Synthesis of (±)-3-Methoxy-6,15-diazaestra-1,3,5,7,9,14-hexaene

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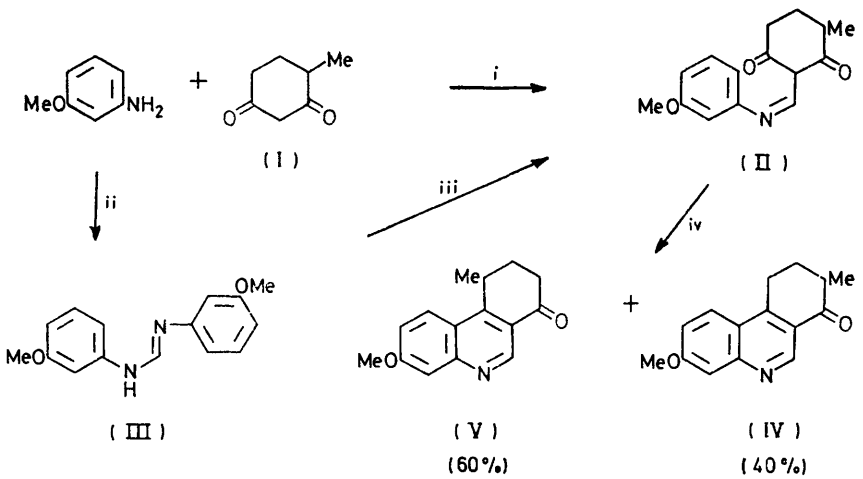
(±)-3-Methoxy-6,15-diazaestra-1,3,5,7,9,14-hexaene (IX) has been synthesised from 3-methoxy-8-methyl-9,10-dihydrophenanthridin-7(8*H*)-one (IV) *via* a modified Curtius rearrangement of the intermediate Michael condensation product (VI).

MANY modified steroids in which one or more carbon atoms are replaced by hetero-atoms have been synthesised in recent years, and such molecules, particularly those containing nitrogen, may act as endocrine agents with a novel spectrum of biological activity.[1,2] Recently, Morgan and his co-workers [3] have synthesised an equilenin-like azasteroid which combines the steroid and indole nuclei in a single structure. We report here a similar synthesis of a 6,15-diazaequilenin derivative (IX) which incorporates quinoline and indole systems.



SCHEME 1 Reagents: i, $(EtO)_3CH$, 120—130°; ii, $(EtO)_3CH$, EtOH, reflux; iii, (I), 130—135°; iv, polyphosphoric acid

The required dihydrophenanthridinone (IV) was prepared from *m*-anisidine and 4-methylcyclohexane-

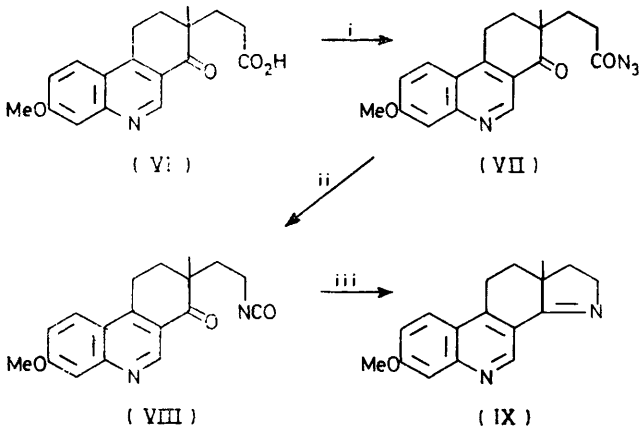
[1] A. Burger, 'Medicinal Chemistry,' 3rd edn., Wiley–Interscience, New York, 1970, p. 1141; M. Alauddin and M. Martin-Smith, *J. Pharm. Pharmacol.*, 1962, **14**, 325; M. Martin-Smith and F. Surgue, *ibid.*, 1964, **16**, 568; S. D. Levine, *J. Medicin. Chem.*, 1965, **8**, 537.

