946. *The Alkaloids of the Amaryllidaceae. Part III.** *Hœmanthamine (Natalensine).*

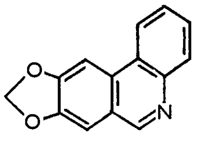
By F. L. Warren and Winifred G. Wright.

Hæmanthamine from *Haemanthus natalensis* is fully characterised and its formula elaborated to $C_{15}H_{13}N(CH_2O_2)(OMe)(OH)$ with a tertiary nitrogen atom and one double bond. Zinc-dust distillation gives methylenedioxyphenanthridine (I). Oxidation with potassium permanganate gives the series of compounds, 1 : 2 : 3 : 4-tetrahydro-3-oxo-6 : 7-methylenedioxy-*iso*quinoline-4-carboxylic acid (II), 4 : 5-methylenedioxy-2-oxalylbenzoic acid (III), and hydrastic anhydride (IV). Hofmann degradation gives *N*-methyl-2-phenylpiperonylamine (VIII) and 2-phenylpiperonaldehyde (V). These findings are accommodated in formula (X) for hæmanthamine.

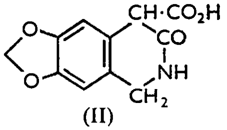
HÆMANTHAMINE, $C_{17}H_{19}O_4N$, was isolated by Boit[1] from *Haemanthus hybrid "King Albert"* and, as natalensine, from *H. natalensis* and *H. puniceus* by Wildman and Kaufman[2] and in our laboratories.[2] Since then it has been found in twenty-two natural species[3] and a large number of cultivated hybrids.[4]

In spite of its wide occurrence little was known about this alkaloid. There is one methoxyl and one methylenedioxy-group, and the other oxygen is present as a hydroxyl group (strong absorption in carbon tetrachloride at 3617 cm.[1] and an acetyl derivative). The formula may accordingly be expanded to $C_{15}H_{13}N(CH_2O_2)(OMe){\cdot}OH$. The alkaloid is readily reduced to dihydrohæmanthamine, $C_{17}H_{21}O_4N$, so that there is one double bond. The nitrogen atom is tertiary in that hæmanthamine and dihydrohæmanthamine readily form methiodides.

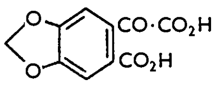
The alkaloid shows a band at 294 mμ (log ε 3·75) with a shoulder at 240 mμ (log ε 3·55), resembling safrole [$\lambda_{max.}$ 285 mμ (log ε 3·6), shoulder at 240 mμ (log ε 3·65)]. This and the fact that the ultraviolet extinction curve is unchanged after reduction show that the double bond is not conjugated with the benzene nucleus.



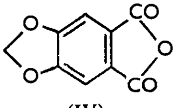
(I)



(II)



(III)



(IV)

Zinc-dust distillation of the alkaloid gave 6 : 7-methylenedioxyphenanthridine (I). Oxidation with potassium permanganate at 0° gave a crystalline compound, $C_{11}H_9O_5N$ (II), but at room temperature gave hydrastic acid isolated as its anhydride (IV), an acid,

---

* Part II, *J.*, 1957, 2537.

[1] Boit, *Chem. Ber.*, 1954, **87**, 1339.

[2] Wildman and Kaufman, *J. Amer. Chem. Soc.*, 1955, **77**, 1245; and references therein.

[3] Boit *et al.*, *Chem. Ber.*, 1954, **87**, 724; 1955, **88**, 1590; 1956, **89**, 163, 1129; 1957, **90**, 727, 1827, 2203.

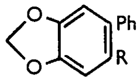
[4] Boit, *ibid.*, 1957, **90**, 2197.

$C_{10}H_6O_7$, presumed to be 2-oxalyl-4 : 5-methylenedioxybenzoic acid (III), and a nitrogenous acid. The formulation of the last acid as 1 : 2 : 3 : 4-tetrahydro-3-oxo-6 : 7-methylenedioxy*iso*quinoline-4-carboxylic acid ((II) accounts for its non-basic character, for its being a possible intermediate in the formation of the other products (III) and (IV), and for its origin from a reduced phenanthridine.

