287. *Akuamma Alkaloids. Part IV.* The Decomposition of Akuammicine in Methanol.*

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Akuammicine (VII) has been shown to break down to the quaternary pyridinium compound (I) in methanol at 80° and to 3-ethylpyridine and 2-hydroxycarbazole at 140°.

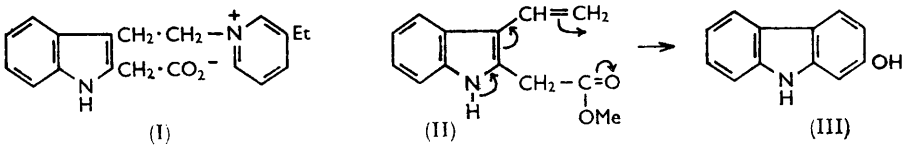
The identification of ψ-akuammicine with racemic akuammicine led us to explore the possibility of racemisation of akuammicine during the extraction process. To this end, akuammicine was heated in methanol under reflux: very slow decomposition was observed. This decomposition was appreciably faster in a sealed tube at 80°, 30% of the akuammicine being decomposed in 3 hr. The total ether-soluble material from this was shown to be essentially pure akuammicine: on the basis of the molecular weight and $\varepsilon_{330m\mu}$ of akuammicine, the specific rotation of the material in this fraction absorbing at 330 mμ was calculated to be −728°. This shows that no racemisation of akuammicine had occurred. Of the ether-insoluble portion of the reaction, 30% was intractable water- and ether-insoluble tar, and 70% was water-soluble with a well-defined ultraviolet spectrum. This water-soluble material yielded a crystalline betaine, $C_{19}H_{20}N_2O_2$, with complex absorption in the NH and OH stretching region but no C=O band; it formed a picrate $C_{19}H_{20}N_2O_2,C_6H_3N_3O_7$ with bands 3400m (NH), 3300—2300w (diffuse; OH), and 1703s cm.$^{-1}$ (C=O). The ultraviolet spectrum of the betaine is shown in the Figure: the small peak at 290 mμ and the intense peak at 223 mμ strongly suggested an indole nucleus, and the band at 268 mμ, unchanged by acid or alkali, suggested a pyridinium nucleus. In fact the absorption was almost identical with that of an equimolar mixture of 2,3-dimethylindole and β-picoline ethobromide, as shown. On the basis of the known structure of akuammicine (VII) and the above data, the decomposition product has structure (I), and the various salts are quaternary pyridinium salts containing a carboxylic acid group.

Heating akuammicine in methanol to 100° for 3 hr. resulted in 80% decomposition and the isolation of a 70% yield of the picrate of (I), so at this temperature the same decomposition occurs, but much more rapidly.

When akuammicine was heated at 140° in methanol for 2 hr., decomposition was complete, and the only products which could be isolated were 3-ethylpyridine (48%) and 2-hydroxycarbazole (III) (60%). The formation of 3-ethylpyridine follows simply from

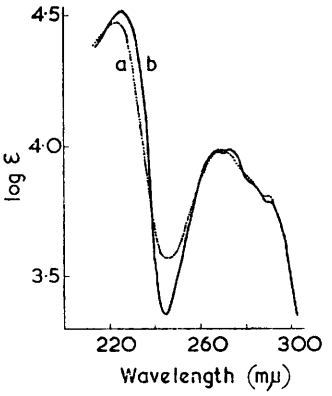
* Part III, Edwards and Smith, *Proc. Chem. Soc.*, 1960, 215.

the methyl ester of (I) (XII; R = Me, X = OMe) (see below). The other immediate product of the elimination should be methyl 3-vinyl-2-indolylacetate (II). This compound was, however, not found. We believe that the 2-hydroxycarbazole (III) is likely to be a transformation product of (II), produced by nucleophilic attack of the vinylogous enamine methylene on the ester-carbonyl carbon, followed by loss of methoxide ion and proton, and by enolisation.



