# 821. *Cularine and Related Compounds. Part VI.*[1] *A Total Synthesis of (±)-Cularine.*[2]

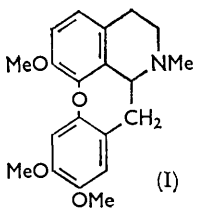
By T. KAMETANI and K. FUKUMOTO.

The Leuckart reaction of 2,3,6-trimethoxydibenzo[*b*,*f*]oxepin-10(11*H*)-one (II) in the presence of formic acid afforded the 10-formamido-derivative (III) in 59% yield (together with some basic by-products whose structures were also elucidated). Attempted condensation of the derived amine (IV) with several halogeno-carboxylic acid derivatives failed, probably because of the weak basicity of amino-group, but chloroacetyl and trichloroacetyl derivatives of the amine were prepared, the cyclization of which, however, was unsuccessful. Then, as a model experiment for a total synthesis of cularine, the cyclization of various *N*-substituted aminoethanol and glycine derivatives was investigated.

A synthesis of (±)-cularine is finally described, confirming Manske's structure for the alkaloid.

CULARINE (I), $C_{20}H_{23}NO_4$, was isolated from *Corydalis claviculata* and from *Dicentra cucullaria, D. eximia, D. formosa,* and *D. oregana* by Manske.[3,4] He [4] showed it to be a benzylisoquinoline alkaloid with the unusual feature that the benzyl ring is joined to 8-position of the isoquinoline by an ether linking, as in (I).

The purpose of the present investigation was to study the Leuckart reaction of ketone (II)[5,6] in order to obtain the corresponding amino-derivative (IV) as a possible intermediate for the synthesis of cularine; reactions of 3,4-dimethoxy-α-methylbenzylamine derivatives and of the amine (IV) with halogeno-carboxylic acid derivatives were also studied, leading eventually to a synthesis of cularine that supports the structure (I).



(I)

Formamide and ammonium formate are generally used in the Leuckart reaction,[7] and preliminary experiments were carried out to determine which will be the reagent of choice for our purpose.

Use of 4—18 mol. of either reagent with one mol. of the ketone at 160—180° (5 hr.) yielded the formamido-derivative (III) in a poor yield. Use of 90 mol. of formamide at 180° (5 hours) led to 32% of the formamido-derivative together with a yellowish-orange compound that is believed to have structure (VIII); if heating was prolonged (15 hours) the yield of amide (III) was very small whereas that of compound (VIII) increased and in addition a small amount of a substance (X) was isolated.

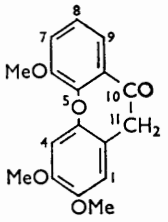
Crossley and Moore [8] reported that when benzyl ketones are treated with formamide under Leuckart conditions the methylene group enters into reaction with formamide in preference to the ketone group, giving abnormal products of unknown structure. In our case the ketone (II) would be expected to react with formamide to form the compound (V) and then the usual Leuckart reaction should yield the formamido-derivative (VII); intramolecular dehydration would then give the dihydropyrimidine derivative (VIII). On the other hand, the intermediate (V) may react with the starting material to give a material (IX) which cyclizes with loss of water to form the pyridine (X). The compounds

[1] Part V, *Chem. and Pharm. Bull.* (*Japan*), 1963, **11**, in the press.
[2] This forms Part LXXXV of "Studies on the Syntheses of Heterocyclic Compounds" by T. Kametani.
[3] Manske, *Canad. J. Res.*, 1940, **18**, *B*, 97.
[4] Manske, *J. Amer. Chem. Soc.*, 1950, **72**, 55.
[5] Kulka and Manske, *J. Amer. Chem. Soc.*, 1953, **75**, 1322.
[6] Kametani, Fukumoto, and Nakano, *J. Pharm. Soc. Japan*, 1962, **82**, 1548.
[7] Moore, *Org. Reactions*, 1949, **3**, 301.
[8] Crossley and Moore, *J. Org. Chem.*, 1944, **9**, 529; Novelli, *Anales Asoc. quím. argentina*, 1939, **27**, 161 (*Chem. Abs.*, 1940, **34**, 1659); Davidson, Weiss, and Jelling, *J. Org. Chem.*, 1937, **2**, 328.

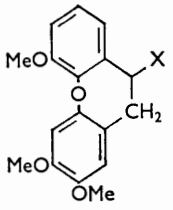
(VIII) and (X) gave elemental analyses agreeing with the formulations, which are also supported by infrared results. The spectrum of compound (VIII) shows a maximum at 1613 (C=N stretching), 1560 (NH deformation), and 806 cm.$^{-1}$ (C=H deformation in di-substituted pyrimidine [9]). Compound (X) lacks NH absorption but has maxima at 1613 (C=N in pyridine) and 1200 cm.$^{-1}$ (pyridine nucleus).

The yield of formamido-derivative (III) was improved to 59% at the cost of the by-products (VIII and X) by using a 1 : 3 : 18 molar mixture of ketone, formic acid, and formamide. The formamido-derivative (III) was converted into the amine (IV) by heating it with hydrochloric acid.

