TRYPTOPHAN DERIVED PYRIDINIUM SALTS: PREPARATION, REDUCTIVE CYANATION AND ADDITION REACTIONS

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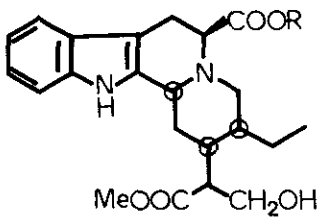
Abstract - Tryptophan derived pyridinium salts 8 can be prepared from methyl 2-tosyloxy-3-(3-indolyl)propionate 6d. The salt formation was usually accompanied by rearrangement in the indole side chain. Behaviour of the pyridinium salts under reductive cyanation conditions and in nucleophilic addition reactions were studied.

INTRODUCTION

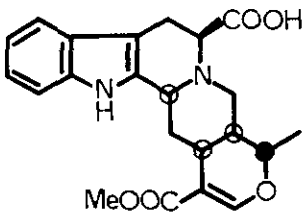
Recent findings of alkaloids such as adirubine 1a[1], 5β-carboxytetrahydroalstonine 2[2] and 5β-carboxycorynanthine 3[3] show beyond doubt that the tryptophan unit is incorporated as such into indole alkaloids. Furthermore, 5β-carboxystrictosidine, a naturally occurring plant base, has been postulated to have a central place in the biosynthesis of the vast group of sarpagine-ajmaline type indole alkaloids.[4] Tryptophan-derived alkaloids and alkaloid model compounds have been the subject of surprisingly few synthetical studies. Starting from tryptophan methyl ester van Tamelen synthesized the methyl ester of adirubine 1b[5] during his research on Adina alkaloids. The synthesis was based on the same methodology as his elegant synthesis of ajmaline[6] which was designed to give support to his postulate on the biogenesis of the sarpagane ring skeleton[7].

Cook has studied 1,3-disubstituted 1,2,3,4-tetrahydro-β-carbolines 4[8] for the synthesis of biologically active compounds. For the cyclization of the C-ring, he successfully employed the Pictet-Spengler reaction in aprotic media[9].

Synthetic studies on indole alkaloid model compounds conducted in our laboratory[10-12] have traditionally been based on a methodology employing pyridinium salts to circumvent the severe stereochemical problems often encountered in the preparation of the acyclic starting materials. For these reasons, it was desirable to find an efficient method to synthesize alkaloid model compounds 5 from the corresponding pyridinium salts.



1a R=H
1b R=Me



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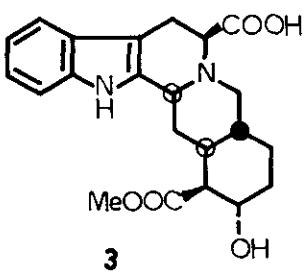

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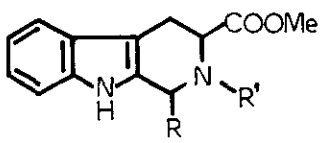

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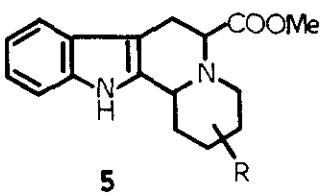

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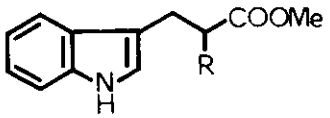
RESULTS AND DISCUSSION

For the preparation of the desired pyridinium salts of the type 8, synthesis of the unsubstituted tryptophyl bromide 6b was attempted from methyl β-indolyllactate 6a. When alcohol 6a was subjected to the Hoshino bromination conditions[13] usually employed in similar reactions, a mixture of isomeric bromides 6b and 7 was produced with the rearranged product 7 being the predominating one*.

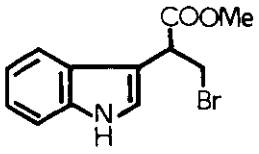
Since this method was plagued by the easy rearrangement of the bromide via a spirosubstituted cyclopropylium intermediate[15], preparation of tosylate 6d was undertaken. Harnden[15] has reported that mesylate 6c lacking an electron donating substituent β to the ester moiety can be prepared without rearrangement. Indeed, the tosylate was obtained cleanly in yields of up to 85 % uncontaminated with the rearrangement product.

To have access to the tetracyclic indoloquinolizidine system 5, the method based on Kröhnke's studies on nucleophilic γ-addition to pyridinium salts[16] and later introduced to alkaloid chemistry by Wenkert[17] was initially adopted. Thus, the tosylate 6d was reacted with 3-acetylpyridine to achieve the salt 8a (vide infra). The salt was then subjected to the alkylation-cyclization conditions described by Wenkert[18] in the expectation of achieving the tetracyclic triester 10. Various modifications of reaction conditions were examined but invariably the

* The same observation was made by Rapoport[14] during his studies on iminium salt cyclization.



