[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF BRANDEIS UNIVERSITY]

Picrotoxin. III.[1] α-Picrotoxininic and Bromopicrotoxininic Acids; Apopicrotoxininic Dilactone

BY HAROLD CONROY

RECEIVED JULY 30, 1956

Arguments are presented allowing delineation of the structures of the α-picrotoxininic and bromopicrotoxininic acids, long known as degradation products of picrotoxinin. Evidence for their formulation as complex glycidic acids is drawn primarily from several remarkable transformations yielding the new derivatives designated as dihydro-β-bromopicrotoxininic acid and as apopicrotoxininic dilactone.

Although the structures of several important simpler degradation products of picrotoxinin have been elucidated, these have been formed in reactions sufficiently complex or drastic to make dubious any detailed structural correlation with the parent compound. The fundamental relationships among picrotoxinin, its bromination products and the picrotoxininic and bromopicrotoxininic acids as set forth in the figure were first studied by Meyer and Bruger[2] and by Horrmann.[3] Adduction of structure proof for these more intimately related but more complicated substances, and as well of picrotoxic acid,[4] Schlittler's "compound C"[5] and neopicrotoxinin,[6] is still desired.[7]

picrotoxinin, $C_{15}H_{16}O_6$

Br_2 ↓ ↑ Zn

α-bromopicrotoxinin, $C_{15}H_{15}O_6Br$ — β-bromopicrotoxinin, $C_{15}H_{15}O_6Br$

↓ OH^- — ↓ OH^-

α-bromopicrotoxininic acid $C_{15}H_{17}O_7Br$, monobasic — β-bromopicrotoxininic acid $C_{15}H_{17}O_7Br$, monobasic

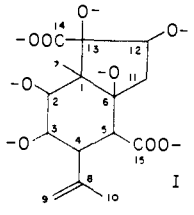
Zn ↓ ↑ Br_2

α-picrotoxininic acid, $C_{15}H_{18}O_7$, monobasic

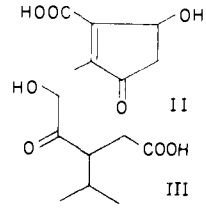
↓ H_2 — ↓ H^+

dihydro-α-picrotoxininic acid, $C_{15}H_{20}O_7$, monobasic — β-picrotoxininic acid, $C_{15}H_{18}O_7$, monobasic

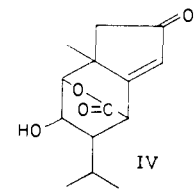
We have drawn the carbon–oxygen framework (I)[1] from three sets of degradation products: (a) picrotic acid, picrotonol and hydroxynorpicrotic acid[8]; (b) the alkaline cleavage products[9] (II and III); and (c) picrotoxinide[1] (IV), the product of pyrolysis of dihydro-α-picrotoxininic acid. The evidence for the functional groups present in picrotoxinin suggests that from the skeleton (I) must be constructed two lactone systems, one hydroxyl group and one ether linkage. The hydroxyl group appears to be tertiary, for picrotoxinin cannot be acetylated by usual procedures, nor can it be oxidized to any corresponding ketone; moreover this tertiary hydroxyl must be located within bonding distance of the isopropenyl group of I, because it participates in bromination[10,1] and is no longer present in the bromopicrotoxinins.[11] The skeleton (I) contains two oxygens (*i.e.*, at C-6 and C-13) which might qualify as the hydroxyl, and that at C-6 could well, configurations permitting, be expected to bridge to the double bond on bromination. The mechanism of the consecutive dealdolizations[1] leading to the formation of the Schlittler cleavage products (II and III)[9] requires that the C-6 oxygen be not bound in a stable oxide bridge in the compounds which do undergo the cleavage, and



I



II III



IV

(1) The previous articles in this series appear in THIS JOURNAL, **74**, 491 (1952); **74**, 3046 (1952).

(2) R. J. Meyer and P. Bruger, *Ber.*, **31**, 2985 (1898).

(3) P. Horrmann, *ibid.*, **45**, 2090 (1912); **46**, 2793 (1913).

(4) P. Horrmann, *Ann.*, **411**, 273 (1916).

(5) M. Sutter and E. Schlittler, *Helv. Chim. Acta*, **33**, 902 (1950).

(6) D. Mercer and A. Robertson, *J. Chem. Soc.*, 288 (1936); S. N. Slater, *ibid.*, 806 (1949); S. N. Slater and A. T. Wilson, *Nature*, **167**, 324 (1951).

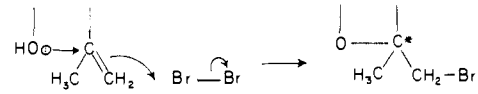
(7) In a brief preliminary report [H. Conroy, THIS JOURNAL, **73**, 1889 (1951)] structures for picrotoxinin, α-picrotoxininic acid and picrotoxic acid were proposed on the basis of the very limited evidence then available. The problems of the structures of picrotoxinin and picrotoxic acid will be treated subsequently.

(8) F. Angelico, *Gazz. chim. ital.*, **41**, ii, 337 (1911); A. Oglialoro, *ibid.*, **21**, ii, 213 (1891); J. C. Harland and A. Robertson, *J. Chem. Soc.*, 937 (1939); D. Mercer, A. Robertson and R. S. Cahn, *ibid.*, 997 (1935).

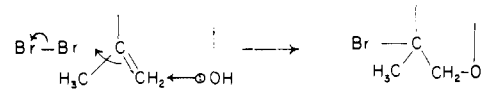
(9) M. Sutter and E. Schlittler, *Helv. Chim. Acta*, **30**, 403 (1947); *ibid.*, **30**, 2102 (1947); *ibid.*, **32**, 1855 (1949); *ibid.*, **32**, 1860 (1949).

(10) R. W. H. O'Donnel, A. Robertson and J. C. Harland, *J. Chem. Soc.*, 1261 (1939).

(11) The bromopicrotoxinins contain a new β-bromoether linkage. The fact that two compounds are formed was interpreted on the basis that a new asymmetric center is introduced:

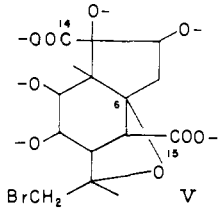


An alternative explanation would lie that one of the bromo derivatives is formed as given above while the other arises from addition in the reverse sense, as shown:



There seems to be no evidence whatsoever at present to decide between these possibilities; the particular bromoether system portrayed in this paper as representing the "β" series is chosen arbitrarily.

since in contrast to these the bromopicrotoxinins and the bromopicrotoxininic acids do not undergo such cleavage, we consider the tempting hypothesis that it is the C-6 oxygen which is the free hydroxyl in picrotoxinin and the same C-6 oxygen which appears as part of the β-bromoether system in the brominated derivatives. As the first step in the development of a working model for the bromopicrotoxininic acids we write V.

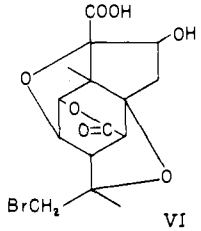


V

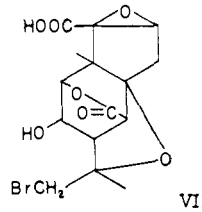
The picrotoxininic acids appear to contain one lactone function in addition to the carboxylic acid group. Since it is C-14 which is lost as carbon dioxide in the formation of picrotoxinide (IV), we must assign C-14 to the carboxylic acid group and C-15 to the lactone carbonyl in dihydro-α-picrotoxininic acid.[12] The lactone band near 1755 cm.$^{-1}$ (5.70 μ) in the infrared spectrum of α-picrotoxininic acid and the similar peaks given by dihydro-α-picrotoxininic acid and β-bromopicrotoxininic acid[13] suggest that this lactone system is not five-membered and moreover that it is constituted identically to the transannular δ-lactone in picrotoxinide.

