989. *Picrotoxin. Part VI.* Picrotoxic Acid and its Derivatives.*

By P. I. Burkhill, J. S. E. Holker, Alexander Robertson, and J. H. Taylor.

Reduction of methyl picrotoxate with potassium borohydride gave a compound, $C_{16}H_{22}O_7$, and, from an examination of this compound and its transformation products in conjunction with the properties of picrotoxic acid and its derivatives, the structure (III; R = H) has been deduced for the latter acid. It is shown that the formation of picrotoxic acid from picrotoxinin can be explained rationally on the basis of the stereochemical description by Conroy [1] of β-bromopicrotoxininic acid with the further assumption that picrotoxinin has the same relative stereochemistry. This work adequately supports the elegant structural deductions of Conroy.

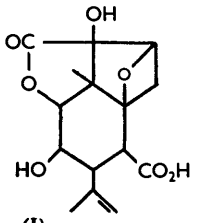
In continuation of our investigations on picrotoxinin and its transformation products (cf. Part V*) some reactions of picrotoxic acid and its derivatives have been studied. This monobasic acid, the methyl ester, and methyl *O*-methylpicrotoxate have been prepared directly from picrotoxinin. Horrmann [2] obtained picrotoxic acid by hydrolysis of picrotoxinin with dilute sulphuric acid, and methyl picrotoxate by treatment of picrotoxinin with potassium hydroxide or sodium methoxide in methanol. The application of the latter reagent has also been studied by Benstead *et al.*[3] who emphasised that in the methanolysis the nature of the product was in the main determined by the concentration of the sodium methoxide; thus with relatively large amounts of the reagent methyl picrotoxate was the only product, but when catalytic amounts were employed methyl picrotoxinindicarboxylate was the major component of the reaction mixture. In our hands the use of a catalytic amount of methoxide invariably produced methyl picrotoxate and methyl picrotoxinindicarboxylate in approximately equal proportions. Methyl *O*-methylpicrotoxate is formed by the action of ethereal diazomethane containing a trace of aqueous potassium hydroxide [3,4] on picrotoxinin but in the absence of alkali methyl picrotoxinindicarboxylate is also produced.[3] By analogous hydrolytic methods dihydropicrotoxinin is converted into dihydropicrotoxic acid or its methyl ester,[3] identical with the products obtained by hydrogenation of picrotoxic acid and methyl picrotoxate respectively. Methyl picrotoxate and dihydropicrotoxate give monoacetates with acetic anhydride–pyridine, monomethyl ethers with diazomethane or methyl sulphate [3] and alkali, and dimethyl ethers by the methyl iodide–silver oxide method.[5] The infrared absorption spectrum of methyl di-*O*-methylpicrotoxate does not show hydroxyl absorption and it therefore appears that methyl picrotoxate contains two hydroxyl groups of which one is sufficiently acidic to be methylated with diazomethane. Further, methyl picrotoxate and its dihydro-derivative are immediately soluble in cold dilute aqueous sodium hydroxide and are precipitated unchanged on acidification, a property which has been utilised to separate methyl picrotoxate from non-acidic methyl picrotoxinindicarboxylate formed in the methanolysis of picrotoxinin. The acidity of methyl picrotoxate is attributed to a hydroxyl group rather than to the opening of a lactone ring with alkali because methyl *O*-methylpicrotoxate is insoluble in alkali. Dihydropicrotoxic acid is stable to sodium dichromate in dilute sulphuric acid at 100°, to evaporation with concentrated nitric acid,[3] or to lead tetra-acetate and it therefore appears that both the hydroxyl groups in picrotoxic and dihydropicrotoxic acid are tertiary, and are not present in an α-glycol system. As in the methylation, the ease of acetylation of a tertiary hydroxyl group in methyl picrotoxate

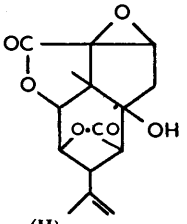
* Part V, *J.*, 1957, 3746.

[1] Conroy, *J. Amer. Chem. Soc.*, 1957, **79**, 1726.
[2] Horrmann, *Annalen*, 1916, **411**, 273.
[3] Benstead, Gee, Johns, Martin-Smith, and Slater, *J.*, 1952, 2292.
[4] Sutter and Schlittler, *Helv. Chim. Acta*, 1950, **33**, 902.
[5] Mercer and Robertson, *J.*, 1936, 288.

is attributed to the acidic nature of the group affected and accordingly the resulting monoacetate is insoluble in alkali.

The formula (I) proposed for picrotoxic acid by Benstead *et al.*[3] on the basis of Conroy's structure [6] (II) for picrotoxinin contains a secondary hydroxyl group and consequently is not in agreement with the observed stability of dihydropicrotoxic acid towards oxidising agents.


