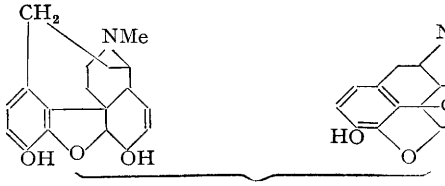
210. *The Synthesis of Analgesic Substances.*

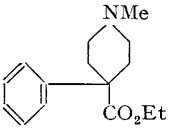
By J. A. Barltrop.

Existing analgesics are briefly reviewed. The preparation is described of α- and β-amino-ketones derived from 5 : 6-dimethoxy- and 5 : 6-methylenedioxy-hydrindone. The introduction of basic side chains into coumarone and *iso*coumaranone and β-tetralone nuclei has been effected by a variety of methods. 5- and 4-(o-*Methoxyphenoxy*)iso*quinoline* have been prepared.

This investigation was undertaken in an attempt to discover synthetic analgesics free from the habit-forming propensities of morphine. Of existing analgesics, the best known, apart from morphine (I) and its derivatives, is pethidine (dolantin, demerol) (II). Many amino-ketones and amino-alcohols derived from partially hydrogenated condensed carbocyclic systems have been tested and found to possess morphine-like activity (cf. Mosettig and van de Kamp, *J. Amer. Chem. Soc.*, 1933, **55**, 3448; Burger and Mosettig, *ibid.*, 1934, **56**, 1745; 1935, **57**, 2189; Mosettig and May, *J. Org. Chem.*, 1940, **5**, 528). Among heterocyclic systems whose deriv-



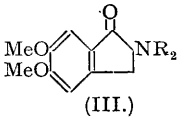
(I.)



(II.)

atives have been found to be analgesic are coumarone (Bovet, Simon, and Depierre, *Compt. rend. Soc. Biol.*, 1934, **117**, 961), dibenzfuran (Kirkpatrick and Parker, *J. Amer. Chem. Soc.*, 1935, **57**, 1123), benzdioxan (Bovet, *Anesthésie et analgésie*, 1935, **1**, 21), and carbazole (Eddy, *J. Pharm. Exp. Ther.*, 1939, **65**, 294).

In particular, 2-*N*-piperidino-6-methoxy-α-tetralone is claimed to be a morphine substitute. In view of the activity of the latter, and since morphine is a catechol derivative, hydrindones of types (III), (IV), and (V) have been synthesised and tested.



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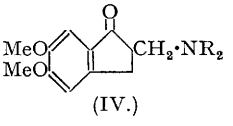

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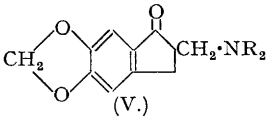
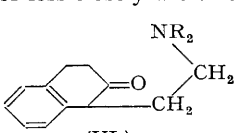


(V.)

5 : 6-Dimethoxyhydrindone (Perkin and Robinson, *J.*, 1907, **91**, 1081) was brominated and condensed with various secondary amines to give 2-*amino-α-hydrindones* (III, NR_2 = piperidyl, morpholyl, and 1 : 2 : 3 : 4-tetrahydro*iso*quinolyl).

5 : 6-Methylenedioxyhydrindone was prepared from the corresponding phenylpropionic acid (*a*) by cyclisation with phosphoric oxide in benzene (Perkin and Robinson, *J.*, 1907, **91**, 1084), and (*b*) by treatment with phosphorus pentachloride in benzene, followed by stannic chloride. It is noteworthy that Perkin and Robinson (*loc. cit.*), by the action of aluminium chloride on 5 : 6-methylenedioxyphenylpropionyl chloride, obtained the hydrindone in only 15% yield; with stannic chloride a 92% yield was obtained.

By following more or less closely the directions of Harradence and Lions (*J. Proc. Roy. Soc. N.S.W.*, 1938,



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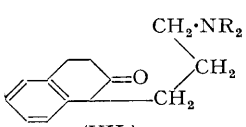


(VII.)

72, 284), 5 : 6-methylenedioxy- and 5 : 6-dimethoxy-hydrindone were condensed with paraformaldehyde and various secondary amines to give the Mannich *bases* (IV) and (V). All these compounds were active, the most promising being (III, NR_2 = piperidyl) and (V, NR_2 = 1 : 2 : 3 : 4-tetrahydro*iso*quinolyl).

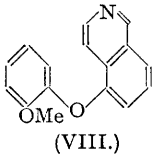
Morphine can be seen to contain a tetralin nucleus alkylated in the 2-position with a dialkylaminoethyl group. In view of the accessibility of β-tetralone obtained by the reduction of 2-methoxynaphthalene (Cornforth, Cornforth, and Robinson, *J.*, 1942, 690), attempts were made to alkylate it with the formation of compounds of types (VI) and (VII).

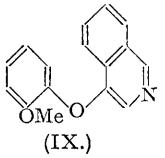
The above authors have shown (*loc. cit.*) that β-tetralone can be alkylated by means of methyl iodide and sodium *iso*propoxide, but in an attempt to obtain (VI, R = Et) by use of diethylaminoethyl chloride only very small yields were obtained even after prolonged refluxing. Eisleb (*Ber.*, 1941, **74**, 1433), however, has demonstrated that basic side chains of this type may be introduced into compounds containing a reactive methylene group by means of sodamide, and application of this method to β-tetralone resulted in the formation in good yield of the *compounds* (VI, NR_2 = piperidyl, and diethylamino) and (VII, NR_2 = piperidyl).

Alternative dissection of the morphine molecule reveals a 5-phenoxy*iso*quinoline skeleton. 5-(o-*Methoxyphenoxy*)iso*quinoline* (VIII) has been synthesised by an Ullmann reaction between guaiacol and 5-iodo*iso*quinoline. The latter was obtained by nitration of *iso*quinoline followed by hydrogenation over Raney nickel catalyst, diazotisation, and treatment with potassium iodide.

Similarly, condensation between guaiacol and 4-bromo*iso*quinoline afforded 4-(o-*methoxyphenoxy*)iso*quinoline* (IX), but owing to the difficulty of obtaining *iso*quinoline under present conditions the series was not further investigated.

Attention was next turned to coumarones with basic side chains. 2-Methoxy- and 3-methoxy-phenoxyacetone (characterised as 2 : 4-*dinitrophenylhydrazones*) were prepared from the corresponding phenol and


(VIII.)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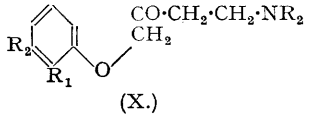
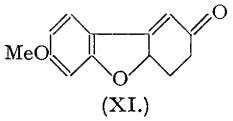
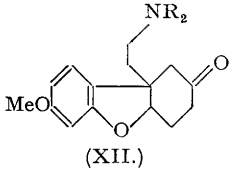

(X.)

chloroacetone in the presence of potassium carbonate (cf. Curd and Robertson, *J.*, 1933, 714), but attempts at preparation of the Mannich bases (X) gave only small yields of products which could not be purified. The ultimate cyclisation to coumarones was not investigated.

6-Methoxycoumaranone seemed a convenient starting substance for investigations in this series and was prepared by the method of Auwers and Pohl (*Annalen*, 1914, **405**, 265). Stannic chloride, which was found to be effective in the hydrindone series, was used to prepare the substance from 3-methoxyphenoxyacetic acid, but the yields were unsatisfactory. Aluminium chloride was not tried in view of the poor yields obtained by Bridge, Heyes, and Robertson (*J.*, 1937, 285) in the cyclisation of α-(3 : 5-dimethoxyphenoxy)*iso*valeryl chloride to the coumaranone.


