and dried *in vacuo*, and recrystallized from 900 ml. of ethyl alcohol; yield of IV as a pale yellow solid 6.84 g. (76%), m.p. 94–95°.[15]

Anal. Calcd. for $C_{16}H_{28}N_2O_2S_6$: C, 40.64; H, 5.97; S, 40.69. Found: C, 40.40; H, 5.88; S, 40.96.

1,5,7,11-Tetrathiaspiro[5.5]undecane (VI).—A solution of 2.1 g. (20 mmoles) of freshly distilled 2,2′-iminodiethanol in 50 ml. of ethyl alcohol was added to a solution of 3.0 g. (20 mmoles) of trimethylene trithiocarbonate[20] in 150 ml. of the same solvent. The resulting solution was evaporated under reduced pressure at 55–60° to a yellow oil, which was kept at this temperature for 3 hr. *in vacuo*. The white crystals that formed were collected, washed with cold propyl alcohol, and dried *in vacuo* over phosphorus pentoxide; yield 0.73 g. (33%),[21] m.p. 116°,[17] nitroprusside test for thiol negative (even after boiling briefly in dilute acid or base). Recrystallization from ethyl alcohol afforded a sample of VI for analysis as white crystals, m.p. 116–117°,[15] 117°;[17] $\nu_{\max}^{\mathrm{KBr}}$ (major bands) 2905 (s.), 1410 (s.), 1270 (s.), 1000 (m.), 905 (m.), 880 (s.), 770 (m.-s.), 740 (s.) cm.$^{-1}$. The n.m.r. spectrum (Fig. 1) was measured on a Varian A 60 n.m.r. spectrometer.

Anal. Calcd. for $C_7H_{12}S_4$: C, 37.46; H, 5.39; S, 57.15; mol. wt., 224. Found: C, 37.66; H, 5.39; S, 57.10; mol. wt., 230.

Acknowledgment.—The authors are indebted to Dr. W. C. Coburn, Jr., for determination and interpretation of the n.m.r. spectra; and to the Analytical Section of Southern Research Institute for the analyses reported.

[21] Additional crystals, not included in the yield figures, were deposited in the oily residue obtained by evaporation of the filtrate *in vacuo;* the residual oil gave a positive nitroprusside test. The crude oily thiols obtained from other runs also deposited crystals on long standing when seeded with VI.

The Structure of Ceanothic Acid[1]

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Received May 3, 1962

The medicinal plant *Ceanothus americanus*, fam. *Rhamnaceae* (Jersey Tea), has until quite recently escaped thorough chemical investigation although it has been known to contain numerous compounds of unknown structure.[2] During the last two years four groups have reported work on this plant.[1,3–5] Roscoe and Hall[3] have noted the presence of eight alkaloids in the root bark while others[1,4,5] have investigated the nonalkaloid fractions of the plant.

De Mayo[4] as well as this writer,[1] have been able to confirm the presence of ceanothic acid as first reported by Julian, Pikl, and Dowson[6] in 1938. Ceanothic acid was described by Julian as a hydroxy dicarboxylic acid in which both carboxyl groups were hindered. On melting it lost one equivalent of carbon dioxide and also one of water.

In this paper experiments are reported leading to structure Ia for ceanothic acid. For the sake of simplicity the entire discussion will be presented in terms of the eventually established structure.

An improved extraction procedure led to the easy separation of ceanothic acid, m.p. 356–358°, $[\alpha]_D$ +38°. Dimethyl ceanothate (Ib) showed an average molecular weight of 503 (Rast). Equivalent weight value of 248 was obtained for the free acid by titration using alkali; ceanothic acid is therefore dibasic. The infrared spectra of Ia and of Ib suggested the presence of a vinylidene group (1642 and 885 cm.$^{-1}$). On catalytic hydrogenation Ib absorbs one mole of hydrogen giving dimethyl dihydroceanothate (II) in which these two bands have disappeared. Repeated analyses of all compounds fitted a $C_{30}H_{46}O_5$ formula for ceanothic acid. Such an empirical formula requires a pentacyclic skeleton. On boiling with acid[7] followed by esterification of the remaining free carboxyl group Ia gave III which has a five-membered lactone ($\nu_{\max}$ 1770 cm.$^{-1}$) but no vinylidene group. A reaction of this type is well known in the lupeol series.[7] In view of the empirical formula, the presence of the vinylidene group and the nature of the lactonization reaction (Ia → III) it seemed plausible that ceanothic acid is a triterpene of the lupeol group. The hydroxyl group, known to be present in the molecule, was assumed, on the basis of rather abundant analogies, to occupy the C-3 position. One of the carboxylic groups could be placed at C-17, in view of the lactonization reaction.

