Derivatives of 6,11-Dihydropyrrolo[1,2-*b*][2,5]benzodiazocine [1]

By **G. De Martino,* S. Massa, M. Scalzo,** and **R. Giuliano,** Istituto di Chimica Farmaceutica e Tossicologica, 2ª Cattedra, Università di Roma, 00100 Roma, Italy
M. Artico, Istituto di Chimica Farmaceutica e Organica, Università di Camerino, 62032 Camerino, Italy

Cyclisation of 1-(2-acylaminomethylbenzyl)pyrroles by the action of phosphoryl chloride led to 6,11-dihydropyrrolo[1,2-*b*][2,5]benzodiazocine derivatives. The parent nucleus was synthesised through the alkaline hydrolysis of 1-(2-acetamidomethylbenzyl)pyrrole-2-carbaldehyde.

DURING studies on polycyclic ring systems of pharmaceutical significance, we reported the preparation of 5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine (the parent nucleus of the antitumour antibiotic anthramycin) and some of its derivatives by intramolecular cyclisation of *o*-substituted 1-benzylpyrroles.[2]

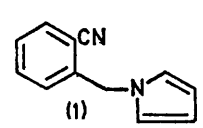
We have now extended this reaction to the synthesis of derivatives of 6,11-dihydropyrrolo[1,2-*b*][2,5]benzodiazocine, a new heterocyclic system, from 1-(2-acylaminomethylbenzyl)pyrroles.

o-Bromomethylbenzonitrile, prepared by treatment of *o*-toluonitrile with *N*-bromosuccinimide in carbon tetrachloride,[3] reacted with potassium pyrrolide in anhydrous tetrahydrofuran to give 1-(2-cyanobenzyl)-pyrrole (1). Reduction of this compound with excess of lithium aluminium hydride afforded 1-(2-aminomethylbenzyl)pyrrole (2) in high yield, and this was transformed into the amides (3) and (4) on treatment with cold acetic anhydride and benzoyl chloride, respectively.

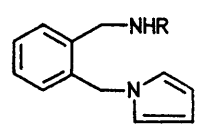
Cyclisation to 6,11-dihydro-4-methylpyrrolo[1,2-*b*]-[2,5]benzodiazocine (5) and its 4-phenyl analogue (6) was carried out with phosphoryl chloride.

The amine (2) was also utilised to prepare 6,11-dihydropyrrolo[1,2-*b*][2,5]benzodiazocin-4(5*H*)-one (8) by reaction with ethyl chloroformate followed by intramolecular cyclisation of the product (7) with zinc chloride in boiling *o*-dichlorobenzene.

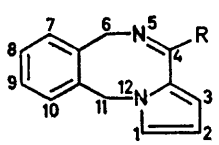
The foregoing scheme could not be used for the synthesis of the parent nucleus (10) because we were unable to obtain the formyl derivative of (2). However compound (10) was obtained through the alkaline hydrolysis of 1-(2-acetamidomethylbenzyl)pyrrole-2-carbaldehyde (9), prepared by Vilsmeier–Haack formylation of



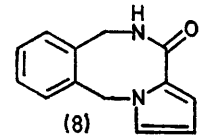
(1)



(2) R = H
(3) R = Ac
(4) R = Bz
(7) R = CO_2Et



(5) R = Me
(6) R = Ph
(10) R = H



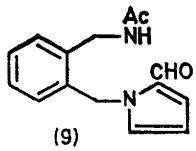
(8)

1-(2-acetamidomethylbenzyl)pyrrole (3). The latter reaction gave different results depending on the experimental conditions. Reaction at room temperature for 3 h gave the expected aldehyde (9), whereas reaction at 120° for 2 h gave compound (10) directly.

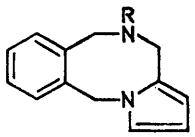
Compound (10) was reduced with sodium borohydride in boiling methanol to the 4,5,6,11-tetrahydro-compound (13), which readily yielded the 5-acetyl compound (14). The n.m.r. spectrum ($CDCl_3$) of the tetrahydro-compound (13) showed signals at δ 1·07br (s, exchangeable NH), 3·72 (s) and 3·78 (s) (4- and 6-H_2), 5·57 (s, 11-H_2),

[1] Preliminary communication, G. De Martino, S. Massa, M. Scalzo, R. Giuliano, and M. Artico, *Chem. Comm.*, 1971, 1549.
[2] M. Artico, G. C. Porretta, and G. De Martino, *J. Heterocyclic Chem.*, 1971, **8**, 283, and references therein.
[3] Fa-Ki Tcheou, Yu-Tsun Shih, and Kwan-Liang Lee, *J. Chinese Chem. Soc.*, 1950, **17**, 150 (*Chem. Abs.*, 1953, **47**, 3254g).

