HETEROCYCLES, Vol 8 1977

PROFILE AND SCIENTIFIC CONTRIBUTIONS OF PROFESSOR SHIGEHIKO SUGASAWA

Yoshio Ban
Faculty of Pharmaceutical Sciences, Hokkaido University,
Sapporo, 060 Japan

Professor Shigehiko Sugasawa was born in Osaka on April 2, 1898, as the second son of Dr. Takesaburo Sugasawa, one of the most distinguished ophthalmologists in Japan. He started to go to the primary school one year earlier than the regular school age, and graduated from Kitano Middle School of illustrious traditions in March, 1915. While he was a student at the Third High School in Kyoto which was founded and administered by the Federal Government, he used to play baseball as a regular member of the school team, in which I hear he was a tough slogger. Although he had been to go to the Medical School to succeed his father's profession after graduation from the high school, he was intrigued by organic chemistry rather than human anatomy. Thus, he entered the Pharmaceutical Institute, Medical School, Tokyo Imperial University, in April, 1919, because the Institute had the great fame in the field of organic chemistry in Japan. After he finished the undergraduate course at the University, which has been called "University of Tokyo" after the War, he entered the graduate course of the same University, in April, 1922, making research under a direction of Professor Katsuzaemon Keimatsu.

His first paper published with Professor Keimatsu, was concerned with studies on the synthesis of dl-glutamic acid, the method of which includes the step of β-formylpropionic acid [$OHC\text{-}CH_2CH_2COOH$(I)] as a key intermediate strarting from acrolein as is shown in Chart 1.

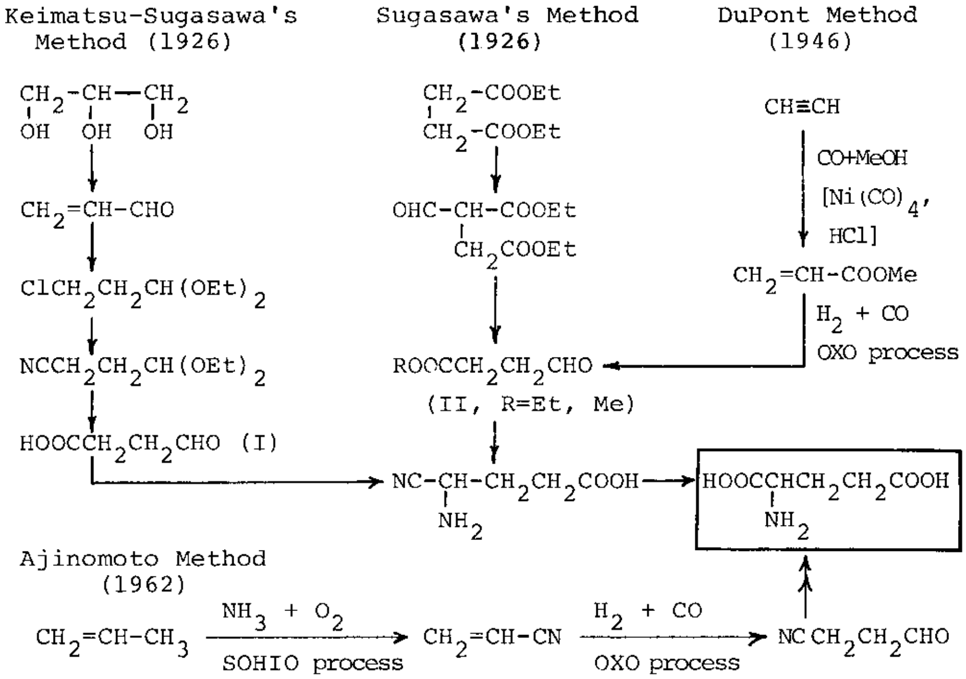


Chart 1. Syntheses of dl-Glutamic Acid

A disadvantage of this method was to use acrolein as a starting material, since it was very difficult to be produced at that time and unpleasant on handling, of course. Therefore, Professor Sugasawa modified the method to effect formylation of ethyl succinate, followed by hydrolysis with water in a sealed tube heated at 120-130° for 2.5-3 hrs, which efficiently furnished ethyl β-formylpropionate(II, R=Et). The product had been erroneously assigned by the former workers to be the corresponding carboxylic acid(I). These methods were not realized in a large scale for the industrial production, but the creativity involved in these methods attracted much attention after the oxo process was first effected by Smith(1930) and substantially developed in Germany during World War II. Inasmuch as the above starting substances have been readily available at present by means of oxo process, several new methods have been invented and industrially operated for large production of sodium l-glutaminate via β-formylpropionic acid or its equivalents[$MeOOCCH_2CH_2CHO$(II, R=Me)(DuPont Method) and $NCCH_2CH_2CHO$(Ajinomoto Method)], which are very similar to Sugasawa's Method before the war and demonstrated in Chart 1 for comparison. These works constituted a part of his dissertation for Ph. D. degree(1928), and were suggestive of Professor Sugasawa's ingenious and productive activities in organic syntheses thereafter.

In Europe in those days, Sir Robert Robinson was presenting his ingenious idea for alkaloid biogenesis via the Mannich reaction. Sir Robert envisioned tropinone arising in the plant by a symmetrical two-part Mannich reaction from succinic dialdehyde, methylamine, and acetone[or its equivalents, for example, calcium acetonedicarboxylate(IV, $R^1=R^2=1/2Ca$)]. To test the possibility of this idea(1917), he mixed these three compounds in water at room temperature and was able to isolate authentic tropinone(V) from the mixture(Chart 2). These experiments were extremely fascinating for young Dr. Sugasawa, since a previous synthesis of tropinone(V) had required a laborious multi-step sequence.

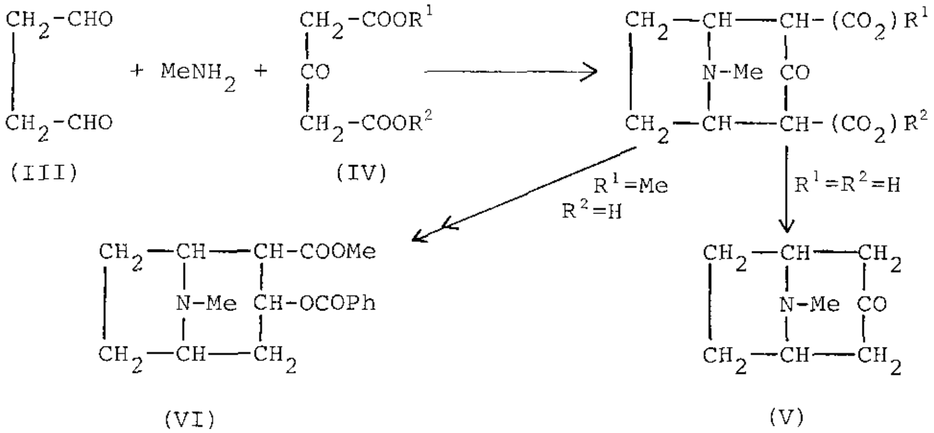


Chart 2

Incidentally, Professor Keimatsu ordered Dr. Sugasawa to make the productive synthesis of cocaine(VI). The superiority of the Robinson's method using IV($R^1=Me$, $R^2=K$) to any other syntheses was obvious, and only one problem was how to prepare succinic dialdehyde(III) in an advantageous way, since the preparation of this aldehyde had been complicated by any known methods. Professor Sugasawa exploited the following excellent method for synthesis of succinic dialdehyde(III) to solve this problem.

$$CH_3COOEt + HCOOEt \xrightarrow{Na} NaOCH{=}CHCOOEt \xrightarrow{EtOH + HCl}$$

$$(EtO)_2CHCH_2COOEt \xrightarrow{KOH} (EtO)_2CHCH_2COOK$$

$$\xrightarrow{\text{Kolbe electrolysis}} (EtO)_2CHCH_2CH_2CH(OEt)_2 \longrightarrow \text{succinic dialdehyde (III)}$$

Chart 3

Professor Keimatsu was completely satisfied at this fine work.

It seems to be natural that Professor Sugasawa went to England in 1929 to work under a direction of Sir Robert Robinson at University College in London(1929-1930) and later at Oxford University(1930-1932).

The very impressive story about his brilliant work on dehydrogenation of laudanosoline hydrochloride in relation to the biogenesis of morphine alkaloids published with Sir Robert Robinson during his stay in England, has been well known in any text book of the chemistry on natural products, as Lord Todd described it in his congratulatory address of this issue.

After he returned to Japan from England in 1932, Dr. Sugasawa was appointed the Assistant Professor of Tokyo Imperial University in 1932 and later promoted to the Full Professor of the same University in 1937, succeeding the chair of Professor Keimatsu.

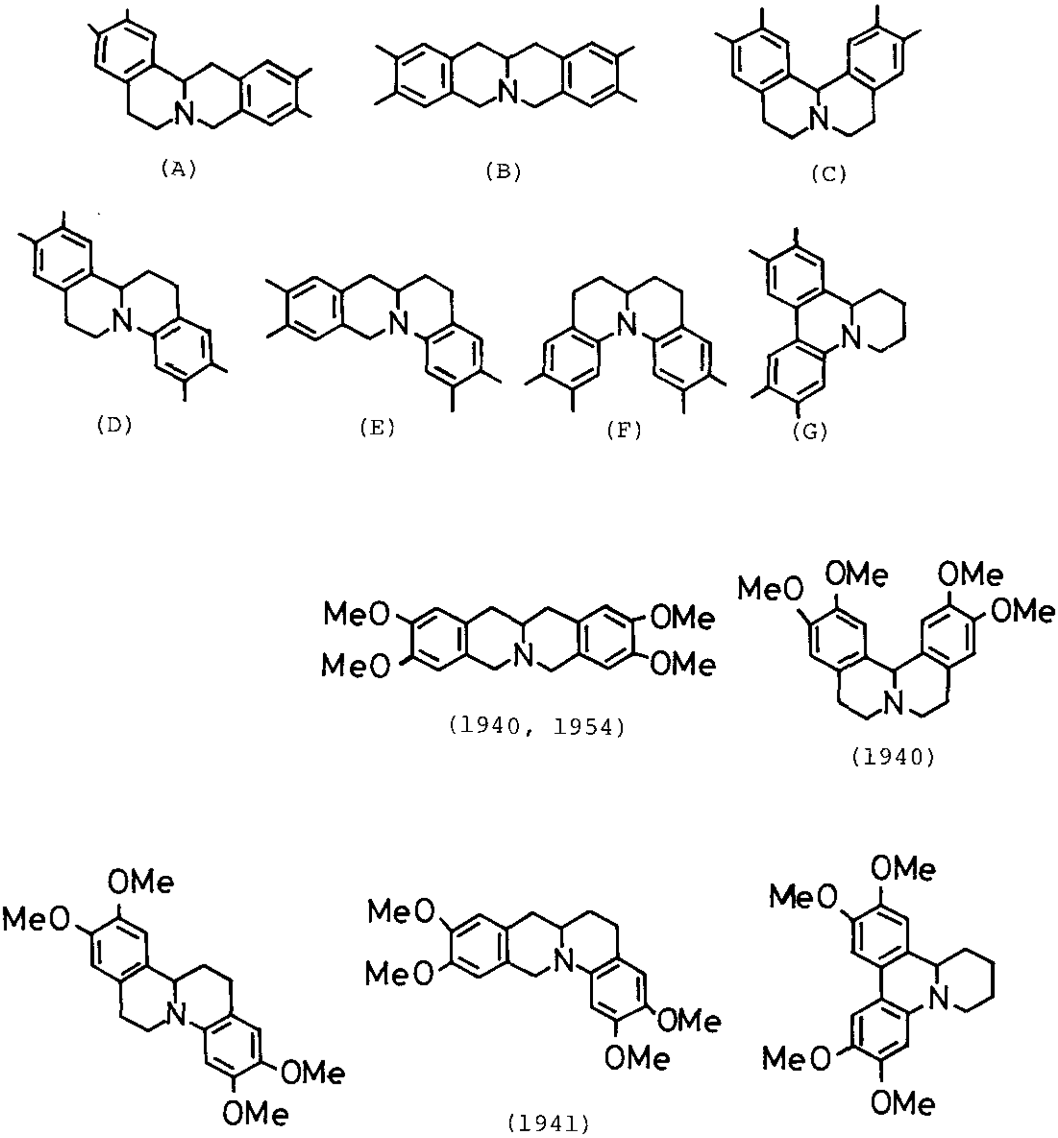
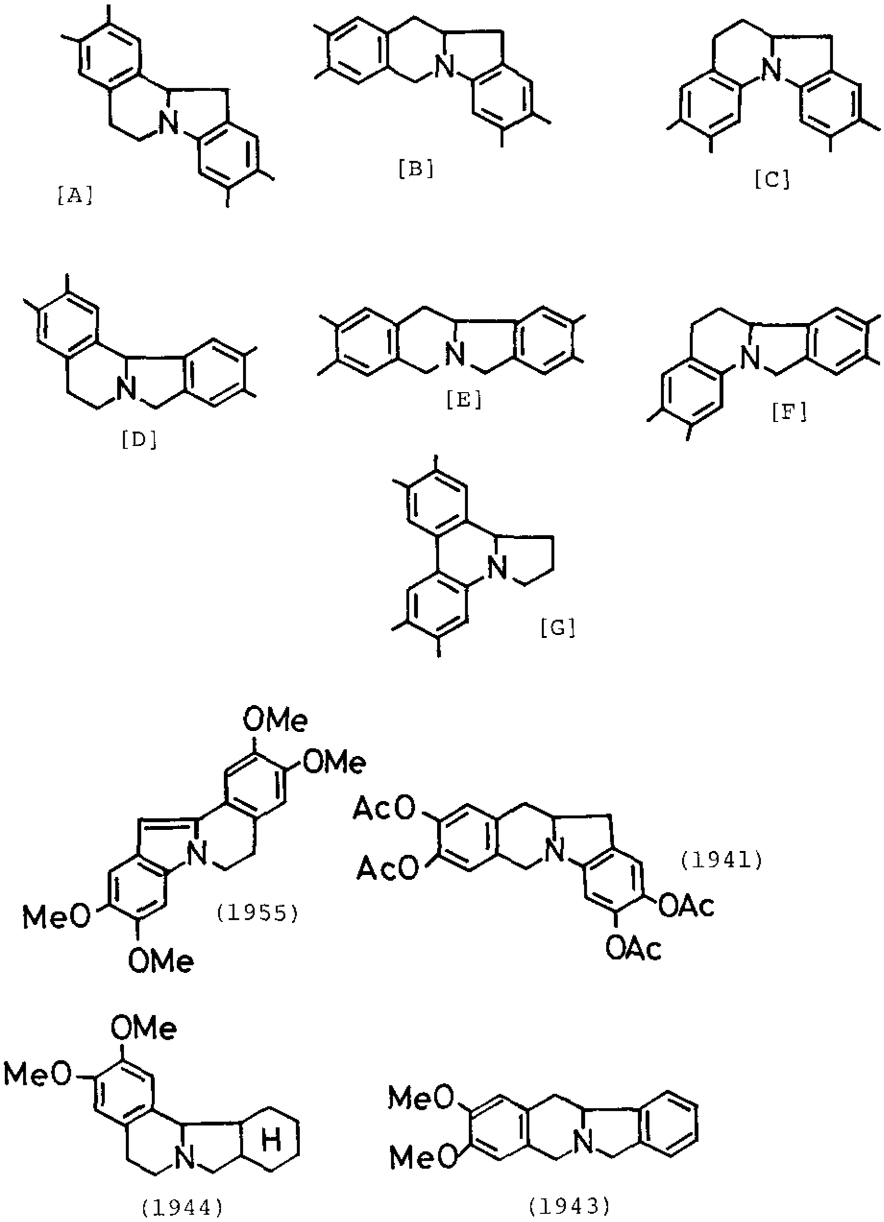

