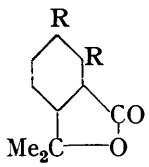
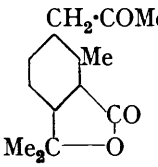
63. *Picrotoxin. Part II. Picrotone and Picrotonol.*

By Donald Mercer and Alexander Robertson.

By the hydrolytic fission of the ketone $C_{14}H_{16}O_3$, formed along with picrotic acid and now named picrotone, Angelico (*Gazzetta*, 1911, **41**, ii, 343; 1912, **42**, ii, 540) obtained acetic acid and a neutral compound which he considered to be α : α : 3 : 4-tetramethylphthalide (I, R = Me), a conclusion in agreement with the oxidation of the ketone to the acid $C_{12}H_{10}O_6$ recently shown to have the structure (I, R = CO_2H) (Part I; J., 1935, 997). The constitution of picrotone was subsequently studied by Horrmann and Bischof (*Arch. Pharm.*, 1921, **259**, 165), who suggested that the compound was represented by formula (II) or (III), a view with which Angelico disagreed (*Gazzetta*, 1923, **53**, 800).


(I.)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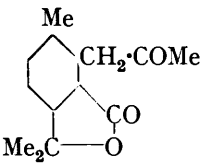
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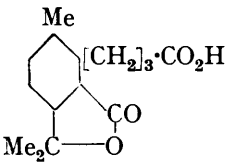
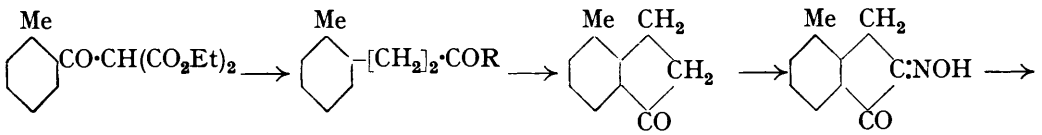

(IV.)

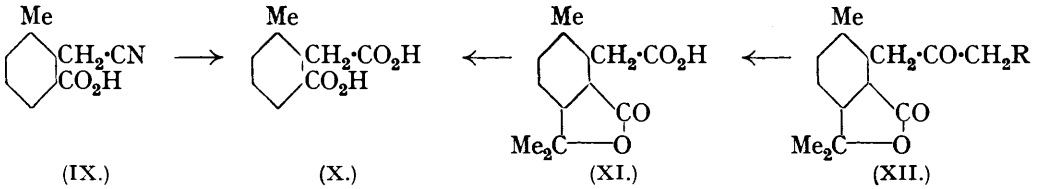
When, however, the experimental results of these authors are taken into account, it follows as a corollary to the structure of picrotic acid (IV),* clearly established in Part I, that picrotone has formula (III).†

On boiling α-picrotinic acid with 25% sulphuric acid, Angelico (*Gazzetta*, 1910, **40**, i, 391) obtained an α-ketol, $C_{14}H_{16}O_4$, which we have named picrotonol. According to Angelico oxidation of picrotonol gave an acid, $C_{14}H_{16}O_4$, m. p. 165°, devoid of ketonic properties, but Horrmann and Hagendorn (*Arch. Pharm.*, 1921, **259**, 7) considered this to be impossible and stated that the acid had the composition $C_{13}H_{14}O_4$. On repeating this work, we confirmed Horrmann and Hagendorn's observations and found that on decarboxylation the acid $C_{13}H_{14}O_4$ yields the tetramethylphthalide (I, R = Me), identical with a specimen derived from picrotone. Further, in accordance with the behaviour of αα-dimethylphthalides, fission of this monobasic acid with 50% aqueous potassium hydroxide results in the production of acetone and a dibasic acid, $C_{10}H_{10}O_4$, identical with authentic 6-*methylhomophthalic acid* (conveniently characterised by conversion into the *anhydride*) synthesised by the following method :


(V.) (VI.) (VII.) (VIII.)

* In formula (VII) of Part I (*loc. cit.*), –CO—CO– should read –CO—O–.