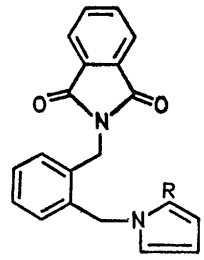
6·10 (t, 2- and 3-H), 6·41 (t, 1-H), and 7·0—7·4 p.p.m. (4H, m, aromatic).



(9)



(13) R = H
(14) R = Ac



(11) R = H
(12) R = CHO

An alternative route to compound (10) (but with lower overall yield) involved preparation of 1-(2-phthalimidomethylbenzyl)pyrrole (11) by treatment of the amine (2) with phthalic anhydride, and formylation of (11) to give the aldehyde (12), followed by alkaline hydrolysis.

EXPERIMENTAL

M.p.s were taken on a Fisher–Johns apparatus. I.r. spectra were recorded for Nujol mulls with a Perkin-Elmer Infracord model 157. N.m.r. spectra were measured on a Varian A-60 instrument with tetramethylsilane as internal standard. The alumina and silica gel used for chromatographic purifications were Merck II—III sec. Brockmann and Merck 0·05—0·2 mm (70—352 mesh ASTM), respectively. Elemental analyses were performed by A. Bernhardt, Elbach (Germany).

1-(2-*Cyanobenzyl*)*pyrrole* (1).—A solution of *o*-bromobenzonitrile (34·3 g) in dry tetrahydrofuran (100 ml) was added dropwise to a stirred suspension of potassium pyrrolide [from pyrrole (18·2 g) and potassium metal (8·19 g)] in the same solvent (150 ml). The mixture was heated under reflux for 6 h then poured on ice. The water-insoluble material was extracted into ethyl acetate. The extracts were dried (Na_2SO_4) and evaporated; the oily residue (30·9 g) was purified on an alumina column (benzene as eluant) to give 1-(2-*cyanobenzyl*)*pyrrole* (24·0 g, 75%), m.p. 43—44° [from petroleum (b.p. 75—120°)] (Found: C, 79·0; H, 5·4; N, 15·25. $C_{12}H_{10}N_2$ requires C, 79·1; H, 5·55; N, 15·4%), $\nu_{max.}$ 2230 (C≡N) cm^{-1}.

1-(2-*Aminomethylbenzyl*)*pyrrole Picrate*.—A solution of the nitrile (1) (2·3 g) in dry ether (30 ml) was added to a stirred suspension of lithium aluminium hydride (1·0 g) in dry ether (30 ml). The mixture was stirred at room temperature for 2 h, then cooled and carefully decomposed with ice. The organic layer was separated, dried (Na_2SO_4), and evaporated. The residue was chromatographed on alumina with benzene as eluant to give oily 1-(2-aminomethylbenzyl)pyrrole (2·1 g; 92%). Its *picrate* had m.p. 168—169° (from water) (Found: C, 52·15; H, 4·25; N, 16·75. $C_{18}H_{17}N_5O_7$ requires C, 52·05; H, 4·15; N, 16·85%).

1-(2-*Acetamidomethylbenzyl*)*pyrrole* (3).—Acetic anhydride (20 ml) was dropped into a cooled flask containing 1-(2-aminomethylbenzyl)pyrrole (16 g). The solution was left at room temperature for 1 h, then poured on ice and neutralized with sodium hydrogen carbonate solution. The precipitated *amide* (3) crystallised from water (15·3 g, 78%), m.p. 99—100° (Found: C, 73·5; H, 6·95; N, 12·45. $C_{14}H_{16}N_2O$ requires C, 73·65; H, 7·05; N, 12·25%), $\nu_{max.}$ 3300 (NH) and 1640 (C=O) cm^{-1}.

1-(2-*Benzamidomethylbenzyl*)*pyrrole* (4).—A solution of benzoyl chloride (3·36 g) in dry dioxan (10 ml) was dropped with stirring into a cooled solution of the amine (2) (4·0 g) and triethylamine (2·2 g) in dry dioxan (20 ml). The mixture was left at room temperature for 2 h and then poured on ice. The precipitate was collected, dried, and crystallised from benzene to give the *amide* (4) (3·8 g, 61%), m.p. 113—114° (Found: C, 78·6; H, 6·4; N, 9·85. $C_{19}H_{18}N_2O$ requires C, 78·6; H, 6·25; N, 9·65%), $\nu_{max.}$ 3300 (NH) and 1640 (C=O) cm^{-1}.