(A)
(B)
(C)
(D)
(E)
(F)
(G)
MeO
MeO
OMe
OMe
(1940, 1954)
MeO
OMe
OMe
OMe
(1940)
OMe
MeO
OMe
OMe
(1940)
MeO
MeO
OMe
OMe
(1941)
OMe
MeO
MeO
OMe
(1942)

Chart 4.

Studies on the Synthesis of Dibenzoindolizine Derivatives



[A] [B] [C]

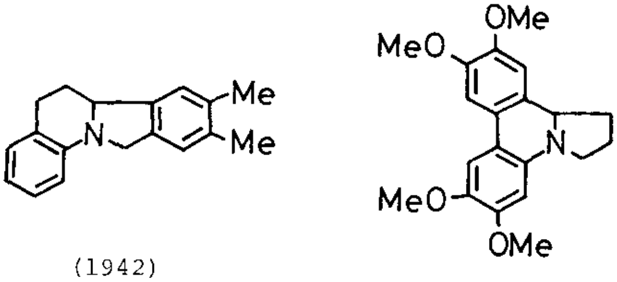
[D] [E] [F]

[G]

(1955) (1941)

(1944) (1943)

Chart 5(1).



(1942)

(1942)

Chart 5(2).

The subject of instruction for this position was officially "Industrial and Pharmaceutical Chemistry".

Professor Sugasawa was naturally enchanted with Sir Robert Robinson's marvellous idea about the structural relations of natural products. In connection with the above elegant work, he attempted the syntheses of seven types[(A)∼(G) in Chart 4] of dibenzoquinolizine derivatives, all of the theoretically possible isomers, which were accomplished unbelievably fast except type(F). [Type(A), the fundamental skeleton of berberine, had been synthesized before his works]. And at the same time, dibenzoindolizines[(A)∼(G) in Chart 5] were synthesized except type(C). The latter halves of Charts 4 and 5 indicate the major compounds synthesized by Professor Sugasawa. For these outstanding works, he was conferred the Award of Imperial Academy in 1943, which is one of the highest awards in science in this country.

As it is impossible for any one to state here all of his numerous publications in limited pages, I would like to illustrate the principal compounds synthesized by Professor Sugasawa consecutively according to the classification appeared in *"The Collection of Papers Dedicated to Professor Shigehiko Sugasawa on Celebration of His 75th Birthday" edited by S. Yamada (1972, Hirokawa Publishing Co., Tokyo).*

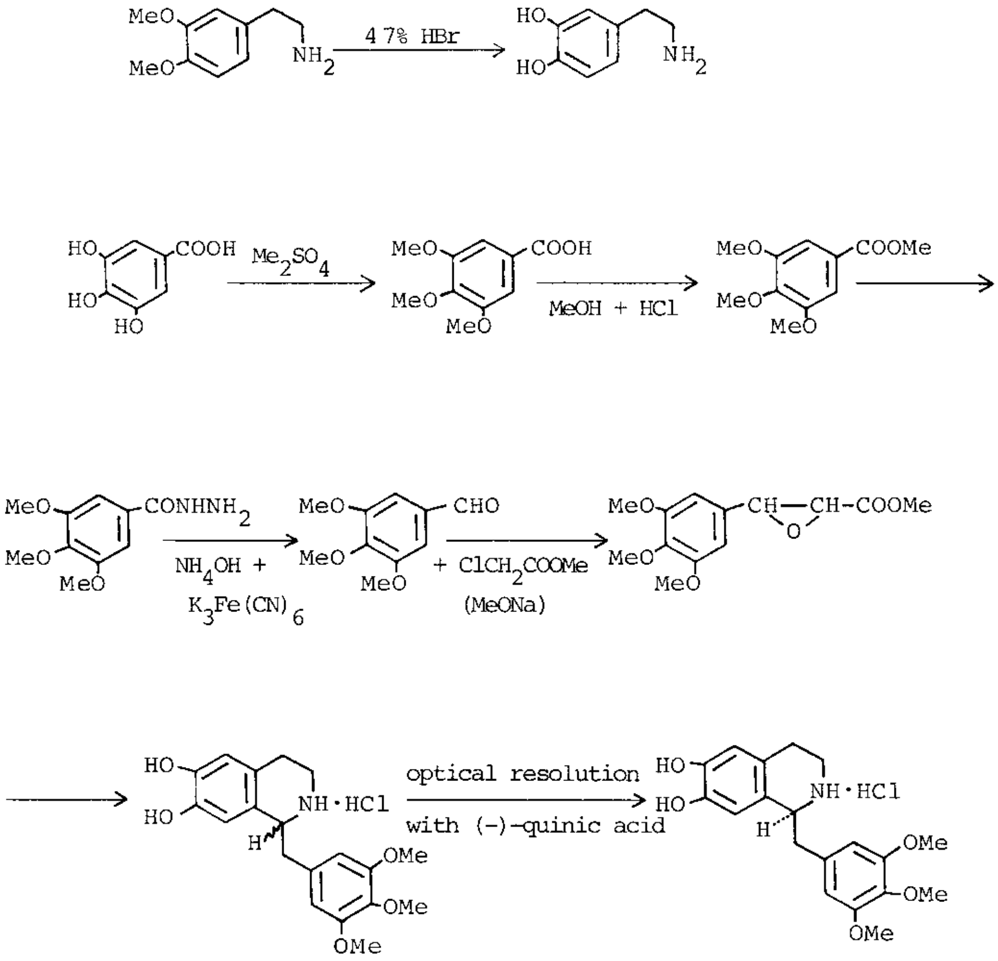
The classification of the works done by Professor Shigehiko Sugasawa is in the following:

I. Studies on Syntheses of Amino Acids, Indoles, Morphine Alkaloids and Flavones. (1926-1937).
II. Studies on the Synthesis of Isoquinoline Derivatives
  II-1. Syntheses of Isoquinoline Derivatives
  II-2. Syntheses of Diisoquinolyl Derivatives
  II-3. Synthesis of 2,2'-Polymethylene-bis(*Py*-tetrahydroisoquinoline) Derivatives
  II-4. Studies on Synthetic Curariform Substances
III. Studies on the Synthesis of Quinoline Derivatives
IV. Studies on the Synthesis of Indole Derivatives
V. Studies on the Synthesis of Dibenzoquinolizine Derivatives (See Chart 4).
VI. Studies on the Synthesis of Dibenzoindolizine Derivatives (See Chart 5).
VII. Studies on the Synthesis of Benzoquinolizine Derivatives

In addition to these contents, the reactions which were discovered or developed by Professor Sugasawa are compiled under R-numbers, but they are rather arbitrarily selected, and therefore I am afraid that his much more significant and interesting reactions might be overlooked. Also, a few synthetic works effected by Professor Sugasawa are simply demonstrated together with the above reactions. All of these reactions and syntheses are arranged on the subsequent pages to the above chapters. I am sure you can enjoy these beautiful works by yourself.

Professor Emeritus Shigehiko Sugasawa, University of Tokyo, has been still engaged in chemical research and working hard with young people at Research Laboratories, Tanabe Pharmaceutial Co., these nearly twenty years since his retirement from the University in 1959. During this period he and his coworkers synthesized about sixty 1-substituted 6,7-dihydroxy-1,2,3,4-tetrahydroisoquinolines for pharmacological evaluation. 1-(3',4',5'-Trimethoxybenzyl) derivative(VII) thus prepared was found to be the most active bronchodilator both *in vitro* and *vivo* test hitherto described in the literature. The synthetic scheme of this compound(VII, AQL-208, See Chapter II-1) is shown in Chart 6.

He has been a member of Japan Academy since November , 1975, which needless to say, is the greatest honor for the scientist in this country.



(VII) (AQL 208)
mp 151-153°(decomp.)
$[\alpha]_D^{21}$ -30.5°(MeOH)

Chart 5. Synthesis of (-)-1-(3',4',5'-Trimethoxybenzyl)-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline(VII)

Apart from scientific activities, may I say that Professor Sugasawa is bright, humorous, generous and frank. He likes neither smoking nor drinking any alcoholic beverage at all. He is very strict in differentiation between public and private affairs. He loves sports, looking and doing them himself. Particularly, he likes playing golf. He won the amateur championship of Japan twice to get "Trophies of Higashikuninomiya Prince" before the War, which have been placed in his study.

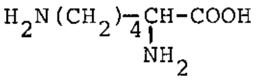
Mrs. Sugasawa passed away in August, 1958. She was an accomplished and compassionate lady. She was very kind to everybody working under a direction of Professor Sugasawa. He has two excellent sons, who are very active in their jobs. Furthermore, Professor Sugasawa has many "chemical and pharmaceutical" sons and "talented" daughters, who have ever worked in his laboratory and are active in various fields.

At the end of this report, I am honored and privileged to have studied under Professor Sugasawa's pertinent tutelage. I would like to offer my sincere congratulations to Professor Sugasawa on his 80th birthday and send him my best wishes for his personal and scientific future with deepest gratitude.

Yoshio Ban

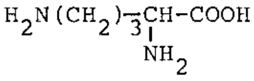
THE MAJOR COMPOUNDS
SYNTHESIZED BY
PROFESSOR SHIGEHIKO SUGASAWA

I. Studies on Syntheses of Amino Acids, Indoles, Morphine Alkaloids and Flavones. (1926~1937)



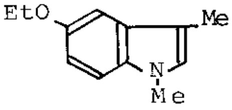
$\mathrm{H_2N(CH_2)_4\underset{NH_2}{\underset{|}{C}}H{-}COOH}$

dl-lysine(1927)

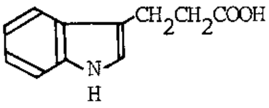


$\mathrm{H_2N(CH_2)_3\underset{NH_2}{\underset{|}{C}}H{-}COOH}$

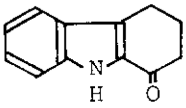
dl-ornithine(1928)



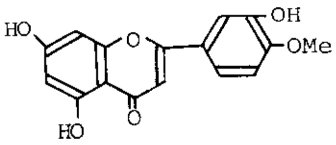
physostigmol-ethylether(1928)



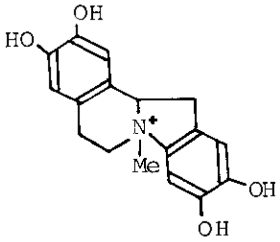
(1928)



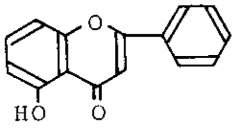
(1928)



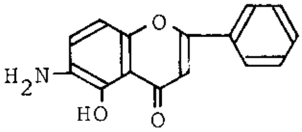
diosmetine
(with Sir Robert Robinson)
(1930)



(with Sir Robert Robinson)
(1932)



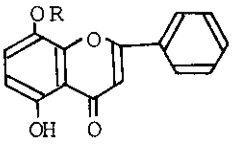
5-hydroxyflavone
(1934)



5-Hydroxy-6-aminoflavone
(1936)

The synthesis of primetinemonomethylether(I, R=Me) was accomplished by Z. Horii under a direction of Professor Sugasawa, which work established the structure for primetine(I, R=H).

