Picrotoxin and tutin. Part IX

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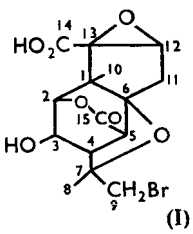
26. *Picrotoxin and Tutin. Part IX.**

By R. M. Carman, Ghulam Hassan, and R. B. Johns.

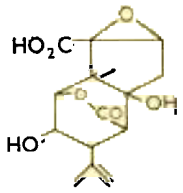
Evidence is presented which establishes the relative positions of the carboxylic acid, lactone, and secondary hydroxyl groups, and one point of attachment of the ether linkage, and the potential α-glycol unit in β-bromopicrotoxinic and α-picrotoxinic acid. These results confirm substantially Conroy's structure for picrotoxinin.

In recent papers,[1] plausible structures based on mechanistic and stereochemical arguments have been presented for picrotoxinin and its more important derivatives. Nevertheless, the evidence for the contentious aspect of picrotoxinin chemistry, *viz.*, the function and position of the ether-oxygen link, is still indirect rather than positive. Before our recent publication [2] there had been no confirmation of the relative position of any of the oxygen atoms within the molecule as the result of stepwise degradation. This paper describes further experiments of this nature which also have a direct bearing on the position of the ether function in picrotoxinin.

β-Bromopicrotoxinic acid is formed from β-bromopicrotoxinin under alkaline conditions by the irreversible opening of one lactone ring to give the carboxylic acid, together with a change of the remaining lactone from a five- to a six-membered system.[1] One hydroxyl group only is present in β-bromopicrotoxinic acid [1] and by oxidation with chromic acid in acetic acid [3] or, better, in acetone the corresponding keto-acid, showing no infrared hydroxyl absorption, is obtained in good yield. Conroy [1] has formulated β-bromopicrotoxinic acid and the reversibly related α-picrotoxinic acid as (I) and (II) respectively, the evidence being largely spectral and stereochemical; the position of the epoxide ring is the result of arguments of elimination rather than otherwise.



(I)



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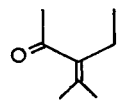

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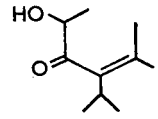


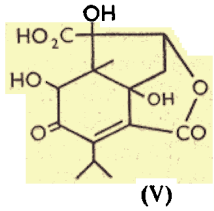
(IV)

Reduction [2] of β-bromopicrotoxinic acid with lithium aluminium hydride, followed by oxidation with periodate, giving a small-ring cyclic ketone and formaldehyde, suggests that the lactone giving rise to the carboxyl group is that shown in (I), and experiments with Grignard reagents on methyl β-bromopicrotoxinate, discussed more fully below, confirm our result. In agreement with Conroy,[4] we find that β-bromopicrotoxinic acid is recovered after treatment with lead tetra-acetate and consequently the hydroxyl group cannot be in an α-position to the carboxyl group. The retention of the ether linkage in both acids (I) and (II), on the basis of the available chemical evidence bearing directly on the functional groups of these compounds, seems reasonable. Debromination of oxo-β-bromopicrotoxinic acid, $C_{15}H_{15}O_7Br$, leads to the expected product, $C_{15}H_{16}O_7$, m. p. 219°, which, like α-picrotoxinic acid, is unstable to warm alkali, together with an alkali-stable acid, $C_{15}H_{18}O_8$, m. p. 251°. The acid of m. p. 219° shows infrared maxima 1764 cm.$^{-1}$ (lactone), 1732 cm.$^{-1}$ (CO_2H), 1708 and 1615 cm.$^{-1}$ (unsaturated ketone) and ultraviolet maxima at 260 and 340 mμ consistent with the presence of a fully substituted αβ-unsaturated ketone with the double bond exocyclic to the six-membered ring. These facts, together with the formation of acetone by ozonolysis, enable us partially to formulate the acid as (III).

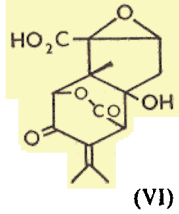
* Part VIII, *J.*, 1956, 4715.

