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THE TOTAL SYNTHESIS OF RESERPINE*

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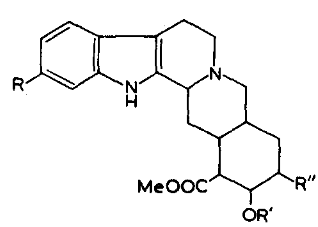
FOR centuries, the Indian snake-root, *Rauwolfia serpentina* Benth., has enjoyed a favorable reputation in its habitat as a valuable medicinal agent. The problem of defining the scope of its utility in terms of modern Western medical standards was complicated by the fact that the plant produces a very large number of closely related alkaloids, of which those present in larger relative measure are not those with the more interesting physiological properties.[1] Only five years ago, Schlittler first isolated reserpine, and demonstrated that this new alkaloid was largely responsible for the hypotensive activity associated with crude *Rauwolfia* extracts.[2] This discovery, and the remarkable effect which reserpine was subsequently found to exert upon the central nervous system, rapidly won for the alkaloid an important place in the treatment of hypertensive, nervous, and mental disorders.

Schlittler and his colleagues took structural studies in hand at once, and were soon able to propose for reserpine the structure (I : R = MeO, R′ = Me, R″ = 3,4,5-$(MeO)_3C_6H_2COO$).[3] Thus, it was early clear that reserpine is a member of the



I

great alkaloidal group of which yohimbine (I : R = R′ = R″ = H) is the prototype and oldest known member. There remained a stereochemical problem of no mean dimensions, and in view of the stereochemical abandon with which Nature has constructed the members of the yohimbine group—at least eight stereoisomers of yohimbine itself have so far been isolated from natural sources[1d]—few clues were at hand. But by summer of 1955, the Ciba group, and a number of independent investigators as well, had completed a series of elegant investigations which permitted the

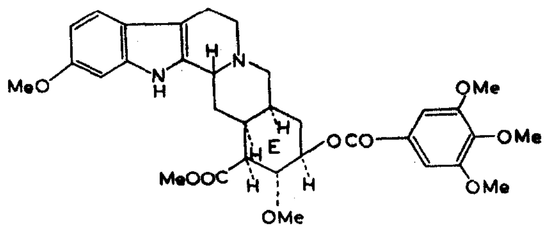
* For preliminary communications, see *J. Amer. Chem. Soc.* **78**, 2023, 2657 (1956).

[1a] A. Chatterjee *Fortschr. Chem. Org. Naturst.* **10**, 390 (1953); [b] A. Chatterjee, S. C. Pakrashi and G. Werner *Ibid.* **13**, 346 (1956); [c] E. Schlittler, J. A. Schneider and A. J. Plummer, *Angew. Chem.* **66**, 386 (1954); [d] J. E. Saxton, *Quart. Rev. Chem. Soc.* **10**, 128 (1956).

[2] J. M. Müller, E. Schlittler and H. J. Bein *Experientia* **8**, 338 (1952).

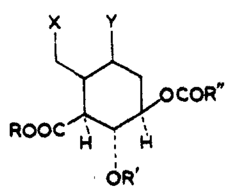
[3a] L. Dorfman, C. F. Huebner, H. B. MacPhillamy, E. Schlittler and A. F. St. André *Experientia* **9**, 368 (1953); [b] L. Dorfman, A. Furlenmeier, C. F. Huebner, R. Lucas, H. B. MacPhillamy, J. M. Mueller, E. Schlittler, R. Schwyzer and A. F. St. André *Helv. Chim. Acta* **37**, 59 (1954).

elaboration of the full structure (II) for reserpine.[4] The stage was now set for rational synthetic efforts.

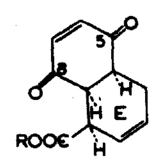


II

From the first, we looked upon the synthesis of reserpine as an exercise in stereochemistry. It will be noted that Ring E of the alkaloid is the site of an unusually heavy concentration of asymmetry. Indeed, five of the six asymmetric carbon atoms present are there disposed in a single consecutive chain. Consequently, it was our design to construct first an assemblage of the type (III), with the five groups attached



III



IV

to the single *cyclo*hexane ring suitably chosen in respect to function, and properly oriented.