β-Bromopicrotoxininic acid contains, in addition to the carboxyl, one free hydroxyl group. This would be expected from its composition, which corresponds to a chemical hydrate of the bromopicrotoxinin (which has no hydroxyl); furthermore the bromoacid gave a monoacetylated acid with acetic anhydride and pyridine. With thionyl chloride the acetyl-β-bromopicrotoxininic acid was converted to a crystalline acid chloride of the expected composition whose infrared spectrum shows no hydroxyl absorption. The alcoholic hydroxyl group of β-bromopicrotoxininic acid is secondary,[5] since chromic acid oxidation gave a ketone $C_{15}H_{15}O_7Br$, which had undergone no skeletal change for it was convertible by reduction to dihydro-α-picrotoxininic acid; the acetylated acid was found stable to chromic acid.[5]

Incorporation of these deductions into the working model allows, with the reservations of footnote 11, only two possibilities: the formal representations (VI and VII). Aside from the comment



VI



VII

that VI is sterically badly strained, if not impossible we may reject it on other grounds. β-Bromopicrotoxininic acid, containing only one alcoholic hydroxyl, would not be expected to react with periodate, and it does not. But when the bromoacid was warmed with an excess of dilute alkali and the mixture subsequently neutralized, the resulting solution reacted readily with periodate (*vide infra*). The system HO–C–C–O–CO– postulated in VII, which could hydrolyze to a free vicinal glycol, is consistent with the observation, but any structure, as VI, containing an alkali-stable oxide bridge at once blocking *both* of the two pairs of vicinal oxygen atoms of I is excluded.

Thus the constitution of β-bromopicrotoxininic acid implied in VII can be deduced by a reasonable and orderly argument; nevertheless the argument as given is somewhat involved, and it requires a number of incompletely proved assumptions, the negation of any one of which might radically alter the outcome. The oxirane grouping occurs in natural products so exceedingly rarely that its proposal merits exceptional concern. Worse yet, in fact the substance is markedly resistant to acid hydrolysis,[14] a property which can hardly be said to support the proposed structure. Nowhere in the extensive literature describing picrotoxinin and its degradation products is there to be found a pair of compounds clearly appearing to bear, one to another, the simple relationship of epoxide and vicinal glycol. These facts have formed a basis

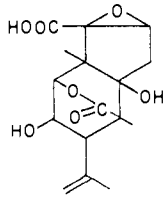
(12) The alternative proposition that C-14 is present in a lactone ring in dihydro-α-picrotoxininic acid would, with the loss of carbon dioxide, require the elimination from the skeleton of an oxygen atom which actually is not eliminated. In the formation of picrotoxinide the oxygen atoms at C-6 and at C-13 are lost, but neither of these can be involved with C-14 in the lactone ring of dihydro-α-picrotoxininic acid; C-13 would then require the absurd formulation of an α-lactone while the conceivable γ-lactone involving C-6, inconsistent as it is with the above working hypothesis that the C-6 oxygen is part of the β-bromoether system in the bromopicrotoxininic acids and hence should be present as a free tertiary hydroxyl in α-picrotoxininic acid, is excluded by the infrared data.[1]

(13) β-Bromopicrotoxininic acid is dimorphous and the infrared spectra of the two forms in the solid state (potassium bromide disks) are very different. The form obtained by crystallization from a more dilute aqueous solution in the cold gave broad carbonyl bands at 1742 and 1705 cm.$^{-1}$. The form obtained by crystallization from a hot concentrated solution showed sharp absorption at 1769 and 1745 cm.$^{-1}$. It is believed that the 1742 band in the first and the 1745 band in the second are associated with the δ-lactone, while the 1705 and 1769 bands represent the carboxyl group in greater and lesser states of hydrogen bonding, respectively. This view is in accord with the known wide variation in carbonyl stretching frequency of carboxylic acids, with the value of 1770 cm.$^{-1}$ reported [R. S. Rasmussen in "Progress in the Chemistry of Organic Natural Products," Vol. V, Springer Verlag, Vienna, 1948] due to the free monomeric carboxyl group in the gas phase or in very dilute solution; it is supported here by the presence of a sharp carboxyl OH band at 3360 cm.$^{-1}$ in addition to that of the alcohol at 3510 cm.$^{-1}$ in the latter polymorph while the former substance gives a single 3510 band and the weak, broad and indistinct absorption (2700–3300 cm.$^{-1}$) typical of the associated carboxyl.

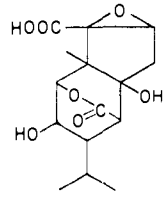
(14) The compound can be recovered from long standing with concentrated hydrochloric acid in the cold, while it resists the action of hot dilute hydrochloric acid saturated with magnesium chloride, a reagent known to be particularly efficacious at cleavage of oxirane systems. It is however reported [J. Sielisch, *Ber.*, **45**, 2563 (1912)] that a "chlorobromopicrotoxininic acid," $C_{15}H_{15}O_7BrCl$, is formed by the prolonged action of boiling concentrated hydrochloric acid. The observation would be immediately significant were it not for the vigorous conditions involved which may have led to deep seated changes. Nevertheless we have been able to repeat the preparation of chlorobromopicrotoxininic acid and find its properties to coincide with those reported; while further study is needed definitely to assign a structure, the possibility that the substance is simply the expected chlorohydrin is not excluded.

for serious criticism leveled by the New Zealand group.[15] However, it is believed that this seeming inconsistency will find explanation in the evidence to be presented. The likelihood of fantastic differences in behavior between isolated functions in simple molecules and similar groups held within bonding distances in complex, rigid, caged systems is not to be underestimated.

The constitutions of α-picrotoxininic acid and its dihydro derivative are represented by VIII and IX, respectively; hence the formation of picrotoxinide (IV) from IX is viewed as the thermal de-



VIII



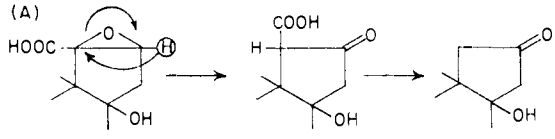
IX

composition of a glycidic acid to a ketone and carbon dioxide, followed by the loss of the elements of water from the resulting β-hydroxyketone.[16] The structures are consistent with the lack of reactivity toward periodate shown by those compounds and with the obtention of the cleavage products (II and III)[5,9] from IX with dilute alkali by the mechanism shown (IX → II → III).

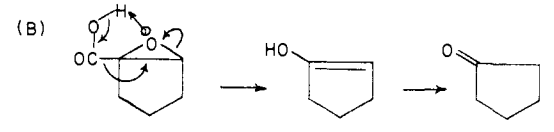
We turn now to a stereochemical description of β-bromopicrotoxininic acid. It was concluded[1] from the behavior of tetrahydrodesoxypicrotoxinide in elimination reactions that the C-3 hydroxyl group is *trans* to the isopropyl in that substance. The possibility of inversion at centers 3 or 4 during the several transformations seems remote, so that we write the C-3 hydroxyl as *trans* to the β-bromo-

(15) J. C. Benstead, H. V. Brewerton, J. R. Fletcher, M. Martin-Smith, S. N. Slater and A. T. Wilson, *J. Chem. Soc.*, 1042 (1952).