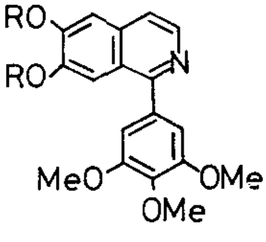
Yakugaku Zasshi, **59**, 552 (1939).



(I, R=Me, H)

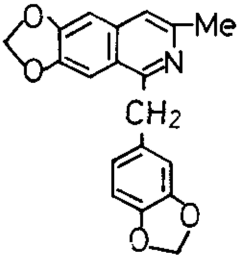
II. Studies on the Synthesis of Isoquinoline Derivatives

II-1. Syntheses of Isoquinoline Derivatives

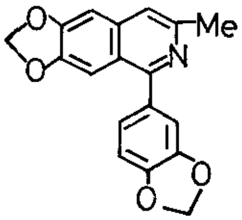


R = Et, n-Pr

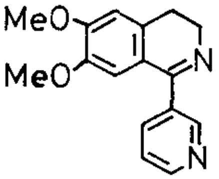
(1935)



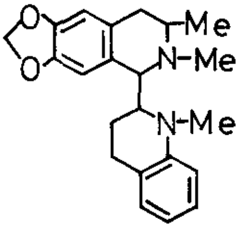
(1936)



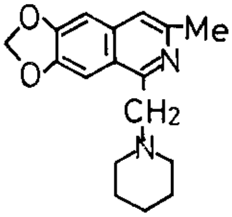
(1936)



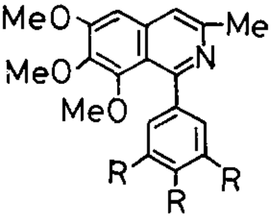
(1936)



(1940)

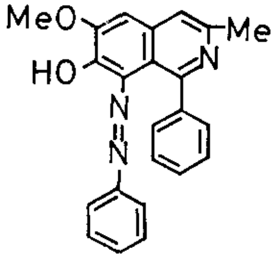


(1940)

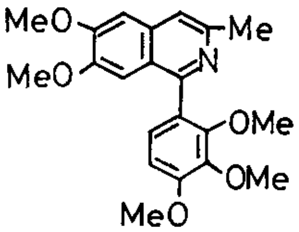


R = H, OMe

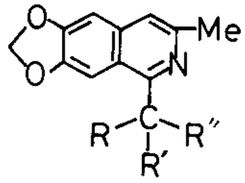
(1937)



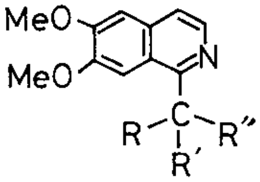
(1938)



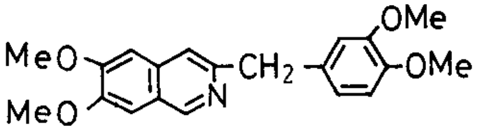
(1942)



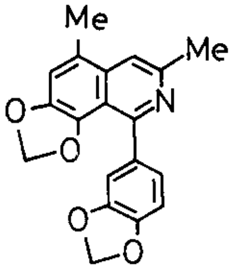
(1954)



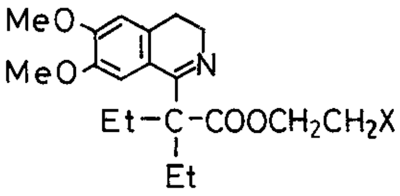
(1958)



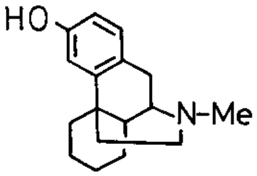
(1954)



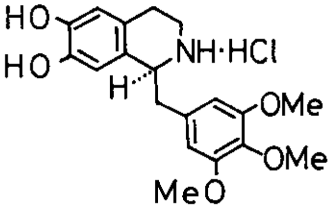
(1954)



X=Cl, NEt_2
(1958)

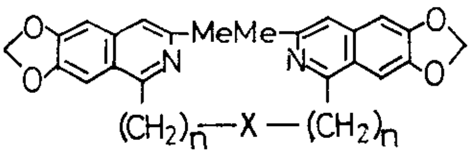


(1959)



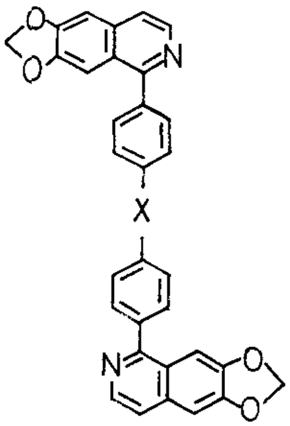
AQL-208 (1966)

II-2. Syntheses of Di-isoquinolyl Derivatives



X = S, SO, SO_2: n = 1, 2

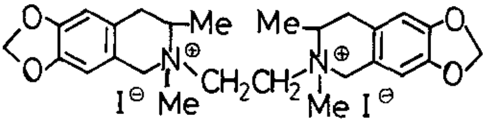
(1944)



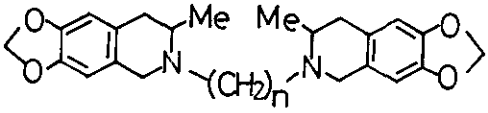
X = S, SO

(1944)

II-3. Synthesis of 2,2'-Polymethylene-bis(*Py*-tetrahydroisoquinoline) Derivatives



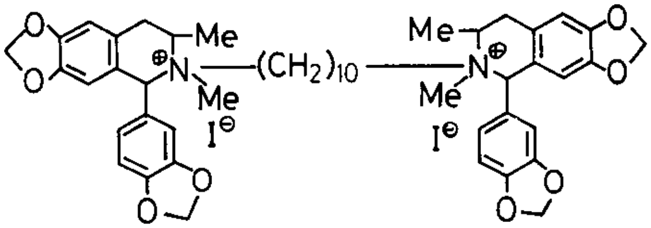
(1953)



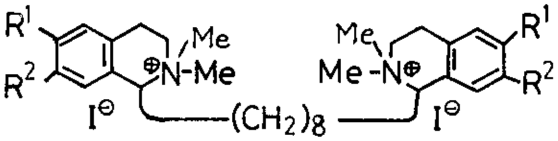
n = 6,7,8,9,10,11,12

(1954)

II-4. Studies on Synthetic Curariform Substances

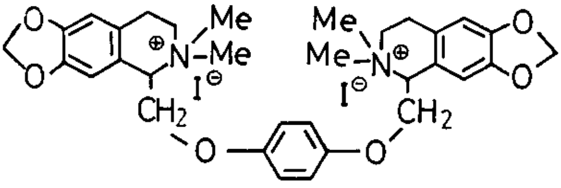


(1954)

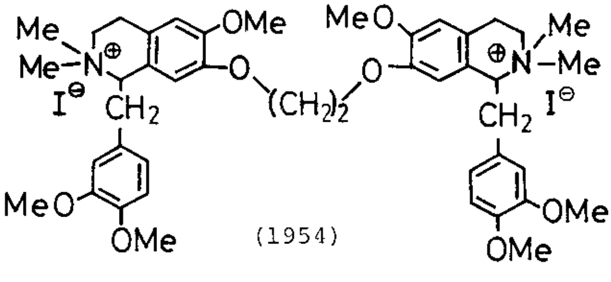


R^1-R^2 = O-CH_2-O; R^1, R^2 = OMe
R^1 = OMe, R^2 = H

(1954)

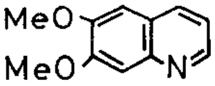


(1954)

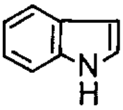


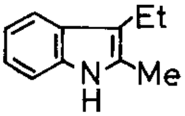
(1954)

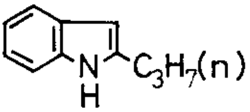
III. Studies on the Synthesis of Quinoline Derivatives

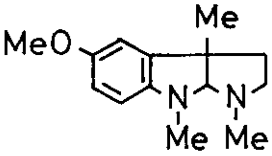

(1938)

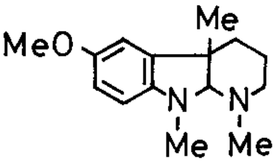
IV. Studies on the Synthesis of Indole Derivatives

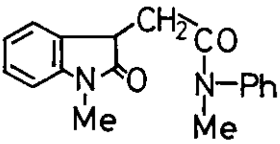

(1938)

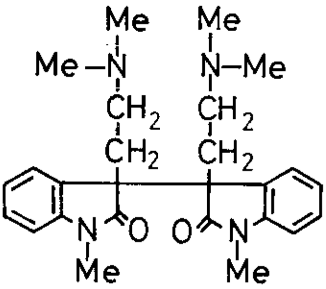

(1953)

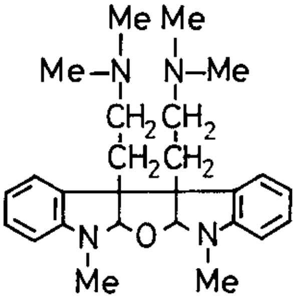

(1953)

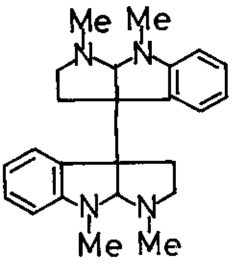

esermethole
(1958)


homoesermethole
(1958)


(1960)

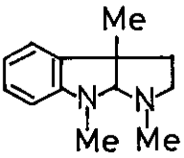

(1961)


(1961)

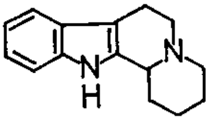


dl-folicanthine

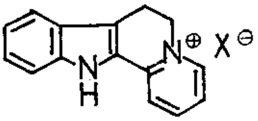
(1963)



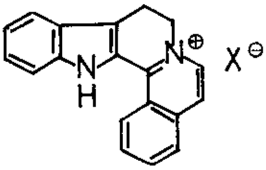
(1963)



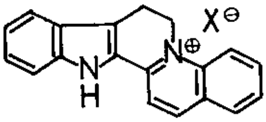
(1956)



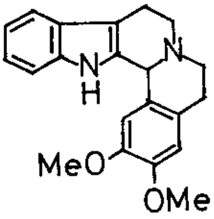
(1956)



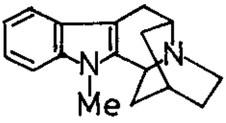
(1959)



(1959)



(1960)

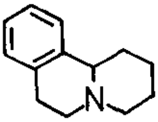


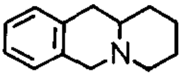
(1965)

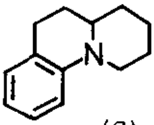
V. Studies on the Synthesis of Dibenzoquinolizine Derivatives (See Chart 4).

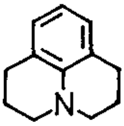
VI. Studies on the Synthesis of Dibenzoindolizine Derivatives (See Chart 5).

