The Synthesis of 4*H*-Pyrrolo[2,1-*c*][1,4]benzoxazine

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Tricyclic heteroaromatic systems with a bridgehead nitrogen atom have been recently reinvestigated following the discovery that mitomycin C and anthramycin, two antibiotics possessing interesting antitumor properties, were derivatives of 9*H*-pyrrolo[1,2-*a*]indole (I) and 5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine (II) respectively.

New methods for the synthesis of 9*H*-pyrrolo[1,2-*a*]indole and its derivatives, including those related to mytosane, have been reported by others in recent years (1-8) and very recently we have reported the synthesis of 5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine and some of its derivatives (9-11).

Furthermore, pyrrolo[1,2-*a*]quinoxaline (III) chemistry was the object of intensive study by Cheeseman and coworkers (12-16) and a new synthetic pathway leading to substituted pyrrolo[1,2-*a*]quinoxalines has been described by us in some previous studies (17,18).

Until now 4*H*-pyrrolo[2,1-*c*][1,4]benzoxazine (IV), a nucleus with structural features which resemble the above mentioned systems, was unknown and only a few of its derivatives have been reported in the literature.

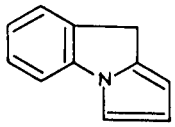
Kumashiro (19) reported the formation of a 4-oxo-4*H*-pyrrolo[2,1-*c*][1,4]benzoxazine derivative by treating the ethyl ester formed from the condensation of *o*-aminophenol with ethyl 2-oxoglutarate with phosphoryl chloride in the presence of *N*,*N*-dimethylformamide.

Later in 1969 we described the preparation of some alkyl derivatives of 1,2,3,3a-tetrahydro-4*H*-pyrrolo[2,1-*c*][1,4]benzoxazine while developing research on new potential antitumor drugs (20,21). Following studies on these nitrogen polycyclic compounds, we now report the synthesis of 4*H*-pyrrolo[2,1-*c*][1,4]benzoxazine (IV) and its 4-oxoderivative (VII).

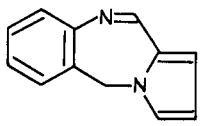
Compound VII was obtained as follows. When *o*-aminophenol and 2,5-diethoxytetrahydrofuran were refluxed in boiling glacial acetic acid, 1-(*o*-hydroxyphenyl)pyrrole (V) was formed as an oil which solidified after purification by column chromatography and subsequent storage in a cool place for several days.

Treatment of the sodium salt of 1-(*o*-hydroxyphenyl)-pyrrole (V) with ethyl chlorocarbonate in anhydrous tetrahydrofuran afforded 1-(*o*-ethoxycarbonyloxyphenyl)-pyrrole (VI) which was then converted into the 4-oxo-4*H*-pyrrolo[2,1-*c*][1,4]benzoxazine (VII) by the action of anhydrous zinc chloride in boiling *o*-dichlorobenzene.

Similar methods of intramolecular electrophilic substitutions on the pyrrole ring which have been successfully employed in the synthesis of a variety of polycyclic compounds with a bridgehead nitrogen (5,9,10,12,13,22,23,24,25) could not be used for the preparation of the title compound nor did 4-oxo-4*H*-pyrrolo[2,1-*c*][1,4]benzoxazine (VII) appear to be a useful intermediate to the parent nucleus.



I



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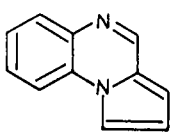

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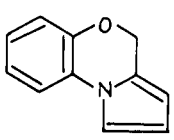
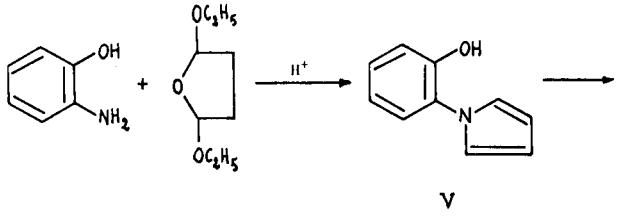
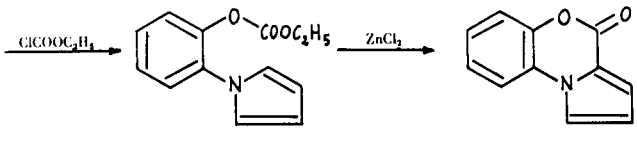


