793. *Cularine and Related Compounds. Part VIII.*[1] *A Modified Total Synthesis of* (±)-*Cularine Methiodide.*[2]

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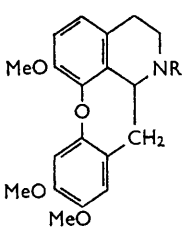
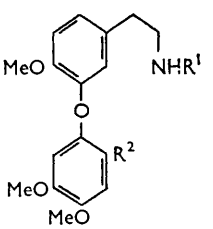
Hydrolysis of the azlactone (V) with various reagents was examined and the dibenzoxepin (IX) was obtained by heating the azlactone with concentrated barium hydroxide solution. Lederer–Manasse reaction of the intermediate (VIb) in the presence of base gave the dibenzoxepin (IX) in excellent yield; methylation then gave the dimethylamino-derivative (X). Hofmann degradation of the methiodide (XI), and oxidation of the methine as above, gave the tricarboxylic acid (XIV) and the mono-acid (XIII), which support structure (X) for the dimethylamino-compound. Compound (X) was converted into (±)-cularine methochloride (IV) by cyclization with thionyl chloride. Treatment of the methochloride with potassium iodide gave cularine methiodide (III), the infrared spectrum of which was identical with that of racemic cularine methiodide.

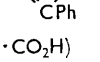
A TOTAL synthesis of cularine has already been described,[3] confirming Manske's structure (I) [5,6] for the alkaloid, but the yield was poor. The present Paper describes an alternative synthesis by which (±)-cularine methiodide (III) is obtained in better yield.



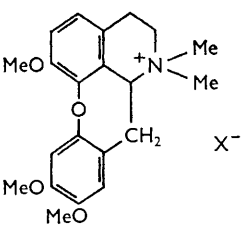
(I: R = Me)
(VII: R = H)



(II R^1 = COMe, R^2 = CHO)
(V R^1 = COMe, R^2 = CH=C—C=O)



(VIa: R^1 = H, R^2 = $CH_2 \cdot CO \cdot CO_2H$)
(VIb: R^1 = H, R^2 = $CH_2 \cdot CHO$)

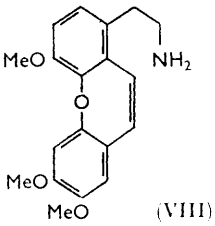


(III: X = I)
(IV: X = Cl)

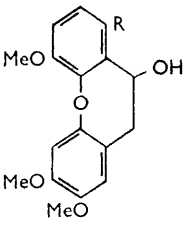
[1] Part VII, Kametani, Fukumoto, and Masuko, *J. Pharm. Soc. Japan*, 1963, **83**, 1052.
[2] This forms Part XCIX of "Studies on the Syntheses of Heterocyclic Compounds," by T. Kametani.
[3] Kametani and Fukumoto, *Chem. and Ind.*, 1963, 291; *J.*, 1963, 4289.
[4] Kametani, Fukumoto, and Ogasawara, *J. Pharm. Soc. Japan*, 1963, **83**, 180.
[5] Manske, *Canad. J. Res.*, 1940, **18**b, 97.
[6] Manske, *J. Amer. Chem. Soc.*, 1950, **72**, 55.

Acid hydrolysis of the azlactone (V) did not give the expected cularimine (VII), and hydrolysis with aqueous sodium hydroxide did not produce the α-keto-acid (VIa). However, when the azlactone (V) was heated with concentrated aqueous barium hydroxide it was converted into a product which, on chromatography, yielded the hydroxy-amine (IX) and a second fraction which was probably the anhydro-compound (VIII), since it showed an absorption band at 1630 cm.$^{-1}$ (C=C stretching) which was lacking in the spectrum of (IX).

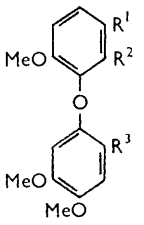
Eschweiler–Clarke methylation of the base (IX) gave a crude *NN*-dimethyl derivative (X), which, with methyl iodide, yielded the methiodide (XI) [also obtainable in poor yield from (IX) and methyl iodide]. Hofmann degradation gave the nitrogen-free methine (XII), the structure of which was confirmed by oxidation to the tricarboxylic acid (XIV) described by Manske,[6] and to a monocarboxylic acid (XIIIa). Under mild oxidation conditions the latter is the main product; similar resistance of the secondary alcohol group to oxidation is shown by compound (XIIIc).[7] Since the analytical figures did not differentiate sufficiently clearly between structure (XIIIa) and other possible structures such as (XVI) and (XX), the latter were synthesized and shown to be different from the oxidation product. Formation of the acid (XIIIa) confirms the dibenzoxepin structure of the dimethylamine (X).