† Evidence for this structure and that of the important related ketol has been deduced by Tettweiler and Drishaus (*Annalen*, 1935, **520**, 163), whose memoir appeared after the completion of the present work, which formed part of a Thesis submitted by one of us (D. M.) for the degree of Doctor of Philosophy of the University of Liverpool in September, 1935. The experimental proofs now recorded differ from those subscribed by these authors, who, it may be noted, have recorded unpublished data from Dissertations submitted to the University of Kiel which have not been available to us.



(IX.) (X.) (XI.) (XII.)

The interaction of *o*-toluoyl chloride and ethyl sodiomalonate yielded the keto-ester (V), which by successive reduction, hydrolysis, and elimination of carbon dioxide gave rise to β-*o*-tolylpropionic acid (VI, R = OH). Cyclisation of the acid chloride (VI, R = Cl) with aluminium chloride in benzene gave 4-methyl-α-hydrindone (VII) in good yield, from which the *oximino*-derivative (VIII) was obtained in the usual manner. By means of *p*-toluenesulphonyl chloride according to the method of Chakravarti (*J. Indian Chem. Soc.*, 1934, **11**, 105), the last compound was readily transformed into the *acid nitrile* (IX), which on hydrolysis furnished 6-methylhomophthalic acid (X).

That the monobasic acid $C_{13}H_{14}O_4$ must have the structure (XI) clearly follows from its established relationship to the tetramethylphthalide (I, R = Me) and to 6-methylhomophthalic acid and hence picrotonol must be a primary alcohol having formula (XII, R = OH). Further, since picrotone has been degraded to the phthalide (I, R = Me) and to the acid (I, R = CO_2H) (*loc. cit.*), and since the osazone obtained from picrotonol has been found by us to be identical with the osazone (Horrmann and Bischof, *loc. cit.*) derived from bromopicrotone which is formed from picrotone by the action of sodium hypobromite, therefore bromopicrotone is represented by the structure (XII, R = Br) and picrotone by (III).

Although the studies in progress in these laboratories on the hydrogenation of picrotoxinin and of the hydration products (acids) derived therefrom are not yet complete, it seems desirable in view of the communication by Tettweiler and Drishaus (*loc. cit.*) to record the results obtained from this line of attack which have some bearing on the formation of picrotonol. In accordance with the experiment recorded by these authors we have found that picrotoxinin is readily hydrogenated in acetic acid with hydrogen at atmospheric pressure and a platinum catalyst, forming a dihydro-derivative, m. p. 252°, which we have named α-dihydropicrotoxinin. On treatment with warm 5% sulphuric acid this compound is quantitatively converted into dihydropicrotoxic acid, identical with a specimen obtained from picrotoxic acid by means of a palladium–charcoal catalyst. On the other hand, reduction of picrotoxinin with a palladium–charcoal catalyst in absolute ethyl acetate gives β-*dihydropicrotoxinin*, m. p. 255—256°, which so far we have been unable to hydrate with mineral acids to the corresponding dihydro-acid, but which, like the α-dihydro-derivative, retains the reducing properties exhibited by picrotoxinin. If, however, the reduction with a palladium catalyst (with or without charcoal) is carried out in aqueous alcohol in the presence of small amounts of hydrochloric acid, a mixture is obtained which in the majority of experiments could be crystallised from a small volume of alcohol as an apparently homogeneous compound, m. p. varying from 227° to 232—234°, but which, according to Mr. O'Donnell (private communication), contains at least three compounds. Of special interest is the fact that treatment of this mixture with 2% or 5% sulphuric acid leads to the formation of dihydropicrotoxic acid and picrotonol, being the first recorded production of the latter substance from picrotoxinin. In addition, this result affords an example of the conversion of the hydroaromatic ring system of picrotoxinin into the aromatic type under milder conditions than have hitherto been possible.

Although picrotoxinin and the majority of its hydration products, as Horrmann's results show (*Annalen*, 1916, **411**, 273), give unsatisfactory values for hydroxyl estimation by the Zerewitinoff method (*e.g.*, picrotoxinin gives OH, 1·5), the value obtained for picrotoxic acid indicates the presence of an indifferent oxygen atom. This view is confirmed by the properties of *methyl O-dimethyldihydropicrotoxate*, which is obtained by the methylation of dihydropicrotoxic acid or its methyl ester by the Purdie method, does not exhibit ketonic properties, and does not react with phosphorus pentachloride or with

thionyl chloride; the oxygen atoms are accounted for thus: two in two methoxyl groups, two in an ester group, two in the lactone group, and one in an oxide ring. Although the changes involved in the conversion of picrotoxinin into picrotoxic acid are still obscure, it is not unlikely that picrotoxinin contains an oxide ring system, because the high result (OH, 1·5) obtained by Horrmann (*loc. cit.*) in the Zerewitinoff determination on this compound is in all probability due to water of crystallisation (approximately $0{\cdot}5H_2O$) retained by material dried in a vacuum at 100° (see experimental section).

