199. *Picrotoxin. Part III.*

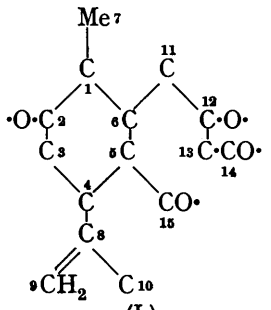
By JAMES C. HARLAND and ALEXANDER ROBERTSON.

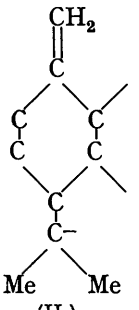
On being boiled with hydriodic acid and red phosphorus, picrotoxinone and picrotoxinonic acid give rise to a mixture from which a phenolic *ketone* $C_{13}H_{16}O_2$, nor*picrotic acid*, and hydroxy*nor*picrotic acid have been isolated. On reduction the ketone gave rise to a phenol identical with 1-methyl-4-ethyl-5 : 6 : 7 : 8-tetrahydro-β-naphthol, the synthesis of which and that of the isomeric 4-methyl-1-ethyl-5 : 6 : 7 : 8-tetrahydro-β-naphthol are described. From the structure of the phenol the positions of the ethylenic linkage and of an oxygen atom in picrotoxinin and picrotoxic acid are deduced. The possible significance of the formation of a naphthalene derivative from a picrotoxinin degradation product is discussed and structural formulæ for *nor*- and hydroxy*nor*-picrotic acid have been developed.

IN Part II (J., 1936, 288) it was shown that the formation of picrotoxinone and of picrotoxinonic acid from picrotoxinin and picrotoxic acid, respectively, is accompanied by the production of considerable amounts of formaldehyde and hence the double bond in the parent compounds is present as a vinyl group. On the assumption that the *C*-skeleton * of picrotoxinin and its derivatives is essentially that obtaining in picrotic acid (J., 1935, 997) there are only two possible positions for the latter group, *viz.*, those represented by the partial formulæ (I) and (II), and in this connexion it may be noted that Horrmann (*Ber.*, 1916, **49**, 1557) claimed to have obtained a lactonic dibasic acid by the oxidation of picrotoxinonic acid according to the scheme

$$C_{11}H_{12}O_4\begin{cases}-OH\\-CO\\-CH_2\\-CO_2H\end{cases}\longrightarrow\begin{cases}-OH\\-CO_2H\\-CO_2H\\-CO_2H\end{cases}\longrightarrow\begin{cases}-O\\-CO\\-CO_2H\\-CO_2H\end{cases}$$

a result which may now be interpreted as indicating that picrotoxinone and picrotoxinonic acid have either formula type (III) or (IV). If Horrmann's results are accepted, the latter structure implies that the methylene group, which is adjacent to the carbonyl and undergoes oxidation in the course of the formation of the lactonic acid, would form part of a second cyclic system in picrotoxinonic acid and therefore in all probability in picrotoxinin and picrotoxic acid. In support of the structure type (IV) for picrotoxinone and hence type (I) for picrotoxinin we found that, unlike the latter compound, picrotoxinone did not give rise to acetone on being heated with potassium hydroxide at 310—320°. Before attempting to confirm the formation of Horrmann's acid and to elucidate its structure it seemed highly desirable to establish the position of the double bond in the picrotoxinin *C*-skeleton by an independent procedure and the most direct method of attaining this objective appeared to be by the conversion of picrotoxinone into an aromatic system analogous to the formation of picrotic acid from picrotoxinin.


(I.)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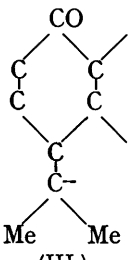
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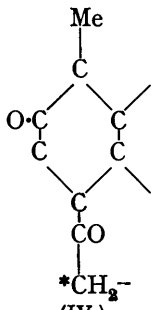
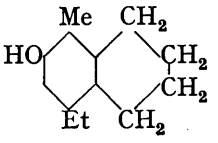

(IV.)

* Until decisive experimental evidence opposing this view is available we propose, in discussing experimental results and in formulating the changes undergone by picrotoxinin and its degradation products, to employ this working hypothesis.

In the course of preliminary experiments in this direction it was found that the carbonyl group in picrotoxinone or in picrotoxinonic acid could not be reduced by catalytic methods, and Clemmensen's method gave rise to a water-soluble product which proved intractable. When, however, picrotoxinone or picrotoxinonic acid was heated with hydriodic acid and red phosphorus, a complex mixture resulted from which a phenolic *ketone* $C_{13}H_{16}O_2$ and two acids, nor*picrotic acid* and *hydroxy*nor*picrotic acid*, were isolated. These compounds were accompanied by smaller amounts of neutral oil, which could not be resolved into individual substances, together with a small amount of a solid insufficient for complete examination and a considerable quantity of an amorphous product.



