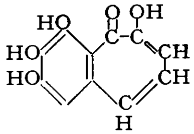
121. *Purpurogallin. Part IV. Some Properties of Tropolones.*

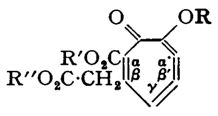
By Robert D. Haworth and John D. Hobson.

An improved preparation of 2-carboxy-4-hydroxy-3-keto*cyclo*heptatrienylacetic acid (II; $R = R' = R'' = H$) and 2-hydroxy-6-methyl*cyclo*heptatrienone (IV; $R = H$; $R' = Me$) from purpurogallin is recorded. Isomeric methyl and *p*-nitrobenzyl ethers of (IV; $R = H$; $R' = Me$) have been prepared; oxidation of the former to 6-formyl-2-hydroxy*cyclo*heptatrienone (IV; $R = H$; $R' = CHO$) and the corresponding 6-carboxylic acid is described, and decarboxylation of the latter has yielded the parent 2-hydroxy*cyclo*heptatrienone (tropolone) (IV; $R = R' = H$). Some substitution reactions of the tropolones are described, and some ultra-violet and infra-red spectroscopic results are included together with a brief discussion of the tropolone ring system.

In Part I (*J.*, 1948, 1045) it was shown that alkaline solutions of purpurogallin (I) were oxidised by an air-stream to α-carboxy-β-carboxymethyltropolone (2-carboxy-4-hydroxy-3-keto*cyclo*heptatrienylacetic acid) (II; $R = R' = R'' = H$)* which, when heated above its melting point, was converted into β-methyltropolone (2-hydroxy-6-methyl*cyclo*heptatrienone) (IV; $R = H$, $R' = Me$) by loss of two molecular proportions of carbon dioxide. As structure (I) for purpurogallin has since been confirmed synthetically (*Chem. and Ind.*, 1950, 149; *J.*, 1950, 1631), structures (II; $R = R' = R'' = H$) and (IV; $R = H$, $R' = Me$) are securely established, and their preparation from purpurogallin represents a synthesis of representatives of the 2-hydroxy*cyclo*heptatrienone (tropolone) (Dewar, *Nature*, 1945, **155**, 50, 141, 479) group. It has been found that the oxidation of purpurogallin is improved considerably by employing hydrogen peroxide, and the acid (II; $R = R' = R'' = H$), obtained in 30% yield, has therefore been made readily accessible for further investigation.



(I.)



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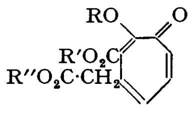

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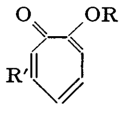

(IV.)

Several relatively simple tropolone derivatives have been isolated from natural sources. In 1936, Nozoe (*Bull. Chem. Soc., Japan*, 1936, **11**, 295) reported the isolation of hinokitiol from the acid portion of the essential oil of *Chamaecyparis taiwanensis*, and later studies (Iinuma, *J. Chem. Soc., Japan*, 1943, **64**, 742; Nozoe and Katsura, *J. Pharm. Soc., Japan*, 1944, **64**, 181,

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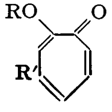
* The structure (II; $R = R' = R'' = H$) and the tautomeric 2-carboxy-3-hydroxy-4-keto*cyclo*heptatrienylacetic acid structure (III; $R = R' = R'' = H$) are regarded as equivalent and the dual nature of all hydroxy*cyclo*heptatrienones (tropolones) is implied throughout this communication. The α, β, γ enumeration of the tropolone positions, as in (II), will in general be used. Ethers corresponding to (II) and (III) (or *vice versa*) have been isolated in several cases (p. 563) and here we ascribe a suffix-A to the higher-melting and less soluble ether, and a suffix-B to its isomer, until the structures can be determined.

and unpublished results *) indicate the identity of hinokitiol and β-thujaplicin (IV; $R = H$, $R' = Pr^i$) isolated together with the α- (VI) and γ- (VII) isomers from the heartwood of red cedar (*Thuja plicata* Don.) by Erdtman and his co-workers (*Nature*, 1948, **161**, 719; *Acta Chem. Scand.*, 1948, **2**, 625, 639, 644). As originally suggested by Dewar (*loc. cit.*, pp. 50, 479), puberulic and stipitatic acids, isolated by Raistrick and his co-workers (*Biochem. J.*, 1932, **26**, 441; 1942, **36**, 242) from the culture media of *Penicillium puberulum* and *P. stipitatum* respectively, have been shown to be the tropolones (VIII; $R = OH$) and (VIII; $R = H$) respectively (Corbett, Hassall, Johnson, and Todd, *J.*, 1950, 1; Corbett, Johnson, and Todd, *ibid.*, pp. 6, 147). In view of the increasing interest in the chemistry of these simple tropolones it appeared desirable to communicate the results of one of several investigations in progress which have (*a*) provided evidence in favour of structure (II; $R = R' = R'' = H$) and (IV; $R = H$, $R' = Me$), (*b*) illustrated the tautomerism of the ketol grouping and the stability of the tropolone ring system, and (*c*) led to the preparation of the parent 2-hydroxy*cyclo*heptatrienone (tropolone) (IV; $R = R' = H$). These results were discussed during a lecture to the Bedson Club at King's College, Newcastle-on-Tyne, on March 10th, 1950, and also to the Chemical Society at St. Andrews on 7th April, 1950, and a brief account of the synthesis of tropolone has appeared in *Chem. and Ind.*, 1950, 441. Announcements of the preparation of tropolone (IV; $R = R' = H$) have also been made by Cook, Gibb, Raphael, and Somerville (*Chem. and Ind.*, 1950, 427) and by Doering and Knox (*J. Amer. Chem. Soc.*, 1950, **72**, 2305).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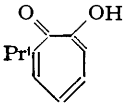
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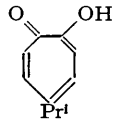
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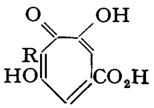
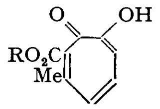

(VIII.)


