571. *The Aporphine Series. Part III.* Corydine and* iso*Corydine.*

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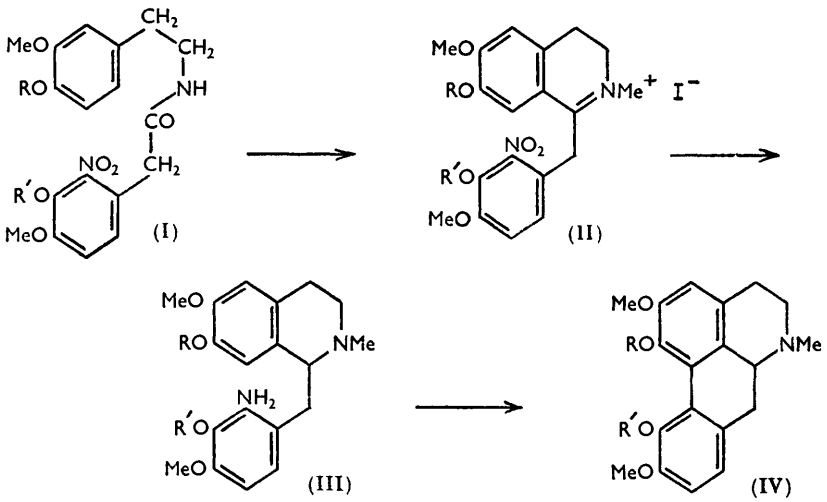
The structure assigned to corydine has been confirmed by a total synthesis by the Bischler–Napieralski–Pschorr method in which the phenolic hydroxyl group was protected by benzylation. An attempted synthesis of *iso*corydine on similar lines failed at the penultimate stage.

The isomeric alkaloids corydine and *iso*corydine, which often appear together in various plants of the *Corydalis*, *Dicentra*, and *Glaucium* species, are 3 : 4 : 5 : 6-tetra-substituted derivatives of aporphine containing three methoxyl and one hydroxyl groups. The location of these groups in the aporphine structure has been established by Späth and Berger [1] by relating them to the known structures of the alkaloids corytuberine and bulbocapnine and by degradation. Confirmation of these structures has never been established by synthesis. No synthesis of a phenolic alkaloid of the aporphine series has, in fact, yet been achieved, although two hydroxyaporphines and one hydroxy*nor*aporphine have been



prepared. Kondo and Ishiwata [2] have reported the synthesis of 6-hydroxy-3 : 4-dimethoxy*nor*aporphine and Hey and Lobo [3] that of 3-hydroxy-4-methoxy-5 : 6-methylenedioxyaporphine and 3-hydroxy-2-methoxy-5 : 6-methylenedioxyaporphine. Routes for the synthesis of phenolic alkaloids of the aporphine series were investigated by Gulland and his co-workers,[4-7] but with little success.

The synthesis of a phenolic aporphine requires the protection of the free hydroxyl group (or groups) throughout a multi-stage synthesis by a group which is stable under the range of experimental conditions, yet one which can be readily removed at the final stage under conditions which will leave the rest of the molecule unaffected. In the synthesis of

* Part II, *J.*, 1956, 4123.

[1] Späth and Berger, *Ber.*, 1931, **64**, 2038.
[2] Kondo and Ishiwata, *Ber.*, 1931, **64**, 1533.
[3] Hey and Lobo, *J.*, 1954, 2246.
[4] Gulland, *J.*, 1931, 2872.
[5] Gulland, Ross, and Virden, *J.*, 1931, 2881.
[6] Gulland, Ross, and Smellie, *J.*, 1931, 2885.
[7] Douglas and Gulland, *J.*, 1931, 2893.

the three phenolic derivatives referred to above, the hydroxyl group was protected by benzylation. In an attempt to confirm by synthesis the structures assigned to corydine and *iso*corydine, the present communication describes the results obtained by using benzylation for the protection of the free hydroxyl group.

