17. *Experiments in the Piperidine Series. Part III.*

By R. M. Anker and A. H. Cook.

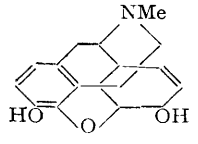
3-Carbethoxy-1-methyl-4-piperidone and the corresponding 3-cyano compound have been condensed with resorcinol to give isomeric 3 : 4-3′ : 4′-tetrahydropyridocoumarins (V, VI) which were converted into *gem*-dimethylpyran derivatives (VII, VIII). 7-Alkyl derivatives of (VI) and (VIII) were obtained by using orcinol or olivetol in place of resorcinol but similar reactions with 4-*n*-hexylresorcinol were unsuccessful. The 7-amyl analogue of (VIII) was reduced to the hexahydropyrido compound which was of special interest as a possible analgesic in view of a skeletal similarity to hexahydrocannabinol and a spatial similarity to morphine.

Consideration of the structural formulæ of morphine (I) and dolantin (II) suggested that their analgesic action might have been conditioned at least in part by the feature, common to both, of an aromatic grouping in the 4-position of a piperidine ring and maintained in two-dimensional angular relationship to it. In dolantin the relationship may be assumed because of the bulk of the *tert.*-ester group preventing free rotation, and it is possibly significant that active piperidines related to dolantin (Schaumann, *Arch. f. exp. Path. Pharm.*, 1940, **196**, 109) contain, in addition to the 4-aryl group, a large ester or ketone grouping in the 4-position which may have a similar function. In morphine the relationship is necessitated by the additional rings. Similar piperidines which would be constrained to possess a rigid three-dimensional structure can be evolved, the synthesis of which would help to test the correctness of this hypothesis. For example, by discarding atomic groupings in (I) which are probably unessential for analgesic action, the structure (III) can be devised with the postulated angularity; the lactone (IIIa) would be of this type. Consideration was given to this structure and its synthesis during the present work, but as experiments in a rather similar direction have already been reported (Bergel, Haworth, Morrison, and Rinderknecht, *J.*, 1944, 261), their prosecution has been discontinued. It is a short step, however, to the related but still angular structure (IV), and experiments towards this objective are now reported. Additional interest is lent to the ring-structure present in (IV) by the occurrence of a sterically similar system in hexahydrocannabinol, and the synthetic route adopted in the present work was analogous to one which has been extensively used in the cannabinol field.

Ethyl 1-methyl-4-piperidone-3-carboxylate hydrochloride was condensed with resorcinol in presence of concentrated sulphuric acid and phosphorus oxychloride. The pseudo-acidic product was analytically in agreement with the structure (V) and it contained a free hydroxyl group giving a *monomethyl ether*. The orientation (V), rather than the alternative (VI), seemed correct, as the compound failed to give a positive indophenol reaction (Gibbs, *J. Biol. Chem.*, 1927, **72**, 649).

A previous communication (Cook and Reed, *J.*, 1945, 399) described the preparation of 4-imino-3-cyano-1-methylpiperidine and 3-cyano-1-methyl-4-piperidone and, since it was more convenient to obtain these than the ester used above, their reaction with resorcinol was examined. The former piperidone derivative could not be condensed with resorcinol satisfactorily, but the latter gave a *compound* isomeric with (V) above. There could be little doubt that this compound was also a coumarin for the preparation of coumarins from resorcinols and β-ketonitriles is well known (see, for example, Pechmann, *Ber.*, 1883, **16**, 2126; Baker, *J.*, 1927, 2898); moreover a xanthone structure, the only reasonable alternative, was disproved by lactonic properties and the results of reaction with methylmagnesium iodide (see below). Although decomposing at about the same temperature as its isomeride, the new compound showed by contrast with (V) a strongly positive indophenol reaction and was therefore assumed to contain a hydroxyl with a free *p*-position. It yielded a characteristic