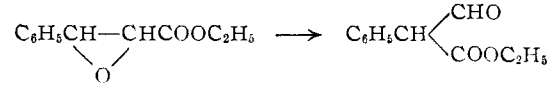
(16) This glycidic acid decarboxylation gives the uncommon result that the carbonyl group of the product ketone is situated beta to the original carboxyl, not, as usual, alpha. The mechanism A could involve prior rearrangement of the epoxide to a β-ketoacid, with hydrogen migration, followed by decarboxylation of the β-ketoacid; the preference for this process over the more common mechanism B leading to the α-ketone would arise from the fact that the stereoelectronic requirements (the desirability of a *trans*-coplanar orientation

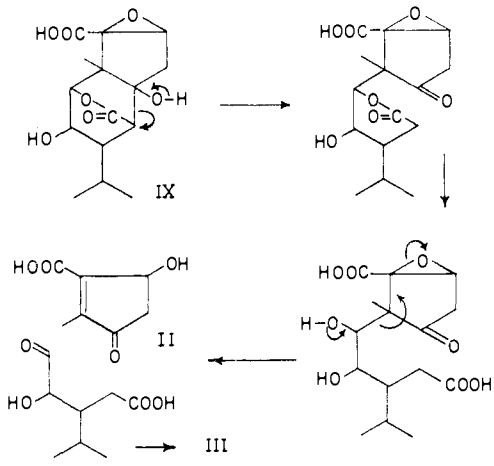


of eliminated groups, etc.) of this decarboxylation–elimination (B) seem to be poorly met at best. Subtle influences might lead to its abdication and here operation of mechanism B would require the in-



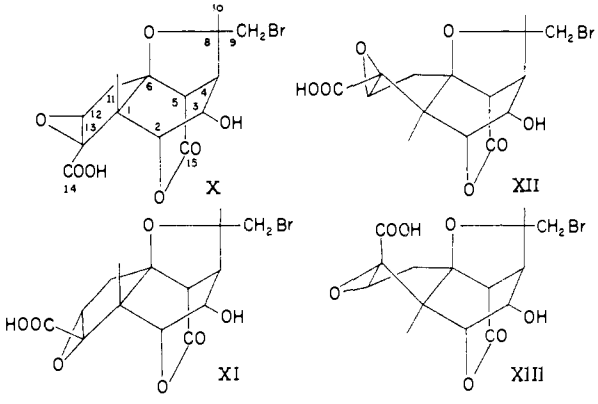
clusion of a double bond in the five-membered ring while (A) allows the formation of the more favorable exocyclic carbonyl bond in the rate-determining step. Apparently no analogous glycidic acids have been studied, but at least one glycidic *ester* [Tiffeneau and Levy, *Anales soc. quim. argentina*, **16**, 144 (1928); *C. A.*, **24**, 2450 (1930)] is reported to rearrange on heating to give a β-dicarbonyl system





IX II III

ether bridge in VII. The transannular –O–CO– chain in VII must be *trans* to the β-bromoether bridge because the alternative configuration is sterically impossible. The relative configurations at centers 2,3,4,5 and 6 are thereby established, and since the oxirane must be *cis* locked, we need consider only the four diastereoisomeric structures (X, XI, XII and XIII). The two (XII and XIII) which have the cyclopentane ring *trans* fused

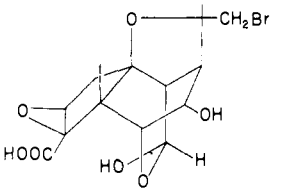


X XII XI XIII

to the rigid oxabicyclo[2.2.2]octanone are badly distorted, but they should not be dismissed on this ground; the others (X and XI) are essentially free of angle strain, except of course for the epoxide. Evidence to be discussed that certain related compounds contain a stable γ-lactone in which C-14 and the C-2 oxygen become bonded will allow a choice; these atoms can become close only when centers 1 and 13 have the configurations implied in X. That stereoisomer is proposed as an hypothesis, satisfactory to this point, upon which to base discussion of the remaining reactions and properties of β-bromopicrotoxininic acid.

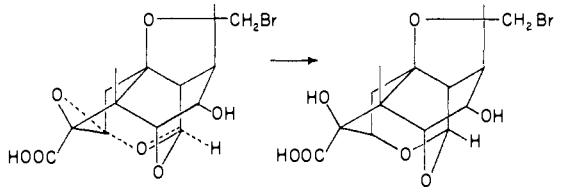
The expression (X) is in fact fully equipped to explain the remarkable stability of the epoxide toward acid hydrolysis. An imaginary line drawn through the oxirane oxygen, bisecting the three-membered ring and extended beyond by a length of about *two angstroms* would intersect the line of centers of the lactone carbonyl groups. The necessity of rearward attack, or at least rearward solvation, in epoxide ring opening is now well recognized, while here the caged structure makes backside approach of an external nucleophile a near impossibility.

But it will develop that this lactone bridge which is so effective at preventing external attack, when properly transformed can, by virtue of its proximity to the rear face of C-12, act as a powerful intramolecular displacing agent in itself. β-Bromopicrotoxininic acid was treated with a large excess of aqueous sodium borohydride at room temperature; from the ensuing slow reaction there was isolated in good yield a nicely crystalline substance whose analysis indicated the number of hydrogen atoms to have been increased by two. This dihydro-β-bromopicrotoxininic acid, which was indeed found to be still acidic, gave an infrared spectrum containing a single, very sharp carbonyl band at 1736 cm.$^{-1}$ (5.76 μ), which can be due only to the carboxylic acid group. (The starting bromoacid gives a split peak,[13] associated with both lactone and carboxyl functions; clearly the lactone has disappeared.) We reject the simple hypothesis of the hemiacetal[17] XIV, implying, as it does, easy reversion to an aldehyde and vicinal glycol, for the substance gave no 2,4-dinitrophenylhydrazone, no Tollens test and would not react with periodic acid or lead tetraacetate under any normal conditions. Instead we regard dihydro-β-bromopicrotoxininic



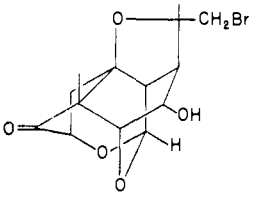
XIV

acid as XV, formed by a concerted, geometrically expedient process wherein the carbonyl accepts a hydride ion while simultaneously the carbonyl oxygen employs its accumulating charge for rearward displacement of the oxirane linkage



XV

In support of the formulation XV it was found that dihydro-β-bromopicrotoxininic acid readily gave a diacetate, where β-bromopicrotoxininic acid gives only a monoacetate. And in spite of the negative lead tetraacetate result with this α-hydroxyacid, lead dioxide–acetic acid mixture caused rapid and quantitative oxidation of XV to carbon dioxide and a C_{14}-ketone (XVI). Under the same conditions, β-bromopicrotoxininic acid did not react with lead dioxide.[18] The C_{14}-ketone absorbed in the infrared at 3470 cm.$^{-1}$ (2.88 μ) and 1770 cm.$^{-1}$ (5.65 μ) and in the ultraviolet at a λ_{max} 302 mμ (ε 34) and was characterized by its 2,4-dinitrophenylhydrazone, which showed no carbonyl band in the infrared, and its monoacetate, which showed no hydroxyl absorption but peaks at 1760 cm.$^{-1}$ (5.68 μ) and 1746 cm.$^{-1}$ (5.73 μ). The 1770 cm.$^{-1}$ ketone band is somewhat higher than that (1745 cm.$^{-1}$) taken as typical for cyclopentanones, but the shift is easily accounted for on the basis either of the polarity of the α-substituted group or of the small additional strain imposed by fusion in the pentacyclic system. The structure



XVI

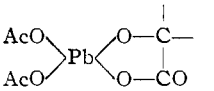
XVI contains no methylene adjacent to the carbonyl; accordingly the ketone was recovered from attempts to form an α-benzylidene derivative under conditions equivalent to or more vigorous than those succeeding in the preparation of dibenzylidenedihydropicrotoxinide.[1] The acetate of XVI was also obtained in another way, by pyrolysis of the diacetate of XV, when acetic acid and carbon monoxide were formed.

