715. *Akuamma Alkaloids. Part VI.* The Reactions of Picraline.*

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Several reactions of picraline are described: on the basis of these reactions, structure (III; R = CO·Me) is advanced for picraline as a working hypothesis.

The isolation of picraline from *Picralima klaineana* was first reported by Robinson and Thomas;[1] we have isolated it from the same source in 0·05% yield and have found it to have the molecular formula $C_{23}H_{26}N_2O_5$. It is a weak monoacidic base with pK_a 5·65 (in 50% aqueous ethanol), contains one methoxycarbonyl group, one *O*-acetyl group, and no *N*-methyl group. The infrared spectrum reveals the presence of an NH group (3400 cm.$^{-1}$, in chloroform), and the ultraviolet spectrum shows the alkaloid to be an indoline largely unprotonated on N(a) in dilute acid and changing reversibly into a 3*H*-indolium system in concentrated perchloric acid. Ozonolysis yields acetaldehyde, isolated as the *p*-nitrophenylhydrazone in 18% yield, strongly suggesting the presence of an ethylidene group.

Mild acid hydrolysis converts picraline into deacetylpicraline, $C_{21}H_{24}N_2O_4$, a base which we have also isolated from the akuamma seeds (0·01%). This hydrolysis simply involves the loss of the *O*-acetyl group, deacetylpicraline thus shows both OH (3560 cm.$^{-1}$) and NH (3387 cm.$^{-1}$) absorption in the infrared spectrum. Attempts to reacetylate the molecule to picraline failed, the products being amorphous and consisting largely of *N*(a)-acetylated material (ultraviolet and infrared spectral evidence).

Treatment of both bases with aqueous alcoholic potassium hydroxide at 80° for a short time yielded the same product, $C_{20}H_{22}N_2O_3$, formed by the loss of the elements of formaldehyde from deacetylpicraline. This base, picrinine, still contains the methoxycarbonyl ($\nu_{max.}$ 1737 cm.$^{-1}$ in chloroform; 6·37 τ) and ethylidene groups (quartet centred at 4·65 τ and doublet centred at 8·52 τ, $J = 15$), but contains no hydroxyl group; the third oxygen must therefore be present as an ether, since the infrared spectrum does not indicate a second carbonyl group. Since picrinine, with an indoline-type ultraviolet

* Part V, Joule and Smith, *J.*, 1962, 312.

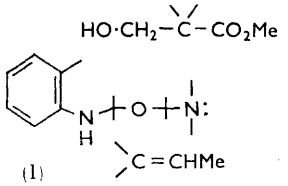
[1] A. F. Thomas, D.Phil. Thesis, Oxford, 1954.

absorption, still gives the 3*H*-indolium type of ultraviolet absorption in concentrated perchloric acid, this ether oxygen must be attached to the indoline α-position. The loss of formaldehyde is very likely to be a retroaldol type of reaction involving a $HO{\cdot}CH_2{-}C{-}CO_2Me$ grouping. If it is a retroaldolisation, it occurs with unusual ease; echitamine,[2] akuammidine,[3] and isodihydro-ψ-akuammigine [4] require much more vigorous conditions. The reaction in fact resembles a deformylation [5] much more closely. This possibility is ruled out by the oxidation of deacetylpicraline by chromic acid in acetone to picralinal, $C_{21}H_{22}N_2O_4$, which contains an aldehyde group ($\nu_{max.}$ 2700 and 1720 cm.$^{-1}$ in chloroform), NH (3420 cm.$^{-1}$) and no hydroxyl group. Short warming of picralinal with methanolic potassium hydroxide gives a quantitative yield of picrinine, and it is reduced by potassium borohydride to deacetylpicraline.

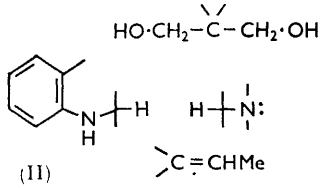
More vigorous reduction of deacetylpicraline with potassium borohydride gives a non-crystalline basic product which has not yet been analysed. Since this product shows indoline-type ultraviolet absorption, changed to anilinium in concentrated perchloric acid, the Ar–N–C–O system of deacetylpicraline has been reduced. Acetylation now gives a product with an acetylarylamine-type of ultraviolet absorption, establishing the presence of N(a)–H in the alkaloid.

