282. *The Structure of Tazettine. A Synthesis of the Emde Degradation Product derived from Tazettamide.*

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The compound (VI; R = OMe, R′ = H) has been synthesised by a stereospecific route. Its identity with the Emde degradation product of an amine derived from tazettamide has provided further confirmation of the detailed structure of tazettine.

We have shown earlier [1] that tazettine, an alkaloid occurring in many plants of the *Amaryllidaceae*, can best be represented by the formula (I; R = OMe, R′ = H, R″ = Me, R‴ = OH). The degradative sequence leading to (VI; R = OMe, R′ = H) (see Chart 1) started from tazettamide (II; R = OMe, R′ = H, R″ = Me), a product of the manganese dioxide oxidation of tazettine.[2]

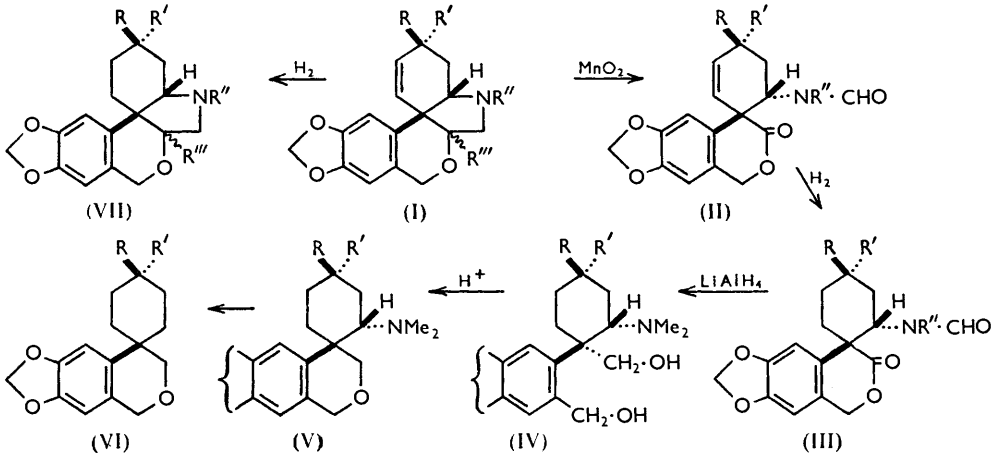
We have recently found that two further compounds are formed during the initial oxidation. One of them is 6-*p*-hydroxyphenylpiperonaldehyde, as shown by synthesis, and the other is *N*-demethyltazettamide (II; R = OMe, R′ = R″ = H), identical with the product obtained by manganese dioxide oxidation of nortazettine (I; R = OMe, R′ = R″ = H, R‴ = OH) which in turn was prepared by alkaline rearrangement [3] of hæmanthidine.[4] Such an elimination of a methyl group attached to nitrogen has also been demonstrated by Henbest and Thomas.[5]

We have further noted that when tazettamide was reduced catalytically over palladium–charcoal, demethoxydihydrotazettamide (III; R = R′ = H, R″ = Me) was produced

[1] Ikeda, Taylor, Tsuda, Uyeo, and Yajima, *J.*, 1956, 4749.
[2] Highet and Wildman, *Chem. and Ind.*, 1955, 1159.
[3] Fales, Highet, Uyeo, and Wildman, unpublished observation.
[4] Uyeo, Fales, Highet, and Wildman, *J. Amer. Chem. Soc.*, 1958, **80**, 2590.
[5] Henbest and Thomas, *J.*, 1957, 3032.

as a by-product which can be satisfactorily separated from the major product, dihydrotazettamide (III; R = OMe, R′ = H, R″ = Me), only by chromatography. Re-examination of the hydrogenation products of tazettine and deoxytazettine (I; R = OMe, R′ = R‴ = H, R″ = Me) has afforded similar results, *viz.*, that demethoxydihydrotazettine (VII; R = R′ = H, R″ = Me, R‴ = OH) and demethoxydeoxydihydrotazettine (VII; R = R′ = R‴ = H, R″ = Me), respectively, were invariably accompanied by dihydrotazettine (VII; R = OMe, R′ = H, R″ = Me, R‴ = OH) and deoxydihydrotazettine (VII; R = OMe, R′ = R‴ = H, R″ = Me), respectively.

Chart I.



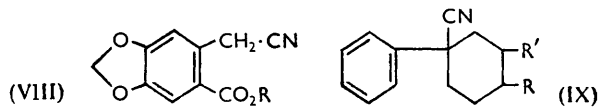
An allylic acetoxyl group was found to be eliminated even more readily by hydrogenation. Thus diacetyltazettinol (I; R = R‴ = OAc, R′ = H, R″ = Me) or diacetyl-*iso*tazettinol (I; R = H, R′ = R‴ = OAc, R″ = Me) over palladium–charcoal in acidic solution gave the same products, acetyldemethoxytazettine (I; R = R′ = H, R″ = Me, R‴ = OAc) and demethoxydihydrotazettine (VII; R = R′ = H, R″ = Me, R‴ = OH), but monoacetyl*iso*tazettinol (I; R = H, R′ = OAc, R″ = Me, R‴ = OH) was converted into demethoxytazettine (I; R = R′ = H, R″ = Me, R‴ = OH), subsequent hydrogenation of which over platinic oxide furnished its dihydro-derivative (VII; R = R′ = H, R″ = Me, R‴ = OH). Hydrogenolysis also occurred with platinic oxide since diacetyl-*iso*tazettinol afforded dihydro*iso*tazettinol, demethoxydihydrotazettine, and demethoxydeoxydihydrotazettine (VII; R = R′ = R‴ = H, R″ = Me). Because of the above type of side reaction, the Emde product (VI; R = OMe, R′ = H) derived from dihydrotazettamide was sometimes contaminated by its demethoxylated derivative (VI; R = R′ = H), unless chromatographically purified dihydrotazettamide was used as a starting material.

For the synthesis of compounds related to (VI), the most logical starting material seemed to be the ester (VIII; R = Me) which was readily obtained from the known acid [6] (VIII; R = H). Attempts to condense the ester with methyl β-bromopropionate or β-bromopropionitrile in the presence of sodium amide or sodium hydride in a variety of solvents under various conditions were fruitless. The model compound, benzyl cyanide, on the other hand, readily condensed in good yields with the above reagents in toluene in the presence of excess of sodium amide to afford in one step the compounds (IX; R = NH, R′ = CN; and R = O, R′ = CO_2Me, respectively), both of which were convertible into 4-cyano-4-phenyl*cyclo*hexanone (IX; R = O, R′ = H) by strong acid.

[6] Edwards, *J.*, 1926, 813.

Michael condensation of the ester (VIII; R = Me) with acrylonitrile or methyl acrylate also failed and hence the use of this compound as the starting material was abandoned.

Next, we tried unsuccessfully to condense 3 : 4-methylenedioxybenzyl cyanide (X) with β-bromopropionitrile or methyl β-bromopropionate in the presence of sodium amide



(VIII) (IX)

or sodium hydride. On the other hand, the compound (X) reacted readily with acrylonitrile or methyl acrylate in the presence of alkaline reagents such as sodium methoxide or Triton B, yielding γ-cyano-γ-(3 : 4-methylenedioxyphenyl)pimelonitrile (XI) or the analogous dimethyl ester (XII; R = Me). The best yield of the latter (XII; R = Me) was obtained by the use of Triton B in boiling *tert.*-butyl alcohol. Hydrolysis of the trinitrile (XI) in concentrated hydrochloric acid furnished an acid shown to be an imidocarboxylic acid (XIII; R = H) from the infrared spectrum and its non-identity with the acid (XII; R = H) obtained by saponification of the ester (XII; R = Me). This was not surprising since Campbell [7] observed that γ-cyano-γ-phenylpimelonitrile was smoothly converted into α-2-carboxyethyl-α-phenylglutarimide by treatment with sulphuric acid and Mariella, Clutter, and Ebner [8] showed that γ-cyano-γ-ethoxycarbonylpimelonitrile and γγ-dicyanopimelonitrile, among other compounds, gave with concentrated hydrochloric acid α-ethoxycarbonyl-α-2-carboxyethylglutarimide and 2 : 8-diaza*spiro*-[5 : 5]hendecane-1 : 3 : 7 : 9-tetraone [3 : 3'-*spiro*bi(piperidine-2 : 6-dione)], respectively. The acid (XIII; R = H) gave with diazomethane an *N*-methyl ester (XIII; R = Me), as proved by analysis and by the absence of NH absorption in the 3 μ region. The ester (XIII; R = Me) thus formed was converted into an amido-ketone (XIV; R = H), albeit in a low yield, by treatment with sodium methoxide followed by strong acid, as a result of methanolysis of the imide linkage to an amide diester followed by cyclisation under Dieckmann conditions and decarboxylation of the resulting β-keto-ester (XIV; R = CO_2Me). An attempt to convert the acid (XIII; R = H) into the ketone (XV; R = H) under the Blanc conditions by first refluxing it with acetic anhydride and then heating it at 200° under reduced pressure gave only a minute amount of the desired product which showed correct analytical values and infrared absorption bands at 2252 (CN) and 1724 $cm.^{-1}$ (CO).

The same ketone (XV; R = H) was made in far better yield by Dieckmann cyclisation of the diester (XII; R = Me) followed by decarboxylation in a strong acid. Formation of a diethyl ketal (XVIII; R = Et) of the ketone as a by-product was sometimes observed when ethanol was used as a solvent.