These results, whereby it is shown that in a single transformation addition to the C-15 carbonyl is linked with the production of an α-hydroxyacid, i.e., the appearance of a new hydroxyl at C-13, are viewed as compelling evidence not only for the general propriety of the glycidic acid formulation but as well for the geometry expressed in X; establishment of a new bridge joining C-12 and C-15 would have been out of the question with the other stereoisomers (XI, XII and XIII).

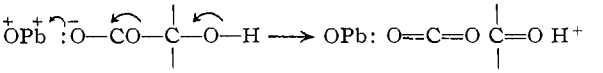
A somewhat similar example was uncovered in a study of the hydrolysis of β-bromopicrotoxininic acid. As mentioned, the acid itself does not react with periodate, but when it is at first heated with excess dilute potassium hydroxide, the resulting solution, after neutralization, does react with the eventual consumption of *three* equivalents of periodate. The bromoacid is clearly changed to some other species by hot alkali, even though it can be recovered from its solution in excess *cold* base and despite the report[15] drawn from conductimetric

(17) For analogies to the sodium borohydride reduction of lactone to hemiacetal see M. L. Wolfrom and H. B. Wood, THIS JOURNAL, **73**, 2933 (1951); M. L. Wolfrom and K. Anno, *ibid.*, **74**, 5583 (1952).

(18) The startling difference in behavior of XV with lead tetraacetate compared to lead dioxide–acetic acid requires comment. Lead tetraacetate did actually react with XV but only under the special circumstance that enough water was added to the acetic acid medium to cause a brown coloration and virtual precipitation of lead dioxide, when it was obvious that lead tetraacetate is not the reactive species. If we accept the idea, in analogy to the glycol cleavage reaction, that normal lead tetraacetate oxidation of α-hydroxyacids proceeds through a covalently bonded five-membered cyclic intermediate containing a tetravalent, tetrahedral lead atom in the ring



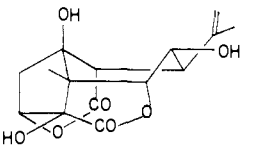
then it is clear that the formation of such an intermediate from XV would suffer serious steric interference by the adjacent quaternary carbon and its attached groups. The relative ease of the lead dioxide oxidation here lends support to the non-occurrence of a cyclic intermediate with lead dioxide; the following simple decomposition of the Pb^{IV} salt would have minimal steric requirements



titrations that this acid is cleanly monobasic. Except for a small trace of unchanged β-bromopicrotoxininic acid, we have been unable to isolate any crystalline products directly from the neutralized alkali degradation mixtures, the substance(s) in question having been obtained only as a water-miscible sirup. However, when the solution was subjected to the zinc and ammonium chloride debromination (a reaction used previously for the conversions of bromopicrotoxinin to picrotoxinin and β-bromopicrotoxininic acid to α-picrotoxininic acid), there was isolated in good yield a sparingly soluble, remarkably well crystallized and high melting solid. It gives analyses corresponding to $C_{15}H_{18}O_7$, so it is isomeric with α-picrotoxininic acid or contains the elements of one molecule of water more than picrotoxinin, *but it is not acidic.* The substance will dissolve in strong alkali and is precipitated unchanged upon acidification. It is insoluble in sodium bicarbonate solution in the cold. We designate this substance "apopicrotoxininic dilactone" in accord with its infrared spectrum indicating two sharp carbonyl peaks at 1792 cm.$^{-1}$ (5.58 μ) and 1724 cm.$^{-1}$ (5.80 μ) as well as a weak band at 1642 cm.$^{-1}$ (6.09 μ) for the isopropenyl group.

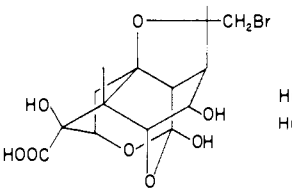
The presence of the isopropenyl group was further shown by catalytic hydrogenation; the dihydroapopicrotoxininic dilactone, m.p. 325°, gave a spectrum similar in the carbonyl region, but lacking the 1642 cm.$^{-1}$ band. Dihydroapopicrotoxininic dilactone was acetylated readily with acetic anhydride and pyridine, and the acetate still absorbed strongly in the hydroxyl region of the infrared, indicating the presence of *at least* two differently situated hydroxyls in the original apopicrotoxininic dilactone. No two of the hydroxyls are vicinal, however, since the dilactone does not react with periodate.[19]

No reasonable alternative to structure XVII fits the properties described and at the same time meets

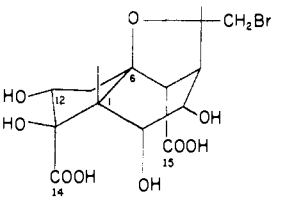


XVII

those stereochemical requirements we can impose through knowledge of the configurational assignment of β-bromopicrotoxininic acid. The initial attack of hydroxide ion upon X, by direct analogy to the addition of hydride, would be expected to give the ortho acid XVIII which unlike its counterpart XV would be susceptible to further attack by



XVIII



XIX

base ultimately to give the salt of the tetrahydroxydiacid XIX. The difficulty in isolation of crystalline XIX is not surprising in view of its expected very high water solubility; XIX contains two different vicinal glycol systems, one of which upon periodate cleavage would yield an α-ketoacid, so the uptake of exactly three equivalents of periodate by this solution is readily understandable.[19] Upon zinc debromination of XIX the β-bromoether linkage is broken and the resulting pentahydroxydiacid reverts to the dilactone XVII.

This interpretation raises questions concerning the relative stabilities of the various lactone systems. The facts insist that the dilactone system is formed only after the debromination, for if the neutralized alkali degradation mixture actually contained a stable brominated dilactone, this should be isolable (*vide infra*); moreover, the solution would presumably not have reacted with periodate since XVII does not react as such. But the dilactone system of XVII is stable enough to form spontaneously, and the compound is precipitated unchanged upon acidification of its solution in alkali. We propose a conformational argument in explanation of this remarkable influence of the bromoether bridge upon the lactones: In the stable conformation XIX it would be reasonable to expect closure of the γ-lactone of XVII, but when this occurs the C-12 hydroxyl is locked quasi-equatorial on the five-membered ring and cannot move into the quasi-axial orientation required for cyclization of the second lactone. Such motion would force the C-14 carbonyl into the quasi-equatorial configuration and badly distort the γ-lactone already present. However upon debromination, when the isopropyl group is no longer bonded through oxygen to C-6, a new *boat* form for the cyclohexane ring becomes possible, as in XVII; this must be comparatively very favorable because now both the bulky isopropenyl group and the angular methyl group can be equatorial while the heavily substituted, hitherto eclipsed centers, C-1 and C-6, have become staggered. It is apparent from a study of the model that if this new *boat* form is maintained, then the C-12 oxygen and the C-15 carbonyl are held rigidly together at the bonding distance and in such wise that both lactones can become properly coplanar.

