378. *The Constitution of Conessine. Part III.**

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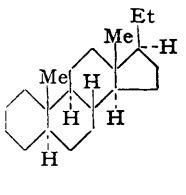
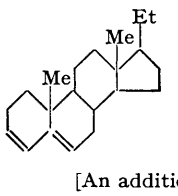
The hydrocarbon, $C_{21}H_{36}$, obtained by reduction of the hydrocarbon, $C_{21}H_{30}$, m. p. 74—76°, and first isolated by Späth and Hromatka, has been further examined, and has now been shown by repeated chromatography to be a mixture of 5-*allo*pregnane and pregnane. A number of metho-salts of conessine derivatives have yielded methine bases, which are quaternised by acid treatment. This indicates the presence of a pyrrolidine nucleus, and the bearing of these and other observations on the constitutional problem is discussed.

Proof for the steroid nature of conessine was given in Part I of this series (Haworth, McKenna, and Singh, *J.*, 1949, 831) and it was concluded that the structural formula of the alkaloid was derived from 5-*allo*pregnane (I) by the insertion of a dimethylamino-group, a cyclic methylimino-group, and one double bond. In Part II (Haworth, McKenna, and Whitfield, *J.*, 1949, 3127), it was suggested that the pregnatriene, $C_{21}H_{30}$, m. p. 74—76°, first isolated by Späth and Hromatka (*Ber.*, 1930, **63**, 126) by Emde degradation of *apo*conessine had formula



(I.)



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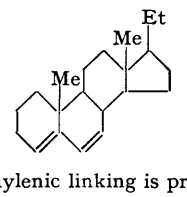
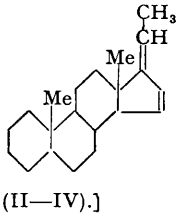


(III.)



(IV.)

[An additional ethylenic linking is present in (II—IV).]

(II), (III), or (IV), with an additional isolated, but unlocated, double bond. The conjugated diene system present in *apo*conessine and the pregnatriene was shown to be derived from the original double bond of conessine, and the double bond introduced during the elimination of trimethylamine by Hofmann degradation. We have not as yet succeeded in fixing the position of any one of the functional groups of the alkaloid but the experimental work has reached a stage where a further discussion appears opportune.

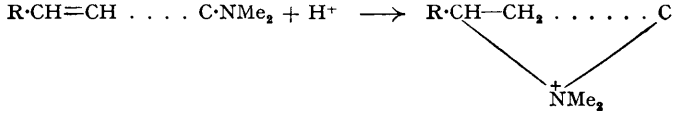
Späth and Hromatka (*loc. cit.*) obtained, by catalytic reduction of the pregnatriene, $C_{21}H_{30}$, in acetic acid solution, a hexahydro-derivative, $C_{21}H_{36}$, m. p. 56—58°, which was separated by Haworth, McKenna, and Singh (*loc. cit.*) into 5-*allo*pregnane, m. p. 83—84°, $[\alpha]_D^{20}$ +15° (in chloroform), and an isomer. m. p. 56—58°, $[\alpha]_D^{20}$ +17° (in chloroform), apparently identical

* Part II, *J.*, 1949, 3127.