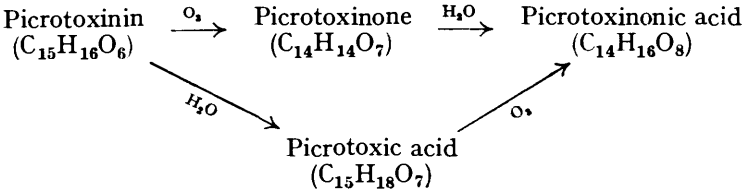
Although on the basis of the *C*-skeleton for picrotic acid and the structure of picrotonol several graphic expressions may be written which can account for some of the main transformations hitherto recorded for picrotoxinin and its hydration products, it must be admitted that sufficient analytical evidence has not so far been published to warrant a choice as a working hypothesis, *e.g.*, step-wise degradation. Nevertheless certain salient points may be usefully commented on at this stage.

(1) In the conversion of picrotoxinin into picrotic acid migration of the carboxyl groups is unlikely and therefore their relative positions may be regarded as fixed. The production of picrotonol from a reduction (?) product under comparatively mild conditions lends support to the *C*-skeleton of picrotoxinin being essentially the same as that of picrotic acid.

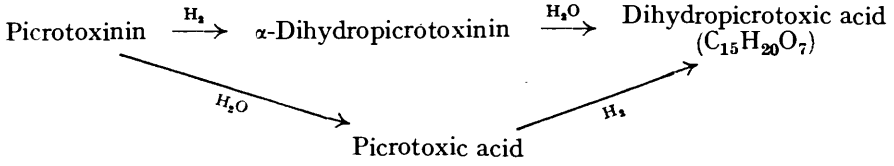
(2) From hydrogenation and ozonisation experiments, picrotoxinin and picrotoxic acid contain only one double bond; prolonged ozonisation of picrotoxinin yields only picrotoxinone. Therefore, on the basis of the *C*-skeleton and if the presence of an oxide ring is accepted, it is probable that these compounds contain a second *C*-ring system, *e.g.*, a bridge of the sabinene or pinene type.

(3) The double bond is present as a vinyl group. Horrmann and his collaborators (*Ber.*, 1916, **49**, 1554; *Arch. Pharm.*, 1920, **258**, 200) maintained that decomposition of the ozonides of picrotoxinin and picrotoxic acid gave only formic acid together with picrotoxinone in one case and picrotoxinonic acid in the other. We, however, have always found that decomposition of these ozonides is also accompanied by the production of formaldehyde, which was isolated as the 2 : 4-dinitrophenylhydrazone in amounts of about 20—25% of that theoretically possible, a result in agreement with the findings of Clemo and MacDonald for the ozonisation of vinyl derivatives (J., 1935, 1294). The formation of formaldehyde in this manner excludes the possibility of picrotoxinin or picrotoxic acid having the group :C:CH—O–.

(4) In the conversion of picrotoxinin into picrotoxic acid the double bond does not appear to be involved, because, as Horrmann (*loc. cit.*) has found, the following scheme holds:



This is corroborated by the fact that a similar scheme holds when the double bond is suppressed by hydrogenation:



(5) The six oxygen atoms of picrotoxinin are accounted for thus: four in two lactone groups, one as an oxide ring, and one as an alcoholic hydroxyl group, in all probability tertiary. Apart from the two carbonyl oxygen atoms of the lactone groups, the points of

attachment of the hydroxyl, oxide ring, and the potential hydroxyl groups of the lactones have not been determined. It seems reasonably certain, however, that one of the oxygen atoms of the lactone or oxide groups appears as the primary alcoholic group in picrotonol and it is equally probable that the *C*-atom of picrotoxinin appearing in the β-position to the primary alcohol group of picrotonol, *i.e.*, in the γ-position of the picrotoxinin side chain, does not carry an oxygen atom (compare Tettweiler and Drishaus, *loc. cit.*). Further, we are of the opinion that picrotoxinin (and also picrotin) contains a potential keto-group, which under certain conditions, not yet clearly defined, appears as the keto-group of picrotonol and of picrotone. This potential keto-group is in the β-position to a lactone and in the process of conversion into the ketones there is formed at some stage a β-ketonic acid which immediately loses carbon dioxide.

