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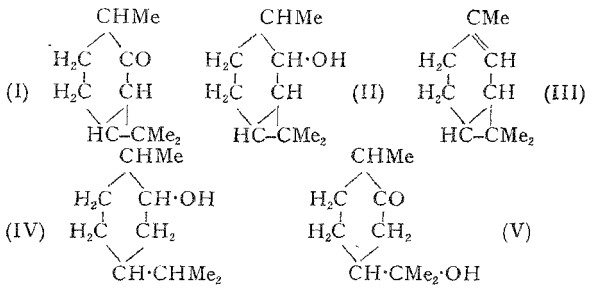
CONTENTS.

I. THE CATALYTIC HYDROGENATION OF CARONE.[1]

By Subramania Narayana Iyer and John Lionel Simonsen.

During the course of his researches on the terpenes Baeyer (*Ber.*, 1894, **27**, 1913) prepared the dicyclic ketone carone (I), and until the separation of the two hydrocarbons Δ^3- and Δ^4-carene from the essential oils obtained from *P. longifolia* and *A. Jwarancusa* (J., 1920, **117**, 570; 1922, **122**, 2292) this was the only known substance of the terpene group possessing this dicyclic structure. In view of the probable wide occurrence of these dicyclic hydrocarbons in nature it appeared to us of interest to attempt the synthesis of Δ^4-carene (III). The simplest method available would be the elimination of water from the secondary alcohol (II) which should result from the reduction of carone.



It was shown by Baeyer (*Ber.*, 1895, **28**, 1601) that when carone in moist ethereal solution was reduced with sodium *p*-menthan-2-ol (IV) was produced, whilst treatment of the cyclic ketone with sodium and amyl formate with subsequent decomposition of the hydroxymethylene derivative yielded the corresponding monocyclic ketone. A further indication of the marked instability of the dicyclic system was the fact, also observed by Baeyer (*Ber.*, 1896, **29**, 16), that in the presence of dilute sulphuric acid carone was converted into *p*-menthan-8-ol-2-one (V). It was obvious from these experiments that carone behaved more like an $\alpha\beta$-unsaturated ketone than a dicyclic ketone, but it seemed to us that it might prove possible to hydrogenate it catalytically to the secondary alcohol (II).

[1] Reprinted from the *Journal of the Chemical Society*] 1926, 2049.

Unfortunately, this was found not to be the case. Under the conditions described in the experimental section, after the absorption of 1 mol. of hydrogen, the product consisted mainly of *p*-menthan-2-one mixed with unchanged carone and other substances; on complete reduction (2 mols. of hydrogen), *p*-menthane (in small quantity), *p*-menthan-2-ol (IV), and *l*-*p*-menthane-2 : 8-diol were obtained.

The *p*-menthan-2-ol (IV) obtained was optically inactive and differed in one particular only from the racemic alcohol described by Wallach (*Annalen*, 1893, **277**, 132)—the phenylurethane melted at 107° and not at 75–76°. This discrepancy is in all probability due to the fact that the two alcohols are stereoisomeric, since four racemic forms are possible.

The formation of *l*-*p*-menthane-2 : 8-diol during the hydrogenation is of some interest and it would appear to have been formed by the hydration of the *cyclo*propane ring by the very dilute hydrochloric acid present in the reaction mixture, the hydroxy-ketone subsequently undergoing reduction.

It is somewhat remarkable that no evidence was obtained of the presence of *m*-cymene derivatives, nor does there appear to be any tendency for *cyclo*heptane derivatives to be formed. Although these experiments have not proceeded in the desired direction, they are not without interest since they show quite clearly the great tendency of carone to behave like an $\alpha\beta$-unsaturated ketone. It is proposed to investigate other reactions with carone in order to determine how far this property is general.

EXPERIMENTAL.

The carone required for these experiments was most conveniently prepared in quantity by the method of Kondakov and Gorbanov (*J. pr. Chem.*, 1897, **56**, 256). It had b. p. 150–153°/100 mm., d_{30}^{30} 0·9468, n_D^{30} 1·4739, and $[\alpha]_D^{30}$ — 250°.