(XI.)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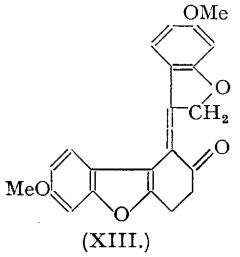
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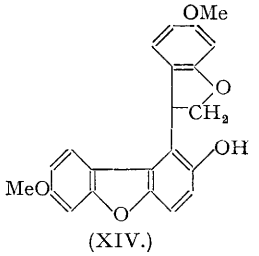
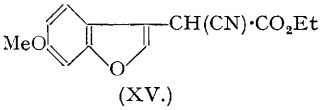

(XIV.)

Attempts were next made to prepare the compound (XII) containing a basic side chain in the angular position occurring in morphine, by Michael addition of ethyl cyanoacetate to the compound (XI) followed by hydrolysis, decarboxylation, reduction, and alkylation. 6-Methoxycoumaranone underwent a Robinson–Mannich reaction with the methiodide of diethylaminobutanone to give an unsaturated *ketone* which, during the subsequent Michael addition, isomerised to a *phenol*. It seems probable that the ketone actually possesses the structure (XIII), being produced by the migration into the furan nucleus of the double bond in the initially formed condensation product (XI), followed by condensation with another molecule of 6-methoxycoumaranone. The isomeric phenol would then be (XIV).

6-Methoxycoumaranone was next condensed with ethyl cyanoacetate according to the directions of Cope *et al.* (*J. Amer. Chem. Soc.*, 1941, **63**, 3452) with the formation of *ethyl* 6-*methoxycoumarone*-3-α-*cyanoacetate* (XV). The yield was poor, and, in view of the more promising trend of subsequent experiments, the projected hydrolysis, decarboxylation, reduction, and alkylation were not carried out. The position of the double bond is not definitely known, but it is considered improbable that it is conjugated with the carbethoxy-group.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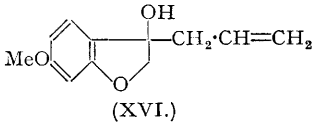
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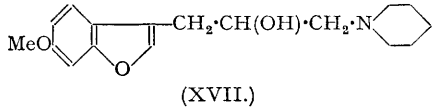
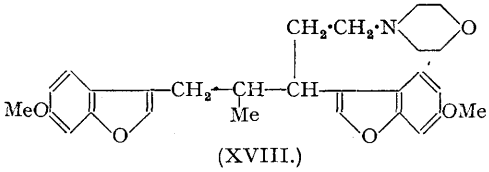

(XVII.)

Reaction of allylmagnesium bromide with 6-methoxycoumaranone produced 3-*hydroxy*-6-*methoxy*-3-*allyl*-*coumaran* (XVI). In this preparation, the order of addition of the reagents was found to be important. The allyl compound was converted into the iodohydrin, and this was treated with piperidine. Piperidine hydriodide was precipitated, indicating the formation of the amino-alcohol (XVII), but this could not be isolated. The free base decomposed on distillation, and attempts at purification through its picrate and picrolonate resulted in hydramine fission and the almost quantitative recovery of piperidine picrolonate. Since a compound as unstable as this would almost certainly be rapidly broken down in the body and thus be inactive, the series was not investigated further.

Addition of hydrogen bromide to the double bond of the hydroxyallylcoumaran by reaction in glacial acetic acid in the presence of benzoyl peroxide gave a bromo-compound, which, when heated with excess morpholine, furnished 6-methoxy-3-morpholinopropylcoumarone, characterised as its *picrate*. When the reaction was repeated on a larger scale the main product was a compound $C_{28}H_{33}O_5N$ (isolated as *hydrochloride*), thought to be (XVIII), containing one morpholine group to two coumarone nuclei.



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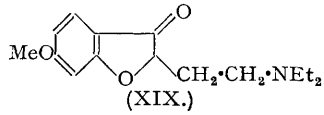
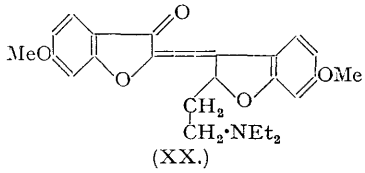


(XIX.)

Alkylation of 6-methoxycoumaranone with diethylaminoethyl chloride in the presence of sodamide afforded, not the desired 6-methoxy-2-β-diethylaminoethylcoumaranone (XIX), but a compound $C_{24}H_{27}O_5N$ (isolated as *hydrochloride*) containing two coumarone nuclei to one basic side chain, whose probable structure is either (XX)



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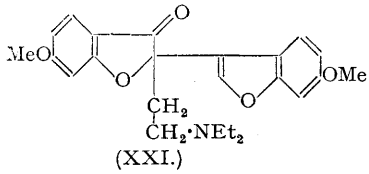
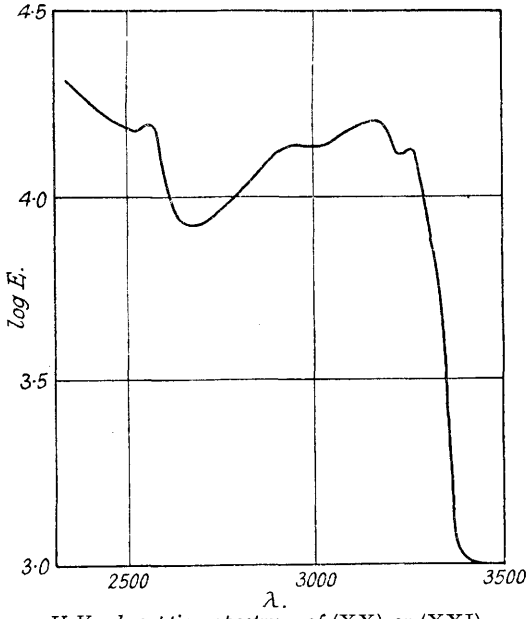


(XXI.)

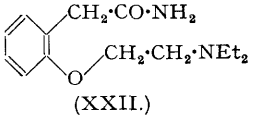
or (XXI). The ultra-violet absorption spectrum of the substance, while not affording conclusive evidence, points to (XX) as the more probable.



U.V. absorption spectrum of (XX) *or* (XXI).

Attention was next turned to *iso*coumaranones, which, it was thought, might be alkylated in the 3-position with dialkylaminoalkyl halides. The compounds so produced would be especially interesting in that the molecule would contain the reactive groups of pethidine (II) in the same relative position, and in addition, would be stabilised by ring formation.

2-Hydroxy-3-methoxyphenylacetic acid was prepared from 2-*hydroxy*-3-*methoxybenzylidene azlactone*. It is noteworthy that the hydroxyl group is so sterically hindered that acetylation did not take place in the azlactone formation. Attempts at cyclisation of the phenylacetic acid were unsuccessful. Even the most drastic conditions failed to produce an appreciable yield of the *iso*coumaranone—another instance of the steric hindrance associated with this hydroxyl group. At this point it was decided to carry out model experiments on *iso*coumaranone itself. Alkylation of this compound with diethylaminoethyl chloride and sodamide gave, not the desired 3-diethylaminoethyl*iso*coumaranone, but 2-β-*diethylaminoethoxyphenylacetamide* (XXII) by opening of the ring followed by alkylation of the resulting sodium aryloxide.