(VIII)



(IX) R = $[CH_2]_2NH_2$
(X) R = $[CH_2]_2NMe_2$
(XI) R = $[CH_2]_2\overset{+}{N}Me_3I^-$
(XII) R = $CH{:}CH_2$
(XIIIa) R = CO_2H
(XIIIb) R = CO_2Me
(XIIIc) R = H



(XIV) $R^1 = R^2 = R^3 = CO_2H$
(XV) $R^1 = CHO$, $R^2 = R^3 = H$
(XVI) $R^1 = CO_2H$, $R^2 = R^3 = H$
(XVII) $R^1 = R^3 = CHO$, $R^2 = H$
(XVIII) $R^1 = R^3 = CO_2H$, $R^2 = H$
(XIX) $R^1 = R^2 = H$, $R^3 = CHO$
(XX) $R^1 = R^2 = H$, $R^3 = CO_2H$

Treatment of the *NN*-dimethylamino-derivative (X) with thionyl chloride and pyridine caused cyclisation to (±)-cularine methochloride (IV), which was converted into the methiodide (III). The product was identical with material synthesised previously.[3,4]

Experimental

4-[2-(5-2′-*Acetamidoethyl*-2-*methoxyphenoxy*)-4,5-*dimethoxybenzylidene*]-2-*phenyloxazol*-5-*one* (V).—The aldehyde [4] (II) (2·7 g.), hippuric acid (1·4 g.), acetic anhydride (3 g.), and potassium hydrogen carbonate (1 g.) were heated on a water-bath for 2 hr. The acetic anhydride was decomposed with hot water, the precipitate collected and washed with 5% sodium hydrogen carbonate solution and water, and the *azlactone* crystallized from benzene, orange needles (3·2 g., 88·9%), m. p. 203—205° (Found: C, 67·4; H, 5·5; N, 5·7. $C_{29}H_{28}N_2O_7$ requires C, 67·4; H, 5·5; N, 5·4%), $\nu_{max.}$ (KBr) 3301 (NH), 1790 (lactone C:O), and 1645 cm.$^{-1}$ (amide C:O).

Hydrolysis of the Azlactone (V).—The azlactone (5·9 g.) and barium hydroxide octahydrate (33 g.) were heated in water (115 ml.) under reflux for 8 hr. The mixture was set aside overnight and extracted with benzene. The extract was washed with saturated sodium chloride solution and dried (Na_2SO_4). Removal of the solvent yielded a pale, yellow-green, viscous oil (3·1 g.). After the barium hydroxide had been filtered off from the above aqueous solution, the filtrate was acidified with 10% hydrochloric acid and extracted with ether. Removal of the dried (Na_2SO_4) solvent gave benzoic acid (1·2 g.).

The above crude oil (0·7 g.) was dissolved in hot 20% hydrochloric acid (3·5 ml.). On

[7] Kametani and Fukumoto, *Chem. and Pharm. Bull. Japan*, 1963, **11**, 1322.

cooling, the mixture was washed with benzene and the acidic solution was basified with 10% ammonium hydroxide. The brown oil which separated was extracted with benzene, and the extract was washed with saturated sodium chloride solution, dried (K_2CO_3), and distilled under reduced pressure, affording a yellow-orange, viscous oil (0·6 g.) having a violet fluorescence. Alumina chromatography of the base in benzene afforded two fractions. The first fraction gave the dibenzoxepin (VIII) (0·1 g.), $\nu_{max.}$ ($CHCl_3$) 1630 cm.$^{-1}$ (C:C), $\lambda_{max.}$ (EtOH) 277 and 320 mμ (log ε 3·87 and 3·43). The second, larger fraction had a violet fluorescence, and distillation of the solvent gave 9-2′-*aminoethyl*-10,11-*dihydro*-10-*hydroxy*-2,3,6-*trimethoxydibenz*[b,f]*oxepin* (IX) (0·4 g.) as an oil which did not solidify, $\nu_{max.}$ ($CHCl_3$) 3450 and 3350 cm.$^{-1}$ (OH and NH), $\lambda_{max.}$ (EtOH) 283 and 345 mμ (log ε 3·82 and 2·08). The *picrate* formed needles, m. p. 202° (subl.) (from methanol) (Found: C, 53·3; H, 4·15; N, 10·05. $C_{25}H_{26}N_4O_{11}$ requires C, 53·75; H, 4·65; N, 10·05%). Overall yield of (IX) from (V) was 48%.