The acid of m. p. 251° also showed light absorption typical of an αβ-unsaturated ketone (1745 cm.$^{-1}$, lactone), (1712 cm.$^{-1}$, CO_2H), (1675 and 1600 cm.$^{-1}$, unsaturated ketone). Ultraviolet maxima at 247 and 318 mμ are consistent with an endocyclic double bond and this is confirmed by the fact that no volatile product could be detected on ozonolysis. The higher-melting acid could be obtained from the lower-melting one in good yield under the usual conditions of debromination. The acid of m. p. 251° possesses reducing properties but is alkali-stable, a distinction from the acid of m. p. 219°, and, whilst the latter is stable to periodic acid, the former reacts with uptake of one equivalent. Disappearance of maxima associated with the αβ-unsaturated ketone in the infrared and the ultraviolet spectrum of the periodate product, isolated as the 2 : 4-dinitrophenylhydrazone, indicates periodate fission of the original acid to have involved the carbonyl group. This fact, taken in conjunction with its reducing properties, allows a partial formulation (IV) to be advanced for the acid, m. p. 251°; *i.e.*, it is an α-ketol. The hydrazone, $C_{21}H_{20}O_{11}N_4$, contains a molecule of water less than would be expected. It is probable that lactonisation with a suitably placed hydroxyl group has occurred, removing the carboxyl function generated by the periodate oxidation. (This is supported by the appearance of infrared bands at 1775 and 1725 cm.$^{-1}$.) The double bond in the acid, m. p. 219°, exocyclic to the six-membered ring establishes the position of the carbonyl group, and hence the secondary hydroxyl group at position 3 in both β-bromopicrotoxinic and α-picrotoxinic acid. Likewise the formation of an α-ketol confirms the presence of a further oxygen atom at position 2. (These two oxygen atoms presumably form the glycol system in picrotoxinindicarboxylic acid.) That this second oxygen atom is a potential hydroxyl group in the acid derivatives under discussion is clear from a consideration of the relation between the acids of m. p. 251° and 219°. In the bromopicrotoxinic acids, α-picrotoxinic acid, and the unsaturated ketonic acids the same lactone gives rise to the carboxyl function. From published evidence,[2] supported by further work described below, this is the 14-carbonyl group. In the acid of m. p. 251°, however, the δ-lactone has isomerised (the 1764 cm.$^{-1}$ lactone band in the acid of lower m. p. has been replaced by one at 1745 cm.$^{-1}$) and from stereochemical considerations of a system containing an endocyclic double bond, as in (IV), lactonisation between the 15-carbonyl and a 2-hydroxyl group is unlikely. Simultaneous formation of the α-ketol and isomerisation of the δ-lactone strongly suggests that it is this 2-hydroxyl group in β-bromopicrotoxinic acid which is free in the acid, m. p. 251°, and bound in the lactone systems of the acid, m. p. 219°, and α-picrotoxinic and β-bromopicrotoxinic acid. If this view is accepted and considered in conjunction with the carbon skeleton established by the formation of picrotoxadiene,[5] the δ-lactone system in these acids may be unequivocally placed within the molecules as in (I) and (II). The evidence outlined above establishes the relative positions in the six-membered ring of the potential glycol system, the *iso*propenyl substituent and the 15-lactone carbonyl group of β-bromopicrotoxinic acid and hence also of picrotoxinin itself.

The acids of m. p. 219° and m. p. 251° differ formally from each other by a molecule of water. It is tempting to suggest that in the latter the ether linkage has opened and a



(V)



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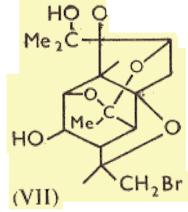
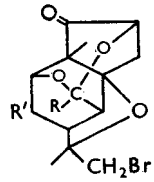


(VII)



(VIII)

relactonisation occurred to form (V) (on the basis of Conroy's structure for picrotoxinin); the acid of m. p. 219° would then be (VI). The position of the lactone in (V) is similar to that proposed by Conroy for *apo*picrotoxinic dilactone.[1] Like this compound, after

treatment with alkali, the acid (V) reacted with two equivalents of periodic acid, which is consistent with the view that in the corresponding diacid there is a glycol unit in addition to the original α-ketol system.