Reduction of deacetylpicraline with lithium aluminium hydride in refluxing tetrahydrofuran gives picralinol, $C_{20}H_{26}N_2O_2$, in good yield. This base contains no ester group, shows OH and NH absorption in the infrared spectrum, and gives an isopropylidene derivative showing only NH absorption in the OH–NH stretching region in the infrared spectrum. The ultraviolet absorption is that of indoline, quenched to anilinium in concentrated perchloric acid, indicating that the Ar–N–C–O system has been reduced. The formation of an isopropylidene derivative strongly suggests that the two oxygens in picralinol are present as a 1,3-diol system produced by the reduction of the ester group in $HO{\cdot}CH_2{-}C{-}CO_2Me$. That the molecule contains no other oxygen indicates that the other two C–O bonds have been hydrogenolysed. Ultraviolet spectral data show that one of these bonds is associated with N(a), the ease of the hydrogenolysis suggests that the other C–O bond is associated with N(b), also as an N–C–O system. This finds strong support in the basicity of picralinol, the pK_a of which is 8·15 (in 50% aqueous ethanol), and closely resembles that of ψ-aluammigol.[6,7]

The above data lead to the partial formula (I) for deacetylpicraline and (II) for picralinol.



(I)

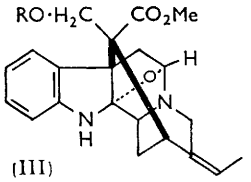


(II)

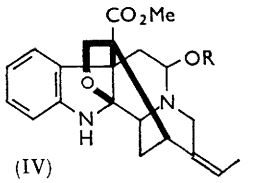
A very close structural relationship between picralinol and ψ-akuammigol is strongly suggested by the close similarity of the infrared spectra of the isopropylidene derivatives of the two bases. Attempts to methylate the N(a)-H of picralinol have so far failed. Assuming the identity of the skeletons of picraline and ψ-akuammigine, and using the structure for the latter alkaloid suggested by Janot, Le Men, and Lévy,[4] one arrives at structure (III; R = CO·Me) for picraline as a plausible working hypothesis. [*Added*

[2] Conroy, Bernasconi, Brook, Ikan, Kurtz, and Robinson, *Tetrahedron Letters*, 1960, No. 6, 1.
[3] Lévy, Le Men, and Janot, *Compt. rend.*, 1961, **253**, 131.
[4] Lévy, Le Men, and Janot, *Bull. Soc. chim. France*, 1961, 1658.
[5] Gosset, Le Men, and Janot, *Bull. Soc. chim. France*, 1961, 1033; Kiang and Smith, *Proc.*, 1962 298.
[6] Robinson and Thomas, *J.*, 1954, 3522.
[7] Joule and Smith, *J.*, 1962, 312.

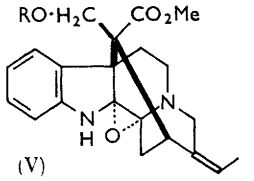
October 5th, 1962. From a study of the mass spectra of picralinol, ψ-akuammigol, and *O*-methylakuamminol, Dr. G. Spiteller (University of Vienna) considers that the skeletons



(III)



(IV)



(V)

in the three bases are identical.] Structure (IV) must also be considered, although it is much less likely; it is possible that, in deacetylpicraline, which would then have structure (IV; R = H), retroaldolisation and oxidation occur by initial or synchronous displacement of the N(a)–C–O ether oxygen by the N(b)–C–OH hydroxyl. The only point in favour of structure (IV; R = H) is that the mass spectrum is anomalous in that the parent peak is missing, and the first peak appears at M-18, indicating easy loss of the elements of water (fairly common with alcohols [8]).

Closure of the N(a)–C–O–C–N(b) ether on the N(b)-allyl methylene is excluded on steric grounds. The only other possible arrangement on the given carbon skeleton is shown in (V), and this is excluded by the presence of a band in the nuclear magnetic resonance spectrum at 5·19 τ which corresponds very well with a $\gtrless$N–$\overset{|}{C}$H–O– hydrogen. This band is also present in picraline (5·20 τ) and in picrinine (5·21 τ).

