28. *Akuamma Alkaloids. Part II.*[1] *The Structure of Akuammicine.*

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Akuammicine is shown to have structure (I) by conversion into the amino-ester (V), prepared from the Wieland–Gumlich aldehyde (II).

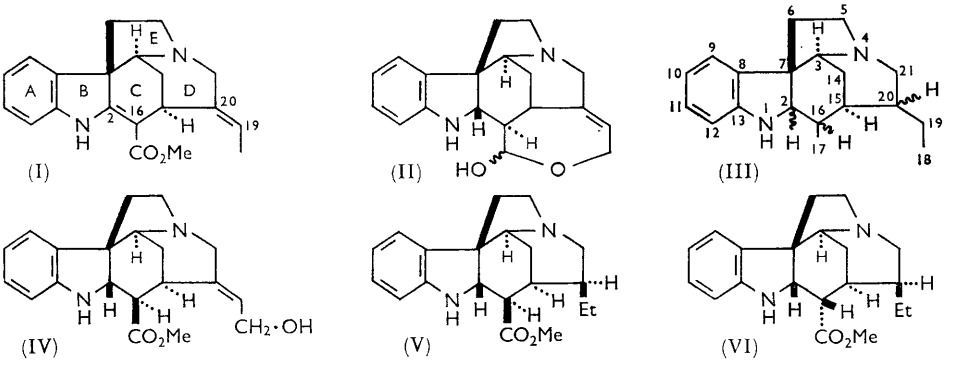
In a previous communication [1] we described a degradation of akuammicine which led to the proposal of a partial structure compatible with (I), the structure suggested for the alkaloid by Sir Robert Robinson and Aghoramurthy.[2] Since the prospects of a complete proof of structure by a continuation of the above degradative approach did not appear to be promising, we turned our attention to conversion of akuammicine into a compound which might in its turn be prepared from strychnine.

Akuammicine is quantitatively reduced by zinc and methanolic sulphuric acid to a dihydro-derivative, $C_{20}H_{24}O_2N_2$, in which the akuammicine ultraviolet absorption, with a long-wavelength maximum at 329 mμ, has been replaced by absorption characteristic of an indoline base, and in which the ester-carbonyl infrared absorption has moved to the usual region around 1730 cm.$^{-1}$. This means that the product is, on the basis of structure (I), 2,16-dihydroakuammicine. The reduction thus proceeds in a manner completely analogous with that of fluorocurarine.[3] The dihydro-base takes up one mol. of hydrogen

[1] Smith and Wróbel, *J.*, 1960, 792.
[2] Robinson and Aghoramurthy, *Tetrahedron*, 1957, **1**, 172.
[3] Von Philipsborn, Bernauer, Schmid, and Karrer, *Helv. Chim. Acta*, 1959, **42**, 461.

in the presence of Adams catalyst to give 2,16,19,20-tetrahydroakuammicine, $C_{20}H_{26}O_2N_2$. The same tetrahydro-base is obtained by reduction of 19,20-dihydroakuammicine with zinc and methanolic sulphuric acid.

Treatment of the tetrahydroakuammicine with sodium methoxide and magnesium methoxide in methanol at 100° results in epimerisation of the methoxycarbonyl group with the formation of isotetrahydroakuammicine.



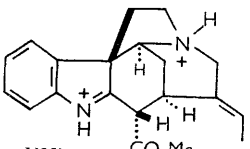
The well-known strychnine degradation product, the Wieland–Gumlich aldehyde [4] (II), was used as the starting point for a synthesis of isotetrahydroakuammicine. Attempts to oxidise the lactol grouping in the *N*-acetyl derivative of (II), diaboline,[5] with manganese dioxide in chloroform or benzene,[6] or with aqueous chromic acid at 100°, failed. An indirect method, however, was successful. The oxime [4] of the Wieland–Gumlich aldehyde was dehydrated by acetic anhydride in pyridine and from the mixed products chromatography on alumina gave a sharp non-crystalline fraction (about 65%) whose infrared and ultraviolet spectra showed it to consist largely of the expected 18-acetoxy-1-acetyl-16-cyano-17-nor-2β,16α-cur-19-ene.* Alkaline hydrolysis of this product, followed by esterification with methanolic hydrochloric acid and chromatography on alumina, gave crystalline methyl 18-hydroxy-2β,16α-cur-19-en-17-oate (IV) in about 30% yield (based on the oxime). The stereochemistry of this product (IV) was fixed by reduction with lithium aluminium hydride which gave 2β,16α-cur-19-ene-17,18-diol (the Wieland-Gumlich diol [8]). The methoxycarbonyl group of the curenoate (IV) was not epimerisable. Attempts to remove the allylic hydroxyl group by hydrogenolysis [7] of the corresponding bromide with zinc and acetic acid failed; on the other hand hydrogenolysis of the ester (IV) with hydrogen and Adams catalyst in methanolic perchloric acid resulted in the uptake of 1·6 mol. of hydrogen and the formation of methyl 2β,16α,20α-curan-17-oate, $C_{20}H_{26}O_2N_2$, identical with isotetrahydroakuammicine. This base must have structure (V); hence tetrahydroakuammicine has structure (VI) (methyl 2β,16β,20α-curanoate), and akuammicine has structure (I), with only the stereochemistry of the ethylidene double bond to be established.