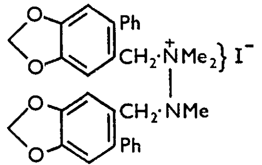
The hydrastic anhydride was not obtained in sufficient quantities for analysis; but it showed similar melting-point characteristics and identical infrared spectra when compared with the product obtained from a similar oxidation of lycorine and with a synthetic sample kindly given by Drs. Reeve and Myers.

Hofmann degradation of hæmanthamine methiodide gave a mixture, which with acid readily gave red gums and a small quantity of *N*-methyl-4 : 5-methylenedioxy-2-phenylbenzylamine (VIII), as well as 4 : 5-methylenedioxy-2-phenylbenzaldehyde (V), isolated as its 2 : 4-dinitrophenylhydrazone, which changed its crystalline form when heated (discrepancies in the melting points of 2 : 4-dinitrophenylhydrazones have been commented on by other workers).[5] The same aldehyde is prepared by oxidation of 4 : 5-methylenedioxy-2-phenylbenzyl alcohol (VI) with potassium permanganate and on oxidation gave 4 : 5-methylenedioxy-2-phenylbenzoic acid (VII).

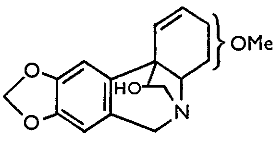
Formulation of the Hofmann product as (VIII) receives support from its oxidation to 4 : 5-methylenedioxy-2-phenylbenzaldehyde (V). When the secondary amine (VIII) was treated with methyl iodide there was formed in small quantities a compound, $C_{16}H_{18}O_2NI$, and a compound, $C_{17}H_{20}O_2NI,H_2O$ formulated as *NN*-dimethyl-4 : 5-methylenedioxy-2-phenylbenzylamine hydriodide and methiodide respectively, but the main product appeared from analyses to be a " semimethiodide " $(C_{15}H_{14}O_2N)_2,CH_3I,2H_2O$, formed presumably by the oxidation of the secondary amine to a tetrasubstituted hydrazine (IX), a type of oxidation previously observed by Goldschmidt and Voeth.[6]



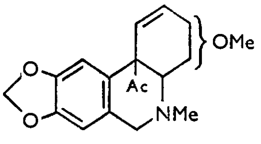
(V) : R = CHO
(VI) : R = $CH_2 \cdot OH$
(VII) : R = CO_2H
(VIII) : R = $CH_2 \cdot NHMe$



(IX)



(X)



(XI)

The elimination of two carbon atoms in the Hofmann reaction is to be understood if hæmanthamine has structure (X). The initial product of the reaction would be a base which would be expected to become aromatic by eliminations similar to those envisaged for Hofmann degradation of tazettine.[7] The aldehyde (V) would result from the fission of the hydroxy-amine formed by oxidation of the secondary amine (VIII). This formulation (X) shows the double bond and the methoxy-group in the same position as in tazettine,[7] with which hæmanthamine is closely associated in several species. Further, the large change in molecular rotation of the base and its methiodide after hydrogenation indicates the close proximity of the double bond to an asymmetric centre. The isolation of the intermediate oxidation product (II) supports structure (X), for the oxidation of the *iso*quinoline nucleus at position 4 would be arrested by the absence of a hydrogen atom there. The same structure has been advanced by Fales and Wildman on different evidence.[8]

---

[5] Campbell, *Analyst*, 1936, **61**, 391; Bredenck and Fritzche, *Ber.*, 1932, **65**, 1833; 1937, **70**, 802; Lange and Houtman, *Rec. Trav. chim.*, 1946, **65**, 891.

[6] Goldschmidt and Voeth, *Annalen*, 1924, **435**, 265.

[7] Wiesner and Valenta, *Chem. and Ind.*, 1956, R 36; Ikeda, Taylor, Tsuda, and Uyeo, *Chem. and Ind.*, 1956, 411.

[8] Fales and Wildman, *Chem. and Ind.*, 1958, 561.

EXPERIMENTAL

Extraction.—The sliced bulbs of *H. natalensis* were extracted once with alcohol, dried (1100 g.), ground, and re-extracted with alcohol. The extract was concentrated, steam-distilled, made alkaline, and extracted with chloroform. The chloroform extract was passed through an alumina column, the chloroform eluate separated, and then the residual alkaloids were washed out with 1 : 19 ethanol–chloroform.