(±)-Corydine (IV; R = H, R′ = Me) has now been synthesised from 4-benzyloxy-3-methoxyphenethylamine and 3 : 4-dimethoxy-2-nitrophenylacetic acid by the conventional Bischler–Napieralski–Pschorr procedure, thus providing the first example of the total synthesis of a naturally occurring phenolic aporphine alkaloid. Benzylvanillin was converted into 4-benzyloxy-3-methoxy-ω-nitrostyrene, which was reduced with lithium aluminium hydride to 4-benzyloxy-3-methoxyphenethylamine in excellent yield. The cyclodehydration of the *N*-(4-benzyloxy-3-methoxyphenethyl)-3 : 4-dimethoxy-2-nitrophenylacetamide (I; R = $PhCH_2$, R′ = Me) was effected in chloroform with phosphorus pentachloride at room temperature over a period of several days (cf. Gulland and Haworth [8]). The hydrochloride of the resulting dihydro*iso*quinoline was soluble in chloroform. The free base was converted into the methiodide (II; R = $PhCH_2$, R′ = Me), which was reduced with zinc and hydrochloric–acetic acid at 0°. The 1-(2-amino-3 : 4-dimethoxybenzyl)-7-benzyloxy-1 : 2 : 3 : 4-tetrahydro-6-methoxy-2-methyl*iso*quinoline (III; R = $PhCH_2$, R′ = Me) on diazotisation and treatment with copper powder gave (±)-benzylcorydine (IV; R = $PhCH_2$, R′ = Me), which was debenzylated with hot hydrochloric acid. The resulting (±)-corydine (IV; R = H, R′ = Me) was isolated as the hydrochloride, since it is known that the free base is susceptible to atmospheric oxidation.

Colour tests on the synthetic (±)-corydine hydrochloride and with naturally occurring (+)-corydine hydrochloride, reported in the experimental section, provide convincing evidence of their structural identity. Whereas the hydrochloride of the (±)-isomer crystallised with one molecule of water of crystallisation, that of the (+)-isomer crystallised with half a molecule of ethanol of crystallisation. The ultraviolet absorption spectra of synthetic (±)-corydine hydrochloride and natural (+)-corydine hydrochloride were identical. At the same time, ultraviolet absorption spectroscopy is unable to distinguish between corydine and *iso*corydine. On the other hand, the infrared spectra of (±)-corydine hydrochloride and (+)-corydine hydrochloride are somewhat different, as would be expected from their different states of solvation. Inspection of the infrared spectra for (+)-corydine and (+)-*iso*corydine hydrochlorides shows appreciable differences in the regions 9·80—10·16 and 11·09—12·15 μ. In these regions the spectrum of (+)-corydine shows sharp peaks at 9·80, 10·34, 11·69, and 12·15 μ, whereas for (+)-*iso*corydine maxima occur at 9·98, 10·16, 11·09, and 12·35 μ. In the spectrum of the synthetic (±)-corydine the peaks which appear to be characteristic of the (+)-corydine molecule are reproduced at 9·75, 10·37, 11·66, and 12·12 μ, respectively, whereas those characteristic of *iso*corydine are absent.

A synthesis of *iso*corydine (IV; R = Me, R′ = H) along similar lines failed at the penultimate stage. The reaction of 3 : 4-dimethoxyphenethylamine with the diazoketone prepared from 3-benzyloxy-4-methoxy-2-nitrobenzoyl chloride gave 3-benzyloxy-4-methoxy-2-nitrophenyl-*N*-(3 : 4-dimethoxyphenethyl)acetamide (I; R = Me, R′ = $PhCH_2$). Treatment of this amide in chloroform with phosphorus pentachloride at room temperature gave the hydrochloride of 1-(3-benzyloxy-4-methoxy-2-nitrobenzyl)-3 : 4-dihydro-6 : 7-dimethoxy*iso*quinoline. The free base was converted into the methiodide (II; R = Me, R′ = $PhCH_2$), which was reduced with zinc and hydrochloric–acetic acid at 0° to give 1-(2-amino-3-benzyloxy-4-methoxybenzyl)-1 : 2 : 3 : 4-tetrahydro-6 : 7-dimethoxy-2-methyl*iso*quinoline (III; R = Me, R′ = $PhCH_2$). The free base was diazotised and on the addition of copper powder nitrogen was evolved. The product was obtained as a brown oil, which liberated benzyl chloride on treatment with hot hydrochloric acid. From the resulting solution a chloroform-soluble hydrochloride was obtained in good yield, but the analysis and ultraviolet absorption spectrum of this compound did

[8] Gulland and Haworth, *J.*, 1928, 581.

not correspond with the requirements of *iso*corydine. The identity of this compound is not known.