with the product of Späth and Hromatka. This lower-melting isomer, however, did not correspond in properties to any of the steroid hydrocarbons, $C_{21}H_{36}$, then known, *viz.* : (*a*) pregnane, m. p. 83—84°, $[\alpha]_D^{20}$ +20° (in chloroform), (*b*) 14-*iso*-17-*iso*pregnane, m. p. 105—106°, $[\alpha]_D$ +18° (in chloroform) (Meyer, *Helv. Chim. Acta*, 1947, **30**, 2025), (*c*) 14-*iso*-17-*iso*-5-*allo*pregnane, m. p. 74—77°, $[\alpha]_D^{19}$ +25° (in chloroform) (Press and Reichstein, *ibid.*, p. 2127), (*d*) 17-α-methyl-D-homoandrostane, m. p. 108—109°, $[\alpha]_D^{19}$ −3° (in dioxan) (Ruzicka and Mehldahl, *ibid.*, 1940, **23**, 364; Shoppee and Prins, *ibid.*, 1943, **26**, 185), (*e*) 17-α-methyl-D-homoætiocholane, m. p. 86—88°, $[\alpha]_D^{17}$ 0° (in acetone) (Shoppee, *ibid.*, 1944, **27**, 8), and (*f*) urane (17-methyl-D-homoandrostane), m. p. 128° (Marker, Kamm, Oakwood, Whittle, and Lawson, *J. Amer. Chem. Soc.*, 1938, **60**, 1066; Klyne, *Nature*, 1950, **166**, 559). More recently the synthesis of 17-*iso*-5-*allo*pregnane, m. p. 57—58°, $[\alpha]_D^{18}$ −33° (in chloroform), has been reported by Casanova and Reichstein (*Helv. Chim. Acta*, 1949, **32**, 647), and we are greatly indebted to Professor Reichstein for a small sample of this hydrocarbon which gave a large melting-point depression when mixed with the hydrocarbon, m. p. 56—58°, obtained from conessine. Only one epimeric configuration at $C_{(8)}$, $C_{(9)}$, $C_{(10)}$, and $C_{(13)}$ has been established among natural or synthetic sterols (cf. Klyne, *loc. cit.*) and four of the seven possible stereoisomers of 5-*allo*pregnane are listed above epimeric at the three remaining asymmetric centres, $C_{(5)}$, $C_{(14)}$, and $C_{(17)}$. The optical-rotation values of the isomers already prepared suggested that the rotation of those not yet known should differ considerably from that of the hydrocarbon, m. p. 56—58°, prepared from conessine.

These and similar considerations led us therefore to examine the possibility that the unidentified hydrocarbon, m. p. 56—58°, from conessine was in fact a mixture. Continued recrystallisation from acetic acid and methanol had no effect on the physical constants of the hydrocarbon, and although repeated chromatography on activated alumina yielded a small fraction, m. p. 60—62°, depressed by 5-*allo*pregnane to 56—58°, the bulk of the product remained unchanged. Finally, chromatography in nine successive stages on active charcoal led to a separation of the hydrocarbon, m. p. 56—58°, into 5-*allo*pregnane, m. p. 83—85°, and pregnane, m. p. 83—84°. The latter which appeared to form about one-third of the mixture was identified by comparison with an authentic specimen prepared from progesterone. Although our analysis of the hydrocarbon mixture has not been quantitative, no evidence for the presence of a third isomer has been obtained. The formation of pregnane and 5-*allo*pregnane in the proportions mentioned above by hydrogenation of the pregnatriene, m. p. 76°, is more readily explained on the basis of (II) or (III) than of (IV), as a conjugated system (diene or unsaturated ketone) involving $C_{(5)}$ generally gives both *cis*- and *trans*-isomers on reduction. Reduction of structure (IV), with an isolated double bond in position 4 : 5 or 5 : 6 could theoretically yield pregnane and 5-*allo*pregnane, but in practice reduction, in acid solution, of a double bond in either of these positions usually gives the *trans*-isomer only (cf. Fieser and Fieser, " Natural Products related to Phenanthrene," Third Edn., New York, 1947, pp. 121, 545).

In Part II (*loc. cit.*, p. 3129) a methoacetate of the base, $C_{22}H_{37}N$, was encountered during catalytic reduction of *apo*conessine in glacial acetic acid and we have now found that quaternisation reactions of the type



occur when methine bases of the conessine series are warmed with acetic acid. Thus *apo*conessine, $C_{23}H_{35}N$, gives a quantitative yield of the methoacetate of the base, $C_{22}H_{33}N$, after being boiled for a short time in acetic acid solution. The methoacetate absorbed two mols. of hydrogen in the presence of a palladium catalyst, and Hofmann decomposition of the corresponding quaternary hydroxide led to regeneration of *apo*conessine. The corresponding methiodide is identical with the methiodide, $C_{22}H_{33}N,CH_3I$, previously obtained in Part II (*loc. cit.*, p. 3128) by partial Hofmann decomposition of conessine. The identity of the two methiodides, established by mixed melting points, correspondence in optical rotatory powder, and by *X*-ray powder photographs which were examined in a microphotometer and shown to correspond exactly, proves that the methoacetate is produced from *apo*conessine by addition of the elements of acetic acid and re-formation of the original conessine heterocyclic ring. The unsaturated methine, $C_{25}H_{44}N_2$ (Part II, *loc. cit.*, p. 3128), produced by rupture of the heterocyclic ring of dihydroconessine had m. p. 66—70°, which could not be improved by re-