6,11-*Dihydro*-4-*methylpyrrolo*[1,2-b][2,5]*benzodiazocine Picrate*.—A mixture of the amide (3) (2·0 g) and phosphoryl chloride (15 ml) was heated under reflux for 1 h. Excess of phosphoryl chloride was removed by distillation and the residue was treated with ice. The aqueous solution was decolourised with charcoal and then made alkaline with sodium hydroxide solution. The water-insoluble material was extracted into ethyl acetate and the extracts were washed with water, dried (Na_2SO_4), and evaporated. The residue (1·6 g) was dissolved in ethanol and treated with an excess of alcoholic picric acid. On dilution with water the *picrate* of 6,11-*dihydro*-4-*methylpyrrolo*[1,2-b]-[2,5]*benzodiazocine* precipitated as a yellow solid (2·2 g, 60%), m.p. 166—167° (from water) (Found: C, 54·45; H, 4·1; N, 15·8. $C_{20}H_{17}N_5O_7$ requires C, 54·65; H, 3·9; N, 15·95%), δ [$(CD_3)_2SO$] 2·35 (3H, s, Me), 4·27 (2H, s, 6-H_2), 5·72 (2H, s, 11-H_2), 6·30 and 6·58 (1H, 2 × 2t, 2- and 3-H), 7·1—7·6 (5H, m, aromatic), 8·33br (1H, s, OH), and 8·66 (2H, s, picrate) p.p.m. Efforts to transform the picrate into the free base were unsuccessful.

6,11-*Dihydro*-4-*phenylpyrrolo*[1,2-b][2,5]*benzodiazocine Picrate*.—Similar cyclisation of the amide (4) (2·0 g) led to compound (6); its *picrate* (2·0 g, 60%) had m.p. 181—182° (from aqueous ethanol) (Found: C, 59·75; H, 4·0; N, 13·75. $C_{25}H_{19}N_5O_7$ requires C, 59·9; H, 3·8; N, 13·95%).

1-(2-*Ethoxycarbonylaminomethylbenzyl*)*pyrrole* (7).—A solution of ethyl chloroformate (3·0 g) in dry tetrahydrofuran (10 ml) was slowly added with stirring to a cooled solution of 1-(2-aminomethylbenzyl)pyrrole (5·0 g) and triethylamine (2·7 g) in dry tetrahydrofuran (20 ml). The mixture was then left at room temperature for 15 min. The solid was filtered off and the filtrate evaporated. Distillation of the residue at 0·18 mmHg gave the *ester* (7) (5·0 g, 72%), b.p. 190—195° (Found: C, 69·7; H, 7·15; N, 10·7. $C_{15}H_{18}N_2O_2$ requires C, 69·75; H, 7·0; N, 10·85%), $\nu_{max.}$ 3350 (NH) and 1710 (C=O) cm^{-1}.

6,11-*Dihydropyrrolo*[1,2-b][2,5]*benzodiazocin*-4(5H)-*one* (8).—A mixture of the ester (7) (3·0 g), anhydrous zinc chloride (5·0 g), and *o*-dichlorobenzene (20 ml) was heated under reflux for 30 min; it was then steam-distilled until the distillate no longer contained *o*-dichlorobenzene. The residue was treated with a few drops of hydrochloric acid and extracted into chloroform. The extracts were washed with water, dried (Na_2SO_4), and evaporated.

The crude material (1·5 g) was then treated with benzene to leave the *ketone* (8) (0·5 g, 20%), m.p. 220—221° (from benzene) (Found: C, 73·7; H, 5·55; N, 13·05. $C_{13}H_{12}N_2O$ requires C, 73·55; H, 5·7; N, 13·2%), $\nu_{max.}$ 3110 (NH) and 1645 (C=O) cm^{-1}.

1-(2-*Acetamidomethylbenzyl*)*pyrrole*-2-*carbaldehyde* (9).—

Phosphoryl chloride (1·6 g) was dropped onto ice-cooled dimethylformamide (0·8 g). After 15 min a solution of 1-(2-acetamidomethylbenzyl)pyrrole (2·5 g) in dimethylformamide (20 ml) was slowly added. The mixture was left at room temperature for 3 h, poured on ice, and then made alkaline with concentrated ammonia. The precipitate was filtered off, washed with water, dried, and purified by passing it through an alumina column (chloroform as eluant). The resulting oil (1·5 g, 54%) promptly solidified to give the *aldehyde* (9), m.p. 95—96° (from cyclohexane) (Found: C, 70·15; H, 6·3; N, 10·85. $C_{15}H_{16}N_2O_2$ requires C, 70·3; H, 6·3; N, 10·95%), $\nu_{max.}$ 3330 (NH), and 1670 and 1650 (C=O amide and C=O aldehyde) cm^{-1}.