6a R=OH
6b R=Br
6c R=OMs
6d R=OTs
6e R=OMe



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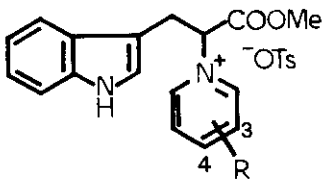
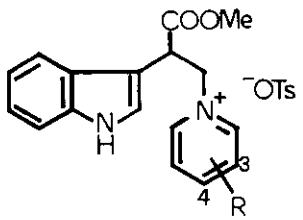


8a R=3-$COCH_3$
8b R=4-CH_2COOMe
8c R=3-Et
8d R=4-Me

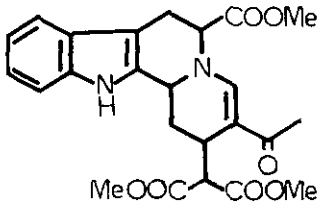


9a R=3-$COCH_3$
9b R=4-CH_2COOMe
9c R=3-Et
9d R=4-Me

triester 11 and β-indolyl acrylate 12 were the only products isolated. The same problem with nucleophilic addition to pyridinium salts has been encountered in the literature.[19]

This approach therefore proved unsuitable and another strategy had to be adopted. The reductive cyanation of pyridinium salts[20] has gained widespread attention in indole alkaloid chemistry[21]. However, the method has not previously been applied to compounds carrying an alkoxycarbonyl substituent at the exocyclic α position. We were therefore prompted to investigate the outcome of this reaction with the ester 8b which, after acid cyclization of the C ring[22], was expected to give rise to the desethyl compound 13. When the transformation was carried out without isolation of the cyano intermediate 21a (i.e. $NaBH_4$ reduction in the presence of NaCN followed by treatment with 1 : 1 AcOH : H_2O)[23], the major product exhibited characteristics not attributable to the tetracycle 13. Instead, the ^1H and ^{13}C NMR spectra were supportive of the open structure 15a with rearranged skeleton (vide supra).

The preparation of the salts 8 from the tosylate 6d was first carefully studied. The product mixture was consistently found to contain two components as judged by TLC. Because their separation could not be satisfactorily achieved, the compound mixture was subjected to catalytic hydrogenation. Starting from 4-methylpyridine, the two compounds 16 and 17 were isolated after hydrogenation of the salts 8d and 9d. The structures 16 and 17 were fully confirmed by their



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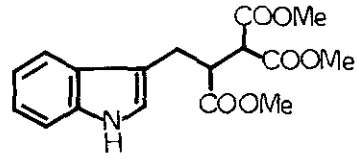

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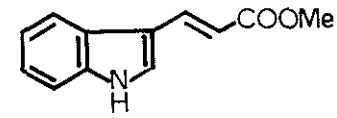

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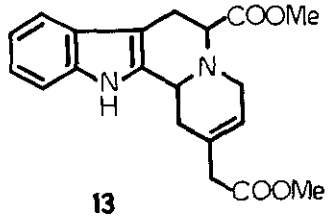

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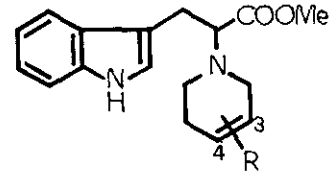
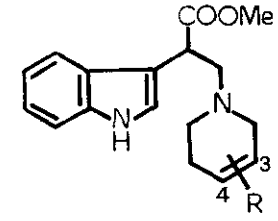
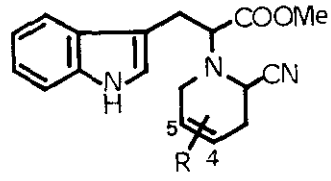


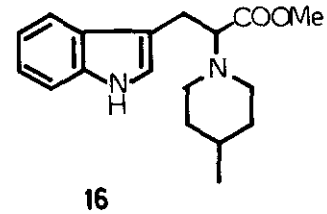
14 **a** R=4-CH_2COOMe
b R=3-Et
c R=4-Me



15 **a** R=4-CH_2COOMe
b R=3-Et
c R=4-Me



21a R=4-CH_2COOMe
21b R=5-Et
21c R=4-Me



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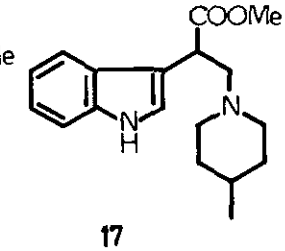