The trinitrile (XI) underwent a Ziegler cyclisation in good yield, but in a preliminary experiment difficulties were encountered in saponifying and decarboxylating the product (XVI) to the ketone (XV; R = H) and hence this compound was not further investigated. The cyano-ketone (XV; R = H) was reduced with sodium borohydride in methanol to 4-cyano-4-(3 : 4-methylenedioxyphenyl)*cyclo*hexanol (XVII). The experimental conditions used were such that we were able to isolate only one of the possible isomers: the bulkiness of the aryl group probably determines the preferred conformation and, since the reduction method would be expected to yield an equatorial hydroxyl group, this would be expected to be in *trans*-position to the aryl residue, as shown in (XVII). The reduction gave the dimethyl ketal (XVIII; R = Me) as by-product: no other analogous case is known to us. This ketal exhibited no absorption in the 3 μ region but there was a strong absorption at about 1100 $cm.^{-1}$ and further it regenerated the parent ketone when heated with acid.

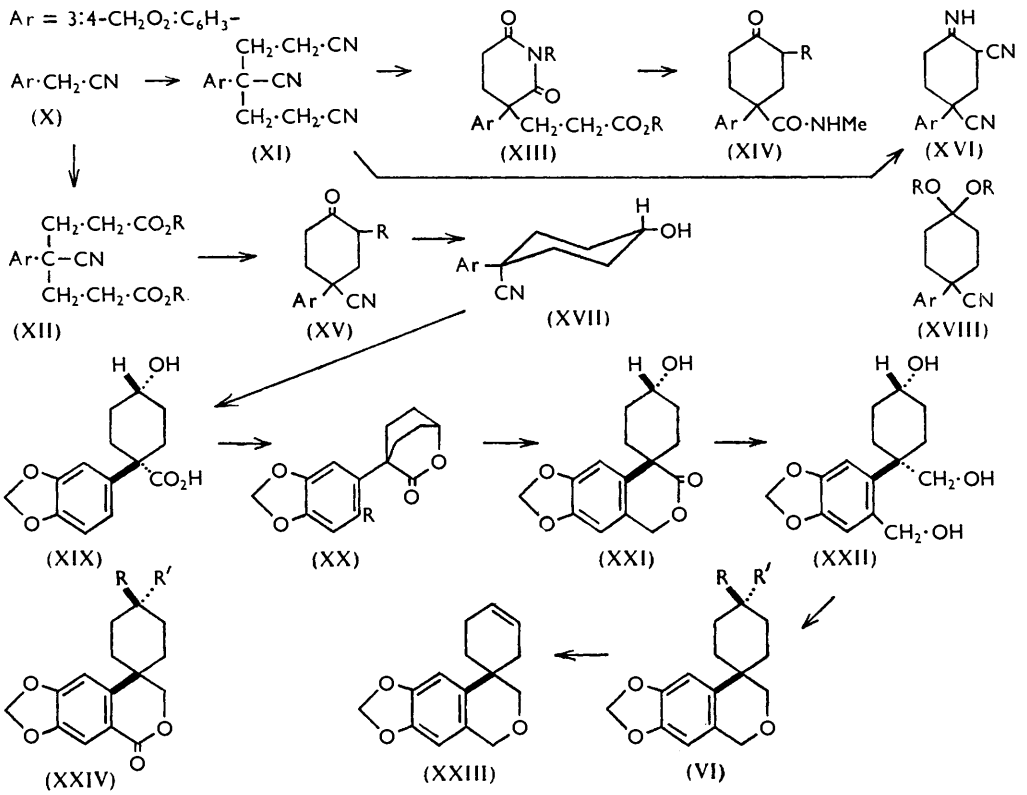
The hydroxy-nitrile (XVII) was then hydrolysed with potassium hydroxide in boiling

[7] Campbell, *J.*, 1954, 1377; cf. Hey and Nagdy, *J.*, 1954, 1204; Blair and Hey, *J.*, 1957, 2921.
[8] Mariella, Clutter, and Ebner, *J. Org. Chem.*, 1955, **20**, 1702.

diethylene glycol, to give the hydroxy-acid (XIX) which with acetic anhydride, in agreement with the stereochemical assignment, passed into the lactone (XX; R = H) (>C=O band at 1739 cm.$^{-1}$). The hydroxy-acid was regenerated on alkaline hydrolysis of the lactone.

A methylene group was then introduced into the position 6 of the aryl nucleus by heating the hydroxy-acid (XIX) or the lactone (XX; R = H) with paraformaldehyde in

Chart 2.



concentrated hydrochloric acid, a chloromethyl compound (XX; R = CH_2Cl) being formed. Alkaline hydrolysis of this, followed by relactonisation, afforded a compound, $C_{15}H_{16}O_5$, for which two alternative structures (XXI) or (XX; R = CH_2OH) were possible: the energetically more stable (XXI) was preferred and in agreement the lactone band at 1724 cm.$^{-1}$ was at a slightly longer wavelength than for the lactones described above. The hydroxy-lactone (XXI) was reduced with lithium aluminium hydride to a triol (XXII) which readily underwent acid-catalysed cyclisation to the hydroxy-ether (VI; R = H, R′ = OH).

If our ideas concerning the structure of tazettine were correct, the same compound was theoretically derivable from *iso*tazettinol by the degradative sequence sketched in Chart 1. Hydrogenation of *iso*tazettinol (I; R = H, R′ = R‴ = OH, R″ = Me) gave dihydro-*iso*tazettinol (VII; R = H, R′ = R‴ = OH, R″ = Me) which was oxidised with manganese dioxide to give an amide-lactone (III; R = H, R′ = OH, R″ = Me). This was converted smoothly into the ether (VI; R = H, R′ = OH) in a manner similar to that employed for the analogous compound (III; R = OMe, R′ = H, R″ = Me). The product thus obtained was, as expected, optically inactive and identical with the synthetic compound.

The synthetic compound (VI; R = H, R′ = OH) was converted into the degradation

product of tazettine by way of the *O*-toluene-*p*-sulphonate which underwent S_N2 replacement with methoxide ion, the expected olefinic by-product (XXIII) being also formed.

Experimental

Ultraviolet absorption spectra were determined for 95% ethanol solutions, and infrared spectra were taken on Nujol mulls unless otherwise stated.

Isolation of Hippeastrine and Hæmanthidine from Lycoris radiata.—The mother-liquor (33 g.) of an extract of *Lycoris radiata* from which most of the lycorine, lycorenine, homolycorine, tazettine, lycoramine, galanthamine, and phenolic alkaloids had been separated, was dissolved in 5% hydrochloric acid (1 l.), washed with chloroform, brought to pH 7·2 with potassium carbonate, and extracted with ethyl acetate (1·5 l.). The dried extract was evaporated to dryness and the residue (7 g.) crystallised from ethanol to give tazettine (2 g.). The mother-liquor from the crystallisation of tazettine was chromatographed in benzene over alumina (50 g.), yielding the following fractions: (i) Benzene eluate (500 ml.), an oil (2 g.). (ii) Ethyl acetate–benzene eluate (1 : 19, 500 ml.; and 1 : 9, 500 ml.), tazettine (0·8 g.). (iii) Ethyl acetate–benzene (1 : 1) eluate (1 l.), hippeastrine [9] (1 g.), prisms (from acetone), m. p. 214—215°, $[\alpha]_D$ +147° (*c* 0·9 in EtOH) {lit.,[10] m. p. 214—215°, $[\alpha]_D$ +160° (in $CHCl_3$)}, $\lambda_{max.}$ 227, 268, and 308 mμ (log ε 4·51, 3·86, and 3·89) (Found: C, 64·6; H, 5·4; N, 4·4. Calc. for $C_{17}H_{17}O_5N$: C, 64·8; H, 5·4; N, 4·4%); a mixed m. p. and comparison of the infrared spectra completed the identification of this alkaloid. (iv) A fraction eluted with ethyl acetate (1·5 l.) was taken up into chloroform; a small portion (20 mg.) remained undissolved. The solution was evaporated to dryness and the residue crystallised from ethyl acetate to furnish hæmanthidine (0·2 g.), m. p. 187—189°, $[\alpha]_D$ −43° (*c* 0·88 in $CHCl_3$) {lit.,[11] m. p. 189—190°, $[\alpha]_D$ −41° (in $CHCl_3$)}, $\lambda_{max.}$ 241 and 293 mμ (log ε 3·46 and 3·62) (Found: C, 63·8; H, 5·9; N, 4·4. Calc. for $C_{17}H_{19}O_5N$: C, 64·3; H, 6·0; N, 4·4%); the m. p. was undepressed on admixture with the authentic alkaloid and the infrared spectrum was identical with that of hæmanthidine; the picrate formed yellow needles, m. p. 207—208° (decomp.) [lit.,[11] m. p. 208° (decomp.)].

