670. *Alkaloids of* Glycosmis arborea. *Part I. Isolation of Arborine and Arborinine: The Structure of Arborine.*

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Arborine, $C_{16}H_{14}ON_2$, and arborinine, $C_{16}H_{15}O_4N$, have been isolated from the leaves of *Glycosmis arborea* in 0·5% and 0·12% yield respectively. The former is identified by degradation and synthesis as 2-benzyl-1-methylquinazol-4-one.

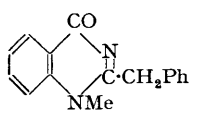
Mature leaves of *Glycosmis arborea* Correa are extensively used in the Ayurvedic system of medicine as, *e.g.*, a febrifuge and anthelmintic. From them arborine, $C_{16}H_{14}ON_2$ (m. p. 155—156°), and arborinine, $C_{16}H_{15}O_4N$ (m. p. 175—176°), were isolated in 0·5% and 0·07% yield, respectively, by R. N. Chakravarti and S. C. Chakravarti (*J. Inst. Chem., India*, 1952, **24**, 96); the yield of the latter has now been raised to 0·12%.

Chatterjee and Ghosh Majumdar (*Science and Culture*, 1952, **17**, 306) reported isolation of skimmianine (m. p. 175—176°) (yield, 0·03%) and an unidentified alkaloid (m. p. 225°) (yield, 0·003%) from leaves of a plant termed by them *G. pentaphylla*. Leaf fragments kindly supplied by them have been identified by us as *G. arborea* (Narayanswami, *Rec. Bot. Survey India*, 1941, **14**, No. 2; cf. Chakravarti and Chakravarti, *loc. cit.*), and 6 g. thereof yielded 20 mg. of arborine. This has been confirmed by Chatterjee and Ghosh Majumdar (*Science and Culture*, 1953, **18**, 505), who however used the name "glycosin" and ascribe to the alkaloid the erroneous formula $C_{15}H_{12}ON_2$.

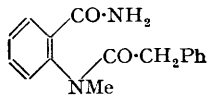
Arborine is optically inactive and contains one *N*-methyl but no methoxyl group. It is a weak monoacid tertiary base, yielding a picrate and a hydrochloride, the latter losing hydrochloric acid at 140° in a vacuum. When heated with selenium, arborine decomposes, without formation of hydrogen selenide, to yield a minute amount of an unidentified material. On distillation with soda-lime it yields ammonia, toluene, and methylaniline, indicating the presence of two benzene rings in the molecule.

Arborine is stable to water at 180° (10 hours) and to boiling concentrated hydrochloric acid (12 hours) and 50% sulphuric acid. In boiling 20% aqueous potassium hydroxide it affords 1 mol. each of *N*-methylanthranilic acid, phenylacetic acid, and ammonia, along with 0·05 mol. of a product, arboricine, $C_{16}H_{13}O_2N$. Use of aqueous barium hydroxide or alcoholic potassium hydroxide led to similar products, except that with shorter reaction times some of the *N*-methylanthranilic acid was recovered as its amide. Arborine thus contains the groupings (*o*-)NMe·C_6H_4·C$\leqslant$ and Ph·CH_2·C$\leqslant$.

Hydrogenation converts arborine into a dihydro-derivative which has ill-defined basic character, separating unchanged on dilution of its solution in concentrated hydrochloric acid. Dihydroarborine is extremely stable to alkali but is hydrolysed by hot dilute hydrochloric acid, giving phenylacetaldehyde almost quantitatively, together with small amounts of *N*-methylanthranilic acid and the amide thereof. Arborine thus is 2-benzyl-1-methylquinazol-4-one (I), and dihydroarborine is the 2 : 3-dihydro-derivative thereof.



(I)



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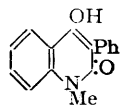

(III)

This identification was confirmed by synthesis. Phenylacetyl chloride and N^4-methylanthranilamide in cold pyridine gave the derivative (II), which when heated at 170—190° for ½ hour afforded arborine in almost quantitative yield.