The chloroform eluate gave crystals (0·94 g.) which were washed with cold acetone and crystallised twice from acetone, to give hæmanthamine, m. p. 204·5° (Boit [1] and Wildman and Kaufman [2] give m. p. 200—201° and 199—200° respectively) (Found: C, 68·3, 68·4; H, 6·3, 6·6; N, 4·1, 4·6; OMe, 11·0; active H, 0·35. Calc. for $C_{17}H_{19}O_4N$: C, 67·8; H, 6·3; N, 4·7; OMe, 10·3; 1 active H, 0·35%). The *picrate* formed needles (from water), m. p. 220—222°, with change in crystalline form at 150° and without loss of weight at 160° (Found: C, 51·2; H, 4·3; N, 10·7. $C_{23}H_{22}O_{11}N_4,\frac{1}{2}H_2O$ requires C, 51·2; H, 4·3; N, 10·4%) [Boit gives m. p. 221° (unanalysed)], and the *styphnate*, separating from hot water, had m. p. 148—151° (Found: C, 50·2; H, 4·2. $C_{23}H_{22}O_{12}N_4$ requires C, 50·0; H, 4·2%).

The ethanol–chloroform eluate yielded a mixture of alkaloids (1·0 g.), and a water-soluble hygroscopic gum (8·3 g.).

Acetylhæmanthamine Picrate.—Hæmanthamine and excess of acetic anhydride were refluxed for 30 min. The product worked up in the usual way gave an oil, b. p. 150°/0·3 mm. This gave *acetylhæmanthamine picrate* which, recrystallised twice from ethanol, yielded needles, m. p. 175°, recrystallising without loss of weight at 178°, and remelting at 189° (Found: C, 52·5; H, 4·6. $C_{25}H_{24}O_{12}N_4$ requires C, 52·4; H, 4·2. $C_{25}H_{24}O_{12}N_4$ requires C, 52·4; H, 4·2%).

Hæmanthamine Methiodides.—Hæmanthamine (2·25 g.) in chloroform (40 ml.) and methyl iodide (5 ml.) were refluxed on a water-bath for 30 min. and set aside overnight. The crystalline deposit was boiled in water with Norit and filtered, to give, while still hot, *hæmanthamine methiodide* as needles, m. p. 204—206°, $[\alpha]_D^{22}$ +13·8° (*c* 2 in methanol) (Found: C, 47·1; H, 4·8; N, 3·0; OMe, 6·4; NMe, 5·5. $C_{18}H_{22}O_4NI,H_2O$ requires C, 46·8; H, 5·2; N, 3·0; OMe, 6·7; NMe, 6·3%).

The mother-liquor, set aside for some hours, deposited another *form* (needles), m. p. 192—194°, $[\alpha]_D^{22}$ +13·4° (*c* 1·6 in methanol) (Found: C, 47·3; H, 5·0; N, 3·1; OMe, 6·3; NMe, 5·5%).

A methyl alcohol solution of the methiodide, m. p. 204—206°, on evaporation deposited the substance (0·5 g.), m. p. 204°, which, dissolved in sufficient water to keep it in solution until cool and then set aside, gave successive crops of crystals (0·4 g.), m. p. 192°. A mixture of the two forms had m. p. 190—200°.

Dihydrohæmanthamine.—Hæmanthamine in ethanol, hydrogenated in the presence of Adams's catalyst, absorbed 0·98 mol. of hydrogen. The filtered solution, allowed to evaporate, gave *dihydrohæmanthamine* as needles, m. p. 222—223°, $[\alpha]_D^{24}$ +67·0 (*c* 0·8 in ethanol) (Found: C, 67·3; H, 7·0. $C_{17}H_{21}O_4N$ requires C, 67·3; H, 6·9%). The *picrate* (from ethanol) had m. p. 208—210° (Found: C, 51·9; H, 4·8; N, 11·81. $C_{23}H_{24}O_{11}N_4$ requires C, 51·9; H, 4·5; N, 10·5%).