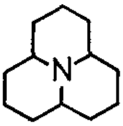
VII. Studies on the Synthesis of Benzoquinolizine Derivatives


(A)

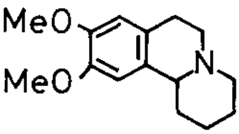

(B)

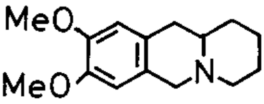

(C)

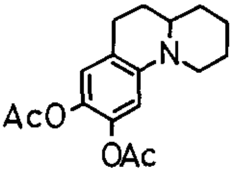

(D)

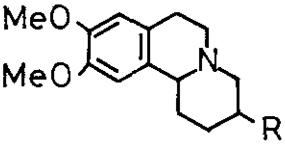

(E)

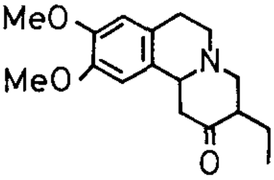
VII-1. Syntheses of Benzoquinolizine Derivatives

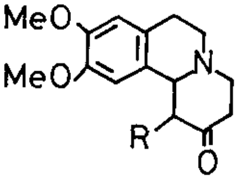

(1939)


(1956)

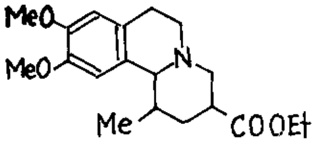

(1943)


$R=(CH_2)_2COOEt$
$R=(CH_2)_2CONMe_2$
$R=(CH_2)_3COOEt$
$R=(CH_2)_3CONMe_2$
(1959)

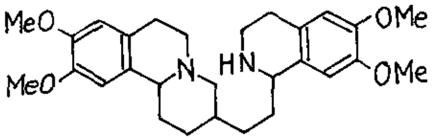

(1959)


R=Me, Et, n-Pr,
n-Bu, i-Bu
(1962)

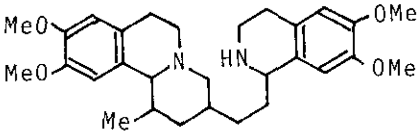
VII-2. Studies on the Synthesis of Emetine



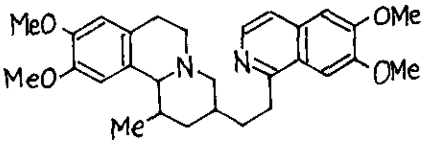
(1942)



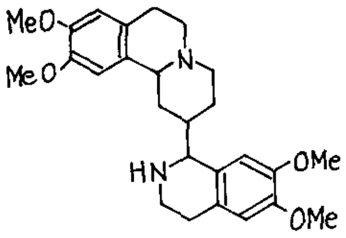
(1942, 1959)



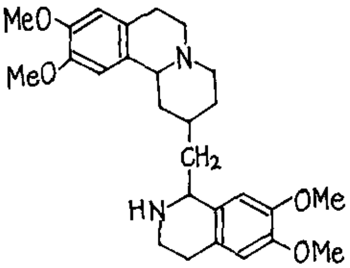
(1949)



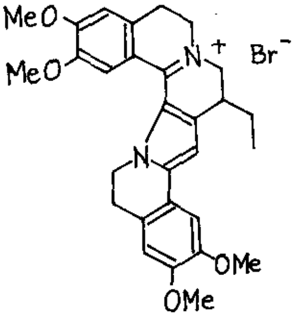
(1949)



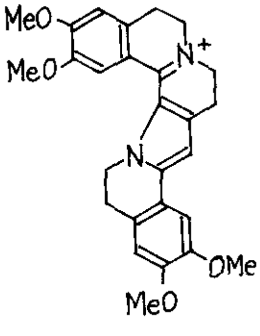
(1953)



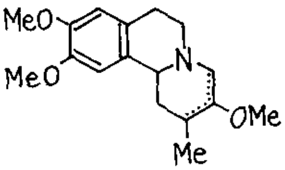
(1954)



(1955)

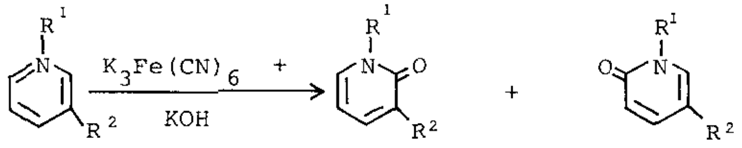


(1959)

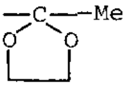
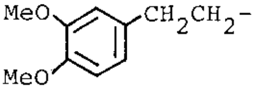


(1958)

VII-3. Oxidation of 3-Substituted 1-Alkyl- or 1-Aralkylpyridinium Salt with Potassium Ferricyanide



(I) (II) (III)

Compound(I)		Product ratio		Yield (%)
R^1	R^2	(II) :	(III)	[(II) + (III)]
Me	Et	89	11	76 1)
Me	Ph	0	100	66 2)
$PhCH_2CH_2$	Ph	0	100	53 2)
Me		0	100	85 3)
	Me	94	6	76 4)
	Et	88	12	71
	n-Bu	74	26	44
	iso-Pr	71	29	79
	$PhCH_2$	69	31	71
	Ph	13	87	50

1) Yakugaku Zasshi, **72**, 1336 (1952). Chem. Pharm. Bull. (Tokyo), **4**, 139 (1955).

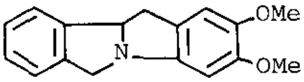
2) Chem. Pharm. Bull. (Tokyo), **3**, 187 (1955).

3) Chem. Pharm. Bull. (Tokyo), **3**, 190 (1955).

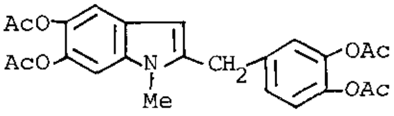
4) The data were provided by Dr. T. Fujii.
Chem. Pharm. Bull. (Tokyo), **25**, 2072 (1977).

VIII. Miscellaneous

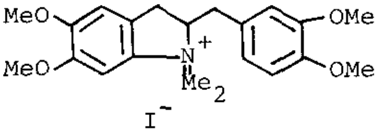
VIII-1. Application of the Robinson Dehydrogenation Reaction (See R-32).



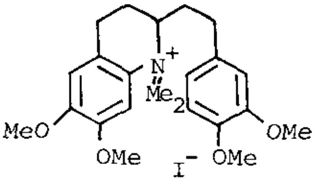
(1955)



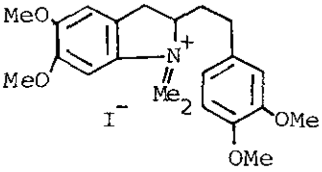
(1959)



(1959)

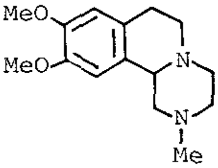


(1959)

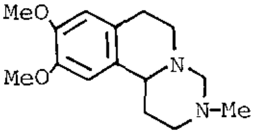


(1959)

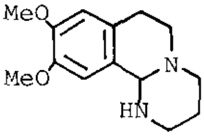
VIII-2. Synthesis of the Azabenzoquinolizine Group



(1959)

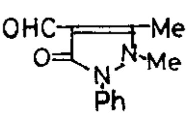


(1959)

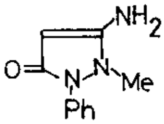


(1959)

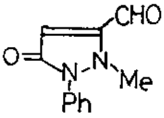
VIII-3. Synthesis of Pyrazolone Derivatives



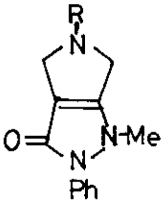
(1956)



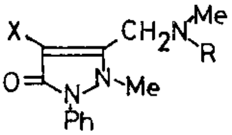
(1956)



(1956)



(1957)



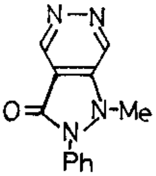
X=Br, R=Me

X=H, R=Me

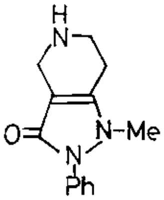
X=Br, R=H

X=H, R=H

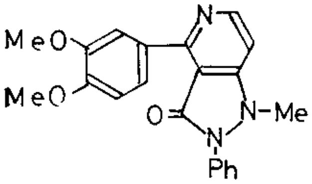
(1956)



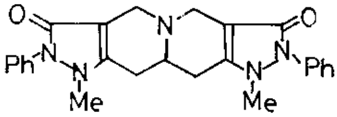
(1957)



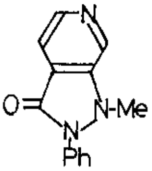
(1956)



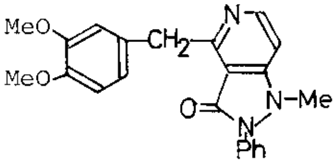
(1956)



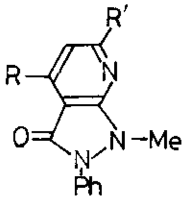
(1961)



(1961)



(1961)



R=Me, R'=H

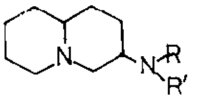
R=H, R'=Me

(1961)

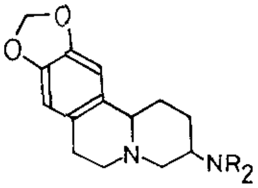
VIII-4. Extension of Bischler-Napieralski Reaction

(See R-13, R-14, R-15, R-16, R-17, R-18, R-19).

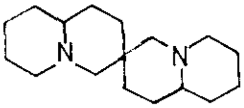
VIII-5. Synthesis of Quinolizine Derivatives



R=R'=H
R=R'=Me (1959)
R=H, R'=Me

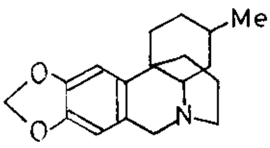


R=H, Me
(1959)

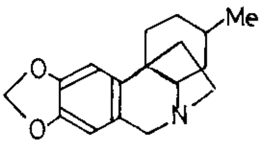


(1959)

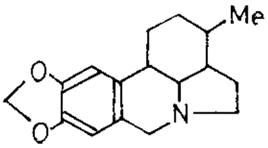
VIII-6. Studies on the Utilization of Safrole as Medicinal Raw Material



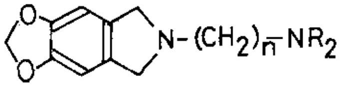
(1962)



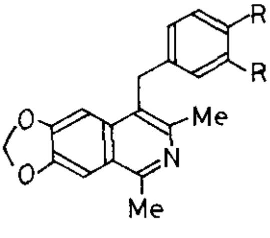
(1962)



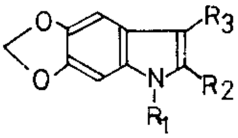
(1962)



n= 2, 2, 3, 3 (1959)
R=Me, Et, Et, Et

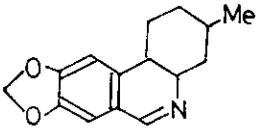


R=H, OMe
(1959)

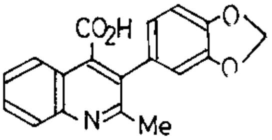


$R_1=R_3=H$, $R_2=Me$
$R_1=R_2=Me$, $R_3=H$
$R_1=R_2=R_3=Me$
$R_1=H$, $R_2=R_3=Me$

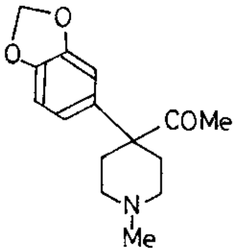
(1959)



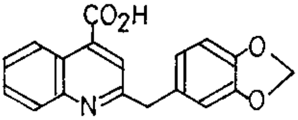
(1959)



(1959)

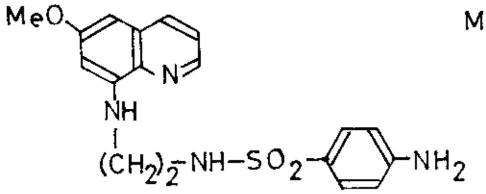


(1959)

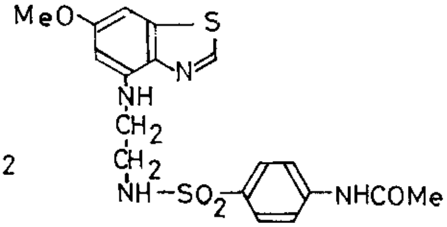


(1959)

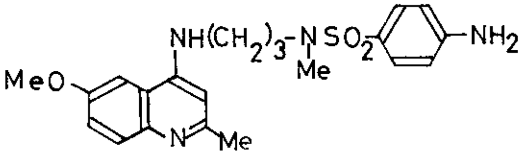
VIII-7. Studies on Synthetic Antimalarial Drugs



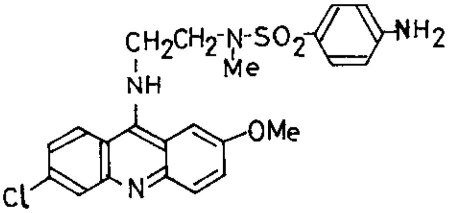
(1942)



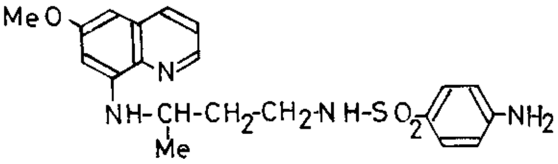
(1943)



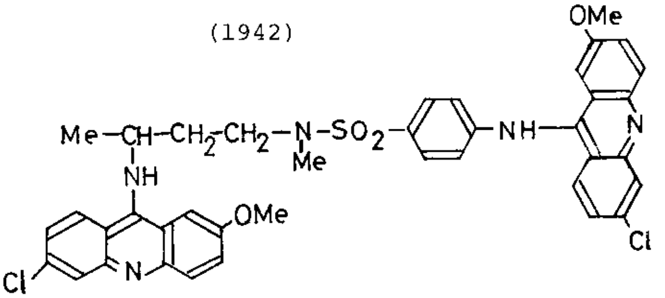
(1942)



(1942)



(1942)



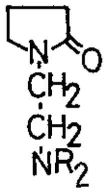
(1943)

VIII-8. The Reaction of Formamide

(See R-7, R-8, R-9, R-10, R-11).