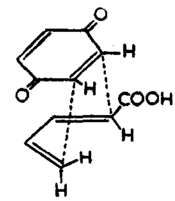
We chose as first step the reaction of vinylacrylic acid with quinone. The addition proceeded relatively smoothly in hot benzene solution, to give the adduct (IV : R = H). It will be noted that the newly formed six-membered ring of the adduct was destined to become Ring E of reserpine, that it contains already a felicitously placed carboxyl group, a double bond of good augury for the introduction of oxygen atoms at appropriate positions, *and three asymmetric carbon atoms properly oriented.* The well-known stereospecificity of the Diels–Alder reaction enabled us to assume with complete assurance that the two rings of the adduct were *cis*-locked, and it was only slightly less certain that the hydrogen atom at the third of the asymmetric centers created in the addition reaction would be on the same side of the molecular plane as those at the points of ring juncture. Thus, the only known form of vinylacrylic acid possesses a *trans* Δ^3 double bond,[5] and the combination of that isomer with quinone, proceeding through an intermediate (V) of the geometrical type generally accepted for the Diels–Alder reaction,[6] can lead only to an adduct with the stereochemistry defined in (IV).

[4a] C. F. Huebner, H. B. MacPhillamy, E. Schlittler and A. F. St. André *Experientia* 11, 303 (1955); [b] E. Wenkert and L. H. Liu *Ibid* 11, 302 (1955); [c] C. F. Huebner and E. Wenkert *J. Amer. Chem. Soc.* 77, 4180 (1955); [d] P. A. Diassi, F. L. Weisenborn, C. M. Dylion and O. Wintersteiner *Ibid.* 77, 4687 (1955); [e] E. E. van Tamelen and P. D. Hance *Ibid.* 77, 4692 (1955).

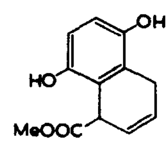
[5] The configuration follows from the oxidation of the acid, by permanganate, to *dl*-tartaric acid (O. Doebner *Ber Dtsch. Chem. Ges.* 35, 1141 (1902)).

[6] K. Alder, M. Schumacher and O. Wolff *Liebigs Ann.* 564, 81 (1949); K. Alder *Ibid.* 571, 157 (1951).

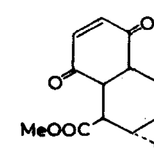
Some preliminary studies with the adduct (IV : R = H) served for the characterization of various of its functions. With diazomethane, the corresponding ester (IV : R = Me) was produced, albeit only in moderate yield; addition of diazomethane



V

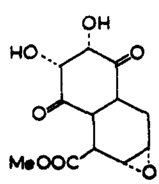


VI

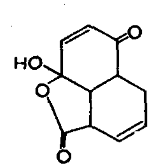


VII

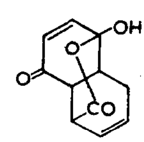
to the carbon-carbon double bond of the ene-dione system was obviously a complicating factor. Attempts to prepare the ester by acid-catalyzed esterification with methanol led only to the aromatic isomer (VI), and emphasized the necessity for the use of gentle methods in effecting further elaboration of our key intermediate. The ester (IV : R = Me) was best prepared by the direct reaction of quinone with methyl vinylacrylate. The attack of perbenzoic acid on the ester was expected to, and did, involve preferential attack upon the isolated, and consequently relatively electron-rich, double bond, with formation of the oxide (VII). In its turn, the double bond of the ene-dione system was attacked by hydrogen peroxide in the presence of osmium tetroxide with the formation of the diol (VIII).



VIII

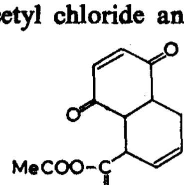


IX

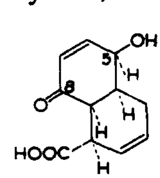


X

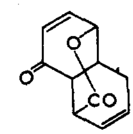
The structure of the adduct deserves some further comment in detail at this point. *A priori*, the possibility was present that one or another of the ring-chain tautomeric species (IX) or (X) might surpass the doubly ketonic structure (IV) in stability. In fact, no evidence for the presence of such molecules, even as minor participants in tautomeric equilibria could be found in the case of the free adduct. In particular, (IX) was easily excluded, through the absence of absorption in the infrared spectrum of the adduct in the 5·6–5·7 μ region. Further, the spectrum exhibited strong absorption of the characteristic carboxyl type at 2·8–4·2 μ, and the presence in the ultraviolet spectrum of bands at 224 and 355 mμ (log ε = 11,300 and 71) indicated that the system —CO—CH=CH—CO— was present.[7] Finally, with acetyl chloride and acetic anhydride, the adduct was converted to a simple



XI



XII

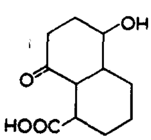


XIII

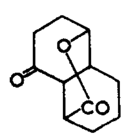
[7] Cf. D. H. R. Barton and A. S. Lindsay *J. Chem. Soc.* 2989 (1951).

mixed anhydride (XI), rather than to a lactol acetate derived from (IX) or (X). None the less, the facts shortly to be detailed suggest that some kind of interaction between the carboxyl group and the carbonyl group at C.8 occurs in certain circumstances.*