Of the exact nature of this potential keto-group, nothing definite is known. The view has been expressed (compare Tettweiler and Drishaus, *loc. cit.*) that under the influence of acids the keto-group may arise from a potential trihydroxybutyric acid by the following series of changes :

$$\cdot CH(OH)\cdot CH(OH)\cdot CH(OH)\cdot C: \longrightarrow \cdot CH{:}C(OH)\cdot CH(OH)\cdot C: \longrightarrow \cdot CH_2\cdot CO\cdot CH(OH)\cdot C:$$

but although this type of change finds analogy in the terpene series in cases where the hydroxyl groups are attached to a ring system, *e.g.*, in the conversion of *p*-menthane-1 : 2 : 4-triol into carvenone (Wallach, *Annalen*, 1893, **277**, 122), we consider this mechanism to be highly improbable in the present instance. Moreover, it does not allow of a conventional explanation of the strong reducing properties exhibited by α- and β-dihydropicrotoxinin as well as picrotoxinin itself in alkaline media. As an alternative we suggest that one or other of the following schemes affords a more satisfactory explanation :

(*a*) $C_{11}{-}CH_2\cdot\underset{-O}{C}(OH)\cdot CH(O\cdot)\cdot C: \longrightarrow C_{11}(OH){-}CH_2\cdot CO\cdot CH(OH)\cdot C:$

(*b*) $C_{11}\cdot CH_2\cdot\underset{O}{\overset{|}{C}}\cdot CH(O\cdot)\cdot C: \longrightarrow \cdot CH_2\cdot C(OH)_2\cdot CH(OH)\cdot C: \longrightarrow \cdot CH_2\cdot CO\cdot CH(OH)\cdot C:$

(*c*) $C_{11}\cdot CH_2\cdot\overset{-O}{C}\cdot CH(O\cdot)\cdot C: \longrightarrow \underset{H}{C_{11}}\cdot CH{:}\overset{-O}{C}\cdot CH(O\cdot)\cdot C: \longrightarrow \underset{C_{11}(H)}{CH_2}\cdot C(OH)_2\cdot CH(OH)\cdot C: \longrightarrow \underset{C_{11}(H)}{CH_2}\cdot CO\cdot CH(OH)\cdot C:$

Experimental.

Picrotoxinin.—This was prepared from picrotoxin according to Horrmann and Prillwitz (*Arch. Pharm.*, 1920, **258**, 200). Crystallised from water or alcohol and dried in a vacuum at 100°, it retained water of crystallisation (Found : C, 60·6; H, 5·8. Calc. for $C_{15}H_{16}O_6,0{\cdot}5H_2O$: C, 60·0; H, 5·7%). Anhydrous material was obtained by drying in a high vacuum at 120°/0·1 mm. over phosphoric oxide (Found : C, 61·6, 61·6; H, 5·6, 5·8. Calc. for $C_{15}H_{16}O_6$: C, 61·6; H, 5·5%). The retention of crystal water in this manner may account for Horrmann's failure to obtain analytical results consistent with the now accepted formula for picrotoxinin, which he himself finally adopted (*Ber.*, 1913, **46**, 2793). Meyer and Bruger (*Ber.*, 1898, **31**, 2958) and Bakunin and Giordani (*Rend. Acad. Sci. Fis. Mat. Napoli*, 1924, iii, **30**, 166) also record analytical figures in agreement with the formula $C_{15}H_{16}O_6$.