peated crystallisation or chromatography. Catalytic reduction in the presence of a platinic oxide catalyst, however, gave the dihydromethine $C_{25}H_{46}N_2$, m. p. 85—86°, in high yield. The wide range of the melting point of the unsaturated base may indicate that this is composed of a mixture of isomers differing in the positions of the double bond or that it may be contaminated with traces of dihydroconessine or dihydro*hetero*conessine. The methine, $C_{25}H_{44}N_2$, could not be degraded further by Hofmann decomposition or Emde reduction of its metho-salts, but it was also found to undergo cyclisation with hot glacial acetic acid. The cyclised product was converted into the corresponding dimethiodide which proved to be identical with dihydroconessine dimethiodide in melting point, specific rotation, and *X*-ray powder pattern. In this case also re-formation of the original conessine heterocyclic ring has occurred. Many examples of the ready formation of the pyrrolidine ring on treatment of unsaturated tertiary bases with acids are recorded (cf. Merling, *Annalen*, 1891, **264**, 310; Jacobi and Merling, *ibid.*, 1894, **278**, 8). The presence of a pyrrolidine ring in conessine and related alkaloids has been suspected since a pine-shaving reaction was reported (Haworth, *J.*, 1932, 631) on the products of pyrolysis of dihydroxynorconessine, and the ring closure of the methine bases reported above confirms this for conessine.

In Part II (*loc. cit.*, p. 3128) some results of an examination of the ultra-violet absorption spectra of *apo*conessine, the methiodide $C_{22}H_{33}N,CH_3I$, and hygroscopic methochloride, $C_{22}H_{33}N{\cdot}CH_3Cl$, were reported. A re-examination of the spectra of *apo*conessine in ethanol with a stronger light source has shown that, in addition to the main peak at 2350 A. ($\log \varepsilon$ 4·3), subsidiary peaks or points of inflexion occur at 2290 and 2430 A. at lower extinction values. The hygroscopic methochloride, $C_{22}H_{33}N,CH_3Cl$, previously obtained in small yield, but now prepared in larger quantities and in a pure state, shows a similar ultra-violet extinction curve, which is in agreement with that reported by Staveley and Bergmann (*J. Org. Chem.*, 1937, **1**, 567) for cholesta-3 : 5-diene, which we have confirmed. This correspondence in ultra-violet spectrum between *apo*conessine and cholesta-3 : 5-diene may be significant, particularly as only one peak is recorded for the corresponding 4 : 6-diene (compare formula III). Unfortunately no steroid 15 : 17-diene (compare formula IV) has been prepared but, if this structure (IV) is excluded by the results of the catalytic reduction of the pregnatriene, then these ultra-violet studies support structure (II) instead of (III) for the pregnatriene, m. p. 76°. With the diene system in this position it would follow that the original double bond and dimethylamino-group of conessine are both situated near $C_{(5)}$.

Some experiments have been carried out with the base *neo*conessine, $C_{24}H_{40}N_2$, m. p. 128°, prepared by isomerising conessine with a mixture of sulphuric and acetic acids as described by Siddiqui and Vasisht (*J. Sci. Ind. Res. India*, 1945, **3**, 559). A solution of this base in dilute sulphuric acid was unsaturated to potassium permanganate, and liberated iodine immediately from potassium iodate at room temperature in contrast to conessine which requires several hours for appreciable reaction with iodate under the same conditions. *neo*Conessine could not be reduced by hydrogen at atmospheric pressure in the presence of a platinum or palladium catalyst, possibly because the double bond is in one of the positions (7 : 8, 8 : 9, or 8 : 14) in the steroid nucleus known to be very resistant to hydrogenation. The base, however, did not isomerise under hydrogenation conditions or on treatment with hydrogen chloride and it was not degraded by attempted Emde reduction of the dimethochloride. However, Hofmann decomposition of the dimethohydroxide gave the new base, *neo*conessimethine, $C_{25}H_{42}N_2$, m. p. 105—106°, which was reduced catalytically to dihydro*neo*conessimethine, $C_{25}H_{44}N_2$, m. p. 83—85°. The latter is, like *neo*conessine, unsaturated to permanganate and iodate, but could not be hydrogenated further. *neo*Conessimethine is clearly produced by opening of the heterocyclic ring, and the double bond thus introduced, but not the original unsaturated group, undergoes catalytic reduction. *neo*Conessimethine was not degraded by Hofmann decomposition. During attempts to improve the preparation of *neo*conessine it was discovered that conessine reacted with hydrogen chloride in methyl alcohol giving chlorodihydroconessine, m. p. 175°, which was converted into dihydroconessine by hydrogenation in the presence of a platinum catalyst and calcium carbonate.