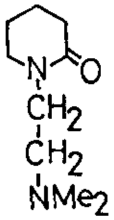
VIII-9. Studies on the Synthesis of Antihistamines

(See R-26).

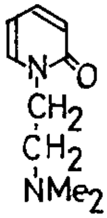


R=Me, Et

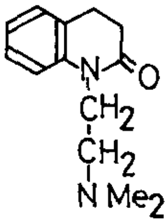
(1950)



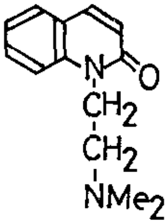
(1950)



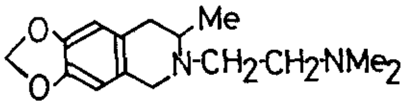
(1950)



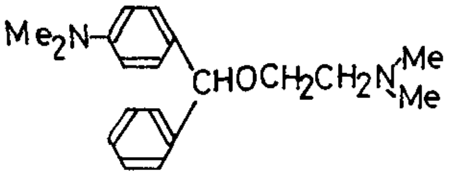
(1950)



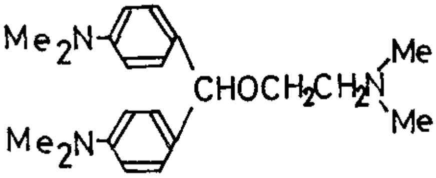
(1950)



(1950)

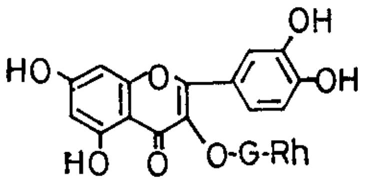


(1950)



(1950)

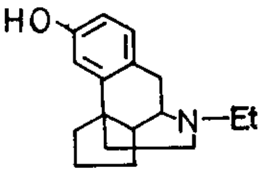
VIII-10. Chemical and Pharmacological Studies on Rutin Derivatives



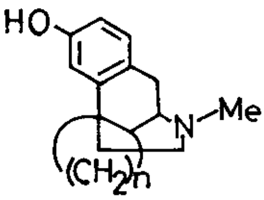
(1951)
G = Glucose
Rh = Rhamnose

VIII-11. Application of the Ball Reaction on Aromatic Alcohol (See R-30).

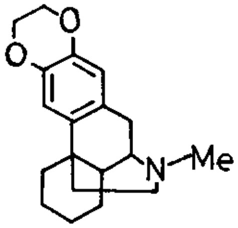
VIII-12. Synthesis in the Morphinan Group



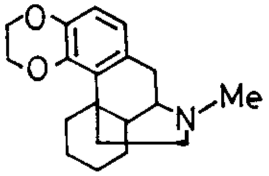
(1956)



n=3, 5.
(1956)

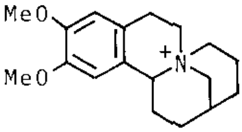


d and *l*
(1960)

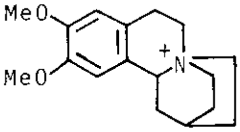


d and *l*
(1960)

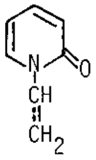
VIII-13. Miscellaneous



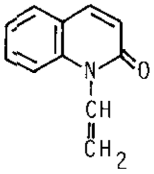
(1959)



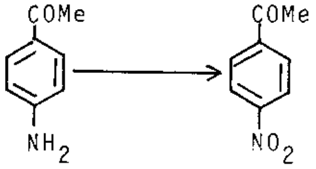
(1959)



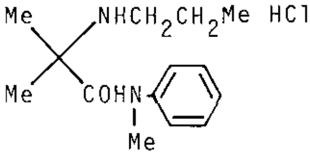
(1950)



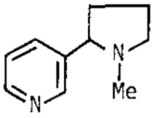
(1950)



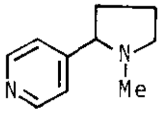
(1951)



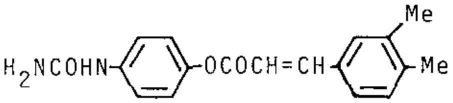
(1969)



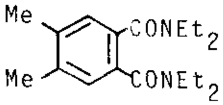
(1954, 1961)



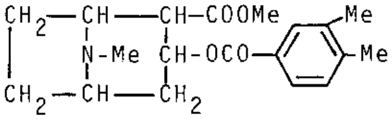
(1954)



(1941)



(1941)



(1941)

REACTIONS AND SYNTHESES

BY

PROFESSOR SHIGEHIKO SUGASAWA

R-1 Modified Curtius Degradation. I.

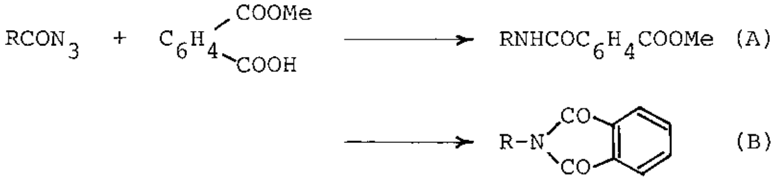
$$RCOOH \longrightarrow RCONHNH_2 \longrightarrow RCON_3 \longrightarrow$$

$$RNHCOOC_7H_7 \longrightarrow RNH_2 + C_6H_5CH_3 + CO_2$$

Proc. Imp. Acad.(Tokyo), **20**, 137 (1944).
Yakugaku Zasshi, **64**(**B**), 20 (1944).

The hydrogenolysis of the benzylurethane was effected with palladium black or Raney nickel under high pressure of hydrogen. If the amine generated is a weak base like aniline, addition of alcoholic alkali was recommended to avoid dilution of hydrogen by carbon dioxide.

R-2 Modified Curtius Degradation. II.



$$RCON_3 + C_6H_4\begin{matrix}COOMe\\COOH\end{matrix} \longrightarrow RNHCOC_6H_4COOMe \quad (A)$$

(B)

An equimolar mixture of an azide and phthalic acid ester in benzene was boiled in a water bath to give the amide(A), which was further heated at 130-140° to furnish the N-substituted phthalimide(B) in an excellent yield.

Yakugaku Zasshi, **68**, 65 (1948).

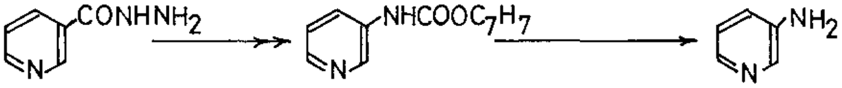
R-3 Modified Curtius Degradation. III.

$$RNHCOOC_7H_7 \longrightarrow RNH_2 + C_7H_7OH + CO_2$$

Yakugaku Zasshi, **72**, 152 (1952).

The use of the mixed acid[20%HCl + CH_3COOH(1:1)] was recommended on heating for this reaction.

Example:



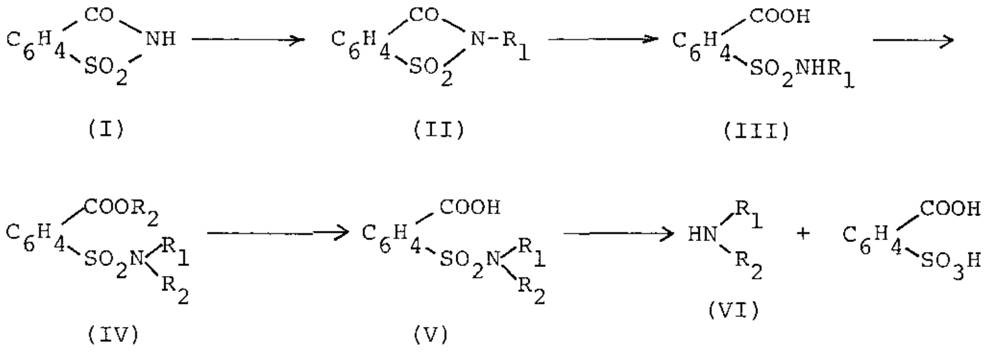
R-4 Reduction of Aliphatic Unsaturated Nitriles with Raney Cobalt Catalyst

$$\underset{\text{(I)}}{PhCH{=}CH{-}CH_2CN} \longrightarrow \underset{\text{(II)}}{PhCH{=}CH{-}CH_2CH_2NH_2}$$

Yakugaku Zasshi, 81, 1563 (1961). Cf. ibid., 76, 351 (1956).

Raney cobalt alloy (Kawakami Kenkyusho OD 4016: Co, 44%; Fe, 0.4%) was submitted to the preparation procedure(W-7) of Raney Ni to afford Raney Co, which was washed with the solvent used for the reduction three times. The use of benzene gives better result than methanol as a solvent in the high pressure catalytic hydrogenation of 4-phenyl-3-propenonitrile(I) to afford 1-phenyl-4-amino-1-butene(II). When methanol is used, a fair amount of 1-amino-4-phenylbutane was found to be formed as a by-product. A few kinds of unsaturated nitriles were submitted to reduction under these conditions and the corresponding unsaturated amines were obtained in good yields.

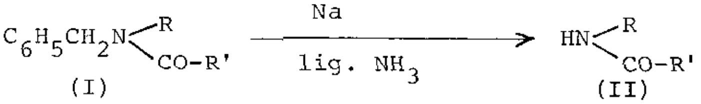
R-5 A New Method for the Preparation of Secondary Amines (Saccharine Method)



Saccharine(I) was found to be a suitalbe starting material for the preapration of alkyl and aralkyl secondary amines(VI). It is not necessary to isolate intermediates(III, IV and V).
The readiness of the last stage hydrolysis(V ⟶ VI), when compared with that of usual arylsulfone dialkylamide, is to be emphasized.

Yakugaku Zasshi, 72, 270 (1952).

R-6 Debenzylation of N-Benzyl-acylamides



Chem. Pharm. Bull.(Tokyo), 6, 587 (1958).

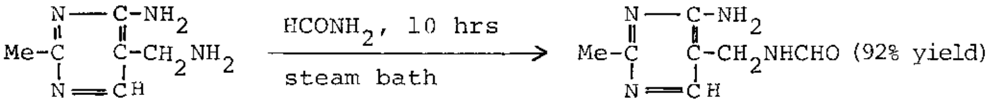
The inability of activated hydrogen to cleave the benzyl group from N-benzyl-acyl-amides(I), as is reported in literature, was confirmed. Metallic sodium in liquid ammonia was now found to be an excellent combination to debenzylate the above-mentioned type of compounds. Several N-benzyl-acylamides and N-benzyl-lactams were thus cleaved to yield the debenzylated products in good yields. The benzyl moiety was recovered as toluene and the presence of dibenzyl in the reaction product was not traced.

R-7 The Formylation of the Amines with Formamide

$$R\text{-}CH_2NH_2 + HCONH_2 \longrightarrow RCH_2NHCHO$$

Examples:

$$C_6H_5CH_2NH_2 \xrightarrow[\text{steam bath}]{HCONH_2,\ 6\ hrs} C_6H_5CH_2NHCHO \text{ (98\% yield)}$$



An equimolar mixture of the amine and formamide is heated in an oil bath until the cease of evolution of ammonia to yield the formyl derivative usually in crystalline forms in excellent yields. Eleven examples are reported.

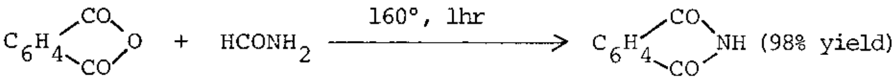
Yakugaku Zasshi, 62, 531 (1942).

R-8 The Amidation of Carboxylic Acids with Formamide

$$R\text{-}COOH + HCONH_2 \longrightarrow RCONH_2 + (HCOOH)$$

Examples:

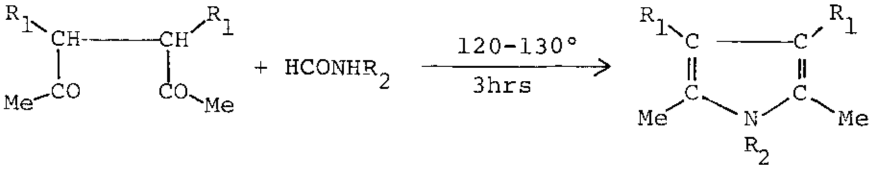
$$PhCH_2COOH + HCONH_2 \xrightarrow{160\text{-}180°,\ 8\ hrs} PhCH_2CONH_2 \text{ (92\% yield)}$$



Yakugaku Zasshi, 62, 532 (1942).