The minor degradation product, arboricine, $C_{16}H_{13}O_2N$, was shown to be 1 : 2-dihydro-4-hydroxy-1-methyl-2-oxo-3-phenylquinoline (or its diketo-tautomer) by synthesis from ethyl phenylmalonate and *N*-methylaniline. Its formation from arborine probably occurs by way of (II) and the corresponding acid.

The alkaloid, arborinine, contains one methoxyl as well as one *N*-methyl group, and is optically inactive, but its structure is not further known.

Quinazolones are rare in Nature. Others isolated are evodiamine, rutaecarpine, and febrifugine (Koepfli, Mead, and Brockman, *J. Amer. Chem. Soc.*, 1949, **71**, 1048; Hutchings, Gordon, Ablondi, Wolf, and Willams, *J. Org. Chem.*, 1952, **17**, 19).

Experimental

Arborinine and Arborine.—Air-dried, powdered, mature leaves (1 kg.) of *Glycosmis arborea* (Chakravarti and Chakravarti, *loc. cit.*) were percolated with 90% alcohol. The residue obtained on evaporation of the solvent under reduced pressure was extracted with 2% hydrochloric acid (1 l.), and the acid extract (A) was washed with ether. The ethereal solution on evaporation gave yellow needles of almost pure arborinine. The pasty residue left after acid extraction was washed free from acid, treated with some alcohol, mixed with paper pulp, dried, and extracted (Soxhlet) first with light petroleum (b. p. 40—60°) for 8 hr. and then with ether for 16 hr. The petroleum extract on evaporation gave a dark viscous oil (32 g.), and the ethereal extract gave a dark sticky mass containing yellow needles. The ethereal extract was dissolved in hot concentrated hydrochloric acid (25 c.c.), allowed to cool, and filtered; this process was repeated until the acid filtrate was only light green. The residue, consisting of yellow needles with some adhering dark material, was washed with water, dried, and chromatographed in chloroform on aluminium oxide, with chloroform as the eluant. Evaporation of the chloroform gave a second crop of yellow needles of arborinine. The yields of the individual crops varied greatly but the total yield was usually about 0·12%. When purified by crystallisation from a large volume of absolute alcohol, it had m. p. 175—176° [Found : C, 67·3, 67·6; H, 5·2, 5·3; N, 5·1, 5·2; NMe, 10·2; OMe, 12·5%; *M* (Rast), 283. Calc. for $C_{16}H_{15}O_4N$: C, 67·4; H, 5·3; N, 4·9; 1NMe, 10·2; 1OMe, 10·9%; *M*, 285]. Arborinine gives a deep green colour with alcoholic ferric chloride; it readily dissolves in cold concentrated hydrochloric acid but immediately separates on dilution in small yellow needles which appear to be those of arborinine.

The acid extract (A) was treated as described previously (Chakravarti and Chakravarti, *loc. cit.*) for the isolation of arborine. Arborine (5 g.) obtained in this way was purified by repeated crystallisation from benzene containing a little absolute alcohol (charcoal). It crystallises in colourless rhombic plates with one molecule of benzene which it loses when kept. The solvent-free product melts at 155—156°. Arborine does not give any marked colour with aqueous or alcoholic ferric chloride, is a weak tertiary base, and does not react with nitrous acid. It has a slightly bitter taste and is highly soluble in alcohol [Found in material dried at 80° : C, 76·6, 76·7; H, 5·7, 5·8; N, 11·1, 11·2; NMe, 8·6; OMe, 0%; *M* (Rast), 276. Calc. for $C_{16}H_{14}ON_2$: C, 76·8; H, 5·6; N, 11·2; 1NMe, 11·6%; *M*, 250].