10,11-*Dihydro*-10-*hydroxy*-2,3,6-*trimethoxy*-9-2′-*dimethylaminoethyldibenz*[b,f]*oxepin* (X).—To a solution of the above base (IX) (0·8 g.) in formic acid (2 ml.), 35% formalin (2 ml.) was added, and the mixture was heated on a water-bath for 4 hr. After cooling, 10% hydrochloric acid was added, and the mixture was washed with benzene. A brown oil, which separated upon treatment of the mixture with 10% ammonium hydroxide, was extracted with benzene. The extract was washed with saturated sodium chloride solution. Removal of the dried (K_2CO_3) solvent left an oil (0·7 g.). This was chromatographed on alumina, but no crystalline substance was obtained. Distillation *in vacuo* afforded a pale yellow oil (X) (0·55 g., 63·6%) having a violet fluorescence, b. p. 180—182°/0·1 mm. (Found: C, 68·3; H, 7·5; N, 3·95. $C_{21}H_{27}NO_3$ requires C, 67·55; H, 7·2; N, 3·75%), $\nu_{max.}$ ($CHCl_3$) 3556 (OH) and 2800 cm.$^{-1}$ (NMe), $\lambda_{max.}$ (EtOH) 283 and 342 mμ (log ε 3·83 and 2·82). Gas chromatography of the distilled base (X) (2 m. column, 240°, 3% SE 30 on Celite, 40 ml./min. helium) showed a peak with a retention time of 21·5 min. and no other peak was observed.

The *picrate* formed needles, m. p. 150—152° (from acetone–ethanol–ether) (Found: C, 53·75; H, 4·35; N, 9·85. $C_{27}H_{30}N_4O_{12}$ requires C, 53·8; H, 5·0; N, 9·3%).

Preparation of the Methiodide (XI).—(*a*) *From the amine* (IX). The mixture of the base (IX) (0·6 g.), freshly distilled methyl iodide (0·5 g.), and methanol (1 ml.) was set aside at room temperature overnight. The precipitate, after washing with 10% hydrochloric acid to remove the hydriodide of (IX), gave the methiodide (XI) (0·5 g.) as colourless prisms, m. p. 231·5—232° (from methanol) (Found: C, 51·65; H, 5·85; N, 2·85. $C_{22}H_{30}INO_5$ requires C, 51·25; H, 5·85; N, 2·7%), $\lambda_{max.}$ (EtOH) 283 mμ (log ε 3·89). The Beilstein halogen test was positive.

(*b*) *From the dimethylamine* (X). The dimethylamine (4·4 g.), methyl iodide (5 g.), and methanol (5 ml.) were set aside overnight. The methiodide (XI) separated and was recrystallized from methanol as colourless prisms (3·1 g., 81%), identified by mixed m. p. and infrared and ultraviolet spectra.

Hofmann Degradation of the Methiodide (XI).—The methiodide (2·2 g.) was suspended in water (30 ml.) and heated on a water-bath with potassium hydroxide (6 g.) for several hours. The turbidity did not disappear. The mixture was heated by a naked flame until the solid precipitate changed to an oil, which was extracted with ether. Removal of the washed and dried (Na_2SO_4) solvent afforded a brown oil (1·1 g.). Trituration of this oil with ether gave the methine (XII) as a colourless powder, m. p. 120—125°, $\nu_{max.}$ ($CHCl_3$) 1640 (C:C) and $\delta_{max.}$ 990, 905 cm.$^{-1}$ (CH:CH_2). During the reaction, a vigorous evolution of a gas having an amine-like odour was observed. A test for nitrogen in (XII) by sodium fusion was negative.

10,11-*Dihydro*-10-*hydroxy*-2,3,6-*trimethoxydibenz*[b,f]*oxepin*-9-*carboxylic Acid* (XIIIa) *and* 4′,5′,6-*Trimethoxyphenoxybenzene*-2,2′,3-*tricarboxylic Acid* (XIV).—(*a*) The above methine (XII) (1·0 g.) was dissolved in acetone (6 ml.) and treated with finely powdered potassium permanganate (3 g.) until a permanent pink colour was obtained. Water (10 ml.) was added, the solvent was removed under reduced pressure, and the mixture filtered. The cooled filtrate was acidified with hydrochloric acid. The pale brown oil which separated was extracted with ether. The solvent was washed with water, dried (Na_2SO_4), and removed by distillation, yielding a white powder (0·5 g.). Recrystallization from ethanol–n-hexane gave the *monocarboxylic acid* (XIIIa), white prisms, m. p. 178° (Found: C, 62·7; H, 5·55. $C_{18}H_{18}O_7$ requires C, 62·4; H, 5·25%), $\nu_{max.}$ (KBr) 3500 cm.$^{-1}$ (OH).