[2] For a review, see H. Singh, S. Padmanavan, and V. Parashar, *J. Proc. Inst. Chem., India*, 1967, **39**, 54.

[3] J. G. Morgan, K. D. Berlin, N. N. Durham, and R. W. Chesnut, *J. Org. Chem.*, 1971, **36**, 1599.

1,3-dione [4] by the route [5] shown in Scheme 1. The final product was a mixture of two ketones (IV) and (V), the latter predominating. This mixture was submitted to a Claisen condensation with ethyl formate whereby compound (V) was converted into an alkali-soluble α-hydroxymethylene derivative [6] while the other (IV) was unchanged and was isolated in *ca.* 40% yield. Hydrolysis of the hydroxymethylene compound afforded the other ketone (V). The n.m.r. spectra of the two ketones differed in the position of the methyl doublets [τ 8·67 and 8·78 in (IV) and 8·45 and 8·57 in (V)] and allowed an estimation of their relative abundance in the cyclised product. The preponderance of the ketone (V) was unexpected and the reason for it is obscure, since its formation involves a more crowded transition state.

The ketone (IV) was condensed with ethyl acrylate and the resultant keto-ester hydrolysed to the propionic acid (VI) in good yield. This was converted into the diazasteroid (IX) by Curtius arrangement as modified by Weinstock [7] (Scheme 2) in an overall yield of 40%. The structure of the diazasteroid (IX) was confirmed by its n.m.r. spectrum (see Experimental section).



SCHEME 2 Reagents: i, $ClCO_2Et$, Et_3N, NaN_3; ii, heating in toluene; iii, HCl–AcOH, reflux

EXPERIMENTAL

N.m.r. spectra were measured with a Varian 60 MHz spectrometer for solutions in [^{2}H]chloroform with tetramethylsilane as internal standard. Petroleum refers to the fraction of b.p. 60—80°. All organic extracts were dried over anhydrous sodium sulphate.

4-Methylcyclohexane-1,3-dione (I).—Ethyl 2-methyl-3-oxobutyrate (43·2 g, 0·3 mol) was condensed with ethyl acrylate (33·0 g, 0·33 mol) in the presence of sodium ethoxide [from sodium (0·23 g, 0·01 mol)] in dry ethanol (25 ml). After 24 h at room temperature, the product was worked up to yield diethyl 2-acetyl-2-methylglutarate, b.p. 124—125° at 0·6 mmHg (68·0 g, 93%) (Found: C, 59·2; H, 8·5. Calc. for $C_{12}H_{20}O_5$: C, 59·0; H, 8·2%). The ester was hydrolysed, the resultant keto-acid re-esterified to methyl 4-methyl-5-oxohexanoate, and the latter cyclised to 4-methylcyclohexane-1,3-dione (I) with sodium ethoxide according to a previous procedure.[4] The diketone was a low-melting solid, b.p. 125—128° at 1 mmHg (Found: C, 66·3; H, 8·3. Calc. for $C_7H_{10}O_2$: C, 66·7; H, 7·9%).

2-m-Methoxyphenyliminomethyl-4-methylcyclohexane-1,3-dione (II).—(*a*) A mixture of *m*-anisidine (4·92 g, 0·04 mol), ethyl orthoformate (5·92 g, 0·04 mol), and 4-methylcyclohexane-1,3-dione (5·0 g, 0·04 mol) was heated in an oil-bath at 120—130° until the ethanol formed was completely distilled off (1 h). The residue (10·5 g) could not be crystallised and was used directly for cyclisation.

(*b*) A mixture of *m*-anisidine (4·92 g), ethyl orthoformate (4·74 g), and ethanol (20 ml) was refluxed for 18 h. Ethanol was partly removed and the residue chilled to give a solid which crystallised from methanol to furnish *NN'*-bis-*m*-methoxyphenylformamidine (III) as needles (5·4 g), m.p. 111—112° (lit.,[5a] 108—109°). The formamidine (4·5 g, 0·018 mol) and 4-methylcyclohexane-1,3-dione (2·26 g, 0·018 mol) were heated together at 130—135° for 2 h. The product was taken up in ethyl acetate, washed successively with aqueous 10% hydrochloric acid, 2% sodium hydrogen carbonate, and water, and dried. The residue (3·65 g) after removal of the solvent was used for the subsequent reaction.