(I)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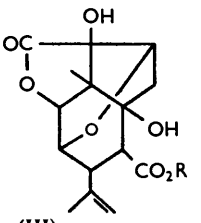
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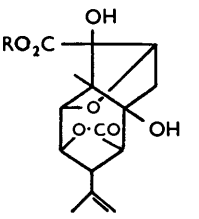
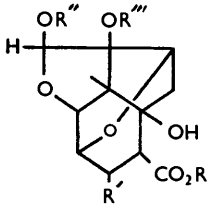

(IV)

On the assumption that the structure (II) for picrotoxinin has the correct carbon skeleton and placement of oxygen functions and that both hydroxyl groups of picrotoxic acid are tertiary, two possible formulations, (III and IV; R = H), may be devised for this compound. It should be noted that on either of these formulations methyl picrotoxate (III or IV; R = Me) would contain an α-hydroxy-ester system [*i.e.*, α-hydroxy-lactone in (III; R = Me)] in which the hydroxyl group would be expected to have acidic properties.[7,8] In an attempt to differentiate between the structures (III and IV; R = Me) methyl picrotoxate was reduced with potassium borohydride, giving a product, $C_{16}H_{22}O_7$, which contained two more hydrogen atoms than the starting material and has been named methyl picrotoxolate. Comparison of the infrared absorption spectra of this compound and of methyl picrotoxate (in mineral oil mull) indicated that although both spectra had peaks at 1745 (methyl ester) and 1650 cm.$^{-1}$ (double bond of the *iso*propenyl system), the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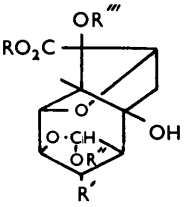
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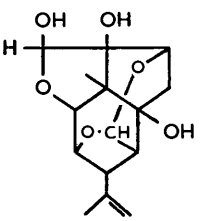
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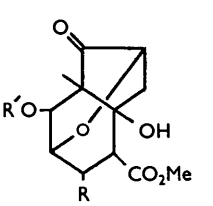

(VIII)

band at 1802 cm.$^{-1}$, present in the spectrum of methyl picrotoxate and attributed to a γ-lactone system, was absent from the spectrum of methyl picrotoxolate and it therefore seems probable that the formation of methyl picrotoxolate involves the reduction of a lactone ring to a hemiacetal system. In agreement with this hypothesis methyl picrotoxolate readily regenerated methyl picrotoxate on oxidation with sodium dichromate in dilute sulphuric acid and thus on the basis of the alternative structures (III or IV; R = Me) methyl picrotoxolate would be represented by (V or VI; R = Me, R′ = ·CMe:CH_2, R″ = R‴ = H). The latter ester, the solubility of which in dilute aqueous sodium hydroxide is attributed to the presence of an acidic hydroxyl group of a hemiacetal system, gave a diacetate (V or VI; R = Me, R′ = ·CMe:CH_2, R″ = R‴ = Ac) and on treatment with methanolic hydrogen chloride or methyl sulphate and alkali a monomethyl ether,

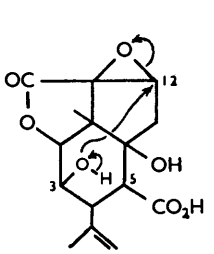
[6] Conroy, *J. Amer. Chem. Soc.*, 1952, **74**, 491, 3046.
[7] Benstead, Brewerton, Fletcher, Martin-Smith, Slater, and Wilson, *J.*, 1952, 1042.
[8] Schmidt *et al.*, reported by Eistert in "Newer Methods of Preparative Organic Chemistry," Interscience, London, 1948, p. 520; *Ber.*, 1934, **67**, 2120, 2127.

methyl *O*-methylpicrotoxolate formulated as the acetal (V or VI; R = R″ = Me, R′ = ·CMe:CH_2, R‴ = H) which formed a monoacetate (V or VI; R = R″ = Me, R′ = ·CMe:CH_2, R‴ = Ac) and on alkaline hydrolysis gave rise to *O*-methylpicrotoxolic acid (V or VI; R = R‴ = H, R′ = ·CMe:CH_2, R″ = Me).

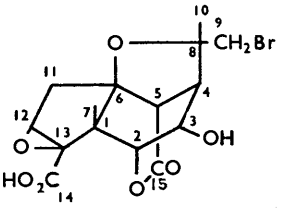
On hydrogenation methyl picrotoxolate gave methyl dihydropicrotoxolate (V or VI; R = Me, R′ = $CHMe_2$, R″ = R‴ = H), which was identical with the product obtained by reduction of methyl dihydropicrotoxate with potassium borohydride. This dihydro-derivative regenerated methyl dihydropicrotoxate on oxidation with sodium dichromate in dilute sulphuric acid, and, like methyl picrotoxolate, formed a diacetate (V or VI; R = Me, R′ = $CHMe_2$, R″ = R‴ = Ac).