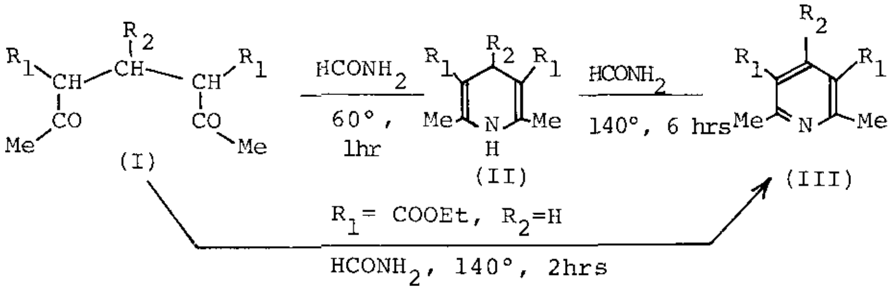
An equimolar mixture of the carboxylic acid and formamide is heated in an oil bath. Nineteen examples are described. Sodium sulfate is an effective catalyst in some cases to improve the yield as well as boric acid.

R-9 The Reaction of Formamide with 1,4-Diketones. Formation of Pyrrole Derivatives



Yakugaku Zasshi, **64**, 192 (1944).

R-10 The Reaction of Formamide with 1,5-Diketones

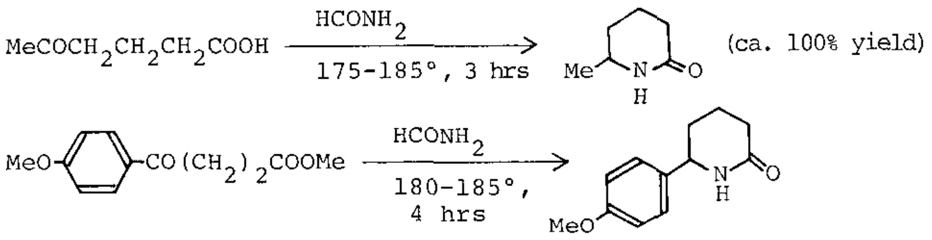


Yakugaku Zasshi, **64**, 192 (1944).

The modified procedure using formamide instead of ammonia for synthesis of pyridine derivatives by Hantsch's method, is as follows. A mixture of ethyl acetoacetate(26 g), paraformaldehyde(3 g) and formamide(25 g) was heated at 140° for 5 hrs, during which time the reaction vessel was occasionally shaken.

On cooling, the mixture was poured on water to yield the basic product(III, 14.5 g) after the usual work-up. When paraaldehyde or benzaldehyde was used in place of paraformaldehyde in the above procedure, the corresponding products(II) were obtained.

R-11 The Reaction of Formamide with Keto-acids and Keto-esters



Yakugaku Zasshi, **64**, 199 (1944).

R-12 A Modified Emde Degradation (Reductive Cleavage of Quaternary Ammonium Salts by Raney Nickel)

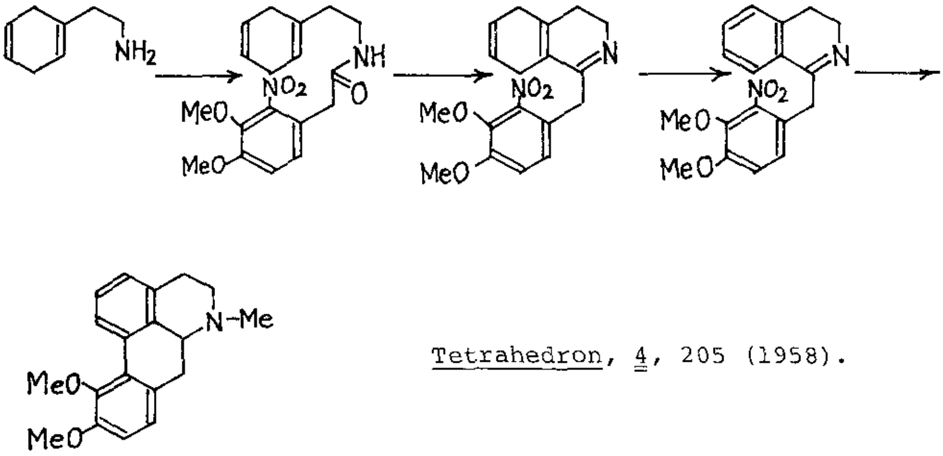
$$PhCH_2CH_2\overset{+}{N}Me_3 \longrightarrow PhCH_2CH_3(85\%) + Me_3N(87\%)$$

A modified Emde degradation in which a combination of Raney nickel and sodium hydroxide solution was used as the reaction agent in place of sodium amalgam in the original Emde reaction.

Chem. Pharm. Bull.(Tokyo), **6**, 601 (1958).

R-13 Extension of Bischler-Napieralski Reaction. I.

A Synthesis of rac-Apomorphine Dimethyl Ether



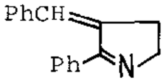
Tetrahedron, 4, 205 (1958).

The scope of Bischler-Napieralski reaction has now been extended to include acyl cyclohexa-1,4-dienylethylamine types, which cyclize smoothly to yield various isoquinolines after dehydrogenation. 1(2-Nitro-3,4-dimethoxybenzyl)-3,4-dihydroisoquinoline, hitherto difficulty accessible, could be prepared and converted to rac-apomorphine dimethyl ether.

R-14 Extension of Bischler-Napieralski Reaction. II.

Synthesis of Pyrroline Derivatives

PhCH=CH-CH_2CH_2NHCOPh ⟶

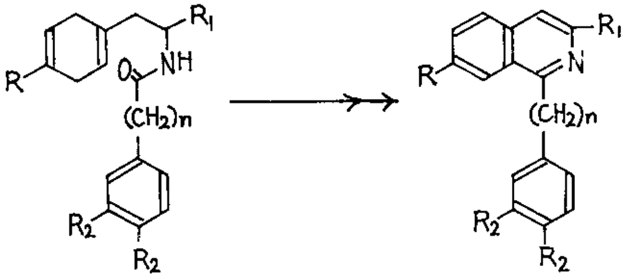


Acyl derivatives of 4-phenyl-but-3-enylamine(I) on treatment with phosphoryl chloride gave good yields of pyrrolines(II). Pyridine or benzazepine derivatives were not obtained.

Tetrahedron, 5, 48 (1959).

R-15 Extension of Bischler-Napieralski Reaction. III.

A Synthesis of Some Isoquinolines Related to Papaverine.



(I) (IIa,b,c,d)

Tetrahedron, 7, 118 (1959).

a: $R=R_1=H$, $R_2=OMe$, n=1

b: $R=H$, $R_1=Me$, $R_2-R_2=O-CH_2-O$
n=1

c: $R=H$, $R_1=Me$, $R_2-R_2= O-CH_2-O$
n=0

d: $R=R_2=OMe$, $R_1=H$, n=1

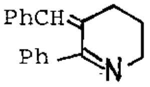
The Bischler-Napieralski reaction has been applied to the synthesis of several isoquinoline derivatives related to papaverine but devoid of one or two methoxyl groups in positions 6 and 7.

R-16 Extension of Bischler-Napieralski Reaction. IV.

Synthesis of Pyridine Derivatives

$PhCH=CH-CH_2CH_2CH_2NHCOPh \xrightarrow{POCl_3}$

(I)

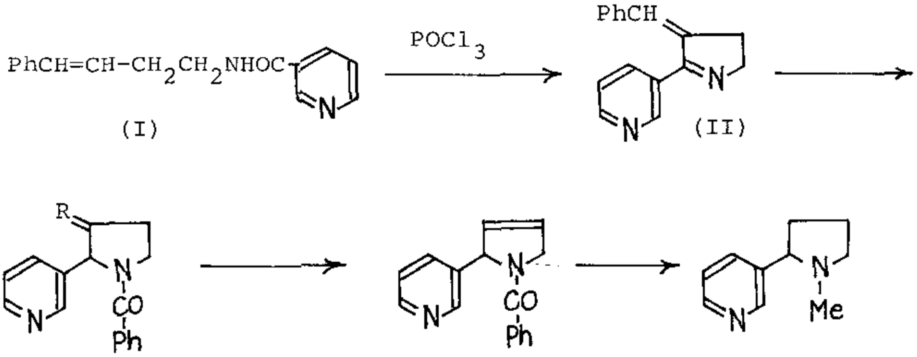


Tetrahedron, 7, 185 (1959).

Acyl derivatives of 5-phenylpent-4-enylamine(I) were cyclized to give 2-substituted 3-benzal-3,4,5,6-tetrahydropyridines in good yields. This is a new synthesis of pyridine derivatives.

R-17 Extension of Bischler-Napieralski Reaction. V.

A New Synthesis of *rac*-Nicotine



(I)

(II)

(IIIa) R=PhCH

(IIIb) R=O

(IIIc) R=TsNHN

(IV)

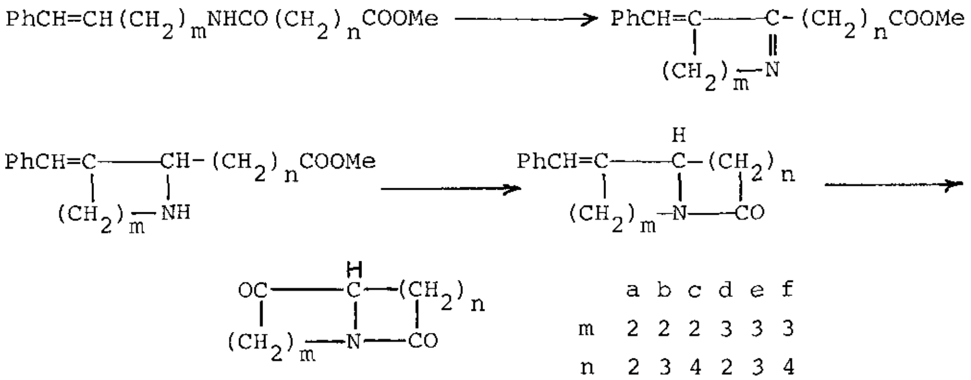
(V)

Chem. Pharm. Bull. (Tokyo), **9**, 818 (1961).

R-18 Extension of Bischler-Napieralski Reaction. VI.

Synthesis of 1-Azabicyclo[x,y,0]alkanediones

$PhCH{=}CH(CH_2)_mNH_2 + ClOC(CH_2)_nCOOMe \longrightarrow$



$$PhCH{=}CH(CH_2)_mNHCO(CH_2)_nCOOMe \longrightarrow \begin{array}{l} PhCH{=}C\text{---}C\text{-}(CH_2)_nCOOMe \\ \qquad\;\; | \qquad\quad \| \\ \quad (CH_2)_m\text{---}N \end{array}$$

$$\begin{array}{l} PhCH{=}C\text{---}CH\text{-}(CH_2)_nCOOMe \\ \qquad\;\; | \qquad\quad | \\ \quad (CH_2)_m\text{---}NH \end{array} \longrightarrow \begin{array}{l} \qquad\qquad\quad\;\; H \\ PhCH{=}C\text{---}C\text{-}(CH_2)_n \\ \qquad\;\; | \qquad\; | \qquad | \\ \quad (CH_2)_m\text{-}N\text{---}CO \end{array} \longrightarrow$$

$$\begin{array}{l} \qquad\qquad\quad H \\ OC\text{---}C\text{---}(CH_2)_n \\ \;\;| \qquad\;\; | \qquad\;\; | \\ (CH_2)_m\text{---}N\text{---}CO \end{array}$$

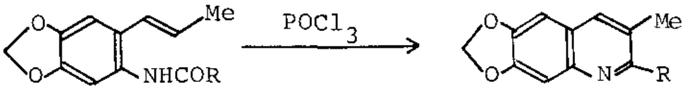
	a	b	c	d	e	f
m	2	2	2	3	3	3
n	2	3	4	2	3	4

Chem. Pharm. Bull. (Tokyo), **10**, 366 (1962).

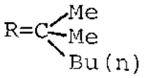
4-Phenyl-3-butenyl- and 5-phenyl-4-pentenyl-amine were acylated with chloride of methyl hydrogen succinate, glutarate and adipate yielding six kinds of ester amide(Ia,b,c,d,e,f), all of which except(Id) were cyclized with ease on being treated with $POCl_3$ in boiling benzene, giving three pyrrolines(IIa,b,c) and two hydropyridines(IIe,f). These were reduced and converted into the corresponding lactams(IIIa,b,c,e,f) from which benzylidene group was removed by ozonization furnishing 5 kinds of title compounds(IVa,b,c,e,f). Their structures were supported by converting one(IVe) of them to the known 1-quinolizidinone, which was identified with the authentic specimen.

R-19 Extension of Bischler-Napieralski Reaction. VII.

Synthesis of Quinoline Derivatives

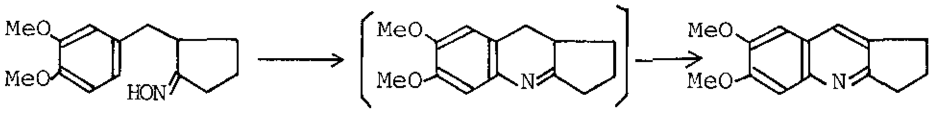


Yakugaku Zasshi, 85, 231 (1965).