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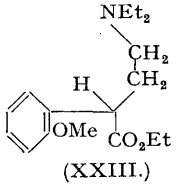

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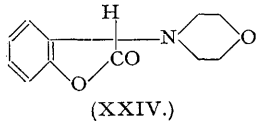
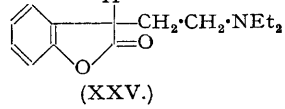


(XXIV.)



(XXV.)

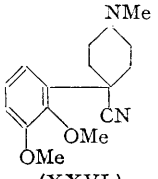
The *hydrobromide* of 3-*morpholino*iso*coumaranone* (XXIV) was obtained by interaction of morpholine and 3-bromo*iso*coumaranone.

2-Methoxybenzaldehyde was hydrogenated with Woodward's (*J. Amer. Chem. Soc.*, 1940, **62**, 1480) activated platinum oxide catalyst to the benzyl alcohol, which was converted into 2-methoxybenzyl cyanide *via* the bromide. This was alkylated in good yield with diethylaminoethyl chloride and sodamide with the formation

of 2-methoxy-α-(β-diethylaminoethyl)benzyl cyanide, characterised as its *oxalate*. Hydrolysis of the cyanide followed by esterification gave *ethyl 2-methoxy-α-(β-diethylaminoethyl)phenylacetate* (XXIII).

Simultaneous demethylation and hydrolysis of the alkylated cyanide furnished a syrupy amino-acid hydrobromide which on distillation with fused sodium acetate was converted into 3-β-diethylaminoethyl*iso*coumaranone (XXV), characterised as its *picrate*.

2 : 3-Dimethoxybenzaldehyde was condensed with rhodanine (cf. Julian and Sturgis, *J. Amer. Chem. Soc.*, 1935, **57**, 1127), and the resulting 2 : 3-*dimethoxybenzylidenerhodanine* was hydrolysed to 2 : 3-*dimethoxyphenylthiopyruvic acid*. This on oximation and dehydration with acetic anhydride furnished 2 : 3-dimethoxybenzyl



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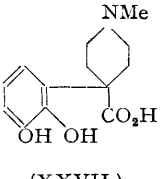
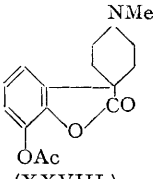


(XXVII.)



(XXVIII.)

cyanide, which was also obtained from the aldehyde *via* the alcohol (crossed Cannizzaro reaction) and bromide. Alkylation of the cyanide with methyl-2 : 2′-dichlorodiethylamine and sodamide gave 4-cyano-4-(2′ : 3′-dimethoxyphenyl)-1-methylpiperidine (XXVI), which has since been described by Bergel, Haworth, Morrison, and Rinderknecht (*J.*, 1944, 262). Simultaneous hydrolysis and demethylation of the cyanide afforded the *hydrobromide* of 4-*carboxy*-4-(2′ : 3′-*dihydroxyphenyl*)-1-*methylpiperidine* (XXVII). This acid was cyclised with acetic anhydride with the production of the *spiro*piperidino*iso*coumaranone (XXVIII) (characterised as *oxalate* and *picrate*), which not only contains a system occurring in the morphine molecule but is also a ring-closed modification of the pethidine molecule.

Experimental.

2-Bromo-5 : 6-dimethoxyhydrindone (cf. Perkin, Rây, and Robinson, *J.*, 1926, 948).—Bromine (5 g.), dissolved in chloroform (5 c.c.), was slowly added with stirring and ice-cooling to a solution of the dimethoxyhydrindone * (5 g.) in chloroform (10 c.c.). After being stirred for 30 mins. at 0°, the paste was kept at room temperature for 30 mins. and then cooled to 0°. The bromo-ketone was precipitated with ligroin, collected, washed with ligroin, and extracted (Soxhlet) with ligroin (b. p. 40—60°); it was obtained as a pale yellow powder (6·9 g.), m. p. 157°.

Condensation of Bromodimethoxyhydrindone with Secondary Amines.—The bromohydrindone (2 g.), dissolved in acetone (40 c.c.), was added to a solution of the secondary amine (2·1 mols.) in acetone (5 c.c.). After several hours, addition of ether (200 c.c.) precipitated the secondary amine hydrobromide, which was collected. The amino-ketone hydrochloride was obtained by passing hydrogen chloride over the surface of the filtrate, collection, and crystallisation. 2-N-*Piperidino*-5 : 6-*dimethoxyhydrindone hydrochloride* (1·95 g.) crystallised from ethanol–ethyl acetate in colourless needles, m. p. 236° (Found: C, 61·2; H, 7·0; N, 3·9. $C_{16}H_{21}O_3N$,HCl requires C, 61·6; H, 7·1; N, 4·5%). 2-N-*Morpholino*-5 : 6-*dimethoxyhydrindone hydrochloride* (1·5 g.) crystallised from ethanol in colourless needles, m. p. 212° (vac.) (Found: C, 56·7; H, 6·3; N, 4·9. $C_{15}H_{19}O_4N$,HCl requires C, 57·4; H, 6·4; N, 4·5%). 2-N-(1′ : 2′ : 3′ : 4′-*Tetrahydroisoquinolino*)-5 : 6-*dimethoxyhydrindone hydrochloride* (2 g.) crystallised from ethanol in colourless needles, m. p. 188° (Found: C, 63·9; H, 6·2; OMe, 16·5; Cl, 9·4. $C_{20}H_{21}O_3N$,HCl,H_2O requires C, 63·6; H, 6·4; OMe, 16·4; Cl, 9·4%).

2-Morpholinomethyl-5 : 6-dimethoxyhydrindone (Harradence and Lions, *loc. cit.*).—The hydrochloride crystallised from aqueous ethanol in radiating clusters of fine yellow needles, m. p. 183° (yield, 35%).

5 : 6-Methylenedioxyhydrindone.—To a solution in benzene (20 c.c.) of 3 : 4-methylenedioxyphenylpropionic acid (3·9 g.) (prepared in almost quantitative yield by hydrogenating the corresponding cinnamic acid over Raney nickel in dioxan solution at 80°) was added phosphorus pentachloride (5 g.), and the whole was kept at room temperature for 2 hours and then cooled in ice. Stannic chloride (5 g.), dissolved in benzene (8 c.c.), was added, and the mixture shaken for 10 minutes, during which time a yellow solid was gradually deposited. After the mixture had been poured on ice and concentrated hydrochloric acid (30 c.c.) and extracted several times with ether, the combined extracts were washed successively with 10% hydrochloric acid (3 times), water, 10% sodium hydroxide solution (twice) and water, and dried. On evaporating the solvents, colourless crystals of the hydrindone (3·2 g., 92%) remained and were purified by extraction (Soxhlet) with ether. It crystallised in colourless plates, m. p. 161—162° alone or mixed with an authentic specimen.

Preparation of Mannich Bases from 5 : 6-Methylenedioxyhydrindone.—The hydrindone (3 g.), paraformaldehyde (0·9 g., 1·76 mols.), secondary amine hydrochloride (1 mol.), and ethanol (15 c.c.) were refluxed on the steam-bath for the times given below. The Mannich base hydrochloride was gradually deposited, and after cooling was collected and crystallised.

2-N-*Morpholinomethyl*-5 : 6-*methylenedioxyhydrindone*. Refluxed for 1 hour. The *hydrochloride* (4·0 g.) crystallised from aqueous ethanol in glistening, rectangular plates, m. p. 183° (vac.) (Found: C, 57·3; H, 6·0; N, 4·9. $C_{15}H_{17}O_4N$,HCl requires C, 57·5; H, 5·75; N, 4·5%).