Experimental

4-Benzyloxy-3-methoxyphenethylamine.—A mixture of benzylvanillin (25 g.) (prepared by the method of Dickinson, Heilbron, and Irving [9]), nitromethane (7 g.), methylamine hydrochloride (1 g.), sodium carbonate (1 g.), and ethanol (50 c.c.) was warmed until a clear solution was obtained. It was then left at room temperature in a stoppered flask for 5 days. The 4-benzyloxy-3-methoxy-ω-nitrostyrene (28 g.), which separated, was collected and washed successively with ethanol and water. It was obtained in prisms, m. p. 120—121°, after crystallisation from acetone. Kobayashi [10] reported m. p. 122—123°. The nitrostyrene (14·25 g.) was placed in a Soxhlet thimble; the flask below contained lithium aluminium hydride (9·35 g.) in dry ether (100 c.c.). Extraction was continued with stirring until no more nitrostyrene was extracted from the thimble (54 hr.) (cf. Nystrom and Brown [11]). After cautious addition of 1·5N-sulphuric acid with stirring and cooling, the ether layer was separated and the aqueous solution was made strongly alkaline with sodium hydroxide solution. The alkaline solution was repeatedly extracted with ether and the extract was dried and concentrated. Addition of saturated dry ethereal hydrogen chloride precipitated 4-benzyloxy-3-methoxyphenethylammonium chloride (13 g.) in fine white needles, m. p. 169—171°. Kobayashi [10] reported m. p. 173—175°.

N-(*4-Benzyloxy-3-methoxyphenethyl*)-3 : *4-dimethoxy-2-nitrophenylacetamide.*—A solution of 3 : 4-dimethoxy-2-nitrophenylacetyl chloride [prepared from the acid [3] (2 g.) and phosphorus pentachloride (2·1 g.)] in dry benzene was added portionwise and alternately with 20% aqueous sodium hydroxide (10 c.c.) to a cooled aqueous solution of 4-benzyloxy-3-methoxyphenethylamine hydrochloride (1·5 g.), made just alkaline with sodium hydroxide solution. After an hour's shaking, the mixture was extracted with chloroform and the chloroform solution was washed with dilute hydrochloric acid, dried, and evaporated. Crystallisation of the residue from ethanol gave N-(*4-benzyloxy-3-methoxyphenethyl*)-3 : *4-dimethoxy-2-nitrophenylacetamide* in fine buff needles, m. p. 118—119° (Found: C, 65·0; H, 5·8; N, 5·3. $C_{26}H_{28}O_7N_2$ requires C, 65·0; H, 5·8; N, 5·8%). A further quantity of this product was obtained from the mother liquors by chromatographic adsorption. The total yield was 2·3 g.

*7-Benzyloxy-1-(3 : 4-dimethoxy-2-nitrobenzyl)-3 : 4-dihydro-6-methoxy*isoquinoline *Hydrochloride and Methiodide.*—A solution of the above amide (4·8 g.) in dry chloroform (50 c.c.) was added, slowly and with shaking, to a strongly cooled suspension of phosphorus pentachloride (15 g.) in chloroform (80 c.c.). The mixture was kept in the refrigerator overnight and then at room temperature for 8 days. The resulting solution was added slowly to crushed ice (300 g.) and concentrated hydrochloric acid (10 c.c.) and, after the addition of a small quantity of methanol to break the emulsion, the mixture was repeatedly extracted with chloroform. The dried extract was concentrated and addition of cold ether deposited *7-benzyloxy-1-(3 : 4-dimethoxy-2-nitrobenzyl)-3 : 4-dihydro-6-methoxy*isoquinolinium *chloride* (4·7 g.), which crystallised from ethanol in pale yellow needles, m. p. 219—200° (with decomp.) (Found: C, 62·0; H, 5·5; N, 5·2. $C_{26}H_{26}O_6N_2$,HCl requires C, 62·6; H, 5·4; N, 5·6%). A solution of the hydrochloride (4·7 g.) in warm ethanol (50 c.c.) was neutralised with 10% ammonia solution, and the precipitation of the free base completed by cooling and the addition of water. The free base (3·9 g.), white needles, m. p. 81—83°, was dried and then boiled under reflux with excess of methyl iodide (50 c.c.) for 3 hr. The mixture was cooled and the precipitated *methiodide* (4·6 g.) crystallised from ethanol, forming yellow needles, m. p. 181—183° (with decomp.) (Found: C, 53·6; H, 4·9. $C_{27}H_{29}O_6N_2I$ requires C, 53·6; H, 4·8%).