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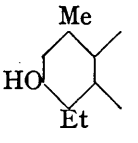
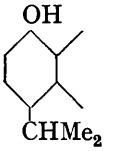


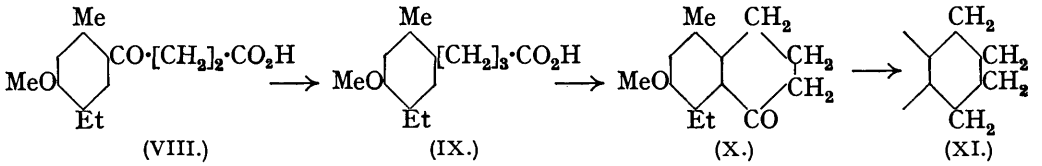
(VI.)



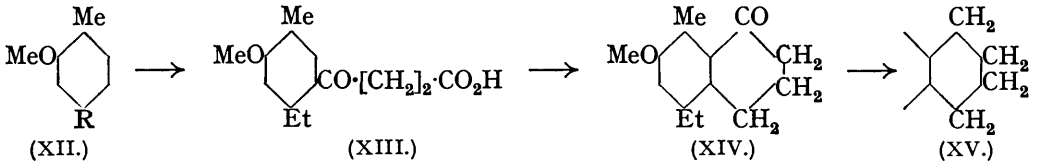
(VII.)

The alkali-soluble ketone $C_{13}H_{16}O_2$, which did not give a ferric reaction and was conveniently characterised by the formation of a *semicarbazone* and a 2 : 4-*dinitrophenylhydrazone*, appeared to be a saturated compound and on reduction by Clemmensen's method gave rise to a saturated *phenol*, $C_{13}H_{18}O$, which readily formed a p-*nitrobenzoate*. From the empirical formulæ of the ketone and its reduction product it appeared clear that in addition to the benzenoid system both compounds contained a second carbocyclic system. Further, from a consideration of the *C*-skeleton of picrotoxinin in conjunction with the feasible partial structure types (III) and (IV) suggested for picrotoxinone it seemed possible that the phenol might be a tetrahydronaphthol having formula (V), (VI), or type (VII) where the hydroxyl group could be in the *o*-, *m*-, or *p*-position to the *iso*propyl residue. Although, in view of the structure of picrotic acid, in which carboxyl groups may be considered to originate from the dilactone system which has been attributed to picrotoxinin, the evidence for the tetrahydronaphthol formula was somewhat slender, it was decided to undertake the synthesis of the aforementioned tetrahydronaphthol types.

Since the starting material, 5-methyl-2-ethylphenol, was readily available, the synthesis of 4-*methyl*-1-*ethyl*-5 : 6 : 7 : 8-*tetrahydro*-β-*naphthol* (VI) by way of the stages (VIII), (IX), (X), and (XI) was carried out first and although this compound closely resembled the natural phenol the two compounds were not identical.



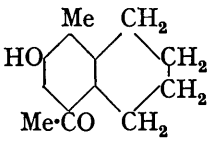
(VIII.) (IX.) (X.) (XI.)

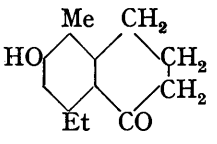


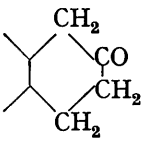
(XII.) (XIII.) (XIV.) (XV.)

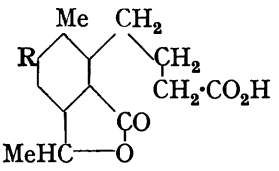
1-*Methyl*-4-*ethyl*-5:6:7:8-*tetrahydro*-β-*naphthol* (V) was then synthesised from the ketone (XII, R = Ac) in a similar manner by way of the stages (XII, R = Et), (XIII), (XIV), and (XV) and found to be identical with the natural phenol, a result which was confirmed by comparison of the *p*-nitrobenzoates; on account of this successful issue the preparation of the tetrahydronaphthols type (VII) was not proceeded with. In connexion with these syntheses it may be noted that the orientation of the intermediate β-anisoylpropionic acids, (VIII) and (XIII), follows on general grounds and from the fact that the compounds were successfully converted into the tetralones (X) and (XIV) respectively.

