78.—*A New Alkaloid from* Holarrhena antidysenterica *Seeds.*

By Robert Downs Haworth.

Stenhouse (*Pharm. J.*, 1864, **5**, 493) isolated the alkaloid conessine from the seeds of *Holarrhena antidysenterica*, and the purification of the alkaloid by means of its hydrogen oxalate is described by Kanga, Ayyar, and Simonsen (J., 1926, 2123) and by Späth and Hromatka (*Ber.*, 1930, **63**, 126), both of whom give references to the earlier work.

Owing to the kindness of Professor J. L. Simonsen, the author was supplied with an extract of the seed, in a state sufficiently pure for direct conversion into conessine hydrogen oxalate as described by previous workers. The hydrogen oxalate separated from the alcoholic solution in colourless prisms, m. p. 260° (decomp.), and recrystallisation from alcohol or water did not affect the melting point. As pure conessine hydrogen oxalate melts at 280° (decomp.), the oxalate, m. p. 260°, was basified and the product crystallised from acetone. Pure conessine was obtained, but the mother-liquors contained a second base, which was detected by means of its dimethiodide. It was then found that this new base was present in larger quantity in the alcoholic oxalic acid liquors from which the hydrogen oxalate, m. p. 260°, had been separated. These were basified and extracted with ether, and the product was distilled at 0·7 mm.; a viscous oil was then obtained. This still contained some conessine, which was removed by a rather tedious fractional crystallisation of the hydrogen oxalates. The tail fractions yielded the hydrogen oxalate of the new base in colourless nodules, m. p. 225° (decomp.), from which the base $C_{23}H_{38}N_2$ has been obtained as a colourless oil, b. p. 240°/0·7 mm., which has not been obtained in the crystalline state. The base, which is dextrorotatory in alcoholic solution, contains three methylimino-groups and is diacid. The salts, of which the *dihydrogen dioxalate* and *dihydrochloride* have been obtained crystalline, are very soluble in alcohol and water. The new base is not identical with any of the bases isolated from the bark of *Holarrhena antidysenterica* (Ghosh and Ghosh, *J. Indian Chem. Soc.*, 1928, **4**, 477) and owing to its similarity to conessine the name *norconessine* is suggested.

Norconessine is converted into *dihydroxynorconessine* by the action of potassium iodate and dilute sulphuric acid, a reaction which in the case of conessine is assumed to be due to addition to an ethylenic bond (Giemsa and Halberkann, *Arch. Pharm.*, 1918, **256**, 201). When dihydroxynorconessine is heated above its melting

point, it decomposes and the vapours give the pyrrole reaction with a pine shaving.

The most characteristic derivative of norconessine is its *dimethiodide*, which is very different from conessine dimethiodide in crystalline form and solubility, but resembles it closely in its behaviour on exhaustive methylation. Thus, on evaporation, the corresponding dimethohydroxide solution loses trimethylamine and water and yields *aponorconessine*, $C_{22}H_{33}N$, b. p. 190—192°/0·2 mm., from which a crystalline *picrate*, *methiodide*, and *methochloride* have been prepared. The metho-salts of aponorconessine resemble those of apoconessine and the nitrogen cannot be removed by treatment with silver oxide or sodium hydroxide. Späth and Hromatka (*loc. cit.*) obtained a hydrocarbon by the action of sodium amalgam on apoconessine methochloride, but aponorconessine methochloride under similar conditions was converted into a quaternary salt, presumably dihydroaponorconessine methochloride, which, when distilled, yielded *dihydroaponorconessine*, b. p. 190°/0·3 mm., from which a crystalline *picrate* has been obtained.

Owing to the kindness of Dr. T. A. Henry the physiological action of norconessine dihydrochloride has been examined at the Wellcome Research Laboratories and the pharmacological results will be published elsewhere by Dr. A. C. White. The pharmacological properties of norconessine resemble those described for conessine by Burn (*J. Pharm. Exp. Ther.*, 1914, **6**, 305) and by Chopra, Gopta, David, and Ghosh (*Indian Med. Gaz.*, 1927, **62**, 132). In experiments made by Dr. G. M. Findlay, norconessine was less active than conessine in killing the *Entamœba histolytica* on a buffered serum medium and both were much less active than emetine.

Experimental.

The crude conessine extract obtained from Professor Simonsen was made as follows: The seeds were exhausted with light petroleum, until free from oil, and mixed with excess of milk of lime, and the alkaloid extracted with petroleum. Although slower, this method gives a cleaner product than the alcohol extraction method described in J., 1926, 2123. The total bases were removed with dilute hydrochloric acid and after basification were taken up in ether and dried, and the solvent removed.