Nortazettamide from Hæmanthidine.—Hæmanthidine (0·16 g.) in 10% methanolic sodium methoxide (5 ml.) was heated under reflux for 40 min. The methanol was evaporated, and the residue in water (20 ml.) was extracted with chloroform after saturation with ammonium chloride. The chloroform extract afforded nortazettine (0·15 g.) as a gum which was characterised as its hydrochloride, needles, m. p. 198—200° (lit.,[3] m. p. 197—201°) (from ethanol–acetone). Nortazettine (90 mg.) in chloroform (12 ml.) was stirred with manganese dioxide (1 g.) at room temperature for 15 hr. The manganese dioxide was filtered off and washed with chloroform and the combined filtrate and washings were shaken with 5% hydrochloric acid and water and concentrated to dryness. Crystallisation of the residue from ethanol gave nortazettamide (II; R = OMe, R′ = R″ = H) (50 mg.) as prisms, m. p. 180—181° from ethanol.

Manganese Dioxide Oxidation of Tazettine.—Tazettine (1·3 g.) was oxidised with manganese dioxide and worked up as described previously,[1] to afford a crude product which was chromatographed in benzene over alumina (10 g.). Tazettamide (0·45 g.) was eluted with benzene (50 ml.) and crystallised from ethanol, then having m. p. 174°. Further elution with the same solvent (450 ml.) furnished *nortazettamide* (0·15 g.), prisms (from ethanol), m. p. 179—181°, $[\alpha]_D$ +250° (*c* 1·0 in EtOH), $\lambda_{max.}$ 245 and 290 mμ (log ε 3·66 and 3·76), $\nu_{max.}$ 3125 (NH), 1748 (lactone), 1661 and 1618 (amide), and 1555 cm.$^{-1}$ (NH) in Nujol mull and 3413 (NH), 1732 (lactone), and 1687 cm.$^{-1}$ (amide) in chloroform (Found: C, 61·7; H, 5·2; N, 4·3; OMe, 9·4. $C_{17}H_{17}O_6N$ requires C, 61·6; H, 5·2; N, 4·2; OMe, 9·4%). The m. p. was not depressed on admixture with a sample derived from nortazettine. Further elution with benzene (1 l.) gave 6-p-*hydroxyphenylpiperonaldehyde* (55 mg.), plates, m. p. 170—172° (from dilute ethanol), $\lambda_{max.}$ 245, 270, and 330 mμ (log ε 4·31, 4·17, and 3·79), $\nu_{max.}$ 3225—3125 (OH), 1653 (CO), and 1616 cm.$^{-1}$ (benzene) (Found: C, 69·4; H, 4·1. $C_{14}H_{10}O_4$ requires C, 69·4; H, 4·2%).

The aldehyde, with acetic anhydride in pyridine, gave an *acetate*, needles, m. p. 164—165° after crystallisation from dilute ethanol (Found: C, 67·0; H, 4·3. $C_{16}H_{12}O_5$ requires C, 67·6;

[9] We are indebted to Dr. W. C. Wildman, National Institutes of Health, Maryland, U.S.A., for authentic samples of hippeastrine and hæmanthidine.

[10] Boit, *Chem. Ber.*, 1956, **89**, 1129.

[11] *Idem, ibid.*, 1954, **87**, 1339.

H, 4·3%), and afforded on reduction with sodium borohydride in methanol 2-*p*-hydroxyphenyl-4 : 5-methylenedioxybenzyl alcohol, m. p. and mixed m. p. 186—188°.[1]

Hydrogenation of Tazettine.—Tazettine (1·65 g.) in ethanol (15 ml.) and acetic acid (7 ml.) was hydrogenated in the presence of platinum oxide (0·4 g.). After 5 hr. the solution was filtered, evaporated and extracted with ether after basification with aqueous ammonia. The ethereal extract was concentrated and the residue crystallised from ether to give dihydrotazettine[12] (0·97 g.), prisms, m. p. and mixed m. p. 165—167°. Evaporation of the mother-liquor and chromatography in benzene over alumina gave *demethoxydihydrotazettine* (VII; R = R′ = H, R″ = Me, R‴ = OH) (0·19 g.), prisms, m. p. 168—169° (from ether), $[\alpha]_D$ +22·4° (*c* 0·3 in $CHCl_3$) (Found: C, 67·5; H, 7·1; OMe, 0. $C_{17}H_{21}O_4N$ requires C, 67·3; H, 7·0%). The *picrate* formed needles, m. p. 200—202° (decomp.), from ethanol (Found: C, 51·6; H, 4·3. $C_{17}H_{21}O_4N,C_6H_3O_7N_3$ requires C, 51·9; H, 4·4%). Further elution with chloroform afforded an additional crop (0·1 g.) of dihydrotazettine.

Hydrogenation of Deoxytazettine.—Deoxytazettine (I; R = OMe, R′ = R‴ = H, R″ = Me) (0·5 g.) in ethanol (10 ml.) and acetic acid (5 ml.) was hydrogenated for 5 hr. The crude product was converted into a mixture of picrates which was separated in acetone into a slightly soluble and a more soluble compound. The less soluble one was crystallised from acetone, to yield *demethoxydeoxydihydrotazettine picrate* (VII; R = R′ = R‴ = H, R″ = Me) (70 mg.), yellow needles, m. p. 225—227° (decomp.) (Found: C, 53·5; H, 4·7; N, 11·1; OMe, 0. $C_{17}H_{21}O_3N,C_6H_3O_7N_3$ requires C, 53·5; H, 4·7; N, 10·9%). The free base regenerated from the picrate by filtration in chloroform through a column of alumina was an oil, $[\alpha]_D$ +46° (*c* 3·55 in EtOH), whose *methiodide* crystallised from ethanol as prisms, m. p. 294° (decomp.) (Found: C, 49·8; H, 5·6; N, 3·4. $C_{17}H_{21}O_3N,CH_3I$ requires C, 50·4; H, 5·6; N, 3·2%). The more soluble picrate was crystallised from ethanol, affording deoxydihydrotazettine picrate[1] (VII; R = OMe, R′ = R‴ = H, R″ = Me) (0·15 g.), m. p. and mixed m. p. 190—191° (decomp.).

Hydrogenation of Tazettamide.—Tazettamide[1] (0·3 g.) in ethanol (20 ml.) was hydrogenated over 10% palladium–carbon (0·25 g.) at room temperature for 15 hr. After removal of the catalyst and concentration to dryness, the residue (0·285 g.) was crystallised four times from ethanol, to furnish dihydrotazettamide[1,2] (20 mg.), m. p. and mixed m. p. 156—157°. The mother-liquors were evaporated to dryness and chromatographed in benzene over acid-washed alumina. A benzene eluate gave an additional quantity of dihydrotazettamide (0·15 g.). Elution with benzene–chloroform (1 : 1) afforded a mixture, m. p. 148—152, and further elution with chloroform yielded *demethoxydihydrotazettamide* (III; R = R′ = H, R″ = Me) (10 mg.), needles, m. p. 213—215° (from ethanol), $\nu_{max.}$ 1715 (lactone), and 1661 cm.$^{-1}$ (amide) (Found: C, 62·8; H, 6·0; OMe, 0. $C_{17}H_{19}O_5N,\frac{1}{2}H_2O$ requires C, 62·6; H, 6·2%). The combined mother-liquors and intermediate fractions were rechromatographed as above and additional quantities of dihydrotazettamide (65 mg.) and demethoxydihydrotazettamide (12 mg.) were isolated. Demethoxydihydrotazettamide was also obtained by the hydrogenation of *demethoxytazettamide* (II; R = R′ = H, R″ = Me), prisms, m. p. 205—206° (from ethanol, $\nu_{max.}$ 1731 (lactone) and 1667 cm.$^{-1}$ (amide) in chloroform (Found: C, 64·4; H, 5·5. $C_{17}H_{17}O_5N$ requires C, 64·8; H, 5·4%), which in turn was prepared by the manganese dioxide oxidation of demethoxytazettine (see below).

Hydrogenation of Nortazettamide.—Nortazettamide (0·15 g.) was hydrogenated in ethanol (20 ml.) over 10% palladium–carbon (0·15 g.) for 8 hr. Chromatography of the crude product in benzene over acid-washed alumina gave *demethoxydihydronortazettamide* (III; R = R′ = R″ = H) (85 mg.), prisms, m. p. 190—191° (from benzene), $[\alpha]_D$ −104·7° (*c* 0·6 in EtOH), $\nu_{max.}$ 3289 (NH), 1733 (lactone), 1681, and 1661 cm.$^{-1}$ (amide) (Found: C, 63·2; H, 5·5; OMe, 0. $C_{16}H_{17}O_5N$ requires C, 63·4; H, 5·7%).

Hydrogenation of Di-O-acetyltazettinol.—Diacetyltazettinol (I; R = R‴ = OAc, R′ = H, R″ = Me) (0·11 g.) in 2% hydrochloric acid (20 ml.) was hydrogenated in the presence of 15% palladium–carbon (0·1 g.) for 7 hr. The resulting crude product was chromatographed in benzene over alumina. The benzene eluate gave O-*acetyldemethoxytazettine* (I; R = R′ = H, R″ = Me, R‴ = OAc) (30 mg.), needles, m. p. 170—171° from light petroleum (b. p. 60—80°), $\nu_{max.}$ 1742 cm.$^{-1}$ (acetyl) (Found: C, 66·7; H, 6·1. $C_{19}H_{21}O_5N$ requires C, 66·5; H, 6·2%). Further elution with chloroform gave demethoxydihydrotazettine (VII; R = R′ = H, R″ = Me, R‴ = OH) (60 mg.), prisms, m. p. and mixed m. p. 167—168° (from ether).

[12] Kondo, Ikeda, and Taga, *Ann. Report ITSUU Lab.*, 1954, **5**, 72.