2-N-*Piperidinomethyl*-5 : 6-*methylenedioxyhydrindone*. Refluxed for 4 hours. The *hydrochloride* (2·6 g.) crystallised from ethanol–ethyl acetate in colourless needles, m. p. 172—173° (vac.) (Found: C, 62·1; H, 6·5; N, 4·55. $C_{16}H_{19}O_3N$,HCl requires C, 62·0; H, 6·45; N, 4·5%).

2-N-(1′ : 2′ : 3′ : 4′-*Tetrahydroisoquinolinomethyl*)-5 : 6-*methylenedioxyhydrindone*. Refluxed for 30 minutes in ethanol (10 c.c.). The *hydrochloride* after several crystallisations from aqueous ethanol formed colourless needles (1·2 g.), m. p. 172° (vac.) (Found: C, 66·85; H, 5·7; N, 4·2. $C_{20}H_{19}O_3N$,HCl requires C, 67·1; H, 5·6; N, 3·9%).

2-Keto-1-(β-diethylaminoethyl)-1 : 2 : 3 : 4-tetrahydronaphthalene.—(A) Sodium (0·845 g.) was dissolved in dry *iso*propyl alcohol (20 c.c.). Air was displaced from the apparatus by nitrogen, and β-tetralone (6·05 g.), dissolved in dry *iso*propyl alcohol (10 c.c.), was added, followed by diethylaminoethyl chloride (5·8 g.). After being heated on the steam-bath for

* Sir Robert Robinson has drawn the author's attention to the fact that the m. p. of 5 : 6-dimethoxyhydrindone is incorrectly given (Perkin and Robinson, *J.*, 1907, **91**, 1084) owing to a clerical error. This has been examined and it is found that the substance, crystallised from ethanol, has m. p. 120°.

28 hours, during which time a little sodium chloride was deposited, the mixture was diluted with water and acidified with hydrochloric acid out of contact with air. The solvent was removed under reduced pressure and the unchanged β-tetralone extracted with ether. The aqueous layer was basified, and the liberated amine isolated with ether and distilled in bulbs. The diethylaminoethyltetralone (30 mg.), a colourless oil, was collected at 100—140°/0·1 mm. It gave an oily picrate. The oxalate had m. p. 146° undepressed by the oxalate described in (B).

(B) β-Tetralone (5·0 g.) and diethylaminoethyl chloride (4·6 g.) were dissolved in toluene (25 c.c.). Air was displaced from the apparatus with nitrogen, and finely powdered sodamide (1·4 g.) added gradually with agitation. The temperature was kept below 35° during the addition, and then slowly raised to 85° and maintained there for 5 hours, stirring being continued. The mixture was finally boiled under reflux for 1 hour and extracted with hydrochloric acid. The aqueous extract was washed several times with ether, basified, and the liberated base isolated with ether and fractionated in a vacuum. The amino-ketone (6·0 g.), a colourless liquid with a pale blue fluorescence, was collected at 128°/0·08 mm. The compound gives a green coloration with concentrated sulphuric acid and darkens on keeping. The *oxalate* crystallised from ethanol in fine, colourless needles, m. p. 146° (Found: C, 64·6; H, 7·6; N, 4·15. $C_{15}H_{23}ON,C_2H_2O_4$ requires C, 64·5; H, 7·4; N, 4·2%). Raising the temperature more rapidly in this and the other alkylations described below reduces the yield.

2-*Keto*-1-(β-*piperidinoethyl*)-1 : 2 : 3 : 4-*tetrahydronaphthalene*.—β-Tetralone (4·9 g.) and piperidinoethyl chloride (5·0 g.), dissolved in toluene (50 c.c.), were treated with sodamide (1·55 g.) as in the preceding experiment, with cooling. When heat evolution had ceased, the mixture was heated to 40° for 1 hour, then 75° for 1 hour, 85° for 1 hour, 100° for 1½ hours and finally refluxed for 1½ hours. The product was worked up as in the preceding experiment. The *piperidinoethyltetralone* (4·8 g.), a viscous pale yellow oil, was collected at 148—152°/0·06 mm. (Found: C, 78·9; H, 8·8. $C_{17}H_{23}ON$ requires C, 79·4; H, 8·95%). The product boils with decomposition.

2-*Keto*-1-(γ-*piperidinopropyl*)-1 : 2 : 3 : 4-*tetrahydronaphthalene*.—Sodamide (1·6 g.) was added with agitation as in experiment (B) above to a mixture of β-tetralone (5·0 g.), piperidinopropyl chloride (6·1 g.) (Hromatka, *Ber.*, 1942, **75**, 131), and toluene (50 c.c.). After 2 hours' heating at 100°, piperidinopropyl chloride (3 g.) was added, and the mixture boiled under reflux for 2 hours. The product was isolated as in the preceding experiments. The *piperidinopropyltetralone* (4·0 g.), a very viscous, pale yellow oil, was collected at 170°/0·18 mm. (Found: C, 79·3; H, 9·2; N, 5·1. $C_{18}H_{25}ON$ requires C, 79·7; H, 9·2; N, 5·2%). The oxalate, hydrochloride, picrate, and picrolonate were oily.

5-*Amino*iso*quinoline*.—5-Nitroisoquinoline (10 g.) (Claus and Hofmann, *J. pr. Chem.*, 1893, **47**, 252), dissolved in ethanol, was hydrogenated over Raney nickel for 6 hours at 80° with initial pressure 130 atmospheres. The product was isolated in the usual manner and distilled. 5-Aminoisoquinoline (7·5 g., 95%) was collected at 196°/18 mm

5-(o-*Methoxyphenoxy*)iso*quinoline*.—5-Iodoisoquinoline [prepared from 5-aminoisoquinoline (Edinger, *J. pr. Chem.*, 1896, **53**, 379)] (4·3 g.), potassium hydroxide (3·8 g.), guaiacol (8·6 g.), and a trace of copper powder were heated for 4 hours in an oil-bath at 230°. After the aqueous layer had been acidified, extracted with ether, and basified, the liberated oil was isolated with ether and distilled in bulbs. The phenoxyisoquinoline (0·65 g.), a colourless oil, was collected at 90° (bath temp.)/0·15 mm. The *picrate* crystallised from ethanol in yellow needles, m. p. 206° (Found: C, 54·7; H, 3·2. $C_{16}H_{13}O_2N,C_6H_3O_7N_3$ requires C, 55·0; H, 3·3%).

4-(o-*Methoxyphenoxy*)iso*quinoline*.—4-Bromoisoquinoline (7·6 g.) (prepared by rearranging the perbromide), guaiacol (5·7 g.), potassium hydroxide (2·05 g.), and activated copper powder (0·1 g.) were heated in an oil-bath at 190° till the reaction started and then at 210—230° for 2 hours. The product was taken up in dilute hydrochloric acid, washed with ether, and basified, and the liberated amines were isolated with ether and distilled in bulbs. The phenoxyisoquinoline, a colourless oil (2·7 g.), was collected at 130—140° (bath temp.)/0·06 mm. The *picrate* crystallised from much ethanol in fine, yellow needles, m. p. 223° (Found: C, 54·8; H, 3·3; N, 11·65. $C_{16}H_{13}O_2N,C_6H_3O_7N_3$ requires C, 55·0; H, 3·3; N, 11·7%).