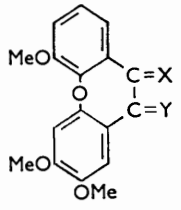
However, the attempts to synthesise cularine from this amine by Schlittler–Müller's method with glyoxal hemiacetal under a variety of conditions failed. As model experiments, attempts to cyclize *N*-substituted α-methylbenzylamine derivatives to isoquinoline or isoquinolone derivatives were therefore made. In general, intramolecular cyclization can be effected between an aromatic nucleus and a hydroxy- or halogeno-side-chain attached to it through an amine or amide linkage. For instance, *N*-2-bromoethyl-*N*-methylaniline affords 1-methylindoline (30—35%) in the presence of aluminium chloride.[10,11] However, 2-(α-methylbenzyl)ethylaminoethanol [12] (XI) (obtained by



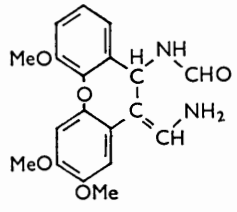
(II)



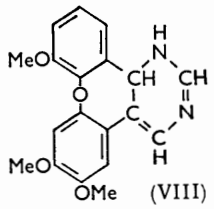
(III: X = NH·CHO)
(IV: X = $NH_2$)



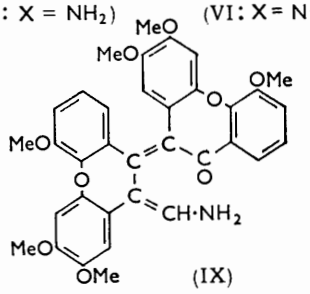
(V: X = O, Y = :CH·$NH_2$)
(VI: X = N·CHO, Y = :CH·$NH_2$)



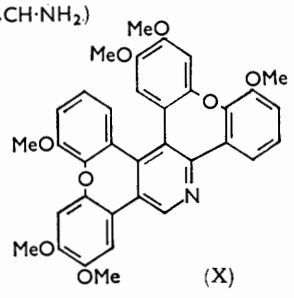
(VII)



(VIII)



(IX)



(X)

catalytic hydrogenation of a mixture of acetophenone with 2-aminoethanol) yielded an unidentified product when heated with polyphosphoric acid at 170—180°, or with phosphoryl chloride–phosphorus pentoxide in xylene; a Friedel–Crafts reaction of the chloride (XII) gave the same product, but it was recovered after being heated with polyphosphoric acid at <100° or with 90% sulphuric acid.

In order to activate the aromatic ring, the corresponding 3,4-dimethoxy-alcohol (XIII) was prepared from acetoveratrone, but again attempts at cyclodehydration failed, and a Friedel–Crafts reaction of the analogous chloride was also unsuccessful.

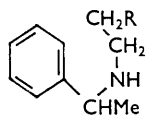
An extension of Stollé's oxyindole synthesis [13] was next investigated. 3,4-Dimethoxy-α-methylbenzylamine, obtained from acetoveratrone through its oxime [14] or through the

[9] Bellamy, "The Infra-red Spectra of Complex Molecules," Methuen, London, 2nd edn., 1958, p. 283.
[10] von Braun, Heider, and Müller, *Ber.*, 1917, **50**, 1613.
[11] Julian and Printy, *J. Amer. Chem. Soc.*, 1949, **71**, 3206.
[12] Cope and Hancock, *J. Amer. Chem. Soc.*, 1942, **64**, 1503.
[13] Stollé, *J. prakt. Chem.*, 1928, **105**, 137.
[14] Rohrmann and Shonle, *J. Amer. Chem. Soc.*, 1944, **66**, 1519.

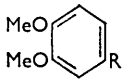
*N*-formylamine, was chloroacetylated and the product (XIV) was treated with aluminium chloride; only a small amount of an unidentified substance was obtained.

A small amount of the isoquinoline derivative (XV) was, however, obtained, together with 3,4-dimethoxystyrene, when *N*-(3,4-dimethoxy-α-methylbenzyl)glycine was heated with polyphosphoric acid. The glycine was prepared by alkaline hydrolysis of the ester which was obtained by heating the 3,4-dimethoxy-α-methylbenzylamine with chloroacetic ester. When, however, the ester was heated with concentrated alkali for a long time there was obtained a considerable amount of 3,4-dimethoxystyrene, as was demonstrated by its characteristic infrared absorption. Such fragility of the glycine toward both acid and base seems to make its intramolecular cyclization difficult, although somewhat different results have been reported by Manson and Winder [15] and by Mannich and Kupphal.[16]

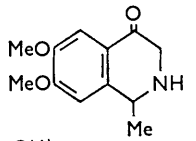
The above isoquinoline synthesis was then applied to the amine (IV). However, this amine failed to condense with ethyl chloroacetate or bromomalonic ester or acid. On attempted cyclization (cf. Mayer [17]) of the amide (XVI) (obtained from the amine and chloroacetyl chloride) by aluminium chloride in refluxing carbon disulphide, the amide was recovered quantitatively. Further, the trichloroacetyl derivative with aluminium chloride in nitromethane at 0—5° (cf. Stollé[18]) gave only a small amount of brown resin.



