Heterocyclic Systems. II. Synthesis of 4*H*,6*H*-Pyrrolo[1,2-*a*][4,1]benzoxazepine (1)

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The reduction of 1-(2-methoxycarbonylphenyl)pyrrole-2-carboxaldehyde by lithium aluminum hydride led to 1-(2-hydroxymethylphenyl)-2-hydroxymethylpyrrole, which was in turn transformed into 4*H*,6*H*-pyrrolo-[1,2-*a*][4,1]benzoxazepine through intramolecular dehydration. The reductive action of sodium borohydride, instead, allowed the preparation of 6-oxo-4*H*-pyrrolo[1,2-*a*][4,1]benzoxazepine.

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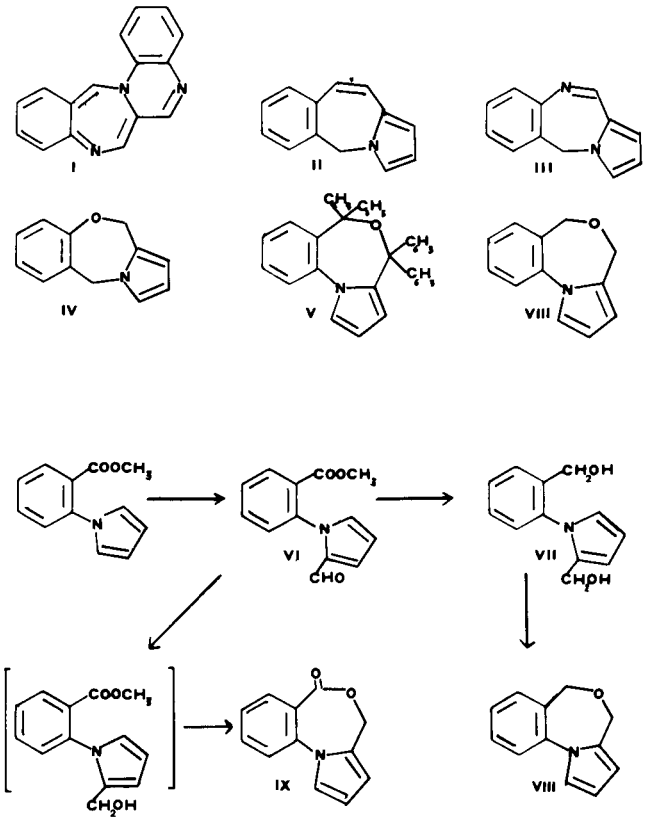
In previous papers (2-4) concerning some studies on nitrogen heterocyclic compounds, the synthesis of derivatives of quinoxalino[2,1-*c*][1,4]benzodiazepine I, 5*H*-pyrrolo[1,2-*b*][2]benzazepine II and 5*H*-pyrrolo[2,1-*c*][1,4]-benzodiazepine III were described. These substances are of interest for both their structural relationship with natural anticancer products and their tested activities on the central nervous system.

As an extension of this research, we have now devoted our attention to the study of pyrrolobenzoxazepine ring systems. Few references concerning these ring systems are available in the literature; these references chiefly concern the synthesis of derivatives of pyrrolo[2,1-*c*][1,4]benzoxazepine IV which was shown to be pharmacologically active (5-7). Only one example of the pyrrolo[1,2-*a*][4,1]benzoxazepine system exists. It is the 4,4,6,6-tetraphenyl derivative V, obtained by Cheeseman, *et al.*, in the identification by reaction with the benzophenone of 2,2'-dilithio-1-phenylpyrrole (8). The objective of our research was the synthesis of the basic ring system (VIII); this aim was achieved through a sequence which was easy to follow and profitable because of its yield.

Vilsmeier-Haack formylation of 1-(2-methoxycarbonylphenyl)pyrrole (9) gave 1-(2-methoxycarbonylphenyl)pyrrole-2-carboxaldehyde VI which was reduced by lithium aluminum hydride to 1-(2-hydroxymethylphenyl)-2-hydroxymethylpyrrole VII. The intramolecular dehydration of VII by phosphorus pentoxide led to the desired compound, 4*H*,6*H*-pyrrolo[2,1-*a*][4,1]benzoxazepine VIII. This same product was also prepared by direct heating of VII, as already observed by Cheeseman, while preparing V.

Starting from VI, the selective reduction of the formyl group followed by intramolecular cyclization produced 6-oxo-4*H*-pyrrolo[2,1-*a*][4,1]benzoxazepine (IX).



EXPERIMENTAL

All melting points were taken on a Fisher-Johns apparatus and are uncorrected. Infrared spectra were run on a Perkin-Elmer model 279 spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Varian EM-390 instrument (TMS as internal standard).