IV



V



VI VII

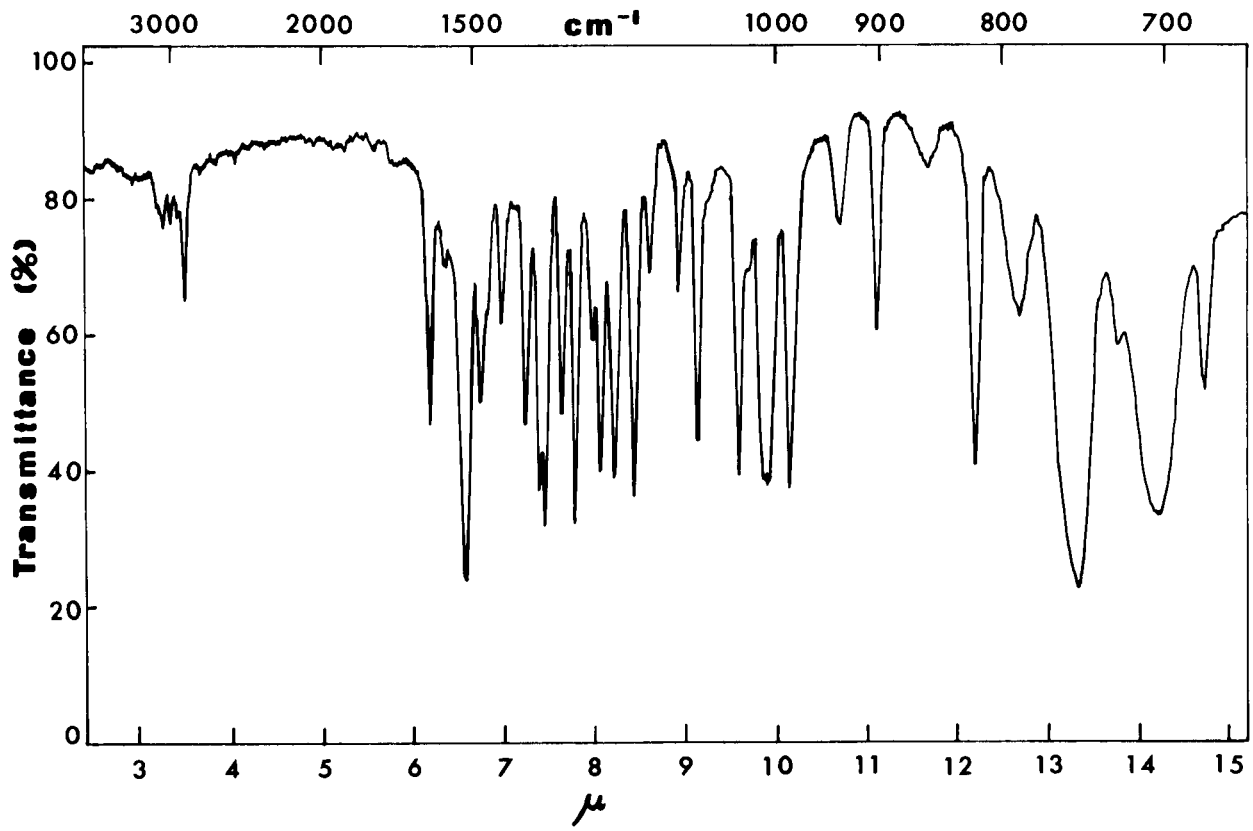
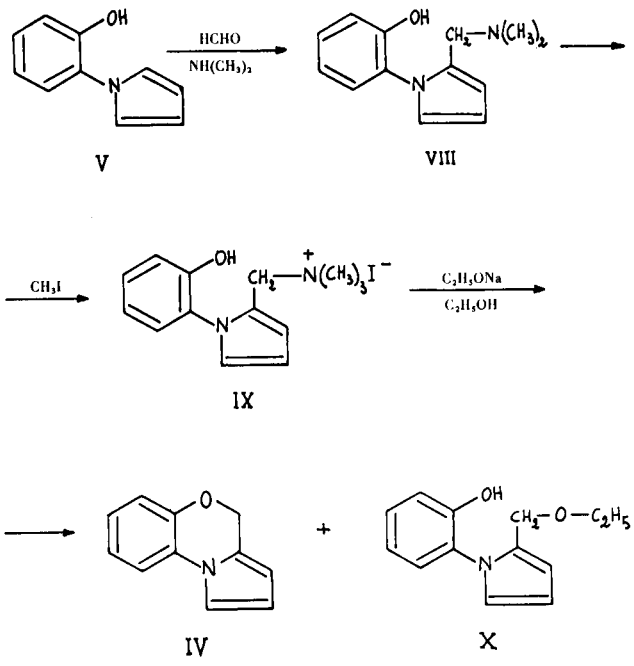