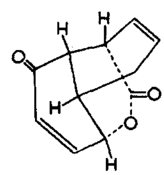
We now wished to find a reaction which would differentiate the two similarly placed carbonyl groups in (IV : R = H), and one was soon found in the reduction of the adduct by sodium borohydride in water to the dihydro derivative (XII). Although we were prepared to make use of the opportunity which would be presented by the selective reduction of *either* carbonyl group, it was of course necessary at this point to establish which of the groups had in fact suffered reduction in the case at hand. The issue was readily resolved through conversion of the reduction product into the corresponding transannular lactone (XIII), the six-membered nature of whose lactone ring was evident from the presence in its infrared spectrum of a strong band at 5·74 μ. Since there was a possibility that the concentration of divers functional groups in (XIII) might lead to abnormalities in the positions of infrared bands, the dihydro derivative also was converted by hydrogenation into the hexahydro compound (XIV), and thence into the saturated keto-lactone (XV), which could be prepared alternatively by the direct reduction of the doubly unsaturated lactone. The infrared



XIV



XV

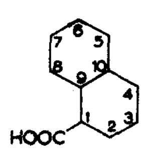


XVI

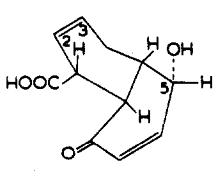
spectrum of the saturated lactone possessed a normal ketonic carbonyl band at 5·85 μ, and a second band at 5·80 μ, characteristic of the carbonyl group of a six-membered lactone ring.

The formation of the lactone (XIII ≡ XVI) may serve for the introduction of a number of stereochemical points of great importance. First, it will be noted (cf. XVI) that the lactone can be formed at all only if the hydroxy acid from which it was obtained possesses the structure (XII) in regard to all stereochemical details. Consequently, the experiment demonstrates rigorously that *the asymmetric carbon atoms of the original adduct are in fact oriented in the manner hitherto deduced only on theoretical grounds*. Secondly, it will be noted that the lactone does not form spontaneously from the hydroxy acid. This fact demonstrates that of the two possible conformations (XVII) and (XVIII), the hydroxy acid assumes the former, in which the groups attached to the ring skeleton are disposed in the energetically favorable *quasi*-equatorial orientation. Consequently, in order to bring about lactonization, energy must be put into the system in order to bring about conversion of the hydroxy

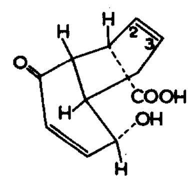
* The carbon atoms of the bicyclic derivatives in this paper are numbered according to the annexed scheme.



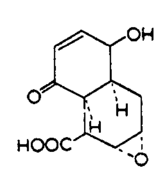
acid molecules into the less favored conformation (XVIII), with axially disposed carboxyl and hydroxyl groups. Conversely, it may be noted that *the co-operation of those groups in the formation of a lactone function serves to freeze the molecular framework in an otherwise relatively unfavorable conformation, with important stereochemical consequences for operations on the periphery of the molecule.* A third theoretical point of importance is brought to light by a consideration of the fact that the addition of hydrogen in the reduction of the carbonyl group at C.5 of the adduct (IV : R = H) takes place from the same side of the molecule on which the two bridgehead hydrogen atoms are located (cf. XVII). The known preference for the formation of equatorial hydroxyl groups in hydride reductions of relatively unhindered carbonyl groups[8] would have suggested in any case that (XII ≡ XVII) would be formed, but it should be emphasized in addition that to the extent that steric factors are operative in directing the reduction, the same product would be expected. For, *all* cis *decalin derivatives*



XVII



XVIII



XIX

possess cage-like structures, to which access is severely obstructed on the concave face;* it will be clear from the subsequent narrative that we have made much use of this simple steric property of our *cis* decalin derivatives.

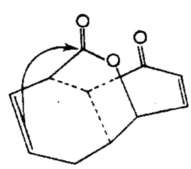
Before leaving the discussion of the dihydro adduct (XII), some further comment is necessary upon the selectivity of the reduction. Even in the presence of a large excess of the reducing reagent the carbonyl group at C.8 is not saturated. This result was hardly anticipated, nor is it even now entirely clear to what it should be attributed. Certain it is that the C.8 carbonyl group is much the more hindered of the two present; but sodium borohydride is not notably subject to ordinary steric effects, and it seems possible either that the carboxylate ion, proximate as it is to the relevant carbonyl group (cf. XVII), exerts electrostatic repulsion upon the borohydride ion, or perhaps interacts electronically with the carbonyl group in such wise as to effect the virtual saturation of the latter.