The most satisfactory method of hydrogenation is the following: The ketone (10 g.) was dissolved in acetic acid (20 c.c.), platinic chloride solution (Pt. 10 per cent.; 5 c.c.) and gum arabic solution (gum arabic, 2 per cent.; 20 c.c.) were added, and the bottle containing the mixture was evacuated and filled with hydrogen. A solution of colloidal palladium (1 c.c.) was added, the apparatus again evacuated, and filled with hydrogen at a pressure of 2 atmospheres. The mixture was mechanically shaken; hydrogen was rapidly absorbed during 2–2½ hours until approximately 2 litres (2 mols.) had been taken up. The mixtures from a number of such experiments were

combined and, after separation of the platinum, the oil was taken up with ether, the ether washed with sodium carbonate solution until free from acetic acid, dried, and evaporated. The residual oil partly crystallised on keeping. The solid (A) was collected, and the filtrate distilled under diminished pressure (100 mm.); three main fractions were then obtained, (i) 105–115°, (ii) 135–140°, (iii) 140–180°. The small residue crystallised and was added to (A).

p-*Menthane*.—Fraction (i) was repeatedly distilled over sodium; it then had b. p. 168–169°/685 mm., d_{30}^{30} 0·7984, n_D^{30} 1·435, was optically inactive, had a smell resembling that of light petroleum and was not attacked by warm alkaline permanganate (Found: C, 86·0; H, 13·9. Calc.: C, 85·7; H, 14·3 per cent.). The small quantity available did not permit the preparation of crystalline derivatives, but there would appear to be no doubt that the substance is *p*-menthane.

p-*Menthan-2-ol*.—The higher fractions were kept for some days in the ice-box and after removal of the solid deposited (this was added to A), the filtrate was heated with alcoholic potassium hydroxide to hydrolyse any acetyl derivative present. The cyclic alcohol was distilled in steam and then under diminished pressure; b. p. 143–144°/100 mm., d_{30}^{30} 0·9004, n_D^{30} 1·457. It was optically inactive (Found: C, 76·9; H, 12·6. Calc.: C, 76·9; H, 12·8 per cent.). The *phenylurethane* crystallised from light petroleum in needles, m. p. 107–108° (Found: N, 5·4. Calc.: N, 5·1 per cent.)

The alcohol (10 g.) was oxidised in acetic acid solution with a slight excess of chromic acid; the *p*-menthan-2-one obtained, b. p. 146–148°/100 mm., was identified by means of the oxime, m. p. 105°, and the semicarbazone, m. p. 194–195°, which were compared with authentic specimens.

On oxidation with alkaline permanganate the ketone gave *β-iso*propyladipic acid, which was purified through the calcium salt and recrystallised from water, from which it tended to separate as an oil. The acid was very difficult to purify and melted at 78–80° (Found for the silver salt: Ag, 54·1. Calc.: Ag, 53·7 per cent.) Previous workers (Wallach and Koehler, *Annalen*, 1905, **339**, 113; Wallach, *ibid.*, 1906, **343**, 33; 1917, **414**, 287) also have found the acid difficult to crystallise.

1-p-*Menthane*-2 : 8-*diol*.—The solid (A) crystallised from ethyl acetate in large, glistening prisms, m. p. 155–156°, $[\alpha]_D^{30°}$ −40° in chloroform (Found: C, 69·7; H, 11·4. Calc.: C, 69·8; H, 11·6 per cent.). It was identified with *l*-*p*-menthane-2 : 8-diol (Wallach, *Annalen*, 1917, **414**, 195) (1) by treating it with an acetic acid solution

of hydrogen bromide for some days; the solid obtained on addition of water crystallised from methyl alcohol in plates, m. p. 57–58°, and was shown by direct comparison to be terpinene dihydrobromide, (2) by oxidising it in acetic acid with a slight excess of chromic acid; *p*-menthan-8-ol-2-one was obtained, and identified by means of the semicarbazone, m. p. 149° (Found: N, 18·6. Calc.: N, 18·5 per cent.).