The action of 3N-hydrochloric acid on either picraline or deacetylpicraline unexpectedly gives a yellow crystalline base, flavopicraline $C_{19\,(or\,20)}\,H_{20}N_2O_3$, with a long-wavelength maximum at 390 mμ changing to 438 mμ in dilute acid. The infrared spectrum shows that the ester group has been converted into what is probably γ-lactone (1761 cm.$^{-1}$ in Nujol). This compound has not yet been thoroughly investigated, but is clearly of great interest. It is reduced by sodium borohydride to a base, $C_{19\,(or\,20)}H_{24}O_3N_2$, which has a simple indolic ultraviolet absorption, and still shows a high carbonyl absorption (1760 cm.$^{-1}$ in chloroform). Both in the presence of a γ-lactone function and in the ease of reduction with sodium borohydride to an indolic compound, flavopicraline shows a parallelism with apo-ψ-akuammigine.[7]

Experimental

Picraline.—The alkaloid crystallises from benzene–pentane as needles, m. p. 160—162° (lit.,[1] m. p. 160—161°) (Found: C, 67·6; H, 6·4; N, 6·85; OMe, 7·4; *C*-Me, 6·24; *N*-Me, 0·0. $C_{23}H_{26}N_2O_5$ requires C, 67·3; H, 6·4; N, 6·85; OMe, 7·55; 2*C*-Me, 7·3%); pK_a (50% aqueous EtOH), 5·65; $\lambda_{max.}$ (EtOH) 237, 289 mμ (ε 7400, 3200), (0·2N-ethanolic HCl) 235, 287 mμ (ε 7400, 3200), (70% perchloric acid) 241, 246, 310 mμ (ε 5500, 5400, 6200), $\nu_{max.}$ ($CHCl_3$) 3400, 737broad cm.$^{-1}$ (NH and C=O str.).

Picraline picrate crystallises from methanol as yellow prisms, m. p. 162—164° (Found: C, 54·35; H, 4·9; N, 10·65; *C*-Me, 4·1. $C_{29}H_{29}N_5O_{12}$ requires C, 54·3; H, 5·3; N, 10·95; 2*C*-Me, 4·7%).

Deacetylpicraline.—Picraline (66 mg.) in 4N-hydrochloric acid (10 c.c.) was left at room temperature for 24 hr. Basification (K_2CO_3) followed by extraction with chloroform (3 × 3 c.c.) yielded a product (53 mg., 88%) which gave *deacetylpicraline*, m. p. 196—198° (from benzene–pentane), identical with the base of the same m. p. isolated from *Picralima klaineana* seeds (Found: C, 68·6; H, 6·6; N, 7·65; OMe, 8·35; *C*-Me, 1·9; *N*-Me, 0·0. $C_{21}H_{24}N_2O_4$ requires C, 68·45; H, 6·55; N, 7·6; OMe, 8·4; *C*-Me, 4·2%); pK_a (50% aqueous ethanol), 5·80; $\lambda_{max.}$ (EtOH) 236, 289 mμ (ε 7000, 2800), (0·2N-ethanolic HCl) 234, 287 mμ (ε 7000, 2800), (70% perchloric acid) 241, 246, 310 mμ (ε 5800, 5600, 5900); $\nu_{max.}$ ($CHCl_3$) 3560, 3387, 1737 cm.$^{-1}$ (OH, NH, and C=O str.).

[8] Beynon, "Mass Spectrometry," Elsevier, Amsterdam, 1960, 345.

Deacetylpicraline picrate crystallised as needles, m. p. 147—149° (from methanol) (Found: C, 53·9; H, 4·6. $C_{27}H_{27}N_5O_{11}$ requires C, 54·2; H, 4·5%).

Ozonolysis of Picraline.—A slow stream of ozonised oxygen was passed through a solution of picraline (62 mg.) in 2% aqueous acetic acid at 0°. Zinc dust was then added, excess of ozone was removed by a stream of nitrogen, and the whole was steam-distilled into a solution of *p*-nitrophenylhydrazine in hydrochloric acid. The *p*-nitrophenylhydrazone crystallised from aqueous ethanol as yellow needles, m. p. 124—127° (undepressed by admixture with authentic acetaldehyde *p*-nitrophenylhydrazone).

Picrinine.—A solution of deacetylpicraline (517 mg.) in 20% aqueous methanolic potassium hydroxide (15 c.c.) was warmed on the steam-bath for 10 min. A white solid separated out and after cooling was filtered off (380 mg., 82%). Crystallisation from benzene–pentane yielded *picrinine* as prisms, m. p. 222—224° (Found: C, 71·15; H, 6·7; N, 7·8; OMe, 8·95; *C*-Me, 4·4. $C_{20}H_{22}N_2O_3$ requires C, 71·0; H, 6·55; N, 8·25; OMe, 9·1; *C*-Me, 4·45%); pK_a (50% aqueous ethanol), 5·70; $\lambda_{max.}$ (EtOH) 237, 288m (ε 7500, 2900), (0·2N-ethanolic HCl) 235, 286 mμ (ε 7500, 2900); (70% perchloric acid) 239, 244, 304 mμ (4500, 4500, 4700); $\nu_{max.}$ ($CHCl_3$) 3400, 1737 cm.$^{-1}$ (NH and C=O str.).

