INTERMOLECULAR TRAPPING BY INDOLE OF A SPIROINDOLENINE INTERMEDIATE FORMED DURING THE BISCHLER-NAPIERALSKI CYCLISATION OF N-ACETYLTRYPTAMINE

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This publication is dedicated to Professor Sir Derek H.R. Barton on the occasion of his 70th birthday.

Abstract - The Bischler-Napieralski cyclisation of N-acetyltryptamine (1a) in the presence of indole (15) affords a moderate yield of the diastereomeric spiroindolines 9 and 10 suggesting the intermediacy of a spiroindolenine 2a in this reaction. Evidence is provided to show that the minor reaction products 2-methyltryptamine (11), tris-(3-indolyl)methane (12) and 6-[(o-aminophenyl)methyl]-5,11-dihydroindolo[3,2-b]carbazole (13) are derived from the spiroindolines 9 and 10.

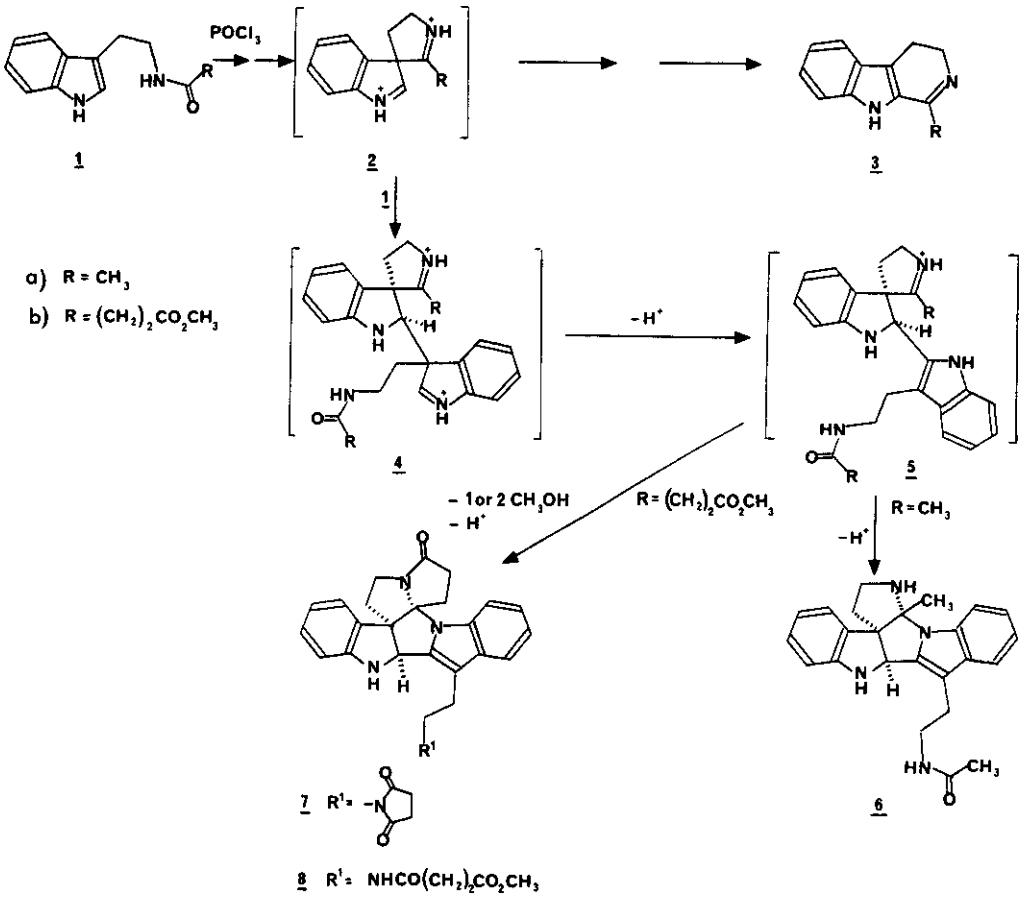
In 1985 we reported [1] that during the phosphorus oxychloride-induced Bischler-Napieralski cyclisation of N-acetyltryptamine (1a) to the 3,4-dihydro-β-carboline 3a (see scheme 1) a small amount of the novel polycyclic heterocycle 6 was formed. Two related heterocycles, 7 and 8, were obtained in combined yields of over 50%, as determined by HPLC, from the acylated tryptamine 1b.