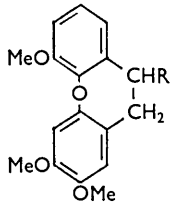
(XI: R = OH)
(XII: R = Cl)



(XIII: R = CHMe·NH·$[CH_2]_2$·OH)
(XIV: R = CHMe·NH·CO·$CH_2Cl$)



(XV)



(XVI: R = NH·CO·$CH_2Cl$)
(XVII: R = NH·CO·$CCl_3$)

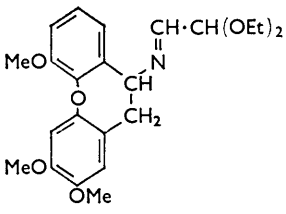
Accordingly, we reverted to Schlittler–Müller's method.[19] The amine (IV) was condensed with glyoxal hemiacetal and the Schiff base (XVIII) was directly treated with 76% sulphuric acid at 0° to −10°, but it gave only a small amount of brown basic powder. Next, the ketone (II) was condensed with aminoacetal azeotropically in toluene and the resulting Schiff base (XIX) was treated with 75% sulphuric acid. The basic product was chromatographed on alumina. In one of nine experiments an 8·35% yield of the desired base (XX) was obtained in a crystalline state. In the other cases yields were inferior (1·25—4·86%) and the products did not solidify. Recovery of the starting *ketone* (II) ranged from 40% to 65%.

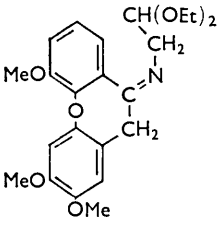
The crystalline isoquinoline (XX) gave a crystalline methiodide that was reduced to crystalline (±)-cularine with the correct analysis and an infrared spectrum (in chloroform) superimposable on that of natural cularine. Both specimens showed a NMe stretching vibration at 2809 cm.$^{-1}$ (in $CHCl_3$) and that of biphenyl ether at 1212 cm.$^{-1}$ (in KBr). They behaved similarly on paper chromatography.

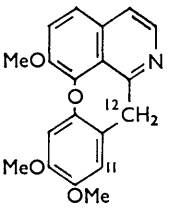
It seems to have been fortuitous that one of the nine attempts to carry out the Pomeranz–Fritsch reactions[20] with the amine (IV) gave a crystalline product (XX). In the other runs the oily bases gave oily methiodides whose further processing was unrewarding. The high recovery of starting ketone suggests competitive fission and cycliz-

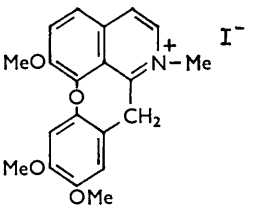
[15] Manson and Winder, *J.*, 1894, **65**, 190.
[16] Mannich and Kupphal, *Ber.*, 1912, **45**, 314.
[17] Mayer, van Zütphen, and Philippo, *Ber.*, 1927, **60**, 858.
[18] Stollé, *J. prakt. Chem.*, 1930, **128**, 1; G.P. 341,112.
[19] Gensler, *Org. Reactions*, 1951, **6**, 191.
[20] Perkin and Robinson, *J.*, 1914, **105**, 2376; Fritsch, *Annalen*, 1903, **329**, 37; Schlittler and Müller, *Helv. Chim. Acta*, 1948, **31**, 914; Inubushi and Fujitani, *J. Pharm. Soc. Japan*, 1958, **78**, 486.

ation of the Schiff base. When the oily product was processed as in the case of the solid, the product again was oily; attempted purification at this stage, including chromatography on alumina, led to a small amount of crystalline (±)-cularine. The oily residue in the mother-liquor showed an infrared ketonic band at 1720 cm.$^{-1}$, probably due to oxidation of the methylene group during chromatography; Clemmensen reduction


(XVIII)


(XIX)


(XX)


(XXI)

removed this band. Ready oxidation of active methylene groups is well known.[21] We noticed that chromatography of 3,4-dihydropapaverine on alumina led to recovery of 3,4-dihydropapaveraldine as the result of oxidation accelerated by alumina.[22] We therefore suggest that the difficulties in the cularine synthesis arose from oxidation of the methylene group in one or more of the intermediates, *e.g.*, the base (XX) or its methiodide, perhaps aided by the alumina used in chromatography.

Finally, hydrogenation of the isoquinoline (XX) gave a base, m. p. 106—107°, presumably (±)-cularimine (pyridine ring reduced), but the natural product (m. p.[23] 102°) was not available for comparison.

## Experimental

10-*Formamido*-10,11-*dihydro*-2,3,6-*trimethoxydibenzo*[b,f]*oxepin* (III).—(*a*) *Reaction with formamide.* The ketone (II) (3 g.) and formamide (8 g.) were heated at 160—180° for 5 hr., then poured into water (100 ml.), and the amorphous precipitate was extracted with chloroform. Drying ($Na_2SO_4$) and evaporation gave an amorphous substance (3·6 g.) that, on treatment with a small amount of warm ethyl acetate, yielded yellow crystals (1·7 g.). Recrystallization of this *formamido-derivative* from ethanol or benzene gave colourless needles (1·2 g., 33%), m. p. 192° (Found: C, 65·6; H, 5·9; N, 4·1. $C_{18}H_{19}NO_5$ requires C, 65·6; H, 5·8; N, 4·25%). The mother-liquor yielded starting material (0·3 g.) and a resin.