(IX.)

β-Methyltropolone (IV; $R = H$, $R' = Me$) is a weak acid, dissolving slowly in aqueous sodium hydrogen carbonate to give a yellow solution from which the tropolone may be partly recovered by ether. Addition of lead acetate to an aqueous solution of β-methyltropolone gave an insoluble lead complex, and the copper salt, likewise precipitated from aqueous solution, crystallised from chloroform. β-Methyltropolone and its derivative (II; $R = R' = R'' = H$) had no ketonic properties, and in this respect, as well as in their positive ferric tests, they closely resembled the thujaplicins (Erdtman *et al.*, *locc. cit.*), and stipitatic, puberulic, and puberulonic acids (Corbett *et al.*, *locc. cit.*). Fusion of β-methyltropolone with potassium hydroxide resulted in the production of *m*-toluic acid. The yield was not high and, although similar benzilic acid changes occur with other tropolones, it should be noted that structural factors play an important part. The change appears to occur with great ease in the colchicine-*allo*colchicine transformation (Lettré, *Angew. Chem.*, 1947, **59**, A, 218; Šantavý, *Helv. Chim. Acta*, 1948, **31**, 821; Fernholz, *Annalen*, 1950, **568**, 63), becomes more difficult with purpurogallin (*J.*, 1949, 3271), stipitatic acid, and γ-thujaplicin, and has not been observed with α- and β-thujaplicins (Erdtman *et al.*, *locc. cit.*) or puberulic acid (Corbett *et al.*, *locc. cit.*); on the other hand Nozoe (*loc. cit.*) reports that dinitrohinokitiol (dinitro-β-thujaplicin) is converted by merely warming it with water into a dinitro*iso*propylbenzoic acid.

As in the cases of purpurogallin and its methyl ethers, the catalytic reduction of β-methyltropolone was very sensitive to modifications in the quality of the catalyst. For an acetic acid solution in the presence of platinic oxide, the hydrogen uptake corresponded to 3·5 molecular proportions, and the oily product, unlike the starting material, was a non-acidic mixture containing some ketonic material which gave an amorphous 2 : 4-dinitrophenylhydrazone. The oil, probably a mixture of *cyclo*heptanediols and hydroxy*cyclo*heptanones, consumed approximately one molecular proportion of periodic acid, and yielded 4-methylnonanedial which was isolated as the bis-2 : 4-dinitrophenylhydrazone. Further oxidation of the oily dialdehyde with potassium permanganate gave β-methylpimelic acid which was identified by comparison of the acid, m. p. 45—48°, the anilide, m. p. 137° (Einhorn and Ehret, *Annalen*, 1897, **295**, 180, 80), and the *S*-benzylthiuronium salt, m. p. 172—173°, with specimens prepared from 3-methyl*cyclo*hexanone by methods based on those employed (*a*) by Kötz and Hesse (*Annalen*, 1905, **342**, 314) and (*b*) for the conversion of *cyclo*hexanone into pimelic acid. Condensation of 3-methyl*cyclo*hexanone with ethyl oxalate gave ethyl 2-keto-4-methyl*cyclo*hexylglyoxylate, which when heated yielded ethyl 2-keto-4-methyl*cyclo*hexanecarboxylate, and alkaline hydrolysis of the last gave β-methylpimelic acid.

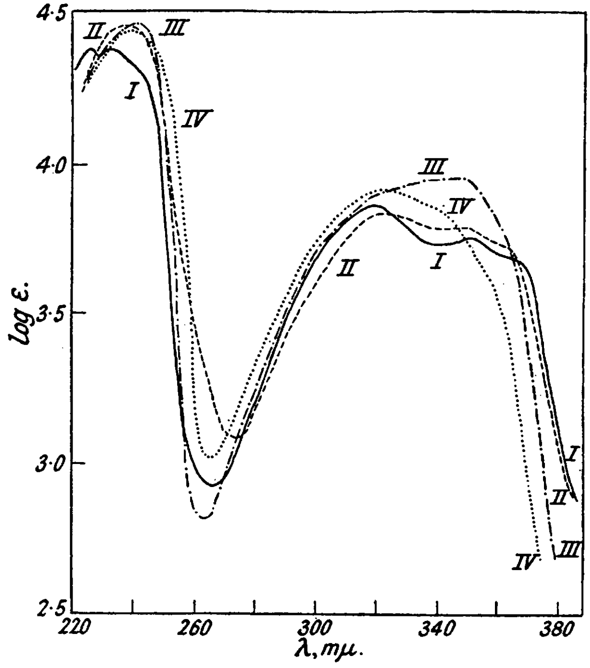
[*] Most of the work was done at Taikoku Imperial University, Formosa, between 1940 and 1948.