Arborine hydrochloride crystallises from water in colourless prisms, which melt partially at 106—108°, then resolidify, and remelt at 215° [Found : C, 58·9; H, 6·2; N, 9·5%; equiv. (titration with NaOH), 315·2. $C_{16}H_{14}ON_2,HCl,2H_2O$ requires C, 59·5; H, 5·9; N, 8·7%; equiv., 322·5]. As this salt is easily purified, the base can be conveniently purified through it.

Arborine picrate crystallises from alcohol in yellow needles, m. p. 172—173° (Found : C, 55·6; H, 3·6; N, 15·0. $C_{16}H_{14}ON_2,C_6H_3O_7N_3$ requires C, 55·1; H, 3·6; N, 14·6%).

Soda-lime Distillation of Arborine.—Benzene-free arborine (5·0 g.) and dry soda-lime (50 g.) were heated with a free flame in a distilling flask provided with a thermometer, the side arm being connected as for a distillation. The temperature was kept at about 100° for some time and then at 180—190°. The distillate, consisting of water and some oil and smelling strongly of ammonia, was shaken with ether. The ethereal solution was washed with water to remove ammonia, then extracted with 10% hydrochloric acid (acid extract B). The ethereal solution, after a final washing with water, was fractionated, giving a colourless liquid, b. p. 108—110° (0·4 g.), shown to be toluene by oxidation to benzoic acid with potassium permanganate.

The acid extract B was made alkaline with aqueous sodium hydroxide and the precipitated oil was taken up in ether, washed with water, and dried (Na_2SO_4). The oily liquid obtained on evaporation was distilled, giving a liquid, b. p. 190—191° (1·0 g.), identified as methylaniline by conversion into *N*-methylacetanilide.

Selenium Dehydrogenation of Arborine.—Arborine (1·0 g.) and selenium powder (3·0 g.) were heated gradually to 300° and then kept at 300—320° for 4 hr. No hydrogen selenide could be detected. A minute quantity of solid was deposited near the bottom of the condenser, and after resublimation and crystallisation from aqueous alcohol had m. p. 220—235° The amount was insufficient for further work.

Hydrolysis of Arborine with Alkali.—Arborine (5·0 g.) was refluxed for 5 hr. with 10% alcoholic potassium hydroxide. The alcohol was then evaporated off with occasional addition of water to keep the volume constant. Much ammonia was evolved. On cooling, colourless needles of N^4-methylanthranilamide separated. These were collected (0·6 g.) (filtrate C); recrystallised from aqueous alcohol (charcoal), they had m. p. and mixed m. p. 160° (Found: C, 64·4; H, 6·7; N, 18·4; NMe, 16·5. Calc. for $C_8H_{10}ON_2$: C, 64·0; H, 6·7; N, 18·6; 1NMe, 19·3%). They gave a nitroso-compound with nitrous acid and lost ammonia when heated in concentrated aqueous sodium hydroxide.

The aqueous solution (C) was extracted three times with ether, and the aqueous solution (D) was kept for further treatment. The ethereal solution was extracted with 5% hydrochloric acid (15 c.c.) and then washed with a little water. On evaporation, a minute quantity of a neutral solid was obtained having a fragrant smell, but this was not identified. The acid extract, when made alkaline with sodium hydroxide solution and extracted with ether, gave N^4-methylanthranilamide (0·05 g.).

The aqueous solution (D) was strongly acidified with concentrated hydrochloric acid. Arboricine, which was precipitated, was collected (0·2 g.) (filtrate E) and crystallised from aqueous alcohol (charcoal) in colourless needles, m. p. 221—222° [Found: C, 76·4; H, 5·2; N, 5·5; NMe, 9·5%; *M* (Rast), 257. Calc. for $C_{16}H_{13}O_2N$: C, 76·5; H, 5·2; N, 5·6; NMe, 11·5%; *M*, 251]. It does not evolve carbon dioxide from sodium hydrogen carbonate solution but dissolves in sodium hydroxide solution. It dissolves in hot concentrated hydrochloric acid from which it crystallises unchanged on cooling.