Grignard reagents may react with epoxides [6] in the manner: $>C\overset{O}{\text{---}}C< + RMgX \longrightarrow >C(OMgX)\cdot CR<$. The advantages of labelling one point of attachment with an alkyl radical are obvious, and in the hope of providing positive evidence for the presence and position of the oxiran ring methyl β-bromopicrotoxinate was treated with methylmagnesium iodide. The major product, $C_{18}H_{27}O_6Br$, showed only hydroxyl absorption in the infrared spectrum and formed a monoacetate which still had maxima in the hydroxyl region. The compound itself reacted cleanly with one equivalent of periodate under acidic or slightly basic conditions and with neutral lead tetra-acetate to give in good yield a product, $C_{15}H_{19}O_5Br$, possessing infrared (1767 $cm.^{-1}$) and ultraviolet (301 mμ) absorption maxima consistent with the presence of a five-membered ring ketone, together with acetone isolated in high yield as its 2 : 4-dinitrophenylhydrazone. This confirms the view [2] that it is the 14-carbonyl group of picrotoxinin which in β-bromopicrotoxinic and related acids is present as the carboxyl function. The ketone was unchanged by further treatment with periodate, did not form a benzylidene derivative under the usual conditions, and was recovered after treatment with selenium dioxide. From this it may be concluded that there is no methylene group α to the carbonyl function.

The formation of a mol. of acetone at varying pH's can occur only if in the Grignard product there is an actual, rather than a potential, hydroxyl group at position 13. The reaction of the methoxycarbonyl group to give the grouping $Me_2C(OH)\cdot C(OH)<$ necessary for the formation of acetone accounts for two of the three molecules of methane formally added to the original molecule. The remaining equivalent must have reacted with the lactone-carbonyl group since the infrared spectrum of the product showed no absorption in this region. Similarly, because of the absence of hydroxyl absorption in the spectrum of the monoacetate of the cyclic ketone, in which the 3-hydroxyl group is acetylated, the Grignard reagent could not have formed the expected hemiketal. The original lactone system, however, must remain essentially unchanged since there is no free 2-hydroxyl group. These facts are explained by assuming that a ketal rather than a hemiketal group has been generated, but such a system requires the presence in the molecule of a new ether linkage. The formation of a 13-hydroxyl group, reaction of the 15-lactone carbonyl group to give a ketal, and the presence of a substituted methylene group α to the cyclic ketone, find a plausible explanation on the basis of the opening of an oxiran ring in the manner postulated by Conroy [1] to account for the reduction with sodium borohydride of β-bromopicrotoxinic acid and accepted by Robertson [7] to account for the products of reduction of picrotoxinin by lithium aluminium hydride. These considerations provide important, but only indirect, evidence, for the position and function of the ether linkage. The Grignard product may accordingly be formulated as (VII) and the ketone as (VIII; R = Me, R′ = OH).

β-Bromopicrotoxinic acid with methylmagnesium iodide gives results similar to those described for the methyl ester. The only product, isolated in small yield, was a compound $C_{16}H_{21}O_7Br$. Its stability to periodic acid but ready oxidation with lead tetra-acetate to a cyclic ketone, identical with that obtained *via* the methyl ester, shows that the Grignard attack on the lactone had given rise to a 15-ketal and a 13-hydroxyl group. From these results we may conclude that in β-bromopicrotoxinic acid, in its methyl ester, and hence in picrotoxinin itself, there is an oxygen atom present in some ether function, of which one point of attachment is position 13.