The conversion of β-methyltropolone into β-methylpimelic acid provides conclusive evidence for structure (IV; R = H, R′ = Me) or its tautomeric modification. The existence of such tautomerism in the tropolones is supported by the isolation of isomeric diacetyl and trimethyl derivatives of stipitatic acid (Raistrick *et al.*, *locc. cit.*), the formation of two readily hydrolysable *O*-methyl ethers, *viz.*, colchicine and *iso*colchicine, by methylation of colchiceine (Johanny and Zeisel, *Monatsh.*, 1888, **9**, 873; Lettré and Fernholz, *J. physiol. Chem.*, 1943, **273**, 175; Meyer and Reichstein, *Pharm. Acta Helv.*, 1944, **19**, 127; Sorkin, *Helv. Chim. Acta*, 1946, **29**, 246), and further examples have been encountered in the present investigation. Methylation of α-carboxy-β-carboxymethyltropolone (II; R = R′ = R″ = H) with diazomethane gave two isomeric trimethyl derivatives, -A, m. p. 110°, and -B, m. p. 73°, which are (II; R = R′ = R″ = Me) and (III; R = R′ = R″ = Me) or *vice versa*; the ether-A has been reported previously (*J.*, 1948, 1045). Methylation of (II; R = R′ = R″ = H) with methyl sulphate in alkaline solution gave a compound, which is regarded as the dimethyl ester α-carbomethoxy-β-carbomethoxymethyltropolone (II; R = H, R′ = R″ = Me) on account of its positive ferric reaction. Hydrolysis of the isomeric trimethyl derivatives and of the dimethyl ester took place very readily with cold sodium hydroxide solution and yielded in all cases the same dibasic acid, which gave a positive ferric test and must be either α-carbomethoxy-β-carboxymethyl- (II; R = R″ = H, R′ = Me) or α-carboxy-β-carbomethoxymethyl-tropolone (II; R = R′ = H, R″ = Me). The latter structure is however very improbable as the mild hydrolytic conditions are unlikely to affect the tertiary 2-carbomethoxy-group, but we failed to obtain experimental evidence by reaction with phenylmagnesium bromide as unrecognisable products were produced. The acid ester (II; R = R″ = H, R′ = Me) did not condense with piperonaldehyde, and was recovered after prolonged treatment with selenium dioxide, but it readily lost carbon dioxide at the melting point. The resulting α-carbomethoxy-β-methyltropolone (IX; R = Me) was soluble in sodium hydrogen carbonate solution, gave a positive ferric test, and was converted by prolonged boiling with 20% potassium hydroxide solution into α-carboxy-β-methyltropolone (IX; R = H) which yielded β-methyltropolone (IV; R = H, R′ = Me) on decarboxylation.

Two isomeric *p*-nitrobenzyl ethers (-A, m. p. 172°; -B, m. p. 160°) of β-methyltropolone have been prepared; on hydrolysis, both were reconverted into β-methyltropolone. In the same way methylation with diazomethane gave a mixture of β-methyltropolone methyl ether-A, m. p. 97°, and -B, m. p. 46°, which were separated by fractional crystallisation of their picrates. Both ethers gave β-methyltropolone on hydrolysis with alkali, but they showed remarkable differences in behaviour towards selenium dioxide in boiling dioxan. The low-melting methyl ether-B, which is markedly hygroscopic, was converted into a mixture of β-formyltropolone methyl ether-B (IV; R = Me, R′ = CHO, or its isomer) and a small amount of β-carboxytropolone methyl ether-B, but the higher-melting methyl ether-A was oxidised much more slowly and underwent simultaneous hydrolysis with the production of β-formyltropolone. The more rapid oxidation of the methyl ether-B may be indicative of a shorter conjugated system between the carbonyl and the methyl group, but, although this may be used as an argument in favour of structure (IV; R = R′ = Me), we prefer to regard the assignment of formulæ to the tautomeric forms as arbitrary at the present time. Further oxidation with sodium hydroxide and silver oxide (cf. Pearl, *J. Amer. Chem. Soc.*, 1946, **68**, 429) converted β-formyltropolone methyl ether-B in goods yields into β-carboxytropolone (IV; R = H, R′ = CO_2H), which was also obtained by alkaline hydrolysis of β-carboxytropolone methyl ether-B. The aldehydes (IV; R = H, R′ = CHO) and (IV; R = Me, R′ = CHO), and the corresponding acids, offer numerous synthetical possibilities which are under investigation. β-Carboxytropolone has been decarboxylated with copper powder in boiling quinoline, to give the parent tropolone (IV; R = R′ = H), m. p. 50°, which dissolves slowly in aqueous sodium hydrogen carbonate to give a yellow solution, gives with neutral ferric chloride a dark red colour which becomes green on dilution or acidification, yields a characteristic copper salt, and is devoid of ketonic properties.

Although no systematic study of the substitution reactions of the tropolones has been reported, it is evident from a number of observations that considerable aromaticity is displayed. Thus Raistrick (*Biochem. J.*, 1942, **36**, 242) showed that stipitatic acid was substituted by bromination in 80% acetic acid solution, and Nozoe (*locc. cit.*) mentions several mono-, di-, and tri-halogen and -nitro-substitution products of hinokitiol. We have observed that β-methyltropolone reacts with bromine in chloroform to give a red complex which is readily decomposed by water, yielding a difficultly separable mixture of mono- and di-bromo-substitution products. Although the structures of these derivatives have not been established, largely because of failure to achieve the benzilic acid transformation with them, the stability towards aqueous or alcoholic potassium hydroxide suggests that substitution has occurred in the tropolone nucleus and not in the methyl group. It is probable that substitution occurs in a position activated by the hydroxyl group, particularly as the tropolones will condense with diazonium compounds in alkaline solution. Diazotised aniline gave red precipitates with alkaline solutions of tropolone or the β-methyl derivative, and the latter gave a crystalline red azo-dye, $C_{15}H_{14}O_2N_2$, m. p. 177—178° (decomp.), with diazotised *p*-toluidine. This azo-dye has been reduced by sodium dithionite (hydrosulphite) to a yellow aminotropolone, m. p. 224°, which was converted into a hydroxytropolone, m. p. 232—233° (decomp.), by the action of nitrous acid. Further investigations of the amino- and hydroxy-compound are in progress.