Dihydrohæmanthamine (2 g.) and methyl iodide (4 ml.) were refluxed for 30 min. and allowed to cool slowly overnight. Larger prisms of a *solvated methiodide* were deposited, which lost solvent of crystallisation at 178° for 2 hr. (Found: Loss of weight, 22. $C_{18}H_{24}O_4NI,CHCl_3$ requires $CHCl_3$, 21%). There was no loss in weight after two hours' heating at 105°, but the chloroform was immediately freed in boiling water. This substance was dissolved in water and set aside overnight, to give large oblong prisms of a *sesquihydrate* which rapidly became opaque in air and lost solvent at 20°/0·2 mm. (Found: Loss of wt., 2, 2·5. $C_{18}H_{24}O_4NI,1\frac{1}{2}H_2O$ requires $\frac{1}{2}H_2O$, 1·9%), leaving *dihydrohæmanthamine methiodide monohydrate*, m. p. 186°, $[\alpha]_D^{21}$ +50° (*c* 2·9 in methanol) (Found: C, 46·7; H, 5·72; OMe, 8·5; NMe, 6·5. $C_{18}H_{24}O_4NI,H_2O$ requires C, 46·6; H, 5·65; OMe, 6·7; NMe, 6·3%). This substance in water deposited, on cooling, large pointed prisms of a fourth *solvate*, which became slightly opaque in air and lost solvent of crystallisation at 20°/0·2 mm. (Found: Loss of wt., 5·8, 4·6. $C_{18}H_{24}O_4NI,2\frac{1}{2}H_2O$ requires $1\frac{1}{2}H_2O$, 5·51%), giving the monohydrate, m. p. 200°, $[\alpha]_D^{20}$ +57·7° (*c* 2·9 in methanol) (Found: C, 47·3; H, 5·3; OMe, 7·2; NMe, 5·9%).

Distillation of Hæmanthamine with Zinc Dust.—Hæmanthamine (0·1 g.) in zinc dust (3 g.) was gently distilled through a layer of heated zinc dust. The cooled mixture was lixiviated with alcohol, the alcohol evaporated, and the residue in benzene chromatographed over alumina.

The first eluates gave oils, and the later fractions a solid which sublimed at 120°/2 mm., to give 6 : 7-methylenedioxyphenanthridine as needles, m. p. 149°, subliming at 120°. The picrate was sublimed at 130°/0·2 mm. and recrystallised from ethanol as needles, m. p. 290° (Found: C, 52·7; H, 2·7. Calc. for $C_{20}H_{12}O_9N_4$: C, 53·1; H, 2·7%). Kondo *et al.*[9] give m. p. 142° and for its picrate m. p. 257°. The picrate, observed under the microscope, started to sublime to a yellow oil at 257°, and the residual crystals showed m. p. 290°, f. p. 288°, and decomposed at 291°.

Oxidation with Potassium Permanganate.—(*a*) Hæmanthamine (2·53 g.) was dissolved in 0·1N-hydrochloric acid, the solution was neutralised to pH 8 with sodium hydroxide and cooled to 0°, and 1% potassium permanganate solution (450 ml.) was added slowly. The solution was acidified and extracted with ether. The ether solution gave a wax which recrystallised from benzene and sublimed at 130°/760 mm., giving 1 : 2 : 3 : 4-*tetrahydro*-6 : 7-*methylenedioxy*-3-*oxo*iso*quinoline*-4-*carboxylic acid* as diamond-shaped needles (17 mg.), acid to litmus, not to Congo Red. Twice resublimed at 130°/0·2 mm. it gave needles, changing form at 190—200°, m. p. 220° (Found: C, 55·9; H, 3·5; N, 6·35. $C_{11}H_9O_5N$ requires C, 56·2; H, 3·8; N, 6·0%).

(*b*) Hæmanthamine (0·84 g.) was dissolved in 0·1N-hydrochloric acid (35 ml.), and 0·1N-sodium hydroxide added until the solution had pH 9. Potassium permanganate was run in with stirring until an excess was present (406 ml.). The solution was filtered, set aside overnight, extracted with ether, acidified to pH 2, and re-extracted with ether. The second ethereal extract gave a product which sublimed at 109°/760 mm. to crystals, m. p. 173—174° (in capillary tube). It showed similar m. p. characteristics to, and identical infrared spectra with, hydrastic anhydride, obtained by similar oxidation of lycorine and also a synthetic sample kindly sent by Drs. Reeve and Myers. For hydrastic anhydride Kondo, Katsura, and Ogami [9] give m. p. 173°, and Reeve and Myers [10] give m. p. 179—180°. Observed under a microscope, the crystals changed form at 140° and, when they had been held at that temperature until the change was complete, the m. p. was 185—186°, crystallisation occurred immediately after melting, and remelting at 190°.