Positive evidence for an oxygen attachment at position 12 would be obtained if the ketal group in (VIII; R = Me, R′ = OH) could be opened to give an α-ketol. Attempts to bring about partial or complete fission under a variety of conditions gave unchanged

ketone or intractable oils. It is probable that the stereochemical requirements of the oxygen bridge formed during bromination preclude a simple opening of the ketal under the conditions used. A comparison of the carbonyl absorptions of the various ketones described in this paper (see Table) emphasises the considerable steric strain and molecular rigidity inherent in the brominated structures. Both the infrared and the ultraviolet

Substance	Light absorption maxima: Ultraviolet (mμ)	Infrared (cm.$^{-1}$): Six-membered	Infrared (cm.$^{-1}$): Five-membered
β-Bromo-oxopicrotoxinic acid	316	1744	—
β-Bromopicrotoxinic acid + $LiAlH_4$ + HIO_4 [1]	302—305	—	1768
Acetate of above ketone [2]	—	—	1762
Methyl-β-bromopicrotoxinate + MeMgI + HIO_4	301	—	1767
Methyl-β-bromopicrotoxinate + MeMgI + HIO_4 + CrO_3	316	1749	1769
2 : 4-DNP of diketone above	—	1749	—
β-Bromopicrotoxinic acid + $LiAlH_4$ + HIO_4 debrominated	301—302	—	1753
Me_2 picrotoxinin dicarboxylate + CrO_3 [2] *	299	1699	—

[1] Part VIII, *J.*, 1956, 4715. [2] Carman, Johns, and Slater, unpublished work. * This is an α-hydroxy-ketone, which would account for a further small shift of the absorption maximum.

absorption maxima, although self-consistent, are considerably displaced from the range in which five- or six-membered ring ketones normally absorb. Consistent with this view is the return to lower frequencies in the debromination products or in structures such as picrotoxinindicarboxylic acid. Accordingly, debromination of the ketone was attempted, but owing to the small yield this approach was abandoned in favour of the debromination of the related ketone (VIII; R = H, R′ = OH) obtained by reduction of methyl β-bromopicrotoxinate with lithium aluminium hydride and subsequent treatment with periodate. This route gave a 25% yield of the desired compound which reacted with 0·5 mol. of periodic acid at room temperature in 24 hours, a result which could be explained by partial hydrolysis of the acetal under acid conditions.

Oxidation of the alcohol (VII) under acid conditions with chromic oxide in acetone [8] proved complex. The major product was a diketone $C_{15}H_{17}O_5Br$, also obtained from the monoketone (VIII; R = Me, R′ = OH) by further oxidation. Absorption in the infrared (1769 and 1749 cm.$^{-1}$) and the ultraviolet (316 mμ) region suggests that both five- and six-membered ring ketone groupings are present in the molecule, hence it is formulated as (VIII; R = Me, R′ = O). Two further ketones, whose analyses best fit formulæ $C_{17}H_{21}O_7Br$ (C:O absorption at 1741 cm.$^{-1}$ and 315 mμ; presumably six-membered ring) and $C_{18}H_{25}O_6Br$ (max. at 1755, 1732, and 1701 cm.$^{-1}$; 299 mμ), were also isolated. In both cases the poor yield precluded close investigation. Further experiments, which it is hoped will elucidate the nature of the substitution on the three remaining carbon atoms $C_{(6)}$, $C_{(11)}$, and $C_{(12)}$, are in progress.

Experimental

Oxidation of β-Bromopicrotoxinic Acid.—A solution of β-bromopicrotoxinic acid (1 g.) in acetone (3 ml.) was treated at <10° with an excess of a solution of chromic acid [8] (5 ml.) and kept overnight at room temperature, then diluted with water (100 ml.) and kept in a refrigerator for 4 hr. *β-Bromo-oxopicrotoxinic acid* crystallised (0·9 g.). Recrystallised from ethanol it had m. p. 173—174° (Found: C, 45·7; H, 4·1. $C_{15}H_{15}O_7Br$ requires C, 46·4; H, 4·1%). The ketone reduced Tollens's reagent immediately and ammoniacal silver nitrate more slowly. It had $\lambda_{max.}$ 316 mμ (log ε 1·63 in ethanol) and $\nu_{max.}$ (in Nujol) 3478 w, 2645 w, 1744 s, 1720 s, and 1622 w cm.$^{-1}$.

The methyl ester, prepared by means of ethereal diazomethane, had m. p. 151° (Sutter and Schlittler [3] give m. p. 151—152°).