The simultaneous dehydration and decarboxylation occurring at the melting point of ceanothic acid[6] suggested that the second carboxyl group is located beta to the hydroxyl group. Indeed oxidation of the hydroxyl group to a ketone, gave a keto monocarboxylic acid (IVa), presumably obtained on decarboxylation of a labile β-keto acid intermediate. The infrared spectrum of this substance showed the presence of the vinylidene group (1640 and 882 cm.$^{-1}$) and of two bands in the carbonyl region at 1740 and 1720 cm.$^{-1}$. The 1740-cm.$^{-1}$ band suggested a five-membered ring ketone.

The triterpene emmolic acid was isolated in 1958 by Simes and coworkers[8] from *Emmenospermum alphitonioides* F. *Muell* (fam. Rhamnaceae)

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[1] Preliminary communication: R. Mechoulam, *Chem. Ind.* (London), 1835 (1961).

[2] For leading references to work prior to 1960 see ref. 3 and 5.

[3] C. W. Roscoe and N. A. Hall, *J. Am. Pharm. Assoc., Sci. Ed.*, **49**, 108 (1960).

[4] P. de Mayo and A. N. Starratt, *Tetrahedron Letters*, **7**, 259 (1961).

[5] R. A. Abramovitch and G. Tertzakian, *Can. J. Chem.*, **39**, 1733 (1961).

[6] P. L. Julian, J. Pikl, and R. Dowson, *J. Am. Chem. Soc.*, **60**, 77 (1938).

[7] *Cf.* V. Bruckner, J. Kovács, and I. Koczka, *J. Chem. Soc.*, 951 (1948); G. S. Davy, T. G. Halsall, and E. R. H. Jones, *ibid.*, 2696 (1951).

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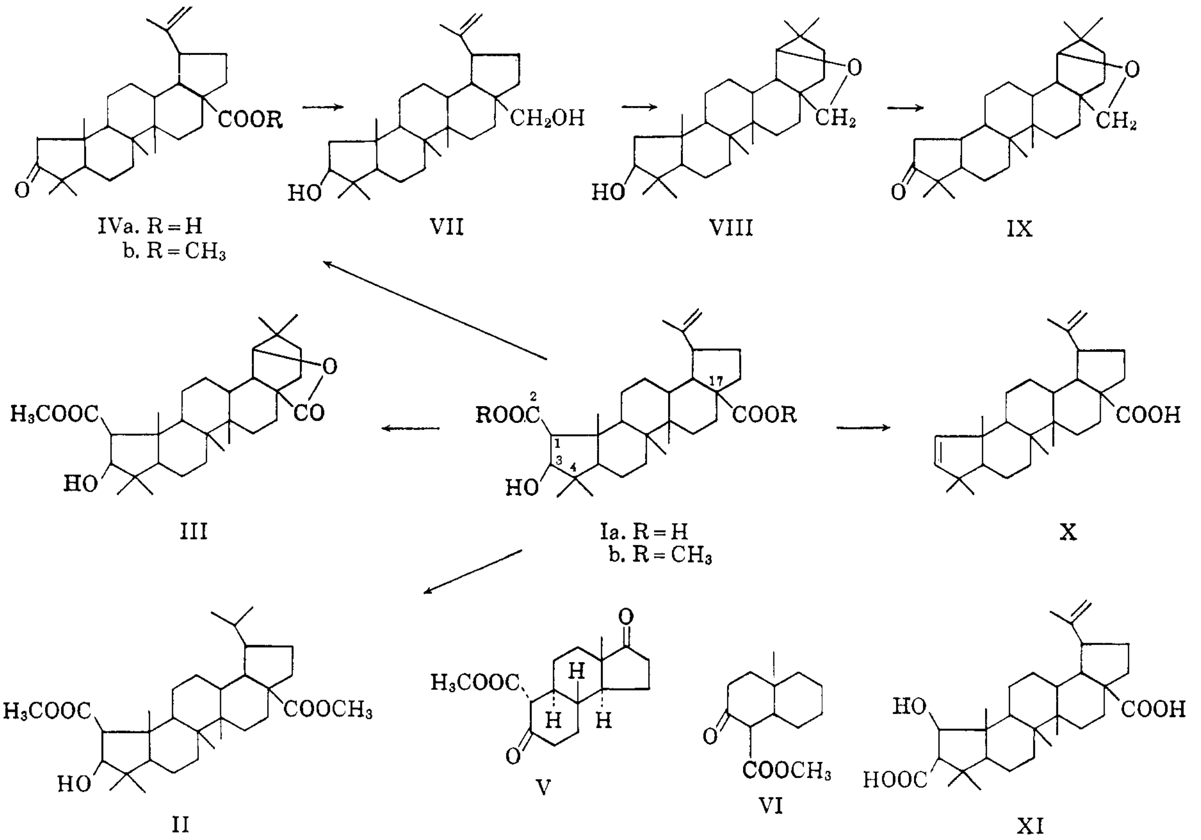