Figure 1. I.R. spectrum (liquid film) of 4*H*-pyrrolo[2,1-*c*][1,4]benzoxazine.

However, the title compound was successfully prepared by the following pathway. Reaction of 1-(*o*-hydroxyphenyl)pyrrole (V) with formaldehyde and dimethylamine *via* the Mannich reaction gave 1-(*o*-hydroxyphenyl)-2-dimethylaminomethylpyrrole (VIII) in good yield. The latter compound was then transformed into the ammonium salt (IX) by treatment with methyl iodide in anhydrous tetrahydrofuran.

Treatment of 1-(*o*-hydroxyphenyl)-2-dimethylaminomethylpyrrole methiodide (IX) with sodium ethoxide in boiling anhydrous ethanol under a nitrogen atmosphere afforded two products which were identified as 4*H*-pyrrolo-[2,1-*c*][1,4]benzoxazine (IV) and 1-(*o*-hydroxyphenyl)-2-ethoxymethylpyrrole (X) respectively. Separation of IV + X was easily accomplished due to the acidic property of 1-(*o*-hydroxyphenyl)-2-ethoxymethylpyrrole (X) and each compound was purified by passing it through a column of partially deactivated alumina.

4*H*-Pyrrolo[2,1-*c*][1,4]benzoxazine (IV) was obtained from IX in 30% yield. Its NMR spectrum showed the methylenic protons at δ = 4.98 ppm (2H) and β protons of the pyrrole nucleus in the range δ = 5.8-6.3 ppm (2H); a broad spectrum of signals in the range δ = 6.7-7.3 ppm (5H) supported the presence of α pyrrole and benzene protons.



1-(*o*-Hydroxyphenyl)-2-ethoxymethylpyrrole (X) (40% yield from IX) showed in the NMR spectrum the following signals: a triplet at δ = 1.07 ppm (3H) for the methyl