The formation of compounds 6, 7 and 8 was rationalised by the mechanism depicted in scheme 1, in which a spiroindolenine intermediate 2 is intercepted inter-molecularly by unconsumed starting material present in the reaction mixture. A rearrangement and subsequent cyclisation reactions then lead to the isolated polycyles.

It was of interest to ascertain whether the spiroindolenine intermediate 2 could be intercepted by other nucleophiles and, in this regard, the Bischler-Napieralski cyclisation of N-acetyltryptamine (1a) in the presence of excess indole (15) is described (see scheme 2).

Indole (15) was chosen for this study, because it would be expected to retain its nucleophilicity under the acid reaction conditions. Furthermore, since its 3-substituent is hydrogen and not an acylaminoalkyl group, its reaction with a spiroindolenine would be expected to lead to different reaction products.[2]

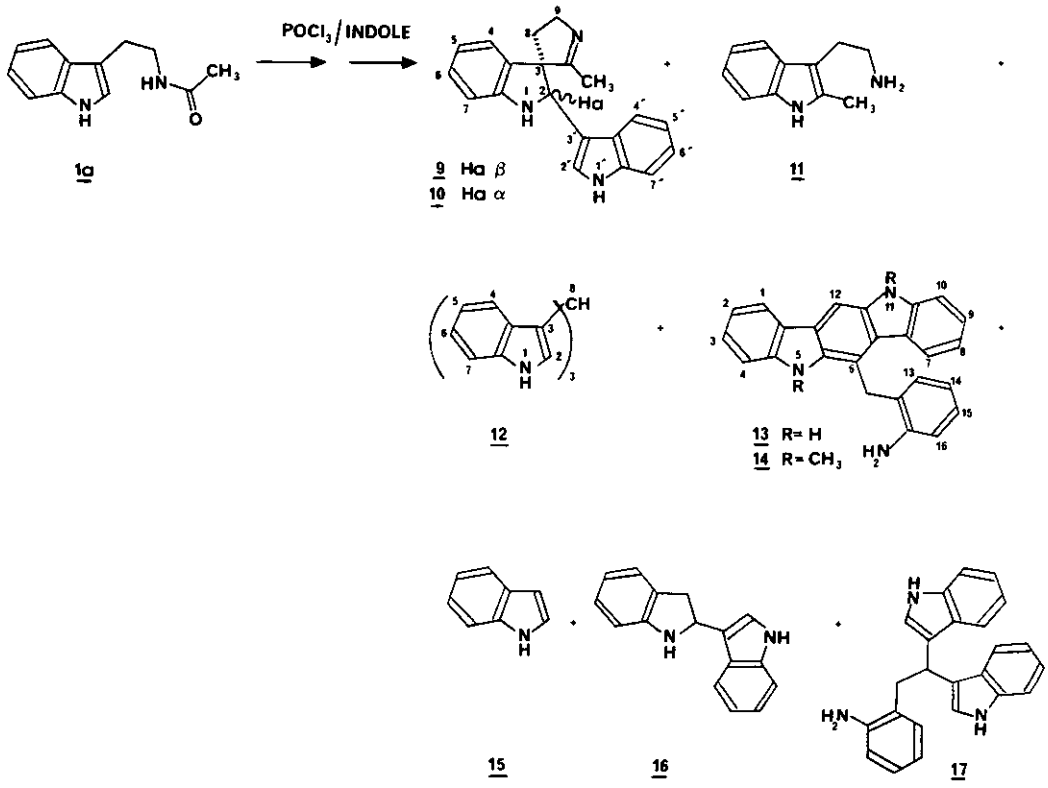
SCHEME 1



In a typical experiment, N-acetyltryptamine (1a) (50 mmol) was refluxed for 15 min in acetonitrile (100 ml) containing phosphorus oxychloride (150 mmol) and indole (15) (150 mmol). After cooling the solvent was evaporated under reduced pressure, the residue was basified carefully with 10% aqueous ammonia and the mixture was extracted with ethyl acetate (600 ml). Removal of the solvent and column chromatography (silica gel) of the residue afforded a ca. 3:1 mixture (as determined by ^{1}H nmr and HPLC) of diastereomeric adducts 9 and 10 (52.4% yield) as a white solid. This mixture was crystallised from methanol as a methanolate and characterised fully by physical methods. The stereochemistry of 9 and 10 was determined by NOE experiments and mass spectrometry (HPLC-FAB-MS-MS) performed on the mixture. [3]Various attempts to separate 9 from 10 on a preparative scale failed. Minor products of the reaction were: 2-methyltryptamine[4] (11) (9.6%), tris-(3-indolyl)methane[5] (12) (0.8%) and 6-[(o-aminophenyl)methyl]-5,11-dihydroindolo[3,2-b]carbazole[6] (13) (3.5%).