The aqueous filtrate (E) was nearly neutralised (litmus) with sodium hydroxide solution. A colourless precipitate was collected (0·5 g.) (filtrate F), and recrystallised from aqueous alcohol (charcoal), colourless needles being obtained, m. p. 179—180°, showing a blue fluorescence in ethereal, alcoholic, or aqueous solution. The fluorescence of the aqueous solution becomes deeper on addition of alkali and is discharged by acid. This product was amphoteric and was identified as *N*-methylanthranilic acid (mixed m. p.) (Found: C, 63·4; H, 5·8; N, 9·2; NMe, 14·1. Calc. for $C_8H_9O_2N$: C, 63·5; H, 5·9; N, 9·2; NMe, 19·2%).

The aqueous filtrate (F) was repeatedly extracted with ether. The semi-solid residue obtained on evaporation was dissolved in a minimum of hot 2% hydrochloric acid, filtered, and then cooled in ice. Phenylacetic acid which separated was collected (0·5 g.), and from the filtrate a further crop of *N*-methylanthranilic acid (0·06 g.) was obtained after neutralisation followed by extraction with ether. The phenylacetic acid was purified by several crystallisations from water (charcoal), and had m. p. and mixed m. p. 76° (Found: C, 70·5; H, 6·0. Calc. for $C_8H_8O_2$: C, 70·6; H, 5·9%).

In one experiment, hydrolysis of benzene-free arborine (1·0 g.) was carried out with hot 20% aqueous potassium hydroxide solution (25 c.c.) for about 4 hr. and the ammonia evolved was determined after absorption in standard acid (Found: NH_3, 6·9. Calc. for $C_{16}H_{14}ON_2$: 1NH_3, 7·0%). From the alkaline solution approx. one molecular proportion each of *N*-methylanthranilic acid and phenylacetic acid along with a small quantity (0·05 g.) of arboricine were isolated.

Hydrolysis of arborine with hot saturated aqueous barium hydroxide gave smoothly *N*-methylanthranilic acid, N^4-methylanthranilamide, phenylacetic acid, and arboricine.

Dihydroarborine.—Purified benzene-free arborine (1·131 g.) was shaken in absolute alcohol (25 c.c.) with Adams catalyst (0·1 g.) under hydrogen [absorption, complete in 2·5 hr.: 104 c.c. (N.T.P.); one double bond requires 102 c.c.]. Crystals separated as soon as the hydrogen atmosphere above the solution was replaced by air. These were again brought into solution by the addition of sufficient amount of chloroform and heating. The mixture was then filtered and the filtrate was heated on the water-bath to remove most of the chloroform. On cooling, *dihydroarborine* separated in colourless plates, m. p. 199—200° (1·012 g.), and was purified by recrystallisation chloroform–alcohol [Found: C, 75·8; H, 6·1; N, 11·3%; *M* (Rast), 246. $C_{16}H_{16}ON_2$ requires C, 76·2; H, 6·3; N, 11·1%; *M*, 252]. It is insoluble in water and alcohol, slightly soluble in ether, and somewhat more soluble in chloroform and glacial acetic acid. It is insoluble in aqueous alkalis and in dilute acids, but dissolves in concentrated hydrochloric acid with the formation of a pale yellow solution from which it separates unchanged on dilution. In chloroform or ether it shows a violet fluorescence.

Dihydroarborine was also prepared by heating a solution of arborine in 10% hydrochloric acid at 45—50° for 24 hr. in presence of granulated zinc. A white precipitate which separated was extracted with chloroform. Evaporation to a small bulk and dilution with absolute alcohol gave a very small yield of dihydroarborine.

