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A CONVENIENT SYNTHESIS OF NEW AMINOPYRROLOINDOLES VIA AN IMMINIUM SALT

S. Rault, M. Cugnon de Sévricourt, A.M. Godard and M. Robba
Laboratoire de Chimie Thérapeutique, U.E.R. des Sciences Pharmaceutiques
Université de Caen, 1, rue Vaubénard, 14032 Caen Cédex - France.

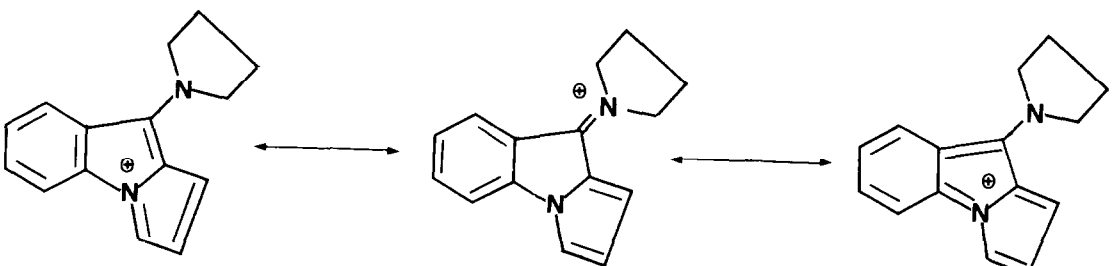
ABSTRACT : Cyclization of pyrrolidinocarboxamide derivative of 2-(1-pyrrolyl) benzoic acid leads to an imminium salt which conduct to N-substituted 9-imino (and amino) 9H-pyrrolo[1,2-a]indoles.

In continuation of our work on the synthesis of heterocyclic systems by cyclization of appropriate N-substituted pyrroles [1], we have recently published the synthesis of some thienopyrrolizines [2] starting from Vilsmeier salts of N-disubstituted amide derivatives of pyrrolylthenoic acids. We wish to describe now the first application of this method to the preparation of new pyrroloindoles [3] : N-substituted 9-imino (and amino) 9H-pyrrolo[1,2-a]indoles.

Treatment of 2-(1-pyrrolyl) benzoic acid [4] 1 with ethyl chloroformate in the presence of triethylamine leads to the symmetrical anhydride 2 (not to the expected unsymmetrical) which gives by reaction with pyrrolidine in chloroform the pyrrolidinocarboxamide 3.

Cyclization of this latter compound in boiling phosphoryl chloride affords the imminium salt 4 ; the crude salt is a mixture of chloride and phosphonodichloridate, as shown by its microanalysis. It can be purified by treatment first by sodium bicarbonate, then by perchloric acid to give the perchlorate 5.

The structure of these salts is clearly established by NMR spectroscopic data.