Picrinine picrate formed yellow needles, m. p. 170—173° (from methanol) (Found: C, 54·85; H, 4·35; N, 11·95; *C*-Me, 2·24. $C_{26}H_{25}N_5O_{10}$ requires C, 55·0; H, 4·45; N, 12·35; *C*-Me, 2·65%).

Picralinal.—A solution of deacetylpicraline (200 mg.) in acetone (20 c.c.) was titrated with an 8N-solution of chromium trioxide in aqueous sulphuric acid until a faint brown colour persisted. Water (20 c.c.) was added, and the solution was basified (K_2CO_3), and extracted with chloroform (3 × 15 c.c.). After having been washed with 10% aqueous potassium carbonate, the extract yielded a crystalline product (180 mg.) two recrystallisations of which from benzene–pentane yielded needles of *picralinal*, m. p. 156—158° (Found: C, 68·75; H, 6·35; N, 7·45; OMe, 8·3; *C*-Me, 3·2. $C_{21}H_{22}N_2O_4$ requires C, 68·85; H, 6·05; N, 7·65; OMe, 8·45; *C*-Me, 4·2%); $\lambda_{max.}$ (EtOH) 237, 291 mμ (ε 6000, 3000), (0·2N-ethanolic HCl) 235, 289 mμ (ε 6000, 3000), (70% perchloric acid) 241, 245, 311 mμ (ε 4000, 3600, 4700); $\nu_{max.}$ ($CHCl_3$) 3405, 2700, 1740sh, 1720 cm.$^{-1}$ (NH, aldehyde, CH, ester C=O, aldehyde C=O str.).

Picralinal picrate crystallised from methanol as yellow needles, m. p. 170—172° (Found: C, 53·85; H, 4·4; N, 11·75. $C_{27}H_{25}N_5O_{11}$ requires C, 54·4; H, 4·2; N, 11·75%).

Action of Alkali on Picralinal.—Picralinal (9 mg.) in 10% aqueous methanolic potassium hydroxide was warmed on the steam-bath for 5 min. On cooling, picrinine, m. p. 220—225°, separated. The infrared spectra in Nujol of this product and of picrinine obtained from deacetylpicralidine were identical.

Potassium Borohydride Reduction of Picralinal.—A solution of picralinal (22 mg.) in aqueous methanol containing a large excess of potassium borohydride was left at room temperature for 3 hr. and then worked up for chloroform-soluble material. This (18 mg.) crystallised from acetone as needles, m. p. 194—198°, identical (mixed m. p. and infrared spectra) with deacetylpicraline, m. p. 196—198°.

Potassium Borohydride Reduction of Deacetylpicraline.—Deacetylpicraline is not reduced by potassium borohydride at room temperature. Potassium borohydride (a very large excess) was added in small portions during 24 hr. to a refluxing solution of deacetylpicraline (60 mg.) in methanol (40 c.c.), and the reaction mixture worked up for chloroform-soluble material. This was a resin (55 mg.) which failed to yield any crystalline derivative; $\lambda_{max.}$ (EtOH) 243, 298 mμ (qualitative), unchanged in 0·2N-ethanolic hydrochloric acid, but becoming benzenoid, $\lambda_{max.}$ 261, 268 mμ (qualitative), in concentrated hydrochloric acid; $\nu_{max.}$ ($CHCl_3$) 3400, 1737 cm.$^{-1}$ (NH, C=O str.).

Acetylation with acetic anhydride and triethylamine at room temperature, and working up for basic material, yielded a resin with an acetylarylamine-type of ultraviolet absorption, $\lambda_{max.}$ 253, $\lambda_{infl.}$ 280 mμ (qualitative), unchanged in acid; $\nu_{max.}$ ($CHCl_3$) 1737, 1650 cm.$^{-1}$ (ester C=O and amide C=O str.); there was no absorption in the OH–NH region.

Picralinol.—Deacetylpicraline (580 mg.) in dry tetrahydrofuran (25 c.c.) was added to a solution of lithium aluminium hydride (2 g.) in tetrahydrofuran (150 c.c.). The mixture was refluxed for 6 hr. and then cooled, and the excess of reagent decomposed with ethyl acetate and then with 10% aqueous sodium hydroxide. The phases were separated, and the aqueous phase extracted with ether and then with chloroform. The combined organic phases yielded a crystalline product (400 mg.), which gave *picralinol* as blades, m. p. 229—232° (from

methanol) (Found: C, 73·45; H, 8·05; N, 8·5; OMe, 0·0. $C_{20}H_{26}N_2O_2$ requires C, 73·6; H, 8·05; N, 8·6%); pK_a (50% aqueous EtOH), 8·15; $\lambda_{max.}$ (ethanol 244, 295 mμ (ε 7200, 3400), unchanged in 0·2N-ethanolic HCl, (in 70% perchloric acid), 260, 268 mμ (ε 540, 500); $\nu_{max.}$ (Nujol) 3450, 3300 cm.$^{-1}$ (OH and NH stretching).