3-*Methoxyphenoxyacetone*.—3-Methoxyphenol (43 g.), chloroacetone (47 g.), potassium carbonate (86 g.), and acetone (160 c.c.) were refluxed on the steam-bath for 2 hours. Most of the acetone was removed, excess of sodium hydroxide solution added, and the ketone isolated with ether. The brown oil so obtained was fractionated in a vacuum, the phenoxyacetone (27 g.), a yellow oil, being collected at 138—149°/11 mm. The 2 : 4-*dinitrophenylhydrazone* crystallised from ethanol in fine orange needles, m. p. 140·5—141·5° (Found: C, 53·2; H, 4·7; N, 15·35. $C_{16}H_{16}O_6N_4$ requires C, 53·3; H, 4·4; N, 15·55%).

2-*Methoxyphenoxyacetone*.—Guaiacol (10 g.), chloroacetone (11 g.), potassium carbonate (20 g.), and acetone (40 c.c.) were refluxed on the steam-bath for 2 hours. The product was isolated as in the preceding experiment. The fraction, b. p. 135—138°/11 mm. (9·3 g.), was collected and refractionated. The phenoxyacetone (9·0 g.), a yellow oil, was collected at 138°/11 mm. The 2 : 4-*dinitrophenylhydrazone* crystallised from ethanol in spherical clusters of fine, orange needles, m. p. 141·5° (Found: C, 53·3; H, 4·4; N, 15·8. $C_{16}H_{16}O_6N_4$ requires C, 53·3; H, 4·4; N, 15·55%).

Attempted Preparation of 1-N-*Morpholino*-3-*keto*-4-(o-*methoxyphenoxy*)*butane*.—2-Methoxyphenoxyacetone (4·63 g.), paraformaldehyde (1·0 g.), morpholine hydrochloride (3·09 g.), and ethanol (15 c.c.) were refluxed on the steam-bath for 6 hours. Water (20 c.c.) was added and the ethanol removed under reduced pressure. The aqueous layer was extracted several times with ether to remove unchanged ketone, filtered, and evaporated under reduced pressure to give the crude hydrochloride as an orange syrup which could not be crystallised. It was converted into the free base, which was freed from morpholine by washing with water, and thence into the picrate, picrolonate, and oxalate. These were also intractable oils. Attempts at distillation of the free base in high vacuum caused complete decomposition.

Attempted Preparation of 1-N-*Morpholino*-3-*keto*-4-(m-*methoxyphenoxy*)*butane*.—3-Methoxyphenoxyacetone (12 g.), paraformaldehyde (1·5 g.), morpholine hydrochloride (6·1 g.), and ethanol (45 c.c.) were refluxed on the steam-bath for 7 hours. The product was worked up as in the preceding experiment. From the ether extracts unchanged phenoxyketone (9·2 g.) was recovered. The free base gave no crystalline derivatives, and distillation in high vacuum caused extensive decomposition; the few drops of distillate obtained gave an oily hydrochloride and picrate.

6-*Methoxycoumaranone*.—(A) The coumaranone was obtained in 84·5% yield from 2-hydroxy-4-methoxychloroacetophenone (see Auwers and Pohl, *Annalen*, 1914, **405**, 265).

(B) Phosphorus pentachloride (6·9 g.) was added to *m*-methoxyphenoxyacetic acid (Koelsch, *J. Amer. Chem. Soc.*, 1931, **53**, 304) (5 g.) suspended in dry benzene (50 c.c.). After being kept for 1 hour and finally warmed gently, the solution was cooled in ice and treated with a cold solution of stannic chloride (3·7 c.c.) in benzene (10 c.c.). A cerise-coloured precipitate gradually formed. After 1 hour at room temperature, the mixture was poured on ice and extracted with ether. The extract was washed with water, sodium carbonate solution, and again with water, and finally dried and evaporated. The residual pink solid (0·95 g.) when crystallised twice from ethanol formed yellow needles, m. p. 119° alone and when mixed with an authentic specimen of 6-methoxycoumaranone.

Condensation of 6-*Methoxycoumaranone with* 1-*Diethylamino*-3-*ketobutane Methiodide*.—6-Methoxycoumaranone (6·6 g.) and sodamide (1·56 g.) were stirred in dry ether (30 c.c.) for 4 hours at room temperature in a stream of nitrogen. The mixture darkened. The methiodide of diethylaminobutanone, prepared from amine (9·6 g.) and methyl iodide (11·4 g.), was dissolved in dry ethanol and added slowly. Agitation was continued at room temperature for 3 hours, and the mixture was then kept overnight and boiled under reflux for 1½ hours. Hydrochloric acid and ether were added

and the product, a black tarry syrup, was isolated with ether. It was dissolved in ethanol and filtered, and the ethanol evaporated. The dark oil was distilled in bulbs. An orange resin (1·8 g.) collected at 200—260° (bath temp.)/0·4 mm., and crystallised on scratching with warm ethanol. The *product* crystallised from ethanol in pale yellow needles, m. p. 184—185° (Found: C, 72·9; H, 5·0. $C_{22}H_{18}O_5$ requires C, 72·9; H, 5·0%). It immediately decolorised potassium permanganate solution and gave a 2 : 4-dinitrophenylhydrazone.

Isomerisation of the above Robinson–Mannich Condensation Product.—The above unsaturated ketone (0·22 g.), ethyl cyanoacetate (0·116 g.), and 0·46 c.c. of a solution of sodium (0·75 g.) in dry ethanol (15 c.c.) were heated on the steam-bath for 6 hours, kept overnight, and refluxed for a further 3 hours. The reaction mixture was diluted with water (20 c.c.) containing acetic acid (0·9 g.) and extracted twice with ether, and the extracts were dried and evaporated. The *compound* (0·15 g.) crystallised from ethanol in long, lemon-yellow needles, m. p. 184—185°, depressed by the Robinson–Mannich condensation product (Found: C, 72·7; H, 5·0; *M*, 335. $C_{22}H_{18}O_5$ requires C, 72·9; H, 5·0%; *M*, 362). The product was sparingly soluble in sodium hydroxide, and gave a brown coloration with ferric chloride. It did not form a 2 : 4-dinitrophenylhydrazone and did not decolorise potassium permanganate.

Ethyl 6-Methoxycoumarone-3-α-cyanoacetate.—6-Methoxycoumaranone (10 g.), ethyl cyanoacetate (7·1 g.), ammonium acetate (1 g.), acetic acid (3 g.), and benzene (15 c.c.) were heated in an oil-bath at 130—150° in a flask fitted with a continuous water separator. Heating was continued for 9 hours. After being cooled and washed with water, the benzene layer was dried and evaporated, and the black residual oil crystallised by trituration with ethanol–ligroin. The solid (7·2 g.), m. p. 112—119°, was collected and distilled in bulbs. The main fraction (6·0 g.) was collected at 120° (bath temp.)/0·03 mm. as a colourless solid, m. p. 119—120° alone and when mixed with an authentic specimen of 6-methoxycoumaranone. The other fraction (0·4 g.), an orange sublimate, was collected at 130—150° (bath temp.)/0·03 mm. The *coumarone-cyanoacetate* crystallised from ethanol in pale orange needles, m. p. 174—175° (Found: C, 64·9; H, 5·15; N, 5·1. $C_{14}H_{13}O_4N$ requires C, 64·9; H, 5·0; N, 5·4%); it gave a deep rose colour with concentrated sulphuric acid, becoming yellow on warming.