There can be drawn from this two predictions subject to experimental proof: (i) Reformation of the β-bromoether bridge by bromination of XVII with its equatorial isopropenyl group should be exceptionally difficult, and (ii) the bromoapopicrotoxininic dilactone, if obtained, should be un-

(19) That is, apopicrotoxininic dilactone does not react with periodate in neutral or weakly acidic solution, under which conditions both lactone rings are preserved. An experiment designed to test the reactivity of the corresponding tetrahydroxy-acid or pentahydroxy-diacid to periodate gave the expected positive result. The solution obtained when the dilactone was heated in aqueous sodium bicarbonate took up 1.8 equivalents of periodate after 16 hr. at 25° or 3.7 equivalents after 38 hr. at 25°. We may anticipate the uptake of one equivalent for each of the two potential vicinal glycol systems in XVII; the product of these cleavages would be an α-ketoacid, which would account for the third equivalent. The fragment remaining, a hydroxytrialdehydo-diacid, would be likely to undergo further changes, *e.g.*, dealdolization, which could result in the formation of α-formylpropionic acid. The latter, in analogy to the behavior of acetoacetic acid [C. F. Huebner, S. R. Ames and E. C. Bubl, THIS JOURNAL, **68**, 1621 (1946)], should take up a further considerable number of equivalents of periodate

stable to hydrolysis. Both were confirmed. While the brominations of picrotoxinin and of α-picrotoxininic acid in acetic acid solution occur nearly instantaneously at 25°, under corresponding conditions XVII required 1 hr. for full decolorization of an equivalent amount of bromine, and in acetic acid even at 100° the reaction took several minutes: moreover, from various runs three separate, non-isomeric products were isolated, in complete contrast to the clean course usually taken. The constitutions of two of these are still under study but one appears to contain an acetoxyl group while the other gives analytical figures corresponding either to a polybromide or to a monobromide with loss of carbon. The third compound, formed in only 24% yield, appears to be the true bromoapopicrotoxininic dilactone. It gave lactone bands in the infrared at 1792 cm.$^{-1}$ (5.58 μ) and 1739 cm.$^{-1}$ (5.75 μ); the shift of the latter upward from 1724 cm.$^{-1}$ as in XVII is not inconsistent with the additional strain implied and finally, as anticipated, this bromodilactone gradually dissolved in hot water to give an acidic solution, which upon subsequent treatment with periodate, consumed 2.8 equivalents thereof after 16 hr.[20]

We have put forth unequivocal evidence that an ether bridge in the picrotoxininic acids occurs no longer in the apopicrotoxininic dilactones; the transition, *i.e.*, the simple fact of an oxide ring easily opened by internal attack, even in itself provides substantial support for the oxirane formulation.

Acknowledgment.—We wish to thank Mr. Harry Morrison, Mr. Ira Levine and Miss Harriet Thurman for technical assistance and S. B. Penick & Co. for generous gifts of picrotoxin.

Experimental[21]

β-Bromopicrotoxininic Acid.—The compound was prepared[2,3] by the action of hot alkali on bromopicrotoxinin. It was recrystallized from methanol–water in the cold and had m.p. 247° dec. It was dried *in vacuo* for analysis.

Anal. Calcd. for $C_{15}H_{17}O_7Br$: C, 46.29; H, 4.41; Br, 20.53. Found: C, 46.63; H, 4.77; Br, 20.49.

Infrared spectrum: 3484(m), 2941(m), 1742(s), 1705(s), 1431(m), 1387(m), 1314(w), 1292(w), 1248(m), 1236(sh), 1211(m), 1185(sh), 1148(w), 1134(w), 1125(w), 1098(w), 1065(sh), 1040(vs), 1020(m), 970(m), 952(w), 926(m), 916(m), 882(m), 857(w), 824(m), 774(w), 724(m), 703(w), 690(sh), 683(m), 647(w).

The other crystal form, obtained by hot evaporation of a saturated aqueous solution, had m.p. 245–247° dec.

Infrared spectrum: 3510(m), 3360(m), 2963(w), 2923(w), 1769(vs), 1745(vs), 1461(w), 1435(sh), 1424(m), 1388(m), 1348(m), 1330(m), 1309(w), 1294(w), 1260(m), 1229(m), 1213(m), 1160(w), 1141(m), 1129(m), 1090(m), 1059(m), 1033(s), 1024(s), 978(w), 964(m), 935(m), 928(sh), 908(w), 902(m), 887(m), 829(m), 815(w), 785(m), 750(w), 737(m), 722(m), 700(m), 666(m).

Periodate Determination.—A sample (0.1798 g.) of the compound was dissolved in 10 ml. of water containing 0.5 ml. of acetic acid and 1.0 g. of sodium acetate trihydrate. The solution was stirred with potassium metaperiodate (0.2226 g.) for 20 hr. at 25°. The unreacted periodate was titrated by the arsenite method and the periodate uptake was calculated to be 0.0 ± 2% of one equivalent. Similar experiments in which the acetic acid or the sodium acetate or both were omitted gave identical results with zero periodate uptake.

Periodate Determination on the Alkaline Hydrolysis Solution.—A sample (0.1839 g.) of β-bromopicrotoxininic acid was boiled for ten minutes with a solution of 300 mg. of sodium hydroxide in 10.0 ml. of water. The solution was brought to the *p*H 5 by dropwise addition of acetic acid. Potassium metaperiodate (0.4271 g.) was added and the suspension was stirred for 20 hr. at 25°. After titration the periodate uptake was found to be 2.98 ± 0.02 equivalents.

Acetyl-β-bromopicrotoxininic Acid.—Fifteen grams of β-bromopicrotoxininic acid, m.p. 247° dec., 30 ml. of acetic anhydride and 30 ml. of pyridine were mixed and allowed to stand 24 hr. The mixture was poured into ice and the clear, colorless solution was acidified with 2.5 *N* hydrochloric acid; the product, precipitated in crystalline condition, was filtered, washed with cold water and dried at 50°. The yield was 15.11 g. (91%). An additional 0.50 g. (3%) of crystalline material was obtained by ether extraction of the filtrate. The combined material was recrystallized from acetone–petroleum ether; a first crop yield of 12.84 g. (77%), m.p. 250–252° dec. with gas evolution, was obtained. For analysis samples were recrystallized from acetone–petroleum ether; the m.p.'s were unchanged.[22]

Anal. Calcd. for $C_{17}H_{19}O_8Br$: C, 47.34; H, 4.44; Br, 18.53. Found: C, 47.49, 47.15; H, 4.52, 4.57; Br, 19.71, 18.62.