From the established structure of the naphthol (V) it is clear that the parent ketone $C_{13}H_{16}O_2$ is either the *C*-acetyltetrahydronaphthol (XVI) or a tetralone for which four expressions are possible, and of the latter formulæ (XVII) and (XVIII) are considered to be the more likely in view of the structures of picrotone and picrotic acid. Although the evidence available does not enable us to make a choice between the orientations possible for the ketone $C_{13}H_{16}O_2$, nevertheless the position of the ethylenic linkage in picrotoxinin and picrotoxic acid can be deduced from the formation of the tetrahydronaphthol (V). Since the possible positions for the double bond are limited to two, indicated by formulæ (I) and (II), comparison of the *C*-skeleton (I) of picrotoxinin and picrotic acid with that of the naphthol (V) shows that in the latter the C_{10}-atom is missing (C_{14} or C_{15} would be lost as carbon dioxide; compare formation of picrotone and picrotonol, *loc. cit.*), *i.e.*, the ethyl group of the naphthol (V) must originate by removal of a methylene group by ozonolysis from the *iso*propyl residue of picrotoxinin which appears as the phthalide group of picrotic acid. Hence it follows that the double bond in picrotoxinin and in picrotoxic acid has the position indicated in (I) and that picrotoxinone and picrotoxinonic acid may be represented by the formula type (IV), in which we consider the *C-atom to be present as a methyl and not as a methylene group, a point which we hope to clarify when an examination of Horrmann's lactonic dibasic acid is completed. Further, on the assumption, which appears justifiable at present, that the hydroxyl group of the phenol does not arise by a secondary reaction (*e.g.*, hydration) in the formation of the aromatic system, this group clearly indicates the position of attachment of an oxygen atom in picrotoxinone and hence in picrotoxinin and, since it is reasonably certain that the latter does not contain a secondary alcohol group, this oxygen atom must be present either as a tertiary alcohol group or (more probably) in an ether system (compare Part II, *loc. cit.*); from the evidence afforded by picrotic acid, picrotone and picrotonol, carbon atoms C_{12}, C_{13}, and C_{14} in (I) would appear to carry oxygen atoms. In this connexion it must be noted that the position of the double bond now established definitely excludes the possibility that the lactone system, appearing as the αα-dimethylphthalide group in picrotone, picrotonol, and picrotic acid, can exist in picrotoxinin or picrotoxic acid and it would seem, therefore, that in all probability the phthalide group in these derivatives arises by hydration of the *iso*propylene residue with subsequent lactonisation.

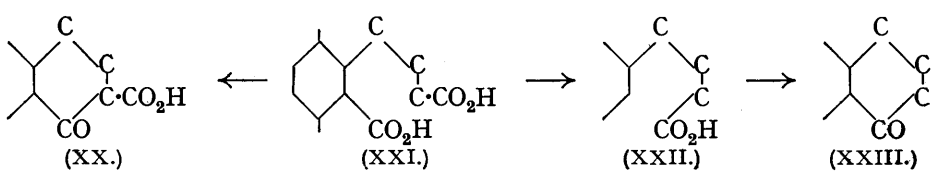

(XVI.)


(XVII.)


(XVIII.)


(XIX.)

Because of the conversion of picrotoxinin into picrotic acid and picrotoxinindicarboxylic acid it has generally been assumed that picrotoxinin contains two lactone groups, but the formation of the dicyclic ketone $C_{13}H_{16}O_2$ raises the question as to whether one of the carboxyl groups of these compounds is originally present in picrotoxinin as a latent carbonyl group in the β-position to a lactone group. Of significance in this connexion are the strong reducing properties exhibited by picrotoxinin and picrotoxic acid, which, however, are absent in picrotoxinindicarboxylic acid and are therefore, presumably, not due to the potential carbonyl group which appears in picrotone and picrotonol (Part II, *loc. cit.*). On this hypothesis the reducing properties may be attributed to the presence of a ·CO·C(OH)—CO—O· group, the hydroxyl of which becomes the primary alcoholic group in picrotonol.


(XX.) (XXI.) (XXII.) (XXIII.)

Alternatively, on the dilactone hypothesis the production of a naphthalene derivative must arise from picrotoxinone either by a Dieckmann type of cyclisation from an intermediate dibasic acid, *i.e.*, conversion of type (XXI) into (XX) and subsequent decarboxylation of the latter to form (XXIII), or by extrusion of a carboxyl group and the cyclisation of the resulting acid type (XXII) to give (XXIII). Though not strictly comparable, the relatively mild conditions required to convert β-phenylpropionic acid-2-acetic acid into β-tetralone (Hückel, *Annalen*, **1925**, **441**, 1) may be quoted in support of the former mechanism, and for the latter the tendency for γ-phenylbutyric acids to form α-tetralones (Krollpfeiffer and Schäfer, *Ber.*, **1923**, **56**, 620).