α : α : 4-*Trimethylphthalide-3-acetic Acid* (XI).—Oxidation of picrotonol was effected by the following modification of Angelico's method (*loc. cit.*) : Concentrated sulphuric acid (13·6 c.c.) was added to a mixture of ketol (6 g.) and water (50 c.c.), and the mixture boiled; a part of the ketol dissolved and the remainder formed a fine suspension. The mixture was diluted with water (25 c.c.), cooled to 0°, and treated with 3% aqueous potassium permanganate (300 c.c.) added during 2 hours with very vigorous stirring, which was then continued for 4 hours. The solution was cleared, and the acid precipitated with excess of sulphur dioxide, forming needles from water, m. p. 165° (Found : C, 66·8; H, 6·0. Calc. for $C_{13}H_{14}O_4$: C, 66·7; H, 6·0%).

A solution of this acid (0·7 g.) in quinoline (40 c.c.) containing Kahlbaum's "Naturkupfer C"

(5 g.) was refluxed for 40 minutes, cooled, mixed with ether (600 c.c.), and filtered. The ethereal solution was freed from quinoline with dilute hydrochloric acid and evaporated, the residue distilled with steam, and the oily product isolated with ether and distilled in a vacuum, giving a fraction (0·3 g.), b. p. 170—180°/18 mm., consisting mainly of α : α : 3 : 4-tetramethylphthalide. Recrystallised from alcohol (charcoal), this compound formed colourless prisms, m. p. 79—80°, identical with a specimen obtained from picrotone according to the directions of Horrmann and Bischof (*loc. cit.*) (Found : C, 75·8; H, 7·4. Calc. for $C_{12}H_{14}O_2$: C, 75·9; H, 7·6%).

β-o-*Tolylpropionic Acid.*—A solution of *o*-toluoyl chloride (41 g.) in ether (50 c.c.) was gradually added to ethyl sodiomalonate (from 45 c.c. of ethyl malonate and 4·6 g. of sodium) in ether (250 c.c.). One hour later the mixture was refluxed for 1 hour, washed with water, dried, and evaporated, leaving a residue, from which ethyl *o*-toluoylmalonate was obtained by distillation in a high vacuum as a colourless oil (40 g.), b. p. 225°/1 mm., giving a deep red ferric chloride reaction. This ester (5 g.) was boiled with acetic acid containing amalgamated zinc dust (25 g.), ammonium acetate (20 g.), and concentrated hydrochloric acid (75 c.c., added during 4 hours) for 7 hours. The mixture was filtered, the greater part of the acetic acid distilled in a vacuum, and the solution extracted with ether. The residue left on evaporation of the dried extracts was heated at 140° for ½ hour, and the resulting β-*o*-tolylpropionic acid separated from *o*-toluic acid by distillation in a vacuum. The fraction, b. p. 160—170°/20 mm., consisted of almost pure β-*o*-tolylpropionic acid, forming plates, m. p. 104—105°, from water (Young, *Ber.*, 1892, **25**, 2104, gives m. p. 102°).

2-*Oximino*-4-*methyl*-1-*hydrindone* (VIII).—To a cooled solution of β-*o*-tolylpropionyl chloride (prepared from 3·7 g. of the acid with phosphorus pentachloride) in benzene (20 c.c.), aluminium chloride (5 g.) was added in three portions during 40 minutes. 24 Hours later the mixture was refluxed for ½ hour, cooled, and treated with ice and dilute hydrochloric acid. Isolated by steam distillation and subsequent extraction from the distillate with ether, the hydrindone (VII) formed stout needles from light petroleum (b. p. 60—80°), m. p. 103—104° (Found : C, 82·1; H, 6·9. Calc. for $C_{10}H_{10}O$: C, 82·2; H, 6·9%) (Young, *loc. cit.*, gives m. p. 95°).

Concentrated hydrochloric acid (0·5 c.c.) was added to a solution of the hydrindone (2 g.) in alcohol (12 c.c.) and amyl nitrite (4 c.c.), and the mixture kept at 40—50° for 20 minutes. The resulting *oximino*-derivative (VIII) (2 g.) was drained from the alcoholic liquors and recrystallised from alcohol, forming colourless needles, m. p. 215° (decomp.) (Found : N, 8·0. $C_{10}H_9O_2N$ requires N, 8·0%).