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II. CONESSINE.[1]

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The alkaloid conessine has been obtained from the bark and seeds of *Holarrhena antidysenterica* and from the bark of *H. africana* and *H. congolensis*. It has formed the subject of a considerable number of communications,[2] but little is known regarding its chemistry beyond the fact that it has the empirical formula $C_{24}H_{40}N_2$ and contains two tertiary -NMe groups.

We had planned an extended investigation on this alkaloid, since, in addition to the intrinsic value attaching to the determination of its constitution, there was the added interest that there is a considerable body of clinical evidence indicating that the bark of *H. antidysenterica* is of value in the treatment of diseases of the dysenteric type (compare Henry and Brown, *Trans. Roy. Soc. Trop. Med. Hyg.*, 1923–4, **17**, 61, 381). Unfortunately our experiments had to be terminated at an early stage, as certain derivatives of conessine had an extremely toxic effect on one of us (J. L. S.), giving rise to a severe attack of giant urticaria. We prepared a few new derivatives of conessine, and record the results of our work in the hope that they may be of assistance to other investigators.

Giemsa and Halberkann observed (*loc. cit.*, p. 212) that when the ammonium base formed by treating an aqueous solution of conessine dimethiodide with silver oxide was heated at 200° under diminished pressure, trimethylamine was evolved, leaving a crystalline base. We have examined this reaction in some detail and have found the residue to consist of a mixture of at least two bases. One of these, for which the name apo*conessine* is proposed, has the formula $C_{22}H_{33}N$, having been formed by the elimination of trimethylamine, water and methyl alcohol from conessinedimethyl-ammonium hydroxide. It was characterised by the preparation of the crystalline *hydrogen*

[1] Reprinted from the *Journal of the Chemical Society*, 1926, 2123.

[2] The following would appear to be a complete list of the references to conessine in the literature: Haines (*Trans. Med. Soc. Bombay*, 1858, **4**, 28, as nereine); Stenhouse (*Pharm. J.*, 1864, **5**, 493); Haines (*ibid.*, 1865, **6**, 432); Wulfsberg (*Gött. Nachr.*, 1878, No. 3); Keidel, *Dissert.*, Göttingen, 1878 ('Physiologische Wirkung des Conessine'); Dutt (Calcutta Chemical Examiner's Report, 1880); Warnecke (*Ber.*, 1886, **19**, 60); Polstorff and Schirmer (*ibid.*, p. 78); Polstorff (*ibid.*, p. 1682); Blondel (*J. Pharm. Chem.*, 1887, **16**, 391); Warnecke (*Arch. Pharm.*, 1888, **226**, 248, 281); Ulrici (*ibid.*, 1918, **256**, 57); Giemsa and Halberkann (*ibid.*, p. 201); Pyman (J., 1919, **115**, 163).

sulphate and *picrate*. The crystalline *methiodide* was reconverted into the original base on treatment with silver oxide.

We have also made some preliminary experiments on the action of alkali on conessine dimethosulphate and obtained a very hygroscopic, crystalline base, $C_{26}H_{44}N_2$; this is apparently a dimethyl derivative of conessine formed by the loss of 2 mols. of water from the ammonium base which is evidently the first product of the reaction.

In the preparation of conessine dimethosulphate (compare Giemsa and Halberkann, *loc. cit.*), in addition to the crystalline dimethosulphate, a thick, extremely hygroscopic oil was obtained which, on treatment with alkali, gave a *base* for which a simple formula could not be found; possibly this was due to the presence of some impurity, but we could not repeat the preparation.

Experimental.