Hydrogenation of Diacetylisotazettinol.—(*a*) Di-*O*-acetyl*iso*tazettinol (I; R = H, R′ = R‴ = OAc, R″ = Me) (0·13 g.) in 1% hydrochloric acid (20 ml.) was hydrogenated over 15% palladium–carbon (0·1 g.) for 7 hr. After working up as above, *O*-acetyldemethoxytazettine (30 mg.) and demethoxydihydrotazettine (75 mg.) were isolated.

(*b*) Diacetyl*iso*tazettinol (0·2 g.) in ethanol (5 ml.) and acetic acid (5 ml.) was hydrogenated over platinum oxide (0·11 g.) for 7 hr. The crude product was chromatographed in benzene over alumina, and the benzene eluate gave demethoxydeoxydihydrotazettine (VII; R = R′ = R‴ = H, R″ = Me) as its picrate (20 mg.), m. p. and mixed m. p. 225—227° (decomp.). Benzene–chloroform (1 : 1) and chloroform eluates were combined and rechromatographed. Elution with chloroform then gave demethoxydihydrotazettine (20 mg.), m. p. and mixed m. p. 162—165°. Chloroform–acetone and acetone eluates from the second column were combined and rechromatographed to furnish dihydro*iso*tazettinol (see below) (5 mg.), m. p. and mixed m. p. 246—248°.

Mono-O-acetylisotazettinol (I; R = H, R′ = OAc, R″ = Me, R‴ = OH).—*iso*Tazettinol (I; R = H, R′ = R‴ = OH, R″ = Me) (80 mg.) in pyridine (2 ml.) and acetic anhydride (1 ml.) was kept at 10° overnight. After addition of water (10 ml.) and sodium carbonate, the mixture was extracted with ether, and the ether dried and evaporated to give a gum which crystallised from benzene to give *mono-O-acetylisotazettinol*, plates, m. p. 193—194°, $[\alpha]_D$ +308° (*c* 0·6 in $CHCl_3$), $\nu_{max.}$ 3436 (OH) and 1712 cm.$^{-1}$ (acetyl) (Found: C, 63·7; H, 5·8. $C_{19}H_{21}O_6N$ requires C, 63·5; H, 5·9%). Chromatography of the mother-liquors gave from the benzene eluate diacetyl*iso*tazettinol (20 mg.), m. p. and mixed m. p. 148—150°, and an additional crop of monoacetyl*iso*tazettinol from the chloroform eluate (total yield, 50 mg.). Monoacetyl*iso*tazettinol regenerated *iso*tazettinol on hydrolysis in 3% methanolic potassium hydroxide.

Hydrogenation of Monoacetylisotazettinol.—Monoacetyl*iso*tazettinol (65 mg.) in ethanol (3 ml.) and 1% hydrochloric acid (20 ml.) was hydrogenated over 5% palladium–carbon (0·1 g.) for 3 hr. The catalyst was removed and the filtrate made alkaline with aqueous ammonia and extracted with ether, which was dried and evaporated, to yield *demethoxytazettine* (I; R = R′ = H, R″ = Me, R‴ = OH) (50 mg.) as needles, m. p. 193—194° (from ethanol), depressed to 160—170° on admixture with the starting material (Found: C, 67·7; H, 6·5. $C_{17}H_{19}O_4N$ requires C, 67·8; H, 6·4%). The picrate crystallised from ethanol as yellow needles, m. p. 200°. The acetate (I; R = R′ = H, R″ = Me, R‴ = OAc) was prepared by use of sodium acetate in acetic anhydride on a water-bath for 2 hr. It formed needles from light petroleum (b. p. 60—80°) and had m. p. and mixed m. p. 170—171°.

Hydrogenation of Demethoxytazettine.—Demethoxytazettine (40 mg.) in ethanol (8 ml.) was hydrogenated over platinum oxide (40 mg.) for 6 hr., to furnish demethoxydihydrotazettine (VII; R = R′ = H, R″ = Me, R‴ = OH), prisms (from ether), m. p. and mixed m. p. 167—168°.

Demethoxydeoxydihydrotazettine (VII; R = R′ = R‴ = H, R″ = Me).—Demethoxydihydrotazettine (40 mg.) obtained as above was reduced in refluxing tetrahydrofuran with excess of lithium aluminium hydride in 3 hr. The crude diol was heated in 5% sulphuric acid (20 ml.) for 2 hr. on a water-bath. Basification followed by extraction with ether gave an oil (VII; R = R′ = R‴ = H, R″ = Me) characterised as its picrate, needles, m. p. and mixed m. p. 225—227° (decomp.) from acetone.

Demethoxydeoxytazettine (I; R = R′ = R‴ = H, R″ = Me).—Demethoxytazettine (30 mg.) was treated with lithium aluminium hydride, and the resulting diol dehydrated with sulphuric acid in the way similar to that described above. Demethoxydeoxytazettine was isolated as its *picrate*, yellow needles, m. p. 242—244° (decomp.) (from ethanol) (Found: C, 53·6; H, 4·2; N, 10·6. $C_{17}H_{19}O_3N,C_6H_3O_7N_3$ requires C, 53·7; H, 4·3; N, 10·9%).

Dihydroisotazettinol (VII; R = H, R′ = R‴ = OH, R″ = Me).—*iso*Tazettinol (0·55 g.) in ethanol (40 ml.) and acetic acid (2 ml.) was hydrogenated over platinum oxide (0·15 g.) for 2·5 hr. After working up, *dihydroisotazettinol* (0·5 g.) was isolated as prisms, m. p. 250° (from ethanol) (Found: C, 64·5; H, 6·5; N, 4·6. $C_{17}H_{21}O_6N$ requires C, 63·9; H, 6·6; N, 4·4%). The hydrochloride, needles from ethanol–ether, had m. p. 186° (decomp.).

Deoxydihydroisotazettinol (VII; R = R‴ = H, R′ = OH, R″ = Me).—(*a*) Dihydro*iso*tazettinol (0·1 g.) was refluxed for 5 hr. in tetrahydrofuran (5 ml.) with excess of lithium aluminium hydride. The resulting triol was heated in 5% sulphuric acid (20 ml.) on the water-bath for 2 hr. The acidic solution was basified with aqueous ammonia and extracted with ether to give an oil (63 mg.) whose *picrate* had m. p. 198° (from ethanol) (Found: C, 52·2; H, 4·5. $C_{17}H_{21}O_4N,C_6H_3O_7N_3$ requires C, 51·9; H, 4·4%). The picrate in acetone–chloroform

was filtered through a column of alumina, yielding the free *base* as prisms, m. p. 155° (from ether–light petroleum; b. p. 60—80°) (Found: C, 67·2; H, 6·8. $C_{17}H_{21}O_4N$ requires C, 67·3; H, 7·0%). (*b*) Deoxy*iso*tazettinol [1] (I; R = R‴ = H, R′ = OH, R″ = Me) (50 mg.) in ethanol (10 ml.) was hydrogenated over platinum oxide (50 mg.) for 4 hr. The catalyst was removed and the filtrate concentrated to dryness, to furnish deoxydihydro*iso*tazettinol, characterised as its picrate, m. p. 198°.

Reduction of Dihydrotazettamide.—The treatment of dihydrotazettamide with lithium aluminium hydride and subsequent cyclisation of the resulting diol (IV; R = OMe, R′ = H) were re-investigated. Starting with chromatographically purified dihydrotazettamide, the amino-ether (V; R = OMe, R′ = H) was obtained as an oil which was converted into its picrate. This formed yellow needles, m. p. 238—240° (decomp.) [lit.,[1] m. p. 226—228° (decomp.)], on crystallisation from acetone and then methanol.

Emde Degradation of the Amino-ether (V; R = OMe, R′ = H).—This reaction was also reinvestigated with a sample of the amino-ether regenerated from its picrate obtained as above. The *methiodide* of the amino-ether crystallised as deliquescent needles, m. p. 220—221°, $[\alpha]_D$ −50° (*c* 0·4 in MeOH), from methanol–ether (Found: C, 48·5; H, 6·1. $C_{18}H_{25}O_4N,CH_3I,\frac{1}{2}H_2O$ requires C, 48·5; H, 6·2%). The methiodide (0·37 g.) was subjected to the Emde degradation under the conditions described in the previous paper.[1] The resulting oil (0·18 g.) was passed in benzene through a column of alumina, concentrated, and kept in a refrigerator, to give the ether (VI; R = OMe, R′ = H) as prisms, m. p. 49—53°. On seeding with a synthetic sample of (VI; R = OMe, R′ = H) (m. p. 89—90°) (see below), this material crystallised from ethanol as prisms, m. p. and mixed m. p. 89—90° (Found: C, 69·9; H, 7·3. Calc. for $C_{16}H_{20}O_4$: C, 69·5; H, 7·3%). The infrared spectrum was identical with that of the synthetic compound.