Infrared spectrum: 3425(sh), 3236(s), 2994(w), 1763(sh), 1747(vs), 1730(sh), 1462(w), 1429(s), 1381(s), 1370(s), 1323(m), 1302(s), 1276(sh), 1259(vs), 1243(s), 1230(s), 1189(s), 1152(m), 1122(w), 1096(m), 1037(vs), 1002(w), 987(w), 973(w), 941(w), 926(w), 911(w), 886(w), 879(w), 870(w), 826(s), 776(w), 747(w), 741(w), 724(m), 675(s), 653(w).

Acetyl-β-bromopicrotoxininic Acid Chloride.—A suspension of recrystallized acetyl-β-bromopicrotoxininic acid in 25 ml. of thionyl chloride and 50 ml. of benzene was refluxed for 3 hr., the solid dissolving in the course of this time. The solvent was removed under reduced pressure, the residue taken up in 40 ml. of benzene and this was removed. The solid residue was dissolved in 20 ml. of hot benzene, 30 ml. of petroleum ether was added, when crystallization commenced. The first crop yield was 10.93 g. (87.5%) of material with the m.p. 170–171°. For analysis a sample was recrystallized from ethyl acetate–petroleum ether; the m.p. was unchanged.

Anal. Calcd. for $C_{17}H_{18}O_7BrCl$: C, 45.40; H, 4.03; Br, 17.77; Cl, 7.88. Found: C, 45.34; H, 4.36; 17.40 mg. of sample gave 12.85 mg. of mixed silver halides. On the assumption that Br:Cl = 1, this corresponds to Br, 17.83; Cl, 7.91.

Infrared spectrum: 2985(w), 2933(w), 1786(vs), 1754(vs), 1445(m), 1383(m), 1372(m), 1323(w), 1300(m), 1285(w), 1272(m), 1232(vs), 1203(s), 1151(m), 1139(m), 1110(w), 1098(m), 1041(vs), 1032(sh), 991(w), 975(w), 939(w), 923(sh), 912(m), 880(m), 856(w), 829(m), 820(sh), 804(s), 750(w), 726(m), 713(w), 685(m), 678(m), 656(w).

Dihydro-β-bromopicrotoxininic Acid (XV).—β-Bromopicrotoxininic acid (2.09 g.) was added in portions to a solution of 3.0 g. of sodium borohydride in 40 ml. of water with stirring at 0°. The clear solution, evolving hydrogen, was allowed to stand at 25° for 20 hr.; 6 *N* hydrochloric acid was added until the mixture was acidic (*p*H 2) when the product began to precipitate. The suspension was stirred at 0° for 1 hr., the solid was centrifuged and washed with several 10-ml. portions of water. The product was recrystallized by hot evaporation of its solution in 250 ml. of boiling water; the crystals were removed when the volume had decreased

(20) It might have been expected that an alternative and direct preparation of apopicrotoxininic dilactone would be the result of alkaline hydrolysis of α-picrotoxininic acid in a way similar to that described with the bromoacid; because the C-6 hydroxyl is free in α-picrotoxininic acid extensive dealdolization intervenes (*vide supra*). Nevertheless a similar transformation has been observed in other circumstances; a compound found to be identical with dihydroapopicrotoxininic dilactone was isolated in significant amount from the *acidic* aqueous mother liquor obtained in a preparative catalytic hydrogenation of α-picrotoxininic acid to its dihydro derivative.

(21) All melting points are corrected. Infrared spectra were determined with a Perkin–Elmer model 21 double beam recording spectrophotometer upon potassium bromide disks unless otherwise noted; strong, medium and weak bands and prominent shoulders are reported, very weak bands and indistinct shoulders are in general omitted. Analysis was done by Dr. S. M. Nagy and associates of the Massachusetts Institute of Technology.

(22) Sutter and Schlittler reported dec. 232–233° (ref. 5).

to about 20 ml. The yield was 1.51 g. (73%) of nicely crystalline material which had no well defined m.p. but which gradually darkened and sintered in decomposition in the range 225–250°. For analysis a sample was recrystallized from hot water.

Anal. Calcd. for $C_{15}H_{19}O_7Br$: C, 46.05; H, 4.90; Br, 20.43. Found: C, 46.22; H, 5.18; Br, 20.91. Calcd. for $C_{15}H_{21}O_7Br$: C, 45.81; H, 5.38; Br, 20.32.

Infrared spectrum: 3367(s), 2985(m), 2941(sh), 1736(vs), 1458(m), 1418(w), 1387(s), 1377(sh), 1353(m), 1340(m), 1333(sh), 1305(m), 1282(m), 1253(m), 1229(m), 1209(m), 1200(m), 1188(m), 1157(s), 1140(w), 1119(s), 1096(m), 1073(w), 1033(vs), 1025(sh), 1010(vs), 988(m), 968(m), 954(s), 900(w), 879(w), 865(m), 838(s), 834(s), 814(m), 722(w), 707(w), 698(s), 673(m).

Periodate Determination.—A sample (0.1277 g.) of the compound was dissolved in 5.0 ml. of hot acetic acid; the solution was cooled and 4.00 ml. of 0.312 *N* sodium metaperiodate solution was added. After standing at 25° for 25 hr. the unreacted periodate was titrated. The periodate uptake was calculated to be 1.2 ± 2% of one equivalent, *i.e.*, zero within experimental error.

2,4-Dinitrophenylhydrazine Reaction.—The compound (52 mg.) was refluxed with 30 mg. of 2,4-dinitrophenylhydrazine and four drops of concentrated sulfuric acid in 5 ml. of ethanol for 1 hr. There was no evidence of hydrazone formation and about 40 mg. of unchanged starting material was recovered by filtration.

Diacetyldihydro-β-bromopicrotoxininic Acid.—Dihydro-β-bromopicrotoxininic acid (57 mg.) was added to 1.0 ml. of acetic anhydride and 0.5 ml. of pyridine. The mixture was allowed to stand at 25° for three days with occasional stirring; the initially insoluble starting material dissolved in the course of this time. The volatile components were evaporated at 100° under a nitrogen stream. The colorless sirup was taken up in 6 ml. of hot water, crystalline material being obtained on cooling. A recrystallization from hot water gave needles, m.p. 244–246° dec. with gas evolution.

Anal. Calcd. for $C_{17}H_{21}O_8Br$ (monoacetate): C, 47.12; H, 4.89; Br, 18.45. Calcd. for $C_{19}H_{23}O_9Br$ (diacetate): C, 48.01; H, 4.88; Br, 16.82. Found: C, 47.99; H, 5.03; Br, 17.58.

Infrared spectrum: 3289(m), 2976(w), 2941(sh), 1742(vs), 1715(s), 1451(m), 1389(m), 1368(m), 1292(w), 1277(m), 1259(vs), 1244(vs), 1215(m), 1205(m), 1182(m), 1163(m), 1127(m), 1096(w), 1064(w), 1052(m), 1029(s), 1010(vs), 965(m), 950(m), 916(w), 888(w), 875(w), 838(m), 805(m), 789(w), 747(w), 718(w), 696(w), 673(w), 645(m).

Pyrolysis.—The nearly colorless residue remaining when a small sample of the diacetate was heated at 250° until the gas evolution ceased was found by infrared spectroscopic examination to be identical with the monoacetate of the C_{14}-ketone (*vide infra*). The liquid distillate from this pyrolysis was identified by odor as acetic acid.