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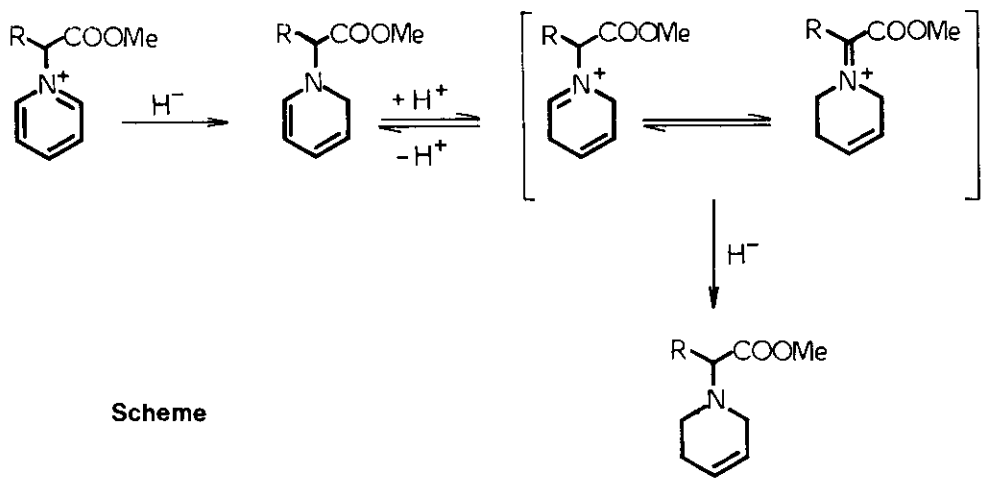
spectral characteristics (IR, ^{1}H NMR, ^{13}C NMR and MS)[24]. Since the catalytic hydrogenation conditions (H_2 - Pd/C, 1 atm, room temperature, MeOH) are mild enough not to cause rearrangement, it is quite doubtless that the salt formation already leads to a mixture of the rearranged products. When the mixture of salts 8b and 9b was subjected to the reductive cyanation[20] followed by acid treatment to the effect cyclization, the desired tetracycle 13 was not achieved (vide infra). The intermediate aminonitrile 21a could not be isolated either. This rather perplexing result prompted us to study the fate of starting materials under the reaction conditions. We first studied the reaction using indolic starting materials 8c and 9c. The results from various experiments are shown in Table 1, along with the results from reduction of 8d and 9d.

In no case were we able to isolate any of the desired nitriles 21b and 21c. In the absence of added hydrochloric acid the reaction mixtures were frequently contaminated with the ether 6e. In these cases, the reaction medium would be basic enough to promote substitution of the pyridine (a good leaving group itself) by methoxide ion. The absence of the desired nitriles in the product mixtures is due to rapid equilibration of the endocyclic β,γ- (more stable) and the exocyclic α,β-unsaturated esters[25] (Scheme).

Table 1. Reduction of Pyridinium Salts 8c,9c and 8d,9d

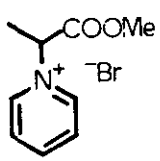
Starting material	T/°C	Solvent	HCl	Products (Yield, %)[a]
8c,9c	+ 5	H_2O	+	14b (34), 15b (18)
8c,9c	+20	H_2O	-	14b (68), 15b (11)
8c,9c	0	MeOH:H_2O	+	14b (43), 15b (18)
8c,9c	0	MeOH:H_2O	-	14b (60), 15b (25)
8d,9d	0	MeOH:H_2O	+	14c (29), 15c (26)
8d,9d	-10	MeOH:H_2O	-	14c (58), 15c (28)

[a] Yields are given for purified products.



Scheme

To test this hypothesis we performed the same reaction on the simple model compound 18 using $NaBD_4$ in place of $NaBH_4$ (19b vs. 19a). Deuterium incorporation in the exocyclic α position was unambiguous as judged by ^1H and ^{13}C NMR.



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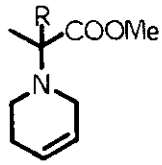
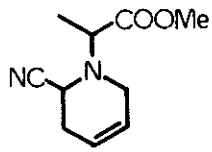


19a R=H
19b R=D



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When the results of this study are compared to those of our previous studies[25] we can conclude that the specific reaction conditions have dramatic effects on the reaction outcome. Whereas the modified Polonovski reaction of 19a[25] did not lead to any of exocyclic iminium ion formation, under the present reaction conditions the exocyclic iminium ion was the predominating one due to facile equilibration.

EXPERIMENTAL

Experimental conditions for spectroscopic characterisation are reported previously.[25] The flash chromatography method[26] was employed for all CCG separations. Thin layer chromatography plates were precoated with either Silica gel 60 $PF_{254+360}$ or Aluminium oxide $PF_{254+360}$, both purchased from Merck. Dragendorff-Munier reagent[27] was used to locate the reaction components.

Methyl 8-indolyllactate 6a

8-Indolyllactic acid[28] (5.13 g, 25 mmol) and p-toluenesulfonic acid (4.30 g, 25 mmol) were refluxed in MeOH (100 ml) for 17 h after which time MeOH was evaporated and the residue dissolved in EtOAc (100 ml). The organic solution was washed with 5 % Na_2CO_3 (40 ml) and water (2 x 30 ml). Drying and evaporation gave a light brown oil which was crystallized from ether-petroleum to give 6a as an amorphous white solid (5.10 g; 93 %). IR: 3410 cm^{-1} (br) (NH), 3350 cm^{-1} (br) (OH), 1740 cm^{-1} (s) (COOMe). ^1H NMR ($CDCl_3$, 60 MHz) δ 3.22 (d, 5 Hz, 2 H), 3.70 (s, 3 H), 4.52 (t, 5 Hz, 1 H), 6.95-7.70 (m, 5 H), 8.10 (br s, 1 H). ^{13}C NMR ($CDCl_3$, 60 MHz) δ 30.3 (t), 52.3 (q), 70.8 (d), 110.1 (s), 111.1 (d), 118.8 (d), 119.5 (d), 122.0 (d), 123.1 (d), 127.5 (s), 136.0 (s), 174.6 (s). MS m/z (rel. int.): 219 (M^+, 15 %), 160 (5 %), 130 (100 %). Anal. Calcd. for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.68; H, 6.02; N, 6.34.