Cyclisation of the Anil (II).—The preceding anil (II) (3·6 g) was intimately mixed with polyphosphoric acid, prepared from phosphorus pentoxide (25 g) and 90% phosphoric acid (30 g), and was heated at 130—140° for 2 h. The cooled mixture was decomposed with ice–water and basified with aqueous 25% sodium hydroxide. The organic matter was extracted with chloroform, and the extract was washed with water, dried, and evaporated to furnish a gum. This on trituration with ether afforded a light brown solid (3·0 g) which crystallised from benzene–petroleum in light yellow plates (2·2 g), m.p. 123—140°. The n.m.r. spectrum showed it to be 40 : 60 mixture of the ketones (IV) and (V) which were separated as described below.

3-Methoxy-8-methyl-9,10-dihydrophenanthridin-7(8H)-one (IV).—The foregoing mixture (2·0 g) and ethyl formate (3·64 g) were added dropwise to an ice-cooled suspension of alcohol-free sodium ethoxide (1·25 g) in dry benzene (40 ml) with stirring under nitrogen, and the mixture was left overnight at room temperature. It was then decomposed with ice–water, and the benzene layer was separated and washed twice with aqueous 2% sodium hydroxide. The mother liquor and the alkali washings were set aside and the benzene extract was evaporated to give the *ketone* (IV) (0·80 g, 40%), m.p. 155—156°. It crystallised from ethyl acetate in light yellow plates, m.p. 160° (Found: C, 74·6; H, 6·4; N, 5·5. $C_{15}H_{15}NO_2$ requires C, 74·7; H, 6·2; N, 5·8%); $\nu_{max.}$ (Nujol) 1666, 1610, and 1590 cm^{-1}; τ 0·60 (1H, s, 6-H), 2·10 (1H, d, *J* 8 Hz, 1-H), 2·67 (2H, m, ArH), 6·03 (3H, s, OMe), 6·62 (2H, m, 10-H_2), 7·20 (1H, m, 8-H), 7·75 (2H, m, 9-H_2), and 8·67 and 8·78 (3H, d, *J* 7 Hz, Me).

3-Methoxy-10-methyl-9,10-dihydrophenanthridin-7(8H)-one (V).—The mother liquor and the alkali washings from the previous reaction were neutralised with 1N-hydrochloric acid and then acidified with acetic acid. The crude solid

[4] G. Pyne, R. C. Bannerjee, and D. Nasipuri, *J. Indian Chem. Soc.*, 1963, **40**, 199.

[5] (*a*) P. E. Cross and E. R. H. Jones, *J. Chem. Soc.*, 1964, 5916; (*b*) J. H. Burkhalter and H. Watanabe, *Chem. Eng. News*, 1963, **41**, 40; S. V. Sunthankar and S. D. Mehenddale, *Indian J. Chem.*, 1973, **11**, 84.

[6] W. J. Bailey and M. Mardoff, *J. Amer. Chem. Soc.*, 1954, **76**, 2707.

[7] J. Weinstock, *J. Org. Chem.*, 1961, **26**, 3511; M. Fetizon and M. Golfier, *Bull. Soc. chim. France*, 1966, 870.