6-*Methylhomophthalic Acid* (X).—(A) *p*-Toluenesulphonyl chloride (3 g.) was added to the yellow solution of the aforementioned oximino-compound (2 g.) in 10% aqueous sodium hydroxide (21 c.c.), and the mixture (agitate) heated to 100° in the course of 10 minutes and then kept at this temperature for a further 7 minutes. The cooled solution was treated with charcoal, filtered, and acidified with hydrochloric acid, yielding o-*tolylacetonitrile*-3-*carboxylic acid* (2 g.), which separated from water in colourless needles, m. p. 142—143° (Found : N, 7·7. $C_{10}H_9O_2N$ requires N, 8·0%). Hydrolysis of this nitrile (2 g.) with boiling 20% aqueous sodium hydroxide (20 c.c.) for 5 hours gave an almost theoretical yield of 6-*methylhomophthalic acid*, which formed needles (2 g.) from water, m. p. 195—196° (Found : C, 62·0; H, 5·4. $C_{10}H_{10}O_4$ requires C, 61·8; H, 5·2%).

(B) α : α : 4-Trimethylphthalide-3-acetic acid (2 g.) was heated with 50% aqueous potassium hydroxide (2 c.c.) in a small distilling flask to 300—315° in the course of 15 minutes (temperature, 150° after 5 minutes; 220° after 10 minutes) and then maintained at this temperature for 15 minutes. The acetone, which was completely evolved at 300° in about 10 minutes, was collected and converted into the 2 : 4-dinitrophenylhydrazone, m. p. 128°, identified by comparison with an authentic specimen.

Acidification of a solution of the alkaline residue in water (10 c.c.) with hydrochloric acid precipitated 6-methylhomophthalic acid, which separated from water in needles, m. p. 192—194°, undepressed by admixture with an authentic specimen. Treatment of this material (0·3 g.) with warm acetyl chloride (3 c.c.) for 15 minutes gave rise to the *anhydride* which, after the removal of the acetyl chloride and acetic acid in a vacuum, crystallised from benzene in needles, m. p. 150°, identical with a specimen prepared from the synthetic acid in the same manner (Found : C, 68·0; H, 4·9. $C_{10}H_8O_3$ requires C, 68·2; H, 4·6%).

Ozonisation of Picrotoxinin and of Picrotoxic Acid.—A stream of ozone and oxygen was led into a solution of anhydrous picrotoxinin (2 g.) in chloroform (200 c.c.) for 24 hours; the ozonide gradually separated in colourless prisms. After the removal of the chloroform in a vacuum the solid was decomposed by being heated with water (200 c.c.), and the solution distilled with the addition of more water (200 c.c.) as required. About 300 c.c. of aqueous distillate were collected

and on treatment with excess of 2 : 4-dinitrophenylhydrazine hydrochloride in 2*N*-hydrochloric acid gave a precipitate of formaldehyde-2 : 4-dinitrophenylhydrazone, which was collected 5 hours later, washed, and crystallised from aqueous alcohol, forming orange-yellow needles, m. p. 164—165°, undepressed by admixture with an authentic specimen, m. p. 165—166°. Yield of formaldehyde, *ca.* 20% of the theoretical.

The ozonisation of picrotoxinin (6 g.) was also carried out with absolute ethyl acetate (150 c.c.) as the solvent; the ozonide was decomposed with water (100 c.c.) at room temperature, the precipitate of α-picrotoxinone (5·5 g.) collected, and the formaldehyde isolated from the aqueous liquors by steam distillation and converted into the 2 : 4-dinitrophenylhydrazone, m. p. 164—165°; yield of formaldehyde, *ca.* 20—25% of the theoretical. α-Picrotoxinone was characterised by conversion into the β-form, m. p. 252—253°.

Ozonisation of picrotoxic acid and of methyl picrotoxate was carried out under similar conditions and gave formaldehyde in addition to picrotoxinonic acid and its methyl ester (compare Horrmann and Wächter, *Ber.*, 1916, **49**, 1554).

Hydrogenation of Picrotoxinin with a Platinum Catalyst.—Picrotoxinin (5 g.) was hydrogenated in acetic acid (200 c.c.) with a platinum catalyst and hydrogen at atmospheric pressure; absorption (1 mol.) was complete in about 5 minutes. After isolation, α-dihydropicrotoxinin crystallised from alcohol in colourless plates, m. p. 252°, $[\alpha]_D^{20°}$ — 4·02° in acetone (Found: C, 61·2; H, 6·1. Calc. for $C_{15}H_{18}O_6$: C, 61·2; H, 6·1%). This compound (1 g.) was recovered unchanged after treatment with acetic anhydride (4 c.c.) and pyridine (2 c.c.) at room temperature for 10 days.