The finely-crushed seeds of *H. antidysenterica* (500 g.) were extracted in a copper Soxhlet apparatus with light petroleum (b. p. 40–60°) to remove the fixed oil (19 per cent.), and having been freed from solvent by a current of air, were mixed with milk of lime (CaO, 100 g.). The whole was exposed to the air over-night and then extracted with 88 per cent. alcohol for about 18 hours. The deep brown extract was freed from alcohol by distillation, finally under diminished pressure, and the residue shaken with dilute hydrochloric acid. Ether removed non-basic impurities from the filtered acid solution, from which ammonia then precipitated the crude alkaloid. This was extracted with ether, and from the dried extract the alkaloid was obtained as a viscid, brown oil which partly crystallised on keeping (yield 1 per cent.). The oil, dissolved in the minimum quantity of alcohol, was warmed with a concentrated alcoholic solution of sufficient oxalic acid for the formation of the hydrogen oxalate. The salt crystallised in colourless prisms on cooling and was recrystallised from alcohol.[1] The recovered base melted at 120–121°, and at 125° after crystallisation from acetone (Found: C, 80·6; H, 11·4. Calc.: C, 80·0; H, 11·3 per cent.).

Conessine was not attacked when boiled in sulphuric acid solution for some time with manganese dioxide. It was, however, slowly converted by an acetic acid solution of mercuric acetate into a base

[1] Since crystallisation of the base from acetone is always accompanied by considerable loss of material, when working with large quantities it is more convenient to recrystallise the hydrogen oxalate; the base is then readily obtained pure enough for experimental purposes and does not require to be recrystallised.

which crystallised from dilute alcohol in fine needles. This reaction would appear to be worthy of further investigation.

apo*Conessine*.—A solution of conessine dimethiodide (35 g.) in water (400 c.c.) was shaken with an excess of freshly-precipitated silver oxide, the silver iodide and the excess of the oxide were removed, and the colourless filtrate was evaporated on the water-bath. The concentrated, faintly yellow solution was heated under diminished pressure, finally at 200°, vigorous frothing taking place. The deep brown, viscid oil thus obtained was dissolved in chloroform, filtered from a little carbonaceous matter, and the solvent removed. The residual oil on trituration with a little alcohol rapidly crystallised, and on recrystallisation from absolute alcohol apo*conessine* was obtained in needles several centimetres in length; m. p. 68·5° (Found: C, 84·9; H, 10·6; N, 5·0. $C_{22}H_{33}N$ requires C, 84·9; H, 10·6; N, 4·5 per cent.). This base is insoluble in water, very sparingly soluble in cold alcohol, and more readily soluble in hot. It is readily soluble in benzene, chloroform, or ethyl acetate, and somewhat readily soluble in light petroleum. Its port-wine coloured solution in concentrated sulphuric acid becomes colourless on the addition of water. It dissolves in nitric acid with a deep red colour, which rapidly changes to yellow.

The *hydrochloride* and *hydrobromide* were sparingly soluble, amorphous solids; the *hydrogen sulphate*, which was readily soluble in hot water, much more sparingly soluble in cold, crystallised in glistening leaflets, m. p. 107–108°. The salt crystallised apparently with $7\frac{1}{2}$ mols. of water of crystallisation (Found: H_2O, 11·0. $C_{22}H_{33}N$, H_2SO_4, $7\frac{1}{2}H_2O$ requires $3\frac{1}{2}H_2O$, 11·6 per cent.), $3\frac{1}{2}$ of which were lost on drying in a vacuum (Found: S, 6·4. $C_{22}H_{33}N$, H_2SO_4, $4H_2O$ requires S, 6·6 per cent.). After drying, the salt began to soften at 138°, gradually darkened and decomposed, but was not completely liquid at 280°.

The *picrate* crystallised from alcohol in fine, yellow needles, m. p. 110–111° (Found: C, 62·0; H, 7·0. $C_{28}H_{36}O_7N_4$ requires C, 62·2; H, 6·7 per cent.). The *methiodide* was prepared by heating a mixture of the base (1 g.), methyl alcohol (5 c.c.), and methyl iodide (1 g.) in a sealed tube at 100° for 3 hours. It separated on cooling, and more was obtained on evaporation of the mother-liquor. It crystallised from ethyl acetate-methyl alcohol in prismatic needles; these sintered at 245° to a viscid resin which became clear at 283–285° (Found: I, 28·1. $C_{23}H_{36}NI$ requires I, 28·0 per cent.). When the methiodide was treated with silver oxide in aqueous solution, *apo*conessine was re-formed.