The lack of ethylenic and ketonic properties, and the weak acidic properties of the tropolones are understandable on the basis of their structure in which the carbonyl and hydroxyl groups, separated by a triene system, may be considered to be a trivinyl analogue of a carboxylic acid. The ready hydrolysis of the tropolone ethers (see pp. 566, 568) is also explicable by their constitutional resemblance with the ester of a carboxylic acid. It is probable however, that a detailed elucidation of the structure of the tropolone ring system must await further physical measurements.



I. Tropolone in methanol.
II. β-Methyltropolone in methanol.
III. β-Methyltropolone methyl ether-B in methanol.
IV. β-Methyltropolone methyl ether-A in methanol.

Mr. H. J. V. Tyrrell and Mr. O. S. Mills have shown that in *cyclo*hexane and benzene solutions, β-methyltropolone (IV; R = H, R′ = Me) is not associated at concentrations at which carboxylic acids are almost completely dimerised. Nozoe (*locc. cit.*) suggested that the relatively high boiling point of hinokitiol was indicative of a bimolecular structure, but our molecular weight determinations do not support this view. On the other hand they indicate a considerable degree of intramolecular hydrogen bonding of some type.

The ultra-violet absorption spectra of a number of tropolone derivatives have been measured, and the results, shown in the figure, resemble closely those, reported during the course of our work, for the thujaplicins (Erdtman *et al., locc. cit.*), and stipitatic, puberulic, and puberulonic acids (Corbett *et al., locc. cit.*). The results quoted by Cook, Gibb, Raphael, and Somerville (*loc. cit.*) are in close agreement with our observations. Those of Doering and Knox (*loc. cit.*) show some discrepancies (their solvent is not stated).

The ultra-violet spectra indicate the general aromatic nature of the tropolone ring; the shift of the spectrum of the methyl ethers to shorter wave-length relative to the tropolone band and the disappearance of the vibrational structure in the longer-wave absorption of the methyl ether show marked similarity with the results of Morton and Earlam (*J.*, 1941, 159) on 1-hydroxy- and 1-methoxy-anthraquinones and suggest some type of internal hydrogen bonding.

Tarbell and his co-workers (*J. Amer. Chem. Soc.*, 1950, **72**, 240, 243, 379) have examined the infra-red absorption of γ-thujaplicin and β-methyltropolone and interpret the results as indicating a large shift in the carbonyl stretching frequency on account of conjugation but they fail to detect internal hydrogen bonding. We are greatly indebted to Mrs. Broomfield, Imperial Chemical Industries Limited, Billingham Division, for the following report on the infra-red spectra of four tropolone derivatives. "The spectra of four tropolones were recorded in chloroform solution over the region of 6—7 μ. (1300—1700 cm.$^{-1}$), and the following maxima were observed :

Tropolone	1300	1437	1474	1550	1610
β-Methyltropolone *	1396	1450	1474	1542	1610
β-Methyltropolone methyl ether-A	1474	1508	1560—70	1600	1630
β-Methyltropolone methyl ether-B	1474	1498	1560—70	1605	1630

* These values agree with those cited by Scott and Tarbell (*loc. cit.*).

"The infra-red absorption bands are not easy to assign to specific bonds or groups in the tropolone ring. The band in the 1610-cm.$^{-1}$ region for β-methyltropolone was assigned by Scott and Tarbell (*loc. cit.*) to the carbonyl stretching vibration, which is known to occur at much lowered frequency when involved in a highly conjugated system. It is interesting to note that in the parent tropolone this band occurs in exactly the same position, while a somewhat different picture is presented by the two isomeric monomethyl ethers, apparently indicating some effect of the proximity of the hydroxyl on the carbonyl group. The hydroxyl group in tropolone and β-methyltropolone is characterised by a weak broad band around 3200 cm.$^{-1}$, which, since a completely free hydroxyl group is known to give a band above 3500 cm.$^{-1}$, would almost certainly indicate some type of internal hydrogen bonding. It is doubtful if " zwitterionisation " would lead to such a markedly low hydroxyl frequency."

The isolation of tautomeric forms of the ethers of unsymmetrical tropolones (p. 563), but the non-existence of more than one form of β-methyltropolone, are also probably best interpreted at the present time by internal hydrogen bonding.

Some preliminary measurements made by Mr. Mills and Mr. Tyrrell have shown that β-methyltropolone and the methyl ether-A have dipole moments in benzene solution of 3·9 and 4·9 D. respectively. This greater value for the methyl ether indicates a considerable contribution from polar structures, which also accounts for the increased water solubility of the tropolone methyl ethers. These dipole moment measurements are being continued, but it is difficult to devise a satisfactory explanation for the high dipole moment of β-methyltropolone itself.

Antibiotic tests have been carried out with several tropolone derivatives by Dr. Elsden and Mr. Marshall of the Bacteriology Department, Sheffield University, who find that in Fleming's medium β-methyltropolone inhibits the growth of *Staph. aureus* at dilutions of 1 : 160,000, and of *B. coli* at 1 : 20,000, but that other derivatives are less active. These and other biological results will be described more fully later.

EXPERIMENTAL.

Purpurogallin, prepared in 60—70% yield by oxidation of pyrogallol with potassium iodate (Evans and Dehn, *J. Amer. Chem. Soc.*, 1930, **52**, 3647), was purified by vacuum sublimation or by crystallisation from anisole; red prisms, m. p. 276° (decomp.), were obtained.