1-(*2-Amino-3 : 4-dimethoxybenzyl*)-*7-benzyloxy-1 : 2 : 3 : 4-tetrahydro-6-methoxy-2-methyl*isoquinoline *Dipicrolonate.*—Concentrated hydrochloric acid (25 c.c.) and zinc dust (15 g., portionwise and with shaking) were added to a solution of the methiodide (2 g.) in acetic acid (100 c.c.) and water (25 c.c.) at 0°. The mixture was kept in the refrigerator overnight after which more hydrochloric acid (25 c.c.) and zinc dust (5 g.) were added. After being kept for a further

[9] Dickinson, Heilbron, and Irving, *J.*, 1927, 1895.
[10] Kobayashi, *Sci. Papers Inst. Phys. Chem. Res., Tokyo*, 1927, **6**, 149.
[11] Nystrom and Brown, *J. Amer. Chem. Soc.*, 1947, **69**, 1197; 1948, **70**, 3738.

24 hr. at 0—10°, the solution was filtered from unchanged zinc and poured, dropwise and with stirring, into ice-cold aqueous ammonia (300 c.c.) covered by a layer of ether. The alkaline solution was exhaustively extracted with ether, and the ethereal extract dried and evaporated. 1-(2-Amino-3 : 4-dimethoxybenzyl)-7-benzyloxy-1 : 2 : 3 : 4-tetrahydro-6-methoxy-2-methyl*iso*-quinoline (1·41 g.) was obtained as a pale yellow oil with a blue fluorescence. The *dipicrolonate* (2·7 g.), prepared in ethanol solution, separated from that solvent in yellow needles, m. p. 151—152° (Found : C, 56·9; H, 4·9; N, 13·8. $C_{27}H_{32}O_4N_2,2C_{10}H_8O_5N_4$ requires C, 57·8; H, 4·9; N, 14·3%).

(±)-*Corydine Hydrochloride*.—To the above dipicrolonate (2 g.) suspended in methanol (10 c.c.) in a small mortar was added a cold solution of concentrated sulphuric acid (2 c.c.) in methanol (10 c.c.) dropwise with grinding. The picrolonic acid (0·98 g.) which separated was filtered off and washed with cold methanol (5 c.c.). To the methanol solution at 0° a solution of sodium nitrite (0·14 g.) in water (4 c.c.) was added with stirring. The resulting diazonium solution was kept overnight in the refrigerator, after which " catalytic " copper powder (0·5 g.) was added. The mixture was kept at room temperature for an hour, during which time nitrogen was freely evolved. The mixture was then boiled under reflux (30 min.), cooled, and extracted with ether. The aqueous layer was made alkaline with ammonia solution and exhaustively extracted with ether. Evaporation of the dried extract gave crude benzyl-(±)-corydine (0·7 g.) as a brown gum, which was debenzylated by boiling for 30 min. with 15% hydrochloric acid. The diluted solution was extracted successively with ether and chloroform. Evaporation of the dried chloroform extract gave a gum, which was redissolved in dilute hydrochloric acid (20 c.c.) to which was added zinc dust (1 g.) (cf. Späth and Hromatka [12]). Extraction of the filtered solution with chloroform and subsequent evaporation gave (±)-*corydine hydrochloride* (0·25 g.), which crystallised from ethanol–ether in white needles, sintering at 205°, m. p. 228° (with decomp.) (Found : C, 60·6; H, 6·6; N, 3·2. After being dried at 70—80°/0·3 mm. for 16 hr. : C, 60·3; H, 6·6; N, 3·3. $C_{20}H_{23}O_4N,HCl,H_2O$ requires C, 60·6; H, 6·6; N, 3·5%).