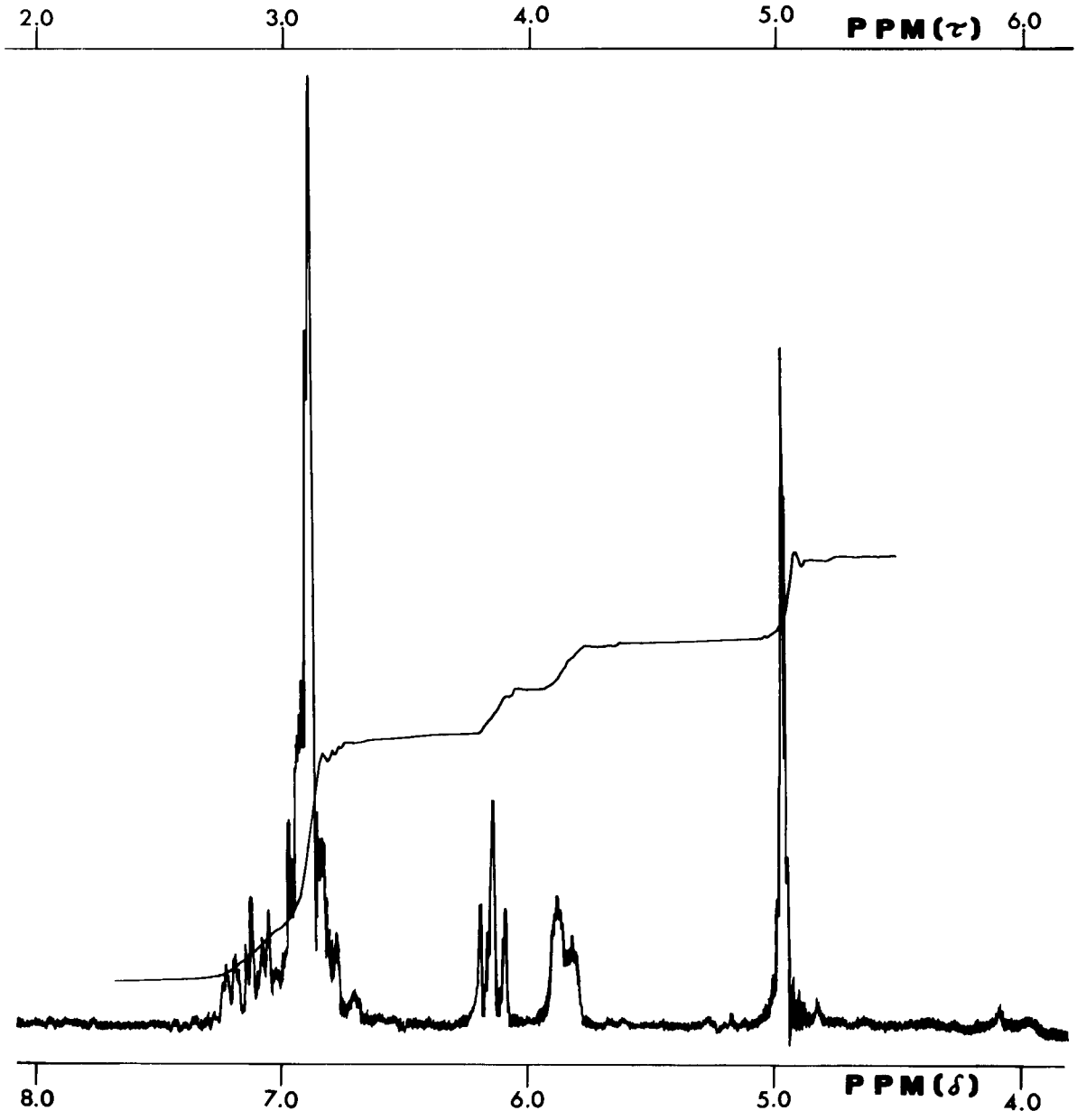


Figure 2. N.M.R. spectrum (CCl_4; TMS internal standard) of 4*H*-pyrrolo[2,1-*c*][1,4]benzoxazine.

protons; a quartet at δ = 3.30 ppm (2H) and a singlet at δ = 4.13 ppm (2H) for the protons of the two methylenic groups; a broad spectrum of signals in the range δ = 6.0-7.3 ppm (8H) accounted for the protons of pyrrole (3H) and benzene (4H) nuclei and for the proton of the phenolic hydroxy group.

Further studies are now in progress with the purpose of preparing new 4*H*-pyrrolo[2,1-*c*][1,4]benzoxazine derivatives of pharmacological interest.

EXPERIMENTAL

All melting points were taken on a Fisher-Johns apparatus and are uncorrected. Infrared spectra (nujol mulls) were run on a Perkin-Elmer model 157 spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Varian A-60 instrument (TMS internal standard). The partially deactivated alumina used for chromatographic purification was prepared by adding dilute acetic acid (10 ml., 10% v/v) to Merck sec. Brockmann alumina (100 g.). Elemental analyses were performed by A. Bernhardt, Elbach (Germany).

1-(*o*-Hydroxyphenyl)pyrrole (V).