When a sample (1·5 g.) of dihydrotazettamide, which had been obtained by one crystallisation of the hydrogenation product of tazettamide, was treated as above and the resulting Emde product crystallised repeatedly from ethanol, the product (VI; R = OMe, R′ = H) (0·5 g.) was isolated as the high-melting form, m. p. and mixed m. p. 89—90°. The mother-liquors (0·2 g.) from the crystallisation were chromatographed in benzene over alumina (30 g.). The first benzene eluate gave leaflets, m. p. 60—62°, and the following benzene eluate gave prisms, (50 mg.), m. p. 89—90°, identical with (VI; R = OMe, R′ = H). The former fraction was rechromatographed in benzene over alumina (50 g.) and 6 : 7-*methylenedioxy*iso*chroman*-4-spirocyclo*hexane* (VI; R = R′ = H) (35 mg.) was isolated from the first benzene eluate. It crystallised from ethanol as prisms, m. p. 56—57°, undepressed on admixture with the synthetic sample (Found: C, 72·7; H, 7·3; OMe, 0. $C_{15}H_{18}O_3$ requires C, 73·1; H, 7·4%). Further elution with benzene gave an additional crop (70 mg.) of (VI; R = OMe, R′ = H).

3 : 4-*Dihydro*-4′-*methoxy*-6 : 7-*methylenedioxy*iso*coumarin*-4-spiro-1′-cyclo*hexane* (XXIV; R = OMe, R′ = H).—Potassium permanganate (0·15 g.) in acetone (10 ml.) was added dropwise with stirring to 4′-methoxy-6 : 7-methylenedioxy*iso*chroman-4-*spiro*-1′-*cyclo*hexane (VI; R = OMe, R′ = H) (50 mg.) in acetone (20 ml.) at 15° during 8 hr. After a further 12 hours' stirring, sulphur dioxide was bubbled into the mixture which was then acidified with 1% sulphuric acid (30 ml.) and extracted with ether. The extract furnished the *lactone* (XXIV; R = OMe, R = H), m. p. 144—146°, prisms (from ether), $\lambda_{max.}$ 226, 267, and 306 mμ (log ε 4·32, 3·73, and 3·76), $\nu_{max.}$ 1715 (lactone), and 1613 cm.$^{-1}$ (benzene) in KBr (Found: C, 66·0; H, 6·2. $C_{16}H_{18}O_5$ requires C, 66·2; H, 6·3%).

3 : 4-*Dihydro*-6 : 7-*methylenedioxy*iso*coumarin*-4-spirocyclo*hexane* (XXIV; R = R′ = H).—6 : 7-Methylenedioxy*iso*chroman-4-*spirocyclo*hexane (20 mg.) and potassium permanganate (0·1 g.) were stirred in acetone (25 ml.) at 15° for 20 hr. A saturated solution of sulphur dioxide and dilute sulphuric acid were added to the mixture which was then extracted with ether. Evaporation of the ether gave a residue which was filtered in benzene through a column of alumina and crystallised from light petroleum (b. p. 60—80°), to afford the *lactone* (XXIV; R = R′ = H) as leaflets, m. p. 125—126°, $\lambda_{max.}$ 226, 267, and 307 mμ (log ε 4·33, 3·75, and 3·79) (Found: C, 69·2; H, 6·2. $C_{15}H_{16}O_4$ requires C, 69·2; H, 6·2%).

Manganese Dioxide Oxidation of iso*Tazettinol.*—*iso*Tazettinol (0·46 g.) and manganese dioxide (4 g.) in chloroform (50 ml.) were stirred for 6 hr. After being set aside overnight, manganese dioxide was filtered off and washed with chloroform. The combined filtrate and washings were extracted with 5% hydrochloric acid which removed some unchanged starting material (275 mg.). Concentration of the chloroform gave the *keto-lactone* (II; R, R′ = O, R″ = Me) (70 mg.), needles, m. p. 214—216° (decomp.) (from acetone or ethanol), $[\alpha]_D$ +250°

(*c* 0·4 in EtOH), $\nu_{max.}$ 1730 (lactone), 1698 (ketone), and 1684 cm.$^{-1}$ (amide) (Found: C, 62·1; H, 4·6; N, 4·4. $C_{17}H_{15}O_6N$ requires C, 62·0; H, 4·6; N, 4·3%). The solid from the mother-liquors was chromatographed in benzene over acid-washed alumina. The first benzene eluate gave an additional crop (10 mg.) of the above keto-lactone, and the second benzene eluate afforded a substance (10 mg.), needles, m. p. 266—267° (Found: C, 62·4; H, 4·7), the structure of which is still to be elucidated. Further elution with chloroform gave the *hydroxy-lactone* (II; R = H, R′ = OH, R″ = Me) (15 mg.), needles, m. p. 207—209° (decomp.) (from ethanol), raised to 216—218° after drying *in vacuo* at 100°, $[\alpha]_D$ +235° (*c* 0·43 in EtOH), $\nu_{max.}$ 3390—3125 (OH), 1721 (lactone) and 1653 cm.$^{-1}$ (amide) in Nujol mull, and 3597 (OH), 1730 (lactone), and 1672 cm.$^{-1}$ (amide) in chloroform (Found: C, 61·4; H, 5·7; N, 4·3. $C_{17}H_{17}O_6N$ requires C, 61·6; H, 5·2; N, 4·2%). The keto-lactone (II; R, R′ = O, R″ = Me) was converted into 2-*p*-hydroxyphenyl-4 : 5-methylenedioxybenzyl alcohol, m. p. and mixed m. p. 186—188°, upon prolonged heating in 15% aqueous potassium hydroxide.

Hydrogenation of the Keto-lactone (II; R, R′ = O, R″ = Me).—(*a*) The keto-lactone (30 mg.) in ethanol (30 ml.) was hydrogenated over 10% palladium–carbon (50 mg.) for 3 hr. The crude product was chromatographed in benzene over acid-washed alumina. The first benzene eluate gave an oil (2 mg.). Further elution with benzene gave the *dihydro-keto-lactone* (III; R, R′ = O, R″ = Me) (25 mg.), prisms, m. p. 185—187° (from benzene), $\nu_{max.}$ 1733 (lactone), 1718 (ketone), and 1667 cm.$^{-1}$ (amide) (Found: C, 61·9; H, 5·3. $C_{17}H_{17}O_6N$ requires C, 61·6; H, 5·2%).

(*b*) The keto-lactone (30 mg.) in ethanol (30 ml.) was hydrogenated over 10% palladium–carbon for 4 days during daylight hours. Chromatography of the resulting product in benzene over acid-washed alumina furnished from a benzene eluate the dihydro-keto-lactone (15 mg.), m. p. and mixed m. p. 185—187° (from benzene), and the dihydro-alcohol (III; R = H, R′ = OH, R″ = Me) (10 mg.), m. p. and mixed m. p. 125—127° (from benzene–ligroin) from a methanol eluate.

*Manganese Dioxide Oxidation of Dihydro*isotazettinol.—Dihydro*iso*tazettinol (0·4 g.) in chloroform (35 ml.) and acetone (5 ml.) was stirred with manganese dioxide (4 g.) at room temperature for 15 hr. Manganese dioxide was removed and washed with chloroform, and the combined filtrate and washings were extracted with 5% hydrochloric acid to remove unchanged starting material (90 mg.). The residue from the chloroform solution was chromatographed in benzene over acid-washed alumina. The benzene eluate gave an oil, and the chloroform and the acetone eluates gave 2′-(N-*formyl*-N-*methylamino*)-4′-*hydroxy*-6 : 7-*methylenedioxy*-3-*oxo*iso-*chroman*-4-spiro-1′-cyclo*hexane* (III; R = H, R′ = OH, R‴ = Me) (0·18 g.), needles, m. p. 125—127° (from benzene), $[\alpha]_D$ +75° (*c* 0·24 in EtOH), $\nu_{max.}$ 3472 and 3225 (OH), 1730 (lactone), and 1686 and 1667 cm.$^{-1}$ (amide) (Found: C, 59·7; H, 6·0. $C_{17}H_{19}O_6N,\frac{1}{2}H_2O$ requires C, 59·7; H, 5·9%). Hydrolysis of this (40 mg.) in 10% potassium hydroxide (2 ml.) on a water-bath for 3 hr., followed by lactonisation in dilute sulphuric acid, gave an *amine* (III; R = H, R′ = OH, R″ = Me, H in place of CHO) (18 mg.), needles, m. p. 185—187° (from ethanol), $\nu_{max.}$ 3521 (OH, NH), and 1724 cm.$^{-1}$ (lactone) (Found: C, 62·7; H, 6·3. $C_{16}H_{19}O_5N$ requires C, 62·9; H, 6·3%).

Reduction of O-*Demethyldihydro*iso*tazettamide* (III; R = H, R′ = OH, R″ = Me).—The amide (0·3 g.) and lithium aluminium hydride (0·25 g.) were heated in tetrahydrofuran (10 ml.) under reflux for 4 hr. The crude oily base isolated was heated in 5% sulphuric acid (20 ml.) for 1·5 hr. Basification and extraction with ether gave an oil (0·2 g.) which was chromatographed in benzene over alumina. The first benzene eluate did not give a crystalline picrate. The second benzene eluate and the benzene–chloroform (1 : 1) eluate gave the *picrate* of an amino-alcohol (V; R = H, R′ = OH) which when crystallised from methanol formed needles (0·13 g.), m. p. 204—207°, raised to 220—222° (decomp.) by drying *in vacuo* (Found: C, 50·8; H, 5·0; N, 10·3. $C_{17}H_{23}O_4N,C_6H_3O_7N_3,\frac{1}{2}H_2O$ requires C, 50·9; H, 5·0; N, 10·3%). The free base regenerated from the picrate was converted into its *carbonate*, m. p. 194° (prisms from benzene) [Found: C, 62·6; H, 6·9. $(C_{17}H_{23}O_4N)_2H_2CO_3$ requires C, 62·5; H, 7·1%]. The 3 : 5-*dinitrobenzoate* of the base formed orange yellow prisms, m. p. 236—238° (from chloroform–ethanol) (Found: C, 57·6; H, 5·0; N, 8·5. $C_{24}H_{23}O_9N_3$ requires C, 58·0; H, 4·6; N, 8·5%).