(*b*) *Reaction with ammonium formate.* The ketone (II) (3 g.) was heated with ammonium formate (8·2 g.) at 180° for 5 hr. After cooling, water (100 ml.) was added. A brown viscous oil that separated was extracted with chloroform, washed, dried ($Na_2SO_4$), recovered, and dissolved in hot ethyl acetate (10 ml.), from which crystals separated as it cooled. Recrystallization from ethanol afforded colourless needles (1·1 g.), m. p. 191—192°. The mother-liquor gave starting material (1·1 g.) and a resin.

(*c*) *Reaction with an excess of formamide for a long time.* After the ketone (3 g.) and formamide (40 g.) had been heated at 160—170° for 15 hr., they were cooled, poured into water (100 ml.), and extracted with chloroform. Removal of the dried ($Na_2SO_4$) solvent gave a dark brown powder (3·5 g.). This was chromatographed with elution by ethyl acetate, dark yellowish crystals (2·5 g.), m. p. 83—123°, being obtained from the first (yellowish-orange) and dark-brown amorphous powders (0·3 g.) from the second (orange) eluate. The former was treated with hot ethanol, leaving some residue. From the filtrate was obtained the *pyrimidine derivative* (VIII) (1·5 g.), m. p. 138—142° [Found: C, 67·5; H, 5·05; N, 7·9%; *M* (Rast), 338. $C_{19}H_{18}N_2O_4$ requires C, 67·4; H, 5·4; N, 8·3%; *M*, 326], which gave a picrate, yellow needles (from ethanol), m. p. 207—208° (Found: C, 51·9; H, 3·9; N, 12·6. $C_{19}H_{18}N_2O_4,C_6H_3N_3O_7,\frac{1}{2}H_2O$ requires C, 52·1; H, 3·8; N, 12·15%). The residue afforded the *pyridine derivative* (X) as yellow prisms (0·1 g.) (from ethyl acetate), m. p. 265° [Found:

[21] Yang, *J. Pharm. Soc. Japan*, 1962, **82**, 804; Kametani, Fukumoto, and Ogasawara, *ibid.*, 1963, **83**, 201.

[22] Kametani and Fukumoto, *J. Pharm. Soc. Japan*, in the press.

[23] Manske, *Canad. J. Res.*, 1938, **16**, *B*, 81.

C, 71·0; H, 4·0; N, 2·7%; *M* (Rast), 599·5. $C_{35}H_{29}NO_8$ requires C, 71·05; H, 4·9; N, 2·4%; *M*, 591·5]. The second eluate gave the formamido-derivative (III) (0·1 g.).

(*d*) *Reaction with formamide and formic acid.* Formamide (26·5 g.) and formic acid (4·6 g.) were added to the ketone (II) (10 g.), and the whole was heated at 180° under reflux for 5 hr.; the solid dissolved and after some time an orange, colloidal substance separated. On cooling, the mixture was poured into much water, and the precipitate was extracted with chloroform, washed with 5% sodium hydrogen carbonate solution and water, dried ($Na_2SO_4$), and recovered as a brown solid (7 g.). Recrystallization from ethyl acetate gave the formamido-derivative (III) (6·5 g., 59%), m. p. 189—190°.

10-*Amino*-10,11-*dihydro*-2,3,6-*trimethoxydibenzo*[b,f]*oxepin* (IV).—Heating the formamido-derivative (III) (1·7 g.) with concentrated hydrochloric acid (17 ml.) for 4·5 hr. gave a mixture containing crystals. After being kept in a refrigerator overnight, the pale yellow crystals were filtered off, washed with chloroform, and dried (2·2 g.; m. p. 248—251°). Recrystallization from water gave the *hydrochloride* as colourless needles, m. p. >285° (Found: C, 58·75; H, 5·9; N, 4·0. $C_{17}H_{19}NO_4,HCl,\frac{1}{2}H_2O$ requires C, 58·8; H, 6·05; N, 4·0%). The mother-liquor was basified with 10% sodium hydroxide solution to liberate the free *base* (IV) which was collected in benzene, washed with saturated sodium chloride solution and water, dried ($Na_2SO_4$), and recovered as a pink, viscous oil (0·1 g.) which solidified. Recrystallization from n-hexane yielded colourless prisms, m. p. 160—161° (Found: C, 68·1; H, 6·1; N, 4·4. $C_{17}H_{19}NO_4$ requires C, 67·8; H, 6·35; N, 4·65%).

2-(N-α-*Methylbenzylamino*)*ethanol* (XI).—A mixture of acetophenone (12·5 g.) and 2-aminoethanol (6·1 g.) in ethanol was shaken with platinum oxide (52·8 mg.) in an atmosphere of hydrogen. Uptake was complete in 9 hr. The mixture was filtered, the solvent was removed, and the residue was distilled *in vacuo*, giving the amino-alcohol (10·8 g.), b. p. 134—135°/6 mm. [picrate, needles (from ethanol–hexane), m. p. 138—141° (lit.,[12] 139—140°)].