methyl ether, distinct from that of (V), but as the light absorption characteristics of the parent condensation products were identical, the same ring system must be postulated for them, and structure (VI) is assigned to the second product.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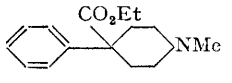
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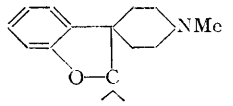
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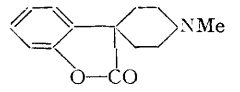
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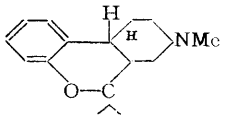
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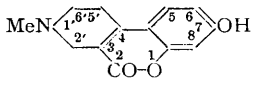
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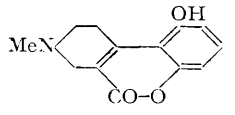
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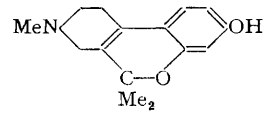
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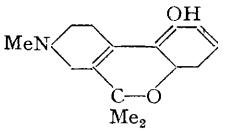
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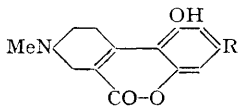
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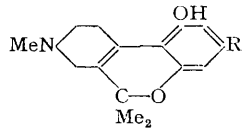
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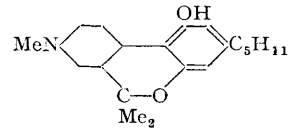
(XI.)

Compounds (V) and (VI) may assume an angular configuration by migration of the isolated double linking. but they need not necessarily do so and indeed their light absorption indicates, as would be expected on other grounds, that this does not occur. Attempts to impose this angular restriction on the molecule by catalytic reduction with platinum at up to 7 atm. were, however, unsuccessful. Furthermore, experiments to obtain the desired hydro-derivatives or isomerides thereof by condensation of the substituted piperidones with dihydroresorcinol, 5-methyl-, or 5 : 5-dimethyl-dihydroresorcinol, or dihydro-orcinol were fruitless. The methods of reduction were restricted in view of the desirability of *cis* reduction, for *trans* isomerides of type (IV) would be virtually uniplanar. Each of the coumarins was treated with excess of methylmagnesium iodide to obtain the *gem*-dimethyl pyran derivatives (VII), (VIII) analogous to tetrahydrocannabinol. Although some of these and the following compounds were tested for analgesic activity by the courtesy of I.C.I. Ltd. (Dyestuffs Division), there was no notable response, but it still appeared desirable to insert alkyl residues into the aromatic ring as have been found favourable in the cannabinol structures.

In the first place, orcinol condensed smoothly with the piperidone ester hydrochloride; the coumarin gave a positive indophenol reaction and had therefore the anticipated structure (IX) (R = Me). This was also converted into the gem-*dimethylpyran derivative* (X) (R = Me). With these models therefore olivetol (Anker and Cook, *J.*, 1945, 311) was similarly condensed to give the lactone (IX) (R = C_5H_{11}) and thence converted into the gem-*dimethylpyran derivative* (X) (R = C_5H_{11}), first obtained as its *hydriodide*. Several attempts were made to hydrogenate the isolated double bond in the earlier *gem*-dimethyl compounds, but these were unsuccessful, perhaps because of the low solubility of the compounds. The compound (X) (R = C_5H_{11}), however, differed markedly in its physical nature from its predecessors and it was fairly readily hydrogenated. The *dihydro-compound*, characterised as its *acetate*, still showed benzenoid light absorption, and was therefore formulated as (XI), having a necessarily angular structure if it be assumed, as is almost certainly the case, that the use of platinum results in *cis*-reduction.

No homogeneous product was obtained from the condensation of phloroglucinol with the piperidone ester hydrochloride using a mixture of sulphuric acid and phosphorus oxychloride. Prior to the conclusion of the synthesis with olivetol an attempt was made to utilise 4-*n*-hexylresorcinol in a similar manner. The only product isolated from its reaction with the piperidone ester hydrochloride in a sulphuric acid medium was a crystalline *compound* $C_{22}H_{31}O_5NS$; the constitution of this material was not elucidated and this part of the project was abandoned.

Experimental.

