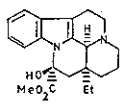

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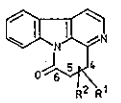
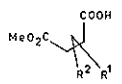
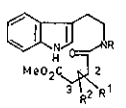


2 R^1 = 4-Et, R^2 = 4-Pr
3 R^1 = 4-Et, R^2 = 4-Me
4 R^1 = 5-Et, R^2 = 5-Pr
5 R^1 = 5-Et, R^2 = 5-Me





6 R^1 = 2-Et, R^2 = 2-Pr
7 R^1 = 2-Et, R^2 = 2-Me
8 R^1 = 3-Et, R^2 = 3-Pr
9 R^1 = 3-Et, R^2 = 3-Me
10 R^1 = 3-Et, R^2 = 3-Pr
11 R^1 = 3-Et, R^2 = 3-Me
12 R^1 = 2-Et, R^2 = 2-Pr
13 R^1 = 2-Et, R^2 = 2-Me

ader programme in this field we focused our attention on the synthesis of their degradation products — 4,5-dihydrocanthin-6-ones — particularly on (—)-4-ethyl-4-propyl-4,5-dihydro-6H--canthin-6-one **2**, which was readily obtained by degradation of (+)-vincamine **1**.

Starting from racemic and optically active 2,2[a] and 3,3-disubstituted 3-methoxycarbonylpropionic acids **6**—**9** the appropriate amid-esters **10**—**13** were prepared, which on Bischler-Napieralskii cyclization followed by selenium dehydrogenation afforded the desired 4,5-dihydrocanthin-6-ones **2**—**5**.

The synthesis of succinic acid-esters **6**—**9** will be discussed briefly together with the physico-chemical properties of tryptamides **10**—**13** and especially of canthin-6-ones **2**—**5**.

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LE I 18

SYNTHESIS OF SUBSTITUTED 1(2H)-ISOQUINOLINONES AND 8-OXOBERBINES FROM HOMOPHTALIC ANHYDRIDES AND AZOMETHINES

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Recently we reported that the reaction of 1,3-isochromandiones (homophtalic anhydrides) with acyclic and cyclic azomethines can be used as a method for synthesis of 4-carboxy-1(2H)--isoquinolinones, 13-carboxy-8-oxoberbines and 14-carboxy-hexadehydroyohimbanes[1,2].

Homophtolic anhydrides **1** react analogously with azomethines of aromatic, heteroaromatic and aliphatic aldehydes and ketones, and aliphatic amines **2**, as well as with 1-alkyl(aryl)-6,7--dimethoxy-3,4-dihydroisoquinolines **4** (refluxing of **1** and **2**, resp. **4** in benzene or dichloroethane, extraction of **3**, resp. **5** with NaOH , aq), where trans-2,3-disubstituted or 2,3,3-trisubstituted-4-carboxy-3,4-dihydro-1(2H)-isoquinolinones **3** (R = H) and 14-alkyl(aryl)-13-carboxy-8-oxoberbines **5** (R = H), resp., are obtained. The relative configuration of **3** is proved chemically and by NMR-investigation of their corresponding methyl esters **3** (R = Me)[1,2]. The spatial structure of C-13 and C-14 can not be established by NMR-analysis of **5** (R = Me).
Only in the case of the reaction between **1** (R^1 = H or MeO) and ethoxymethyleneaniline (**2**, R^2 = H, R^3 = EtO, R^4 = Ph) 4-anilinomethylene-1,3-isochromandiones **6** (R^1 = H or MeO) are obtained. In conditions of alkoline hydrolysis they are converted into 4-carboxy-1(2H)-isoquinolinones **7** (R = H, R^1 = H or MeO, R^2 = Ph). The NMR-spectra of their methyl esters show a great similarity with the spectrum of the ester **7** (R = R^2 = = Me, R^1 = H), which was obtained by us from the known acid **7** (R = H)[3]. In these two cases an aldol condensation between the CH-acidic anhydrides and the azomethine takes place.