and in 1960 by Birch *et al.*[9] from *Alphitonia excelsa* of the same family. The similarity of the physical constants of this triterpene and of its derivatives with ceanothic acid as well as their botanical relationship intimated that they could be identical. A sample of dimethyl emmolate kindly supplied by Dr. J. J. H. Simes was identical with dimethyl ceanothate (mixed melting point and infrared spectra comparison).[10]

On the basis of experiments similar to those reported above, the Australian group[8] have reached the conclusion that emmolic acid contains two hindered carboxylic groups, one double bond in an isopropenyl group and a secondary hydroxyl group on a five-membered ring in a beta position to one of the carboxyl groups. They concluded that the latter is on a quaternary carbon atom as there was no evidence of enolisation in dimethyl ketoemmolate and dimethyl dihydroketoemmolate. They also suggested that emmolic acid is probably pentacyclic with a carbon skeleton different from that of any of the naturally occurring triterpenes.

The argument for the tertiary position of the carboxyl group to the hydroxyl group seems untenable. It has been shown[11] that compounds such as V and VI have also no enolic properties.

A most important point of the above conclusions was the placing of the hydroxyl group on a five-membered ring. This had been assumed on the basis of the infrared spectra of a number of keto derivatives (1750 cm.$^{-1}$ in Nujol). As in these derivatives the ketone is located beta to a carboxylic ester group; such a high frequency in the carbonyl region, which is usually due to a ketone on a five-membered ring, could be due in this case to a ketone beta to an *equatorial* carboxylic ester on a six-membered ring. Such ketones have been reported to absorb in the 1740-cm.$^{-1}$ region.[12]

To clarify this point, ceanothic acid was oxidized to IVa which was then reduced to the diol VII. Boiling with acid converted the diol into VIII. Such a rearrangement has been described in similar compounds in the lupeol series.[13] On oxidation of VIII compound IX was obtained. This monoketone has only one group absorbing in the carbonyl region—at 1740 cm.$^{-1}$, indicative of a ketone on a five-membered ring, proving thereby that the hydroxyl group is on such a ring.

On melting ceanothic acid loses one mole of carbon dioxide and one of water giving, not a lactone as previously assumed,[6] but a monocar-

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[9] A. J. Birch, E. Ritchie, and R. N. Speake, *J. Chem. Soc.*, 3593 (1960).

[10] Prof. E. R. H. Jones and Dr. T. G. Halsall of Oxford University have also reached the same conclusion (personal communication).

[11] F. Sondheimer, R. Mechoulam, and M. Sprecher, *Tetrahedron Letters*, **22**, 38 (1960); G. Stork, P. Rosen, and N. Goldman, *J. Am. Chem. Soc.*, **83**, 2965 (1961); see also R. Hanna and G. Ourisson, *Bull. Soc. Chim. France*, 1945 (1961).