(I) (II) (III)

A number of experiments were carried out in order to throw some light on the very remarkable transformation of akuammicine (VII) into the betaine (I). Akuammicine is completely stable in benzene at 100° and is recovered unchanged after 12 hr.; this suggests



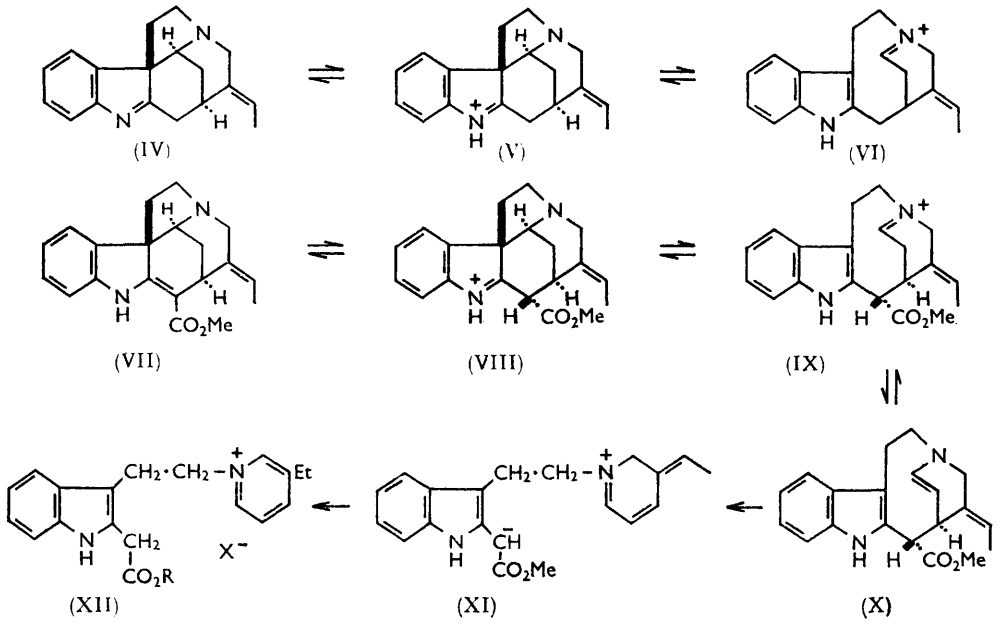
Absorption spectra of: (a) *betaine* (I); (b) *an equimolar mixture of* 2,3-*dimethylindole and* β-*picoline ethobromide* (*both in methanol*).

that the decomposition in methanol may be proton-catalysed. Heating 2,16-dihydroakuammicine in methanol at 100° for 12 hr. leads simply to epimerisation at $C_{(16)}$;[1] the 2,16-double bond therefore plays an essential rôle in the decomposition. Another compound which resists the action of methanol at 100° is akuammicine methiodide. 19,20-Dihydroakuammicine is decomposed in methanol, but much more slowly than akuammicine itself: in methanol at 100° for 5 hr. it is decomposed only to the extent of 10%, and the decomposition product does not contain a pyridinium ion, for it has simple indole absorption in the ultraviolet region; it was not investigated further. About 20% of 19,20-dihydroakuammicine survives being heated in methanol for 3 hr. at 140°; the rest is largely intractable material from which about 10% of 4-ethylpyridine and 10% of 2-hydroxycarbazole can be isolated. This shows that, although the 19,20-double bond is not essential for the decomposition, it greatly facilitates it.

The above results enable us to propose the following sequence of reactions for the overall change of akuammicine into the betaine (I). Bearing in mind the proton-catalysed equilibrium (IV) ⇌ (V) ⇌ (VI), which has been clearly shown to exist in a methanol solution of the product (IV) of acid-hydrolysis of akuammicine, we believe that the first steps in the decomposition of akuammicine are very likely to involve the reversible reactions (VII) ⇌ (VIII) ⇌ (IX). Now if we visualise the further plausible equilibrium involving loss of proton to give the enamine (X), this is nicely constituted to undergo a reverse Michael reaction, by 15,16-bond fission, to give compound (XI). This step may be regarded as irreversible, since it involves the opening of a nine-membered ring. A racemisation of akuammicine to ψ-akuammicine would have to involve the change

[1] Edwards and Smith, *J.*, in the press.

(XI) ⟶ racemic (X), which we regard as highly unlikely. This change would furthermore have to occur more rapidly than aromatisation to the pyridinium system. The final steps are proton addition to the mesomeric carbanion in (XI) and double-bond migration into the pyridine ring. The product expected from this reaction would be the methyl



ester methoxide (XII; R = Me, X = OMe). The fact that the actual product isolated is the betaine (I) is to be explained as saponification due to traces of water in the methanol used, which allows the equilibrium $MeO^- + H_2O \rightleftharpoons MeOH + OH^-$ to be set up.