		Yield(%)
a:	R=Me	51.4
b:	R=Ph	28.4
c:	$R{=}CMe_3$	32.1
d:	 $\mathrm{R{=}C}\begin{matrix}\mathrm{Me}\\\mathrm{Me}\\\mathrm{Bu(n)}\end{matrix}$	42.6
e:	$R{=}CH_2Cl$	43.1

On treating with phosphoryl chloride, acyl derivatives of 6-aminoisosafrole gave quinolines.

R-20 A New Cyclization Reaction of Cyclic Ketoxime



(II)

Chem Pharm. Bull.(Tokyo), 9, 104 (1961).

When treated with phosphoryl chloride in boiling toluene 2-veratrylcyclopentanone oxime suffered an intramolecular dehydration, in which oxime-OH took part, to form 6,7-dimethoxy-2,3,9,9a-tetrahydro1H-cyclopenta[b]quinoline(II). Spontaneous dehydrogenation of the latter resulted in the formation of 6,7-dimethoxy -2,3-dihydro-1H-cyclopenta[b]quinoline as the ultimate product. 2-Veratrylcyclohexanone oxime behaved similarly, but gave an inferior yield of 6,7-dimethoxy-1,2,3,4-tetrahydroacridine. This is a novel dehydration reaction of an oxime.

R-21 Acetalization of the Unstable Formyl Derivatives

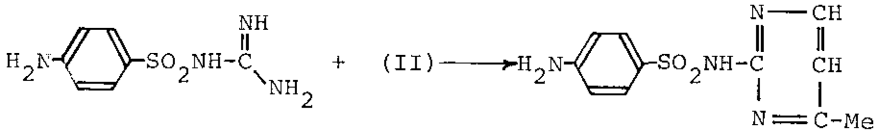
$$\mathrm{NaOCH{=}CHCOOEt} \xrightarrow{\mathrm{EtOH\ +\ HCl}} \mathrm{(EtO)_2CHCH_2COOEt}$$

Yakugaku Zasshi, 47, 551 (1927). (I)

$$\mathrm{NaOCH{=}CHCOMe} \longrightarrow \mathrm{(EtO)_2CHCH_2COMe}$$

Yakugaku Zasshi, 69, 82 (1949). (II)

Utilization of the latter acetal for cyclization to the pyrimidine ring:



R-22 Esterification by 'Melange azeotropique' Method

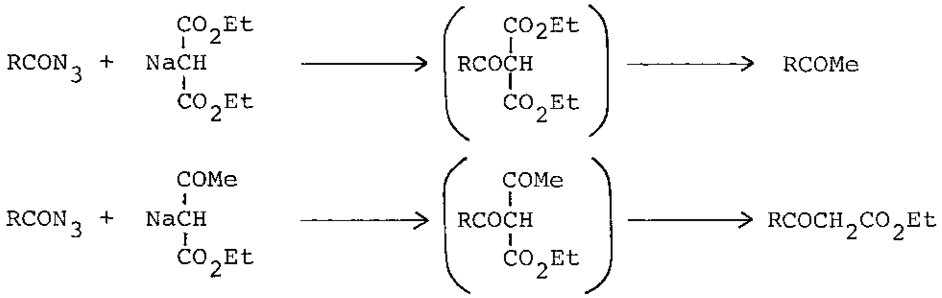
$$RCOOH \xrightarrow[(HCl)]{EtOH + toluene} RCOOEt$$

A typical procedure:

A mixture of ethanol(300 g), toluene(200 g), adipic acid(146 g), 2.5 ml of concentrated hydrochloric acid and ethanol(2 mol, which are required for esterification) was heated in a steam bath to evaporate an zeotropic mixture(bp 75-78°). A similar treatment was repeated by adding the same amount of ethanol and toluene to the residual mixture. The final residue was submitted without washing with water, to the distillation under diminished pressure. $Bp_{177mm}134°$ (85-88% yield). Twelve examples are described.

Yakugaku Zasshi, **47**, 1050 (1927).

R-23 Acid Azide as an Acylating Agent.



$$RCON_3 + \underset{CO_2Et}{\overset{CO_2Et}{NaCH}} \longrightarrow \left(\underset{CO_2Et}{\overset{CO_2Et}{RCOCH}}\right) \longrightarrow RCOMe$$

$$RCON_3 + \underset{CO_2Et}{\overset{COMe}{NaCH}} \longrightarrow \left(\underset{CO_2Et}{\overset{COMe}{RCOCH}}\right) \longrightarrow RCOCH_2CO_2Et$$

Chem. Pharm. Bull.(Tokyo), **3**, 32 (1955).

Diethyl sodiomalonate and ethyl sodioacetoacetate were treated with azides of α-,β-, and γ-pyridine-carboxylic acids in absolute ether, furnishing the corresponding diethyl pyridoylmalonate and ethyl pyridoylacetoacetate in fair yields. Thus, azide of various basic carboxylic acids can advantageously be used for similar purposes, when acid chloride is hard to obtain in a pure state, which is usually the case in various basic carboxylic acid.

R-24 Preparation of Nitrile from Primary Amide

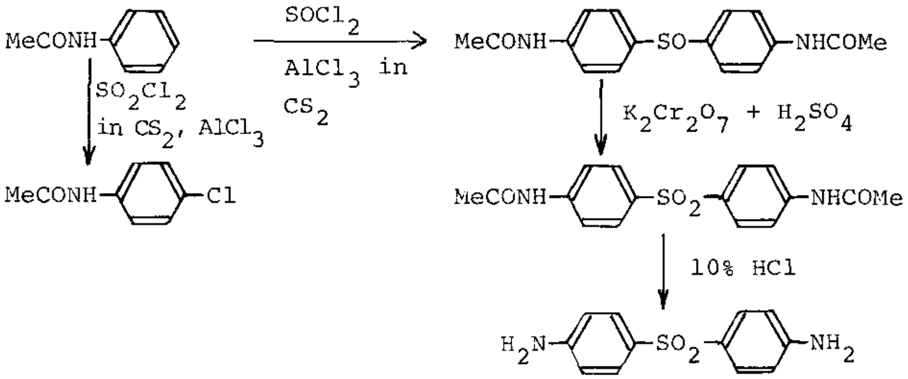
$$PhCONH_2 + PPh_3 + CCl_4 \longrightarrow PhC(Cl){=}NH + O{=}PPh_3 + CHCl_3$$

$$PhC(Cl){=}NH + PPh_3 \longrightarrow PhCN + PPh_3 \cdot HCl$$

Tetrahedron Letters, 4383 (1970).

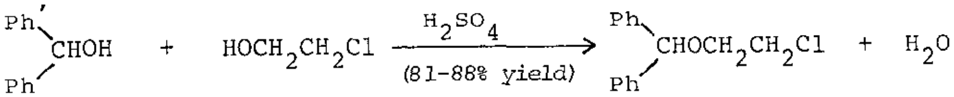
Genral Procedure: A solution of benzamide(1.21 g, 0.01 mole) dissolved in THF(15 ml, dired over Na and distilled) was added to a mixture of PPh_3(5.24 g, 0.02 mole, commercial product used without purification) and CCl_4(15 ml, dried over $CaCl_2$ and distilled) with stirring; a slight evolution of heat was observed. The whole was then warmed at 45-55° to give a clear solution, from which colorless solid begam tp se arate after about 15 min. Warmed altogether for 2 hrs and cooled. A residue obtained after evaporation of filtered solution was distilled to give a colorless liquid of bp_{24}65-70°, yield 0.68 g(83.5%), which was identified with authentic benzonitrile through IR spectral data: ν_{max}^{film} 2280 cm^{-1}(CN).

R-25 The Friedel-Crafts' Reactions with Thionyl Chloride and Sulfuryl Chloride. The Synthesis of 4,4'-Diacetoamino-diphenylsulfone



Yakugaku Zasshi, 60, 22 (1940).

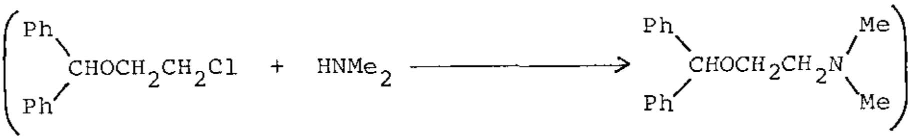
R-26 Synthesis of Benzhydryl β-Chloroethyl Ether



$$Ph_2CHOH + HOCH_2CH_2Cl \xrightarrow[\text{(81-88\% yield)}]{H_2SO_4} Ph_2CHOCH_2CH_2Cl + H_2O$$

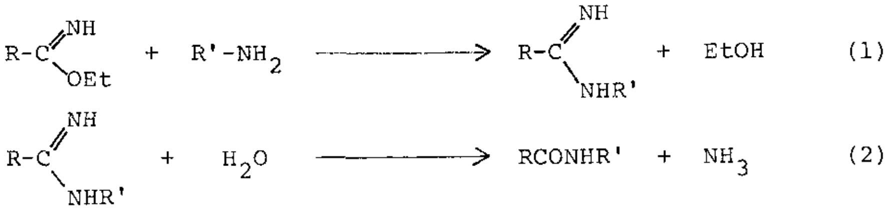
$bp_{1.0}$ 144-148°
colorless viscous oil

Yakugaku Zasshi, 91, 365 (1951). Org. Syn. Coll. Vol., 4, 72 (1963).



$$\left(Ph_2CHOCH_2CH_2Cl + HNMe_2 \longrightarrow Ph_2CHOCH_2CH_2NMe_2 \right)$$

R-27 Synthesis of Several N-Substituted Acid Amides



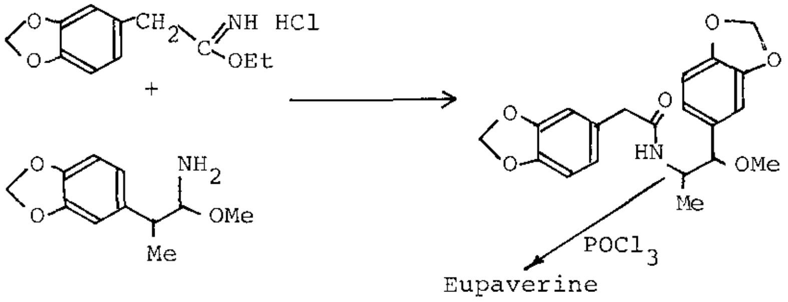
$$R\text{-}C(=NH)OEt + R'\text{-}NH_2 \longrightarrow R\text{-}C(=NH)NHR' + EtOH \qquad (1)$$

$$R\text{-}C(=NH)NHR' + H_2O \longrightarrow RCONHR' + NH_3 \qquad (2)$$

Yakugaku Zasshi, 72, 1036 (1952).

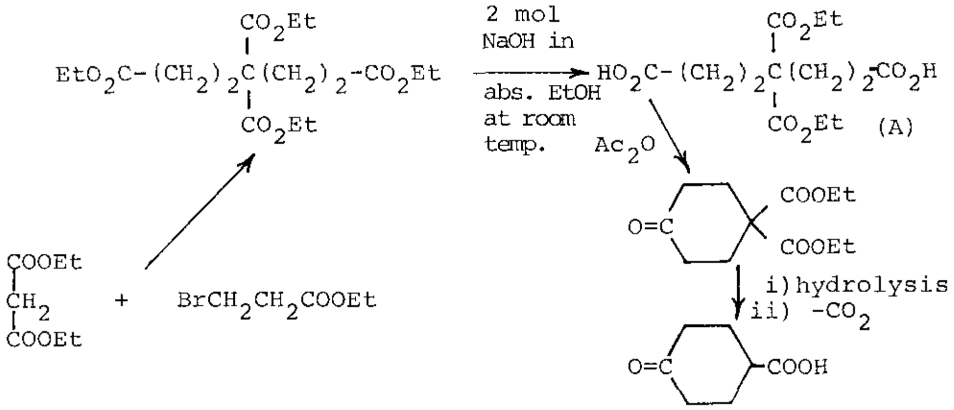
Several N-substituted acid amides were prepared by this method. Both reactions proceed with difficulty where R is an aromatic group as compared with those where R is an aralkyl.

Example:



R-28 Partial Hydrolysis of Diethyl γ,γ-Diethoxycarbonylpimelate.