(*b*) The above methine (XII) (300 mg.) was dissolved in a liberal volume of acetone and the solution treated with finely powdered potassium permanganate (1·5 g.) until a permanent pink colour was obtained. Hot water (15 ml.) was added, the acetone boiled off, and the hot mixture

filtered. The cooled filtrate was acidified with hydrochloric acid and extracted with benzene. The extract was washed with water, dried (Na_2SO_4), and evaporated, leaving a colourless powder (150 mg.). Recrystallization from benzene afforded the monocarboxylic acid as colourless crystals, m. p. 178°. From the mother-liquor the tricarboxylic acid (XIV), m. p. 186—187° (lit.,[6] 187°), $\nu_{max.}$ (KBr) 1695 cm.$^{-1}$ (C:O), was obtained. Since insufficient natural cularine was available, comparison with the Hofmann degradation product (XIV) obtained from (+)-cularine could not be done.

Esterification of the Monocarboxylic Acid (XIIIa).—The acid (100 mg.) was dissolved in methanol and dry hydrogen chloride was passed in. The mixture was refluxed on a water-bath for 0·5 hr. and the solvent was removed, giving a brown oil which was extracted with hot n-hexane. The extract gave crystals on standing. Distillation of the product *in vacuo* afforded a viscous oil, b. p. 200° (bath)/0·05 mm., which solidified. Recrystallization from n-hexane–ethanol gave the *methyl ester* (XIIIb) as colourless cubes, m. p. 66—67° (dried over P_2O_5 at 20°, 24 hr./5 mm.) (Found: C, 63·4; H, 5·85. $C_{19}H_{20}O_7$ requires C, 63·3; H, 5·85%), $\nu_{max.}$ (KBr) 3450 (OH) and 1710 cm.$^{-1}$ (C:O).

3-(3,4-*Dimethoxyphenoxy*)-4-*methoxybenzoic Acid* (XVI).—(*a*) *Ullmann condensation.* Isovanillin (3·1 g.), 4-bromo-1,2-dimethoxybenzene [8] (4·3 g.), copper powder (2·3 g.), potassium carbonate (2·8 g.), and pyridine (1 ml.) were gradually heated for 1 hr. until the temperature of the mixture reached 150° (a vigorous gas evolution was observed at this temperature). The mixture was cooled, extracted with chloroform, and filtered. The solvent was washed with 10% sodium hydroxide, saturated sodium chloride solution, 10% hydrochloric acid, and water, dried (K_2CO_3), and distilled, giving the aldehyde (XV) as a dark brown oil (2·4 g.), which did not solidify.

(*b*) *Oxidation.* The above aldehyde (XV) (2·4 g.) was dissolved in a small amount of acetone, and water (20 ml.) was added. A solution of potassium permanganate (3·6 g.) in water (50 ml.) was added drop by drop to the above solution, with stirring, at 80°. After the pink colour had completely disappeared, the cooled and filtered mixture was acidified with hydrochloric acid and the precipitate filtered off. Recrystallization from ethanol afforded the *acid* (XVI) (0·9 g.) as a colourless powder, m. p. 187—188° (Found: C, 62·9; H, 5·55. $C_{16}H_{16}O_6$ requires C, 63·15; H, 5·3%), $\nu_{max.}$ (KBr) 1680 cm.$^{-1}$ (C:O).

4,5,6′-*Trimethoxyphenoxybenzene*-2,3′-*dialdehyde* (XVII).—Isovanillin (5 g.), 2-bromo-4,5-dimethoxybenzaldehyde [9] (8·0 g.), copper powder (0·3 g.), and potassium carbonate (4·2 g.) were crushed in a mortar, and pyridine (0·5 ml.) was added. The mixture was heated in an oil-bath at 165° for 80 min. until the gas evolution grew weak, extracted with saturated sodium hydrogen sulphate solution, and the aqueous extract was extracted with ethyl acetate to remove non-aldehyde. The resulting solution was basified with 10% sodium hydroxide, heated on a water-bath for 5 min., and extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and evaporated, leaving a dark reddish viscous oil (4 g.) which crystallized on being triturated with a small amount of ethanol to give the *dialdehyde* (XVII) as colourless scales, m. p. 138—140° (from n-hexane–benzene) (Found: C, 64·9; H, 5·15. $C_{17}H_{16}O_6$ requires C, 64·55; H, 5·1%), $\nu_{max.}$ (KBr) 1680 cm.$^{-1}$ (C:O).