The crucial step in the decomposition of akuammicine is thus the irreversible 15,16-bond fission (X ⟶ XI). It is extremely likely that the slowing down of the decomposition of 19,20-dihydroakuammicine occurs at the corresponding step: in akuammicine, the 19,20-double bond actually assists the 15,16-bond fission by leading to the mesomeric immonium system in (XI), longer by one double bond than the corresponding system produced from 19,20-dihydroakuammicine. That the latter compound decomposes at all is an indication that pyridinium ion formation is not essential for the 15,16-bond fission.

Concerning the decomposition of akuammicine at 140°, we have observed that the betaine (I), its hydrochloride (XII; R = H, X = Cl), and the methyl ester of the picrate (XII; R = Me, X = picrate) survive largely undecomposed in methanol at 140° for 3 hr. No carbazole formation was observed. Treatment of the betaine (I), and the methyl ester of the chloride (XII; R = Me, X = Cl), with an excess of sodium methoxide and magnesium methoxide in methanol at 140° for 3 hr. results in decomposition, with the isolation of 3-ethylpyridine from the methanol distillates. Ultraviolet spectroscopic examination of the residues showed in the first case only indole absorption, and, in the second, that only a trace of 2-hydroxycarbazole accompanied the mainly indole product.

The results suggest that the elimination of 3-ethylpyridine from the methyl ester (XII; R = Me, X = OMe) in the actual decomposition of akuammicine in methanol at 140° is brought about by the methoxide ion, and is thus a Hofmann reaction. These results also show that in the presence of a large excess of methoxide ions the simple cyclisation of the vinylindole (II) to 2-hydroxycarbazole is replaced by conversion into an indole, the nature of which has not been investigated.

Experimental

Decomposition of Akuammicine in Methanol at 140°.—A solution of akuammicine (400 mg.) in dry methanol (6 c.c.) was heated in an evacuated sealed tube at 140° for 2 hr. The methanol was distilled from the dark solution, more methanol (10 c.c.) added to the residue, and the solution evaporated again. This process was repeated eight times. The combined distillates were acidified with concentrated hydrochloric acid (0·2 c.c.) and evaporated. The residue was crystalline and deliquescent (85 mg., 48%); treatment with aqueous sodium picrate gave 3-ethylpyridine picrate which, after crystallisation from aqueous methanol, had m. p. and mixed m. p. 124·5—126·5° (Found: C, 46·75; H, 3·75. Calc. for $C_{13}H_{12}N_4O_7$: C, 46·4; H, 3·6%). The non-volatile portion of the reaction mixture (251 mg.) was chromatographed on neutral alumina (10 g.): none of the fractions had an akuammicine-type chromophore, and the 9 : 1 chloroform–methanol fraction yielded the crude 2-hydroxycarbazole (135 mg., 60%). Sublimation at 160°/0·05 mm. followed by crystallisation from benzene–methanol gave pure 2-hydroxycarbazole, m. p. 270—273° (sealed capillary), undepressed by admixture with an authentic specimen [3] (Found: C, 78·6; H, 5·0; N, 7·75; OMe, 0·0. Calc. for $C_{12}H_9NO$: C, 78·7; H, 4·95; N, 7·65; OMe, 0·0%), $\lambda_{max.}$ 235, 258, 301 mμ in EtOH (ε 54,000, 25,000, 15,500 respectively), changed to 243, 330 mμ (ε 48,000, 20,000 respectively) by alkali, $\nu_{max.}$ (in Nujol) 3400 (NH str.), 3220 cm.$^{-1}$ broad (OH str.; hydrogen-bonded). The ultraviolet spectra in neutral and alkaline solution were identical with those of authentic 2-hydroxycarbazole. The picrate forms dark red needles (from benzene), m. p. 182—186° (decomp.). The *O*-acetyl derivative, prepared by the pyridine–acetic anhydride method, forms plates (from methanol), m. p. 185—187°, undepressed by admixture with 2-acetoxycarbazole,[4] $\lambda_{max.}$ 233, 257, 295, 320, 332 mμ in EtOH (ε 39,000, 17,500, 14,800, 4000, 2950 respectively), $\nu_{max.}$ (in Nujol) 3420 (NH str.), 1755 cm.$^{-1}$ (C=O str.).