Indole (15), indole dimer 16 and indole trimer 17 were also isolated from the reaction mixture. Compounds 11, 12, 15, 16 and 17 were identified by comparison of their ^{1}H nmr and/or ir spectra with those of authentic samples. The structure of compound 13 was determined by physical methods and confirmed by NOE experiments done on its 5,11-dimethyl derivative 14.[7]

SCHEME 2

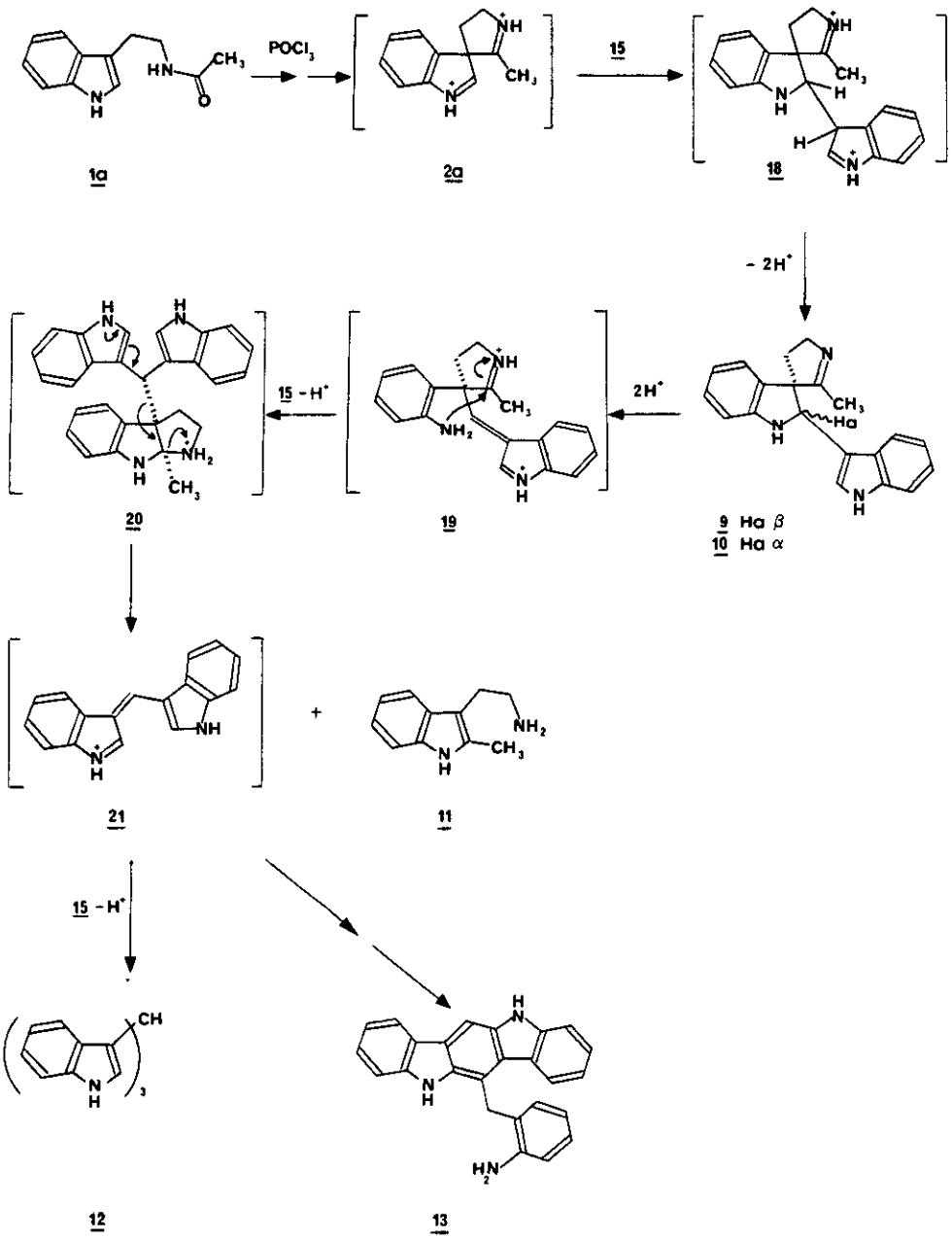


A plausible mechanism for the formation of the reaction products 9, 10, 11, 12 and 13 is shown in scheme 3. The initially formed spiroindolenine 2a is intercepted by indole (15), affording intermediate 18. The latter is analogous to intermediate 4a (scheme 1) obtained on spiroindolenine 2a being intercepted by starting material 1a.