4,5,6′-*Trimethoxyphenoxybenzene*-2,3′-*dicarboxylic Acid* (XVIII).—To a heated (70—80°) suspension of the above aldehyde (XVII) (0·5 g.) in water (5 ml.), a solution of potassium permanganate (1 g.) in water (5 ml.) was added dropwise. The suspension was heated on a water-bath for 2 hr. On cooling, the solution was made alkaline with 10% potassium hydroxide, filtered, and acidified with hydrochloric acid. The precipitate was collected and recrystallized from acetic acid to give the *dicarboxylic acid* (XVIII) as colourless cubes, m. p. 283° (decomp.) (Found: C, 58·05; H, 4·85. $C_{17}H_{16}O_8$ requires C, 58·6; H, 4·65%), $\nu_{max.}$ (KBr) 1695 cm.$^{-1}$ (C:O).

2-(2-*Methoxyphenoxy*)*veratraldehyde* (XIX).—To a mixture of 2-bromo-4,5-dimethoxybenzaldehyde [9] (15·2 g.), guaiacol (9·0 g.), copper powder (16·8 g.), potassium carbonate (10·2 g.), and potassium hydrogen carbonate (6 g.), pyridine (2 ml.) was added, and the mixture was heated in an oil-bath for 1 hr. Copious evolution of gas was observed. The resultant mixture was, while warm, extracted with chloroform, and the extract was washed with 10% sodium hydroxide, saturated sodium chloride solution, 10% hydrochloric acid, and water. Removal of the dried (Na_2SO_4) solvent yielded a dark brown viscous oil (20 g.). Distillation of the oil

[8] Bannard, *Canad. J. Chem.*, 1953, **31**, 953; Buu-Hoï, *Annalen*, 1944, **556**, 1.
[9] Pschorr, *Annalen*, 1912, **391**, 32.

in vacuo afforded the *aldehyde* as a pale yellowish-green oil, b. p. 190—194°/0·18—0·15 mm., which solidified and had m. p. 58—59° (Found: C, 66·3; H, 5·85. $C_{16}H_{16}O_5$ requires C, 66·65; H, 5·6%), $\nu_{max.}$ (liquid) 1685 cm.$^{-1}$ (C:O).

2-(2-*Methyoxyphenoxy*)*veratric Acid* (XX).—The above aldehyde (XIX) (4·3 g.), acetone (6 ml.), and water (40 ml.) were mixed, and a solution of potassium permanganate (6·3 g.) was added dropwise during 1 hr., with stirring, at 80°. The mixture was heated for 2 hr., cooled, basified with 10% potassium hydroxide, and filtered. The filtrate was acidified with 10% hydrochloric acid and the precipitate collected by filtration. Recrystallization from ethanol afforded the *acid* (XX) (3·6 g.) as a colourless powder, m. p. 178—179° (Found: C, 63·45; H, 5·55. $C_{16}H_{16}O_6$ requires C, 63·15; H, 5·3%), $\nu_{max.}$ (KBr) 1695 cm.$^{-1}$ (C:O).

2,3,12,12a-*Tetrahydro*-6,9,10-*methoxy*-1-*methyl*-1H-[1]*benzoxepino*[2,3,4-ij]*isoquinolinium Methiodide* (III).—Thionyl chloride (1 g.) was added dropwise to a solution of the above amine (X) (1·5 g.) in dry benzene (20 ml.) containing an excess of pyridine, and the mixture was refluxed on a water-bath for 4 hr. On cooling, the oily precipitate was separated from the benzene layer, dissolved in a little hot water and filtered. Addition of an excess of crystalline potassium iodide gave a dark brown precipitate, which was again extracted with hot water. Evaporation gave the crude, pale yellow *methiodide* (*ca.* 1·3 g.) which crystallized from methanol–ether (0·3 g., 11·1%), m. p. 218° (Found: C, 50·55; H, 4·9; N, 2·7. $C_{21}H_{26}INO_4,H_2O$ requires C, 50·3; H, 5·65; N, 2·8%), the infrared spectrum of which was identical with that of racemic cularine methiodide obtained from (±)-cularine.[3]

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