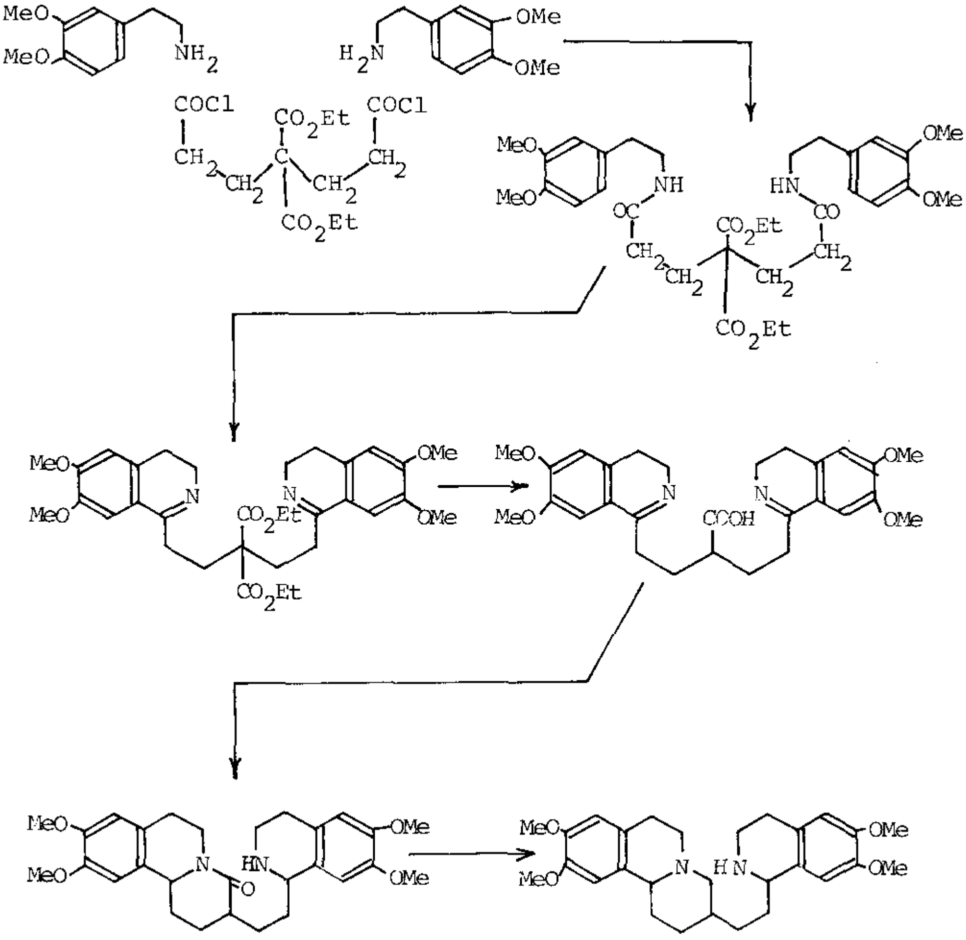
A Method of Preparing γ,γ-Diethixycarbonylpimelic Acid



When one mole of diethyl γ,γ-diethoxy carbonylpimelate was hydrolyzed with exactly two moles of sodium hydroxide in absolute thanolic solution at room temperature, γ,γ-diethoxycarbonylpimelic acid was produced in excellent yield. Its structure was proved beyond doubt by two independent methods.

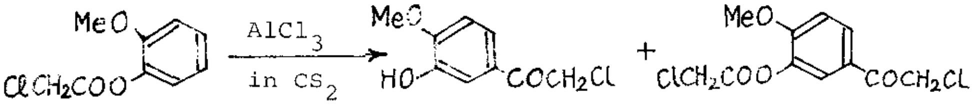
Yakugaku Zasshi, **62**, 82 (1942). Tetrahedron, **3**, 175 (1958).

This acid(A) was used as a starting material for the synthesis of rac-C-nor-emetine (Pyman) in the following:

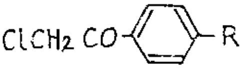


rac-C-nor-emetine(Pyman)
(1942)

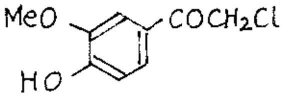
R-29 Fries Transposition of Chloroacetoguaiacol:



(I) (II) (II')



(IV) R=H
(V) R=Me



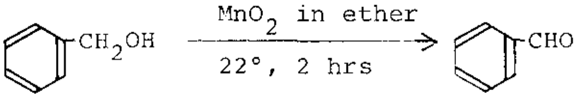
(III)

The Fries rearrangement of ω-chloroacetoguaiacol(I) was found to give mainly ω-chloroisoacetovanillone(II) with a small amount of ω-chloroisoacetovanillone chloroacetate(II'). The expected ω-chloroacetovanillone(III) was not detected in the reaction mixture. The best result was obtained when 2.2 moles of $AlCl_3$ was used with 1 mole of (I) in carbon disulfide at an ordinary temperature(25°).

When the reaction was carried out in benzene or toluene, the only ketonic product isolated was ω-chloroacetophenone(IV) or its *p*-methyl derivative(V), which showed that the Fries rearrangement occurs intermolecularly and not intramolecularly as was earlier assumed. A mechanism for the formation of (II) and (II') was postulated.

Yakugaku Zasshi, **73**, 1102 (1953).

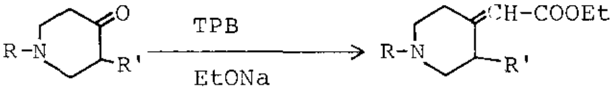
R-30 Application of the Ball Reaction on Aromatic Alcohols.



The oxidation method of Ball, Goodwin, and Morton for polyene alcohols to the corresponding aldehydes, using active MnO_2 in an indifferent solvent, was proved to give satisfactory results when applied on aromatic alcohols, isocyclic and heterocyclic as well. Manganese dioxide prepared according to Attenburrow was recommended for this purpose. Ten examples are described.

Chem. Pharm. Bull. (Tokyo), 2, 341 (1954); 3, 393 (1955).

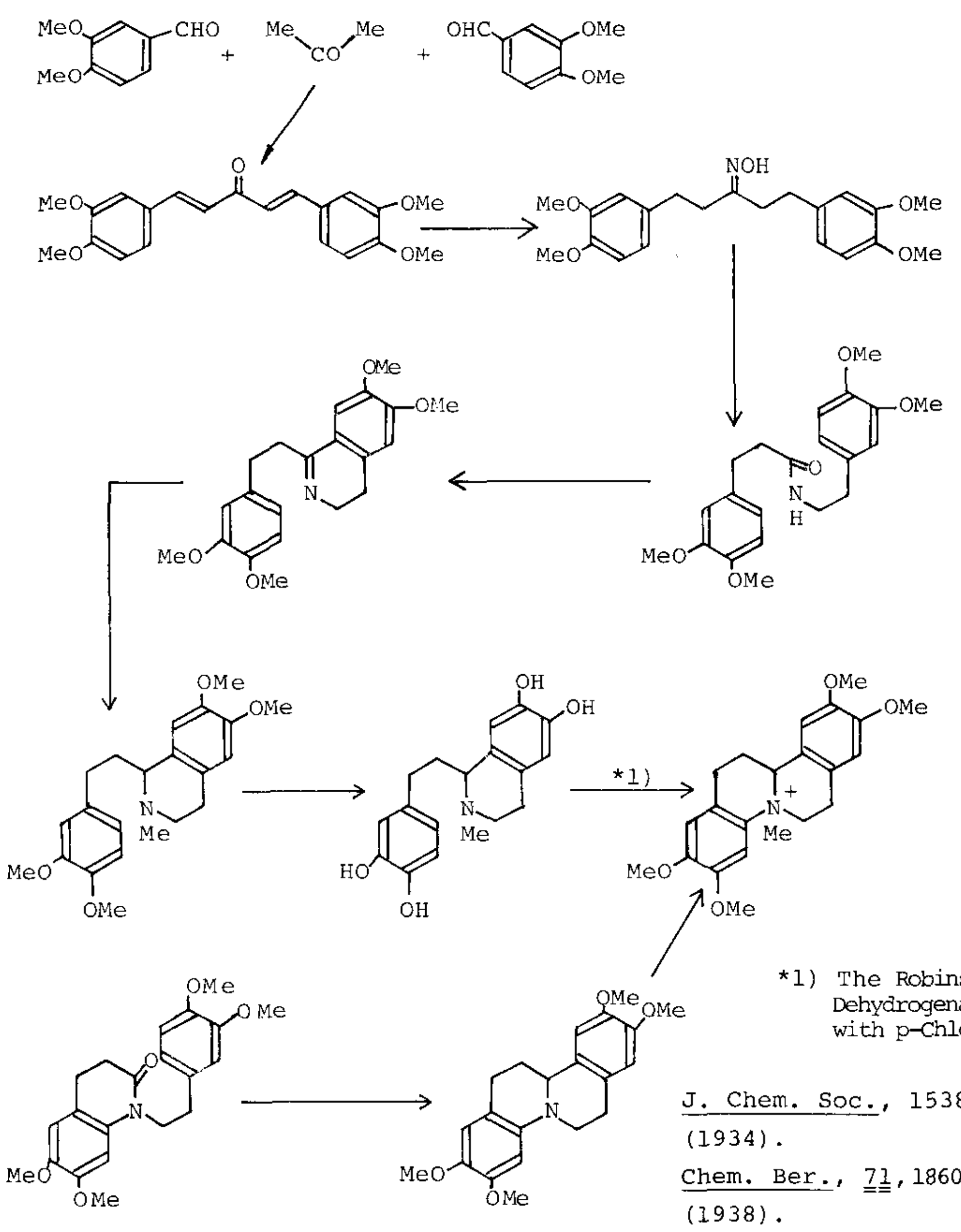
R-31 Synthesis of α,β-Unsaturated Esters by Application of Wittig Reaction



Chem. Pharm. Bull. (Tokyo), 8, 819 (1960).

Thirteen kinds of aldehyde and ketone, including some basic and/or alicyclic carbonyl compounds, were subjected to Wittig reaction, using ethoxycarbonylmethyl-triphenylphosphonium bromide(TPB) and sodium ethoxide in dehyd. ethanol at room temperature in nitrogen atmosphere, and corresponding α,β-unsaturated ethyl esters were formed as expected.

R-32. Synthesis of dl-Homolaudanosoline and Its Dehydrogenation

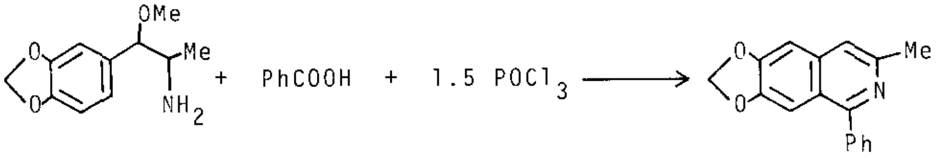


*1) The Robinson Dehydrogenation with p-Chloranil

J. Chem. Soc., 1538 (1934).

Chem. Ber., 71, 1860 (1938).

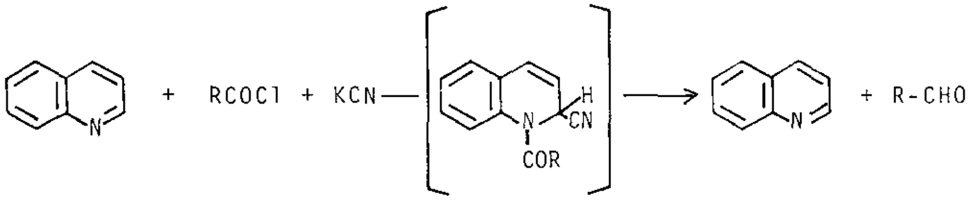
R-33. A Simplified Isoquinoline Synthesis



Yakugaku Zasshi, 72, 252 (1952).

A simplified isoquinoline synthesis is described. In this method one mole each of appropriately substituted β-phenethylamine and acid were mixed under toluene and the mixture was boiled with an excess of phosphoryl chloride, giving isoquinoline in a fair yield. The isolation of the intermediate acid amide in the usual Bischler-Napieralski Perkin method was thus made unnecessary. Eight examples are described.

R-34. The Action of Acid Chloride and Potassium Cyanide onto Quinoline

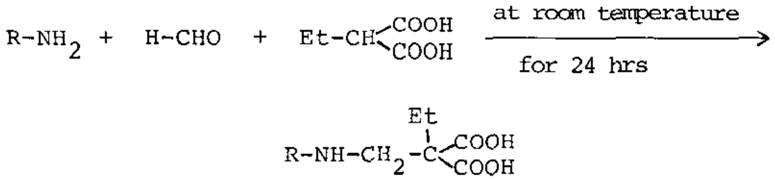


The reaction is not generally applicable to the preparation of aldehydes. Several aromatic aldehydes could be prepared by this method.

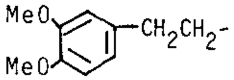
Yakugaku Zasshi, 56, 557 (1936).

Product (R-CHO)	Yield (%)
p-Anisaldehyde	51
Veratrumaldehyde	57
Cinnamaldehyde	34

R-35. The Mannich Reaction of the Primary Amines with Ethylmalonic Acid



$$\text{R-NH}_2 + \text{H-CHO} + \text{Et-CH(COOH)}_2 \xrightarrow[\text{for 24 hrs}]{\text{at room temperature}} \text{R-NH-CH}_2\text{-C(Et)(COOH)}_2$$

R-NH$_2$ (I)	Yield(%) of (II)
R=PhCH$_2$-	89
R= 	93

Chem. Pharm. Bull. (Tokyo), 3, 47, 53 (1955).

The reaction was extended to the total synthesis of dl-rubremetinium Salt. Chem. Pharm. Bull. (Tokyo), 6, 591 (1958). (Cf. R-6).