Debromination of β-Bromo-oxopicrotoxinic Acid.—(*a*) To the acid (2 g.) in boiling 95% ethanol (40 ml.) were added ammonium chloride (0·4 g.), in water (2 ml.), and zinc dust (0·6 g.) in small quantities (three such total additions). The volume of solvent was kept constant and reaction restricted to 10—20 min. The excess of zinc was filtered off, the filtrate was reduced to dryness

in a vacuum and the residue treated with 2N-sulphuric acid (10 ml.) and kept at 0° for 3 hr., then filtered. The filtrate was continuously extracted with ether. The precipitate was extracted with hot absolute ethanol (4 × 20 ml.), the inorganic residue was rejected, and the combined filtrates were taken to dryness in a vacuum. Crystallisation of the resulting solid from water yielded a mixture (0·95 g.), m. p. 190°. The ether extract yielded further solid (0·06 g.). The combined solids on crystallisation from water yielded the *acid* (VI) in needles, m. p. 219° (Found: C, 59·1; H, 5·6. $C_{15}H_{16}O_7$ requires C, 58·4; H, 5·2%), $\lambda_{max.}$ 340 and 260 mμ (log ε 1·82 and 3·99 respectively in ethanol), $\nu_{max.}$ (in Nujol) 3542, 3397 m, 2730 vw, 2660 vw, 1764 s, 1732 s, 1708 s, 1644 w, 1615 cm.$^{-1}$. The acid did not decolorise bromine water quickly but gave a positive Baeyer's test and reduced Tollens's reagent immediately, but ammoniacal silver nitrate more slowly. Warm alkali gave a deep yellow colour. It did not react with periodic acid.

The *methyl ester*, prepared by treatment with diazomethane and sublimed, had m. p. 171° (Found: C, 60·3; H, 5·75. $C_{16}H_{18}O_7$ requires C, 59·6; H, 5·6%.)

(*b*) Debromination of the acid (2 g.) was carried out as in (*a*) but 5 additions of ammonium chloride–zinc dust were made and the time extended to at least 30 min. On working up after crystallisation from water, an acid crystallising in needles (0·63 g.), m. p. 251°, was obtained. The mother-liquors yielded the acid, m. p. 219° (0·1 g.). Ether extraction of the debromination mother-liquors gave a further yield (0·1 g.) of a mixture of both acids. The *acid*, m. p. 251°, was recrystallised from water for analysis (Found: C, 55·1, 55·0; H, 6·16, 5·9. $C_{15}H_{18}O_8$ requires C, 55·2; H, 5·6%). The acid (V) decolorises bromine-water immediately and gives a positive Baeyer's test. Tollens's reagent is immediately reduced but no colour is obtained by heating the acid with concentrated alkali. Neutral ferric chloride gives a deep yellow colour. The acid reacts with 0·9 and 1·4 equivalents of periodic acid after 2 and 24 hr. respectively. When the acid was boiled with an excess of sodium hydrogen carbonate solution and then allowed to react with an excess of sodium metaperiodate, the uptake after 22 and 51 hr. amounted to 1·1 and 2·7 equivalents respectively.

Conversion of Acid of M. p. 219° (VI) *into Acid of M. p.* 251° (V).—The acid (VI), m. p. 219° (0·22 g.), was treated with excess of ammonium chloride and zinc dust in a solution of ethanol as described in method (*b*) above. Working up in the same way and crystallisation from water gave an acid, m. p. 251° (0·19 g.), which showed no m. p. depression with the acid (V) obtained as above and possessed identical ultraviolet absorption.

Ozonolysis of Acid (VI).—The acid (VI), m. p. 219°, in ethyl acetate (5 ml.) in an ice–salt bath was treated with ozone–oxygen for 3 hr., by which time the ultraviolet spectrum showed one maximum only, at 285 mμ. The solvent was removed in a vacuum, the resultant glass dissolved in water, and air passed through it into a dilute aqueous solution of 2 : 4-dinitrophenylhydrazine hydrochloride for 1 hr. A yellow precipitate was obtained which after being collected and recrystallised showed no m. p. depression with a sample prepared from acetone. The ozonised product became yellowish-brown when kept, and under a variety of conditions on working up yielded only an intractable gum, $\lambda_{max.}$ 285 mμ.