After sublimation of the hydrastic anhydride the residue was dissolved in aqueous sodium hydrogen carbonate, decolorised with Norit, filtered, acidified, and extracted with ether. The solution was concentrated, light petroleum added, and the whole set aside, affording 4 : 5-*methylenedioxy*-2-*oxalylbenzoic acid*, m. p. 206° (Found: C, 50·3; H, 2·5. $C_{10}H_6O_7$ requires C, 50·4; H, 2·5%).

The ether–light petroleum solution was chromatographed over alumina, to give crystals changing form at 190—200°, and m. p. 220°, undepressed on admixture with the compound from first oxidation.

Hofmann Degradation of Hæmanthamine Methiodides.—Hæmanthamine methiodide (2·9 g.), m. p. 188—192°, water (50 ml.), and silver oxide [from silver nitrate (10 g.)] were stirred on a water-bath for 2 hr., then filtered, and evaporated under reduced pressure. The dark brown solid was heated at 100°/0·2 mm. for 30 min. and lixiviated with benzene. The residue dissolved in water and gave a *reineckate* (Found: N, 14·7. $C_{21}H_{25}O_4N_7S_4$ requires N, 15·8%). The red benzene solution was extracted with dilute hydrochloric acid until the extract gave no reaction with Meyer's reagent. A copious red oil separated with each extraction and was collected in acetone. The clear acid extract was treated stepwise with sodium hydrogen carbonate. A red tar and then a red solid separated at pH 2—4 and were filtered off separately. The solution was set aside for two days, and filtered from the red deposit. The filtrate was treated stepwise with sodium hydrogen carbonate to give a copious creamy precipitate at pH 6 and then at pH 8 an oil. Sufficient acid was added to dissolve the oil, the solution filtered and made alkaline with sodium hydrogen carbonate, and the precipitated oil extracted with ether. The ether extract gave N-*methyl*-4 : 5-*methylenedioxy*-2-*phenylbenzylamine* as a colourless oil (Found: C, 74·2; H, 6·45; N, 5·8. $C_{15}H_{15}O_2N$ requires C, 74·7; H, 6·3; N, 5·8%). The *hydrochloride* crystallised from acetone in needles (0·4 g.), m. p. 160°. The crystals lost water in air and completely at 20°/0·2 mm. and were dried at 100°/0·2 mm. (Found: Loss of wt., 6·05. $C_{15}H_{16}O_2NCl,H_2O$ requires H_2O, 6·1. Found, for anhydrous material: C, 64·7, 64·5; H, 5·9, 5·9; N, 5·0, 4·9; Cl, 13·0, 13·0. $C_{15}H_{16}O_2NCl$ requires C, 64·8; H, 5·8; N, 5·0; Cl, 12·8%). The hydrochloride in water, with aqueous picric acid, gave the *picrate*, needles, m. p. 148—150°, which recrystallised from hot water as needles, m. p. 95—97°, becoming completely crystalline at 120°, and remelting at 157°

---

[9] Kondo, Katsura, and Ogami, *J. Pharm. Soc. Japan*, 1940, **60**, 619.

[10] Reeve and Myers, *J. Amer. Chem. Soc.*, 1951, **73**, 1371.

(Found, for substance, m. p. 157°: C, 53·0; H, 3·7. $C_{21}H_{18}O_9N_4$ requires C, 53·5; H, 4·1. Found, for substance, m. p. 97°: C, 52·3; H, 4·55; N, 11·3. $C_{21}H_{18}O_9N_4,H_2O$ requires C, 51·7; H, 4·13; N, 11·5%).

4 : 5-*Methylenedioxy*-2-*phenylbenzaldehyde* 2 : 4-*Dinitrophenylhydrazone.*—This substance was obtained on addition of 2 : 4-dinitrophenylhydrazine hydrochloride in alcohol to an alcoholic solution of (i) the brown impurities obtained by washing the hydrochloride of the methine with acetone, (ii) the benzene solution of the Hofmann degradation product, and (iii) the distillate obtained by heating the red oil produced during the Hofmann reaction at 170°/0·2 mm. The colloidal solution formed was evaporated to dryness, dissolved in benzene, and passed through alumina. The first eluate with benzene gave 4 : 5-*methylenedioxy*-2-*phenylbenzaldehyde* 2 : 4-*dinitrophenylhydrazone* which crystallised from benzene in orange needles. The m. p. of the compound depended on the rate of heating. Rapid heating gave m. p. 280°. On a microapparatus it sublimed above 230° to give a mixture of needles and deep red diamond-shaped crystals. At 270—275° the substance slowly changed from the orange needles to the diamond-shaped crystals, and, if subsequent heating was slow enough to complete the change before the m. p. of the mixture was reached, the resultant compound had m. p. 297° (Found: C, 59·6; H, 3·5; N, 14·2. $C_{20}H_{14}O_6N_4$ requires C, 59·1; H, 3·5; N, 13·8%).