A considerable quantity of a new base, $C_{25}H_{42}ON_2$, m. p. 171—173°, was encountered during one preparation of conessine from Kurchi seeds. It was later found that conessine on treatment with formaldehyde and strong formic acid yielded the new base by addition of the elements of formaldehyde, and the production of this compound in the first instance must have been caused by too drastic conditions during the methylation stage (compare Part I, *loc. cit.*, p. 835). A solution of the new base in dilute sulphuric acid is saturated towards cold permanganate and iodate at 100°. The base contains no active hydrogen atoms and, as it does not react with 2 : 4-di-

nitrophenylhydrazine, the oxygen atom is probably present as a cyclic ether. Further experiments with this compound are in progress

In a recent communication Bertho (*Annalen*, 1950, **569**, 1) has suggested a formula for conessine, which involves (*a*) the erroneous assumption that *apo*conessine contains no conjugated diene system although it is admitted that the ultra-violet spectrum was not examined below 2360 A., and (*b*) the location of the conessine double bond in position 7 : 8 by an estimate of the optical contribution of the unsaturated centre. Lack of reference data, particularly for amino- and quaternary ammonium steroid derivatives, hinders the application of the method of molecular-rotation differences (for summary see Barton and Klyne, *Chem. and Ind.*, 1948, 755) in the conessine field, but we hope to discuss the results more fully later. However, our measurements indicate that Bertho (*loc. cit.*) has derived a grossly incorrect value for the optical contribution of the unsaturated centre; we believe the 7 : 8 position for the double bond is not in accordance with the ease of hydrogenation of conessine; and finally we are of the opinion that at the moment there is insufficient evidence for a profitable discussion of the more detailed structural position.

Experimental.

Chromatography of the Hydrocarbon, $C_{21}H_{36}$, *m. p.* 56—58°.—Animal charcoal of technical quality (British Drug Houses) was extracted with alcohol for 2 hours, dried at 160° for 2 hours, suspended in light petroleum (b. p. 40—60°), and used in the preparation of a chromatograph column (dimensions 50 × 6 mm.). A solution of the hydrocarbon, m. p. 56—58° (105 mg.), in light petroleum (b. p. 40—60°; 7 c.c.) was poured on this column, and the chromatogram developed with the same solvent. A hydrostatic pressure of 1·5 m. was applied to the top of the tube. Five or six successive fractions of the eluate were evaporated and the separation followed by observations on the m. p. of the recovered hydrocarbon. In this way a small " head " fraction (*ca.* 6 mg.) was obtained, the m. p. of which was depressed by admixture with 5-*allo*pregnane, m. p. 83—84°; a similar small " tail " fraction (*ca.* 7 mg.) separated, the m. p. of which was undepressed by addition of 5-*allo*pregnane, and a relatively large unresolved middle fraction (*ca.* 90 mg.) was recovered. After the column had been washed with light petroleum (b. p. 40—60°; 200 c.c.), the unresolved middle fraction (90 mg.) was rechromatographed as described above. This process was repeated six times and the " head " fractions divided into fractions (*A*) having m. p. between 66° and 78°, and fractions (*B*) having m. p. between 78° and 84°. The combined fractions (*A*) (16 mg.), on further chromatography, gave a fraction (13 mg.), m. p. 80—84°, which was added to the combined fractions (*B*) (10 mg.). Crystallisation from methyl alcohol now gave colourless prismatic needles, m. p. 83—84°, undepressed by admixture with pregnane, m. p. 82—83°, prepared from pregnane-3 : 20-dione. At the same time combination of appropriate " tail " fractions of m. p. between 68° and 83° gave (*C*) (45 mg.), yielding on further chromatography a fraction (27 mg.), m. p. 83—85°, which separated from methyl alcohol in colourless rectangular prisms, m. p. 83—85°, undepressed on admixture with an authentic sample of 5-*allo*pregnane, m. p. 83—84°.