3-Hydroxy-6-methoxy-3-allylcoumaran.—Powdered magnesium–aluminium alloy (60 g. containing 7% of Al) was covered with dry ether (160 c.c.), a crystal of iodine added, and a solution of allyl bromide (41 c.c.) in ether (200 c.c.) run in during 4 hours with stirring. Agitation was continued for a further 4 hours, and the mixture kept overnight. The ethereal solution of the Grignard reagent was filtered through glass wool and added slowly with stirring to a solution of 6-methoxycoumaranone (18 g.) in ether (700 c.c.). Next day, ice was added and then dilute acetic acid until all the solid dissolved. The ethereal layer was separated, washed with water, dried, and evaporated, and the residual oil fractionated. The *coumaran* (15·2 g., 67%), a pale yellow oil, was collected at 154°/18 mm. (Found: C, 69·6; H, 6·7. $C_{12}H_{14}O_3$ requires C, 69·9; H, 6·8%). It decolorised potassium permanganate solution and gave red colorations with alcoholic picric acid and 1 : 3 : 5-trinitrobenzene.

Increasing the proportion of coumaranone to Grignard reagent diminished the yield somewhat, and reversed addition of the coumaranone to the Grignard reagent gave very little of the condensation product, much coumaranone being recovered.

Attempted Preparation of 6-Methoxy-3-(γ-piperidino-β-hydroxypropyl)coumarone.—(A) The above coumaran (2·06 g.) was shaken in ethanol-free ether with yellow mercuric oxide (1·3 g.) and water (0·2 c.c.). Iodine (2·54 g.) was added in portions during 1 hour and shaking continued for a further 2 hours. The solution was filtered, washed with potassium iodide solution, sodium bisulphite solution, and water, and then dried, and the ether evaporated under reduced pressure. The crude iodohydrin remained as an oil which could not be distilled. To this was added piperidine (3 g.) dissolved in ether (6 c.c.); fine colourless needles of piperidine hydriodide (m. p. 172°) were deposited after standing at room temperature for 16 hours and dilution with ether, the solution was extracted several times with water to remove piperidine and its hydriodide, and the ether evaporated under reduced pressure. The crude base was converted into the picrate, an oil which eventually solidified. Attempts at purification by crystallisation from ethanol caused progressive darkening and decomposition, and only piperidine picrate was isolated.

(B) The coumaran (8·24 g.) was converted into the iodohydrin, and treated with piperidine (6·8 g.). After some time, excess of dry ether was added to precipitate all the hydriodide, which was removed. The condensation product was worked up as above, and kept over concentrated sulphuric acid in a vacuum desiccator until no more piperidine was lost. The residual viscous oil (1·3 g.) was converted into its picrolonate in acetone and crystallised from acetone. Piperidine picrolonate (1·1 g.), m. p. 248° undepressed by authentic salt, was isolated, and also 70 mg. of a picrolonate, m. p. >280°. This on recrystallisation darkened and gave more piperidine picrolonate.

6-Methoxy-3-morpholinopropylcoumarone.—The coumaran (0·94 g.) was added dropwise to 1·4 g. of an ice-cold solution prepared from hydrogen bromide (63 g.) and acetic acid (142 g.), with addition of benzoyl peroxide (0·1 g.). After 24 hours at 0°, the viscous, deep red solution was taken up in chloroform, washed with sodium carbonate solution and with water, then dried and evaporated under reduced pressure. The red, residual oil (1·4 g.) was refluxed with morpholine (2·3 g.) in ethanol (20 c.c.) for 14 hours. The ethanol was distilled, water added, and the base extracted with ether. The ethereal solution was washed several times with water and then extracted with dilute hydrochloric acid. The acid layer was basified, and the amine isolated with ether and converted into the *picrate* (0·2 g.), which crystallised from ethanol in yellow rods, m. p. 177—178° (darkening) (Found: C, 52·3; H, 5·0; N, 11·4. $C_{16}H_{21}O_3N,C_6H_3O_7N_3$ requires C, 52·4; H, 4·8; N, 11·1%).

(B) The coumarane (15 g.) was converted into the bromide and boiled under reflux with morpholine (35 g.) for 3 hours, and the product taken up in ether. The ethereal solution was washed repeatedly with water until the washings were no longer alkaline, and then extracted several times with 10% hydrochloric acid. The aqueous layer deposited a brown oil (*a*) (6 g.), which gradually solidified and was collected. The filtrate was basified and the amine (*b*) (2 g.) isolated with ether.

The substance (*a*) was obtained as its *hydrochloride* in colourless needles, m. p. 270°, by extraction (Soxhlet) with ethyl acetate and crystallisation from ethanol (Found: C, 66·9; H, 7·05; N, 2·9; OMe, 11·4. $C_{28}H_{33}O_5N,HCl$ requires C, 67·3; H, 6·8; N, 2·8; OMe, 12·4%). The amine (*b*) gave an oily picrate from which was isolated a small quantity of the picrate of morpholinopropylcoumarone, m. p. 177—179°.

Alkylation of 6-Methoxycoumaranone with Diethylaminoethyl Chloride.—The finely powdered coumaranone (4·9 g.), diethylaminoethyl chloride (4·4 g.), and toluene (50 c.c.) were stirred, and pulverised sodamide (1·4 g.) was added in portions, the temperature being kept below 35°. When all the sodamide had been added, the temperature was raised gradually to 90° and maintained there for 8 hours, during which time the mixture darkened considerably. The reaction was completed by boiling under reflux for 2 hours. The mixture was washed with water and extracted with 18% hydrochloric acid. The acid extract rapidly deposited crystals of the *hydrochloride*, which crystallised from ethanol in pale yellow needles (5 g.), m. p. 233° (Found: C, 64·4, 64·3; H, 6·3, 6·4; N, 3·4, 2·8; OMe, 13·0. $C_{24}H_{27}O_5N,HCl$ requires C, 64·6; H, 6·3; N, 3·15; OMe, 13·9%).

2-Hydroxy-3-methoxybenzylidene Azlactone.—*o*-Vanillin (100 g.), hippuric acid (140 g.), fused sodium acetate (50 g.), and acetic anhydride (250 c.c.) were heated on the steam-bath for 2 hours. After cooling, the *azlactone* was collected as a salmon-pink solid, which was washed with water; it crystallised from glacial acetic acid in thin, orange plates (132 g.),

m. p. 202°. The analytical specimen when recrystallised was pale yellow and had m. p. 203° (Found: C, 69·1; H, 4·4; N, 5·1. $C_{17}H_{13}O_4N$ requires C, 69·2; H, 4·4; N, 4·75%).

2-*Hydroxy*-3-*methoxyphenylacetic Acid.*—The above azlactone (114 g.) was dissolved in 10% sodium hydroxide solution (1140 c.c.). Air was displaced from the apparatus by nitrogen, and the mixture was boiled under reflux in an atmosphere of nitrogen for 5 hours and then cooled in ice. 6% Hydrogen peroxide (600 c.c.) was added to half the resulting mixture with agitation. The temperature slowly rose. The next day, the solution was acidified with hydrochloric acid and steam-distilled to remove benzoic acid, much tar being formed during the process. The phenylacetic acid was isolated with ether and distilled. The acid (11 g.) was collected at 150—158°/28 mm. as a pale yellow solid, m. p. 124°. Much residue remained in the flask.