*nor*Picrotic acid, $C_{14}H_{16}O_4$, is a saturated, non-reducing, monobasic acid, devoid of hydroxyl or carbonyl groups and on esterification under the usual conditions yields a *monoethyl* ester, which is insoluble in aqueous sodium hydroxide and on hydrolysis regenerates the original acid; excess of diazomethane gives the *methyl* ester, which has the same properties. By analogy with picrotic acid, which is formed under analogous conditions, it seems reasonably certain that the two remaining oxygen atoms of *nor*picrotic acid are present in a lactone system which, in view of the presence of the ethyl group in (V) and the partial structure (IV) for picrotoxinone, is considered to be present as an α-methylphthalide group and hence *nor*picrotic acid may be represented by the expression (XIX, R = H). Unlike picrotic acid and in agreement with this formula, *nor*picrotic acid is unaffected by being heated with potassium hydroxide at 300°, a result in accordance with the observation that only αα-disubstituted phthalides or α-mono-substituted phthalides where the substituent is a higher alkyl radical undergo complete hydrolytic fission under these conditions (Gucci, *Atti R. Accad. Lincei*, **1898**, **7**, i, 215; **10**, i, 470; *Gazzetta*, **1898**, **28**, i, 297). In the course of unsuccessful attempts to effect reductive fission of the phthalide system the compound was also recovered unchanged after having been boiled with hydriodic acid and yellow phosphorus.

The acid $C_{14}H_{16}O_5$, which we have termed hydroxy*nor*picrotic acid, is a saturated compound which does not react with carbonyl reagents. On titration it behaved approximately as a dibasic acid (phenolphthalein as an indicator) but on esterification by the standard methods gave only a *monoethyl* ester, soluble in aqueous sodium hydroxide but insoluble in aqueous sodium bicarbonate. Treatment of the acid with an excess of diazomethane gave rise to a *dimethyl* derivative and on hydrolysis this compound yielded *methoxynorpicrotic acid*, which behaved on titration as a monobasic acid and was not affected by prolonged boiling with concentrated aqueous sodium hydroxide or with hydrazine hydrate. It appeared reasonably certain, therefore, that the acid $C_{14}H_{16}O_5$ was a phenolic acid, in which the hydroxyl group was highly acidic, and this conclusion was clearly established by the fact that in alkaline solution the compound reacted with α-naphthalenediazonium chloride, forming an intense red dye. Like *nor*picrotic acid, on being heated with potassium hydroxide at 300°, hydroxy*nor*picrotic acid does not appear to undergo hydrolytic fission. By analogy with the former acid it seems probable that hydroxy*nor*picrotic acid contains an α-methylphthalide group and therefore may be represented by the expression (XIX, R = OH) in which the position of the hydroxyl group follows from the structure of the naphthol (V) and the enhanced acidity of the phenolic group is due to the lactone carbonyl in the *p*-position.

Experimental.

Reduction of Picrotoxinone with Hydriodic Acid and Phosphorus.—On being gently warmed, α-picrotoxinone (Part II, *loc. cit.*), m. p. 189° (10 g., prepared by ozonolysis of picrotoxinin in ethyl acetate), red phosphorus (4 g.), and hydriodic acid (26 c.c., *d* 1·7) reacted vigorously with much frothing. After this initial reaction had subsided, the mixture was refluxed for 6 hours, cooled, and poured into water (650 c.c.). Next day the supernatant liquid was decanted from the brown viscous residue, saturated with salt, and extracted with ether (10 × 200 c.c.). The combined ethereal extracts were concentrated, and the red-brown residual solution (200 c.c.) decolorised by successive treatment with small amounts of sulphurous acid, washed with water, and then repeatedly extracted with aqueous sodium carbonate, again washed, and dried; this constitutes extract (A). The combined sodium carbonate extracts were treated with charcoal, filtered, and acidified, yielding hydroxy*nor*picrotic acid, $C_{14}H_{16}O_5$, which gradually separated in

the course of about a week. After the isolation of this acid the residual aqueous liquors were extracted with ether; this constitutes extract (B).