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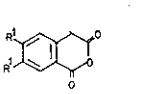

1

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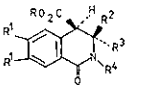
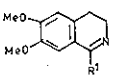


3

R = H or Me; R^1 = H or MeO; R^2 = H or Me;
R^3 = Ph, 2-furyl, Me, Et, iso-Pr etc.
R^4 = $PhCH_2$, $PhCH_2CH_2$, $(MeO)_2CHCH_2$, Me, Et, n-Pr, iso-Pr, cyclohexyl etc.



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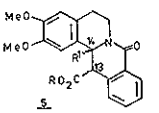
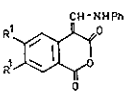


5

R = H or Me
R^1 = Me, Et, $PhCH_2$, Ph



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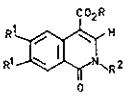

7

R = H or Me
R^1 = H or MeO
R^2 = Me or Ph

LE I 19

ON THE MECHANISM OF THE AMINATION OF 3-SUBSTITUTED DERIVATIVES OF 1,2,4-TRIAZINE WITH POTASSIUM AMIDE IN LIQUID AMMONIA

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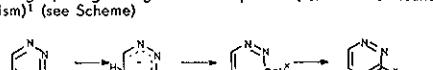
Amination of 3-methylthio-1,2,4-triazine with potassium amide in liquid ammonia at —75 °C yields the corresponding 3-amino compound and in addition 3,3'-bis(methylthio)-5,5'-bi-1,2,4-triazine. It has been proved using the corresponding 3-methylthio-[4-^{15}N]-1,2,4-triazine that amination goes for about 93% via a ring opening - ring closure sequence ($S_NANRORC$-mechanism)[1] (see Scheme)



* = ^{15}N

In order to investigate the generality of this mechanism in the 1,2,4-triazine series, we extended our amination studies to some derivatives containing different leaving groups at C-3 and various substituents at C-5 or C-6 of the triazine ring (see Figure).

1. X = F	R_1 = Ph	R_2 = H	11. X = SCH_3	R_1 = t-Bu	R_2 = H
2. X = Cl	R_1 = Ph	R_2 = H	12. X = SO_2CH_3	R_1 = t-Bu	R_2 = H
3. X = Br	R_1 = Ph	R_2 = H	13. X = $+N(CH_3)_3$	R_1 = t-Bu	R_2 = H
4. X = I	R_1 = Ph	R_2 = H	14. X = Cl	R_1 = H	R_2 = Ph
5. X = OCH_3	R_1 = Ph	R_2 = H	15. X = SCH_3	R_1 = H	R_2 = Ph
6. X = SCH_3	R_1 = Ph	R_2 = H	16. X = Cl	R_1 = Ph	R_2 = Ph
7. X = SO_2CH_3	R_1 = Ph	R_2 = H	17. X = OCH_3	R_1 = Ph	R_2 = Ph
8. X = $+N(CH_3)_3$	R_1 = Ph	R_2 = H	18. X = SCH_3	R_1 = Ph	R_2 = Ph
9. X = Cl	R_1 = t-Bu	R_2 = H	19. X = SO_2CH_3	R_1 = Ph	R_2 = Ph
10. X = OCH_3	R_1 = t-Bu	R_2 = H	20. X = $+N(CH_3)_3$	R_1 = Ph	R_2 = Ph

It was found that besides the corresponding 3-amino compounds as main product, several by-products are formed depending on the nature of the substituents on positions 3 and 5.

With the compounds **2**, **3** and **4** a considerable amount of 2,4-diphenyl-1,3,5-triazine is obtained as by-product together with some of the dehalogenated product 5-phenyl-1,2,4-triazine.

With compound **6**, ring contraction into 3-methylthio-5-phenyl-1,2,4-triazole takes place as side reaction.

