The Synthesis of Some Reduced Pyrido- and Pyrrolo-benzodiazepines

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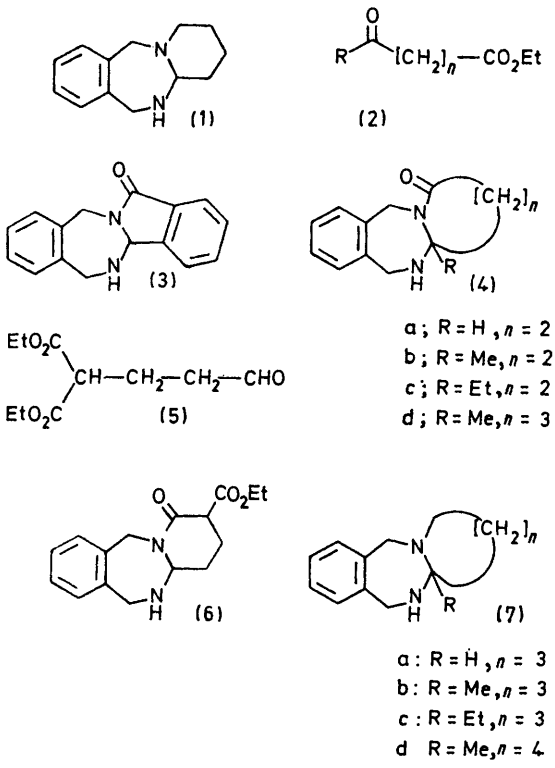
Some 3a-alkyl-2.3.3a.4.5.10-hexahydro-1*H*-pyrrolo[1.2-*b*][2.4]benzodiazepines and 4a-alkyl-1.2.3.4.4a.5.6.11-octahydropyrido[1.2-*b*][2.4]benzodiazepines have been prepared by reduction of the corresponding 1-oxo-compounds. The latter were synthesised by the condensation of *o*-phenylenebismethylamine with the appropriate oxo-ester.

FOLLOWING the synthesis of the 1,2,3,4,4a,5,6,11-octahydropyrido[1,2-*b*][2,4]benzodiazepine system (1),[1] we wished to prepare 4a-substituted analogues for pharmacological evaluation. The original synthesis was not applicable and we therefore examined the condensation of ketonic esters (2) with *o*-phenylenebismethylamine, by analogy with the work of Stevenson and Hatt [2,3] who prepared compound (3) by condensation of the diamine with phthalaldehydic acid. It was found that the pyrrolodiazepines (4; $n = 2$) were formed readily in ethanolic solution but that the pyridodiazepines (4; $n = 3$) could only be obtained under forcing conditions. However, an ester derivative (6) was obtained readily from the diamine and the diester (5). The pyrrolodiazepinones (4a—c) and the pyridodiazepinone (4d) gave the corresponding reduced diazepines (7) on treatment with lithium aluminium hydride.



EXPERIMENTAL

I.r. spectra were determined on a Unicam SP 200 spectrometer, u.v. spectra on a Unicam SP 700 spectrometer (1 cm cells), ^{1}H n.m.r. spectra on a Varian A60-D spectrometer.

o-Phenylenebismethylamine Hydrochloride Hydrate.—Owing to the unsuitability of the literature methods [4-6] for the large scale production of the diamine hydrochloride the following method was devised. Phthalonitrile (300 g) in acetic anhydride (3·5 l) was catalytically hydrogenated (70°; 300 lb in^{-2}; 20% Raney nickel). After uptake had ceased (92%; 4·5 h) excess of solvent was removed *in vacuo* and the resulting brown oil was heated under reflux with concentrated hydrochloric acid (2·5 l) for 5 h. The acid was removed *in vacuo* and the residue was dissolved in water (2 l) and partly clarified with charcoal (2 × 50 g). Removal of the water and trituration with hot ethanol (400 ml) gave the diamine hydrochloride (256 g, 52%) (slow decomp. >300°), identical (i.r. spectrum) with a sample prepared by the literature method [4] (Found: C, 42·7; H, 6·6; N, 12·0. Calc. for $C_8H_{12}N_2,2HCl,H_2O$: C, 42·3; H, 7·1; N, 12·3%).

The free base was liberated by dissolving the diamine

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[3] E. F. M. Stevenson, *J. Chem. Soc.*, 1952, 5024.
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[5] E. F. Elslager, D. F. Worth, N. F. Haley, and S. C. Perricone, *J. Heterocyclic. Chem.*, 1968, **5**, 609.
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hydrochloride in 10N-sodium hydroxide and continuously extracting with ether. This was always carried out immediately before use, owing to darkening and absorption of carbon dioxide by the diamine.