It is of interest to speculate on the stereochemistry of the reduction of the 2,16-double bond in akuammicine by zinc and sulphuric acid. The first step in the reaction must

* The nomenclature used in this paper is based on preliminary proposals received from Professor M.-M. Janot and Dr. J. Le Men (personal communication, July 13th, 1960). Full details of a comprehensive system of nomenclature for β-indole alkaloids will be published by Professor Janot and Dr. Le Men. The curan system is formulated as (III), without specification of stereochemistry at positions 2, 16, and 20. The numbering follows that of Bernauer *et al.*[7]

[4] Wieland and Karizo, *Annalen*, 1933, **506**, 60; Wieland and Gumlich, *ibid.*, 1932, **494**, 191.
[5] Battersby and Hodson, *Proc. Chem. Soc.*, 1959, 126.
[6] Highet and Wildman, *J. Amer. Chem. Soc.*, 1955, **77**, 4399.
[7] Bernauer, Berlage, von Philipsborn, Schmid, and Karrer, *Helv. Chim. Acta*, 1958, **41**, 2293.
[8] Anet and Robinson, *J.*, 1955, 2253.

almost certainly be protonation [9] of $C_{(16)}$ to give the immonium ion (VII). The proton adds to the β-face in order to allow the methoxycarbonyl group to take up the more stable equatorial orientation, ring C being in the boat conformation. Reduction of the $C_{(2)}$ then proceeds by addition of hydrogen again to the β-face, to give an ester (VI) in which the B/C ring junction is the more stable *cis*-form and rings C and D have chair conformations. This forces the methoxycarbonyl group into an axial orientation. Epimerisation of tetrahydroakuammicine to the isomeric base (IV) is then readily understood, for it involves a change of orientation of the methoxycarbonyl group from axial to equatorial. The axial orientation of the ester group in tetrahydroakuammicine brings the ester-carbonyl group within hydrogen-bonding distance of the NH group, which accounts for the twinning (1746, 1726 cm.$^{-1}$) of the carbonyl band in the infrared spectrum of this base. In the iso-base (V) the ester group is well out of reach of the *N*-hydrogen atom, and the infrared carbonyl absorption is a single band at 1732 cm.$^{-1}$.



(VII)

The preparation of Wieland-Gumlich aldehyde has, in our hands and also in the experience of another research group,[10] consistently given a yield (~20%) much lower than that (33%) quoted by earlier workers.[8] In our last two preparations we isolated ~5% of a chloroform- and water-soluble, ether-insoluble by-product which has been shown, by its ready formation from the Wieland-Gumlich aldehyde and bromochloromethane-free chloroform [11] at the boiling point, to be the αα-dichloromethochloride of this base. It follows that the yield of Wieland–Gumlich aldehyde would be appreciably raised by avoiding the use of chloroform during the working up of the reaction mixture.

[*Note, added June 22nd*, 1960.] Methyl 2β,16β,20α-curan-17-oate (VI) was reduced by lithium aluminium hydride to 2β,16β,20α-curan-17-ol, isolated as the crystalline methiodide. Through the courtesy of Professor M.-M. Janot, this methiodide has been shown to be identical with geissoschizoline methiodide, which confirms the structure proposed by Puisieux *et al.*[12] for this geissospermine hydrolysis product. Professor Janot informs us that he has also independently established the structure of geissoschizoline.