The mass spectra were recorded on a Hewlett-Packard 5908-A mass spectrometer. Merck acc. to Brockman alumina was used for chromatographic purifications. Elemental analyses were performed by Microanalytical Laboratory of the Istituto di Chimica Farmaceutica - Università - Padova, Italy.

1-(2-Methoxycarbonylphenyl)pyrrole-2-carboxaldehyde (VI).

Phosphorus oxychloride (3.2 g.) was dropped into *N,N*-dimethylformamide (1.6 g.) cooled in ice-bath while stirring; *N,N*-dimethylformamide (20 ml.) solution of 1-(2-methoxycarbonylphenyl)pyrrole (4 g.) was then gradually added for 30 minutes. The mixture was stirred for 3 hours at room temperature, then poured into crushed ice and made basic by concentrated ammonium hydroxide. The precipitate which formed was purified on an alumina column using benzene as an eluent. 1-(2-Methoxycarbonylphenyl)pyrrole-2-carboxaldehyde (VI) (3.2 g.) was obtained, m.p. 53-55° from ethyl ether; ir: 1670 cm^{-1} (CHO), 1730 cm^{-1} (ester C=O).

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Anal. Calcd. for $C_{13}H_{11}NO_3$: C, 68.11; H, 4.84; N, 6.11. Found: C, 68.37; H, 4.88; N, 6.01.

6-Oxo-4*H*-pyrrolo[1,2-*a*][4,1]benzoxazepine (IX).

To a methanolic solution (50 ml.) of 1-(2-methoxycarbonylphenyl)-pyrrole-2-carboxaldehyde (VI) (4.6 g.), sodium borohydride (0.4 g.) was added under stirring at room temperature. The mixture was stirred for 1 hour at room temperature, and then it was acidified with concentrated hydrochloric acid. The precipitate obtained was collected, washed with water and crystallized from ethanol to give 6-oxo-4*H*-pyrrolo[1,2-*a*][4,1]benzoxazepine (IX) (3.2 g.), m.p. 101-102°, ir: 1710 cm^{-1} (C=O); nmr (deuterochloroform): δ 5.03 (s, 2, CH_2), 6.2-6.4 (m, 2, (2)CH and (3)CH), 7.05-8.1 (m, 5, benzene ring- and (1)CH); ms: m/e 199 (M^+) and 154.

Anal. Calcd. for $C_{12}H_9NO_2$: C, 72.35; H, 4.55; N, 7.03. Found: C, 72.59; H, 4.64; N, 7.03.

1-(2-Hydroxymethylphenyl)-2-hydroxymethylpyrrole (VII).

A tetrahydrofuran solution (20 ml.) of 1-(2-methoxycarbonylphenyl)-pyrrole-2-carboxaldehyde (VI) (2g.) was dropped into a well stirred suspension of lithium aluminum hydride (0.7 g.) in anhydrous tetrahydrofuran (50 ml.). The mixture was stirred for 4 hours at room temperature; crushed ice was then added and the precipitate which formed was filtered.

The organic layer was separated, washed with water and dried (anhydrous sodium sulphate). The residue (1.6 g.) after removal of the solvent was 1-(2-hydroxymethylphenyl)-2-hydroxymethylpyrrole (VII), which was purified by passing it though an alumina column eluting with benzene; ir: 3350 cm^{-1} (OH).

Anal. Calcd. for $C_{12}H_{13}NO_2$: C, 70.91; H, 6.45; N, 6.89. Found: C, 70.83; H, 6.74; N, 7.08.

4*H*,6*H*-Pyrrolo[1,2-*a*][4,1]benzoxazepine (VIII).

A mixture of 1-(2-hydroxymethylphenyl)-2-hydroxymethylpyrrole (VII) (1.6 g.), anhydrous benzene (100 ml.) and phosphorus pentoxide (2 g.) was refluxed for 2.5 hours with stirring. After cooling, the decanted solution was washed with a 5% sodium hydrogen carbonate solution and dried on anhydrous sodium sulphate. The oily residue, after removal of the solvent, was passed through an alumina column eluting with benzene. Pure 4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepine (VIII) (1 g.) was thus obtained. The same product formed by heating VII at 160-180° for a few minutes; nmr (deuterochloroform): δ 4.27-4.29 (double s, 4, (4)CH_2 and (6)CH_2), 6.15 (m, 2, (2)CH and (3)CH), 6.8-7.3 (m, 5, benzene ring and (1)CH); ms: m/e 185 (M^+) and 156.

Anal. Calcd. for $C_{12}H_{11}NO$: C, 77.81; H, 5.99; N, 7.56. Found: C, 77.65; H, 6.11; N, 7.75.

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