Emde Degradation of the Amino-alcohol (V; R = H, R′ = OH).—The foregoing amino-alcohol (0·12 g.) regenerated from its picrate gave with methyl iodide in methanol the methiodide which was immediately converted into its chloride by shaking it with an excess of silver chloride.

The chloride in water (5 ml.) was heated with 5% sodium amalgam (30 g.) on a water-bath for 6 hr. The oil which separated was extracted with chloroform, which was washed with 5% hydrochloric acid and water, dried, and evaporated, to give a neutral product which was chromatographed in benzene–ligroin (1 : 1) over acid-washed alumina. Elution with benzene–ligroin (1 : 1) and benzene gave an oil (8 mg.). The second benzene eluate afforded *4'-hydroxy-6 : 7-methylenedioxyisochroman*-4-spiro-1'-cyclo*hexane* (VI; R = H, R' = OH) (20 mg.) which crystallised from ligroin, then from benzene as prisms, m. p. 146—148° (Found: C, 68·3; H, 6·6. $C_{15}H_{18}O_4$ requires C, 68·7; H, 6·9%). The 3 : 5-dinitrobenzoate had m. p. 278° (pale yellow needles from chloroform–ethanol).

2 : 4-*Dicyano*-1-*imino*-4-*phenyl*cyclo*hexane* (IX; R = NH, R' = CN).—(*a*) To a stirred solution of benzyl cyanide (2 g.) and β-bromopropionitrile (4·8 g.) in toluene (40 ml.) powdered sodium amide (0·8 g.) was added in portions. Stirring was continued at room temperature for 8 hr., then under reflux for 2 hr. After cooling, the excess of sodium amide was destroyed with acetic acid, the precipitated sodium acetate removed by filtration, and the toluene washed with aqueous sodium carbonate, then water, dried, and evaporated under reduced pressure to give the *ketimine* (4 g.) which crystallised from ethanol as needles, m. p. 145—146° (Found: C, 75·3; H, 6·0. $C_{14}H_{13}N_3$ requires C, 75·3; H, 5·9%).

(*b*) Sodium amide (1 g.) was added to γ-cyano-γ-phenylpimelonitrile [13] (2 g.) in toluene (30 ml.), and the mixture refluxed for 5 hr. On working up of the mixture as described above, the same ketimine (0·8 g.) was obtained.

Methyl 3-*Cyano*-6-*oxo*-3-*phenyl*cyclo*hexanecarboxylate* (IX; R = O, R' = CO_2Me).—Sodium amide (2·5 g.) was added in portions with stirring to a mixture of benzyl cyanide (0·9 g.), methyl β-bromopropionate (3 g.), and toluene (30 ml.). Stirring was continued at room temperature for 24 hr., then under reflux for 4 hr. After cooling, a little acetic acid and then water were added and the toluene layer was washed with aqueous sodium carbonate, dried, and evaporated to dryness to give the cyclo*hexanone-ester* (1·5 g.). It crystallised from benzene as needles, m. p. 90—91·5° (Found: C, 70·3; H, 5·9; N, 5·5. $C_{15}H_{15}O_3N$ requires C, 70·0; H, 5·9; N, 5·4%).

Acidic Hydrolysis of the Keto-ester (IX; R = O, R' = CO_2Me).—The keto-ester (0·1 g.) was refluxed in 2% ethanolic sodium hydroxide (20 ml.) containing water (5 ml.) for 4 hr. The mixture was concentrated and the residue in dilute hydrochloric acid was extracted with ether. The organic layer was extracted with aqueous sodium carbonate which was made acid and extracted again with ether. The ethereal extract was dried and evaporated to furnish *γ-cyano-γ-phenylpimelic acid* (0·1 g.), m. p. 167—168°, $\nu_{max.}$ 2237 (CN), 2577—2725 and 1724 $cm.^{-1}$ (CO_2H) (from methanol) (Found: C, 64·4; H, 5·8. $C_{14}H_{15}O_4N$ requires C, 64·4; H, 5·8%). This was not identical (mixed m. p. and infrared spectra) with α-2-carboxyethyl-α-phenylglutarimide.[7]

4-*Cyano*-4-*phenyl*cyclo*hexanone* (IX; R = O, R' = H).—(*a*) The above ketimine (0·5 g.) was heated in acetic acid (15 ml.) containing 30% sulphuric acid (10 ml.) on the water-bath for 10 hr. After cooling, water (20 ml.) was added, and the whole was extracted with benzene which in turn was washed with aqueous sodium carbonate, water, dried, and evaporated to dryness, to give a residue (60 mg.). This was passed in benzene through a column of alumina, affording the *cyano-ketone* (30 mg.), m. p. 114—115°, needles from benzene (Found: C, 78·1; H, 6·5. $C_{13}H_{13}ON$ requires C, 78·4; H, 6·6%).

(*b*) The β-keto-ester obtained as above (0·1 g.) was refluxed in ethanol (20 ml.) and concentrated hydrochloric acid (3 ml.) for 4 hr. The mixture was concentrated under reduced pressure to 10 ml., diluted with water (30 ml.), and extracted with ether. The ether extracts were washed with aqueous sodium carbonate and water, dried, and evaporated to dryness. The residue (70 mg.) gave the ketone, m. p. and mixed m. p. 114—115°, needles from benzene.

γ-Cyano-γ-(3 : 4-methylenedioxyphenyl)pimelonitrile (XI).—(*a*) 30% Methanolic Triton B (0·2 g.) was added dropwise to a stirred mixture of 3 : 4-methylenedioxybenzyl cyanide (1·6 g.) and acrylonitrile (1·5 g.) during 15 min. at 30—40°, the mixture becoming dark brown and viscous. After being heated on the water-bath for 30 min., the mixture was taken up in chloroform (100 ml.), washed with dilute hydrochloric acid, aqueous sodium carbonate, and water, dried, and evaporated to dryness under reduced pressure. The residue crystallised, giving the *trinitrile* as prisms (2·5 g.). After crystallisation from methanol, it had m. p. 91—93° (Found: C, 67·3; H, 4·7; N, 15·3. $C_{15}H_{13}O_2N_3$ requires C, 67·4; H, 4·9; N, 15·7%).

[13] Bruson and Riener, *J. Amer. Chem. Soc.*, 1943, **65**, 23.

(*b*) 30% Methanolic Triton B (0·4 g.) in *tert.*-butyl alcohol (5 ml.) was added dropwise to a stirred solution of 3 : 4-methylenedioxybenzyl cyanide (3 g.) and acrylonitrile (3 g.) in *tert.*-butyl alcohol (10 ml.) at 35—45°. After 1 hour's stirring, the mixture was concentrated, and the resulting residue was taken up in ethylene dichloride, washed with dilute hydrochloric acid, aqueous sodium carbonate, and water, dried, and evaporated to dryness, to give the pimelonitrile (5 g.) which crystallised from methanol as prisms, m. p. and mixed m. p. 91—93°.

α-2-*Carboxyethyl*-α-(3 : 4-*methylenedioxyphenyl*)*glutarimide* (XIII; R = R′ = H).—γ-Cyano-γ-(3 : 4-methylenedioxyphenyl)pimelonitrile (2·7 g.) in acetic acid (15 ml.) containing concentrated hydrochloric acid (30 ml.) and water (5 ml.) was heated on the water-bath for 2·5 hr. during which the mixture became dark brown. On cooling, crystals separated which were collected and recrystallised from aqueous ethanol, to give the *imidocarboxylic acid*, m. p. 220—221° (Found: C, 58·7; H, 4·8; N, 4·7. $C_{15}H_{15}O_6N$ requires C, 59·0; H, 5·0; N, 4·6%), $\nu_{max.}$ 3077—3175 (NH), 2584—2740 (OH of carboxylic acid), 1656, 1712, 1730 cm.$^{-1}$ (CO).

Treatment of the Imidocarboxylic Acid (XIII; R = R′ = H) *with Diazomethane.*—Excess of ethereal diazomethane was added to a suspension of the imidocarboxylic acid (3 g.) in ether (50 ml.) and methanol (10 ml.). This was kept overnight at room temperature, then a little acetic acid was introduced into the mixture to destroy the excess of diazomethane and the mixture was washed with aqueous sodium carbonate, dried, and evaporated to give α-2-*methoxycarbonylethyl*-N-*methyl*-α-(3 : 4-*methylenedioxyphenyl*)*glutarimide*, b. p. 200—230°(bath)/0·03 mm. (Found: OMe, 9·0. $C_{17}H_{19}O_6N$ requires OMe, 9·3%).