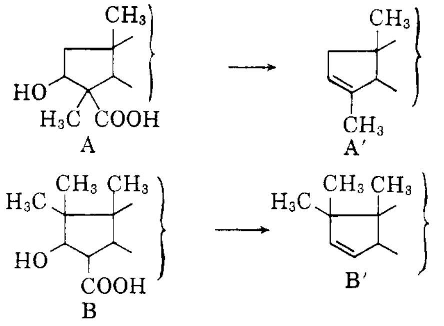
[12] P. A. Stadler, A. Nechvatal, A. J. Frey, and A. Eschenmoser, *Helv. Chim. Acta*, **40**, 1373 (1957); N. A. Nelson and R. N. Schut, *J. Am. Chem. Soc.*, **80**, 6630 (1958).

[13] *Cf.* W. Lawrie, J. McLean, and G. R. Taylor, *J. Chem. Soc.*, 4303 (1960).

boxylic acid (X) which has retained the isopropenyl group (ν_{max}, 1640 and 890 cm.$^{-1}$) and has also an additional *cis* double bond (758 cm.$^{-1}$). A comparison between the n.m.r. spectra of X and of dimethyl ceanothate (Ib) shows that each of them has only one vinylic methyl group (CH_3—$C = CH_2$) with τ values of the methyl protons of 8.32 and 8.38, respectively. This indicates that in ceanothic acid there is no methyl group alpha to the carboxyl group which is eliminated on melting. If such a methyl group were present, it would have appeared as a second methyl vinyl group after the decarboxylation (see A → A′). In addition to the vinyl protons of the isopropenyl group (5.26 τ and 5.40 τ), X has also two vinyl hydrogens, which appear as two doublets centered at 4.52 τ and 4.02 τ. The splitting to doublets only shows that each vinylic hydrogen is split by the adjacent vinylic hydrogen only and that there are probably no hydrogens on the carbon atoms next to the double bond (C-4 and C-10). These observations show that at least two of the carbon atoms of the cyclopentane ring A are tertiary, while the carboxyl and hydroxyl groups on this same ring are secondary.

If no further skeletal rearrangements have occurred, the preceding data indicate that ceanothic acid has structure Ia or the less probable structure XI.

Structures A and B have to be excluded since the pyrolysis product should then have structures A′ and B′ respectively which are incompatible with the n.m.r. data.



At this point of the investigation, the publication of de Mayo *et al.*[4] appeared These authors reached the same conclusions as presented in this paper concerning the structure of ceanothic acid and were able to ascertain them by comparing one of their degradation products with a known compound. In a later paper, published after the present manuscript was submitted for publication, de Mayo[14] established the full stereochemistry of ceanothic acid. Thus the C-1 carobxyl group is beta, as previously suggested by us,[1] while the C-3 hydroxyl group is alpha, showing that the stereochemical assignment for this asymmetric center previously proposed by us[1] was incorrect.

Experimental

Melting points are uncorrected. Rotations were determined at 20–25° in chloroform solution. Infrared spectra were measured on a Perkin-Elmer model 137 Infracord recording infrared spectrometer. N.m.r. spectra were determined at 56.4 Mc. on a Varian V-4300-C spectrometer in deuteriochloroform solution with tetramethylsilane as internal standard.

Isolation of Ceanothic Acid.—The finely powdered, dried root bark (1 kg.) of *Ceanothus americanus* (purchased from Meer Corp., New York) was extracted twice with boiling petroleum ether (b.p. 60–80°). The defatted plant material was continuously extracted with boiling ether for 40 hr. The ether extract was concentrated to a volume of *ca.* 200 cc. and shaken with 100 cc. of 3% sodium hydroxide solution. The aqueous layer was twice extracted with ether, then acidified with ice cold 5% hydrochloric acid solution. The acidic aqueous layer was extracted several times with ether. The ethereal solution was evaporated to dryness and the residue was crystallized four times from methanol giving long fibrous needles of ceanothic acid, m.p. 353–355° (dec.). The total yield was 1.65 g. The analytical sample showed m.p. 356–358°, $[\alpha]_D$ +37° (in ethanol).

Anal. Calcd. for $C_{30}H_{46}O_5$: C, 74.03; H, 9.53. Found: C, 73.68; H, 9.66.

Dimethyl ceanothate (Ib), dimethyl dihydroceanothate (II), and dimethyl 3-oxoceanothate (XI) were obtained as described by Boyer, *et al.*,[8] for the identical derivatives of emmolic acid. All physical constants obtained correspond to those given by the Australian authors.