*2-Carboxy-4-hydroxy-3-keto*cyclo*heptatrienylacetic Acid* (*α-Carboxy-β-carboxymethyltropolone*) (II; R = R′ = R″ = H).—Hydrogen peroxide (25 c.c.; 100-vol.) was added dropwise with stirring to a solution of purpurogallin (10 g.) in 23% potassium hydroxide solution (650 g.) which was preheated to 90—95°. After cooling of the mixture, sodium hydrogen sulphite (5 g.) was added, and the clear deep-red solution was acidified by addition of 40% sulphuric acid (270 c.c.). The deposited potassium sulphate was collected and the filtrate extracted continuously with ether for 40 hours. After being dried, the red extract yielded a dark brown oil from which the acid (II; R = R′ = R″ = H) slowly separated as yellow crystals (2·5—3 g.). After these had been washed with a little ether and crystallised from glacial acetic acid, colourless prisms, m. p. 183—184° (decomp.) (rapid heating) (Part I, *loc. cit.*), were obtained.

An attempt to oxidise the acid in boiling aqueous solution with selenium dioxide gave much tar and a small amount of yellow amorphous solid, gradually darkening between 170° and 190° and yielding with Brady's reagent a red precipitate which was not purified.

Methylation of α-Carboxy-β-carboxymethyltropolone.—Diazomethane (1·5 g.) in ether (50 c.c.) was added slowly to a solution of the acid (2·24 g.) in acetone (50 c.c.). After 16 hours, evaporation of the solvent left a brown oil (2·7 g.) which deposited crystals of α-carbomethoxy-β-carbomethoxymethyltropolone methyl ether-A; recrystallisation from benzene yielded colourless prisms (1·2 g.), m. p. 110°, described previously in Part I (*loc. cit.*). Evaporation of the ethereal mother-liquors gave a pale yellow oil (1·4 g.), which eventually solidified and was repeatedly extracted with light petroleum (b. p. 40—60°). On cooling, the concentrated extract deposited the *dimethyl ester methyl ether-B*, which crystallised from benzene–light petroleum (b. p. 40—60°) in colourless prisms, m. p. 72—73° (Found : C, 58·9; H, 5·3. $C_{13}H_{14}O_6$ requires C, 58·7; H, 5·3%). The isomeric ethers were mixed separately with methyl oxalate in dioxan in presence of potassium methoxide; small yields were obtained of an amorphous yellow acid which could not be purified.

α-Carbomethoxy-β-carboxymethyltropolone (II; R = R″ = H; R′ = Me).—Each of the isomeric ethers-A and -B was quantitatively hydrolysed with cold 2N-sodium hydroxide (5 vols.) to *α-carbomethoxy-β-carboxymethyltropolone* (II; R = R″ = H; R′ = Me), which separated from methyl alcohol or water in colourless elongated plates, m. p. 179—180° (decomp.) (rapid heating) (Found : C, 55·5; H, 4·2. $C_{11}H_{10}O_6$ requires C, 55·5; H, 4·2%), soluble in sodium hydrogen carbonate solution with effervescence and giving a red colour with neutral ferric chloride solution, becoming green on dilution or acidification.

α-Carbomethoxy-β-methyltropolone (IX; R = Me).—The acid (II; R = R″ = H; R′ = Me) described above was decarboxylated by heating it at 180°, and the product, purified first by sublimation and then by crystallisation from *cyclo*hexane, was obtained as colourless prisms, m. p. 122—123° (Found : C, 61·8; H, 5·2. $C_{10}H_{10}O_4$ requires C, 61·9; H, 5·2%), which were slightly soluble in sodium hydrogen carbonate solution and gave a deep red colour with ferric chloride. The *ester* was not oxidised when heated with selenium dioxide in aqueous solution for 18 hours, and could not be condensed with piperonaldehyde in presence of sodium hydroxide. A complex reaction took place when the ester was mixed with excess of phenylmagnesium bromide: the neutral product was precipitated by addition of light petroleum (b. p. 40—60°) to its ethereal solution as a light brown amorphous solid, which gave a negative ferric test but was not further investigated.

α-Carboxy-β-methyltropolone (IX; R = H).—The ester (IX; R = Me) (0·2 g.) described above was refluxed with a solution of potassium hydroxide (1·25 g.) in water (2 c.c.) and methyl alcohol (3 c.c.) for 6 hours. The cooled solution was acidified with hydrochloric acid, and the product, isolated with ether, was taken up in sodium hydrogen carbonate solution, recovered, and extracted with ether. Evaporation of the dried extract gave *α-carboxy-β-methyltropolone* (IX; R = H) (0·15 g.); crystallisation from acetone–light petroleum (b. p. 40—60°) gave colourless prisms, m. p. 186—187° (decomp.) (Found : C, 60·0; H, 4·8. $C_9H_8O_4$ requires C, 60·0; H, 4·5%), which gave a ferric test and was decarboxylated to β-methyltropolone, m. p. 76—77°, by heating it at 190°.

α-Carbomethoxy-β-carbomethoxymethyltropolone.—Methyl sulphate (8·4 c.c.) was added to α-carboxy-β-carboxymethyltropolone (6 g.) dissolved in a solution of sodium hydroxide (3·3 g.) in water (15 c.c.). After 30 hours' shaking the light brown precipitate of *α-carbomethoxy-β-carbomethoxymethyltropolone* (II; R = H; R′ = R″ = Me) (5·5 g.) was collected and crystallised from benzene; colourless prisms, m. p. 107° (Found : C, 57·2; H, 4·9. $C_{12}H_{12}O_6$ requires C, 57·1; H, 4·8%), were obtained, which gave a deep red ferric test, dissolved slowly in sodium hydrogen carbonate solution, and underwent rapid hydrolysis to α-carbomethoxy-β-carboxymethyltropolone, m. p. 179—180° (decomp.), with cold sodium hydroxide solution.