Of the two alternative possible structures for methyl picrotoxolate, formula (V; R = Me, R′ = ·CMe:CH_2, R″ = R‴ = H) contains an α-hydroxy-hemiacetal system in the same environment as that in compound A (VII) derived by the reduction of picrotoxinin with lithium aluminium hydride [9] and it was therefore possible to differentiate between structures (V and VI; R = Me, R′ = ·CMe:CH_2, R″ = R‴ = H) for methyl picrotoxolate by reactions similar to those described in the elucidation of the structure of compound A.[9] Thus methyl picrotoxolate consumed one mol. of sodium metaperiodate rapidly, yielding a formate, $C_{16}H_{20}O_7$, the nature of which was established by hydrolysis with dilute sulphuric acid to the alcohol, $C_{15}H_{20}O_6$, which on subsequent formylation regenerated the parent ester. These products are strictly analogous to the compounds obtained from compound A by similar reactions, indicating that methyl picrotoxolate contains an α-hydroxy-hemiacetal system and therefore must be represented by structure (V; R = Me, R′ = ·CMe:CH_2, R″ = R‴ = H). Accordingly, the sodium metaperiodate product and the derived alcohol are formulated as (VIII; R = ·CMe:CH_2, R′ = ·CHO) and (VIII; R = ·CMe:CH_2, R′ = H) respectively. In agreement with the structure (VIII; R = ·CMe:CH_2, R′ = H) this compound, which did not react with lead tetra-acetate, formed a monoacetate (VIII; R = ·CMe:CH_2, R′ = Ac) and a yellow 2 : 4-dinitrophenylhydrazone. Strictly analogous properties were exhibited by methyl dihydropicrotoxolate. Thus, on treatment with sodium metaperiodate this ester gave the keto-formate (VIII; R = $CHMe_2$, R′ = CHO) which with cold dilute sulphuric acid generated the corresponding keto-alcohol (VIII; R = $CHMe_2$, R′ = H), and this product gave a monoacetate (VIII; R = $CHMe_2$, R′ = Ac] with acetic anhydride—pyridine, formed a 2 : 4-dinitrophenylhydrazone, and with formic acid and acetic anhydride regenerated the parent keto-formate.

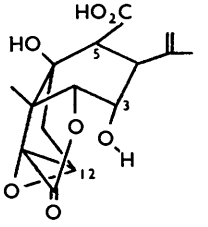
These results provide cogent evidence in favour of the structures (V; R = Me, R′ = ·CMe:CH_2, R″ = R‴ = H) and (V; R = Me, R′ = $CHMe_2$, R″ = R‴ = H) for methyl picrotoxolate and its dihydro-derivative respectively and hence picrotoxic acid may be represented by formula (III; R = H).



(IX)



(X)



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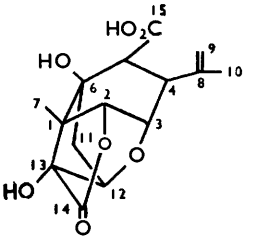


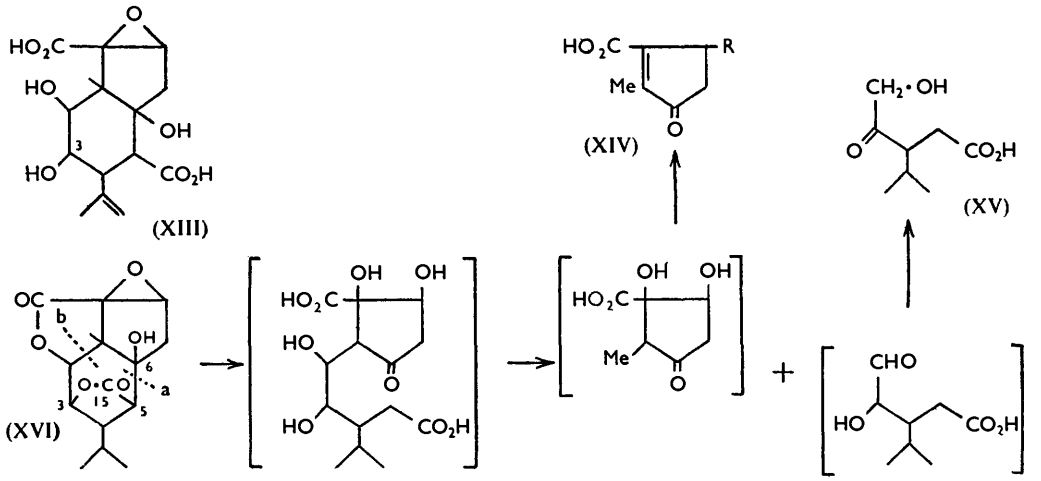
(XII)

In the conversion of picrotoxinin (II) into picrotoxic acid (III; R = H) by hydrolysis it is assumed that the lactone ring bridging $C_{(3)}$ and $C_{(5)}$ is opened and that the 3-hydroxyl

[9] Holker, Holker, McGookin, Robertson, and Sargeant, *J.*, 1957, 3746.

group thus generated is spatially situated in a suitable position for rearward attack at $C_{(12)}$ of the epoxide ring by an internal S_N2 mechanism (expression IX). In a recent publication [1] Conroy has considered the properties of β-bromopicrotoxininic acid and related compounds and on the basis of the original structure (II) for picrotoxinin has derived the stereochemical formulation (X) for this acid. If it is assumed that picrotoxinin has the same relative stereochemical description, it becomes apparent that, when the lactone ring bridging $C_{(3)}$ and $C_{(5)}$ in picrotoxinin is opened, the *cyclo*hexane ring is no longer rigid and can take up the conformation shown in (XI) in which the 3-hydroxyl group is situated in an ideal position for reaction with the epoxide ring as postulated above. Thus, on this basis picrotoxic acid has the stereochemical description (XII) and the mechanism of its formation adequately supports the deductions of Conroy. It should be noted that on the basis of formula (XIII) for picrotoxinindicarboxylic acid proposed by Conroy [6] the 3-hydroxyl group should similarly be in an ideal position for rearward attack on the epoxide ring, and hence this acid should be readily isomerised. This problem is at present under investigation.