Treatment of the Ester (XIII; R = R′ = Me) *with Sodium Methoxide.*—The above ester (3 g.) and sodium methoxide (2 g.) were refluxed in benzene (30 ml.) for 2 hr. The mixture was then acidified with dilute hydrochloric acid, and the benzene layer washed with aqueous sodium carbonate, dried, and evaporated under reduced pressure to give an oil (2·3 g.). This was heated in ethanol (50 ml.) and concentrated hydrochloric acid (20 ml.) under reflux for 10 hr., which was next concentrated under reduced pressure to 15 ml., diluted with water (80 ml.), and extracted with ether. The ethereal extracts were washed with aqueous sodium carbonate and water, dried, and evaporated to dryness and the residue was chromatographed in benzene over alumina. The benzene eluate gave the 1-(3 : 4-*methylenedioxyphenyl*)-N-*methyl*-4-*oxo*cyclo*hexanecarboxyamide* (XIV; R = H) (25 mg.), m. p. 151—152°, as plates from benzene (Found: C, 65·3; H, 6·1; N, 5·1. $C_{15}H_{17}O_4N$ requires C, 65·4; H, 6·2; N, 5·1%), $\nu_{max.}$ 3413 (NH), 1681, 1718 cm.$^{-1}$ (CO). The 2 : 4-*dinitrophenylhydrazone*, m. p. 138—141°, formed needles from ethanol (Found: C, 55·0; H, 5·0. $C_{21}H_{21}O_7N_5$ requires C, 55·4; H, 4·7%).

2 : 4-*Dicyano*-1-*imino*-4-(3 : 4-*methylenedioxyphenyl*)cyclo*hexane* (XVI).—γ-Cyano-γ-(3 : 4-methylenedioxyphenylpimelonitrile (XI) (1 g.) and sodium amide (0·7 g.) in toluene (20 ml.) were heated under reflux for 6 hr. A little acetic acid and then water were added to the mixture, and the toluene layer was washed with aqueous sodium carbonate and water, dried, and evaporated to dryness under reduced pressure. The residue, which solidified, crystallised from benzene to give the *ketimine* (0·8 g.) as needles, m. p. 191—193° (Found: C, 67·1; H, 4·7; N, 15·6. $C_{15}H_{13}O_2N_3$ requires C, 67·4; H, 4·9; N, 15·7%).

Methyl γ-Cyano-γ-(3 : 4-*methylenedioxyphenyl*)*pimelate* (XII; R = Me).—30% Methanolic Triton B (1 g.) in *tert.*-butyl alcohol (2 ml.) was added dropwise to a stirred mixture of 3 : 4-methylenedioxybenzyl cyanide (3·2 g.), methyl acrylate (3·5 g.), and *tert.*-butyl alcohol (10 ml.) during 30 min. at 65—70°. The mixture was heated under reflux for 2 hr. and then the solvent was removed by distillation. The resulting oil was taken up in chloroform, washed with dilute hydrochloric acid, aqueous sodium carbonate, and water, dried, and evaporated to dryness. The residue (6·5 g.) was fractionated by distillation into two portions; the first fraction (1 g.), b. p. 190—210°(bath)/0·01 mm., was discarded; the second fraction (4·8 g.), b. p. 245—255° (bath)/0·005 mm., crystallised overnight. Recrystallisation from ethanol gave the *ester* (XII; R = Me), prisms, m. p. 45—46° (Found: C, 61·5; H, 5·8; N, 4·2; OMe, 18·3. $C_{17}H_{19}O_6N$ requires C, 61·3; H, 5·8; N, 4·2; OMe, 18·6%).

Methyl 5-*Cyano*-5-(3 : 4-*methylenedioxyphenyl*)-2-*oxo*cyclo*hexanecarboxylate* (XV; R = CO_2Me).—The methyl cyanopimelate (4·5 g.) obtained as above and sodium hydride (0·4 g.) were heated in toluene (100 ml.) containing a few drops of methanol under reflux under nitrogen for 4 hr. A little acetic acid was added to the mixture to destroy the excess of sodium hydride, and the mixture was shaken with aqueous sodium carbonate and water, dried, and evaporated under reduced pressure. The residue crystallised from ethanol, to give the cyclo*hexanone-ester*

(3·2 g.) as needles, m. p. 136—137° (Found: C, 63·8; H, 5·0; N, 4·5. $C_{16}H_{15}O_5N$ requires C, 63·8; H, 5·0; N, 4·7%), $\nu_{max.}$ 2242 (CN) and 1675 cm.$^{-1}$ (CO).

γ-Cyano-γ-(3 : 4-methylenedioxyphenyl)pimelic Acid (XII; R = H).—Methyl γ-cyano-γ-(3 : 4-methylenedioxyphenyl)pimelate was hydrolysed in the usual way in alkali to give the *acid*, m. p. 178—179, needles (from ethanol) (Found: C, 59·3; H, 5·1; N, 4·5. $C_{15}H_{15}O_6N$ requires C, 59·0; H, 5·0; N, 4·6%).

4-*Cyano*-4-(3 : 4-*methylenedioxyphenyl*)cyclo*hexanone* (XV; R = H).—(*a*) The imido-carboxylic acid (XIII; R = R′ = H) (2 g.) in acetic anhydride (30 ml.) was heated under reflux for 8 hr. After evaporation of the mixture to dryness under reduced pressure, the residue was kept at 200° under reduced pressure for 20 min. The product was taken up in chloroform, washed with aqueous sodium carbonate, dried, and concentrated to dryness to give an oil (0·4 g.) which was distilled *in vacuo* to give a fraction, b. p. 170—175° (bath)/0·01 mm. This was chromatographed in benzene over alumina, and the eluate furnished 4-*cyano*-4-(3 : 4-*methylenedioxyphenyl*)cyclo*hexanone* as needles (50 mg.), m. p. 134—135°, from benzene (Found: C, 69·4; H, 5·3; N, 5·9. $C_{14}H_{13}O_3N$ requires C, 69·1; H, 5·4; N, 5·8%), $\nu_{max.}$ 2252 (CN) and 1724 cm.$^{-1}$ (CO). The 2 : 4-*dinitrophenylhydrazone* had m. p. 220—223° (from ethanol) (Found: C, 56·9; H, 4·2. $C_{20}H_{17}O_6N_5$ requires C, 56·7; H, 4·1%).

(*b*) The *cyclo*hexanone-ester (XV; R = CO_2Me) (10 g.) was refluxed for 10 hr. in ethanol (200 ml.), concentrated hydrochloric acid (100 ml.), and 25% sulphuric acid (10 ml.). The mixture was concentrated to 100 ml., diluted with water (400 ml.), and extracted with ether. This extract was washed with aqueous sodium carbonate and water, dried, and evaporated to dryness to give a solid (6·5 g.) which was crystallised from benzene, affording the ketone (XV; R = H) (5 g.), m. p. and mixed m. p. 134—135°. The mother-liquor was chromatographed (*A*) in benzene over alumina. The first benzene eluate gave the *diethyl ketal* (XVIII; R = Et) (0·5 g.) of the ketone (XV; R = H); this formed needles, m. p. 127—129° from ethanol (Found: C, 68·2; H, 7·2; N, 4·6; OEt, 28·1. $C_{18}H_{23}O_4N$ requires C, 68·1; H, 7·3; N, 4·4; OEt, 28·4%); it was identical with the ketal prepared from the ketone (XV; R = H) in ethanol in the presence of toluene-*p*-sulphonic acid. The later fractions from the chromatogram (*A*) eluted with the same solvent gave the ketone (0·5 g.).

(*c*) The ketimine (XVI) (1 g.) obtained above was heated on a water-bath for 10 hr. in ethanol (25 ml.) containing 30% aqueous sulphuric acid (15 ml.). The mixture was concentrated to 25 ml., diluted with water, and extracted with ether. The ethereal extract was washed with aqueous sodium carbonate and water, dried, and evaporated, to give an oil (70 mg.) which was chromatographed in benzene over alumina. This afforded the cyano-ketone (XV; R = H) (30 mg.), m. p. and mixed m. p. 134—135° (from carbon tetrachloride).

4-*Cyano*-4-(3 : 4-*methylenedioxyphenyl*)cyclo*hexanol* (XVII).—A suspension of sodium borohydride (1 g.) in methanol (50 ml.) was added in portions to 4-cyano-4-(3 : 4-methylenedioxyphenyl)*cyclo*hexanone (XV; R = H) (4 g.) in methanol (150 ml.) at 0°. After being kept overnight, the mixture was evaporated under reduced pressure, diluted with water, and extracted with ether. The ethereal extract was washed with dilute hydrochloric acid, aqueous sodium carbonate, and water, dried, and evaporated to give a solid, m. p. 96—105° which when crystallised from benzene gave 4-*cyano*-4-(3 : 4-*methylenedioxyphenyl*)cyclo*hexanol* (2 g.), prisms, m. p. 121—122° (Found: C, 69·0; H, 6·1; N, 5·6. $C_{14}H_{15}O_3N$ requires C, 68·6; H, 6·2; N, 5·7%), $\nu_{max.}$ 3534 (OH) and 2247 cm.$^{-1}$ (CN). The mother-liquor from the *cyclo*hexanol was chromatographed over alumina. The first benzene eluate gave 4-*cyano*-4-(3 : 4-*methylenedioxyphenyl*)cyclo*hexanone dimethyl ketal* (XVIII; R = Me) (1 g.), m. p. 107—108° (from methanol) [Found: C, 66·4; H, 6·5; N, 4·8; OMe, 21·4. $C_{14}H_{13}O_2N(OMe)_2$ requires C, 66·4; H, 6·6; N, 4·8; OMe, 21·4%]. This was identical with the ketal prepared from the ketone (XV; R = H) and toluene-*p*-sulphonic acid in methanol. The second benzene eluate gave the *cyclo*hexanol (XVII) (0·5 g.). The *acetyl derivative* of the *cyclo*hexanol formed needles, m. p. 161—162°, from ethanol (Found: C, 66·7; H, 5·9; N, 5·1. $C_{16}H_{17}O_4N$ requires C, 66·9; H, 6·0; N, 4·9%), $\nu_{max.}$ 2247 (CN) and 1733 cm.$^{-1}$ (CO) in a KBr disc. The *toluene*-p-*sulphonate* was obtained when the *cyclo*hexanol (0·2 g.) and toluene-*p*-sulphonyl chloride (0·17 g.) were kept overnight in pyridine (4 ml.) at 30°; the mixture was poured into water and extracted with chloroform, and the chloroform extract washed with dilute hydrochloric acid and evaporated; the residue crystallised from ethanol as needles, m. p. 162—163° (Found: C, 63·0; H, 5·1; N, 3·4. $C_{21}H_{21}O_5NS$ requires C, 63·2; H, 5·3; N, 3·5%).