Methyl 2-tosyloxy-3-(3-indolyl)propionate 6d

The ester 6a (3.54 g, 16 mmol) was dissolved in dry pyridine (35 ml) and the solution cooled to 0°C. Then p-toluenesulfonyl chloride (5.1 g, 27 mmol) was added in one portion, the solution purged with argon and stirred at 0°C until all starting material was in solution (2 h). The resulting reddish solution was stored at -15°C for three days, then poured into ice-water (200 ml) and

extracted with ether (4 x 150 ml). The combined ether extracts were washed with ice-cold 5 M HCl (3 x 75 ml) and ice-water (2 x 150 ml), dried over Na_2SO_4 and evaporated. The resulting solid (5.53 g, 92 %) was dissolved in ether (50 ml), hexane (10 ml) was added and the brown oil formed was separated and discarded. Addition of a further 40 ml portion of hexane gave 6d as pinkish flaky crystals, mp 84-85°C, (5.01 g; 84 %). IR: 3450 cm^{-1} (br) (NH), 1760 cm^{-1} (s) (COOMe), 1360 cm^{-1} (s) (SO_2-OR). ^1H NMR ($CDCl_3$, 60 MHz) δ 2.27 (s, 3 H), 3.24 (d, 7 Hz, 2 H), 3.66 (s, 3H), 4.96 (t, 7 Hz, 1 H), 6.96 (d, 8.4 Hz, 2 H), 7.43 (d, 8.4 Hz, 2 H), 6.86-7.40 (m, 4 H), 6.89 (s, 1 H), 8.22 (br s, 1 H). ^{13}C NMR($CDCl_3$, 15 MHz) δ 21.6 (q), 28.3 (t), 52.6 (q), 77.5 (d), 108.0 (s), 111.2 (d), 118.0 (d), 119.3 (d), 121.8 (d), 123.5 (d), 126.6 (s), 127.4 (d, 2 C), 129.2 (d, 2 C), 132.2 (s), 136.0 (s), 144.5 (s), 169.1 (s). MS m/z (rel. int.): 203 (M-170, 5 %), 172 (45 %), 144 (25 %), 130 (45 %). Anal. Calcd. for $C_{19}H_{19}NO_5S$: C, 61.12; H, 5.13; N, 3.75. Found: C, 61.02; H, 5.08; N, 3.64.

Pyridinium salts 8a and 9a

Tosylate 6d (3.73 g, 10 mmol) and 3-acetylpyridine (1.20 g, 10 mmol) were mixed under an atmosphere of argon and allowed to stand at 50°C for 16 h. The resulting gum was then washed thrice with dry ether and dried *in vacuo* to give 4.90 g (99 %) of a 1:1 mixture of salts 8a and 9a as extremely hygroscopic yellow solid. IR: 3450 cm^{-1} (br) (NH), 1740 cm^{-1} (s) (COOMe), 1710 cm^{-1} (s) (C=O), 1640 cm^{-1} (m) (C=C).

Attempted preparation of 10

Sodium hydride (0.90 g, 36 mmol) in dry dimethoxyethane (50 ml) was cooled to 0°C. Dimethyl malonate (2.70 g, 20.5 mmol) was added and the suspension stirred for 30 min. The above salt mixture (8a and 9a) (6.18 g, 12.5 mmol) was then added and the solution stirred for 25 h allowing the temperature reach room temperature. Thereafter 60 ml benzene presaturated with HCl was added to bring the pH to 3.5 and the acidic solution was stirred for another 1 h. The solution was slowly poured into $NaHCO_3$ in 100 ml CH_2Cl_2 and stirring was continued at room temperature for 2 h. After filtration, the solution was washed with 100 ml 5 % $NaHCO_2$, saturated brine and water. The dried organic phase was evaporated to give a semi-solid yellow oil (4.9 g). The residue was chromatographed on alumina using acetone-hexane (1:1) as eluant. First fractions gave dimethyl malonate (1.8 g), 3-acetylpyridine (0.78 g), triester 11 (0.99 g) and 12 (0.24 g).