Lead Dioxide Oxidation of Dihydro-β-bromopicrotoxininic Acid. The C_{14}-Ketone.—Dihydro-β-bromopicrotoxininic acid (1.03 g.) and 1.0 g. of lead dioxide (commercial reagent grade, assay 91.4%) were suspended in 7.0 ml. of glacial acetic acid. The mixture was heated at 100° for about 45 minutes with occasional stirring, when the carbon dioxide evolution had ceased and the white solid had dissolved. The excess lead dioxide was centrifuged and washed with small portions of acetic acid, and the clear, straw-colored liquid was evaporated to dryness under a stream of nitrogen. The solid residue was taken up in water (6 ml.) and the mixture was extracted with five 4-ml. portions of ethyl acetate. The extract was washed with water and evaporated under a stream of nitrogen. The crystalline residue was recrystallized from a supersaturated solution in 5.0 ml. of ethyl acetate. The first crop yield of white needles, m.p. 200.0–201.2°, was 643 mg. A second crop (185 mg.) had the m.p. 199–200°; the total yield was 91%. For analysis a sample was recrystallized twice more from ethyl acetate–ether and gave colorless needles, m.p. 201.6–202.1°.

Anal. Calcd. for $C_{14}H_{17}O_8Br$: C, 48.71; H, 4.97; Br, 23.15. Found: C, 48.66; H, 5.13; Br, 25.12.

Infrared spectrum: 3472(m), 2959(m), 1770(vs), 1456(m), 1410(m), 1385(m), 1376(m), 1362(m), 1332(w), 1280(sh), 1271(m), 1245(m), 1220(sh), 1214(s), 1172(w), 1148(m), 1119(s), 1111(s), 1082(m), 1053(m), 1041(vs), 1028(m), 998(s), 993(sh), 962(s), 943(w), 935(m), 905(m), 845(w), 826(s), 795(m), 697(w), 681(w), 658(w); ultraviolet spectrum: λ_{max} 302 mμ (ε 34) in ethanol.

The 2,4-dinitrophenylhydrazone was prepared from 26.1 mg. of the ketone, 66 mg. of 2,4-dinitrophenylhydrazine and four drops of sulfuric acid in 5 ml. of ethanol with a 1 hr. reflux period. The derivative was recrystallized once from dioxane–water and once again from hot glacial acetic acid. It formed golden leaflets, m.p. 287° dec.

Anal. Calcd. for $C_{20}H_{21}O_8N_4Br$: C, 45.72; H, 4.03; N, 10.67. Found: C, 46.23; H, 4.60; N, 10.60.

Infrared spectrum: 3484(m), 3325(w), 2941(w), 1623(vs), 1595(s), 1531(sh), 1522(m), 1490(m), 1447(w), 1418(m), 1393(w), 1377(w), 1339(s), 1312(s), 1280(m), 1241(w), 1215(w), 1175(w), 1152(m), 1131(m), 1115(m), 1086(m), 1043(s), 1033(s), 990(m), 959(m), 936(m), 920(w), 906(m), 854(w), 836(m), 821(m), 798(w), 743(m), 706(w), 688(w), 670(w).

The monoacetate was prepared as follows: The ketone (44.3 mg.) was dissolved in a mixture of 0.5 ml. of acetic anhydride and 0.5 ml. of pyridine; the solution was allowed to stand at 25° for 24 hr. The excess volatile reagents were removed by evaporation with a stream of nitrogen and finally in a high vacuum. The residue weighed 49.7 mg.; the calculated weight for a monoacetate is 49.5 mg. The residue was recrystallized from ethyl acetate (1 ml.) and petroleum ether (1 ml.) mixture. The yield of colorless needles was 37.2 mg. A second recrystallization from the same solvent pair gave needles with the m.p. 204.2–205.0°.

Anal. Calcd. for $C_{16}H_{19}O_8Br$: C, 49.62; H, 4.95. Found: C, 49.48; H, 5.20.

Infrared spectrum: 2950(w), 1760(vs), 1746(vs), 1449(m), 1383(m), 1370(sh), 1340(w), 1295(w), 1271(m), 1233(vs), 1220(vs), 1189(w), 1170(w), 1147(m), 1122(w), 1110(m), 1095(w), 1079(w), 1048(s), 1033(s), 1024(sh), 1005(s), 996(m), 971(sh), 960(m), 948(sh), 936(w), 925(w), 907(w), 881(w), 849(w), 824(s), 794(w), 714(w), 694(w), 671(w).

The infrared spectrum in chloroform contained carbonyl bands at 1773(vs) and 1748(vs); it showed no hydroxyl absorption.

Apopicrotoxininic Dilactone.—β-Bromopicrotoxininic acid (10.1 g.) was dissolved in a solution of 6.2 g. of potassium hydroxide in 40 ml. of water; the solution was heated at 100° for 1 hr. and, without cooling, 10.0 ml. of acetic acid was added, followed by 5.0 g. of ammonium chloride and a total of 15 g. of zinc dust in small portions. The mixture was heated for another 10 minutes, when crystals of the dilactone began to appear. The zinc was removed and washed with 15–20 ml. of hot acetic acid. The volume of the combined solution and extract was made up to 110 ml. with hot water. Crystallization was completed when the suspension was kept overnight in the refrigerator. The first crop yield of white needles, m.p. 302–303° dec., was 3.0 g. The filtrate and water washings were combined, concentrated and treated with another 5 g. of zinc dust in case debromination had been incomplete. After removal of the zinc the second crop of dilactone amounted to 0.3 g.; the total yield was 3.3 g. or 41%. For analysis a sample was recrystallized from acetone–water and consisted of needles, m.p. 305° slight dec.

Anal. Calcd. for $C_{15}H_{18}O_7$: C, 58.06; H, 5.85. Found: C, 57.74; H, 5.70.

Infrared spectrum: 3390(s), 3333(s), 3155(m), 2950(sh), 1792(vs), 1724(vs), 1642(w), 1451(w), 1366(m), 1335(w), 1311(w), 1271(m), 1244(s), 1192(m), 1160(vs), 1119(m), 1094(m), 1071(m), 1047(m), 1037(m), 1020(s), 997(m), 974(w), 921(w), 906(s), 860(w), 821(w), 800(w), 757(w), 745(w).

Periodate Determination.—A sample (141.8 mg.) of apopicrotoxininic dilactone was dissolved in a boiling mixture of 10 ml. of acetic acid and 3 ml. of water. The solution was diluted to 35 ml. with cold water, and potassium metaperiodate (0.4399 g.) was added. The suspension was stirred at 25° for 24 hr. After arsenite titration the periodate uptake was calculated to be 0.03 ± 0.02 equivalent.

Periodate Determination of Hydrolysis Solution.—A suspension of 0.1263 g. of apopicrotoxininic dilactone in 10 ml. of water containing 100 mg. of sodium bicarbonate was heated for 0.5 hr. when the solid had dissolved. To the cooled solution was added 321.3 mg. of potassium metaperiodate, and the mixture was stirred for 16 hr. at 25°; titration established an uptake of 1.79 ± 0.02 equivalents.

A similar experiment where the initial heating with dilute bicarbonate was for 1 hr. and the solution was allowed to stand with periodate for 38 hr. indicated a periodate uptake of 3.70 ± 0.02 equivalents.