Compound (XI) (1 g.) was added with cooling to polyphosphoric acid (85% phosphoric acid, 3 ml., phosphorus pentoxide, 5 g.) and heated at 170—180° for 12 hr. The solution was cooled, decomposed with ice–water, basified with concentrated aqueous ammonia, and extracted with benzene. The benzene extract was washed with water, dried ($Na_2SO_4$), and distilled, yielding a dark brown, viscous oil (0·5 g.), giving a picrate, needles (from ethanol), m. p. 236° (decomp.), thought to be 1,4-*di*-(α-*methylbenzyl*)*piperazine picrate* (Found: C, 47·9; H, 4·4. $C_{20}H_{26}N_2,2C_6H_3N_3O_7,3H_2O$ requires C, 47·6; H, 4·7%), $\nu_{max.}$ 3333 cm.$^{-1}$ (water of crystallization).

A mixture of the above amino-alcohol (XI) (1 g.), dry xylene (20 ml.), freshly distilled phosphoryl chloride (4 g.), and phosphorus pentoxide (5 g.) was refluxed for 5 hr. The solvent and excess of condensing agent were removed under reduced pressure. The residue was decomposed with ice–water, basified with concentrated aqueous ammonia, and extracted with benzene. The extract was washed with water, dried ($Na_2SO_4$), and distilled, giving a brown oil (0·7 g.), the preceding picrate, m. p. 229—231°.

The amino-alcohol (XI) (1 g.) was refluxed with thionyl chloride (3·5 g.) for 1 hr., the chloride obtained was refluxed with aluminium chloride (3 g.) in carbon disulphide (5 ml.) for 2 hr., and the mixture was worked up as usual, giving a brown oil (0·4 g.), whose picrate, m. p. 236° (decomp.), was identical with that obtained as above.

2-N-(3,4-*Dimethoxy*-α-*methylbenzyl*)*aminoethanol* (XIII).—A mixture of acetoveratrone (15·7 g.), 2-aminoethanol (5·52 g.), and platinum oxide (114·5 mg.) in ethanol (40 ml.) was hydrogenated. After some time palladium oxide (105·5 mg.) was added. Uptake of hydrogen was almost complete in 80 hr. The mixture was filtered, the solvent removed, and the residue distilled *in vacuo*, giving a pale yellow *alcohol* (XIII) (13·1 g.), b. p. 174—176°/3 mm. (Found: C, 63·3; H, 8·4; N, 6·6. $C_{12}H_{19}NO_3$ requires C, 64·0; H, 8·5; N, 6·2%).

This product (2 g.), methyl iodide (2·5 g.), and potassium carbonate (1·23 g.) were heated for 4 hr. in acetone (10 ml.). The mixture was filtered and the filtrate was allowed to cool. The *methiodide* separated and, crystallized from ethanol, had m. p. 127—128° (Found: C, 44·4; H, 6·4; N, 3·15. $C_{14}H_{23}INO_3$ requires C, 44·1; H, 6·3; N, 3·7%).

N-*Formyl*-3,4-*dimethoxy*-α-*methylbenzylamine*.—Acetoveratrone (15 g.) and formamide (15 g.) were heated at 180—190° for 12 hr., giving a reddish-brown solution. The mixture was poured into water, extracted with benzene, which was then washed with water and dried ($Na_2SO_4$). Removal of the solvent gave the solid *amide* (10·1 g.), which formed a pale yellow powder (from benzene–light petroleum), m. p. 98—101° (Found: C, 62·75; H, 7·0; N, 6·2. $C_{11}H_{15}NO_3$ requires C, 63·2; H, 7·2; N, 6·7%).

3,4-*Dimethoxy*-α-*methylbenzylamine*.—(*a*) The preceding amide (10 g.) and concentrated hydrochloric acid (7·2 ml.) were heated on a water-bath for 3 hr., then poured into water. After the neutral substance had been removed by extraction, the acidic solution was basified with 20% sodium hydroxide solution and extracted with benzene. The extract was washed with water, dried ($Na_2SO_4$), and distilled, *in vacuo* after removal of the solvent, giving a colourless *base* (2 g.), which solidified (Found: C, 62·8; H, 8·9; N, 7·9. $C_{10}H_{15}NO_2,\frac{1}{2}H_2O$ requires C, 63·1; H, 8·5; N, 7·4%). Recrystallization of the *hydrochloride* from ethanol–ether gave colourless cubes, m. p. 215—216° (Found: C, 55·2, 55·3; H, 7·3, 7·4; N, 6·5. $C_{10}H_{15}NO_2,HCl$ requires C, 55·2; H, 7·4; N, 6·4%).

(*b*) Metallic sodium (166·5 g.) was added in small portions to a stirred and refluxed solution of acetoveratrone oxime (XVII) (65 g.) in ethanol, which was refluxed for a further 4—5 hr. A small amount of ethanol was then added to dissolve the excess of sodium. Ethanol was distilled off and the residue was added to water, salted out with much potassium carbonate, and extracted with ether. Distillation of the dried ($Na_2SO_4$) extract gave a pale yellow liquid (40·9 g.), b. p. 120—125°/5 mm.