Oxidation of N-*Methyl*-4 : 5-*methylenedioxy*-2-*phenylbenzylamine* (VIII).—A solution of the hydrogen amine (VIII) hydrochloride (500 mg.) in water was made alkaline with sodium carbonate and extracted with ether. The extract gave an oil which was treated in acetone with a 1% solution of potassium permanganate in acetone (40 ml., 4 equivs. of oxygen) at 0°. After 12 hr. the solution was filtered, decolorised with a drop of formaldehyde, and evaporated. The residue crystallised from light petroleum, to give 4 : 5-methylenedioxy-2-phenylbenzaldehyde in needles (210 mg.), m. p. 89°, subliming at 75° (Found: C, 74·2; H, 4·55. Calc. for $C_{14}H_{10}O_3$: C, 74·3; H, 4·5%). Späth and Kahovec[11] give m. p. 87°. It gives with concentrated sulphuric acid a deep green colour, and a blue precipitate. Piperonaldehyde gives a green colour only, with sulphuric acid. The 2 : 4-dinitrophenylhydrazone had a m. p. which varied as reported above, and an infrared spectrum identical with that from the product of the Hofmann reaction above and with that from the oxidation product of 4 : 5-methylenedioxy-2-phenylbenzyl alcohol.

Reaction of N-*Methyl*-4 : 5-*methylenedioxy*-2-*phenylbenzylamine with Methyl Iodide.*—(*a*) A solution of the amine hydrochloride (0·2 g.) in water was basified with sodium hydrogen carbonate and extracted with ether. The oil so obtained was dissolved in chloroform, and methyl iodide (2 ml.) was added. Iodine was immediately liberated. The solution was refluxed for 1 hr. and evaporated to a gum which solidified on lixiviation with boiling benzene–alcohol (70 : 30) (three times), to leave a white solid, the organic solvent becoming yellow. The yellow solution obtained by the first boiling was concentrated to give NN-*dimethyl*-4 : 5-*methylenedioxy*-2-*phenylbenzylamine hydriodide* as hexagonal crystals (8 mg.), m. p. 206° (Found: C, 49·8; H, 5·02. $C_{16}H_{18}O_2NI$ requires C, 50·1; H, 4·74%).

The white solid was dissolved in alcohol (1 ml.), and one drop of benzene added to give crystallisation immediately in needles (10 mg.), m. p. 144—146°.

(*b*) The amine (250 mg.) in ether and methyl iodide were set aside for one day in the dark at 0°. The gummy precipitate was dissolved in a little alcohol, and a few drops of benzene were added, and the crystalline solid (120 mg.) was recrystallised by the same procedure, to give 1 : 2-*dimethyl*-1 : 2-*di*-(4 : 5-*methylenedioxy*-2-*phenylbenzyl*)*hydrazine monomethiodide*, m. p. 144° (Found: C, 56·4, 56·3; H, 5·6, 5·3. $C_{31}H_{31}O_4N_2I,2H_2O$ requires C, 56·5; H, 5·35%). The mother liquor therefrom was evaporated to dryness and lixiviated with benzene, to leave a residue, m. p. 204°, undepressed by the substance, m. p. 206°, obtained in the first preparation. The benzene solution slowly deposited NNN-*trimethyl*-4 : 5-*methylenedioxy*-2-*phenylbenzylammonium iodide* as one large hexagonal crystal (11·2 mg.), m. p. 132—134° (Found: C, 49·0; H, 4·8. $C_{17}H_{20}O_2NI,H_2O$ requires C, 49·2; H, 5·3%).

The authors gratefully acknowledge grants from the South African C.S.I.R.

Department of Chemistry and Chemical Engineering, University of Natal,
Durban and Pietermaritzburg.
[*Received, July 22nd,* 1958.]

---

[11] Späth and Kahovec, *Ber.*, 1934, **67**, 1501.