Picrotoxinin and α-picrotoxininic acid react with bromine to give insoluble saturated monobromo-derivatives, containing a β-bromo-ether system [3,10] of the type illustrated in structure (X) for β-bromopicrotoxininic acid. Conroy [1] has indicated that in the formation of compounds of this type it is necessary to assume that the tertiary 6-hydroxyl group is within bonding distance of the *iso*propenyl group in picrotoxinin and in α-picrotoxininic acid. Picrotoxic acid and its derivatives do not form monobromo-derivatives and Benstead *et al.*[3] originally proposed structure (I) for picrotoxic acid in an attempt to explain this anomaly. It is now clear from structure (XII) for picrotoxic acid that in the formation of an ether link between $C_{(3)}$ and $C_{(12)}$, the *cyclo*hexane ring has adopted a rigid conformation in which the tertiary 6-hydroxyl group and the 4-*iso*propenyl group are too far apart to take part in the formation of a 6 : 8-ether link. Accordingly, on this basis, picrotoxic acid and its derivatives would not be expected to form monobromo-substitution products.

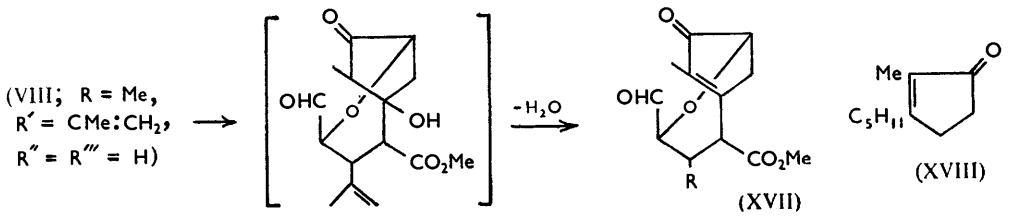


It is known that picrotoxinin, α-picrotoxininic acid, and their respective dihydro-derivatives are degraded by treatment with alkali under very mild conditions. Thus, Sutter and Schlittler [11] have isolated compounds (XIV; R = H), (XIV; R = OH), and (XV) by degradation of α-dihydropicrotoxinin (XVI) with sodium carbonate. On the other hand, picrotoxic acid, picrotoxinindicarboxylic acid, their respective dihydro-

[10] O'Donnel, Robertson, and Harland, *J.*, 1939, 1261.
[11] Sutter and Schlittler, *Helv. Chim. Acta*, 1949, **32**, 1855.

derivatives and methyl esters, as well as β-bromopicrotoxininic acid and its methyl ester, are relatively stable to treatment with alkali. It appears, therefore, that when the $C_{(15}$ atom of the picrotoxinin skeleton is present in a lactone ring and the oxygen function at $C_{(6)}$ in a hydroxyl group, the compounds concerned are alkali-sensitive whereas derivatives in which either of these conditions is not fulfilled are stable. Conroy [6] has postulated that the degradation of dihydropicrotoxinin (XVI) with sodium carbonate proceeds by two successive retro-aldol condensations at (a) and (b) according to the annexed scheme. On the basis of this mechanism it is obvious that the presence of a free 6-hydroxyl group in the picrotoxinin skeleton is necessary for fission of the 5 : 6-bond, and therefore β-bromopicrotoxininic acid (X), in which this oxygen function is present in an ether link, would not be expected to be degraded by alkali. Further, picrotoxic acid, picrotoxinindicarboxylic acid, and their methyl esters, which respectively contain β-hydroxy-acid and β-hydroxy-ester systems, might not be expected to undergo retro-aldol condensation with fission of the 5 : 6-bond since it has been shown [12] that β-hydroxy-acids and their ethyl esters undergo this scission only when there is at least one phenyl residue in the α-position or two in the β-position and even then the use of hot 15—20% aqueous potassium hydroxide seems to be necessary. The stability of picrotoxic acid and its derivatives to alkali thus appears to be in agreement with the structure (XII).