The dried extract (100 g.) in hot alcohol (100 c.c.) was added to a solution of oxalic acid (100 g.) in alcohol (200 c.c.). On cooling, conessine hydrogen oxalate (70 g.), m. p. 260° (decomp.), separated in colourless prisms, which yielded conessine (40 g.), m. p. 121°, after basification and crystallisation from acetone. The mother-liquors were concentrated, diluted with water, sodium hydroxide added,

and the oil extracted with ether, dried, and distilled. The oil (30 g.), b. p. 240—245°/0·7 mm., was again converted into hydrogen oxalate by treatment with oxalic acid (30 g.) : the stout prisms (15 g.), m. p. 245—250°, obtained still contained considerable quantities of conessine hydrogen oxalate. The mother-liquors were reconverted into base (20 g.), which was combined with oxalic acid (20 g.) for the third time; a hydrogen oxalate (15 g.) then separated in stout nodules, m. p. 225—227° (decomp.). *Norconessine*, obtained by the action of sodium hydroxide on the hydrogen oxalate, m. p. 225—227°, is a colourless viscid oil, b. p. 238—240°/0·7 mm. (Found : C, 80·4, 80·5; H, 11·3, 11·0; N, 8·4, 8·5; NMe, 20·6. $C_{23}H_{38}N_2$ requires C, 80·7; H, 11·2; N, 8·2; NMe, 25·4%). It is excessively soluble in the usual organic solvents and in acids, but insoluble in water. In absolute alcoholic solution the base had $[\alpha_D]$ +6·7° (l=1, c=2·245, α_D=0·15°). The *dihydrogen dioxalate* separated from alcohol or from a little water in colourless nodules, m. p. 225—227° (decomp.) (Found : C, 61·8, 61·9; H, 8·5, 8·3. $C_{27}H_{42}O_8N_2$ requires C, 62·1; H, 8·1%). The *dihydrochloride*, precipitated by passing dry hydrogen chloride into an ethereal solution of the base, crystallised from alcohol–acetone in slender needles, m. p. 340° (decomp.) (Found : Cl, 17·5. $C_{23}H_{38}N_2$,2HCl requires Cl, 17·1%). The *dimethiodide* was prepared as follows : Norconessine (5 g.), methyl iodide (5 c.c.), and methyl alcohol (50 c.c.) were heated under reflux for 3 hours. The excess of methyl iodide and some methyl alcohol were removed by distillation and the residue was cooled. Norconessine dimethiodide (7 g.) separated in very pale yellow prisms, m. p. 310—312° (decomp.), and a second crop (1·7 g.) was obtained by concentration of the liquors (Found : C, 47·7; H, 7·7; I, 40·2. $C_{25}H_{44}N_2I_2$ requires C, 47·9; H, 7·1; I, 40·4%). The dimethiodide is almost insoluble in acetone, sparingly soluble in methyl alcohol, and soluble in water.

Dihydroxynorconessine.—Potassium iodate (2 g.) was added to a warm solution of norconessine (2 g.) in dilute sulphuric acid. The iodine, which was rapidly liberated, was removed by boiling the solution, which was then filtered and made alkaline with sodium hydroxide, and the *dihydroxynorconessine* collected and crystallised from aqueous alcohol; small colourless needles, m. p. 264—266°, were obtained (Found : C, 72·8; H, 11·5. $C_{23}H_{40}O_2N_2$ requires C, 72·6; H, 11·6%). Dihydroxynorconessine dissolves in dilute mineral acids and, when heated above its melting point, it decomposes, giving vapours which give a pink colour on a pine shaving moistened with hydrochloric acid.

Aponorconessine.—A solution of norconessine dimethiodide (11 g.) in water (100 c.c.) was shaken with an excess of freshly precipitated

silver oxide, and the filtered liquid evaporated on the water-bath under reduced pressure. The distillate was absorbed in dilute hydrochloric acid and evaporated to dryness, and the residue identified as trimethylamine hydrochloride by conversion into the picrate and chloroaurate. The residue was mixed with water and extracted with ether, and the oil obtained from the dried extract was distilled. *Aponorconessine* (3 g.) was obtained as a colourless oil, b. p. 190—192°/0·2 mm. (Found : C, 85·5; H, 10·0. $C_{22}H_{33}N$ requires C, 84·9; H, 10·6%). This base is readily soluble in organic solvents, including methyl alcohol, in which apoconessine is sparingly soluble. It also dissolves in dilute mineral acids and the salts are much more soluble than those of conessine. The *picrate*, prepared in methyl-alcoholic solution, is sparingly soluble in methyl alcohol, ethyl alcohol, and ethyl acetate and crystallises from glacial acetic acid in long yellow needles, m. p. 244—245° (Found : C, 62·2; H, 6·8. $C_{28}H_{36}O_7N_4$ requires C, 62·2; H, 6·8%). The *methiodide*, prepared by heating the base with methyl iodide in a sealed tube at 100°, was readily soluble in alcohol and crystallised from boiling water, in which it was sparingly soluble, in colourless needles, m. p. 274—276° (Found : C, 61·1; H, 8·1. $C_{23}H_{36}NI$ requires C, 60·9; H, 8·0%). The methochloride, prepared by the action of silver chloride on the methiodide, crystallised from hot water in felted needles. The methiodide was decomposed with silver oxide, and treated as described in the preparation of aponorconessine. No hydrocarbon was obtained and neutralisation of the residue with hydriodic acid yielded aponorconessine methiodide.

When the methochloride in hot aqueous solution was treated with sodium amalgam for 24 hours, no hydrocarbon was produced. The solution was neutralised with hydrochloric acid, potassium iodide added, the precipitate collected and decomposed with silver oxide, and the product distilled. An oil, b. p. 190°/0·3 mm., was obtained, which was converted into a *picrate* : this crystallised from glacial acetic acid in yellow plates, m. p. 260° (decomp.) (Found : C, 61·7; H, 7·0. $C_{28}H_{38}O_7N_4$ requires C, 62·0; H, 7·0%). The analytical figures indicate that the oil, b. p. 190°/0·3 mm., is *dihydroaponorconessine*.

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