2,3,3a,4,5,10-*Hexahydro*-1H-*pyrrolo*[1,2-b][2,4]*benzodiazepin*-1-*one* (4a).—A mixture of the foregoing diamine (6·8 g) and methyl β-formylpropionate (5·8 g) in dry ethanol (75 ml) was heated under reflux in an atmosphere of nitrogen for 72 h. The mixture was treated with charcoal, filtered, and concentrated to an oil. Addition of ether (100 ml) afforded the *pyrrolodiazepine* (5·15 g, 54%), m.p. 173—175° (from benzene) (Found: 71·3; H, 6·8; N, 13·6. $C_{12}H_{14}N_2O$ requires C, 71·3; H, 7·0; N, 13·9%), $\nu_{max.}$ (KBr) 1670 (C=O), 3300 (NH) cm^{-1}, τ (10% $CDCl_3$) 2·8 (4H, m, ArH), 4·8 and 5·5 (2H, ABq, *J* 15 Hz, 10-H_2), 5·08 (1H, t, *J* 6 Hz, 3a-H), 5·8 (2H, ABq, *J* 12 Hz, 5-H_2), 7·7 (3H, m, 2-H_2 + NH as shown by addition of D_2O), and 8·0 (2H, m, 3-H_2). The assignment of the two AB quartets is based on the assumption that the diamagnetic anisotropy of the carbonyl group would separate the components of the quartet due to the methylene protons at C-10 to a greater extent than those associated with the 5-position.

2,3,3a,4,5,10-*Hexahydro*-3a-*methyl*-1H-*pyrrolo*[1,2,-b]-[2,4]*benzodiazepin*-1-*one* (4b) (85%), m.p. 171—172°, was prepared similarly from ethyl levulinate (24 h reaction period) (Found: C, 72·1; H, 7·4; N, 12·9. $C_{13}H_{16}N_2O$ requires C, 72·2; H, 7·5; N, 13·0%), $\nu_{max.}$ (KBr) 1670 (C=O) and 3300 (NH) cm^{-1}, τ(10% $CDCl_3$) 2·8 (4H, m, ArH), 5·0 and 5·8 (2H, ABq, *J* 15 Hz, 10-H_2), 6·0 (2H, s, 5-H_2), 7·8 (5H, m, 2- and 3-H_2 + NH as shown by addition of D_2O), and 8·4 (3H, s, Me). From the occurrence of a singlet at τ 6·0 instead of an AB quartet, it is inferred that the resonance of the 5-protons are coincident. The resonances due to these protons are resolved, however, in the spectrum of the reduction product (7b).

3a-*Ethyl*-2,3,3a,4,5,10-*hexahydro*-1H-*pyrrolo*[1,2-b][2,4]-*benzodiazepin*-1-*one* (4c) (25%), m.p. 125—126° [from benzene–petroleum (b.p. 60—80°)] was prepared similarly from ethyl homolevulinate (24 h reaction period) (Found: C, 73·3; H, 8·0; N, 12·3. $C_{14}H_{18}N_2O$ requires C, 73·1; H, 7·9; N, 12·2%), $\nu_{max.}$ (KBr) 1660 (C=O) and 3300 (NH) cm^{-1}, $\nu_{max.}$ (0·03% in CCl_4) 1689 (C=O) cm^{-1}, τ (10% $CDCl_3$) 2·85 (4H, m, ArH), 5·1 and 5·95 (2H, ABq, *J* 15 Hz, 10-H_2), 6·1 (2H, s, 5-H_2), 7·9 (7H, m, 2- and 3-H_2, MeCH_2, and NH, as shown by addition of D_2O), and 9·1 (3H, t, *J* 6 Hz, CH_3·CH_2).

1,2,3,4,4a,5,6,11-*Octahydro*-4a-*methylpyrido*[1,2-b][2,4]-*benzodiazepin*-1-*one* (4d).—*o*-Phenylenebismethylamine (25 g) and ethyl 5-oxohexanoate (24 g) in 2-ethoxyethanol (250 ml) were heated under reflux in an atmosphere of nitrogen for 72 h. The solvent was removed *in vacuo* and the residue was extracted with boiling ether (500 ml). On cooling, the extract deposited the *diazepine* (9·0 g, 18%), m.p. 134—135° (from benzene–ether) (Found: C, 72·9; H, 8·0; N, 12·2. $C_{14}H_{18}N_2O$ requires C, 73·0; H, 7·9; N, 12·2%), $\nu_{max.}$ (KBr) 1605 (C=O), 3250 (NH) cm^{-1}, $\nu_{max.}$ (0·03% CCl_4) 1640 (C=O) cm^{-1}, τ (10% $CDCl_3$) 2·65 (4H, m, ArH), 4·65 and 5·4 (2H, ABq, *J* 16 Hz, 11-H_2), 5·75 (2H, ABq, *J* 17 Hz, 6-H_2), 7·4—7·95 (7H, m, 2-, 3-, and 4-H_2 and NH as shown by addition of D_2O), and 8·3 (3H, s, Me).