thus obtained was crystallised from ethyl acetate to furnish 8-*hydroxymethylene*-3-*methoxy*-10-*methyl*-9,10-*dihydrophenanthridin*-7(8H)-*one* (1·1 g) in glistening brown needles, m.p. 182—183° (Found: C, 71·4; H, 5·8; N, 5·0. $C_{16}H_{15}NO_3$ requires C, 71·4; H, 5·6; N, 5·2%). This compound (0·3 g) was refluxed with aqueous 5% sodium hydroxide (25 ml) for 1 h. The precipitate was taken up in ether and worked up to afford the *ketone* (V) (0·23 g) which crystallised from ethyl acetate–petroleum in shining flakes, m.p. 147° (Found: C, 74·6; H, 6·3; N, 5·6%); $\nu_{max.}$ (Nujol) 1666, 1610, and 1580 cm^{-1}; τ 0·56 (1H, s, 6-H), 2·05 (1H, d, *J* 8 Hz, 1-H), 2·60 (2H, m, ArH), 6·01 (3H, s, OMe), 6·20 (1H, m, 10-H), 7·30 (2H, t, *J* 5 Hz, 8-H_2), 7·77 (2H, m, 9-H_2), and 8·45 and 8·57 (3H, d, Me). A 50 : 50 mixture of the ketones (IV) and (V) had m.p. 120—140°.

3-(3-*Methoxy*-8-*methyl*-7-*oxo*-7,8,9,10-*tetrahydrophenanthridin*-8-*yl*)*propionic Acid* (VI).—The ketone (IV) (0·65 g, 2·7 mmol) was added to a solution of sodium (0·062 g, 2·7 mmol) in dry ethanol (5 ml) followed by ethyl acrylate (0·27 g, 2·7 mmol). The mixture was refluxed for 6 h under nitrogen. Aqueous 15% sodium hydroxide (5 ml) was then added and the heating continued for 3 h. After removal of ethanol and extraction of neutral matter by ethyl acetate, the alkaline solution was cooled and acidified with 1N-hydrochloric acid followed by acetic acid. The precipitate gave the *propionic acid* (VI) in plates (0·45 g), m.p. 86—88° (from methanol) (Found: C, 68·7; H, 6·3; N, 4·4. $C_{18}H_{19}NO_4$ requires C, 69·0; H, 6·1; N, 4·5%); $\nu_{max.}$ (KBr) 1695 (CO_2H) and 1660 (C=O) cm^{-1}.

(±)-3-*Methoxy*-6,15-*diazaestra*-1,3,5,7,9,14-*hexaene* (IX).—The foregoing propionic acid (VI) (0·4 g, 1·3 mmol) was dissolved in anhydrous acetone (12 ml), chilled to −5°, and triethylamine (0·202 g, 2 mmol) was added with stirring under nitrogen. Ethyl chloroformate (0·217 g, 2 mmol) was then introduced and the mixture stirred in the cold for 30 min. A solution of sodium azide (0·195 g, 3 mmol) in water (1 ml) was added dropwise and the stirring continued for 2 h more at 0°. The milky-white reaction mixture was poured into ice–water to precipitate the azide (VII) as a semi-solid mass. It was taken up in methylene chloride and was used in the next operation.

The residue (0·4 g) after removal of methylene chloride was heated in toluene on a steam-bath for 2 h, toluene was removed under reduced pressure, and the crude isocyanate (VIII) (0·38 g) was refluxed with a mixture of hydrochloric acid (3 ml), acetic acid (3 ml), and water (4 ml) for 24 h under nitrogen. The cooled solution was diluted with water, extracted thoroughly with ether, and then neutralised with aqueous 10% sodium hydrogen carbonate. A dark solid was obtained which was washed with warm aqueous 2% sodium hydroxide to remove any phenolic matter. The residue was sublimed (160—170° at 0·4 mmHg) to furnish the *diazasteroid* (IX) as a crystalline mass (0·14 g, 40%), m.p. 170° (after resublimation) (Found: C, 76·7; H, 7·1; N, 9·9%; M^+, 266. $C_{17}H_{18}N_2O$ requires C, 76·7; H, 6·8; N, 10·5%; *M*, 266); $\nu_{max.}$ (Nujol) 1600 cm^{-1} (C=N); τ 0·53 (1H, s, 7-H), 2·14 (1H, d, *J* 8 Hz, 1-H), 2·66 (2H, m, ArH), 6·05 (3H, s, OMe), 6·70 (2H, m, 11-H_2), 8·05 (4H, m, 2 × CH_2), and 8·90 (3H, s, 13-Me). The alkali-wash on acidification afforded a gummy mass (0·02 g) which was not further investigated.

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