The viscous brown residue was digested with successive portions of ether (5 × 120 c.c.) and the combined brown ethereal extracts were filtered to remove phosphorus, decolorised with sulphurous acid, repeatedly extracted with aqueous sodium carbonate (20 × 25 c.c.), washed with water, and dried; this constitutes extract (C). The combined aqueous sodium carbonate washings were treated with charcoal, filtered, acidified with hydrochloric acid, and extracted with ether (5 × 200 c.c.). The latter extracts were combined with extract (B), dried, and evaporated, leaving a semi-solid viscous residue, which was esterified with excess of boiling alcohol, containing 8% of concentrated sulphuric acid, during 16 hours. The product was separated from a small amount of unchanged acidic material by means of aqueous sodium carbonate and then on distillation in a vacuum gave an oil, b. p. 120—170°/0·1 mm., and a residual solid. By repeated distillation of this oil pure ethyl *nor*picrotate was ultimately isolated. From the residue left on separation of the crude ethyl *nor*picrotate a mixture of hydroxy*nor*picrotic acid and its ethyl ester was isolated by extraction with dilute aqueous sodium hydroxide and then separated by means of aqueous sodium bicarbonate; the formation of hydroxy*nor*picrotic acid at this stage was due apparently to partial hydrolysis of the residual ester fraction in the course of the separation of the ester from a small amount of alkali-insoluble material, which was not further examined.

The ethereal extracts (A) and (C) were combined and evaporated and the resulting semi-solid brown product, which contained phenolic material, was separated by means of 2% aqueous sodium hydroxide into a phenolic fraction consisting of the crude ketone $C_{13}H_{16}O_2$ and a neutral fraction which appeared to be a complex mixture and of which part distilled in a high vacuum, leaving an amorphous residue; a fraction, b. p. 100—150°/0·1 mm., was obtained as a mobile, dark brown oil which did not react with carbonyl reagents and formed a picrate; the second fraction, b. p. 150—185°/0·1 mm., which was too small to permit a complete examination, solidified and on recrystallisation from light petroleum (b. p. 80—100°) had m. p. 90—95°. This product, which was also unreactive towards the aforementioned reagents, appeared to be a complex mixture. 10 G. of picrotoxinone gave 0·4—0·45 g. of the ketone, 1 g. of *nor*picrotic acid, and 0·9 g. of hydroxy*nor*picrotic acid.

When picrotoxinone was replaced by picrotoxinonic acid, the same results were obtained.

The *ketone* $C_{13}H_{16}O_2$ separated from carbon tetrachloride in tiny colourless needles, m. p. 189°, tenaciously retaining solvent of crystallisation, which was removed when the substance was sublimed in a high vacuum at 120° (Found: C, 76·5; H, 7·8. $C_{13}H_{16}O_2$ requires C, 76·5; H, 7·8%). This compound, which was readily soluble in dilute aqueous sodium hydroxide, alcohol, or benzene and did not give a ferric reaction or reduce Fehling's solution on boiling, reduced Tollens' reagent on being warmed and readily formed a 2 : 4-*dinitrophenylhydrazone*, which separated from ethyl acetate in red needles, m. p. 268° (Found: C, 59·4; H, 5·2; N, 14·6. $C_{19}H_{20}O_5N_4$ requires C, 59·4; H, 5·2; N, 14·6%). Interaction of the ketone with excess of aqueous alcoholic semicarbazide acetate in the usual manner in the course of 5 days gave the *semicarbazone*, which, after repeated crystallisation from chloroform and then from dilute alcohol, formed clusters of stout rectangular prisms, m. p. 201° (Found: C, 64·5; H, 7·2; N, 15·8. $C_{14}H_{19}O_2N_3$ requires C, 64·4; H, 7·3; N, 16·1%).

A mixture of the ketone (1 g.), amalgamated zinc (6 g.), alcohol (5 c.c.), and 15% hydrochloric acid (15 c.c.) was refluxed for 6 hours; three portions (each 2 c.c.) of concentrated hydrochloric acid were added at intervals of 1½ hours. On isolation with ether the resulting 2-*hydroxy*-1-*methyl*-4-*ethyl*-5 : 6 : 7 : 8-*tetrahydronaphthalene* (V) was purified by distillation in a high vacuum and then by crystallisation from light petroleum (b. p. 40—60°), being finally obtained in colourless, elongated prisms, m. p. 66·5°, identical with a synthetical specimen (Found: C, 82·1; H, 9·6. $C_{13}H_{18}O$ requires C, 82·1; H, 9·5%). Prepared by interaction of the phenol with excess of *p*-nitrobenzoyl chloride in pyridine at 60° in the course of 100 hours, the p-*nitrobenzoate* was separated from a little *p*-nitrobenzoic acid by means of aqueous sodium bicarbonate, and then repeatedly crystallised from alcohol, forming colourless irregular prisms, m. p. 85°, undepressed by admixture with a specimen prepared from the synthetic phenol (Found: N, 4·3. $C_{20}H_{21}O_4N$ requires N, 4·1%).