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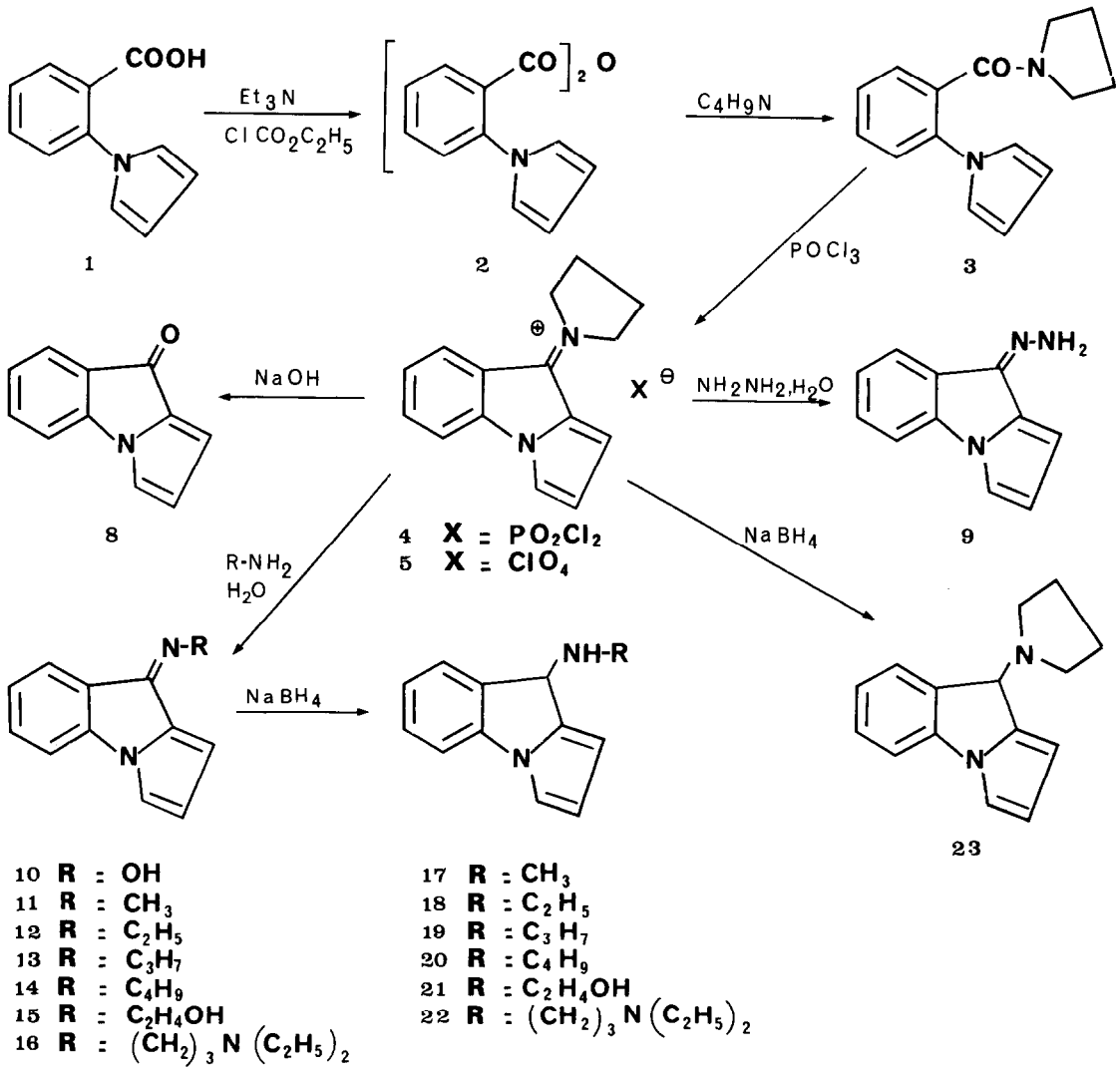

1 2 3

8 4 X = PO_2Cl_2 5 X = ClO_4 9

23

10 R = OH
11 R = CH_3
12 R = C_2H_5
13 R = C_3H_7
14 R = C_4H_9
15 R = C_2H_4OH
16 R = $(CH_2)_3N(C_2H_5)_2$

17 R = CH_3
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19 R = C_3H_7
20 R = C_4H_9
21 R = C_2H_4OH
22 R = $(CH_2)_3N(C_2H_5)_2$

Table : m.p. or b.p. ir and nmr spectroscopic data.