A mixture of ethyl *N*-methyl-4-piperidone-3-carboxylate hydrochloride (McElvain, *J. Amer. Chem. Soc.*, 1924, **46**, 1721) (5·5 g.) with resorcinol (3·5 g.) was treated with concentrated sulphuric acid (9 c.c.) in small portions with stirring and cooling and the solution kept for 24 hours; occasionally a sulphate separated after some hours. The mixture was poured into water, neutralised with a slight excess of sodium bicarbonate, and the precipitated mixture of organic and inorganic products collected and extracted (Soxhlet) with chloroform. *7-Hydroxy-3 : 4-(1′-methyl-1′ : 2′ : 5′ : 6′-tetrahydro-3′ : 4′-pyrido)-coumarin* (V) (yield, 25%) separated from the extract. It could be crystallised with some loss from ethanol, when it formed small pale yellow prisms, m. p. 220° (decomp.) (Found : C, 67·45; H, 5·95. $C_{13}H_{13}O_3N$ requires C, 67·5; H, 5·6%); it gave no indophenol reaction. Light absorption (ethanol) · max. at λ = 217, 324 mμ; $E^{1\%}_{1cm.}$ = 740, 730. The yield was not improved when phosphorus oxychloride or mixtures with sulphuric acid were used; it deteriorated when the compounds were brought into reaction in any order differing from that above. Methylation of (V) in ether with diazomethane was slow, and a compound of indeterminate constitution was obtained in 30% yield after 10 days at room

temperature; after crystallisation from ethyl acetate it had m. p. 155° (decomp.) (Found: C, 74·2; H, 6·2%). Methylation of (V) was, however, rapid in methanol with ethereal diazomethane, though the reaction was complex. Fractional crystallisation of the mixture from ethyl acetate or methyl cyanide gave three apparently pure materials (described in order of decreasing solubility): the *methyl ether*, which separated from ethyl acetate–ligroin in stout prisms, m. p. 134° (Found: C, 68·65; H, 6·2. $C_{14}H_{15}O_3N$ requires C, 68·55; H, 6·1%); the compound, m. p. 155° (decomp.), obtained previously with diazomethane in ether; and a *compound* which separated from ethanol in pale yellow needles, m. p. 210° (decomp.) (Found: C, 58·5; H, 6·7; N, 4·45. $C_{15}H_{21}O_6N$ requires C, 58·4; H, 6·7; N, 4·5%). Compound (V) (4·2 g.) in pyridine (45 c.c.) was slowly added to a Grignard reagent prepared from magnesium (4·5 g.) and methyl iodide (8 c.c.) in anisole (50 c.c.). After 2 hours on the steam-bath the dark blue product was poured into water (200 c.c.) and acidified with concentrated hydrochloric acid (100 c.c.), residual solid (0·5 g.) being rejected. Anisole was removed in steam, and after addition of sodium carbonate (60 g.) pyridine was likewise removed. The solid was extracted with boiling ethanol (3 lots of 100 c.c.) and the extract concentrated to give the pyran derivative (1·8 g.); *7-hydroxy*-3 : 4-(1′-*methyl*-1′ : 2′ : 5′ : 6′-*tetrahydro*-3′ : 4′-*pyrido*)-2 : 2-*dimethyl*-α-*chromen* (VII) separated from ethanol (charcoal) as a pale yellow crystalline powder, m. p. 239° (decomp.) (Found: C, 73·4; H, 7·85. $C_{15}H_{19}O_2N$ requires C, 73·45; H, 7·75%).