β-Methyltropolone (IV; R = H; R′ = Me), prepared by heating α-carboxy-β-carboxymethyltropolone to its m. p., and purified by sublimation, crystallised from light petroleum (b. p. 40—60°) in colourless prisms, m. p. 76—77° (see Part I, *loc. cit.*). The *copper* salt, precipitated by addition of copper acetate to an aqueous solution of (IV; R = H; R′ = Me), separated from concentrated chloroform solution in green prisms containing solvent of crystallisation which was eliminated slowly in the air, or in 1 hour at 100°; the salt had m. p. 280—282° (decomp.) (Found : C, 57·6; H, 4·4. $C_{16}H_{14}O_4Cu$ requires C, 57·6; H, 4·2%). β-Methyltropolone was recovered after being heated with an aqueous solution of selenium dioxide for 2 hours at 160°, and it did not react with piperonaldehyde in a warm alcoholic solution of potassium ethoxide.

Fusion of β-Methyltropolone with Potassium Hydroxide [with Dr. P. L. PAUSON].—The methyltropolone (0·1 g.) was gradually heated to 300° with potassium hydroxide (2 g.) and water (0·5 c.c.), and the mixture was maintained at 300° for 10 minutes. Acidification yielded *m*-toluic acid, which after purification by steam distillation, sublimation, and crystallisation from water had m. p. 110—111°, undepressed by admixture with an authentic specimen. Identification was confirmed by preparation of the *S*-benzylthiuronium salt, which separated from alcohol in needles, m. p. 174° (Found : N, 9·4. Calc. for $C_{16}H_{18}O_2N_2S$: N, 9·3%) (Donleavy, *J. Amer. Chem. Soc.*, 1936, **58**, 1004, gives m. p. 164°), and by conversion in benzene solution into the *benzylammonium* salt, which separated from benzene in colourless needles, m. p. 145—147° (Found : N, 5·9. $C_{15}H_{17}O_2N$ requires N, 5·8%).

Conversion of β-Methyltropolone into β-Methylpimelic Acid.—β-Methyltropolone (0·4 g.) was reduced in glacial acetic acid (15 c.c.) in the presence of freshly prepared platinic oxide (0·02 g.); hydrogen (250 c.c., 3·5 moles) was absorbed during 3 hours, reduction then being complete. Removal of the solvent yielded a neutral amber oil (0·4 g.) which gave an amorphous 2 : 4-dinitrophenylhydrazone. A solution of the neutral reduction product (0·4 g.) in water (25 c.c.) reacted with 0·25M-periodic acid (13 c.c., 1 mole), and the product, isolated with ether, was an oil (0·4 g.) which partly dissolved in sodium hydrogen carbonate solution. The neutral fraction, containing β-methylpimelic dialdehyde, gave a *bis*-2 : 4-*dinitrophenylhydrazone*, which separated from alcohol as an amorphous orange powder, m. p. 155—165° (decomp.) (Found : C, 48·4; H, 4·4; N, 22·0. $C_{20}H_{22}O_8N_8$ requires C, 47·9; H, 4·4; N, 22·3%). The combined neutral and acidic fractions (0·4 g.) were oxidised with 3% potassium permanganate solution (12 c.c.) in cold 10% sodium carbonate solution. After half an hour the liquid was saturated with sulphur dioxide, and extracted with ether. The dried extract yielded a colourless acidic oil (0·3 g.) which gradually solidified, having m. p. 45—48° undepressed on admixture with authentic β-methylpimelic acid (Einhorn and Ehret, *loc. cit.*, give m. p. 48°). The anilide, prepared by refluxing the acid with aniline for 20 hours, crystallised from aqueous alcohol in colourless needles, m. p. 134° (Einhorn and Ehret, *loc. cit.*, give m. p. 137°) undepressed on admixture with an authentic specimen. The S-*benzylthiuronium* salt, precipitated by adding a slight excess of a 15% solution of *S*-benzylthiuronium chloride in alcohol to an aqueous solution of the acid, crystallised from aqueous alcohol in white needles, m. p. 172—173° (decomp.) (Found : C, 57·0; H, 6·7; N, 10·7. $C_{24}H_{34}O_4N_4S_2$ requires C, 56·9; H, 6·7; N, 11·1%), identical with a specimen prepared from synthetic β-methylpimelic acid.

Synthesis of β-Methylpimelic Acid.—An ice-cold mixture of 3-methyl*cyclo*hexanone (45 g.) and ethyl oxalate (58·4 g.) was added during 20 minutes to a well-stirred solution of sodium ethoxide (from sodium, 9·2 g.) in absolute alcohol (120 c.c.) cooled below 10°. The cloudy orange-yellow solution was stirred for 1 hour at <10° and a thick yellow precipitate gradually separated. After a further 4 hours' stirring at room temperature, a mixture of concentrated sulphuric acid (11 c.c.) and ice (100 g.) was added, and the precipitated yellow oil was taken up in ether and washed with water. Unchanged ester and ketone were removed by distillation, and crude ethyl 2-keto-4-methyl*cyclo*hexylglyoxylate (40 g.) was collected at 120—150°/12 mm. This crude ester (40 g.) was heated in an oil-bath at 170°/40 mm. with powdered glass (2 g.) and a trace of iron powder. Slow distillation during 1 hour yielded ethyl 2-keto-4-methyl*cyclo*hexanecarboxylate (32 g.), b. p. 135—148°/40 mm. (Kotz and Hesse, *loc. cit.*, give b. p. 146°/40 mm.), which was added during 1 hour to a well-stirred solution of sodium hydroxide (30 g.) in dry methyl alcohol (90 c.c.) in an oil-bath at 120°. After a further hour, the mixture was diluted with water (150 c.c.), and the methyl alcohol removed. Concentrated sulphuric acid (42 c.c.) was added to the cooled solution which was clarified with charcoal and extracted with ether for 10 hours. The dried extract yielded β-methylpimelic acid (14 g.) as a colourless oil which gradually solidified and was purified by distillation at 215°/10mm., giving a colourless crystalline distillate, which had m. p. 45—48° after remaining in contact with a porous tile for some time. The anilide, m. p. 137°, and *S*-benzylthiuronium salt, m. p. 172—173° (decomp.), were prepared as described above.