N-*Chloroacetyl*-3,4-*dimethoxy*-α-*methylbenzylamine* (XIV).—The preceding amine (3 g.) in acetone (10 ml.) was mixed with 10% sodium carbonate solution (10 ml.) and treated with chloroacetyl chloride (3·9 g.) with cooling and stirring. The mixture was stirred for a further 6 hr., then evaporated under reduced pressure. The residue was diluted with water and extracted with ethyl acetate, and the extract was washed with 10% hydrochloric acid and saturated sodium chloride solution and dried ($K_2CO_3$). Evaporation gave a pale orange liquid (2·6 g.), which solidified. Recrystallization from benzene afforded the *chloroacetamide* as pale yellow crystals, m. p. 96—97° (Found: C, 55·9; H, 6·3; N, 5·5. $C_{12}H_{16}ClNO_3$ requires C, 55·9; H, 6·2; N, 5·4.

N-(3,4-*Dimethoxy*-α-*methylbenzyl*)*glycine Methyl Ester*.—The benzyl amine (10 g.) was heated with methyl chloroacetate (6·6 g.) at 72—82° for 1 hr., pale orange crystals separating. After being kept in a refrigerator for 3 hr., the mixture was diluted with cold ethanol and filtered. Recrystallization from ethanol–ether gave the hydrochloride of recovered material (6·7 g.), m. p. 224—225°. Concentration of the ethanolic mother-liquor gave a brown oil, which was diluted with water (20 ml.), basified with sodium carbonate, and extracted with ether; the extract was washed and dried and the solvent was removed. Distillation of the residue yielded the *glycine ester* (4·4 g.), b. p. 168—178°/7 mm. (Found: C, 62·1; H, 6·9; N, 5·0. $C_{13}H_{19}NO_4$ requires C, 61·6; H, 7·6; N, 5·5%). Recrystallization of its *hydrochloride* from methanol–ether afforded cubes, m. p. 170° (decomp.) (Found: C, 53·6; H, 7·0; N, 4·8. $C_{13}H_{20}ClNO_4$ requires C, 53·9; H, 7·0; N, 4·8%).

N-(3,4-*Dimethoxy*-α-*methylbenzyl*)*glycine*.—The preceding ester (4·3 g.) in ethanol (10 ml.) was refluxed in 10% sodium hydroxide solution (10 ml.) for 5 hr. Evaporation gave a yellow oil, which was extracted with benzene. Removal of the dried ($Na_2SO_4$) solvent yielded a yellow oil (2·2 g.), which was distilled *in vacuo* to give 3,4-dimethoxystyrene, b. p. 117—119°/10 mm. (Found: C, 73·6; H, 7·6. $C_{10}H_{12}O_2$ requires C, 73·1; H, 7·4%) (lit.,[24] b. p. 120—125°/10 mm.), $\nu_{max.}$ 3100—3080 (:$CH_2$), 3020 (:CH·), 1635 (conj. C=C), 1418, 985, 910 (·CH:$CH_2$) cm.$^{-1}$.

The above alkaline solution was acidified with 10% hydrochloric acid and evaporated to dryness. The residue was repeatedly extracted with methanol, and the extract was again evaporated to dryness. This procedure was repeated three times. Recrystallization of the last residue (1 g.) gave the *glycine hydrochloride* as colourless needles, m. p. 210—212° (Found: C, 52·4; H, 6·4; N, 4·9. $C_{12}H_{17}NO_4,HCl$ requires C, 52·3; H, 6·5; N, 5·1%).

1,2,3,4-*Tetrahydro*-6,7-*dimethoxy*-1-*methyl*-4-*oxoisoquinoline*.—(*a*) The glycine ester (1 g.) was added to a mixture of phosphorus pentoxide (10 g.) and 85% phosphoric acid (6·5 ml.), and the whole was gradually warmed in a water-bath. The mixture became pink at 45—50°, and the temperature was raised gradually to 68° and kept there for 2 hr. with occasional stirring, then cooled, poured into ice–water (20 ml.), extracted with ether, basified by concentrated sodium carbonate solution, and extracted with ethyl acetate. The ethyl acetate extract was washed with water, dried ($Na_2SO_4$), and evaporated, giving 1,2,3,4-tetrahydro-6,7-dimethoxy-1-methyl-4-oxoisoquinoline (XV) as a reddish-orange oil (0·5 g.), whose *hydrochloride* recrystallized from methanol–ether in pale yellow needles, m. p. 169—171° (decomp.) (Found: C, 54·2; H, 6·9; N, 5·3. $C_{12}H_{15}NO_3,HCl,\frac{1}{2}H_2O$ requires C, 54·0; H, 6·4; N, 5·25%).

[24] Barger and Jowett, *J.*, 1905, **87**, 972.

Methylation of this isoquinoline with methyl iodide and recrystallization of the product from methanol–ether gave *1,2,3,4-tetrahydro-6,7-dimethoxy-1,2-dimethyl-4-oxoisoquinoline hydriodide* as pale yellow prisms, m. p. 215—217° (Found: C, 38·8, 39·0; H, 5·45, 5·5; N, 4·3. $C_{13}H_{18}INO_3,2H_2O$ requires C, 39·1; H, 5·5; N, 5·25%).