Further transformation products derived from the keto-alcohol (VIII; R = Me, R′ = ·CMe:CH_2, R′ = R″ = H) and its dihydro-derivative have been obtained and although the experimental evidence is, as yet, insufficient for the unequivocal formulation of these compounds, certain structural features have become apparent. Thus, on treatment with boiling water the keto-alcohol or its formate gave an anhydro-compound, $C_{15}H_{18}O_5$, which contains a molecule of water less than the parent alcohol. This anhydro-compound, which formed a dioxime and a yellow mono-2 : 4-dinitrophenylhydrazone, readily reduced Fehling's solution and ammoniacal silver nitrate on warming. On treatment with acetylating agents it was recovered unchanged and in agreement with this the



infrared absorption spectrum showed a total absence of absorption in the hydroxyl region. The ultraviolet spectrum of the compound included a band at 234 mμ (log ε 3·94) and it was readily shown that the *iso*propenyl double bond was not involved in the chromophoric system giving rise to this spectrum since the dihydro-keto-alcohol (VIII; R = Me, R′ = $CHMe_2$, R″ = R‴ = H) and its formate under similar conditions gave an analogous dihydro-anhydro-compound, $C_{15}H_{20}O_5$, the ultraviolet spectrum of which contained a band at 237 mμ (log ε 3·90). Similarly this product formed a dioxime and a yellow mono-2 : 4-dinitrophenylhydrazone. Methoxyl estimations on the compound, $C_{15}H_{18}O_5$, and its dihydro-derivative showed that both contained the methyl ester group known to be present in the parent keto-alcohol, the formate, and the respective dihydro-derivatives.

It is tentatively suggested that the compound, $C_{15}H_{18}O_5$, has the formula (XVII; R = ·CMe:CH_2) and arises from the keto-alcohol (VIII; R = Me, R′ = ·CMe:CH_2) by a reversed aldol condensation with subsequent dehydration as shown in the annexed scheme; the corresponding dihydro-compound, $C_{15}H_{20}O_5$ has the structure (XVII; R = $CHMe_2$). In the formation of the compounds $C_{15}H_{18}O_5$ and $C_{15}H_{20}O_5$ from the formate (VIII;

[12] Ivanov, *Ann. Univ. Sofia, II, Falculté phys.-math., Livre* 2, 1938—1939, **35**, 337; *Chem. Abs.*, 1940, **34**, 2348.

R = Me, R′ = ·CMe:CH_2, R″ = R‴ = H) and its dihydro-derivative respectively it is assumed that the hydrolysis of the formyl group precedes the retro-aldol condensation envisaged in the above scheme. The presence in structures (XVII; R = ·CMe:CH_2) and (XVII; R = $CHMe_2$) respectively of a fully substituted *cyclo*pentenone ring is in agreement with the ultraviolet spectra [dihydrojasmone [13] (XVIII) shows a high-intensity absorption band at 237 mμ] and, although the infrared spectra of the compound, $C_{15}H_{18}O_5$, and its dihydro-derivative are very complex in the carbonyl region, they are not incompatible with the structures proposed. Thus, *e.g.*, the infrared spectrum (in mineral oil mull) of the dihydro-compound, $C_{15}H_{20}O_5$, showed bands at 1733, 1695 (with shoulders at 1706 and 1692), and 1639 cm.$^{-1}$. The absence of carbonyl bands at a higher frequency than 1733 cm.$^{-1}$ indicates that the *cyclo*pentanone structure originally present in the dihydro-keto-alcohol has been modified in the formation of the dihydro-anhydro-compound, $C_{15}H_{20}O_5$. It is probable that the yellow mono-2 : 4-dinitrophenylhydrazones are formed from the formyl group in the retro-aldol condensation products and that the insolubility of these derivatives in the reaction mixtures prevents interaction of the carbonyl group in the *cyclo*pentenone system with the reagent.

Experimental

Ultraviolet absorption spectra were measured in 95% alcohol with a Unicam spectrophotometer and infrared spectra in mineral oil mulls with either a Grubb-Parsons double-beam or a Perkin-Elmer model 21 instrument. The light petroleum used had b. p. 60—80°.

Methyl picrotoxate and dihydropicrotoxate were prepared from picrotoxinin and dihydropicrotoxinin respectively with potassium hydroxide in methanol according to Horrmann's procedure.[2] The infrared spectrum of methyl picrotoxate had bands at 3448 (OH), 1802 (γ-lactone), 1745 (ester), and 1650 cm.$^{-1}$ (double band of *iso*propenyl group).

With acetic anhydride–pyridine methyl picrotoxate gave a *monoacetate* which formed platelets, m. p. 156—157°, from ethyl acetate–light petroleum (Found: C, 59·0; H, 6·1; OMe, 8·7; Ac, 12·1. $C_{18}H_{22}O_8$ requires C, 59·0; H, 6·1; OMe, 8·5; Ac, 11·8%). Similarly formed, the *monoacetate* of methyl dihydropicrotoxate separated from ethyl acetate–light petroleum in needles, m. p. 170—171° (Found: C, 58·8; H, 6·5; Ac, 12·0. $C_{18}H_{24}O_8$ requires C, 58·7; H, 6·6; Ac, 11·7%).