Picralinol picrate crystallised as yellow needles, m. p. 141—143° (from methanol) (Found: C, 54·75, 54·70, 54·65; H, 5·50, 5·65, 5·35; N, 11·95, 12·05. $C_{26}H_{29}N_5O_9,H_2O$ requires C, 54·50; H, 5·40; N, 12·1%).

Isopropylidenepicralinol.—A suspension of picralinol (60 mg.) in dry acetone containing 2% of benzene was treated with two drops of concentrated hydrochloric acid, and the whole heated to 55° in an evacuated sealed tube for 1 hr. The solvents were removed under reduced pressure and the residue partitioned between ether and 10% aqueous potassium carbonate at 0°. The aqueous phase was extracted with ether and the combined ether phases dried and concentrated. This yielded a product (35 mg.) which crystallised from acetone to give *isopropylidenepicralinol* as polyhedra, m. p. 204—210° (Found: C, 75·35; H, 8·2; N, 7·5. $C_{23}H_{30}N_2O_2$ requires C, 75·35; H, 8·25; N, 7·7%); $\lambda_{max.}$ (EtOH) 243, 294 mμ (ε 7000, 3200), (0·2N-ethanolic HCl) 242, 290 mμ (ε 6200, 2600); $\nu_{max.}$ (CCl_4) 3360 cm.$^{-1}$ (NH str.), no OH absorption.

Flavopicraline.—A solution of deacetylpicraline (200 mg.) in 3N-aqueous hydrochloric acid (4 c.c.) was heated in an evacuated sealed tube for 4 hr. at 80°. The solution was then basified (K_2CO_3), and extracted with chloroform (4 × 10 c.c.). The extract yielded a yellow inhomogeneous solid (182 mg.) which was chromatographed on alumina (grade H). Elution with 50% benzene–chloroform yielded deacetylpicraline (80 mg.) and then *flavopicraline* as yellow needles (48 mg.), m. p. 289—291° (decomp.) (Found: C, 70·15; H, 6·0; N, 8·35; OMe, 0·0; *C*-Me, 3·6. $C_{19}H_{20}N_2O_3$ requires C, 70·35; H, 6·2; N, 8·65; *C*-Me, 4·6. $C_{20}H_{20}N_2O_3$ requires C, 71·4; H, 6·0; N, 8·35; *C*-Me, 4·4%); $\lambda_{max.}$ (EtOH) 245, 390 mμ (ε 29,000, 16,000), (0·2N-ethanolic HCl) 240, 264, 270, 438 mμ (ε 17,000, 23,000, 24,000, 21,000), (70% perchloric acid) 270, 443 mμ (ε 14,000, 16,000); $\nu_{max.}$ (Nujol) 3173br, 1761, 1571, 1559 cm.$^{-1}$ (NH and/or OH, γ-lactone C=O, C=N (?) str.).

The same product was obtained by the action of dry methanolic hydrochloric acid on deacetylpicraline under the same conditions.

Reduction of Flavopicraline.—A solution of flavopicraline (18 mg.) in ethanol (10 c.c.) was refluxed with a large excess of potassium borohydride. After removal of the ethanol, the product was partitioned between ether and water. The aqueous phase was extracted with ether, and the combined ether phases yielded material (15 mg.) which gave the *reduction product* as prisms, m. p. 205—208° (from methanol) (Found: C, 69·8; H, 7·4. $C_{19}H_{24}N_2O_3$ requires C, 69·5; H, 7·35. $C_{20}H_{24}N_2O_3$ requires C, 70·55: H, 7·1%); $\lambda_{max.}$ (EtOH) 222, 282, 288 mμ (ε 32,000, 6800, 6800), (0·2N-ethanolic HCl) 220, 270sh, 279, 288 mμ (ε 35,000, 6500, 7200, 6800); $\nu_{max.}$ ($CHCl_3$) 3400, 3250, 1760 cm.$^{-1}$ (indole NH, H-bonded OH, γ-lactone C=O str.).

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