A mixture of 2,5-diethoxytetrahydrofuran (16 g., 0.1 mole), *o*-aminophenol (12 g., 0.11 mole) and glacial acetic acid (35 ml.) was heated under reflux for 4 hours, then poured into crushed ice. The oil which precipitated was taken up in ethyl acetate. The organic solution was washed twice with 5% sodium bicarbonate, then with water, dried over anhydrous sodium sulfate and evaporated. The residual oil (12 g.) was treated with benzene and after filtration the solution was passed through a column of partially deactivated alumina. On elution with benzene an early fraction was obtained which after evaporation of the solvent afforded analytically pure 1-(*o*-hydroxyphenyl)pyrrole, a colorless oil (10 g.). After storage for a few days in a cool place the oil solidified, m.p. 45-47°; infrared absorption (nujol) of phenolic OH max at 3440 cm^{-1}; the NMR spectrum (deuteriochloroform) showed signals at δ = 5.62 ppm (1H, proton of hydroxy group), δ = 6.2-6.4 ppm (2H, β protons of pyrrole) and δ = 6.75-7.35 ppm (6H, α pyrrole and benzene protons).

Anal. Calcd. for $C_{10}H_9NO$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.32; H, 5.76; N, 8.64.

Its *p*-nitrobenzoate ester crystallized from ethanol and melted at 99-100°.

Anal. Calcd. for $C_{17}H_{12}N_2O_4$: C, 66.23; H, 3.92; N, 9.09. Found: C, 66.28; H, 4.10; N, 9.28.

1-(*o*-Ethoxycarbonyloxyphenyl)pyrrole (VI).

To a solution of sodium (0.6 g., 0.025 g.-atom) in anhydrous ethanol (30 ml.) 1-(*o*-hydroxyphenyl)pyrrole (V) (4 g., 0.025 mole) was added. After removal of excess solvent under vacuum, the residue was suspended in anhydrous tetrahydrofuran (30 ml.). A solution of ethyl chlorocarbonate (5.4 g., 0.05 mole) in tetrahydrofuran (20 ml.) was added dropwise while stirring. The mixture was stirred at room temperature for 2 hours and poured into crushed ice. The oil which separated was extracted several times with ether and the combined extracts were dried over anhydrous sodium sulfate. Evaporation of the solvent gave an oil which was purified by distillation under reduced pressure giving 1-(*o*-ethoxycarbonyloxyphenyl)pyrrole, colorless oil, b.p. 108°/0.3 mm (yield 3 g.); infrared absorption of C=O carbonate at 1750 cm^{-1}.

Anal. Calcd. for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.66; H, 5.61; N, 6.13.

4-Oxo-4*H*-pyrrolo[2,1-*c*][1,4]benzoxazine (VII).

A mixture of 1-(*o*-ethoxycarbonyloxyphenyl)pyrrole (VI) (3 g.), anhydrous zinc chloride (6 g.) and *o*-dichlorobenzene (15 ml.) was refluxed for 1 hour. The residue obtained after removal of solvent under vacuum was treated with crushed ice and ethyl acetate (25 ml.). The organic layer was separated, washed with water and dried over anhydrous sodium sulfate. Evaporation of solvent gave a dark solid which was purified by passing through a column of partially deactivated alumina. On elution with benzene and subsequent evaporation of solvent 4-oxo-4*H*-pyrrolo[2,1-*c*]-[1,4]benzoxazine (1.5 g.) was obtained. Crystallization from cyclohexane afforded colorless needles, m.p. 126-127°; infrared absorption of C=O at 1725 cm^{-1}.

Anal. Calcd. for $C_{11}H_7NO_2$: C, 71.35; H, 3.81; N, 7.56. Found: C, 71.24; H, 3.94; N, 7.36.

1-(*o*-Hydroxyphenyl)-2-dimethylaminomethylpyrrole (VIII).

A suspension of 1-(*o*-hydroxyphenyl)pyrrole (V) (4.8 g.) in a mixture of 33% aqueous dimethylamine (8 ml.), 40% of formaldehyde (3.4 ml.) and acetic acid (9 ml.) was stirred at room temperature for 40 hours. The solution was then treated with charcoal, filtered and neutralized with solid sodium bicarbonate. The oil which separated was extracted several times with ethyl acetate, the combined extracts were washed with water and then dried over anhydrous sodium sulfate. Evaporation of the solvent gave an oil which solidified in contact with cyclohexane. After crystallization from the same solvent, 1-(*o*-hydroxyphenyl)-2-dimethylaminomethylpyrrole melted at 103-104° (2.7 g., 45% yield); the NMR spectrum (deuteriochloroform) showed a singlet at δ = 2.28 ppm (6H, protons of dimethylamino group); a singlet at δ = 3.3 ppm (2H, protons of methylene group); signals in the ranges δ = 6.1-6.3 ppm (2H, β protons of pyrrole) and δ = 6.7-7.4 ppm (5H, α proton of pyrrole and the four benzenic protons). A broad signal at δ = 13.1 ppm accounted for the proton of the hydroxyl group.