*nor*Picrotic acid (XIX, R = H) was isolated as the *ethyl* ester, which on repeated distillation in a vacuum was obtained as a colourless oil, b. p. 165°/0·01 mm., insoluble in aqueous sodium hydroxide [Found: C, 69·4; H, 7·7; OEt, 17·3. $C_{14}H_{15}O_3(OEt)$ requires C, 69·5; H, 7·3; OEt, 16·3%]. Hydrolysis of this ester (16·5 g.) with a boiling mixture of 8% aqueous sodium hydroxide (90 c.c.) and alcohol (45 c.c.) for 10 hours gave rise to the *acid* (13 g.), which was

isolated from the acidified hydrolysate with ether and purified by crystallisation from warm water and then dilute alcohol, forming elongated prisms, m. p. 113° (Found for a specimen dried in a high vacuum at 80°: C, 67·8; H, 6·5. $C_{14}H_{16}O_4$ requires C, 67·7; H, 6·5%). Treatment of this acid, which behaved as a saturated compound towards hydrogen in the presence of an active catalyst, with excess of ethereal diazomethane gave rise to a quantitative yield of the *methyl* ester, which, after having been distilled in a high vacuum, separated from light petroleum (b. p. 60—80°) in elongated prisms, m. p. 61° [Found: OMe, 12·3. $C_{14}H_{15}O_3(OMe)$ requires OMe, 11·9%], and on hydrolysis wih alkali regenerated the original acid, m. p. and mixed m. p. 113°.

*Hydroxy*nor*picrotic acid* (XIX, R = OH) was purified by repeated crystallisation from acetone–benzene and then from dilute alcohol, forming glistening plates, m. p. 213°, having a negative ferric reaction and being readily soluble in acetone or alcohol and sparingly soluble in benzene (Found for a specimen dried in a high vacuum at 100°: C, 63·5; H, 6·2. $C_{14}H_{16}O_5$ requires C, 63·6; H, 6·1%). On being titrated with standard aqueous sodium hydroxide, a solution of this compound in aqueous alcohol behaved as a dibasic acid. Esterified by the alcohol–sulphuric acid method, it gave the *ethyl* ester, which separated from benzene in tiny prisms, m. p. 125°, insoluble in aqueous sodium bicarbonate and re-forming the original acid on hydrolysis with alkali [Found for a specimen dried in a high vacuum at 60°: C, 65·9; H, 6·8; OEt, 15·7. $C_{14}H_{15}O_4(OEt)$ requires C, 65·8; H, 6·9; OEt, 15·4%].

On treatment with an excess of ethereal diazomethane this acid (2 g.) gave rise to *methyl methoxy*nor*picrotate* (2 g.), which, after distillation in a high vacuum, crystallised from light petroleum in irregular plates, m. p. 93°, insoluble in aqueous sodium hydroxide [Found: OMe, 20·8. $C_{14}H_{14}O_3(OMe)_2$ requires OMe, 21·2%]. Hydrolysis of this ester (1·2 g.) with boiling 12% aqueous-methyl-alcoholic sodium hydroxide (25 c.c.) for 6 hours and subsequent acidification of the mixture gave *methoxy*nor*picrotic acid* (XIX, R = OMe), which separated from dilute alcohol in slender rods, m. p. 177°, and behaved as a monobasic acid on titration [Found: C, 65·0; H, 6·5; OMe, 11·4. $C_{14}H_{15}O_4(OMe)$ requires C, 64·8; H, 6·5; OMe, 11·2%]. On being boiled with excess of hydrazine hydrate for 10 hours, this compound was recovered unchanged quantitatively, m. p. and mixed m. p. 177°, after having been once crystallised from aqueous alcohol.