Ethyl 1,2,3,4,4a,5,6,11-*Octahydro*-1-*oxopyrido*[1,2-b][2,4]-*benzodiazepine*-2-*carboxylate Hydrochloride Hemihydrate* (6).—*o*-Phenylenebismethylamine (10 g) and diethyl 3-oxopropylmalonate (14·2 g) in ethanol (100 ml) were heated under reflux in an atmosphere of nitrogen for 36 h. Removal of the solvent *in vacuo* and chromatography [silica gel (40 × 3 cm); acetone] of the resulting brown oil gave a fraction which after clarification with charcoal and treatment with ethereal hydrogen chloride gave the *diazepine hydrochloride* (9 g, 37%), m.p. 192—194° [Found: C, 57·4; H, 6·4; Cl, 10·3; N, 8·1; H_2O (Karl Fischer) 2·2. $C_{16}H_{20}N_2O_3$,HCl,0·5H_2O requires C, 57·6; H, 6·7; Cl, 10·6; N, 8·4; H_2O, 2·7%), $\nu_{max.}$ (KBr) 1660 (amide C=O), 1730 (ester C=O), 2800, and 2950 (NH_2^+) cm^{-1}.

2,3,3a,4,5,10-*Hexahydro*-1H-*pyrrolo*[1,2-b][2,4]*benzodiazepine* (7a).—To a solution of 2,3,3a,4,5,10-hexahydropyrrolo[1,2-*b*][2,4]benzodiazepin-1-one (1·5 g) in dry ether (40 ml) was added lithium aluminium hydride (0·7 g) during 5 min. The mixture was stirred and refluxed for 30 min and the inorganic complex was then decomposed at −20° with the minimum volume of water. Evaporation of the ethereal extract gave the *diazepine* (0·8 g, 58%), m.p. 58·5—60° (from n-pentane at −30°) (Found: C, 76·7; H, 8·4; N, 14·7. $C_{12}H_{16}N_2$ requires C, 76·6; H, 8·6; N, 14·9%), $\nu_{max.}$ (KBr) 3250 (NH) cm^{-1}, τ (10% C_6D_6) 3·0 (4H, m, ArH), 6·10 and 6·37 (2H, ABq, *J* 15 Hz, 5- or 10-H_2), 6·20 and 6·47 (2H, ABq, *J* 13·4 Hz, 5- or 10-H_2), 6·6 (1H, t, 3a-H), 7·0—8·8 (7H, m, 1-, 2-, and 3-H_2 NH, as shown by addition of D_2O).

1,2,3,4,4a,5,6,11-*Octahydro*-4a-*methylpyrido*[1,2-*b*][2,4]-*benzodiazepine* (7d) (46%), b.p. 160—170° (bulb-to-bulb distillation at 0·1 mmHg), was prepared similarly (Found: C, 77·4; H, 9·2; N, 13·2. $C_{14}H_{20}N_2$ requires C, 77·7; H, 9·3; N, 13·0%), $\nu_{max.}$ (film) 3300 (NH) cm^{-1}.

2,3,3a,4,5,10-*Hexahydro*-3a-*methyl*-1H-*pyrrolo*[1,2-b]-[2,4]*benzodiazepine* (7b) was prepared similarly. Distillation of the product [b.p. 120—130° (bulb-to-bulb distillation at 0·1 mmHg)] gave the slightly impure *diazepine* (Found: C, 76·7; H, 9·2; N, 13·5. $C_{13}H_{18}N_2$ requires C, 77·2; H, 9·0; N, 13·9%), $\nu_{max.}$ (film) 3300 cm^{-1}, τ (10% $CDCl_3$) 2·9 (4H, m, ArH), 5·6 (2H, ABq, *J* 17 Hz, 5- or 10-H_2), 6·2 (2H, ABq, 5- or 10-H_2), 7·4 (2H, m, 1-H_2), 7·4—8·5 (5H, m, 2- and 3-H_2 and NH), and 8·6 (3H, s, Me).

This product was purified as follows. Ethereal hydrogen chloride was added and the crude precipitated material was decolourised by treatment of a cold aqueous solution with charcoal. Removal of solvent at 30° *in vacuo* gave the *diazepine dihydrochloride* (65%), m.p. 266—267° (softening at 250°) (from ethanol–ether) (Found: C, 55·1; H, 7·3; Cl, 25·4; N, 10·2. $C_{13}H_{18}N_2$,2HCl,0·5H_2O requires C, 54·9; H, 7·4; Cl, 25·0; N, 9·9%). Water determination by the Karl Fischer method was unsatisfactory owing to the insolubility of the product in the reagent; however some water was shown to be present; the i.r. spectrum (KBr) showed multiple peaks at 2400—2900 cm^{-1} ($\overset{+}{N}H_2$, $\overset{+}{N}H$).

3a-*Ethyl*-2,3,3a,4,5,10-*hexahydro*-1H-*pyrrolo*[1,2-b][2,4]-*benzodiazepine* (7c) was prepared similarly as its dihydrochloride hemihydrate (46·5%), m.p. 248—251° (from ethanol–ether) (Found: C, 56·7; H, 7·6; Cl, 23·9; N, 9·1. $C_{14}H_{20}N_2$,2HCl,0·5H_2O requires C, 56·4; H, 7·8; Cl, 23·8; N, 9·4%), $\nu_{max.}$ (KBr) 2600—2800 cm^{-1} ($\overset{+}{N}H_2$, $\overset{+}{N}H$).

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