Methyl 2,3-dimethoxycarbonyl-4-(3-indolyl)butyrate 11

Viscous oil. IR: 3450 cm^{-1} (br) (NH), 1740 cm^{-1}(s) (COOMe). ^1H NMR ($CDCl_3$, 60 MHz) δ 2.58 (m, 1 H), 3.32 (dt, 2.3 Hz, 7 Hz, 2 H), 4.02 (d, 8 Hz, 1 H), 3.62 (s, 6 H), 3.68 (s, 3 H), 6.9-7.8 (m, 4 H), 7.03 (d, 2.3 Hz, 1 H), 8.81 (br s, 1 H). ^{13}C NMR ($CDCl_3$, 15 MHz) δ 31.0 (t), 40.3 (d), 49.4 (d), 51.8 (q, 2 C), 52.3 (q), 111.2 (s), 118.6 (d), 119.3 (d), 121.9 (d), 122.7 (d), 125.8 (s), 136.1

(s), 169.2 (s, 2 C), 173.8 (s). MS m/z (rel. int.): 333 (M^+, 15 %), 301 (25 %), 274 (10 %), 201 100 %), 130 (30 %). Anal. Calcd. for $C_{17}H_{19}NO_6$: C, 61.25; H, 5.75; N, 4.20. Found: C, 61.12; H, 5.78; N, 4.14.

Preparation of the pyridinium salts 8 and 9

The salts were prepared according to the procedure given for the preparation of salts 8a and 9a.

Ester salts 8b and 9b

From tosylate 6d (5.70 g, 15 mmol) and methyl 4-pyridineacetate (2.30 g, 15 mmol). Yield 7.20 g (89 %). IR: 3400 cm^{-1} (br) (NH), 1740 cm^{-1} (s) (COOMe), 1645 cm^{-1} (m) (N-C=C).

3-Ethylpyridinium salts 8c and 9c

From tosylate 6d (1.92 g, 5.1 mmol) and 3-ethylpyridine (0.565 g, 5.1 mmol). Yield 2.47 g (98 %). IR: 3400 cm^{-1} (br) (NH), 1740 cm^{-1} (s) (COOMe), 1640 cm^{-1} (m) (N-C=C).

4-Methylpyridinium salts 8d and 9d

From tosylate 6d (3.63 g, 10 mmol) and 4- methylpyridine (0.93 g, 10 mmol). Yield 4.27 g (94 %). IR: 3400 cm^{-1} (br) (NH), 1740 cm^{-1} (s) (COOMe), 1640 cm^{-1} (m) (N-C=C).

Attempted preparation of 1,4,6,7,12,12a-hexahydro-6-methoxycarbonyl-2-methoxycarbonylmethyl-indolo[2,3-a]quinolizidine 13

To a two-phase mixture of sodium cyanide (3.78 g, 77 mmol) in water (12 ml) layered with ether (30 ml), a mixture of salts 8b and 9b (7.06 g, 13.2 mmol) was added followed by sodium borohydride (600 mg, 16 mmol). The mixture was then stirred at room temperature for 3 h, the ether layer was separated and replaced with another 30 ml portion of ether. After 1 h, the ether was again separated. The combined organic phases were washed once with water (10 ml) and evaporated in vacuo to give a mixture of two components as a pale yellow foam (5.30g). The crude mixture was immediately dissolved in 50 % aq acetic acid (60 ml) and the solution was stirred at room temperature for 36 h. After extraction with benzene (50 ml), the solution was basified under ice-cooling with 15 M NaOH and then extracted with methylene chloride (4 x 100 ml). Chromatography over alumina with ethyl acetate : methylene chloride (7:3) as eluant gave methyl ether 6e (630 g), methyl 4-pyridine-acetate (260 mg) and 15a (437 mg).

Methyl 2-methoxy-3-(3-indolyl)propionate 6e

Viscous oil. IR: 3450 cm^{-1} (br) (NH), 1740 cm^{-1} (s) (COOMe), 1090 cm^{-1} (s) (ROR). ^1H NMR ($CDCl_3$, 60 MHz) δ 3.39 (s, 3 H), 3.56 (d, 7 Hz, 2 H), 3.64 (s, 3 H), 4.18 (t, 7 Hz, 1 H), 6.85-7.80 (m, 4 H), 7.17 (br s, 1 H), 8.59 (br s, 1 H). ^{13}C NMR ($CDCl_3$, 15 MHz) δ 43.2 (t), 51.9 (q) 58.8 (q), 73.6 (d) 107.4 (s), 111.3 (d), 118.6 (d), 119.5 (d), 121.9 (d), 122.4 (d), 125.5 (s), 136.0 (s), 173.8 (s). MS m/z (rel. int.): 233 (M^+, 25 %), 201 (10 %), 174 (15 %), 130 (50 %), 84 (100 %). Anal. Calcd. for $C_{13}H_{15}NO_3$: C, 66.93; H, 6.48; N, 6.01. Found: C, 66.86; H, 6.52; N, 6.04.