Bromination of β-Methyltropolone.—Bromine (2·4 g.) in chloroform (10 c.c.) was added dropwise with stirring to a solution of β-methyltropolone (2·0 g.) in chloroform (10 c.c.); an orange-red solid rapidly separated. The mixture was shaken with water (20 c.c.), the yellow chloroform layer was removed, and the aqueous layer extracted with chloroform. The combined and dried extracts gave a yellow oil (3 g.) which slowly solidified and yielded by fractional crystallisation from light petroleum (b. p. 40—60°) a small quantity of *dibromo*-derivative as cream coloured prisms, m. p. 139—140° (Found : C, 32·7; H, 2·2. $C_8H_6O_2Br_2$ requires C, 32·7; H, 2·1%), and a more soluble *monobromo*-compound (1 g.) as colourless prisms, m. p. 85—86° (Found : C, 44·7; H, 3·3. $C_8H_7O_2Br$ requires C, 44·7; H, 3·3%). This monobromo-derivative was recovered after being heated with potassium hydroxide (4 parts by wt.) in water (10 vols.) and ethyl alcohol (10 vols.) for 4 hours. Fusion with potassium hydroxide (10 parts by wt.) at 260° for half an hour gave a small amount of acidic material which did not give a ferric test, but the yield was insufficient for purification and identification.

*Reaction of Toluene-*p*-diazonium Chloride with β-Methyltropolone.*—*p*-Toluidine (0·4 g.) in N-hydrochloric acid (10 c.c.) was diazotised by addition of sodium nitrite (0·26 g.) in water (2 c.c.), and the solution was poured with stirring into a solution of β-methyltropolone (0·5 g.) in 2N-sodium hydroxide (10 c.c.) and water (35 c.c.). The bright red solid was collected, suspended in water, acidified with dilute hydrochloric acid and the orange-red *azo*-compound crystallised from ethyl alcohol, giving small flat needles, m. p. 177—178° (decomp.) (Found : C, 70·4; H, 5·8; N, 10·9. $C_{15}H_{14}O_2N_2$ requires C, 70·9; H, 5·5; N, 11·0%).

(?-)*Amino-β-methyltropolone.*—A 10% solution of sodium dithionite (*ca.* 100 c.c.) was added to a warm suspension of the above azo-compound (3·0 g.) in acetone (200 c.c.) and water (100 c.c.). The deep-yellow solution was made alkaline by the addition of 2N-sodium hydroxide (10 c.c.) and, after removal of the acetone by distillation, the *p*-toluidine was taken up in benzene. The aqueous solution was made acid to litmus with dilute hydrochloric acid, neutralised with aqueous ammonia, and made faintly acid with acetic acid. Extraction with several portions of ethyl methyl ketone, and subsequent evaporation of the solvent yielded (?-)*amino-β-methyltropolone* (1·0 g.) which, purified by sublimation at 220°/0·5 mm., and crystallisation from ethanol, formed yellow prisms, m. p. 224° (decomp.) (Found : C, 63·4; H, 5·8; N, 9·5. $C_8H_9O_2N$ requires C, 63·6; N, 6·0; N, 9·3%), giving an intense reddish-violet colour with ferric chloride solution. The amine dissolved in dilute alkali, to give a deep-yellow solution, and dissolved in dilute hydrochloric acid to give a pale yellow solution, from which the hydrochloride separated as pale yellow needles, m. p. 205° (decomp.).

(?-)*Hydroxy-β-methyltropolone.*—A solution of sodium nitrite (0·68 g.) in water (5 c.c.) was added dropwise, with stirring, to a solution of the above amino-compound (1·5 g.) in 3N-sulphuric acid (10 c.c.) cooled to 10°. The diazo-compound was decomposed by heating the solution on a water-bath until there was no further evolution of nitrogen, and extraction with ether yielded a crystalline solid (0·4 g.), which was purified by sublimation at 220°/0·1 mm. and crystallisation from water. Cream coloured plates, m. p. 232—233° (decomp.), of (?-)*hydroxy-β-methyltropolone* (Found : C, 63·3; H, 5·3. $C_8H_8O_3$ requires C, 63·2; H, 5·3%) were obtained, giving an intense green colour with ferric chloride solution, and soluble in sodium hydrogen carbonate to give a yellow solution.

Ethers of β-Methyltropolone.—(a) *Methyl ethers.* β-Methyltropolone (3 g.) in ether (40 c.c.) was allowed to react for 20 hours with diazomethane (1·1 g.) in ether (100 c.c.); removal of the solvent gave a yellow oil (3·3 g.), which was dissolved in methanol (10 c.c.) and warmed with a solution of picric acid (5·3 g.) in methanol (10 c.c.). After cooling, the yellow crystalline solid was collected, and fractional crystallisation from methanol yielded *β-methyltropolone methyl ether-B picrate* as yellow prisms, m. p. 130—131° (decomp.) (Found : C, 47·7; H, 3·4; N, 11·1. $C_{15}H_{13}O_9N_3$ requires C, 47·5; H, 3·5; N, 11·3%), and the *isomer-A picrate* as yellow needles, m. p. 160° (decomp.) (Found : C, 47·3; H, 3·7; N, 10·9%). The picrates were decomposed by extracting their chloroform solutions with sodium hydrogen carbonate solution, remaining impurities being removed by passage through an alumina column. Evaporation of the solutions yielded *β-methyltropolone methyl ether-B*, giving on distillation at 114°/0·1 mm. a white crystalline solid, m. p. 46° (Found : C, 71·7; H, 6·8. $C_9H_{10}O_2$ requires C, 72·0; H, 6·7%), and the isomeric *ether-A*, giving on crystallisation from light petroleum (b. p. 60—80°) colourless elongated plates, m. p. 96—97° (Found : C, 71·9; H, 6·5%). The low-melting ether rapidly absorbed moisture and became liquid on exposure to the atmosphere.