(*b*) The substituted glycine (4·4 g.) was added to phosphorus pentoxide (40 g.) and 85% phosphoric acid (30 ml.), and the mixture was heated at 70—80° for 2 hr. On cooling, the mixture was poured into ice–water (40 ml.) and the solution was shaken with ether, basified with 10% sodium carbonate solution, and extracted with ethyl acetate. This extract was washed with water, dried ($Na_2SO_4$), and evaporated to an oil (1 g.), which was characterized as the hydrochloride, m. p. 168—169°.

The above ethereal extract was washed with water. Removal of the dried ($Na_2SO_4$) solvent gave a yellow, brown oil. Purification by chromatography yielded 3,4-dimethoxystyrene (0·1 g.), b. p. 98—101°/4 mm., whose infrared spectrum was identical with that of the product obtained by hydrolysis of the ester. The styrene decolorized 1% potassium permanganate solution in aqueous acetone.

*N-Benzylglycine.*—(*a*) Diethyl bromomalonate (5·5 g.) was added with shaking to an ethanolic solution of benzylamine (3·2 g.) containing sodium (2·1 g.), and the mixture was stirred and refluxed for 4 hr. Ethanol was distilled off, and the residue refluxed with 10% sodium hydroxide solution (65 ml.) for 1·5 hr. After the alkaline solution had been cooled and extracted with ether, it was acidified with hydrochloric acid and evaporated to dryness under reduced pressure. Extraction of the residue with ethanol and removal of the solvent were repeated twice, giving an orange solid. This was heated at 165—185° for 0·5 hr. and basified with 10% sodium hydroxide solution with cooling. The mixture was extracted with ether, acidified with 10% hydrochloric acid, and evaporated under reduced pressure. Extraction of the residue with ethanol, and removal of the solvent yielded *N*-benzylglycine (5·4 g.). Recrystallization from ethanol afforded pale yellow needles (1·8 g.), m. p. 214—216° (lit.,[15] 214—215°).

(*b*) Bromomalonic acid (4·3 g.) was added to a solution of benzylamine (5 g.) in ethanol (20 ml.), and the mixture was refluxed for 4 hr. Ethanol was distilled off, the residue was acidified with 10% hydrochloric acid and extracted with ether. The acidic solution was evaporated to dryness, yielding a yellowish-orange substance, m. p. 157—160° (decomp.). When this was heated in an oil-bath, evolution of carbon dioxide began at 128° and was completed by heating at 135—145° for 15 min. and at 180° for 5 min. The resultant substance was cooled, dissolved in 10% sodium hydroxide solution, and extracted with ether. The alkaline solution was then acidified with 10% hydrochloric acid, evaporated to dryness under reduced pressure, and extracted with ethanol. Removal of the solvent gave a yellow residue (10·8 g.), which was purified from ethanol to give colourless needles (4·0 g.), m. p. 214—216°, identical with the preceding product.

*10-Chloroacetamido-10,11-dihydro-2,3,6-trimethoxydibenzo*[b,f]*oxepin* (XVI).—Chloroacetyl chloride (0·25 g.) was added to a yellow solution of the amine (IV) (0·6 g.) and potassium carbonate (2·1 g.) in acetone (20 ml.), and the mixture was shaken at room temperature (20—25°) for 1 hr. After removal of the solvent, the brown viscous residue was extracted with chloroform. The extract was washed with 10% aqueous sodium carbonate, 10% hydrochloric acid, and water, dried ($Na_2SO_4$), and evaporated, yielding pale yellow prisms (0·5 g.), m. p. 165—167°. Recrystallization from ethanol afforded the *amide* as colourless needles, m. p. 182—183° (Found: C, 60·3; H, 5·45; N, 3·6. $C_{19}H_{20}ClNO_5$ requires C, 60·4; H, 5·3; N, 3·7%).

*10,11-Dihydro-2,3,6-trimethoxy-10-trichloroacetamidodibenzo*[b,f]*oxepin* (XVII).—Trichloroacetyl chloride (4·0 g.) was added to a stirred and cooled solution of the amine (IV) (4·5 g.) in acetone (180 ml.) containing potassium carbonate (15 g.), the mixture was stirred at room temperature for 40 min., then refluxed for 10 min. After filtration, the acetone was distilled off, and the residue was extracted with chloroform. The extract was washed successively with 10% sodium carbonate solution, 10% hydrochloric acid, and water. Removal of the dried ($Na_2SO_4$) solvent gave the *trichloroacetamide* as a yellow solid (1·9 g.). Recrystallization from hexane afforded pale orange prisms, m. p. 139° (Found: C, 49·4; H, 4·6; N, 2·9. $C_{19}H_{18}Cl_3NO_5,H_2O$ requires C, 49·0; H, 4·3; N, 3·0%), $\nu_{max.}$ 3560 cm.$^{-1}$ (in KBr) (water of crystallization).