1-[2-(3-Indolyl)-2-methoxycarbonylethyl]-4-methoxycarbonylmethyl-1,2,5,6-tetrahydropyridine 15a

Viscous oil. IR: 3400 cm^{-1} (br) (NH), 1740 cm^{-1} (s) (COOMe), 1730 cm^{-1} (s) (COOMe), 1680 cm^{-1} (m) (C=C). ^1H NMR ($CDCl_3$, 60 MHz) δ 2.15 (m, 2 H), 2.66 (m, 3 H), 2.96 (br s, 2 H), 3.09 (m, 2 H), 3.27 (dd, 10 Hz, 18 Hz, 1 H), 3.61 (s, 3 H), 3.63 (s, 3 H), 4.24 (dd, 4 Hz, 10 Hz, 1 H), 5.50 (br s, 1 H), 7.04 (br s, 1 H), 7.0-7.8 (m, 4 H), 8.53 (br s, 1 H). ^{13}C NMR ($CDCl_3$, 15 MHz) δ 28.8 (t), 41.2 (d), 42.0 (t), 49.8 (t), 51.6 (q), 51.7 (q), 52.4 (t), 60.3 (t), 111.3 (d), 111.4 (s), 118.5 (d), 119.2 (d), 121.7 (d), 122.2 (d), 123.2 (d), 126.3 (s), 129.3 (s), 126.0 (s), 171.7 (s), 174.4 (s). MS m/z (rel. int.): 356 (M^+, 5 %), 202 (25 %), 130 (40 %). Anal. Calcd. for $C_{20}H_{24}N_2O_4$: C, 67.39; H, 6.79; N, 7.86. Found: C, 67.42; H, 6.72; N, 7.76.

Reductive cyanations of salts 8c and 9c, and 8d and 9d

The reductions were performed according to the procedure given for preparation of 13 and subjected to the modifications indicated in Table 1. (HCl = 6 M HCl, 1.5 eq.)

1-[2-(3-Indolyl)-1-methoxycarbonylethyl]-3-ethyl-1,2,5,6-tetrahydropyridine 14b

Viscous oil. IR: 3450 cm^{-1} (br) (NH), 1740 cm^{-1} (s) (COOMe), 1640 cm^{-1} (m) (C=C). ^1H NMR ($CDCl_3$, 60 MHz) δ 1.02 (t, 7 Hz, 3 H), 1.97 (q, 7 Hz, 2 H), 2.14 (m, 2 H), 2.76 (m, 2 H), 3.15 (m, 4 H), 3.54 (s, 3 H), 3.60 (m, 1 H), 5.44 (br s, 1 H), 6.97 (d, 1.5 Hz, 1 H), 7.0-7.8 (m, 4 H), 8.23 (br s, 1 H). ^{13}C NMR ($CDCl_3$, 15 MHz) δ 12.1 (q), 25.3 (t), 26.3 (t), 27.7 (t), 46.7 (t), 50.9 (q), 52.1 (t), 68.3 (d), 111.1 (d), 111.6 (s), 117.5 (d), 118.5 (d), 119.1 (d), 121.7 (d), 122.6 (d), 127.3 (s), 136.0 (s), 137.8 (s), 172.3 (s). MS m/z (rel. int.): 312 (M^+, 25 %), 253 (20 %), 201 (10 %), 182 (100 %), 130 (80 %). Anal. Calcd. for $C_{19}H_{24}N_2O_2$: C, 73.04; H, 7.74; N, 8.97. Found: C, 73.10; H, 7.68; N, 8.88.

1-[2-(3-Indolyl)-2-methoxycarbonylethyl]-3-ethyl-1,2,5,6-tetrahydropyridine 15b

Viscous oil. IR: 3450 cm^{-1} (br) (NH), 1740 cm^{-1} (s) (COOMe), 1640 cm^{-1} (m) (C=C). ^1H NMR ($CDCl_3$, 60 MHz) δ 0.97 (t, 7 Hz, 3 H), 1.93 (q, 7 Hz, 2 H), 2.10 (m, 2 H), 2.60 (dd, 4 Hz, 9 Hz, 1 H), 2.85 (m, 2 H), 3.00 (br s, 2 H), 3.30 (dd, 9 Hz, 10 Hz, 1 H), 3.56 (s, 3 H), 4.29 (dd, 4 Hz, 10 Hz, 1 H), 5.41 (br s, 1 H), 7.00 (s, 1 H), 7.0-7.9 (m, 4 H), 8.88 (br s, 1 H). ^{13}C NMR ($CDCl_3$, 15 MHz) δ 12.0 (q), 25.3 (t), 27.7 (t), 41.2 (d), 49.9 (t), 51.8 (q), 55.6 (t), 60.6 (t), 111.4 (d), 111.6 (s), 117.5 (d), 118.6 (d), 119.3 (d), 121.9 (d), 122.4 (d), 126.2 (s), 136.1 (s), 137.3 (s), 174.7 (s). MS m/z (rel. int.): 312 (M^+, 5 %), 253 (5 %), 201 (66 %), 188 (15 %), 130 (45 %), 124 (100 %). Anal. Calcd. for $C_{19}H_{24}N_2O_2$: C, 73.04; H, 7.74; N, 8.97. Found: C, 73.02; H, 7.70; N, 8.90.