Methyl Picrotoxolate (V; R = Me, R′ = ·CMe:CH_2, R″ = R‴ = H).—Potassium borohydride (3·5 g.), dissolved in water (15 ml.), was added to a solution of methyl picrotoxate (7 g.) in methanol (80 ml.) and water (80 ml.) at 45° and the mixture kept for 24 hr. at room temperature, added to 2N-hydrochloric acid (50 ml.), and concentrated in vacuum (to 100 ml.). The crystalline precipitate (6 g.) was collected 24 hr. later; further concentration of the mother-liquors gave more solid (2—3 g.) containing large amounts of boric acid and boron complexes. To remove boron compounds the combined crude product was dissolved in methanol (75 ml.), mixed with a solution of mannitol (30 g.) in 0·1N-sulphuric acid (100 ml.), heated under reflux for 2 hr., concentrated (to 100 ml.), and neutralised with sodium hydrogen carbonate. *Methyl picrotoxolate* was isolated by continuous extraction with ether (8 hr.) and crystallised from water and then from ethyl acetate–light petroleum, forming felted needles (3·0 g.), m. p. 166·5—170°, $[\alpha]_D^{21}$ +125° (*c* 1·06 in EtOH); the infrared spectrum had bands at 3413 (OH), 1736 (ester), and 1648 cm.$^{-1}$ (double bond of *iso*propenyl system) (Found: C, 56·3; H, 6·9. $C_{16}H_{22}O_7,H_2O$ requires C, 55·8; H, 7·0%). A sample of the ester was dried at 100°/1 mm. and the resulting hygroscopic powder analysed immediately (Found: C, 59·0; H, 6·8; OMe, 9·6. $C_{16}H_{22}O_7$ requires C, 58·9; H, 6·8; OMe, 9·5%). This compound, which was readily soluble in 2N-aqueous sodium hydroxide was precipitated on acidification with mineral acid, and did not react with ethereal diazomethane, with Fehling's solution, or with Tollens's reagent. Prepared with acetic anhydride and pyridine, the *diacetate* (V; R = Me, R′ = ·CMe:CH_2, R″ = R‴ = Ac) separated from ethyl acetate–light petroleum in rosettes of needles, m. p. 179—180° (Found: C, 58·8; H, 6·7; Ac, 22·9. $C_{20}H_{26}O_9$ requires C, 58·5; H, 6·4; Ac, 21·0%).

Methyl O-*methylpicrotoxolate* (V; R = R″ = Me, R′ = ·CMe:CH_2, R‴ = H) was prepared

[13] Gillam and Stern, "An Introduction to Electronic Absorption Spectroscopy in Organic Chemistry," Arnold, London, 1954, p. 96.

from methyl picrotoxolate with either methanolic hydrogen chloride or methyl sulphate–potassium carbonate in acetone, and formed needles, m. p. 155·5—157° (from ethyl acetate–light petroleum), not immediately soluble in 2N-aqueous sodium hydroxide (Found: C, 59·8; H, 7·2; OMe, 18·2. $C_{17}H_{24}O_7$ requires C, 60·0; H, 7·1; OMe, 18·2%). Prepared with acetic anhydride–pyridine, the *acetate* (V; R = R'' = Me, R' = ·CMe:CH_2, R''' = Ac) separated from ethyl acetate–light petroleum in needles, m. p. 144—146° (Found: C, 59·7; H, 6·9; OMe, 18·5; Ac, 13·5. $C_{19}H_{26}O_8$ requires C, 59·7; H, 6·9; OMe, 16·2; Ac, 11·2%). Hydrolysis of methyl *O*-methylpicrotoxolate with 0·5N-sodium hydroxide and isolation by continuous extraction with ether gave *O-methylpicrotoxolic acid* (V; R = R''' = H, R' = ·CMe:CH_2, R'' = Me) which separated from benzene–ethyl acetate in needles, m. p. 221—222·5° (Found: C, 58·9; H, 6·7; OMe, 9·9. $C_{16}H_{22}O_7$ requires C, 58·9; H, 6·8; OMe, 9·5%). With ethereal diazomethane this acid regenerated methyl *O*-methylpicrotoxolate, m. p. and mixed m. p. 155—157°.

Oxidation of Methyl Picrotoxolate to Methyl Picrotoxate.—Methyl picrotoxolate (0·5 g.), dissolved in water (12 ml.), was added to sodium dichromate (1·5 g.) in water (8 ml.) and concentrated sulphuric acid (1 ml.) at room temperature. Colourless needles (80 mg.) of methyl picrotoxate which separated were collected 23 hr. later; more material (310 mg.) was isolated from the mother-liquors with ether. On purification from benzene this ester formed needles, m. p. and mixed m. p. 168·5—170°, having the requisite infrared absorption spectrum.

Methyl Dihydropicrotoxolate (V; R = Me, R' = $CHMe_2$, R'' = R''' = H).—Reduction of methyl dihydropicrotoxate (4 g.) with potassium borohydride (3 g.) under the conditions used for the preparation of methyl picrotoxolate gave *methyl dihydropicrotoxolate* which separated from ethyl acetate in needles (1·9 g.), m. p. 157—161° (Found, on a sample dried at 80°/0·3 mm.: C, 58·2; H, 7·4; OMe, 9·3. $C_{16}H_{24}O_7$ requires C, 58·5; H, 7·4; OMe, 9·4%). The same compound was formed by the hydrogenation of methyl picrotoxolate in ethyl acetate with a platinum catalyst and had m. p. and mixed m. p. 157—161° and the requisite infrared absorption spectrum. This ester gave a *diacetate* (V; R = Me, R' = $CHMe_2$, R'' = R''' = Ac), forming needles, m. p. 180—181°, from ethyl acetate–light petroleum (Found: C, 58·1; H, 7·1; Ac, 18·1. $C_{20}H_{28}O_9$ requires C, 58·2; H, 6·8; Ac, 20·9%). On oxidation in water (4 ml.) with sodium dichromate (0·5 g.) in 10% sulphuric acid (3 ml.) methyl dihydropicrotoxolate (0·17 g.) gave methyl dihydropicrotoxate (0·09 g.) which separated from benzene in needles, m. p. and mixed m. p. 209—210°.