Experimental

Methyl 2β,16β-*Cur*-19-*en*-17-*oate* (2,16-*Dihydroakuammicine*).—A solution of akuammicine (220 mg.) in 10% absolute methanolic sulphuric acid (100 c.c.) was treated with zinc dust (30 g.), and the mixture heated under reflux for 30 min. with vigorous shaking. The filtered solution was evaporated to small bulk *in vacuo* and treated with water (50 c.c.) and then with sodium carbonate solution to permanent turbidity. Aqueous ammonia (20 c.c.; *d* 0·880) was then added and the whole immediately extracted with ether (5 × 30 c.c.). The ether extract vielded *methyl* 2β,16β-*cur*-19-*en*-17-*oate* (198 mg.) which, after two crystallisations from light petroleum (b. p. 80—100°), formed prisms, m. p. 143—145° (Found: C, 74·1; H, 7·35. $C_{20}H_{24}N_2O_2$ requires C, 74·05; H, 7·45%), $\lambda_{max.}$ 299, 246 mμ (ε 3900, 8700 in MeOH), $\nu_{max.}$ (in CCl_4), 3400w, 1747s, 1729s cm.$^{-1}$.

Methyl 2β,16β,20α-*Curan*-17-*oate* (*Tetrahydroakuammicine*) (VI).—(i) The above base (200 mg.) was hydrogenated in methanolic 10% acetic acid (25 c.c.) in the presence of Adams catalyst (59 mg.). The hydrogen uptake ceased after 30 min (1·1 mol. taken up). Working up the solution for basic material yielded the *curanoate* (189 mg.) which, after two crystallisations from light petroleum, was obtained as needles, m. p. 135—137° (Found: C, 73·55; H, 8·0. $C_{20}H_{26}N_2O_2$ requires C, 73·6; H, 8·05%), $\lambda_{max.}$ 299, 246 mμ (ε 3600, 8300 in MeOH), $\nu_{max.}$ (in CCl_4) 3400w, 1746s, 1726s cm.$^{-1}$.

(ii) 19,20-Dihydroakuammicine (73 mg.) was reduced with zinc and methanolic sulphuric acid under the conditions described above for the reduction of akuammicine. The product formed needles, m. p. and mixed m. p. 134·5—136·5° (65 mg.).

[9] Fritz, *Chem. Ber.*, 1959, **92**, 1809.
[10] Battersby, personal communication.
[11] Williams, *Chem. and Ind.*, 1960, 900.
[12] Puisieux, Goutarel, Janot, Le Men, and Le Hir, *Compt. rend.*, 1960, **250**, 1285.

Methyl 18-*Hydroxy*-2β,16α-*cur*-19-*en*-17-*oate* (IV).—A mixture of the Wieland–Gumlich oxime [4] (2·88 g.), acetic anhydride (30 c.c.), and pyridine (5 c.c.) was heated at 100° for 90 min., the solvent removed *in vacuo*, and the residue partitioned between 20% aqueous sodium carbonate (25 c.c.) and ethyl acetate (15 c.c.). The aqueous phase was extracted further with ethyl acetate (2 × 15 c.c.), the combined extracts were evaporated, and the residue (3·21 g.) was adsorbed on alumina (50 g.) and eluted with chloroform (500 c.c.). The eluate (2·42 g.) did not crystallise [$\nu_{max.}$ (in CCl_4) 3630w, 2260vw, 1748s, 1680s cm.$^{-1}$]. A solution of this product in ethanol (50 c.c.) was refluxed with one of barium hydroxide (9·5 g.) in hot water (100 c.c.) under nitrogen for 16 hr. Sulphuric acid (3·0 g.) was then added, barium sulphate filtered off, and the solution evaporated to dryness. The residue was refluxed with methanolic 5% hydrochloric acid (150 c.c.) for 5 hr., and again evaporated to dryness. The residue was treated with 10% aqueous sodium carbonate (100 c.c.) and the whole extracted with ethyl acetate (4 × 25 c.c.). The dried combined extracts yielded crude *methyl* 18-*hydroxy*-2β,16α-*cur*-19-*en*-17-*oate* (1·32 g.) which after three crystallisations from methanol formed needles, m. p. 152—154·5° (sintering at 110°) (Found, in material dried at room temperature *in vacuo*: C, 68·1; H, 7·4. $C_{20}H_{24}N_2O_3,CH_3OH$ requires C, 67·7; H, 7·6%). The solvent-free *ester* crystallises from benzene as needles, m. p. 154—156° (Found: C, 70·7; H, 7·1. $C_{20}H_{24}N_2O_3$ requires C, 70·55; H, 7·1%), $\lambda_{max.}$ 301, 246 mμ (ε 2600, 6200 in MeOH), $\nu_{max.}$ (in CCl_4) 3550w, 3400w, 1732s cm.$^{-1}$.