3 : 4-*Dimethoxyphenethylamine*.—A suspension of 3 : 4-dimethoxycinnamic acid (31 g.), prepared by Wittmer and Raiford's method,[13] in a solution of sodium hydroxide (75 g.) in water (750 c.c.) was heated to 80—90° and 50% nickel–aluminium alloy (50 g.) was added portionwise with rapid stirring during 3 hr. (cf. Schwenk, Papa, Whitman, and Ginsberg [14]). The mixture was kept at 80—90° for a further hour, then cooled, filtered, and poured dropwise with stirring into concentrated hydrochloric acid (450 c.c.). The precipitated β-3 : 4-dimethoxyphenylpropionic acid (26 g.), m. p. 95—96°, was collected. To a solution of the acid (21 g.) in dry chloroform (70 c.c.) was added thionyl chloride (23·8 g.). After 12 hr. the resulting solution was poured with stirring into a solution of sodium hydroxide (10 g.) in concentrated aqueous ammonia (240 c.c.). The mixture was boiled to remove excess of ammonia and chloroform and sufficient hot water then added to give a clear solution. β-3 : 4-Dimethoxyphenylpropionamide (18·5 g.), m. p. 118—119°, separated on cooling. Pictet and Finkelstein [15] have reported m. p. 120—121° for this compound. The amide (10 g.) was converted by the action of sodium hypochlorite, as described by Buck and Perkin,[16] into 3 : 4-dimethoxyphenethylamine (7·2 g.), a pale yellow oil (picrate m. p. 165—166°, as reported by Kondo, Narita, and Uyeo [17])

3-*Benzyloxy*-4-*methoxy*-2-*nitrophenyl*-N-(3 : 4-*dimethoxyphenethyl*)*acetamide*.—To a solution of 3-benzyloxy-ω-diazo-4-methoxy-2-nitroacetophenone (1·8 g.; m. p. 132—133°), prepared as described by Hey and Lobo,[3] in dioxan (30 c.c.) at 60° was added 3 : 4-dimethoxyphenethylamine (1 g.) and then silver oxide (1 g.). The mixture was kept at 60—70° for 2 hr., further quantities of silver oxide being added until evolution of nitrogen had ceased. It was then boiled under reflux for 30 min., filtered, cooled, diluted with carbon tetrachloride, and extracted repeatedly with dilute nitric acid. Much insoluble tar was formed. The pale carbon tetrachloride solution was washed with dilute sodium hydroxide solution and dried. Removal of the solvent left an oil which solidified on trituration with a little methanol. Repeated crystallisation from aqueous methanol gave 3-*benzyloxy*-4-*methoxy*-2-*nitrophenyl*-N-(3 : 4-*dimethoxyphenethyl*)*acetamide*, (1·9 g.) in fine needles, m. p. 45—46° (Found : C, 62·4; H, 5·9; N, 5·2. After being

[12] Späth and Hromatka, *Ber.*, 1928, **61**, 1334.
[13] Wittmer and Raiford, *J. Org. Chem.*, 1945, **10**, 527.
[14] Schwenk, Papa, Whitman, and Ginsberg, *ibid.*, 1944, **9**, 175.
[15] Pictet and Finkelstein, *Ber.*, 1909, **42**, 1986.
[16] Buck and Perkin, *J.*, 1924, 1679.
[17] Kondo, Narita, and Uyeo, *Ber.*, 1935, **68**, 527.

dried at room temp./0·3 mm. for 16 hr.: C, 62·7; H, 5·6. $C_{26}H_{28}O_7N_2,H_2O$ requires C, 62·6; H, 6·0; N, 5·6%).

1-(3-*Benzyloxy*-4-*methoxy*-2-*nitrobenzyl*)-3:4-*dihydro*-6:7-*dimethoxy*isoquinoline *Hydrochloride and Methiodide*.—The above amide (1·5 g.) was treated with phosphorus pentachloride (5 g.) in chloroform (60 c.c.) as described in the synthesis of (±)-corydine. The reaction was allowed to proceed at room temperature for 14 days. 1-(3-*Benzyloxy*-4-*methoxy*-2-*nitrobenzyl*)-3:4-*dihydro*-6:7-*dimethoxy*isoquinolinium *chloride* (0·65 g.) crystallised from ethanol (charcoal) in pale yellow needles, m. p. 221—223° (with decomp.) (Found: C, 61·8; H, 5·6; N, 5·1. After being dried at 100°/0·3 mm. for 8 hr.: C, 62·4; H, 5·2. $C_{26}H_{26}O_6N_2,HCl$ requires C, 62·6; H, 5·4; N, 5·6. $C_{26}H_{26}O_6N_2,HCl,C_2H_5{\cdot}OH$ requires C, 61·7; H, 6·0; N, 5·1%). The free base, isolated from the hydrochloride (1·1 g.), was converted into the *methiodide* as in the previous example. It separated from ethanol containing a few drops of methyl iodide in yellow needles (1·0 g.), m. p. 124—126° (with decomp.) (Found, after being dried at 80°/0·1 mm. for 8 hr.: C, 53·0; H, 4·8. $C_{27}H_{29}O_6N_2I$ requires C, 53·6; H, 4·8%).