1-(2-*Phthalimidomethylbenzyl*)*pyrrole* (11).—A mixture of 1-(2-aminomethylbenzyl)pyrrole (1·86 g) and phthalic anhydride (1·48 g) was heated at 150° for 15 min; it was then cooled and treated with ice. The precipitate was filtered off, dried, and purified by chromatography on silica gel (elution with benzene). 1-(2-*Phthalimidomethylbenzyl*)*pyrrole* (2·0 g, 63%) had m.p. 142—143° (from ethanol) (Found: C, 75·75; H, 5·05; N, 8·7. $C_{20}H_{16}N_2O_2$ requires C, 75·95; H, 5·1; N, 8·85%), $\nu_{max.}$ 1750 and 1690 (C=O) cm^{-1}.

1-(2-*Phthalimidomethylbenzyl*)*pyrrole*-2-*carbaldehyde* (12).—Vilsmeier–Haack formylation of compound (11) was carried out at 110° for 2·5 h; the product was worked up as described for compound (9). Chromatography on alumina (benzene as eluant) gave the *aldehyde* (12) as a solid (92%), m.p. 122—123° (from carbon tetrachloride) (Found: C, 73·1; H, 4·8; N, 7·85. $C_{21}H_{16}N_2O_3$ requires C, 73·25; H, 4·7; N, 8·15%), $\nu_{max.}$ 1770 and 1710 (C=O phthalimido) and 1660 (C=O aldehyde) cm^{-1}.

6,11-*Dihydropyrrolo*[1,2-b][2,5]*benzodiazocine* (10).—(a) *From compound* (9) *or* (12). Alkaline hydrolysis in boiling aqueous ethanol of amide (9) or (12) afforded the *pyrrolobenzodiazocine* (10) (33 and 17% yield, respectively), m.p. 290—291° (from ethyl acetate) (Found: C, 79·3; H, 6·1; N, 14·6. $C_{13}H_{12}N_2$ requires C, 79·55; H, 6·15; N, 14·3%), $\nu_{max.}$ 1640 (C=N) cm^{-1}.

(b) *From compound* (3).—1-(2-Acetamidomethylbenzyl)pyrrole in dimethylformamide was dropped on to the phosphoryl chloride–dimethylformamide complex. The mixture was heated at 120° for 2 h, then cooled, poured on ice, and made alkaline with concentrated ammonia. The precipitate was extracted into ethyl acetate; the extracts were washed with water, dried ($Na_2SO)_4$, and evaporated. The residue was chromatographed on a column of alumina (elution first with benzene then with ethyl acetate). Partial evaporation of the latter eluate gave compound (10) (31%), m.p. 289—290°, identical (i.r. spectra and mixed m.p.) with the sample prepared as described in (a).

4,5,6,11-*Tetrahydropyrrolo*[1,2-b][2,5]*benzodiazocine* (13).—To a suspension of 6,11-dihydropyrrolo[1,2-*b*][2,5]benzodiazocine (0·4 g) in methanol (40 ml) was added slowly a solution of sodium borohydride (0·4 g) in methanol (30 ml); the mixture was then heated under reflux for 3 h. The solid, which precipitated on cooling, was collected, washed with water, and dried (0·3 g, 74%). The *tetrahydrocompound* (13) crystallised from petroleum; m.p. 224—225° (Found: C, 78·9; H, 7·0; N, 14·05. $C_{13}H_{14}N_2$ requires C, 78·75; H, 7·1; N, 14·15%).

5-*Acetyl*-4,5,6,11-*tetrahydropyrrolo*[1,2-b][2,5]*benzodiazocine* (14).—A mixture of compound (13) (0·25 g) and acetic anhydride (1 ml) was stirred overnight at room temperature; it was then poured on ice–water and sodium hydrogen carbonate solution was added. The *acetyl derivative* was precipitated (0·2 g, 66%); m.p. 279—280° (from aqueous dimethylformamide) (Found: C, 74·8; H, 6·65; N, 11·4. $C_{15}H_{16}N_2O$ requires C, 74·95; H, 6·7; N, 11·65%), $\nu_{max.}$ 1650 (C=O) cm^{-1}.

[2/1003 *Received, 5th May,* 1972]