Lactone (III) from Ceanothic Acid.—Ceanothic acid (100 mg.) was dissolved in a solution of 10 cc. of acetic acid and 7 cc. of hydrochloric acid and heated under reflux for 2 hr. The reaction mixture was poured into water and extracted with ether. The organic layer was washed with water and evaporated to dryness. The residue was dissolved in 10 cc. of ethanol and water was added until a permanent cloudiness persisted. This mixture was heated on a water bath for 2 hr. After cooling, the solution was extracted with ether. The ether solution was concentrated and excess diazomethane in ether was added. The material obtained was boiled with 5% methanolic sodium hydroxide for 1 hr. After the usual work-up 43 mg. of lactone III were obtained. Crystallizations from petroleum ether–benzene (1:1) gave crystals, m.p. 255–257°, $[\alpha]_D$ +90°. J. J. H. Simes and coworkers[8] report m.p. 258–260°, $[\alpha]_D$ +91.

Oxidation of Ceanothic Acid. Methyl 3-Oxo-2-decarboxyceanothate (IVb).—Ceanothic acid (110 mg.) was dissolved in 10 cc. of acetone. Chromic acid (0.2 cc. of a 8 *N* solution in sulfuric acid) was added under nitrogen with stirring over a period of several minutes. Methanol was added to destroy excess reagent. Water and ether were added. The organic layer was washed with water, dried over magnesium sulfate, and the ether evaporated. The residue was dissolved in a 2% solution of potassium hydroxide in ethanol. After boiling under reflux for 2 hr., water and ether were added. The mixture was acidified with 10% hydrochloric acid. The organic layer was washed with water, dried over sodium sulphate, and evaporated to dryness. The solid material obtained (IVa) was not crystallized. On titration with 0.01 *N* sodium hydroxide solution, only one carboxyl group was shown to be present. The amorphous IVa was dissolved in ether and treated with an ethereal solution of diazomethane. The solution was left at room temperature for 12 hr., after which it was evaporated to dryness. The residue was crystallized from methanol, giving 41 mg., IVb, m.p. 118–121°. The analytical sample showed m.p. 123–125°, $[\alpha]_D$ +95°, ν_{max} 1740 cm.$^{-1}$ and 1725 cm.$^{-1}$.

Anal. Calcd. for $C_{30}H_{46}O_3$: C, 79.24; H, 10.20. Found: C, 79.60; H, 10.11.

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[14] P. de Mayo and A. N. Starratt, *Can. J. Chem.*, **40**, 788 (1962); see also R. A. Eade, G. Kornis, and J. J. H. Simes, *Chem. Ind.* (London), 1195 (1962)

Ether (IX) from Methyl 3-Oxo-2-decarboxyceanothate (IVb).—A solution of IVb (250 mg.), m.p. 123°, in dry ether was added to a slurry of lithium aluminum hydride (250 mg.) in ether (30 cc.). The reaction mixture was refluxed for 5 hr. A saturated solution of sodium sulfate was added dropwise until a clear ether solution was obtained. Evaporation to dryness yielded 206 mg. of an oil which was used without further purification. The oil (VII) showed $\nu_{\max}$ 1640 and 886 cm.$^{-1}$ (terminal methylene group).

A solution of 150 mg. of oil VII in ethanol (45 cc.) and hydrochloric acid (7.5 cc.) was boiled under reflux for 5 hr. The solution was cooled with ice and sodium hydroxide (7 gr.) in water (25 cc.) was added. The organic material was extracted with ether. Evaporation of the ether gave 140 mg. of an amorphous compound (VIII), which was used directly for the next stage. Compound VIII showed no absorption bands for terminal methylene or ketone in the infrared spectrum.

Compound VIII (140 mg.) was dissolved in 20 cc. of acetone and oxidized with 0.4 cc. of a 8 *N* solution of chromic acid in sulfuric acid. After 2 min. methanol (5 cc.) was added and the mixture poured over ice. The organic material was extracted with ether. The ether solution was washed with water, dried over sodium sulfate, and evaporated to dryness. The oil obtained was chromatographed on 16 g. of F-20 (basic Alcoa) alumina. The material eluted with petroleum ether: benzene (2:1) was crystallized with methanol giving 57 mg. of compound IX, m.p. 220–224°. The analytical sample showed m.p. 224–226°, $[\alpha]_D$ +155°, $\nu_{\max}$ 1740 cm.$^{-1}$ (ketone on a five-membered ring).