*6,9,10-Trimethoxy-12H-*[*-1-*]*benzoxepino*[*2,3,4-ij*]*isoquinoline* (XX).—Aminoacetal (18 g.) was mixed with a suspension of 2,3,6-trimethoxydibenzo[*b,f*]oxepin-10(11*H*)-one (II) (10 g.) in

toluene (110 ml.) containing 5 drops of pyridine and heated on an oil-bath under reflux for 7 hr., water (0·5—0·6 ml.) being separated. Removal of the solvent gave the Schiff base (XIX) as a dark brown viscous oil.

To 75% sulphuric acid (78 g.) at $< -10°$ was added the Schiff base (XIX), and the mixture was kept at 0° for 63 hr., forming a reddish-brown solution, which was added to ice–water (200 ml.). An amorphous substance that separated was filtered off. The filtrate was extracted with benzene, and removal of the solvent gave the ketone (II) (4·2 g.). The mother-liquor, after being made alkaline with concentrated aqueous ammonia, was extracted with benzene. The extract was washed with water, then dried ($K_2CO_3$), and removal of the solvent yielded a resin (2·8 g.). This was chromatographed in benzene on alumina (72 g.). A benzene filtrate having a violet fluorescence was collected and the solvent was removed, to give a pink-red oil (0·9 g.), which solidified. Recrystallization from ether–light petroleum afforded the *base* (XX) as colourless pillars, m. p. 133° (Found: C, 70·8; H, 5·5; N, 4·65. $C_{19}H_{17}NO_4$ requires C, 70·6; H, 5·3; N, 4·3%), $\nu_{max.}$ 1620 (C=N) and 1403 ($CH_2$) cm.$^{-1}$ (in KBr), $\lambda_{max.}$ 231 (log ε 4·56) and 285 mμ (log ε 3·94) in EtOH.

The *picrate* formed pale yellow needles (from acetone), m. p. 222° (Found: C, 54·2; H, 3·7; N, 10·3. $C_{19}H_{17}NO_4,C_6H_3N_3O_7$ requires C, 54·35; H, 3·5; N, 10·1%).

(±)-*Cularine* (I).—The crystalline isoquinoline (XX) (150 mg.), methyl iodide (2 ml.), and methanol (6 ml.) were refluxed for 1 hr., more methyl iodide (0·5 ml.) was then added, and refluxing continued for an additional 2 hr. More methyl iodide (2 ml.) was added and the whole was set aside overnight. The *methiodide* [150 mg.; m. p. 209—213° (decomp.)], separated and recrystallized from methanol–ether as yellow needles, m. p. 222—223° (Found: C, 48·2; H, 5·0; N, 3·1. $C_{20}H_{20}INO_4,2H_2O$ requires C, 47·9; H, 4·8; N, 2·8%), $\nu_{max.}$ 3497 cm.$^{-1}$ (KBr) (water of crystallization).

Sodium borohydride (0·3 g.) was added in small portions with shaking to a solution of the methiodide (0·15 g.) in methanol (10 ml.) containing 10 drops of water, the yellow solution becoming colourless. After 1·5 hours' refluxing the solvent was distilled off, and the residue treated with ice–water and extracted with benzene. The benzene extract was washed with water, dried ($K_2CO_3$), and evaporated, leaving a yellowish-orange glass (0·1 g.), which crystallized on being triturated with ether (m. p. 104—106°). Recrystallization from ether afforded (±)-*cularine* as pale yellow cubes, m. p. 113—114° (Found: C, 70·6; H, 7·0; N, 4·1. $C_{20}H_{23}NO_4$ requires C, 70·4; H, 6·8; N, 4·1%).

The vitreous residue could also be worked up as follows. It was extracted with warm pentane–ether (10 : 1). The solvent was removed from the extract, and the residue thus obtained was chromatographed, giving a yellow benzene eluate. The residue from the eluate was again extracted with pentane–ether (10 : 1) and the extract was kept in the refrigerator for a long time, giving pale yellow cubes, m. p. 114°, $\lambda_{max.}$ 226 (log ε 4·38) and 285 mμ (log ε 3·92 in EtOH), $R_F$ (synthetic) 0·79, (natural) 0·81 [butanol–acetic acid–water (4 : 1 : 5) as solvent; 1% aqueous potassium permanganate as spray].

Infrared spectra, measured on a Type EPI-2 Hitachi infrared spectrophotometer with sodium chloride optics, of synthetic and natural cularine in chloroform were identical. In KBr, a slight difference in the compounds was observed.

(±)-*Cularimine*.—The base (XX) (0·2 g.) in methanol (70 ml.) was hydrogenated at atmospheric pressure in the presence of Adams catalyst (128·5 mg.) and 2 drops of concentrated hydrochloric acid. Filtration and removal of the solvent *in vacuo* gave a brown oil, which was dissolved in water. The resultant acidic solution was basified with 10% sodium carbonate solution, and extracted with benzene. The solvent was washed with water and dried ($K_2CO_3$). Removal of the solvent gave a brown, viscous substance (0·1 g.), which was triturated with ether to form crystals, m. p. 98—100°. Recrystallization from ether afforded (?) (±)-*cularimine* as yellowish-orange cubes, m. p. 106—107° (Found: C, 69·8; H, 6·0; N, 4·5. $C_{19}H_{21}NO_4$ requires C, 69·7; H, 6·5; N, 4·3%).

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