Dihydroapopicrotoxininic Dilactone. (A) By Hydrogenation of Apopicrotoxininic Dilactone.—One gram of apopicrotoxininic dilactone was hydrogenated in the presence of platinum oxide (50 mg.) at atmospheric pressure. Hydrogen absorption slowed down rapidly, because of the separation of solid product upon the catalyst, but began again when the solution was heated to near the b.p.; absorption stopped after the uptake of 80.7 ml. (at 28°). The calculated volume for one equivalent is 79.6 ml. Enough hot acetone to dissolve the dihydrodilactone was added, the catalyst was removed by filtration, and the solvent was evaporated. The residue was recrystallized from acetone–ether; the first crop yield was 0.750 g. (75%). For analysis a sample was recrystallized from acetone–water and again from methanol–water. It formed short needles, m.p. 325°.

Anal. Calcd. for $C_{15}H_{20}O_7$: C, 57.68; H, 6.46. Found: C, 57.41; H, 6.11.

Infrared spectrum (Nujol mull): 3450(s), 3350(s), 2900(vs), 1780(s), 1727(s), 1450(vs), 1372(s), 1326(w), 1304(w), 1295(w), 1277(m), 1258(m), 1242(m), 1212(w), 1179(sh), 1164(s), 1142(w), 1124(w), 1097(m), 1066(m), 1045(s), 1032(w), 1017(s), 998(w), 979(w), 964(m), 939(w), 914(m), 898(m), 870(w), 846(w), 827(w), 794(w), 752(w), 734(w), 721(w).

The acetate was prepared with excess acetic anhydride and pyridine, as given in the other examples. It was recrystallized from ethanol and formed leaflets, m.p. 330–331° dec. Because the calculated figures are so close, it is unfortunately not possible to distinguish between a mono- or diacetate from the analysis.

Anal. Calcd. for $C_{17}H_{22}O_8$ (monoacetate): C, 57.62; H, 6.26. Calcd. for $C_{19}H_{24}O_9$ (diacetate): C, 57.57; H, 6.10. Found: C, 57.33; H, 6.18.

Infrared spectrum: 3412(m), 2967(w), 1795(vs), 1748(vs), 1723(vs), 1468(w), 1431(w), 1377(m), 1368(m), 1314(w), 1261(vs), 1235(vs), 1220(sh), 1185(w), 1152(w), 1142(m), 1106(w), 1098(m), 1062(m), 1031(s), 1007(w), 921(m), 867(w), 852(w), 826(w).

Dihydroapopicrotoxininic Dilactone. (B) **Isolation from Dihydro-α-picrotoxininic Acid Mother Liquor.**—α-Picrotoxininic acid (10.3 g.) dissolved in 350 ml. of acetic acid containing 1.0 ml. of concentrated hydrochloric acid was hydrogenated in the presence of platinum oxide at atmospheric pressure. The required volume (800 ml.) of hydrogen was absorbed in about 2 hr. The solution was heated until clear, the catalyst was removed by filtration and the filtrate evaporated under reduced pressure. The residue was recrystallized from aqueous acetic acid; the yield of crystalline dihydro-α-picrotoxininic acid was highly variable but was usually in the neighborhood of 3 to 5 g., even though upon occasion none at all could be isolated. The mother liquor, from which it was usually not possible to recover additional dihydro-α-picrotoxininic acid, a sirup being obtained, was set aside. In one run, when the sirup had aged nearly four months, long needles of a sparingly soluble neutral compound separated, which upon recrystallization from ethanol and comparison with mixed m.p. and infrared spectra was found to be identical with the dihydroapopicrotoxininic dilactone prepared by method A.

Bromoapopicrotoxininic Dilactone.—A solution (8.17 ml.) of bromine in acetic acid containing 30.0 mg. of bromine per ml. was added to 475 mg. of apopicrotoxininic dilactone. The suspension was stirred and heated rapidly to 100°; the bromine was decolorized in several minutes. The suspension was cooled and centrifuged immediately. The solid obtained was washed three times with 4-ml. portions of petroleum ether. It weighed 144 mg. (24%) after it was dried *in vacuo* at 25°. The solid was recrystallized for analysis from acetone–petroleum ether; it gave dec. 228–230°.

Anal. Calcd. for $C_{15}H_{17}O_7Br$: C, 46.29; H, 4.41; Br, 20.53. Found: C, 46.06; H, 4.59; Br, 21.67.

Infrared spectrum: 3448(s), 3356(s), 3257(s), 2976(w), 2933(w), 1792(vs), 1739(vs), 1647(vw), 1453(m), 1414(m), 1377(w), 1355(m), 1316(sh), 1304(w), 1280(m), 1267(m), 1241(m), 1222(sh), 1212(m), 1189(m), 1161(s), 1117(m), 1100(m), 1085(m), 1071(m), 1056(w), 1043(m), 1017(s), 1000(m), 986(w), 968(w), 943(w), 928(sh), 923(m), 913(w), 895(w), 856(w), 797(w), 713(w), 705(w), 675(w).

WALTHAM, MASS.

[CONTRIBUTION NO. 1390 FROM STERLING CHEMISTRY LABORATORY, YALE UNIVERSITY]

Chromate Esters. III. Mechanism of Oxidation of 2-Methylfenchol and 1-Methyl-α-fenchene[1]

BY HAROLD H. ZEISS[2] AND FRANCES R. ZWANZIG

RECEIVED AUGUST 24, 1956

Kinetic and ultraviolet evidence are combined with product analysis to show that chromic anhydride oxidation of 2-methylfenchol in acetic acid involves the formation of chromate ester and that the oxidation of the dehydration products of 2-methylfenchyl alcohol, 1-methylcamphene and 1-methyl-α-fenchene, does not, although both reactions lead to the same products. Oxidation of hitherto unknown pure 1-methyl-α-fenchene, obtained by pyrolysis of camphane-2-carbinyl acetate, gives camphor containing little of the rearranged ketonic product, α-fenchone. It is proposed that the oxidation of 2-methylfenchol and 1-methyl-α-fenchene by hexavalent chromium proceeds through a tetravalent chromium intermediate.

In the preceding papers of this series[3] the preparation and reactions of tertiary chromate esters have been discussed, and the proposal of a common oxidation intermediate in the chromic acid oxidation of a tertiary alcohol and its corresponding olefin was made. This hypothesis was based on the experimental fact that 2-methylfenchol and the mixture of its dehydration products, 1-methylcamphene and 1-methyl-α-fenchene, were oxidized in acetic acid to the same products, *i.e.*, camphor, fenchone and a mixture of C_{12}-acids. We wish now to present further evidence for this postulate and for the identity of the oxidation intermediate.

The rate of decomposition of di-2-methylfenchyl chromate (II) was measured in absolute methanol at 25 and at 50° and in 80% aqueous methanol, anhydrous acetic acid and 90% acetic acid at 25°. In all cases first-order kinetic results were obtained (Table I). Regardless of solvent the ultraviolet spectrum of the ester exhibited two distinct maxima, one at 287 mμ and the other at 393 mμ; and strictly comparable rate constants were obtained from data (decrease in optical density) taken at

(1) This work was supported in part by Contract No. DA-19-059-ORD-1494 between the Office of Ordnance Research, U. S. Army, and Yale University. Taken from the doctoral dissertation of F. R. Zwanzig, Yale University, 1955, and published in part as a Communication, *Chemistry & Industry*, 545 (1956).

(2) Monsanto Chemical Co., Dayton 7, Ohio.

(3) (a) Paper I, THIS JOURNAL, **78**, 1694 (1956); (b) paper II, **78**, 3182 (1956).