1-(2-*Amino*-3-*benzyloxy*-4-*methoxybenzyl*)-1:2:3:4-*tetrahydro*-6:7-*dimethoxy*-2-*methyl*isoquinoline *Dipicrolonate*.—As described in the synthesis of corydine, the above methiodide (0·66 g.) was reduced to 1-(2-amino-3-benzyloxy-4-methoxybenzyl)-1:2:3:4-tetrahydro-6:7-dimethoxy-2-methyl*iso*quinoline (0·63 g.), a pale brown oil; its *dipicrolonate* (0·95 g.) formed yellow prisms (from ethanol), m. p. 166—169° (with decomp.) (Found: C, 56·7; H, 4·9; N, 13·7. After being dried at 80°/0·1 mm. for 8 hr.: C, 57·4; H, 4·7; N, 13·9. $C_{27}H_{32}O_4N_2,2C_{10}H_8O_5N_4$ requires C, 57·8; H, 4·9; N, 14·3. $C_{27}H_{32}O_4N_2,2C_{10}H_8O_5N_4,H_2O$ requires C, 56·7; H, 5·0; N, 14·1%). The free base, isolated from the dipicrolonate (2 g.), was diazotised and the product was worked up as described for the synthesis of (±)-corydine. The *hydrochloride* of the product obtained after debenzylation was a white amorphous solid (0·7 g.), which sintered at 205° and melted (with decomp.) at 225° (Found: C, 57·5; H, 6·2; N, 2·3. $C_{20}H_{23}O_4N,HCl$ requires C, 63·5; H, 6·35; N, 3·7%). The identity of this compound is not known.

Colour Reactions.—The authors are indebted to Dr. R. H. F. Manske for authentic specimens of (+)-corydine hydrochloride and (+)-*iso*corydine. (+)-Corydine hydrochloride crystallised from ethanol–ether in small white needles, m. p. 240° (with decomp.) (Found: C, 62·9; H, 6·4; N, 3·2. After being dried at 70—80°/0·3 mm. for 16 hr.: C, 62·7; H, 6·4; N, 3·5. Calc. for $C_{20}H_{23}O_4N,HCl,\frac{1}{2}C_2H_5OH$: C, 62·8; H, 6·7; N, 3·5%). Manske [18] reported that (+)-corydine hydrochloride sinters at 240° and decomposes at 258°. (+)-*iso*Corydine was converted into its hydrochloride by addition of dry hydrogen chloride to a solution of the base in ether. The salt had m. p. 215—218° (with decomp.) (Found: C, 59·9; H, 6·5; N, 3·2. Calc. for $C_{20}H_{23}O_4N,HCl,H_2O$: C, 60·6; H, 6·6; N, 3·5%).

The following colour reactions were performed on the hydrochlorides of synthetic (±)-corydine, (+)-corydine, and (+)-*iso*corydine (cf. Callow, Gulland, and Haworth [19]):

Reagent	(+)-Corydine	(+)-*iso*Corydine	(±)-Corydine
* Mandelin's	Brilliant green	Brownish-purple becoming yellow	Brilliant green
* Frohde's	Bright blue-green	Lilac becoming yellow-green	Bright blue-green
* Erdmann's	Red	Red	Red
* Vitali's	Pale green	Pale pink	Pale green
Conc. sulphuric acid	nil	nil	nil
Conc. nitric acid	Red	Yellow	Pink

* Cf. The Merck Index, 5th edn.

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[18] Manske, *Canad. J. Res.*, 1952, **7**, 258.
[19] Callow, Gulland, and Haworth, *J.*, 1929, 669.