Attempted Cyclisation of 2-*Hydroxy*-3-*methoxyphenylacetic Acid.*—(A) The acid was heated in a metal-bath at 250° for 2 hours and then distilled under reduced pressure. The acid was recovered almost quantitatively. (B) The acid was distilled under atmospheric pressure and was recovered unchanged. (C) The acid (7·8 g.), dissolved in toluene (50 c.c.), was heated on the steam-bath, and phosphoric oxide (20 g.) added in portions. After 3 hours, water was added, the toluene later separated, dried, and evaporated under reduced pressure, and the product distilled. The oil (2 g.) collected at 140—160°/18 mm. solidified to a colourless solid, m. p. 105—115°. Much high-boiling material was obtained. The solid, dissolved in ether, was washed several times with sodium carbonate solution, dried, and evaporated. Only a few mg. of oil were obtained. The sodium carbonate solution on acidification gave the unchanged phenylacetic acid, m. p. 124°.

iso*Coumaranone.*—2-Acetoxybenzylidene azlactone (67 g.) (Erlenmeyer and Stadlin, *Annalen*, 1904, **337**, 290) was boiled under reflux with 10% sodium hydroxide (670 c.c.) for 5 hours, filtered, cooled in ice, treated with 6% hydrogen peroxide (650 c.c.), and left overnight. Addition of hydrochloric acid precipitated the phenylacetic acid and benzoic acid which were isolated with ether and distilled. The fraction (44 g.), b. p. 240—260°, a yellow oil solidifying to a paste, was taken up in ether, washed repeatedly with sodium carbonate solution, and dried. After removal of the ether, the product was distilled under reduced pressure. *iso*Coumaranone (20 g.) was collected at 144°/35 mm., n^{20} 1·547.

Alkylation of iso*Coumaranone with Diethylaminoethyl Chloride.*—*iso*Coumaranone (3·5 g.) and diethylaminoethyl chloride (3·6 g.) were stirred in toluene (30 c.c.) in an atmosphere of nitrogen. Pulverised sodamide (1·25 g.) was added with cooling. After addition of the sodamide, the temperature was raised slowly to 90° and maintained there for 2 hours. The mixture was heated at 100° for 2 hours and finally boiled under reflux for 2 hours. The solution was washed with water and extracted with hydrochloric acid. The acid extract was basified, and the amine isolated with ether and fractionated. 2-*Diethylaminoethoxyphenylacetamide* (3·8 g.) was collected at 168—172°/0·05 mm. as a yellow oil, crystallising in square plates on standing. On slow evaporation of its ethereal solution, the amide crystallised in colourless prisms, m. p. 75° (Found: C, 67·1; H, 8·7; N, 11·4. $C_{14}H_{22}O_2N_2$ requires C, 67·2; H, 8·8; N, 11·2%). The product evolves nitrogen with nitrous acid.

3-*Morpholino*iso*coumaranone.*—*iso*Coumaranone (1·3 g.) and ice chips were shaken, and bromine (1·6 g.) was added dropwise. When the colour of the bromine had disappeared, the product was taken up in ether and washed several times with water. Morpholine (1·8 g.) was added to the dried ethereal layer, and the whole left overnight. Hemispherical clusters of crystals separated and were collected. The 3-*morpholino*iso*coumaranone hydrobromide* crystallised from ethanol in colourless plates (0·5 g.), m. p. 171° (decomp.) (Found: C, 48·4; H, 5·0; N, 5·0. $C_{12}H_{13}O_3N$,HBr requires C, 48·0; H, 4·7; N, 4·7%).

2-*Methoxybenzyl Alcohol.*—2-Methoxybenzaldehyde (10 g.) was hydrogenated over platinum oxide catalyst (0·05 g.) activated with ferrous sulphate (0·5 c.c. of 0·1M.) in ethanol solution (50 c.c.) at atmospheric pressure. When the calculated amount of hydrogen had been absorbed, the catalyst was centrifuged and used again with more of the aldehyde (11 g.). The combined alcoholic solutions were evaporated and distilled. The alcohol (20·5 g.) was collected at 135°/22 mm.

2-*Methoxybenzyl Bromide.*—Prepared according to Lapworth and Shoesmith (*J.*, 1922, **121**, 1396), this bromide, b. p. 112°/12 mm., frequently polymerised on distillation, so the crude compound was used for conversion into the nitrile.

2-*Methoxybenzyl Cyanide* (cf. Pschorr, Wolfe, and Buckow, *Ber.*, 1900, **33**, 166).—The crude undistilled bromide (38 g.) was boiled under reflux for 1 hour with potassium cyanide (15 g.), ethanol (150 c.c.), and water (25 c.c.). Water was added, the ethanol distilled under reduced pressure, and the cyanide isolated with ether and distilled. It was collected as a colourless oil, b. p. 130—140°/14 mm., solidifying to a colourless solid (19·2 g.). On crystallising from benzene–ligroin it formed thin prisms, m. p. 67°.

α-(β-*Diethylaminoethyl*)-2-*methoxybenzyl Cyanide.*—2-Methoxybenzyl cyanide (4·9 g.) was stirred with diethylaminoethyl chloride (6·0 g.) and toluene (50 c.c.). Sodamide (1·6 g.) was added in portions, and the temperature raised slowly to 75°. After 3 hours, the temperature was further raised to 100° for 1½ hours and finally the mixture was boiled under reflux for 1½ hours. The toluene layer was washed with water and extracted with hydrochloric acid. The extract was basified, and the product isolated with ether and distilled. The cyanide (5·3 g.), a colourless oil, was collected at 122°/0·04 mm. The *oxalate* crystallised from ethanol in colourless, glistening plates, m. p. 169° (gas evolution) (Found: C, 60·85; H, 7·2. $C_{15}H_{22}ON_2,C_2H_2O_4$ requires C, 60·7; H, 7·1%).

Ethyl 2-*Methoxy*-α-(β-*diethylaminoethyl*)*phenylacetate.*—The above cyanide (11 g.) was boiled under reflux for 8 hours with 18% hydrochloric acid, evaporated to dryness under reduced pressure, and the residue taken up in ethanol and filtered from the ammonium chloride. The filtrate was evaporated, leaving a viscous brown syrup of the amino-acid hydrochloride. This was dried by heating in a vacuum and esterified with alcoholic hydrogen chloride. The solvent having been distilled, the residue was dissolved in water, basified with sodium carbonate solution, and the *amino-ester* isolated with ether and distilled. The base (7·1 g.), a colourless oil, was collected at 122—128°/0·15 mm., and on redistillation had b. p. 125°/0·13 mm (Found: C, 69·5; H, 9·3. $C_{17}H_{27}O_3N$ requires C, 69·6; H, 9·2%).

3-β-*Diethylaminoethyl*iso*coumaranone.*—The alkylated benzyl cyanide was boiled under reflux for 1¾ hours with 3 parts of glacial acetic acid and 8 parts of hydrobromic acid (*d* 1·5); the solvents were evaporated off under reduced pressure and the semicrystalline paste was dissolved in ethanol, filtered from ammonium bromide, and evaporated. The residual syrup gave a violet ferric chloride colour and a red coloration with benzenediazonium chloride, and consisted presumably of the phenolic amino-acid hydrobromide. The syrup (7·8 g.) was evaporated to dryness with pulverised fused sodium acetate (2·5 g.) and ethanol and then heated at 120° under reduced pressure for 1 hour. On raising the bath temperature to 180°, a yellow oil distilled at 11 mm. and was collected and redistilled. The diethylaminoethyl*iso*coumaranone (4·0 g.), a pale yellow oil, was collected at 166°/10 mm. The *picrate* crystallised from ethanol in yellow, rhombic prisms, m. p. 149° (Found: C, 51·9; H, 4·9; N, 12·0. $C_{14}H_{19}O_2N,C_6H_3O_7N_3$ requires C, 51·9; H, 4·8; N, 12·1%).