The alcoholic filtrate from which *apo*conessine had been separated (see p. 2125) yielded, on removal of the solvent, a viscid, uncrystallisable oil. This was dissolved in an excess of dilute hydrochloric acid (1 : 2), the small quantity of *apo*conessine hydrochloride that separated was filtered off, and the base recovered from the filtrate. It had b. p. 253–255°/11 mm. and was a faintly yellow oil which slowly crystallised at 0° in fine needles. It was readily soluble in all the ordinary solvents and its aqueous solution showed very strong fluorescence. The salts with organic and inorganic acids were readily soluble in water. The picrate was obtained crystalline from ethereal solution, but it was not possible to investigate this method of purification.

Conessine Dimethosulphate.—The base (5 g.) and methyl sulphate (5·6 g.) reacted so vigorously in methyl alcohol (5 c.c.) that the mixture boiled. After about 5 minutes the dimethosulphate began to crystallise in well-formed prisms and after 1 hour acetone (5 c.c.) was added and the crystalline solid collected (yield 6·3 g.); more was obtained (2·6 g.) on evaporating the mother-liquor in a vacuum. The filtrate, after complete removal of the solvent, yielded a viscid, semi-crystalline oil which was extremely hygroscopic and resisted all attempts at purification. The dimethosulphate, after repeated crystallisation from methyl alcohol-acetone, was obtained in glistening prisms which softened at 225° and melted at 240–242° with slight darkening but no decomposition. The prisms effloresced when dried over sulphuric acid (Found : S, 10·6. Calc. : S, 10·5 per cent.).

Action of Potassium Hydroxide on Conessine Dimethosulphate.—The dimethosulphate (6·3 g.) and potassium hydroxide (25 g.) in aqueous solution were heated on the water-bath, a slow stream of air being passed over the solution and through an absorption apparatus containing dilute hydrochloric acid. The hydrochloric acid solution, on subsequent evaporation, yielded no residue, and apparently no volatile base was formed. After 3 hours the pale brown alkaline solution was concentrated on the water-bath; a small amount of a brown oil then separated which was removed in chloroform. (The extract on evaporation yielded 0·5 g. of a brown resin which was not examined.) The aqueous solution, now colourless, was saturated with carbon dioxide and evaporated first on the water-bath and finally to dryness in a vacuum desiccator over sulphuric acid. The crystalline residue was ground with methyl alcohol, the solution filtered from inorganic matter, and the solvent removed, the treatment being repeated until the crystalline residue was completely soluble in cold methyl alcohol.

The *base* remaining after the removal of the alcohol crystallised in needles, but was extremely hygroscopic. It was insoluble in

benzene, very sparingly soluble in acetone, readily in methyl alcohol or water. It gave a *dipicrate* which separated from dilute acetone in fine, yellow needles, m. p. 258–259° (slight decomp.) (Found: C, 54·2, 54·2; H, 5·9, 6·1; N, 13·8. $C_{38}H_{50}O_{14}N_8$ requires C, 54·1; H, 5.9; N, 13·3%). The *dimethiodide* crystallised from hot water in glistening concentric groups of needles when the solution was rapidly cooled, but on slow cooling or evaporation well-formed prisms were deposited. The dimethiodide did not melt at 290°.

The hygroscopic oil obtained during several preparations of the dimethosulphate (see p. 2126) was treated with potassium hydroxide in the way described above. The viscid, brown oil that separated from the concentrated aqueous solution was taken up with chloroform. On removal of the solvent a crystalline solid remained which, after repeated crystallisation from acetone-benzene, was obtained in colourless, silky needles; these rapidly became brown on exposure to the air. As only a small quantity of material was available, it is possible that the substance was not obtained quite free from the large amount of resinous impurity which accompanied it. It melted at 253–254° after sintering at 251°, was readily soluble in water, and its aqueous solution showed a marked fluorescence (Found: C, 63.9, 63·7; H, 8·7, 8·8; N, 9·7%). The *picrate* crystallised from alcohol in small, yellow plates, decomp. about 256°, but it was not prepared in sufficient quantity for analysis.

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