RESERPINE ANALOGUES: SYNTHESIS OF DIBENZOQUINOLIZINE AND ISOQUINOLINE DERIVATIVES

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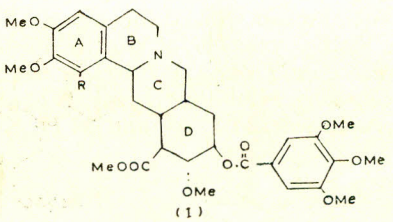
(Received June 21, 1966)

2,3,10,11-Tetramethoxy-12-carbomethoxy-5,6,13,13a-tetrahydro-8H-dibenzo (a,g) quinolizine and two 5-carbomethoxy-6,7-dimethoxyisoquinoline derivatives have been prepared for evaluation as reserpine analogues.

A novel approach to the dibenzo (a,g) quinolizine derivative has been made, the C ring being prepared first as the lactam and the latter cyclized.

Introduction

Apart from the analogues based on the intact reserpine skeleton and the simpler amine esters and amides of trimethoxybenzoic acid the more obvious portions of the reserpine molecule taken as models were the β-carboline and the indole-tryptamine moieties. These compounds did not prove very useful as far as their reserpine-like properties were concerned. Thus the indoloquinolizine and the dibenzoquinolizine analogues, the latter of which may also be described as the despyrroloreserpine derivatives, have been examined of late as reserpine analogues. The dibenzoquinolizine nucleus, which occurs in the physiologically active berberine group of alkaloids, has been examined by several workers. Muller and Allais[1] reported the synthesis of 10-methoxy-despyrroloreserpine (I, R=H). This compound and its 13a-iso derivative, corresponding to 3-iso-resperine, were also reported by Protiva *et al.*[2] Pelz *et al.*[3] went further on to prepare the mescaline analogues of the above (I, R=MeO). According to preliminary pharmacological reports[3] the mescaline derivatives exhibit activity similar to reserpine and isoreserpine. However, all these compounds may be presumed not to have been very effective. The fact that these compounds had the ring fully hydrogenated, coupled with the observations that some dibenzoquinolizine derivatives with the ring D aromatic, e.g., palmatine, have been described as hypotensive agents[4] and there has been interest, of late, in other such derivatives as blood pressure lowering agents, e.g. canadine methocyanate[5] and *N*-methylrhodanide[6] suggested to us that, keeping the ring D aromatic, the siting of a carbomethoxy group at C-12 corresponding to C-16 of reserpine may result in compounds with enhanced reserpine-like properties. The despyrrolo compound IV was therefore prepared. It might be argued that for greater similarity in structure with reserpine it was preferable that the function at C-10 was the trimethoxybenzoyl ester, but from a consideration of the



(I)

results of Logemann *et al.*,[7] confirmed by Nogradi,[8] who had shown that for the analogues having the reserpine skeleton with the ring E aromatic such esterification was contraindicated, the converse argument could likewise be put forward.

In the course of this synthesis a novel approach to the desired dibenzo(a,g)quinolizine derivative has been made, the ring C being prepared first as the lactam and the latter cyclized. The usual method for the preparation of the dibenzoquinolizine derivatives of the protoberberine type, to which the desired compound belongs, consists of condensing the benzylisoquinoline derivatives with formaldehyde. The synthesis of norcorydaline by Walker[9] is a typical example. It can be schematically represented as below (scheme a). In this process rings A, B and D are formed first and the final condensation produces the C ring. Our method (b) consists of the condensation of homoveratrylamine with methyl 2-carbomethoxy-3,4-dimethoxy-6-chloromethylphenyl-acetate (II) to give the lactam III which was cyclized with phosphorous oxychloride to the quaternary salt. Reduction with sodium borohydride furnished the final protoberberine derivative IV. The overall yield in this process was 30% which compares favourably with that in the usual method (ca. 25%), the calculations being based on the initial condensations to give the amide and the lactam. An additional advantage of the new process is that there is no scope of isomerides being formed.

Besides the compounds III and IV, the n-propyl analogue of the former has been prepared by us.

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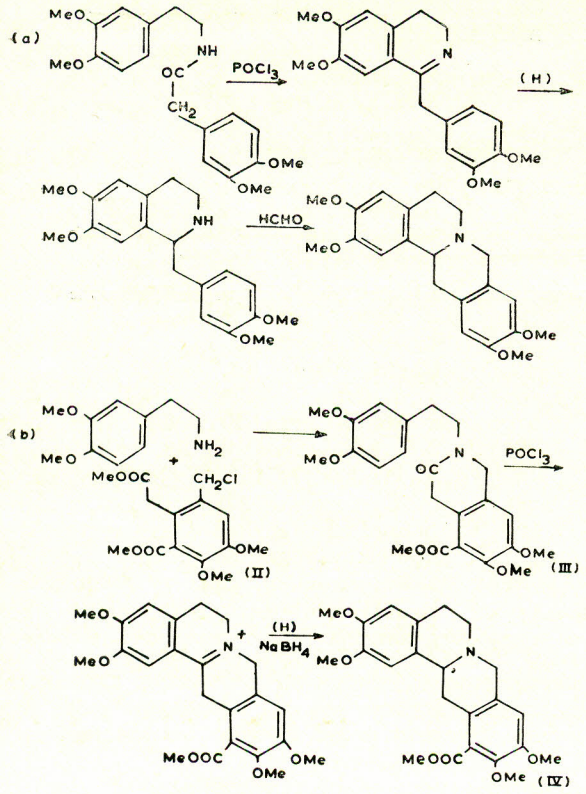

The route chosen also furnishes isoquinoline derivatives with the carbomethoxy group in the 5-position. In themselves they are of interest as reserpine analogues the rings D and E of this alkaloid being represented, the latter being aromatic.