β-3-*Methyl*-6-*ethylanisoylpropionic Acid* (VIII).—A solution of 5-methyl-2-ethylanisole [9·5 g., prepared by methylation of 5-methyl-2-ethylphenol (von Auwers, *Annalen*, 1926, **447**, 178) with methyl sulphate and aqueous sodium hydroxide] and succinic anhydride (5·6 g.) in nitrobenzene (75 c.c.) was treated below 0° with powdered aluminium chloride (10·9 g., added in small portions), kept at room temperature for 70 hours, and poured on crushed ice (300 g.) and concentrated hydrochloric acid (15 c.c.). The mixture was extracted with ether (8 × 180 c.c.), the greater part of the ether evaporated, the residual solution (300 c.c.) repeatedly extracted with aqueous sodium bicarbonate (12 × 50 c.c.) and the combined extracts treated with charcoal, filtered, and acidified with hydrochloric acid. Recrystallised from light petroleum (b. p. 80—100°), the resulting *acid* (15 g.) formed colourless needles, m. p. 107°, readily soluble in alcohol or benzene [Found: C, 67·4; H, 7·3; OMe, 12·1. $C_{13}H_{15}O_3(OMe)$ requires C, 67·2; H, 7·2; OMe, 12·4%]. The *semicarbazone* separated from dilute methyl alcohol in slender prisms, m. p. 186° (Found: N, 13·7. $C_{15}H_{21}O_4N_3$ requires N, 13·9%).

γ-3-*Methyl*-6-*ethylanisylbutyric Acid* (IX).—A mixture of the foregoing keto-acid (13 g.) was boiled with 15% hydrochloric acid (250 c.c.), containing amalgamated zinc (80 g.), for 10 hours; concentrated hydrochloric acid (120 c.c.) was added in six portions at intervals of 1½ hours. On cooling, the hot filtered solution deposited the *acid* as a crystalline crust, which on recrystallisation from light petroleum (b. p. 60—80°) formed colourless plates (10 g.), m. p. 71·5°, readily soluble in alcohol or benzene [Found: C, 71·2; H, 8·6; OMe, 13·1. $C_{13}H_{17}O_3(OMe)$ requires C, 71·2; H, 8·5; OMe, 13·1%].

2-*Hydroxy*-4-*methyl*-1-*ethyl*-5 : 6 : 7 : 8-*tetrahydronaphthalene* (VI).—A mixture of the aforementioned γ-anisylbutyric acid (3 g.) and sulphuric acid (20 c.c., *d* 1·86) was kept at 80° for ½ hour, cooled, and poured into ice-water. The well-washed precipitate was triturated with aqueous sodium bicarbonate, washed, and crystallised from dilute methyl alcohol, giving 2-*methoxy*-4-*methyl*-1-*ethyl*-α-*tetralone* (X) in elongated prisms (2·6 g.), m. p. 75·5—76° [Found: OMe, 14·0. $C_{13}H_{13}O(OMe)$ requires OMe, 14·2%]. The *semicarbazone* separated from dilute alcohol in irregular prisms, m. p. 160° (Found: N, 15·3. $C_{15}H_{21}O_3N_3$ requires N, 15·3%).

Reduction of this tetralone (5 g.) with amalgamated zinc (60 g.) and 15% hydrochloric acid (160 c.c.) during 8 hours with the addition of concentrated hydrochloric acid (75 c.c. in five portions) during the reaction gave rise to the tetrahydronaphthalene methyl ether (XI), which was

obtained as a colourless oil, b. p. 128°/0·1 mm. A mixture of this material (2 g.), hydriodic acid (20 c.c.; *d* 1·7), and acetic anhydride (12·5 c.c.) was boiled (oil-bath at 138—140°) for 1 hour, cooled, and poured into 1% aqueous sodium bisulphite (150 c.c.). The product (1·7 g.), which separated, was recrystallised from light petroleum (b. p. 40—60°), giving the *tetrahydronaphthol* (VI) in elongated prisms, m. p. 67° (Found: C, 82·3; H, 9·3. $C_{13}H_{18}O$ requires C, 82·1; H, 9·5%).

β-2-*Methyl*-5-*ethylanisoylpropionic Acid* (XIII).—Methylation of 2-hydroxy-4-acetyltoluene (Morgan and Pettet, J., 1934, 420) (25 g.) with excess of methyl sulphate and 12·5% aqueous sodium hydroxide gave 2-methoxy-4-acetyltoluene (XII, R = Ac) as a mobile oil (21 g.), b. p. 132—133°/13 mm., which solidified on being kept for a long period and gave a *semicarbazone*, forming diamond-shaped plates, m. p. 205°, from alcohol (Found: N, 19·3. $C_{11}H_{15}O_2N_3$ requires N, 19·0%). Reduction of this ketone (9·2 g.) with amalgamated zinc (40 g.) and 15% hydrochloric acid (100 c.c.) with the addition of four portions of concentrated hydrochloric acid at intervals of 1½ hours gave 2-methoxy-4-ethyltoluene (XII, R = Et) as a mobile oil (7 g.), b. p. 91—93°/14 mm.