1-[2-(3-Indolyl)-1-methoxycarbonylethyl]-4-methyl-1,2,5,6-tetrahydropyridine 14c

Viscous oil. IR: 3450 cm^{-1} (br) (NH), 1740 cm^{-1} (s) (COOMe), 1640 cm^{-1} (m) (C=C). ^1H NMR ($CDCl_3$, 60 MHz) δ 1.68 (br s, 3 H), 2.12 (m, 2 H), 2.78 (m, 2 H), 3.19 (m, 2 H), 3.23 (m, 2 H), 3.52 (s, 3 H), 3.59 (m, 1 H), 5.39 (br s, 1 H), 6.96 (d, 2 Hz, 1 H), 7.0-7.7 (m, 4 H), 8.22 (br s, 1 H).

^{13}C NMR ($CDCl_3$, 15 MHz) δ 22.9 (q), 25.2 (t), 31.2 (t), 46.7 (t), 49.0 (t), 51.0 (q), 68.2 (d), 111.0 (d), 111.6 (s), 118.5 (d), 119.1 (d), 121.7 (d), 122.6 (d), 125.2 (d), 127.3 (s), 132.6 (s), 136.0 (s), 172.3 (s). MS m/z (rel. int.): 298 (M^+, 22 %), 239 (14 %), 154 (87 %), 130 (47 %). Anal. Calcd. for $C_{18}H_{22}N_2O_2$: C, 72.45; H, 7.43; N, 9.39. Found: C, 72.48; H, 7.46; N, 9.28.

1-[2-(3-Indolyl)-2-methoxycarbonylethyl]-4-methyl-1,2,5,6-tetrahydropyridine 15c

Viscous oil. IR: 3450 cm^{-1} (br) (NH), 1740 cm^{-1} (s) (COOMe), 1640 cm^{-1} (m) (C=C). ^1H NMR ($CDCl_3$, 60 MHz) δ 1.64 (br s, 3 H), 2.03 (m, 2 H), 2.62 (t, 5 Hz, 2 H), 2.73 (dd, 4 Hz, 15 Hz, 1 H), 3.08 (br s, 2 H), 3.29 (dd, 10 Hz, 15 Hz, 1 H), 3.62 (s, 3 H), 4.26 (dd, 4 Hz, 10 Hz, 1 H), 5.33 (br s, 1 H), 7.06 (d, 2 Hz, 1 H), 7.0-7.8 (m, 4 H), 8.79 (br s, 1 H). ^{13}C NMR ($CDCl_3$, 15 MHz) δ 22.9 (q), 30.3 (t), 41.2 (d), 50.2 (t), 51.9 (q), 52.5 (t), 60.5 (t), 111.4 (d), 111.9 (s), 118.8 (d), 119.4 (d), 121.9 (d), 122.3 (d), 124.7 (d), 126.3 (s), 132.5 (s), 136.2 (s), 174.5 (s). MS m/z (rel. int.): 298 (M^+, 5 %), 239 (5 %), 201 (100 %), 188 (20 %), 130 (40 %). Anal. Calcd. for $C_{18}H_{22}N_2O_2$: C, 72.45; H, 7.43; N, 9.39. Found: C, 72.42; H, 7.38; N, 9.30.

Reductive cyanation of 1-(1-methoxycarbonylethyl)-pyridinium bromide 18

Pyridinium bromide 18 was subjected to the reaction conditions described above for salts 8 and 9. After work-up, 19a and 20 were obtained in yields of 36 % and 32 %, respectively.

1-(1-Methoxycarbonylethyl)-1,2,5,6-tetrahydropyridine 19a

Oil. IR: 1740 cm^{-1} (s) (COOMe). ^1H NMR ($CDCl_3$, 60 MHz) δ 1.34 (d, 7 Hz, 3 H), 2.14 (m, 2 H),2.68 (m, 2 H), 3.15 (br s, 2 H), 3.40 (q, 7 Hz, 1 H), 3.70 (s, 3 H), 5.67 (br s, 2 H). ^{13}C NMR ($CDCl_3$, 15 MHz) δ 14.3 (q), 26.1 (t), 45.8 (t), 48.2 (t), 50.6 (q), 61.7 (d), 124.5 (d), 124.8 (d), 172.8 (s). MS m/z (rel. int.): 169 (M^+, 15 %), 154 (45 %), 110 (100 %), 82 (20 %). Anal. Calcd. for $C_9H_{15}NO_2$: C, 63.88; H, 8.94; N, 8.28. Found: C, 63.94; H, 8.88; N, 8.16.