2 : 3-*Dimethoxybenzaldehyde.*—From *o*-vanillin (100 g.), sodium hydroxide solution (300 c.c. of 20%), and methyl sulphate (120 g.), following the directions of Rupp and Linck (*Arch. Pharm.*, 1915, **235**, 35), the dimethoxybenzaldehyde (73 g.), b. p. 132°/12 mm., was obtained, and from the mother-liquors unchanged *o*-vanillin (21 g.) was recovered. By using *o*-vanillin (100 g.), 20% sodium hydroxide (450 c.c.), and methyl sulphate (180 g.) the yield was raised to 89 g., *o*-vanillin still being recovered.

2 : 3-*Dimethoxybenzylidenerhodanine.*—2 : 3-Dimethoxybenzaldehyde (84 g.), rhodanine (68 g.) (Julian and Sturgis, *J. Amer. Chem. Soc.*, 1935, **57**, 1127), and glacial acetic acid (340 cc.) were boiled under reflux, and fused sodium acetate (126 g.) was added. The mixture rapidly set to an orange paste. After 30 minutes, addition to water precipitated the *benzylidenerhodanine* (121 g.), which was collected, washed with water, a little ethanol, and finally with ether. The analytical specimen crystallised from ethanol in radiating clusters of fine, lemon-yellow needles, m. p. 209° (Found : C, 51·3; H, 4·2; N, 5·45. $C_{12}H_{11}O_3NS_2$ requires C, 51·3; H, 3·9; N, 5·0%). The product has peculiar electrical properties. It adheres tenaciously to objects, and transference from one vessel to another causes it to scatter in all directions.

2 : 3-*Dimethoxyphenylthiopyruvic Acid.*—The crude benzylidenerhodanine (105 g.) was divided into three batches of 35 g. and each was hydrolysed by heating for 30 minutes in the steam-bath with 15% sodium hydroxide solution (160 c.c.). Cooling in a freezing mixture and rapid addition of cooled 10% hydrochloric acid (160 c.c.) precipitated the *thiopyruvic acid*; it crystallised on standing to a buff-coloured solid, m. p. 118—124°, which was collected and washed with water. (Combined yield 89 g., 99%.) The analytical specimen crystallised from methanol in small, pale yellow needles, m. p. 134° (Found : C, 55·2; H, 5·3. $C_{11}H_{12}O_4S$ requires C, 55·0; H, 5·0%).

2 : 3-*Dimethoxybenzyl Cyanide.*—(A) Hydroxylamine hydrochloride (16·2 g.), dissolved in warm water (15 c.c.), was added to a solution of sodium (5·4 g.) in ethanol (155 c.c.). The sodium chloride having been filtered off, the filtrate was added to the thiopyruvic acid (18 g.) and the mixture boiled under reflux for 20 minutes. The ethanol was removed and the residue taken up in dilute sodium hydroxide solution (39 c.c. of 5%). The sulphur was filtered off, and the filtrate cooled in a freezing mixture and cautiously acidified with 10% hydrochloric acid (39 c.c.). The oximino-acid was precipitated as a viscous yellow syrup which was isolated with ethyl acetate. The crude acid was treated with acetic anhydride (60 c.c.) and heated on the steam-bath for 10 minutes. The acetic anhydride was removed under reduced pressure, and the residue taken up in ether, washed with sodium carbonate solution, dried, and evaporated. The remaining brown oil was distilled, and the cyanide (3·8 g.) collected at 148°/11 mm. (Found : C, 67·4; H, 6·1. Calc. for $C_{10}H_{11}O_2N$: C, 67·8; H, 6·2%).

(B) 2 : 3-Dimethoxybenzyl alcohol (54 g.) (prepared by reduction of the aldehyde with formaldehyde and aqueous methanolic sodium hydroxide; cf. Davidson and Bogert, *J. Amer. Chem. Soc.*, 1935, **57**, 905), dissolved in benzene (100 c.c.), was converted into the bromide with hydrogen bromide, the reaction being carried out in a freezing mixture, and without purification the crude bromide was dissolved in ethanol (240 c.c.) and boiled under reflux for 1½ hours with a solution of potassium cyanide (24 g.) in water (40 c.c.). Water was added, the ethanol evaporated under reduced pressure and the cyanide isolated with ether and distilled. The product (41 g.) was collected at 152°/12 mm. On standing, it crystallised in fine white needles, m. p. 20—21°.

4-*Cyano*-4-(2′ : 3′-*dimethoxyphenyl*)-1-*methylpiperidine.*—An aqueous solution of *N*-methyl-2 : 2′-dichlorodiethylamine hydrochloride (26 g.) was cooled and treated with the calculated amount of sodium hydroxide solution and with saturated potassium carbonate solution, and the free base extracted several times with toluene (total volume, 350 c.c.). The dried (K_2CO_3) toluene layer and 2 : 3-dimethoxybenzyl cyanide (25 g.) were stirred and cooled during the gradual addition of sodamide (10·8 g.). When heat evolution had ceased, the mixture was heated for 1 hour at 70°, 2 hours at 85°, 1 hour at 100°, and finally boiled under reflux for 2 hours. The solution was washed with water and extracted with hydrochloric acid, and the acid layer basified. The liberated amine was isolated with toluene and fractionated in a vacuum. The piperidine (5·6 g.), a colourless oil, was collected at 168—175°/0·2 mm. On keeping, it crystallised in colourless rods, m. p. 96°. The picrate crystallised from much ethanol in microscopic, yellow needles, m. p. 194° (Found : C, 51·8; H, 4·9; N, 14·4. Calc. for $C_{15}H_{20}O_2N_2,C_6H_3O_7N_3$: C, 51·5; H, 4·7; N, 14·3%). Care must be taken to protect the lungs and skin during operations with the dichlorodiethylmethylamine.

4-*Carboxy*-4-(2′ : 3′-*dihydroxyphenyl*)-1-*methylpiperidine.*—The above cyanide (2·2 g.) was boiled under reflux for 2½ hours with hydrobromic acid (20 c.c., *d* 1·5). The acid was evaporated under reduced pressure and the crystalline residue crystallised from ethanol. The *phenylpiperidinecarboxylic acid hydrobromide* (2·2 g.) was obtained in colourless needles, m. p. 272·5° (Found : C, 47·4; H, 5·6; N, 4·5. $C_{13}H_{17}O_4N,HBr$ requires C, 47·0; H, 5·4; N, 4·2%).

7-*Acetoxy*-3-spiro-(N-*methyl*-4′-*piperidyl*)*iso*coumaranone.—The above acid (0·8 g.) was boiled under reflux for 3 hours with acetic anhydride (10 c.c.), acetic acid (3 c.c.), and fused sodium acetate (1·0 g.). The solvents were distilled under reduced pressure, and the residue taken up in water and basified with sodium carbonate solution. The liberated amine was isolated with ether and distilled in bulbs. The *spiro*piperidino*iso*coumaranone (0·32 g.), a colourless glass, was collected at 150°/0·07 mm. It crystallised, on keeping, in colourless rhombic plates. The *oxalate* crystallised from ethanol in clusters of colourless needles, m. p. 196° (Found : C, 55·5; H, 5·5; N, 3·8. $C_{15}H_{17}O_4N,C_2H_2O_4$ requires C, 55·9; H, 5·2; N, 3·8%). The *picrate* crystallised from much ethanol in yellow rhombic platelets, m. p. 250° (decomp.) (Found : C, 48·9; H, 4·2. $C_{15}H_{17}O_4N,C_6H_3O_7N_3,H_2O$ requires C, 48·3; H, 4·2%).

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