Anal. Calcd. for $C_{13}H_{16}N_2O$: C, 72.19; H, 7.46; N, 12.96. Found: C, 72.38; H, 7.32; N, 12.79.

1-(*o*-Hydroxyphenyl)-2-dimethylaminomethylpyrrole Methiodide (IX).

To a stirred solution of 1-(*o*-hydroxyphenyl)-2-dimethylaminomethylpyrrole (VIII) (2.7 g.) in anhydrous tetrahydrofuran (20 ml.) was added a solution of methyl iodide (4 g.) in the same solvent (5 ml.).

The solution was maintained at room temperature while stirring for 3 hours. The precipitate which formed was collected and recrystallized from ethanol. The 1-(*o*-hydroxyphenyl)-2-dimethylaminomethylpyrrole methiodide thus obtained melted at 254-256° and showed the hydroxyl absorption in the infrared spectrum at 3200 cm^{-1}.

Anal. Calcd. for $C_{14}H_{19}IN_2O$: C, 46.92; H, 5.30; I, 35.47; N, 7.82. Found: C, 46.77; H, 5.42; I, 35.64; N, 7.97.

4*H*-Pyrrolo[2,1-*c*][1,4]benzoxazine (IV).

A stirred solution of 1-(*o*-hydroxyphenyl)-2-dimethylaminomethylpyrrole methiodide (IX) (17 g., 0.05 mole) in anhydrous ethanol (250 ml.) was kept under nitrogen atmosphere and a solution of sodium ethoxide (3.4 g., 0.05 mole) in ethanol (80 ml.) was added dropwise. The mixture was refluxed for 16 hours, the solvent was removed under reduced pressure and the residue was treated with crushed ice and stored overnight in a cool place. The aqueous solution was saturated with ammonium chloride and extracted several times with ether. The ethereal extracts were combined and extracted with 2*N* sodium hydroxide until the ethereal layer did not colour an alcoholic ferric chloride solution. The organic solution was dried over anhydrous sodium sulfate and then evaporated *in vacuo*. The residual red oil (2.6 g.) was purified by passing through a column of partially deactivated alumina. Elution with light petroleum ether and evaporation of the central fraction afforded analytically pure 4*H*-pyrrolo[2,1-*c*][1,4]benzoxazine (1.4 g.), light rose-coloured oil which solidified after storage for an extended time in a cool place in the presence of petroleum ether (b.p. 40-70°); m.p. 32-33°; IR and NMR spectra of 4*H*-pyrrolo-[2,1-*c*][1,4]benzoxazine are reported in Figure 1 and Figure 2 respectively.

Anal. Calcd. for $C_{11}H_9NO$: C, 77.17; H, 5.30; N, 8.18. Found: C, 77.03; H, 5.37; N, 8.31.

1-(*o*-Hydroxyphenyl)-2-ethoxymethylpyrrole (X).

This compound was isolated from the combined aqueous alkaline extracts obtained from the above preparation. The alkaline solution was made acidic by adding 2*N* hydrochloric acid to *p*H 5, then saturated with ammonium chloride and extracted with ether. The combined etheral extracts were dried over anhydrous sodium sulfate. Evaporation of the solvent *in vacuo* gave an oil

(3.4 g.) which was chromatographated on a column of partially deactivated alumina eluting with light petroleum ether. From the central fraction, 1-(*o*-hydroxyphenyl)-2-ethoxymethylpyrrole was recovered as an oil (2.1 g.) which on standing for several days on a cool place slowly solidified. After recrystallization from a small quantity of petroleum ether (b.p. 40-70°), compound X melted at 43-45°; IR spectrum: OH (phenol) max at 3330 cm^{-1}.

Anal. Calcd. for $C_{13}H_{15}NO_2$: C, 71.86; H, 6.96; N, 6.45. Found: C, 71.75; H, 6.85; N, 6.32.

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