Both methyl ethers were water-soluble, gave a negative ferric test, and showed no ketonic reactions. They were quantitatively converted into β-methyltropolone, m. p. 76°, by being warmed for 5 minutes with 2N-sodium hydroxide (10 vols.).

(b) p-*Nitrobenzyl ethers.* β-Methyltropolone (2 g.) in 2% sodium hydroxide solution (28 c.c.) was mixed with a solution of *p*-nitrobenzyl bromide (3·2 g.) in ethyl alcohol (25 c.c.), and the mixture was refluxed for 2 hours. Fractional crystallisation of the product from alcohol gave *β-methyltropolone* p-*nitrobenzyl ether-A*, m. p. 172° (Found : C, 66·5; H, 4·7; N, 5·3. $C_{15}H_{13}O_4N$ requires C, 66·4; H, 4·8; N, 5·2%), and the more soluble p-*nitrobenzyl ether-B*, which separated in colourless needles, m. p. 160° (Found : C, 66·2; H, 4·7; N, 5·2%).

Either ether (0·1 g.) in alcohol (3 c.c.) was added to sodium hydroxide (0·4 g.) in water (2 c.c.), and the mixture was warmed in a water-bath for 10 minutes. The deep-red solution was acidified with dilute hydrochloric acid and extracted with ether. The extract was shaken with sodium hydroxide solution, the alkaline layer was acidified, and recovery with ether yielded β-methyltropolone, m. p. 74—76°, after sublimation and crystallisation from light petroleum (b. p. 40—60°).

Oxidation of β-Methyltropolone Methyl Ether-A.—The ether, m. p. 96—97° (1·6 g.), was refluxed with selenium dioxide (1·77 g.) in dioxan (25 c.c.) for 18 hours. The filtered solution was diluted with ether (100 c.c.), decanted from tar, and extracted with sodium hydrogen carbonate solution, and the extract well washed with ether. After acidification, continuous ether-extraction for 20 hours yielded a yellow crystalline solid (0·4 g.) which after several recrystallisations from water and sublimation at 150—160°/12 mm. gave *β-formyltropolone* as pale yellow needles, m. p. 159—160° (Found : C, 63·7; H, 4·0. $C_8H_6O_3$ requires C, 64·0; H, 4·0%). The neutral ether–dioxan liquors from the oxidation yielded a small amount of unchanged ether.

Oxidation of β-Methyltropolone Methyl Ether-B.—The ether, m. p. 46° (2·2 g.), was oxidised with selenium dioxide (2·5 g.) in dioxan (25 c.c.) for 8 hours, and separated into neutral and acidic products as described above. The neutral products gave *β-formyltropolone methyl ether-B* which crystallised from methyl alcohol or benzene in colourless needles (0·6 g.), m. p. 182—183° (Found : C, 65·8; H, 5·1. $C_9H_8O_3$ requires C, 65·8; H, 4·9%), giving a negative ferric test. The 2 : 4-*dinitrophenylhydrazone* separated from acetic anhydride in yellow needles, m. p. 292—295° (decomp.) (Found : C, 52·8; H, 3·5; N, 16·1. $C_{15}H_{12}O_6N_4$ requires C, 52·3; H, 3·5; N, 16·3%). The acidic product was crystallised several times from water; *β-carboxytropolone methyl ether-B* (0·4 g.) was obtained as pale yellow needles, m. p. 258° (Found : C, 60·0; H, 4·4. $C_9H_8O_4$ requires C, 60·0; H, 4·5%), which effervesced with sodium hydrogen carbonate solution, and gave no colour with ferric chloride. This acid was hydrolysed to β-carboxytropolone (see below), m. p. 217°, by warming it for a few minutes with dilute sodium hydroxide solution.

Oxidation of β-Formyltropolone or its Methyl Ether.—The free aldehyde or its ether (0·2 g.) was added to a suspension of freshly precipitated silver oxide (0·30 g.) in 4N-sodium hydroxide (2 c.c.) and warmed on the water-bath for half an hour. The cooled, filtered solution was acidified with dilute hydrochloric acid and extracted continuously with ether. Evaporation of the dried extract gave *β-carboxytropolone* (0·18 g.), which crystallised from dioxan in large prisms containing solvent of crystallisation. The solvent was removed when the substance was heated at 100° for half an hour; a crystalline powder, m. p. 217° (Found : C, 58·2; H, 3·9. $C_8H_6O_4$ requires C, 57·8; H, 3·6%), was obtained.

Decarboxylation of β-Carboxytropolone to Tropolone.—The acid (0·2 g.) was refluxed for 2 hours in quinoline (3 c.c.) in presence of copper bronze (50 mg.). The filtered and acidified solution was extracted with ether, and the tropolone was removed with dilute sodium hydroxide, recovered, and isolated with ether. The product rapidly solidified and crystallised from light petroleum (b. p. 40—60°) in colourless prisms (30 mg.), m. p. 49—50° (Found : C, 69·2; H, 5·1. Calc. for $C_7H_6O_2$: C, 68·9; H, 5·0%). Tropolone was very volatile and was readily lost on exposure to the atmosphere at ordinary temperature. It gave a deep red ferric test, becoming green on acidification, and a green copper salt which dissolved in chloroform, and it dissolved in sodium hydrogen carbonate to give a yellow solution.

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