Decomposition of Akuammicine in Methanol at 80°.—A solution of akuammicine (470 mg.) in dry methanol (10 c.c.) was heated in an evacuated sealed tube at 80° for 3 hr. The orange-red solution was evaporated to a small volume, then benzene (15 c.c.) was added, and the remaining methanol removed completely by evaporation to dryness. The benzene-soluble portion of the residue was chromatographed on neutral alumina. The 49 : 1 ether–methanol fraction (316 mg.) had m. p. 170—179·5°, $[\alpha]_D^{21}$ −680° (*c* 0·19 in MeOH), and an ultraviolet spectrum identical with that of akuammicine–*ψ*-akuammicine, but with ε values about 5·5% low. If we assume a non-rotating contamination the rotation on the basis of the intensity of the akuammicine–*ψ*-akuammicine 330 mμ band in this material is $[\alpha]_D^{21}$ −728°, which is of the order of that of pure akuammicine.

The benzene-insoluble fraction of the decomposition (127 mg.) [$\nu_{max.}$ (in Nujol) 3600—2100s, 1735m; sh,1650m, 1600s cm.$^{-1}$] was dissolved in methanol, and the solution evaporated to dryness *in vacuo*, to yield a foam which was thoroughly digested with water (4 c.c.). Evaporation of the filtered aqueous extract gave 1-[2-(2-*carboxymethyl*-3-*indolyl*)*ethyl*]-3-*ethylpyridinium betaine* as a yellow glass (87 mg.) which crystallised from methanol–acetone as small pale yellow needles with variable decomposition point (between 150° and 180°) (Found, in material dried at room temperature: C, 69·2; H, 6·7. $C_{19}H_{20}N_2O_2,H_2O$ requires C, 69·9; H, 6·8. Found, in material dried at 100° *in vacuo*: C, 73·4; H, 6·75. $C_{19}H_{20}N_2O_2$ requires C, 74·0; H, 6·55%), $\lambda_{max.}$ 223, 268, 290 mμ in MeOH (ε 31,600, 9550, 6300 respectively), $\lambda_{infl.}$ 280 mμ (ε 7600). An equimolar mixture of 2,3-dimethylindole and 3-methylpyridine ethobromide had $\lambda_{max.}$ 225, 268, 273, 290 mμ (ε 33,000, 9800, 9800, 6300 respectively), $\lambda_{infl.}$ 280 mμ (ε 7600).

The betaine formed a *picrate* crystallising from methanol as yellow prisms, m. p. 153—154° (decomp.) (Found, in material dried at room temperature *in vacuo*: C, 55·6; H, 4·4; N, 12·3; OMe, 0·95. $C_{19}H_{20}N_2O_2,C_6H_3N_3O_7,0{\cdot}25CH_3{\cdot}OH$ requires C, 55·6; H, 4·45; N, 12·8; OMe, 1·4. Found, in material dried at 100° *in vacuo*: C, 55·7; H, 4·3; N, 12·85; OMe, 0·65. $C_{19}H_{20}N_2O_2,C_6H_3N_3O_7$ requires C, 55·8; H, 4·3; N, 13·0; OMe, 0·0%), $\nu_{max.}$ (in Nujol) 3400m (NH str.), 3300—2300vw (diffuse; OH stretch), 1703s cm.$^{-1}$ (C=O str.).

Decomposition of Akuammicine in Methanol at 100°.—A solution of akuammicine (330 mg.) in commercial methanol (10 c.c.) was heated in an evacuated sealed tube at 100° for 3 hr. The benzene-insoluble material (263 mg., 80%), when worked up as for the decomposition at 80°,

[2] Joule and Smith, *Proc. Chem. Soc.*, 1959, 322; Smith and Wróbel, *J.*, 1960, 792.
[3] Cummins and Tomlinson, *J.*, 1955, 3475.
[4] I.G. Farbenind, A.-G., Fr. 666,450, Dec. 1928; *Chem. Abs.*, 1930, **24**, 1391.

yielded the betaine (I) (238 mg.) which with methanolic picric acid formed yellow prisms (405 mg., 70%), m. p. 153—154° (decomp.).

Epimerisation of 2,16-*Dihydroakuammicine in Methanol at* 100°.—2,16-Dihydroakuammicine (36 mg.) in dry methanol (1 c.c.) was heated in an evacuated sealed tube at 100° for 12 hr. The product was chromatographed on neutral alumina with ether as the eluant, to give crude starting material, m. p. 125—138° (6 mg.), and the epimerised ester (28 mg.). This product was crystallised twice from methanol–water and once from light petroleum, to give pure *methyl* 2β,16α-*cur*-20-*en*-17-*oate* as needles, m. p. 156·5—158° (Found: C, 73·85; H, 7·55. $C_{20}H_{24}N_2O_2$ requires C, 74·05; H, 7·45%).