Periodate Titration.—The acid (VI) (0·5 g.) was ozonised in ethyl acetate until oxidation was complete. The solvent was removed and the ozonide decomposed with water. 0·3M-Periodic acid (10 ml.) was then added and the solution made up to 25 ml. Carbon dioxide was given off for several hours. The amount of periodate consumed amounted to 0·86 and 1·24 equivalents after 2 and 20 hr. respectively. Working up gave intractable oils.

Periodate Oxidation of Acid (V) *of M. p.* 251°.—The acid (V) (0·3 g.) was dissolved in water (40 ml.), 0·3M-periodic acid (6 ml.) was added, and the solution kept for 2 hr. (iodine was liberated after 10 min.), then extracted with ether (4 × 30 ml.) and then continuously for 12 hr. The ether extracts were combined and washed with 10% sodium thiosulphate solution (5 ml.), dried ($MgSO_4$), and evaporated, to yield a straw-coloured gum (0·16 g.). This residue (0·1 g.), in ethanol (5 ml.), was treated with 2 : 4-dinitrophenylhydrazine (0·1 g.) in sulphuric acid (0·5 ml.) and aqueous ethanol (4·5 ml.) and was kept overnight. The orange-red *hydrazone* (0·065 g.) was filtered off and crystallised from ethanol in two forms; orange-yellow, m. p. 255°, and orange-red, m. p. 264° showing no mixed m. p. depression (Found: C, 49·7; H, 4·3; N, 10·0. $C_{21}H_{20}O_{11}N_4$ requires C, 50·0; H, 4·0; N, 11·1%), $\lambda_{max.}$ 363 and 285 mμ (log ε 4·29 and 3·45 respectively), $\lambda_{max.}$ 1775, 1725, 1624, 1595, and 1587 cm.$^{-1}$.

Methyl β-Bromopicrotoxinate and Methylmagnesium Iodide. Product (VII).—Methyl β-bromopicrotoxinate (0·025 mole) was extracted from a Bolton extractor into refluxing ethereal

methylmagnesium iodide (0·2 mole). Refluxing was continued for 1 hr. after extraction, and the complex then hydrolysed with ice (50 g.) and excess of 4N-sulphuric acid. Sodium hydrogen carbonate was added until the solution was neutral to litmus, the ether layer separated, and the aqueous phase extracted with ether (4 × 50 ml.) and then ethyl acetate (5 × 100 ml.). The combined extracts were dried (Na_2CO_3) and the solvent was removed to give a brown solid (85% yield) which crystallised from chloroform, ethanol, water, or, preferably, ethyl acetate, to give the *alcohol* (VII), prisms, m. p. 227° (Found: C, 50·7, 51·0, 51·2; H, 6·0, 6·4, 5·5; Br, 18·8. $C_{18}H_{27}O_6Br$ requires C, 51·5; H, 6·5; Br, 19·1%), $\lambda_{max.}$ 222 mμ (log ε 2·44), $\nu_{max.}$ (in Nujol) 3543 and 3227 m cm.$^{-1}$, giving negative unsaturation and reducing tests.

The alcohol (VII) (0·1 g.) was kept in pyridine (1 ml.)–acetic anhydride (2 ml.) at room temperature for 24 hr. Addition of water and removal of solvent afforded a gum which on repeated distillation (160°/0·01 mm.) gave a *monoacetate* as a colourless glass, m. p. 82° (Found: C, 51·6; H, 6·2; Br, 17·3. $C_{20}H_{29}O_7Br$ requires C, 52·05; H, 6·3; Br, 17·3%), stable to chromic acid in acetone, $\lambda_{max.}$ 220 mμ (log ε 2·42), $\nu_{max.}$ 3438, 1740 m, and 1700 (infl.) cm.$^{-1}$.