Compound	m.p. or b.p. (°C)	ir(KBr) ν cm^{-1}	NMR DMSO-d_6 δ/TMS ppm
2	80	1780-1720 (C=O)	7.60(m,2H) ; 7.40(m,2H) ; 6.86(m,2H); 6.10 (m,2H)
3	150/5 mm	1630(C=O)	7.36(m,4H) ; 6.86(m,2H) ; 6.20(m,2H); 3.33(m,2H) ; 2.70(m,2H) ; 1.56(m,4H)
4	250(dec)	1630(C=N)	8.20(m,H3,H8) ; 7.90(m,H6,H7) ; 7.30 (m,H5) ; 7.20(dd,H1) ; 6.50(dd,H2) ; 4.30(m,2H) ; 4.00(m,2H) ; 2.20(m,4H)
5	280(exp.)	1650(C=N)	7.70(m,H3,H8) ; 7.63(m,H6,H7) ; 7.20 (m,H1,H5) ; 6.50(dd,H2) ; 4.30 (m,2H); 4.00(m,2H) ; 2.20(m,4H)
11	134	1640(C=N)	7.50-7.40(m,H3,H5,H6,H7,H8) ; 6.60 (dd,H1) ; 6.30 (dd,H2) ; 3.15 (s,CH_3)
12	140/5mm	1630(C=N)	7.50-7.15(m,H3,H5,H6,H7,H8) ; 6.60 (dd,H1) ; 6.30 (dd,H2) ; 3.71 (q,CH_2); 1.30 (t,CH_3)
13	160/5mm	1635(C=N)	7.50-7.10(m,H3,H5,H6,H7,H8) ; 6.60 (dd,H1) ; 6.33(dd,H2) ; 3.60 (t,CH_2); 1.75(m,CH_2) ; 1.03(t,CH_3)
14	120/5mm	1635(C=N)	7.50-7.13(m,H3,H5,H6,H7,H8) ; 6.60 (dd, H1) ; 6.33(dd,H2) ; 3.60(t,CH_2) ; 1.70 (m,CH_2) ; 1.43(m,CH_2) ; 0.90(t,CH_3)
15	112	1625(C=N) 3200(broad OH)	7.50-7.13(m,H3,H5,H6,H7,H8) ; 6.60 (dd, H1) ; 6.33 (dd,H2) ; 3.80(s,2CH_2) ; 4.60 (OH)
16	165/5mm	1635(C=N)	7.50-7.15(m,H3,H5,H6,H7,H8) ; 6.60(dd, H1) ; 6.30(dd,H2) ; 3.60(t,CH_2) ; 2.50 (m,3CH_2) ; 1.80(q,CH_2) ; 0.90(t,2CH_3)
17	145/5mm	3300(NH)	7.30-7.00(m,H5,H6,H7,H8) ; 7.15(dd,H3); 6.21(dd,H2) ; 6.15(dd,H1) ; 4.80(s,H9); 3.48(s,CH_3)
18	145/5mm	3290(NH)	7.30-7.00(m,H5,H6,H7,H8) ; 7.10(dd,H3); 6.15(m,H2,H1) ; 4.80(s,H9) ; 2.50(q,CH_2)
19	195/5mm	3300(NH)	7.30-7.00(m,H5,H6,H7,H8) ; 7.10(dd,H3); 6.15(m,H2,H1) ; 4.80(s,H9) ; 3.20(t,CH_2); 1.60(q,CH_2) ; 1.20(t,CH_3).
20	160/5mm	3300(NH)	7.30-7.00(m,H5,H6,H7,H8) ; 7.20(dd,H3); 6.20(dd,H2) ; 6.06(dd,H1) ; 4.80(s,H9); 3.30(t,CH_2) ; 2.45(m,2CH_2) ; 1.03(t,CH_3);
21	220/5mm	3300(NH,OH)	7.30-7.00(m,H5,H6,H7,H8) ; 7.15(dd,H1); 6.20(dd,H2) ; 6.10(dd,H1) ; 4.80(s,H9); 3.80(s,2CH_2) ; 3.00(NH,OH)
22	145/5mm	3280(NH)	7.30-7.00(m,H5,H6,H7,H8) ; 7.20(dd,H1); 6.20(dd,H2) ; 6.10(dd,H1) ; 4.80(s,H9); 2.40(m,4CH_2) ; 1.50(q,CH_2) ; 0.90(t,2CH_3)
23	160/5mm	-	7.30-7.00(m,H5,H6,H7,H8) ; 7.20(dd,H3); 6.20(dd,H2) ; 6.10(dd,H1) ; 5.03(s,H9) ; 2.45(m,2CH_2) ; 1.60(m,2CH_2)

All compounds synthesized gave satisfactory microanalyses.

The α protons of the pyrrolidine ring appear as two deshielded multiplets at 4.00 and 4.30 ppm which reveal a restricted rotation due to an exocyclic double bond (mesomeric structure 5). However one cannot exclude the two mesomeric structures 6 and 7 which possess a greater electronic delocalisation.

The stable salts 4 and 5 exhibit a high reactivity towards nucleophilic reagents and can conduct in aqueous medium to the indolone [4] 8 by treatment with sodium hydroxide, to the hydrazone [4] 9 by treatment with hydrazine hydrate and to the oxime 10 by treatment with hydroxylamine hydrochloride.

Furthermore, the reaction of 4 or 5 in water with an excess of primary aliphatic amines affords in quantitative yield the N-alkyl 9H-pyrrolo 1,2-a pyrrolizin-9-imines 11-16. Reduction of these latter compounds with sodium borohydride in methanol gives the corresponding secondary amines 17-22.

On the other hand, reduction of the imminium salt 4 with a large excess of sodium borohydride gives the 9-pyrrolidino 9H-pyrroloindole 23.

Further studies concerning these reactions and evaluation of psychotropic activity of the title and related compounds are in progress.

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