4-Imino-3-cyano-1-methylpiperidine (Cook and Reed, *J.*, 1945, 399) (20 g.) was warmed with water (10 c.c.) and concentrated hydrochloric acid (30 c.c.) to effect solution and the whole evaporated to dryness. To it was added resorcinol (16 g.), concentrated sulphuric acid (70 c.c.) and, with stirring, phosphorus oxychloride (50 c.c.). After standing 24 hours, the mixture was poured on to ice and neutralised with sodium bicarbonate. On standing, part of the product separated, and a little more was obtained by extracting the dried salt mixture with pyridine. *5-Hydroxy*-3 : 4-(1′-*methyl*-1′ : 2′ : 5′ : 6′-*tetrahydro*-3′ : 4′-*pyrido*)-*coumarin* (VI) separated from ethanol in small prisms, m. p. 223°, which gave a strong indophenol reaction (Found: C, 67·9; H, 5·6. $C_{13}H_{13}O_3N$ requires C, 67·5; H, 5·6%); light absorption (ethanol): max. at 218, 324 mμ, E_1^1 = 770, 750. The same compound (0·4 g.) was obtained from 3-cyano-1-methyl-4-piperidone hydrochloride (Cook and Reed, *loc. cit.*) (1·6 g.) and resorcinol (1·1 g.) under similar conditions. Treatment with excess of ethereal diazomethane for 3 days gave the corresponding *methyl ether* in 30% yield; it crystallised from ethanol in needles, m. p. 215°, which depressed the m. p. of the parent compound (Found: C, 68·45; H, 5·9. $C_{14}H_{15}O_3N$ requires C, 68·55; H, 6·1%). Compound (VI) (5 g.) in pyridine (50 c.c.) was added to a Grignard reagent prepared from magnesium (4·3 g.), methyl iodide (10·5 c.c.) and anisole (75 c.c.), at 40° and reaction completed at 65—85° for 16 hours and finally at 100° for 2 hours. A little methanol, 2N-sulphuric acid (100 c.c.) and water (350 c.c.) were added and the solid collected. It was dissolved in 4N-hydrochloric acid (300 c.c.), anisole removed in steam, and the base precipitated with sodium bicarbonate, a little pyridine being then removed in steam. The solid (2·4 g.) was collected, dried and sublimed in a high vacuum at 150° when *5-hydroxy*-3 : 4-(1′-*methyl*-1′ : 2′ : 5′ : 6′-*tetrahydro*-3′ : 4′-*pyrido*)-2 : 2-*dimethyl*-α-*chromen* (VIII) (0·5 g.) was collected in microscopic prisms, m. p. 257° (Found: C, 73·0; H, 7·8. $C_{15}H_{19}O_2N$ requires C, 73·5; H, 7·8%).

Orcinol hydrate (5 g.), mixed with ethyl *N*-methyl-4-piperidone-3-carboxylate hydrochloride (7 g.), was treated with cooling with sulphuric acid (16 c.c.) and then with phosphorus oxychloride (6 c.c.). After 24 hours the mixture was poured into excess aqueous sodium bicarbonate and the dried precipitate extracted (Soxhlet) with chloroform. The crude material (5·1 g.) crystallised from butanol or much methyl cyanide and *5-hydroxy*-3 : 4-(1′-*methyl*-1′ : 2′ : 5′ : 6′-*tetrahydro*-3′ : 4′-*pyrido*)-*7-methylcoumarin* (IX, R = Me) separated in small cubes, m. p. 232° (decomp.) (Found: C, 68·85; H, 6·2. $C_{14}H_{15}O_3N$ requires C, 68·55; H, 6·1%). Compound (IX, R = Me) (4·9 g.) in pyridine (45 c.c.) was slowly added to methylmagnesium iodide (magnesium, 4·5 g., methyl iodide, 11 c.c.) in anisole (70 c.c.) and reaction completed at 65° for 16 hours. 4N-Sulphuric acid was added and anisole removed by distillation in steam; pyridine was similarly removed after adding sodium carbonate and the residue collected. The residue (4 g.) crystallised from butanol and *5-hydroxy*-3 : 4-(1′-*methyl*-1′ : 2′ : 5′ : 6′-*tetrahydro*-3′ : 4′-*pyrido*)-2 : 2 : 7-*trimethyl*-α-*chromen hydriodide* separated in rhombic prisms, m. p. 267° (decomp.); it was finally purified by sublimation in high vacuum (Found: C, 49·55; H, 6·0. $C_{16}H_{22}O_2NI$ requires C, 49·6; H, 5·7%).