1-(1-Methoxycarbonylethyl)-2-cyano-1,2,5,6-tetrahydropyridine 20

Oil. IR: 2210 cm^{-1} (w) (CN), 1740 cm^{-1} (s) (COOMe). ^1H NMR ($CDCl_3$, 60 MHz) δ 1.37 (d, 7 Hz, 3 H), 2.50 (m, 2 H), 3.28 (br s, 2 H), 3.41 and 3.47 (q, 7 Hz, 1 H), 3.74 (s, 3 H), 4.06 and 4.17 (dd, 2 Hz, 8 Hz, 1 H), 5.74 (br s, 2 H). ^{13}C NMR ($CDCl_3$, 15 MHz) δ 14.3 and 14.7 (q), 30.1 (t), 44.6 and 45.5 (t), 46.2 and 46.4 (d), 51.2 (q), 60.3 and 60.9 (d), 116.7 (s), 120.8 (d), 125.0 (d), 171.7 (s). MS m/z (rel. int.): 194 (M^+, 2 %), 167 (15 %), 166 (15 %), 135 (100 %), 108 (60 %). Anal. Calcd. for $C_{10}H_{14}N_2O_2$: C, 61.83; H, 7.27; N, 14.42. Found: C, 61.78; H, 7.18; N, 14.34.

Reductive cyanation of 18 with $NaBD_4$

The above experiment was repeated using tetradeuterosodium borohydride in place of sodium borohydride to give the deuterated 19b as a colorless oil. ^1H NMR ($CDCl_3$, 60 MHz) δ 1.34 (s, 3 H), 2.15 (m, 2 H), 2.65 (m), 3.14 (br s, 1 H), 3.70 (s, 3 H), 5.67 (br s, 2 H). ^{13}C NMR ($CDCl_3$, 15 MHz, multiplicities of the noise decoupled spectrum are reported) δ 14.6 (s), 26.3 (s), 46.3 (t), 48.6

(t), 51.3 (s), 61.7 (t), 125.0 (s, 2 C), 173.0 (s).

Catalytic reduction of salts 8d and 9d

A mixture of salts 8d and 9d (0.93 g, 2 mmol) in MeOH (10 ml) was hydrogenated at atmospheric pressure and room temperature over 10 % Pd/C (150 mg) for 5 h to give a pale brown oil (510 mg) which was purified over silica gel plates using 5 % MeOH in chloroform as eluant.

1-[2-(3-Indolyl)-1-methoxycarbonylethyl]-4-methylpiperidine 16

Yield 252 mg (42 %). Viscous oil. IR: 3450 cm^{-1} (br) (NH), 1735 cm^{-1} (s) (COOMe). ^1H NMR ($CDCl_3$, 60 MHz) δ 0.92 (br s, 3 H), 1.52 (m, 5 H), 2.32 (m, 2 H), 2.60 (m, 2 H), 3.17 (m, 2 H), 3.52 (s, 3 H), 3.60 (m, 1 H), 6.94 (d, 2 Hz, 1 H), 7.0-7.8 (m, 4 H), 8.41 (br s, 1 H). ^{13}C NMR ($CDCl_3$, 15 MHz) δ 21.8 (q), 25.1 (t), 30.8 (d), 34.5 (t, 2 C), 48.4 (t), 50.8 (q), 52.3 (t), 69.0 (d), 111.0 (d), 111.7 (s), 118.4 (d), 119.0 (d), 121.6 (d), 122.5 (d), 127.3 (s), 136.0 (s), 172.3 (s). MS m/z (rel. int.): 300 (M^+, 5 %), 241 (5 %), 170 (70 %), 156 (25 %), 149 (35 %), 130 (30 %). Anal. Calcd. for $C_{18}H_{24}N_2O_2$: C, 71.97; H, 8.05; N, 9.33. Found: C, 71.88; H, 8.02; N, 9.26.

1-[2-(3-Indolyl)-2-methoxycarbonylethyl]-4-methylpiperidine 17

Yield 170 mg (28 %). Viscous oil. IR: 3400 cm^{-1} (br) (NH), 1720 cm^{-1} (s) (COOMe). ^1H NMR ($CDCl_3$, 60 MHz) δ 0.90 (br s, 3 H), 1.46 (m, 5 H), 2.34 (m, 3 H), 2.67 (dd, 5 Hz, 12 Hz, 1 H), 3.00 (m, 1 H), 3.30 (dd, 10 Hz, 12 Hz, 1 H), 3.65 (s, 3 H), 4.24 (dd, 5 Hz, 10 Hz, 1 H), 7.07 (br s, 1 H), 7.0-7.8 (m, 4 H), 8.68 (br s, 1 H). ^{13}C NMR ($CDCl_3$, 15 MHz) δ 21.8 (q), 30.6 (d), 34.1 (t), 34.2 (t), 41.2 (d), 51.9 (q), 53.3 (t), 54.5 (t), 61.2 (t), 111.3 (d), 112.0 (s), 118.8 (d), 119.5 (d), 122.0 (d), 122.2 (d), 126.4 (s), 136.1 (s), 174.7 (s). MS m/z (rel. int.): 300 (M^+, 5 %), 241 (5 %), 201 (15 %), 188 (10 %), 130 (25 %). Anal. Calcd. for $C_{18}H_{24}N_2O_2$: C, 71.97; H, 8.05; N, 9.33. Found: C, 71.92; H, 8.10; N, 9.28.

ACKNOWLEDGMENT

Financial support of the work by Orion Corporation Research Foundation is gratefully acknowledged.

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Received, 11th July, 1983