Where the Grignard complex was decomposed by a saturated solution of ammonium chloride, a brown gum was obtained from which, by counter-current distribution between water and ethyl acetate–ether (1 : 1), the alcohol (VII), m. p. 227°, was obtained as the major product and in a minor yield a *ketone*, m. p. 241° (needles from ethanol) (Found: C, 51·2; H, 5·7; Br, 20·2. $C_{17}H_{23}O_6Br$ requires C, 50·6; H, 5·7; Br, 19·8%), $\lambda_{max.}$ 220 and 290 mμ, $\nu_{max.}$ (in Nujol) 3462 s, 2650, 2320, and 1699 s cm.$^{-1}$.

Periodate Oxidation of the Alcohol (VII).—The alcohol (0·98 g.) was stirred in 0·5N-periodic acid (20 ml.) for 24 hr. at 20°. Air was bubled through the solution and passed into a saturated solution of 2 : 4-dinitrophenylhydrazine in N-sulphuric acid. The precipitated acetone dinitrophenylhydrazone (65% yield) had m. p. and mixed m. p. 125°. The reaction solution was extracted with ether (5 × 100 ml.), then ethyl acetate (4 × 100 ml.), and the combined extracts were distilled into a 2 : 4-dinitrophenylhydrazine solution to give a further 16% of acetone derivative. The residual *ketone* (VIII; R = Me, R′ = :O) (0·85 g.) crystallised as needles (from ethyl acetate), m. p. 223° (Found: C, 50·2; H, 5·2. $C_{15}H_{19}O_5Br$ requires C, 50·1; H, 5·3%), $\lambda_{max.}$ 223 and 301 mμ (log ε 2·36 and 1·52 respectively), $\nu_{max.}$ 3488 m and 1767 cm.$^{-1}$.

In a quantitative periodate oxidation the excess of periodic acid was determined in the usual manner by back-titration; 1·01 equivs. were consumed after 2·3 hr. and 1·19 equivs. after 24 hr. Oxidation with sodium periodate or lead tetra-acetate of the alcohol (VII) yielded the ketone, m. p. 223°, described above. The ketone was recovered after treatment with selenium dioxide, or with ethanolic benzaldehyde and sodium ethoxide. It was stable towards 0·2N-sulphuric acid at 100° but gave an intractable brown gum with 2N-acid at 100°. The *acetate*, prepared by reaction with acetic anhydride–pyridine and crystallised from water, had m. p. 144° (Found: C, 51·4; H, 5·0. $C_{17}H_{21}O_6Br$ requires C, 50·9; H, 5·3%), $\lambda_{max.}$ 223 and 300 mμ (log ε 2·32 and 1·48 respectively), $\nu_{max.}$ 1762 s and 1729 cm.$^{-1}$. The acetate (0·01 g.) and 2N-periodic acid (2 ml.) were kept for 15 hr. at room temperature; water (10 ml.) was added and the mixture was shaken with ether; the ether layer was distilled into a solution of 2 : 4-dinitrophenylhydrazine; this solution was then extracted with light petroleum (5 × 100 ml.) and the residue run on a chromatogram to give R_F 0·90 identical with that of acetone 2 : 4-dinitrophenylhydrazone under the same conditions (ether–light petroleum 1 : 19).

Chromic Acid Oxidation of the Ketone (VIII; R = Me, R′ = :O).—The ketone obtained as above (0·05 g.), in acetone (2 ml.), was mixed with chromic anhydride (0·02 g.) and 4N-sulphuric acid (1 ml.). After 24 hr. sodium sulphite solution in excess was added, and the solution extracted with ether. Evaporation of the extract gave a *diketone* (0·03 g.) which, recrystallised from aqueous ethanol, had m. p. 191° (Found: C, 50·25; H, 5·0; Br, 22·5. $C_{15}H_{17}O_5Br$ requires C, 50·4; H, 4·8; Br, 22·4%), $\lambda_{max.}$ 316 mμ (log ε 1·89), $\nu_{max.}$ 1769 m and 1749 m cm.$^{-1}$, stable to further periodic and chromic acid oxidation. The 2 : 4-*dinitrophenylhydrazone* crystallised as needles (from chloroform–ethanol), m. p. 267° (Found: C, 46·0; H, 3·4; Br, 14·9, 15·0; N, 10·1. $C_{21}H_{21}O_8N_4Br$ requires C, 46·9; H, 3·9; Br, 14·9; N, 10·4%).