An intimate mixture of anhydrous olivetol (Anker and Cook, *J.*, 1945, 311) (3·6 g.) and ethyl *N*-methyl-4-piperidone-3-carboxylate hydrochloride (4·5 g.) was treated slowly with concentrated sulphuric acid (10 c.c.) and then with phosphorus oxychloride (2 c.c.) and left for 24 hours. The mixture was decomposed with water and sodium bicarbonate and the whole thoroughly extracted with chloroform. Evaporation of the extract gave *5-hydroxy*-3 : 4-(1′-*methyl*-1′ : 2′ : 5′ : 6′-*tetrahydro*-3′ : 4′-*pyrido*)-7-n-*amylcoumarin* (IX) (R = C_5H_{11}), which separated from ethyl acetate in prisms, m. p. 170° (yield, 3·7 g.) (Found: C, 71·5; H, 7·65; N, 4·55. $C_{18}H_{23}O_3N$ requires C, 71·75; H, 7·7; N, 4·65%); it gave a strongly positive indophenol reaction. Compound (IX, R = C_5H_{11}) (5 g.) in warm anisole (150 c.c.) was added dropwise to a Grignard reagent prepared from magnesium (3·3 g.), methyl iodide (7·5 c.c.) and anisole (45 c.c.); heat was evolved and the reaction was completed at 85° for 2 hours. Anisole was removed in steam after adding water and a large volume of 4N-sulphuric acid; the dried mixture of salts was extracted thoroughly with ether leaving 5-hydroxy-3 : 4-(1′-methyl-1′ : 2′ : 5′ : 6′-tetrahydro-3′ : 4′-pyrido)-2 : 2-dimethyl-7-*n*-amyl-α-chromen (X, R = C_5H_{11}) as its *hydriodide* (6·5 g.) which separated from ethanol in rectangular plates, m. p. 268° (Found: C, 54·25; H, 6·65. $C_{20}H_{30}O_2NI$ requires, C, 54·2; H, 6·85%). On shaking the hydriodide with aqueous sodium bicarbonate and chloroform the free *base* (X, R = C_5H_{11}) was extracted; it separated from ethyl acetate in octahedra, m. p. 169° (Found: C, 76·0; H, 9·0. $C_{20}H_{29}O_2N$ requires C, 76·2; H, 9·2%).

Compound (X) (R = C_5H_{11}) (4 g.) in acetic acid (50 c.c.) was hydrogenated over Adams' catalyst (0·2 g.) at 13 atm.; the theoretical quantity of hydrogen was absorbed after 90 minutes. Removal of solvent under reduced pressure gave the *acetate* of (XI), which separated from ethyl acetate in rhombic plates (1·2 g.), m. p. 162° (Found: C, 69·9; H, 9·35. $C_{22}H_{35}O_4N$ requires C, 70·0; H, 9·4%); light absorption (ethanol): max. at λ = 280 mμ, E_1^1 = 34·3. The free base was obtained by dissolving the acetate in ethanol (10 c.c.), pouring into 10% aqueous sodium hydroxide (30 c.c.) and introducing an excess of carbon dioxide. *5-Hydroxy*-3 : 4-(1′-*methyl*-1′ : 2′ : 5′ : 6′-*tetrahydro*-3′ : 4′-*pyrido*)-2 : 3-*dimethyl*-7-n-*amyl*-α-*chromen* (XI) crystallised in pale yellow microscopic prisms, m. p. 147°, from ligroin (Found: C, 75·9; H, 9·5. $C_{20}H_{31}O_2N$ requires C, 75·7; H, 9·8%).

A mixture of 4-*n*-hexylresorcinol (8·5 g.), ethyl *N*-methyl-4-piperidone-3-carboxylate (10 g.), sulphuric acid (22 c.c.) and phosphorus oxychloride (7 c.c.), after standing for some hours, was poured into water. The *product* (13 g.) after separating from glycol monomethyl ether had m. p. 218°; it contained N and S but no SO_4 ions (Found: C, 62·7; H 7·35; N, 2·95, 3·35. $C_{22}H_{31}O_5NS$ requires C, 62·7; H, 7·4; N, 3·3%).

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