Anal. Calcd. for $C_{29}H_{46}O_2$: C, 81.63; H, 10.87. Found: C, 81.76; H, 10.70.

Pyrolysis of Ceanothic Acid.—Compound X was obtained on pyrolysis of ceanothic acid as described by Julian.[6] Complex X showed m.p. 230–232° (rep. 234°), $\nu_{\max}$ 758 cm.$^{-1}$, 886 cm.$^{-1}$, and 1700 cm.$^{-1}$.

Acknowledgment.—The author is indebted to Professor F. Sondheimer for his interest and to Professor J. J. H. Simes of N.S.W. University of Technology, Sydney, Australia, for a sample of dimethyl emmolate.

Syntheses of 9-Keto- and 10-Hydroxy-*trans*-2-decenoic Acids and Related Compounds

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Received May 7, 1962

The syntheses of 9-keto- and 10-hydroxy-*trans*-2-decenoic acids noted for Queen Substance[1] and Royal Jelly acid,[2] respectively, of the honey bee have been described. A new synthesis of the keto acid as outlined below was found to be satisfactory:

$$\underset{\text{I}}{I(CH_2)_6C{\equiv}CH} \xrightarrow{(CH_3)_3NO} \underset{\text{II}}{OCH(CH_2)_5C{\equiv}CH} \xrightarrow{CH_2(CO_2H)_2}$$

$$\underset{\text{III}}{HO_2CCH{=}CH(CH_2)_5C{\equiv}CH} \xrightarrow[HgSO_4]{HCO_2H,\ H_2O}$$

$$\underset{\text{IV}}{HO_2CCH{=}CH(CH_2)_5COCH_3}$$

The oxidation of 8-iodo-1-octyne (I) with trimethylamine oxide was effected as described for octanal by Franzen and Otto[3] with a yield of 69%, and the 7-octynal (II) obtained was condensed with malonic acid under Doebner's conditions[4] to afford 9-decyne-*trans*-2-enoic acid (III) in 65% yield. When the latter was hydrated by means of formic acid in the presence of mercuric sulfate,[5] 9-keto-*trans*-2-decenoic acid (IV) was obtained in almost quantitative yield. Observed physical constants including infrared spectra as well as analyses supported the constitution.

10-Hydroxy-*trans*-2-decenoic acid was prepared according to the following scheme:

$$\underset{\text{V}}{CH_2{=}CH(CH_2)_6CO_2H} \longrightarrow \underset{\text{VI}}{CH_2{=}CH(CH_2)_7OH} \xrightarrow{HCO_3H}$$

$$\underset{\text{VII}}{CH_2OHCHOH(CH_2)_7OH} \longrightarrow \underset{\text{VIII}}{OCH(CH_2)_7OH} \xrightarrow{CH_2(CO_2H)_2}$$

$$\underset{\text{IX}}{HO_2CCH{=}CH(CH_2)_7OH}$$

Since the condensation of 8-hydroxyoctanal (VIII) with malonic acid has been reported by Fujii and his collaborators,[2c] the description will be confined to the preparation of VIII.

8-Nonenoic acid (V) was prepared by double Barbier-Wieland degradations of 10-undecenoic acid in 25% yield based on the ethyl ester. The preparation of V starting from tetrahydrofurfuryl alcohol[6] required several steps and proved impractical. An alternative method described by Stetter and Dierichs[7] was unsuitable because positive evidence for the migration of the terminal double bond was obtained.

Reduction of the ethyl ester of V with lithium aluminum hydride gave 8-nonenol (VI), which was successively dihydroxylated by means of performic acid[8] to give *dl*-1,2,9-trihydroxynonane (VII) in 80% yield.

Treatment of the triol with periodate[9] gave VIII.[10]

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(4) *Cf.* L. Crombie, *J. Chem. Soc.*, 2999 (1952).

(5) A. Mondon, *Ann.*, **585**, 43 (1954).

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