The above product (4·5 mg.) was hydrogenated in 2 : 1 methanol–acetic acid (3 c.c.) in the presence of Adams catalyst (2 mg.). After 4 hr., the product was worked up, and crystallised from methanol, and then from light petroleum, to give needles, m. p. 148—152°, undepressed by authentic methyl 2β,16α,20α-curan-17-oate.[1]

19,20-*Dihydroakuammicine in Methanol at* 100°.—19,20-Dihydroakuammicine (5·6 mg.) in dry methanol (0·3 c.c.) was heated in an evacuated sealed tube at 100° for 5 hr. The product was extracted with light petroleum: the petroleum extract (5 mg.) crystallised from light petroleum to give needles, m. p. 155—163·5°, undepressed on admixture with the starting material, m. p. 166—167·5°. The petroleum insoluble residue (0·5 mg.) showed an indole-type ultraviolet spectrum.

19,20-*Dihydroakuammicine in Methanol at* 140°.—A solution of 19,20-dihydroakuammicine (41 mg.) in dry methanol (1 c.c.) was heated in an evacuated sealed tube at 140° for 3 hr. The yellow solution was worked up as for the decomposition of akuammicine at 140°. Crude starting material (8 mg.) and 2-hydroxycarbazole (2·4 mg.) were isolated by chromatography of the non-volatile portion; 3-ethylpyridine picrate (4 mg.), m. p. 110—120°, raised to m. p. 115—124° on admixture with an authentic specimen, was isolated from the methanol distillate.

Esterification of the Betaine Picrate.—A solution of the betaine picrate (53 mg.) in 1 : 1 acetone–methanol (3 c.c.) was treated with an excess of diazomethane in ether (3 c.c.), then the dark red solution was evaporated to small volume (1 c.c.) and treated with charcoal and picric acid (5 mg.). The filtered solution deposited orange prisms (45 mg.), m. p. 168—171°. A further crystallisation from acetone–methanol (charcoal) gave the pure *ester picrate* as yellow prisms, m. p. 170—172° (Found, in material dried at 100° *in vacuo*: C, 57·1; H, 4·6; N, 12·4; OMe, 5·6. $C_{26}H_{25}O_9N_5$ requires C, 56·6; H, 4·6; N, 12·7; OMe, 5·6%), $\nu_{max.}$ (in Nujol) 3280m (NH str.), 1744s cm.$^{-1}$ (C=O str.).

Action of Methanolic Methoxide on the Betaine (I).—A solution of the betaine (I) (10 mg.) in methanol (1 c.c.) in which sodium (5 mg.) and magnesium (5 mg.) had been dissolved was heated in an evacuated sealed tube at 140° for 3 hr. The methanol was distilled, then more methanol (3 c.c.) added to the residue, and the solution evaporated again. This process was repeated three times. The combined distillates were acidified with concentrated hydrochloric acid (1 drop) and evaporated; treatment with aqueous sodium picrate gave 3-ethylpyridine picrate (3 mg.), m. p. and mixed m. p. 124—126·5°. The residue showed an indole-type ultraviolet spectrum.

Action of Methanolic Methoxide on the Ester Chloride (XII; R = Me, X = Cl).—A solution of the betaine (8·0 mg.) in methanol (0·1 c.c.) was treated with concentrated hydrochloric acid (1 drop), then the solvent and excess of acid were removed *in vacuo*. The residue was dissolved in methanol (0·5 c.c.) and treated with excess of diazomethane in ether (0·5 c.c.), then evaporated to dryness *in vacuo*. Methanol (1 c.c.), in which sodium (5 mg.) and magnesium (5 mg.) had been dissolved, was added to the residue, and the solution heated in an evacuated sealed tube at 140° for 3 hr. The solution was worked up as described for the action of methoxide on the betaine, to give 3-ethylpyridine picrate (2 mg.), m. p. and mixed m. p. 120—126°. The non-volatile residue was partitioned between saturated sodium hydrogen carbonate (5 c.c.) and chloroform (2 c.c.), then the aqueous phase was re-extracted with chloroform (2 × 2 c.c.) and the combined chloroform extracts were chromatographed on neutral alumina. The 9 : 1 chloroform–methanol fraction (2 mg.) showed an ultraviolet spectrum in methanol with a nearly flat peak from 260 to 300 mμ, which on the addition of alkali developed a peak at 325 mμ.

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