To a solution of 2-methoxy-4-ethyltoluene (12 g.) and succinic anhydride (7·1 g.) in nitrobenzene (90 c.c.), which had been kept for 1½ hours and then cooled to below 0°, powdered aluminium chloride (13·7 g.) was added in five portions in the course of 1 hour, and 80 hours later the reaction mixture was poured on ice (400 g.) and concentrated hydrochloric acid (15 c.c.). The product was isolated by extraction with ether (6 × 250 c.c.), the ethereal solution concentrated, the residual liquid (300 c.c.) extracted with aqueous sodium bicarbonate (12 × 50 c.c.), and the combined extracts treated with charcoal, filtered, and acidified with hydrochloric acid, giving a precipitate of β-2-*methyl*-5-*ethylanisoylpropionic acid* (XIII), which formed slender needles (16 g.), m. p. 129°, from dilute methyl alcohol [Found: C, 67·1; H, 7·4; OMe, 12·2. $C_{13}H_{15}O_3(OMe)$ requires C, 67·2; H, 7·2; OMe, 12·4%]. The *semicarbazone* of this keto-acid separated from ethyl acetate in elongated prisms, m. p. 183° (Found: N, 13·8. $C_{15}H_{21}O_4N_3$ requires N, 13·7%).

γ-2-*Methyl*-5-*ethylanisylbutyric acid* (13·5 g.) was prepared by reduction of the aforementioned keto-acid (14·5 g.) with amalgamated zinc (40 g.) and 15% hydrochloric acid (100 c.c.) during 7 hours with the addition of four portions of concentrated hydrochloric acid (10 c.c.) at intervals of 1½ hours and, on isolation, separated from light petroleum (b. p. 40—60°) in irregular prisms, m. p. 63°, soluble in alcohol or benzene and sparingly soluble in cold water [Found: C, 71·5; H, 8·5; OMe, 12·9. $C_{13}H_{17}O_2(OMe)$ requires C, 71·2; H, 8·5; OMe, 13·1%].

2-*Methoxy*-1-*methyl*-4-*ethyl*-α-*tetralone* (XIV).—Cyclisation of the foregoing acid (3 g.) with concentrated sulphuric acid at 65—70° for 15 minutes and addition of the cooled reaction mixture to ice-water (150 c.c.) gave a precipitate of the *tetralone*. The well-washed product (2·4 g.) was triturated with aqueous sodium bicarbonate for 24 hours, washed, and crystallised from dilute methyl alcohol, forming rectangular prisms, m. p. 64° after sintering at 60° [Found: C, 76·7; H, 8·4; OMe, 14·1. $C_{13}H_{15}O(OMe)$ requires C, 77·1; H, 8·3; OMe, 14·2%]. The *semicarbazone* separated from alcohol in long rectangular prisms, m. p. 208° (Found: N, 15·5. $C_{15}H_{21}O_2N_3$ requires N, 15·3%).

2-*Hydroxy*-1-*methyl*-4-*ethyl*-5 : 6 : 7 : 8-*tetrahydronaphthalene*.—Reduction of the tetralone (XIV) (4·8 g.) with amalgamated zinc (20 g.) and 15% hydrochloric acid (60 c.c.) during 8 hours with the further addition of concentrated acid (60 c.c.) gave the *methyl* ether (XV) of the tetrahydro-β-naphthol, which was treated with 2% aqueous sodium hydroxide to remove traces of alkali-soluble impurities and then purified by distillation in a vacuum, being obtained as a colourless oil (3·2 g.), b. p. 112—116°/0·1 mm. [Found: C, 82·0; H, 9·6; OMe, 15·0. $C_{13}H_{17}(OMe)$ requires C, 82·4; H, 9·8; OMe, 15·2%].

Demethylation of this ether (1·2 g.) was effected with boiling hydriodic acid (14 c.c.) and acetic anhydride (9 c.c.) during 40 minutes, and the resulting tetrahydronaphthol (V) precipitated by pouring the cooled reaction mixture into 1% aqueous bisulphite solution (150 c.c.). Recrystallised from a small volume of light petroleum (b. p. 40—60°), this compound formed slender prisms, m. p. 66·5°, identical in every way with a natural specimen (Found: C, 82·1; H, 9·6%). The *p*-nitrobenzoate separated from alcohol in irregular prisms, m. p. 85° (Found: N, 4·2%).

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UNIVERSITY OF LIVERPOOL. [*Received, March 23rd,* 1939.]