Oxidation of Methyl Picrotoxolate with Sodium Metaperiodate.—A solution of methyl picrotoxolate (1·5 g.) in water (40 ml.) was treated with sodium metaperiodate (3·5 g.) in water (18 ml.) at room temperature and the crystalline precipitate of the *keto-formate* (VIII; R = ·CMe:CH_2, R' = CHO), which started to separate almost immediately, was collected 1 hr. later and crystallised from ethyl acetate, forming prisms (1·3 g.), m. p. 185—202° (decomp.), $[\alpha]_D^{23}$ +125° (*c* 0·80 in $CHCl_3$) $\lambda_{max.}$ 306 mμ (log ε 1·75) (Found: C, 59·6; H, 6·1; OMe, 9·5. $C_{16}H_{20}O_7$ requires C, 59·3; H, 6·2; OMe, 9·6%). The infrared absorption spectrum of this compound had bands at 3436 (OH), 1776 (C:O in five-membered ring), 1730 (Me ester), 1709 (formate ester) and 1653 cm.$^{-1}$ (double bond of *iso*propenyl group). Treatment of the keto-formate (0·5 g.) with concentrated sulphuric acid (3 ml.) in water (100 ml.) at room temperature for 10 days gave the *keto-alcohol* (VIII; R = ·CMe:CH_2, R' = H) which was isolated by continuous extraction with ether and crystallised from ethyl acetate, forming stout needles (0·35 g.), m. p .167—172°, $[\alpha]_D^{25}$ +137° (*c* 0·90 in EtOH), $\lambda_{max.}$ 304 mμ (log ε 1·5) (Found: C, 60·3; H, 7·0; OMe, 10·5. $C_{15}H_{20}O_6$ requires C, 60·8; H, 6·8; OMe, 10·5%). This alcohol showed infrared bands at 3448, 3390 (OH), 1770 (C:O in five-membered ring), 1701 [Me ester; this band is shifted from the more usual frequency at *ca.* 1735 cm.$^{-1}$ and although the reason for this shift is not apparent, the corresponding dihydro-compound (VIII; R = $CHMe_2$, R' = H) shows the normal ester frequency (see below)], and 1645 cm.$^{-1}$ (double bond of *iso*propenyl system). On treatment with acetic anhydride, 95% formic acid, and pyridine this alcohol gave the keto-formate (VIII; R = ·CMe:CH_2, R' = CHO), m. p. and mixed m. p. 185—202° (decomp.), with the requisite infrared absorption spectrum. It formed a *monoacetate* (VIII; R = ·CMe:CH_2, R' = Ac) which separated from ethyl acetate–light petroleum in stout needles, m. p. 135—136° (Found: C, 60·7; H, 6·7; Ac, 12·7. $C_{17}H_{22}O_7$ requires C, 60·3; H, 6·6; Ac, 12·7%), and a 2 : 4-*dinitrophenylhydrazone* in yellow needles, m. p. 228—233° (decomp.), from alcohol (Found: C, 52·9; H, 5·1; N, 11·7; OMe, 7·0. $C_{21}H_{24}O_9N_4$ requires C, 52·9; H, 5·1; N, 11·8; OMe, 6·5%). With a boiling solution of 2 : 4-dinitrophenylhydrazine (150 mg.)

in alcohol (10 ml.) and concentrated hydrochloric acid (0·1 ml.) the keto-formate (VIII; R = ·CMe:CH_2, R′ = CHO) (50 mg.) gave the same 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 228—233°. The keto-alcohol was recovered quantitatively after treatment with sodium metaperiodate, periodic acid, lead tetra-acetate, or boiling toluene for 2 hr.