Experimental

N-2-(3,4-*Dimethoxyphenyl*) *ethyl*-3-*keto*-5-*carbomethoxy*-6, 7-*dimethoxy*-1, 2, 3, 4-*tetrahydroisoquinoline*.—Methyl 2-carbomethoxy-3,4-dimethoxy-6-chloromethylphenylacetate (3 g) (obtained from opianic acid by way of methyl 2-carbomethoxy-3,4-dimethoxyphenylacetate,[10] which on reaction with chloromethyl ether in presence of stannic chloride[11] gave the starting material) and homoveratrylamine (3.1 g; twice molar amount plus 10% excess) were dissolved in dry benzene (30 ml) when there commenced almost immediately the precipitation of homoveratrylamine hydrochloride. After standing for 24 hr the salt was filtered out and washed with a little benzene. The filtrate was extracted with 2% hydrochloric acid, 2% sodium hydrogen carbonate solution and water successively. The organic layer was dried overnight ($MgSO_4$). Next morning it was found to have become light yellow in colour. The drying agent was filtered off and the solvent removed *in vacuo* when a yellow gum was obtained. This could not be crystallised at once, but no standing solidified over a period of two weeks. Recrystallisation of the residue from methanol furnished the lemon yellow lactam (2.2 g.; 63%), m.p. 140°C (Found: C, 64.6; H, 6.3; N, 3.5. $C_{23}H_{27}NO_7$ requires C, 64.3; 6.3; N, 3.3%).

2-(*n-Propyl*)-3-*keto*-5-*carbomethoxy*-6,7-*dimethoxy*-1,2,3,4-*tetrahydroisoquinoline*.—The above chloromethyl ester (225 mg) and n-propylamine (50λ; large excess) in solution in tetrahydrofuran (2 ml) gave the corresponding yellow isoquinoline derivative, m.p. 86–87°C (Found: C, 63.2; H, 6.7; N, 4.6. $C_{16}H_{21}NO_5$ requires C, 62.6; H, 6.8; N, 4.6%).

2,3, 10, 11-*Tetramethoxy*-12-*carbomethoxy*-5, 6, 13, 13*a*-*tetrahydro*-8H-*dibenzo*(*a*,*g*)*quinolizine*.—N-2 (3,4-Dimethoxyphenyl)-ethyl-3-keto-5-carbomethoxy-6,7-dimethoxy-1,2,3,4-terahydroisoquinoline (300 mg) was suspended in freshly distilled phosphorous oxychloride (1 ml) and heated when it dissolved and the solution turned orange-red. After refluxing for 10 min dry ether (25 ml) was added. A red gum separated at once. The solvent was decanted off and the gummy residue freed of the phosphorous oxychloride *in vacuo*. The gum obtained was insoluble in benzene, ethyl acetate and ether and was soluble in water, methanol and ethanol. The red quaternary salt could be crystallised from n-butanol to give a small amount of orange needles, m.p. 200–203°C (decomp. with evolution of gas).

However, the crude, red quaternary salt was dissolved in methanol (50 ml) and treated with sodium borohydride (1.75 g) in portions under vigorous stirring at such a rate that the temperature did not rise above 30°C. After the addition was complete the stirring was continued. After a total of 2 hr the methanol was removed *in vacuo* and the pasty mass remaining taken up in water (100 ml). Though the red colour of the solution had considerably diminished in intensity during the addition of the borohydride it had not disappeared completely and now the resulting aqueous suspension had a reddish tinge. On extraction with ether a light yellow organic layer was obtained. It was separated, washed with saturated brine and dried ($MgSO_4$).

On addition of dry alcoholic hydrochloric acid to the ethereal solution a white flocculent precipitate came down, which was soluble in water. Recrystallisation from dry alcohol–ether gave the

desired compound, m.p. 220-222°C. (Found: C, 61.0; H, 6.5; Cl, 7.6. $C_{23}H_{27}NO_6$, HCl requires C, 61.4; H, 6.3; Cl, 7.9%).

The *picrate* was prepared in dry ethanol and recrystallised from the same solvent. The analytical sample was dried *in vacuo* at room temperature, m.p. 136–138°C. (Found: C, 53.0; H, 5.0; N, 8.1. $C_{29}H_{30}N_4O_{13},H_2O$ requires C, 52.7; H, 4.9; N, 8.5%).

Acknowledgement.—The auther wishes to record his thanks to Professor W.H. Linnell then Dean, School of Pharmacy, University of London, for his help and advice during the course of the work and to the U.K. Government for providing the Colombo Plan Fellowship, during the tenure of which this work was done.

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