Hydrolysis of Dihydroarborine.—Dihydroarborine (0·5 g.) gave a pale yellow solution in concentrated hydrochloric acid (10 c.c.). This was diluted with water (20 c.c.) and distilled on a sand-bath, the volume being kept constant by addition of water. An oil with a fragrant smell (phenylacetaldehyde) collected in the distillate. Heating was stopped when the distillate was free from suspended oil. The distillate was extracted with ether, the extract washed with water, dried (Na_2SO_4), and the solvent evaporated, giving a fragrant light yellow oil. The yield of this appeared to depend on the heating and rate of distillation, but was sometimes almost quantitative. The oil readily gave phenylacetaldehyde semicarbazone, prisms (from dilute alcohol), m. p. 155—156°, and the 2 : 4-dinitrophenylhydrazone, m. p. 121°, identified by mixed m. p.s with authentic specimens.

The aqueous solution remaining in the distilling flask was filtered, extracted with ether (only a trace of gum removed), made alkaline with sodium hydroxide, and again extracted thoroughly with ether (aqueous solution G). On evaporation of the ether N^4-methylanthranilamide (40 mg.), m. p. and mixed m. p. 160° (from benzene or alcohol), were obtained.

The aqueous solution (G) was made just acid to Congo-red with hydrochloric acid and repeatedly extracted with ether, and the extract was washed with water and evaporated, yielding N^4-methylanthranilic acid, m. p. and mixed m. p. 179—180° (from aqueous alcohol) (50 mg.).

N^4-*Methyl*-N^4-*phenylacetylanthranilamide* (II).—*N*-Methylanthranilamide (1·0 g.) in anhydrous pyridine (10 c.c.) was treated at 0° with phenylacetyl chloride (2·0 g.) with shaking and kept overnight at room temperature. The product was treated with ice and set aside for about an hour, then acidified to Congo-red with concentrated hydrochloric acid to keep unchanged *N*-methylanthranilamide in solution. A gum which separated was extracted with chloroform, and the extract was washed successively with 5% hydrochloric acid, saturated aqueous sodium hydrogen carbonate and water, dried (Na_2SO_4), and evaporated. The crystalline residue was recrystallised from benzene, giving N^4-*methyl*-N^4-*phenylacetylanthranilamide* (II) as prisms, m. p. 159—160° (0·9 g.) (Found : C, 72·0; H, 6·0; N, 10·8. $C_{16}H_{16}O_2N_2$ requires C, 71·6; H, 6·0; N, 10·4%).

2-*Benzyl*-1-*methylquinazol*-4-*one* (I).—N^4-Methyl-N^4-phenylacetylanthranilamide (0·25 g.) was heated from 170° to 190° during 20 min. and then kept at 190° for about 10 min. Cyclisation took place with vigorous frothing. The product was dissolved in the minimum of hot absolute alcohol and the solution then diluted with benzene. Some of the benzene was allowed to evaporate, most of the alcohol being thus removed. On cooling, 2-*benzyl*-1-*methylquinazol*-4-*one* separated as colourless rhombic plates, m. p. 155—156° (0·2 g.). The crystals contain one molecule of benzene of crystallisation which they lose gradually. The solvent-free product appears to be amorphous (Found, in material dried at 80° : C, 76·7; H, 5·8; N, 11·3. $C_{16}H_{14}ON_2$ requires C, 76·8; H, 5·6; N, 11·2%).

A mixture of this and arborine in equal proportions melted sharply at 155—156°.

1 : 2-*Dihydro*-4-*hydroxy*-1-*methyl*-2-*oxo*-3-*phenylquinoline*.—Ethyl phenylmalonate (10 g.) and methylaniline (4 g.) were heated at 200—220° for 1½ hr. On cooling, crystals separated. Crystallised from aqueous alcohol these gave the *quinoline* derivative (III) as needles (1·5 g.), m. p. 222°, not depressed on admixture with arboricine (Found : C, 76·5; H, 5·3; N, 5·4. $C_{16}H_{13}O_2N$ requires C, 76·5; H, 5·2; N, 5·6%).

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