Since, however, indole (15) is the nucleophile in the present case, the indolenine moiety of intermediate 18 bears a hydrogen atom at its 3-position, the loss of which permits re-aromatisation, affording the diastereomers 9 and 10.

The minor reaction products 11, 12 and 13 can be envisaged to arise from the adducts 9 and 10 by a ring-opening process involving acid (see scheme 3). Fission of the indoline ring of the spiroindo-

SCHEME 3



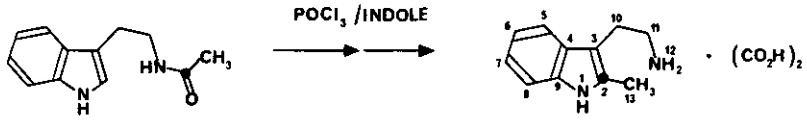
lines 9 and 10 affords intermediate 19, which recyclises as indicated and reacts with indole (15) giving intermediate 20 (cf. indole trimerisation[8]). Finally, the latter undergoes fragmentation affording 2-methyltryptamine (11) and the highly stabilised cation 21.

The conversion of spirocyclic compounds 9 and 10 into 2-methyltryptamine (11) was verified experimentally. Thus, when a ca. 3:1 mixture of compounds 9 and 10 was heated in 1N HCl solution for 30 min, 2-methyltryptamine (11) (isolated as its oxalate salt) was obtained in 20% yield. A small quantity of indole (15) was also isolated from this reaction.

The mechanism proposed in scheme 3 for the formation of 2-methyltryptamine (11) requires the carbonyl carbon of N-acetyltryptamine (1a) to become carbon-2 of the indole moiety of tryptamine 11. In order to verify this hypothesis, acetyl [1-^{13}C] tryptamine (22) was prepared from 90% ^{13}C-enriched acetyl chloride and tryptamine.

The product was submitted to a Bischler-Napieralski reaction of 1 h duration in the presence of indole (15). The ^{13}C-enriched 2-methyltryptamine (23) thus obtained (yield 8.3%) was analysed as its oxalate salt by ^{1}H and ^{13}C nmr spectroscopy (table 1).

Table 1 - ^{1}H and ^{13}C nmr Spectra of Compound 23 in DMSO-D_6



22 23

● = ^{13}C

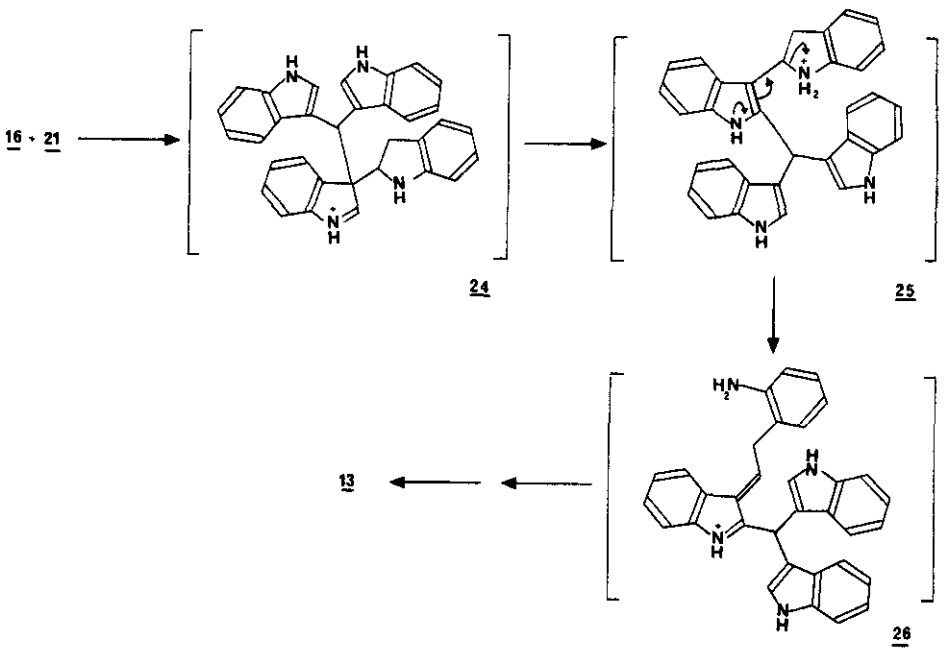
	^{1}H (200 MHz)		^{13}C (50.32 MHz)	
	δ ppm	$J_{^1H,\ ^{13}C}$ Hz	δ ppm	$J_{^{13}C,\ ^{13}C}$ Hz
1	10.90	$^{2}J_{^1H_1,\ ^{13}C_2}$ = 3,8	-	-
2	-		132.64	-
3	-	-	105.17	$^{1}J_{2,3}$ ∿ 72.3
4	-	-	127.81	$^{2}J_{2,4}$ ∿ 4.0
5	7.44	-	116.89	$^{3}J_{2,5}$ ∿ 4.6
6	6.93	-	118.12	-
7	7.00	-	119.92	-
8	7.25	-	110.35	$^{3}J_{2,8}$ ∿ 3
9	-	-	135.22	$^{2}J_{2,9}$ ∿ 5.2
10	2.93	-	22.00	$^{2}J_{2,10}$ ∿ 4.6
11		-	39.41	-
12	8.37	-	-	-
13	2.33	$^{2}J_{^1H_{13},\ ^{13}C_2}$ = 6.6	10.89	$^{1}J_{2,13}$ ∿ 49.3
$(CO_2H)_2$	8.37	-	164.35	-