Production of the Methiodide $C_{22}H_{33}N,CH_3I$ *from* apo*Conessine*.—A solution of *apo*conessine (0·35 g.) in glacial acetic acid (10 c.c.) was refluxed for 20 minutes, evaporated to a low bulk under reduced pressure, and made alkaline with potassium hydroxide. The solution remained clear and no basic material was extracted by ether; addition of potassium iodide, however, gave a white precipitate, which was collected, washed with water, and dried (yield, 0·45 g.). The methiodide evaporated from water in rectangular plates, $[\alpha]_D^{18}$ −38·5° ±1·5° (in chloroform : *c*, 1·30), m. p. 315° (decomp.) (Found : C, 61·2; H, 7·5; N, 3·1; I, 27·6. Calc. for $C_{22}H_{33}N,CH_3I$: C, 60·9; H, 7·9; N, 3·1; I, 28·0%), undepressed on admixture with a sample of the methiodide $C_{22}H_{33}N,CH_3I$ of m. p. 320° (decomp.), $[\alpha]_D^{18}$ −37·7° ± 2·6° (in chloroform : *c*, 0·85), prepared from conessine dimethiodide as described previously (Haworth, McKenna, and Whitfield, *loc. cit.*). The corresponding *methochloride* separated from methanol in colourless needles, m. p. 245—250° (Found : N, 3·8; Cl, 9·4. $C_{22}H_{33}N,CH_3Cl$ requires N, 3·9; Cl, 9·8%). Hofmann decomposition of the methohydroxide by the method described previously (Haworth, McKenna, and Whitfield, *loc. cit.*) gave *apo*conessine.

Reduction of the Methiodide, $C_{22}H_{33}N,CH_3I$.—A solution of the methiodide (0·1 g.) prepared from *apo*conessine in methanol (20 c.c.) and water (10 c.c.) was converted into the methohydroxide in the usual way, acidified with glacial acetic acid, and shaken in a hydrogen atmosphere with 15% palladium–charcoal (0·2 g.) at 30°/760 mm. Hydrogen uptake (12·0 c.c. Calc. for two double bonds, 11·0 c.c.) was complete in 10 minutes. The catalyst was removed, the filtrate evaporated, and the residue treated with potassium iodide. The *dihydro-methiodide* separated from water as irregular plates, m. p. 310° (decomp.) (Found : N, 2·6. $C_{22}H_{37}N,CH_3I$ requires N, 3·1%).

Dihydromethine, $C_{25}H_{46}N_2$.—The unsaturated methine, $C_{25}H_{46}N_2$ (0·141 g.) (prepared as described previously, Haworth, McKenna, and Whitfield, *loc. cit.*), in methanol (5 c.c.) was shaken in a hydrogen atmosphere with platinum oxide catalyst (0·028 g.) at 20°/750 mm. Uptake of hydrogen (8·6 c.c. Calc. for one double bond, 9·2 c.c.) was complete in 8 hours. The *base* (0·146 g.) isolated in the usual way was sublimed at 0·2 mm. (bath-temp., 180°) and formed needles, m. p. 85—86° (Found : C, 80·0; H, 11·7; N, 7·8. $C_{25}H_{46}N_2$ requires C, 80·2; H, 12·3; N, 7·5%), saturated to cold permanganate in acid solution. When the reduction was carried out in glacial acetic acid, some of the methine was found to undergo cyclisation to a quaternary salt (see below).

Cyclisation of the Unsaturated Methine, $C_{25}H_{44}N_2$.—A solution of the unsaturated methine, $C_{25}H_{44}N_2$ (0·285 g.), in glacial acetic acid (5 c.c.) was refluxed for 2 hours, concentrated under reduced pressure, basified with ammonia, and treated with potassium iodide. The white precipitate was extracted with

chloroform, the solvent removed, and the residue (0·335 g.) in methanol (5 c.c.) refluxed with methyl iodide (0·3 c.c.) for 4 hours. The *product* separated from water in rosettes of needles, m. p. 295—305° (decomp.), $[\alpha]_D^{18}$ +27·6° ± 2° (in methanol: *c*, 3·8), undepressed on admixture with a sample of dihydroconessine dimethiodide of the same m. p. and having $[\alpha]_D^{18}$ +25·9° ± 1·5° (in methanol: *c*, 2·7). The m. p. of these quaternary salts depends to some extent on the rate of heating.

neo*Conessine*.—This base was prepared in 16% yield from conessine by the method of Siddiqui and Vasisht (*loc. cit.*) and had m. p. 128° (from acetone). Attempts to isomerise conessine by treatment with Raney nickel in xylene (cf. Chakravarti and Robinson, *J.*, 1947, 78), phosphoric acid, toluene-*p*-sulphonic acid, or hydrogen chloride in acetic acid were unsuccessful, conessine being recovered. Treatment of conessine with hydrogen chloride in methanol gave chlorodihydroconessine described below.