Oxidation of Methyl Dihydropicrotoxolate with Sodium Metaperiodate.—Under the conditions employed for methyl picrotoxolate the oxidation of methyl dihydropicrotoxolate (1 g.) with sodium metaperiodate (1·5 g.) gave the *dihydro-keto-formate* (VIII; R = $CHMe_2$, R′ = CHO) which separated from ethyl acetate in hard prisms (0·65 g.), m. p. 208—211° (decomp.), $\lambda_{max.}$ 307 mμ (log ε 1·4), having infrared absorption bands at 3413 (OH), 1776 (C:O in five-membered ring), 1730 (Me ester) and 1706 cm.$^{-1}$ (formate ester) (Found: C, 58·8; H, 6·8. $C_{16}H_{22}O_7$ requires C, 58·9; H, 6·8%). Hydrolysis of this product (0·5 g.) with sulphuric acid (3 ml.) in water (100 ml.) at room temperature for 10 days gave the *dihydro-keto-alcohol* (VIII; R = $CHMe_2$, R′ = H) which was isolated with ether and crystallised from ethyl acetate, forming stout needles, m. p. 200—204°, $[\alpha]_D^{26}$ +114° (*c* 1·23 in EtOH), $\lambda_{max.}$ 304 mμ (log ε 1·5), infrared absorption bands at 3472, 3436 (OH), 1761 (C:O in five-membered ring) and 1736 cm.$^{-1}$ (Me ester) (Found: C, 60·2; H, 7·2; OMe, 10·3. $C_{15}H_{22}O_6$ requires C, 60·4; H, 7·4; OMe, 10·4%). This product was recovered quantitatively after treatment with sodium metaperiodate, periodic acid, lead tetra-acetate, or boiling toluene for 2 hr. It regenerated the dihydro-keto-formate, m. p. and mixed m. p. 208—211°, and formed an *acetate* (VIII; R = $CHMe_2$, R′ = Ac), which separated from ethyl acetate in prisms, m. p. 184—187° (Found: C, 59·9; H, 7·2; Ac, 12·4. $C_{17}H_{24}O_7$ requires C, 60·0; H, 7·1; Ac, 12·6%), and a 2 : 4-*dinitrophenylhydrazone*, in yellow needles, m. p. 233—234° (decomp.) from methanol (Found: C, 52·3; H, 5·4; N, 11·5. $C_{21}H_{26}O_9N_4$ requires C, 52·7; H, 5·5; N, 11·7%).

Anhydro-compound (XVII; R = ·CMe:CH_2).—Treatment of the keto-alcohol (VIII; R = ·CMe:CH_2, R′ = H) (100 g.) with boiling water (25 ml.) for 40 min. gave the *anhydro-compound* (80 mg.), m. p. 148—150° which separated from methanol in long needles, m. p. 150—152°, $\lambda_{max.}$ 234 mμ (log ε 3·94), infrared absorption bands at 1736, 1701 (with shoulders at 1706 and 1695), and 1653 cm.$^{-1}$ (Found: C, 64·8; H, 6·6; OMe, 11·3. $C_{15}H_{18}O_5$ requires C, 64·7; H, 6·5; OMe, 11·2%). The same compound, m. p. and mixed m. p. 150—152° and identical infrared spectrum, was obtained by boiling the keto-formate (VIII; R = ·CMe:CH_2, R′ = CHO) with water for 3½ hr. It did not react with acetic anhydride and pyridine or lead tetra-acetate, rapidly reduced Fehling's solution and ammoniacal silver nitrate on warming, decolorised cold bromine water, and with 2N-aqueous sodium hydroxide at room temperature gave an intractable gum. The 2 : 4-*dinitrophenylhydrazone* formed yellow needles, m. p. 240—251° (decomp.) (from chloroform–ethanol), $\lambda_{max.}$ 252, 362 mμ (log ε 4·12, 4·46) (Found: C, 55·3; H, 4·9; N, 12·0. $C_{21}H_{22}O_8N_4$ requires C, 55·0; H, 4·8; N, 12·2%), and the *dioxime*, needles, m. p. 214—216° (decomp.), from alcohol (Found: C, 58·0; H, 6·3; N, 8·9. $C_{15}H_{20}O_5N_2$ requires C, 58·4; H, 6·5; N, 9·1%).

Dihydro-anhydro-compound (XVII; R = $CHMe_2$).—On being boiled with water (25 ml.) for 40 min. the dihydro-keto-alcohol (VIII; R = $CHMe_2$, R′ = H) (100 mg.) gave the *dihydro-anhydro-compound* (80 mg.), forming needles, m. p. 161—162° (from light petroleum), $\lambda_{max.}$ 237 mμ (log ε 3·90), infrared absorption bands at 1733, 1695 (with shoulders at 1706 and 1692), and 1639 cm.$^{-1}$ (Found: C, 64·2; H, 7·2; OMe, 11·2. $C_{15}H_{20}O_5$ requires C, 64·3; H, 7·2; OMe, 11·1%). The same compound (0·45 g.), m. p. and mixed m. p. 161—162°, with the same infrared absorption spectrum, was formed by boiling the dihydro-keto-formate (VIII; R = $CHMe_2$, R′ = CHO) (0·7 g.) with water for 2 hr. The 2 : 4-*dinitrophenylhydrazone* separated from chloroform–alcohol in yellow needles, m. p. 221—223° (decomp.) (Found: C, 54·9; H, 5·1; N, 12·1. $C_{21}H_{24}O_8N_4$ requires C, 54·8; H, 5·3; N, 12·2%), and the *dioxime* from alcohol in needles, m. p. 204—206° (decomp.) (Found: C, 57·5; H, 7·3; N, 8·7. $C_{15}H_{22}O_5N_2$ requires C, 58·0; H, 7·2; N, 9·0%).

The analyses were performed by Mr. A. S. Inglis, M.Sc., and his associates in this Department.

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