It has been proved using the corresponding [4-^{15}N]triazines that the formation of the 3-amino compounds occurs by a ring opening - ring closure sequence ($S_NANRORC$) and/or by the more classical addition-elimination mechanism (S_NAE). As proved by nmr spectroscopy the addition of the amide ion to C-5 in 3-X-triazines is more favoured than addition to C-3. However, in cases where a substituent is present at C-3 which has highly electron-attracting properties [$+N(CH_3)_3$, SO_2CH_3], the addition to C-3 is the favourite process. The mechanism of the amination and the ring modifying process will be discussed.

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LE I 20

SOME NOVEL TYPE ELECTRON DEFICIENT HETEROAROMATIC AMMONIOAMIDATES

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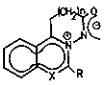
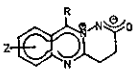
We wish to report on the synthesis of novel type electron deficient heteroaromatic ammonioamidates derived by incorporation of the amidate nitrogen and carbon and of the ammonio nitrogen atoms into a second ring (Compounds **1, 2, 3**).

They key step of the syntheses is based on neighboring-group participation of the nitrogen atom of the starting heteroaromatic system in the cleavage of acyl azide groups.



X = CH **1**
X = N **2**



3

The structures of **1**, **2** and **3** were proved by spectroscopical means and by unambiguous syntheses.

The tautomerism and photochemical behaviour of **1—3** were also investigated.

LE I 21

THE CONDENSATION OF o-AMINOBENZALDEHYDE WITH PYRAZOLE-5-ONES

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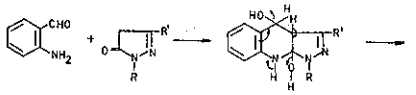
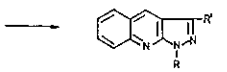
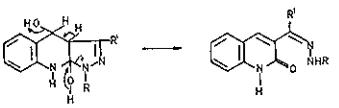
The Friedländer quinoline synthesis was extended to the condensation of o-aminobenzoldehyde with pyrazole-5-one and its derivatives (1a — 1i) in order to obtain pyrozoloquinolines (3)





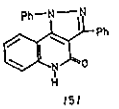
a : R = Ph, R' = Me
b : R = R' = Ph
c : R = Me, R' = Ph
d : R = R' = Me
e : R = H, R' = Ph
f : R = H, R' = Me
g : R = Ph, R' = H
h : R = Me, R' = H
i : R = R' = H

This could be achieved only in few cases. The behavior of the intermediary compound (2) depends on the electronic properties of both the R and R' substituents. When the pyrazole-5-one is not stabilized by R' = Ph the pyrazole moiety in the intermediary compound (2) is cleaved and corresponding hydrazones of 1-H-3-acylquinoline-2-one (4) are formed apart from other products.

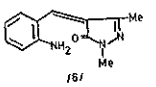


(2) (4)

In the case of 1,3-diphenylpyrazole-5-one (1b) pyrazoloquinoline(5) is also formed by the intramolecular Michael-type addition and subsequent oxidation. 1,3-Dimethylpyrazole-5-one (1d) is much more resistant towards condensation and the major product formed was 1,3-dimethyl-4-(o-aminobenzylidene) pyrazole-5-one (6).

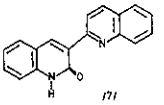


(5)

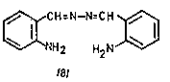


(6)

Moreover, both hydrazones (4a) and (4d) undergo condensation with o-aminobenzaldehyde yielding 3-(2-quinolyl)quinolin-2-one (7). Also benzylidenepyrazole-5-one (6) turns into both pyrazoloquinoline (3d) and quinolylquinoline-2-one (7). 1-H-Pyrazole-5-ones (1f) and (1i) which are not stabilized with R' = Ph can be a source of hydrazine. The latest is formally liberated from pyrazole-5-ones yielding with o-aminobenzaldehyde 2,2'-diaminobenzaldazine (8).



(7)



(8)