The spectra were consistent with the ^{13}C *label being at the C-2 position of the indole moiety*, as required by the proposed mechanism.

Evidence for the existence of cation 21 is provided by the isolation of a small quantity of its reaction product with indole (15), tris-(3-indolyl)methane (12).

Cation 21 is also proposed to be the intermediate for the formation of the isolated indolo[3,2-b]-carbazole 13. Some plausible mechanistic steps are shown in scheme 4. Formally, two further steps lead from 26 to 13 : the cyclisation to the indolo[3,2-b]carbazole and the elimination of an indolyl group (in its protonated form).

SCHEME 4



In conclusion, the formation of the spiroindolines 9 and 10 during the Bischler-Napieralski cyclisation of N-acetyltryptamine (1a) in the presence of indole further corroborates[9] the existence of a spiroindolenine as a central intermediate in this reaction.

ACKNOWLEDGEMENT

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REFERENCES AND NOTES

1. J.R.Frost, B.R.P.Gaudillière, and A.E.Wick, J. Chem.Soc., Chem.Commun., 1985, 895.
2. For example, indole versus skatole dimerisation, see A.H.Jackson and P. Smith, Tetrahedron, 1968, 24, 2227.

3. 9 + 10 (ca. 3:1) Methanolate.

9 (major) ^{1}H Nmr (DMSO-D_6;200 MHz) δ 1.55 (m,1H-8); 2.00 (s,CH_3 and m,1H-8); 2.90 (m,1H-9); 3.48 (m,1H-9); 5.10 (d,J=2.2Hz,H-2); 6.00 (d,J=2.2Hz,H-1) 6.50-7.40 (m,ArH); 7.15 (dd,J=8Hz and 1Hz,H-4'); 7.28 (d,J=2.5Hz,H-2'); 11.00 (br s,H-1').

NOE : irradiation H-2 enhancement CH_3,H-1,H-2',H-4'

: irradiation CH_3 (and one H-8) enhancement H-2, H-2', H-4', other H-8.

10 (minor) ^{1}H Nmr (DMSO-D_6;200 MHz) δ 1.45 (s,CH_3); 5.22 (d,J=2.8Hz,H-2); 6.02 (d,J=2.8Hz,H-1). Other signals obscured by those of 9 and the solvent.

NOE : irradiation CH_3 enhancement H-2'.

CH_3OH of solvation 3.14 (d,J=5Hz,CH_3); 4.07 (q,OH).

EIMS (70 eV, source 200°C) m/z 301 (M^+, 27%), 232 (100).

HPLC - FAB - MS - MS :

- HPLC - micropacked capillary column (0.22 mm x 15 cm, 3 µm ODS2); mobile phase: CH_3CN/H_2O, 50/50 (v/v); flow rate: 3 µl/min; injected solution: 60 nl (1 µg/ml).
- dynamic FAB source - matrix addition: glycerol/water, 15/85 (v/v); flow rate: 2 µl/min; 8 kV Xe gun; temperature 40°C.
- MS-MS - 26 eV Ar collision (EBQ : 3FFR); daughter ions of m/z 302 $(M + H)^+$: 9 m/z 158 = 140% of parent, 10 m/z 158 = 80% of parent.