Hofmann Decomposition of neo*Conessine*.—neo*Conessine dimethiodide* separated from methanol in plates, m. p. 350° (decomp.) (Found: C, 48·5; H, 7·3; N, 4·3; I, 39·3. $C_{24}H_{40}N_2,2CH_3I$ requires C, 48·7; H, 7·2; N, 4·4; I, 39·7%). From this salt (0·1 g.) the quaternary hydroxide was formed in the usual way and heated at 160°/0·5 mm. for 20 minutes. neo*Conessimethine*, isolated with ether and separated from a little *neo*conessine by fractional crystallisation of its dihydriodide, crystallised from acetone in needles (0·035 g.), m. p. 105—106° (Found: C, 80·9; H, 11·0; N, 7·8. $C_{25}H_{42}N_2$ requires C, 81·1; H, 11·4; N, 7·6%).

*Dihydro*neo*conessimethine*.—*neo*Conessimethine (0·23 g.) in ethanol (8 c.c.) was shaken with a platinum oxide catalyst (12·5 mg.) in a hydrogen atmosphere at 19°/760 mm. Hydrogen uptake (14·5 c.c. Calc. for one double bond, 14·8 c.c.) was complete in 2 hours, and the *product* (0·235 g.) isolated in the usual way separated from acetone in colourless needles, m. p. 88—89° (Found: C, 80·2; H, 11·3; N, 7·8. $C_{25}H_{44}N_2$ requires C, 80·6; H, 11·8; N, 7·5%). Neither this base nor *neo*conessimethine showed selective absorption in the ultra-violet.

Chlorodihydroconessine.—A solution of conessine (0·25 g.) in dry methanol (10 c.c.) was saturated with dry hydrogen chloride at 0° and set aside for 3 days. The solvent was then evaporated under reduced pressure at ⩾40°, and the residue basified with ammonia and extracted with ether. The residue from the ether was fractionally crystallised from acetone, giving *chlorodihydroconessine* as needles (0·1 g.), m. p. 175° (decomp.) (Found: C, 73·2; H, 10·2; N, 7·2; Cl, 9·1. $C_{24}H_{41}N_2Cl$ requires, C, 73·4; H, 10·5; N, 7·1; Cl, 9·0%). The mother-liquors yielded a little conessine, m. p. 125°, undepressed on admixture with an authentic specimen. A solution of chlorodihydroconessine in dilute sulphuric acid did not reduce potassium permanganate in the cold. Attempts to remove the elements of hydrogen chloride with pyridine or sodium acetate gave no definite product, but treatment with alcoholic potassium hydroxide gave a small yield of conessine.

Reduction of Chlorodihydroconessine.—Chlorodihydroconessine (49·7 mg.) in ethanol (5 c.c.) was shaken in a hydrogen atmosphere, with platinum oxide (11·5 mg.) and a little calcium carbonate at 22°/760 mm. Hydrogen uptake (2·9 c.c. Calc. for reduction of one chlorine atom, 3·1 c.c.) was complete in 17 hours. The solids were separated, and the filtrate worked up in the usual way, giving dihydroconessine, m. p. 103—106°, undepressed on admixture with an authentic specimen.

Formaldehyde Addition Base.—A solution of conessine (0·5 g.) in 98% formic acid (10 c.c.) and 40% formaldehyde solution (10 c.c.) was concentrated at atmospheric pressure to 6 c.c. 10N-Hydrochloric acid (10 c.c.) was then added and the mixture concentrated to 4 c.c., and this last process repeated. The dark red solution was then basified with sodium hydroxide and extracted with ether. The ethereal solution was washed and evaporated, and the residue purified by several crystallisations from acetone. The *base* separated from acetone in colourless prisms, m. p. 171—173° (Found: C, 77·8, 78·1; H, 10·7, 10·8; N, 7·6, 7·8. $C_{25}H_{42}ON_2$ requires C, 77·7; H, 10·9; N, 7·3%). A solution of the base in dilute sulphuric acid was saturated to cold permanganate and did not liberate iodine on being warmed with potassium iodate. Treatment with boiling 50% hydrobromic acid for 7 hours gave no definite product.

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