It was later found that the formation of the ketal (XVIII; R = Me) in the course of the

sodium borohydride reduction of the ketone could be avoided when tetrahydrofuran was used as a solvent in place of methanol, giving the *cyclo*hexanol (XVII) in an excellent yield.

4-*Hydroxy*-1-(3 : 4-*methylenedioxyphenyl*)cyclo*hexanecarboxylic Acid* (XIX).—4-Cyano-4-(3 : 4-methylenedioxyphenyl)*cyclo*hexanol (0·3 g.) and potassium hydroxide (4·5 g.) were boiled under reflux in diethylene glycol (16 ml.) and water (6 ml.) for 8 hr. A crystalline precipitate appeared after 1 hr., but soon disappeared with liberation of ammonia. After cooling, the mixture was diluted with water (100 ml.) and filtered; the acid (XIX) was precipitated on addition of hydrochloric acid. Crystallisation from ethanol gave the *acid* (0·25 g.), m. p. 220—222° (decomp.), $\nu_{max.}$ 3378 (OH) and 1686 cm.$^{-1}$ (CO_2H) (Found: C, 63·8; H, 6·4. $C_{14}H_{16}O_5$ requires C, 63·6; H, 6·1%). Extraction of the mother-liquors with ethyl acetate yielded a little more acid (0·05 g.).

4-*Hydroxy*-1-(3 : 4-*methylenedioxyphenyl*)cyclo*hexanecarboxylic Lactone* (XX; R = H).—The hydroxy-acid (XIX) (30 mg.) was refluxed in acetic anhydride (5 ml.) for 5 hr. Evaporation under reduced pressure gave the *lactone*, m. p. 219—220°, prisms (from ethanol), $\nu_{max.}$ 1739 cm.$^{-1}$ (six-membered lactone) (Found: C, 68·5; H, 5·7. $C_{14}H_{14}O_4$ requires C, 68·3; H, 5·7%). The lactone regenerated the hydroxy-acid on hydrolysis in alkali.

1-(2-*Chloromethyl*-4 : 5-*methylenedioxyphenyl*)-4-*hydroxy*cyclo*hexanecarboxylic Lactone* (XX; R = CH_2Cl).—(*a*) The hydroxy-acid (XIX) (0·5 g.) and paraformaldehyde (0·5 g.) were heated with stirring in acetic acid (10 ml.) containing concentrated hydrochloric acid (6 ml.) at 70—75° for 10 hr. The mixture was evaporated to dryness under reduced pressure and the residue taken up in chloroform. The chloroform solution was washed with aqueous sodium carbonate and water, dried, and evaporated to give a dark brown oil (0·35 g.) which was chromatographed in benzene over acid-washed alumina. The first fractions eluted with benzene gave the *chloromethyl derivative* (XX; R = CH_2Cl) (0·15 g.). It crystallised from ethanol as leaflets, m. p. 143—145°, $\nu_{max.}$ 1745 cm.$^{-1}$ (six-membered lactone) (Found: C, 61·6; H, 5·5; Cl, 11·4. $C_{15}H_{15}O_4Cl$ requires C, 61·1; H, 5·1; Cl, 12·0%). Later fractions eluted with chloroform gave a substance (50 mg.), m. p. 215—216°, which was not investigated further.

(*b*) The lactone (XX; R = H) (0·5 g.) was similarly chloromethylated, and the chloromethyl derivative, m. p. and mixed m. p. 143—145° (0·2 g.), was obtained along with the starting material (0·15 g.) and the unidentified product, m. p. 215—216°.

The Hydroxy-lactone (XXI).—The chloromethyl-lactone (XX; R = CH_2Cl) (0·1 g.) was heated in 10% aqueous sodium hydroxide (10 ml.) on the water-bath for 10 hr. The mixture was acidified with dilute sulphuric acid, then heated at 100° for a further 8 hr. The mixture was repeatedly extracted with ether and the ethereal extracts were washed with aqueous sodium carbonate and evaporated to dryness, to give the 4′-*hydroxy*-6 : 7-*methylenedioxy*-3-*oxo*iso*chroman*-4-spiro-1′-cyclo*hexane* (XXI) which crystallised from ethanol as prisms (40 mg.), m. p. 156—157°, $\nu_{max.}$ 3448 (OH) and 1724 cm.$^{-1}$ (six-membered lactone) (Found: C, 65·2; H, 5·6. $C_{15}H_{16}O_5$ requires C, 65·2; H, 5·8%).

4′-*Hydroxy*-6 : 7-*methylenedioxy*iso*chroman*-4-spiro-1′-cyclo*hexane* (VI; R = H, R′ = OH).—The hydroxy-lactone (XXI) (0·1 g.) and lithium aluminium hydride (0·1 g.) were boiled under reflux in tetrahydrofuran (8 ml.) for 8 hr. The mixture was treated with a little water, then filtered, and the precipitate washed with methanol. The filtrate and washings were combined and concentrated to dryness, to give an oil which was heated in 3% sulphuric acid (20 ml.) on the water-bath for 3 hr. and then extracted with ether. The ethereal extracts were evaporated and the residue (60 mg.) was chromatographed in benzene over acid-washed alumina to afford the iso*chroman* (VI; R = H, R′ = OH), m. p. 146—147°, plates (from benzene) (Found: C, 68·3; H, 6·6. $C_{15}H_{18}O_4$ requires C, 68·7; H, 6·9%), identical in m. p., mixed m. p., and infrared spectrum with the Emde product derived from *iso*tazettinol described above.

The product (90 mg.) and toluene-*p*-sulphonyl chloride (0·1 g.) in pyridine (3 ml.) were kept overnight at 35°. After addition of crushed ice (10 g.), the mixture was extracted with chloroform, which was washed with dilute hydrochloric acid, aqueous sodium carbonate, and water, dried, and evaporated to dryness. The residue, crystallised from ethanol, gave the *toluene-p-sulphonate* (128 mg.) as needles, m. p. 180—181° (Found: C, 63·4; H, 6·0. $C_{22}H_{24}O_6S$ requires C, 63·5; H, 5·8%).

4′-*Methoxy*-6 : 7-*methylenedioxy*iso*chroman*-4-spiro-1′-cyclo*hexane* (VI; R = OMe, R′ = H).—The above toluene-*p*-sulphonate (0·1 g.) was heated with a solution from sodium (3 g.) in methanol (70 ml.) under reflux for 10 hr., then evaporated under reduced pressure. Water

was added and the mixture extracted with ether. This extract was washed with dilute hydrochloric acid and water, dried, and concentrated to an oil (60 mg.). This was chromatographed in benzene on alumina and eluted with benzene. The first fraction afforded 6 : 7-*methylenedioxy*iso*chroman*-4-spiro-1′-cyclo*hex*-3′-*ene* (XXIII) (32 mg.) which crystallised from ethanol as prisms, m. p. 101—102° (Found: C, 73·7; H, 6·8. $C_{15}H_{16}O_3$ requires C, 73·8; H, 6·6%). The second fraction gave 4′-*methoxy*-6 : 7-*methylenedioxy*iso*chroman*-4-spiro-1′-cyclo*hexane* (20 mg.) which, when dissolved in a little ethanol and seeded with a sample, m. p. 56—58°, of the same structure obtained previously by degradation of tazettamide, formed prisms and had m. p. 52°. But another recrystallisation from the same solvent raised the m. p. to 90° and once the higher-melting polymorph had been obtained the lower-melting form was never recovered during recrystallisation. The compound derived from natural sources showed also the same m. p. when seeded with the synthetic higher-melting form and mixed m. p. showed no depression. The infrared spectra were also identical (Found: C, 69·2; H, 7·5. $C_{16}H_{20}O_4$ requires C, 69·5; H, 7·3%).

6 : 7-*Methylenedioxy*iso*chroman*-4-spirocyclo*hexane* (VI; R = R′ = H).—The *spirocyclo*hexene (XXIII) (4 mg.) was hydrogenated in ethanol (5 ml.) in the presence of platinic oxide (7 mg.). The filtered solution was evaporated and the residue was chromatographed in benzene over alumina. The benzene eluate gave the *spirocyclo*hexane (VI; R = R′ = H) as prisms, m. p. 54—55° which did not depress the m. p. of the product obtained by Emde degradation of (V; R = R′ = H).

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