α-Dihydropicrotoxinin (2 g.) was refluxed with 5% sulphuric acid (100 c.c.) for 20 hours, and the mixture was neutralised with sodium bicarbonate and extracted with ether. Evaporation of the extracts left only slight traces of a residue. Acidification of the aqueous liquors with hydrochloric acid gave dihydropicrotoxic acid, which was isolated with ether and crystallised from ethyl acetate, forming slender needles (1·5 g.), m. p. 252—253°, identical with a specimen obtained by the reduction of picrotoxic acid in water with a palladium–charcoal catalyst (Horrmann and Wächter, *loc. cit.*).

Hydrogenation of Picrotoxinin with a Palladium Catalyst.—(A) By means of a catalyst prepared from palladium (0·3 g.) and charcoal (2 g.) in the usual manner and carefully washed with much water, alcohol, and ethyl acetate, picrotoxinin (5 g.) was hydrogenated in absolute ethyl acetate (200 c.c.) with hydrogen at atmospheric pressure (approximately 400 c.c. absorbed; theoretical for one double bond, 360 c.c.). After isolation, *β-dihydropicrotoxinin* separated from ethyl acetate in prismatic needles, m. p. 256—257°, $[\alpha]_D^{20°}$ — 24·69° in acetone (Found: C, 61·2; H, 6·1%). This compound was recovered unchanged after having been refluxed with 5% sulphuric acid for 24 hours. A mixture of α- and β-dihydropicrotoxinin melted at about 220—225°.

(B) Hydrogen was led into a well-agitated solution of picrotoxinin (5 g.) in alcohol (300 c.c.) and water (100 c.c.) containing palladium chloride (0·4 g.), 2*N*-hydrochloric acid (1 c.c.), and active charcoal (2 g.). Absorption was rapid at first but had almost ceased when, after 2 hours, approximately the theoretical amount of hydrogen for one double bond had been absorbed. The filtered solution was evaporated in a vacuum to about 25 c.c., and the product precipitated with water; the m. p. varied from 227° to 232°; yield, *ca.* 4·5 g. This material could be crystallised from a small volume of alcohol, forming prisms, apparently homogeneous, the m. p. varying with individual preparations from 227° to 234°.

A solution of this product (1 g.) in methyl alcohol containing potassium hydroxide (0·2 g.) was kept for 10 minutes and then evaporated in a vacuum. The residue was dissolved in a small volume of water, neutralised with hydrochloric acid, and extracted with ether. Evaporation of extracts left a product, from which methyl dihydropicrotoxate was isolated by crystallisation from ethyl acetate, m. p. 210°, identical with that of an authentic specimen (Horrmann and Wächter, *loc. cit.*, give m. p. 205°) (Found: C, 58·8; H, 6·8. Calc. for $C_{16}H_{22}O_7$: C, 58·9; H, 6·8%).

Picrotonol.—The material (5 g.), m. p. 228—232°, was boiled with 5% (or 2%) sulphuric acid (200 c.c.) for 18—20 hours, and the cooled solution was filtered from a small amount of crystalline solid, m. p. 255—256° (identified as β-dihydropicrotoxinin), neutralised with sodium bicarbonate, and extracted with ether. Evaporation of the dried extracts left crude picrotonol as a pale brown oil (2—3 g.). Extraction of the aqueous liquors which had been acidified with hydrochloric acid gave dihydropicrotoxic acid, m. p. 252—253° after purification from ethyl acetate.