Chromic Acid Oxidation of Alcohol (VII).—The alcohol (0·97 g.) in acetone (10 ml.) was kept overnight with chromic anhydride (0·5 g.) and 4N-sulphuric acid (5 ml.). An excess of sodium sulphite, in water (50 ml.), was added, and the aqueous solution extracted with ether. The extract was dried (Na_2SO_4), and evaporated. The residue, in ethanol, was passed down an alumina column and crystallised from ethanol–water, to yield the above diketone (0·42 g.), m. p. 191°. From the mother-liquors two further *ketones* were isolated. The first (0·09 g.),

obtained by repeated recrystallisation from aqueous ethanol, had m. p. 209° (Found: C, 48·5; H, 5·1; Br, 18·8. $C_{17}H_{21}O_7Br$ requires C, 48·9; H, 5·1; Br, 19·15. $C_{17}H_{23}O_7Br$ requires C, 48·7; H, 5·5; Br, 19·16%), $\lambda_{max.}$ 315 mμ (log ε 1·36), $\nu_{max.}$ 3608, 3518, 3408, 3318, and 1741 s cm.$^{-1}$, giving no iodoform reaction. The second ketone was obtained by repeated sublimation (150°/0·02 mm.) (about 10% yield) and had m. p. 230° (Found: C, 51·4; H, 5·7; Br, 19·7. $C_{18}H_{25}O_6Br$ requires C, 51·8; 6·0; Br, 19·15%), $\lambda_{max.}$ 299 mμ (log ε 1·72), $\nu_{max.}$ 3363 m, 1755 s, and 1701 s cm.$^{-1}$.

Debromination of Ketone (VIII; R = H, R′ = OH).—The ketone (0·5 g.), in water (10 ml.), was debrominated in the usual manner for 10 min. by zinc (0·3 g.) and ammonium chloride (0·3 g.). The colourless solution was filtered, acidified with 2N-sulphuric acid, and continuously extracted with ether. The debrominated *product* (0·2 g.) was purified by sublimation at 150°/0·02 mm. and crystallisation from water to m. p. 215—218° (Found: C, 63·4; H, 6·7. $C_{14}H_{18}O_5$ requires C, 63·1; H, 6·8%). The compound did not reduce ammoniacal silver nitrate, but decolorised bromine water and after 24 hr. at 18° with periodic acid had consumed 0·45 mole. It had $\lambda_{max.}$ 301 mμ (log ε 1·47) and $\nu_{max.}$ 3426 s and 1753 s cm.$^{-1}$.

β-*Bromopicrotoxinic Acid and Methylmagnesium Iodide*.—The acid (2·12 g. 0·005 mole) was extracted from a thimble into ethereal methylmagnesium iodide (0·05 mole). Refluxing was continued for a further hour after extraction, the mixture was cooled and hydrolysed with N-sulphuric acid (100 ml.), and the ether layer decanted. The aqueous layer was extracted first with ether (3 × 100 ml.) and then with ethyl acetate (3 × 100 ml.), and the combined extracts were reduced to dryness, yielding much iodine and an *acid* (0·05 g.), crystallising as needles, m. p. 215°, from water (Found: C, 47·05; H, 4·4. $C_{16}H_{21}O_7Br$ requires C, 47·4; H, 5·2%). The acid did not react with periodic acid.

Lead Tetra-acetate Oxidation.—The above acid (0·02 g.) and lead tetra-acetate (0·05 g.) were warmed together in glacial acetic acid (2 ml.) at 50° for 1 hr., then kept at room temperature overnight. Addition of water (30 ml.) and ether-extraction gave a yellow oil which on sublimation at 130°/0·02 mm. gave the ketone (VIII; R = Me, R′ = :O) (0·01 g.), m. p. and mixed m. p. 218°.

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VICTORIA UNIVERSITY OF WELLINGTON,
WELLINGTON, NEW ZEALAND.

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