Ir (KBr,cm^{-1}) 1650 (>C=N-). Uv (EtOH 95%) λ max nm (log ε) 320 (3.09), 300 (3.57), 287 (3.95), 279 (3.97), 271 (3.94), 215 (4.62). Anal.Calcd. for $C_{20}H_{19}N_3.CH_3OH$ C=75.65, H=6.95, N=12.60 ; found C=75.79 H=7.04 N=12.93. mp 155-160°.

4. 11 (oxalate salt) ^{1}H Nmr (DMSO-D_6;200MHz) δ 2.35 (s,CH_3); 2.95 (s,$(CH_2)_2$); 6.87-7.05 (2H), 7.25 (1H) and 7.45 (1H) (m,ArH); 8.33 (br s,NH_2 and $(CO_2H)_2$); 10.85 (br s, NH indole). mp and mmp 194-5° (authentic 2-methyltryptamine oxalate salt was prepared from 2-methylindole by treatment with i) oxalyl chloride ii) aqueous ammonia iii) lithium aluminium hydride iv) oxalic acid).

5. 12 ^{1}H Nmr (DMSO-D_6;200MHz) δ 6.06 (s,H-8); 6.84 and 7.01 (ddd,J=8Hz, 8Hz and 1Hz,3H-5 and 3H-6); 6.94 (d,J=2.2Hz,3H-2); 7.34 and 7.41 (br d, 3H-4 and 3H-7); 10.68 (br d,J=2.2Hz, 3H-1). mp and mmp 244-5° (authentic sample prepared by method of Bahner, J. Med. Chem., 1965, 8, 397).

6. 13 ^{1}H Nmr (DMSO-D_6;200MHz) δ 4.58 (s,CH_2); 5.35 (s,NH_2); 6.15-8.26 (m,ArH); 8.08 (s,H-12); 11.00 (1H) and 11.07 (1H) (s,H-5 and H-11).

Ir (KBr)cm^{-1} 3400 (NH),1620,1580,1525,1490,1460 and 1425 (heterocycle). Uv (EtOH 95%) λ max nm (log ε) 400 (3.82), 380 (3.75), 333 (4.78), 317 (4.50), 275 (4.71), 262 shoulder (4.50), 249 (4.49), 242 (4.49), 210 inflection (4.64). EIMS (70 eV, source 200°C) m/z 361 (M^+, 100%), 268 (64) 256 ($M-C_7H_8N+H$, 42). Anal. Calcd. for $C_{25}H_{19}N_3$ C=83.08 H=5.30 N=11.63 ; found C=83.18 H=5.49 N=11.71. mp 353°(as determined by DTA).

7. Methylation of 13 (NaH/DMF/CH_3I) afforded compound 14.

14 ^{1}H Nmr (DMSO-D_6;200MHz) δ 3.86 (s,N_5-CH_3); 3.96 (s,N_{11}-CH_3); 4.78 (br s, CH_2); 5.35 (br s,NH_2); 6.24 (m,H-14); 6.36 (m,H-13); 6.82 (m,H-16); 6.91 (m,H-15); 6.99 (m,H-8); 7.21 (m,H-2); 7.40 (m,H-9); 7.46 (m,H-3); 7.51 (m,H-4); 7.56 (m,H-10); 7.69 (m,H-7); 8.29 (m,H-1); 8.31 (s,H-12).

NOE : irradiation CH_2 enhancement H-7,H-13,NH_2,N_5-CH_3

: irradiation N_5-CH_3 enhancement H-4,H-13,CH_2

: irradiation N_{11}-CH_3 enhancement H-10,H-12.

8. G.F.Smith, Adv. Heterocycl. Chem., 1963,2, 308.

9. As examples of intramolecular trapping of spiroindolenine intermediates see a) J.C.Gaignault, D. Fréchet, and L. Nédelec, Ann. Pharm. Fr., 1978, 36, 401; b) K.M. Biswas and A.H. Jackson, J. Chem. Soc., Chem. Commun., 1983, 85; c) A.H. Jackson, P.V.R. Shannon, and D.J. Wilkins, Tetrahedron Lett., 1987, 28, 4901.

As examples of intermolecular trapping of a spiroindolenine intermediate see:

a) J.R.Frost, B.R.P.Gaudillière, and A.E.Wick, ref. 1; b) K.M. Biswas, A.H. Jackson, and M. Tehrani, J. Chem. Soc., Chem. Commun., 1982, 765.

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