The crude ketol was converted into the semicarbazone, which separated from alcohol in prisms, m. p. 224—226° (Found: C, 58·8; H, 6·2; N, 13·9. Calc. for $C_{15}H_{19}O_4N_3$: C, 59·0;

H, 6·2; N, 13·8%). This derivative was identical with material prepared from authentic ketol obtained from α-picrotinic acid * with 40% sulphuric acid (Horrmann, *loc. cit.*), m. p. and mixed m. p. 224—226°. Decomposition of the semicarbazone (2 g.) with a boiling solution of oxalic acid (2 g.) in water (20 c.c.) during 2 hours gave pure picrotonol, obtained on isolation with ether as a viscous syrup which did not crystallise. On being boiled with 17% acetic acid (70 c.c.) and phenylhydrazine (5 c.c.) for 2 hours, the ketol (1 g.) yielded the osazone, forming golden rods from much alcohol, m. p. 202°, identical with an authentic specimen (Found: C, 73·1; H, 6·4; N, 13·4. Calc. for $C_{26}H_{26}O_2N_4$: C, 73·2; H, 6·1; N, 13·1%). The same osazone was obtained from bromopicrotone by Horrmann and Bischof's method (*loc. cit.*).

A solution of picrotonol (1 g.) and *p*-nitrobenzoyl chloride (2 g.) in pyridine (15 c.c.) was kept at about 70° for 2 days and then mixed with ice-water and excess of dilute hydrochloric acid. The solid was washed with water and thoroughly extracted with aqueous sodium bicarbonate and then with cold water. Crystallised from alcohol, the residual p-*nitrobenzoate* formed slender needles, m. p. 155°, identical with a specimen obtained from authentic ketol by the same method (Found: C, 63·3; H, 4·8; N, 3·7. $C_{21}H_{19}O_7N$ requires C, 63·5; H, 4·8; N, 3·5%).

Picrotonol was also obtained directly from picrotin by the procedure which Horrmann used for the preparation of the compound from α-picrotinic acid; semicarbazone, m. p. and mixed m. p. 224—225°.

Methyl O-Dimethyldihydropicrotoxate.—Dihydropicrotoxic acid (6 g.) was methylated in boiling methyl alcohol (150 c.c.) with excess of methyl iodide and silver oxide, gradually added during 24 hours. The product was isolated and the process repeated (three or four times) without the addition of methyl alcohol, until a product was obtained which was unchanged on further treatment. The *compound* (6 g.) crystallised from methyl alcohol or light petroleum (b. p. 80—100°) in needles, m. p. 146—147°, $[\alpha]_D^{20°}$ + 95·93° in chloroform [Found: C, 61·1; H, 7·5; OMe, 26·6. $C_{15}H_{17}O_4(OMe)_3$ requires C, 61·1; H, 7·3; OMe, 26·2%]. The same ether was obtained by methylation of methyl dihydropicrotoxate by the same procedure. Though it did not appear to be readily hydrolysed with alcoholic potassium hydroxide, the compound (0·4 g.), on being boiled with hydrazine hydrate (10 c.c.) for 2 hours, gave rise to O-*dimethyldihydropicrotoxic acid*, forming needles from water, m. p. 206—207° [Found: C, 59·6; H, 7·2; OMe, 17·6. $C_{15}H_{18}O_5(OMe)_2$ requires C, 60·0; H, 7·1; OMe, 17·9%].

Methyl *O*-dimethyldihydropicrotoxate was recovered unchanged after having been refluxed with excess of thionyl chloride or with phosphorus pentachloride in chloroform.

Appendix.

For 5-methyl-α-tetralone, Tettweiler and Drishaus (*loc. cit.*) give m. p. 63°, but we have always found the m. p. of the synthetic compound to be 50—51° in agreement with Heilbron and his collaborators (J., 1930, 425). Decomposition of the semicarbazone, m. p. 245—246° (for this derivative, Tettweiler and Drishaus give m. p. 242°), with hot aqueous oxalic acid regenerated the tetralone, m. p. 50—51°, unchanged after purification by steam distillation, distillation in a vacuum, and repeated crystallisation from light petroleum (b. p. 40—60°) and aqueous acetic acid.

The authors are indebted to the Department of Scientific and Industrial Research for a maintenance grant to one of them (D. M.).

University of Liverpool. [*Received, December 19th*, 1935.]

* In order to avoid confusion with picrotic acid (Part I, *loc. cit.*) the monobasic acids from picrotin should be named α- and β-picrotinic acid (*Abstracts*, 1910, **98**, i, 404; 1913, **104**, i, 70; 1916, **110**, i, 566) and not α- and β-picrotic acid (*Abstracts*, 1912, **102**, i, 1008).