2β,16α-*Cur*-19-*ene*-17,18-*diol* (*Wieland–Gumlich Diol*).—The preceding ester (56 mg.) in benzene (5 c.c.) was treated with excess of lithium aluminium hydride in ether (150 c.c.), and the mixture refluxed for 24 hr. 20% Aqueous sodium hydroxide (50 c.c.) was added, the whole shaken, and the ether layer separated. The aqueous phase was extracted with chloroform (2 × 50 c.c.). The combined, dried ether and chloroform extracts yielded a gum (50·4 mg.) which crystallised (45 mg.) from benzene–methanol. Two more crystallisations yielded the pure diol as prisms, m. p. 245—248° with some distillation on to the cover slip from 240°. This m. p. was not depressed by the product (identical m. p.) of reduction of the Wieland–Gumlich aldehyde [7] by lithium aluminium hydride. The infrared spectra (Nujol mull) were identical.

Methyl 2β,16α,20α-*Curanoate* (V).—(i) The ester (IV) (351 mg.) in absolute methanol (50 c.c.) containing aqueous perchloric acid (1 c.c.; 60% w/v) was hydrogenated in the presence of Adams catalyst for 3 hr., by which time the rate of hydrogen uptake had slowed very consoderably and 1·6 mol. had been absorbed. The basic product (343 mg.) was passed through neutral alumina (10 g.) by means of ether (100 c.c.). The eluate (207 mg.), crystallised three times from light petroleum, gave the pure *ester* (V) as needles, m. p. 152—153° (165 mg.). Slow crystallisation from light petroleum at room temperature gives a polymorph (prisms), m. p. 129—131° (Found: C, 73·2; H, 7·85; OMe, 9·5. $C_{20}H_{26}N_2O_2$ requires C, 73·6; H, 8·05; 1OMe, 9·5%), $\lambda_{max.}$ 299, 245 mμ (ε 3000, 7200 in MeOH), $\nu_{max.}$ (in CCl_4) 3430w, 1732s cm.$^{-1}$, $[\alpha]_D^{22}$ −139° (*c* 1·1 in MeOH).

(ii) A solution of tetrahydroakuammicine (VI) (47 mg.) in methanol (1 c.c.), in which magnesium (25 mg.) and sodium (10 mg.) had been dissolved, was heated in an evacuated tube at 100° for 3 hr., then treated with water (10 c.c.) and immediately extracted with ether (3 × 20 c.c.). The dried ether extracts yielded a product (47 mg.) which after three crystallisations from light petroleum formed needles, m. p. 151—152·5°, identical (including formation of the polymorph), with the ester (V) obtained as above.

Wieland–Gumlich Aldehyde (II) *and its Dichloromethochloride*.—The preparation was carried out with 112 g. of strychnine, according to Anet and Robinson's directions [8] up to the final chloroform extraction of the total product. Material from this extract was crystallised from chloroform: the first crop consisted of needles which did not melt but gradually decomposed above 200° (3·5 g.); the second crop consisted of impure Wieland–Gumlich aldehyde which on recrystallisation from methanol–acetone gave a product, m. p. 200—215° (10·1 g.). The combined chloroform and methanol–acetone mother-liquors were chromatographed on neutral alumina containing 10% of water: benzene–chloroform (3 : 2) eluted more impure aldehyde (7·0 g.); chloroform–methanol (9 : 1) eluted the quaternary salt, decomp. >200° (1·5 g.). The combined aldehyde fractions were recrystallised twice from methanol–acetone to give the pure product, m. p. 212·5—215° (12 g., 20%).

The combined quaternary salt fractions (5 g., 5%) were recrystallised several times from methanol, giving the *aldehyde dichloromethochloride* as needles, decomp. >200° (Found, in

material dried at room temperature *in vacuo*: C, 51·5, 51·05; H, 5·95, 6·2. $C_{20}H_{23}Cl_3N_2O_2,2H_2O$ requires C, 51·55; H, 5·8%), $\lambda_{max.}$ 293, 239 mμ (ε 2900, 7900 in MeOH), soluble in water.

Interaction of Wieland–Gumlich aldehyde and boiling bromochloromethane-free chloroform [11] gave the same compound.

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