We turned now to the problem of introducing oxygen atoms at appropriate positions of our Ring E progenitor. Our expectation was realized that perbenzoic acid would attack the dihydroadduct (XII ≡ XVII) on the convex face, and preferentially at the isolated double bond, with formation of the oxide (XIX). A point of much theoretical interest emerges from the fact that a similar preferential reaction could not be realized in the case of the lactone (XIII). In that case, oxidation by perbenzoic acid occurred relatively slowly, the consumption of oxidant did not

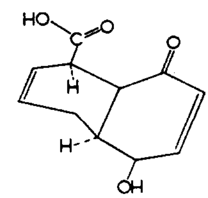
* The term *convex face* is used in the sequel for that side of *cis* decalin derivatives on which the *cis* bridgehead hydrogen atoms are located. The use of this designation, and the complementary *concave face* for the opposite side, obviates the ambiguities inherent in such phrases as "from the *top* side," and "attack from the *rear*."

[8] D. H. R. Barton *J. Chem. Soc.* 1027 (1953); H. R. Nace and G. L. O'Connor *J. Amer. Chem. Soc.* 73, 5824 (1951); J. B. Umland and M. I. Jefraim *Ibid.* 78, 2788 (1956).

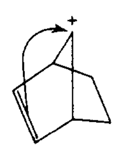
cease after one mole, and no clearly defined products were isolated.* It is clear that in both cases, the *conjugated* double bond is relatively inert to cationoid oxidants as a result of electron withdrawal by the directly attached carbonyl group. The different behavior of the isolated double bonds in the two cases is attributable to the fact that in the lactone, the geometrical prerequisites for *electron release from the isolated double bond to the carboxyl carbonyl group* are better satisfied than in the acid. Thus, in the lactone the relevant carbonyl group is axially disposed, and the opportunity for overlap between the electron-deficient π orbital of that group and the π orbitals of the double bond is relatively favorable (cf. XX, arrow). In marked contrast,



XX



XXI



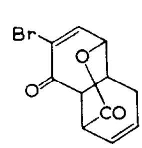
XXII

the equatorial orientation of the carboxyl group in the hydroxy acid provides little occasion for an analogous interaction (cf. XXI). The striking effects which can arise from similar interactions between non-bonded centers may be emphasized by reference to the carbonium ion (XXII), which is stabilized to such an extent by orbital overlap that the corresponding toluenesulfonate is solvolyzed one hundred billion times more rapidly than the saturated analog.[9]

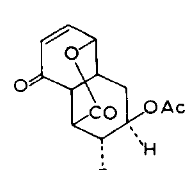
We considered, but regarded as unlikely, the possibility that the attack of perbenzoic acid on (XII) might lead directly to a hydroxy lactone of the type (XXIII).

* Further, very striking, evidence of the deactivation of the $\Delta^{2,3}$ double bond in the lactone (XIII) was found in the observation that the substance was converted by one mole of bromine to the α-bromo-α, β-unsaturated ketone (i).

On the other hand, preferential attack at the non-conjugated center of unsaturation was achieved with iodine and silver acetate in acetic acid, which converted the lactone into the iodoacetate (ii).



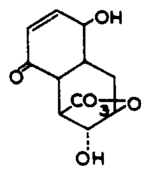
i



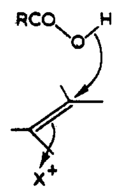
ii

[9] S. Winstein, M. Shatavsky, C. Norton and R. B. Woodward *J. Amer. Chem. Soc.* **77**, 4183 (1955).

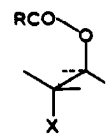
While it is true that unsaturated acids frequently undergo changes of the sort (XXIV → XXV) on attack by electron-deficient reagents, it is clear that the equatorial dispo-



XXIII



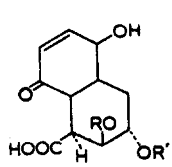
XXIV



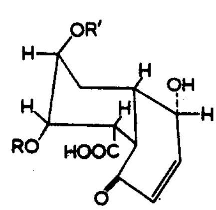
XXV

sition of the carboxyl group in the most stable conformational isomer of (XII ≡ XVII) places that function at such remove from the terminal carbon atom (C.3) of the double bond that a concerted reaction of the type under discussion cannot occur. Of course, the geometry of the unstable conformational isomer (XVIII) is favorable for the concerted reaction, and since conformational changes are no doubt rapid, the hydroxy lactone could be formed, if the relevant double bond ($\Delta^{2,3}$) of (XVIII) were more reactive than the corresponding unsaturated center in (XVII); but the discussion of the preceding paragraph indicates that the double bond with the adjacent axially oriented carboxyl group will be the *less* reactive of the pair.

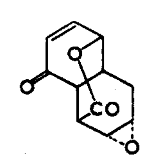
We now came to grips with the problem of opening the 2,3-oxide ring. The cleavage of the oxide ring of (XIX) by hydrolytic reagents would be expected to lead to a *trans* diol derivative of the undesirable stereostructure (XXVI), since it is well



XXVI



XXVII

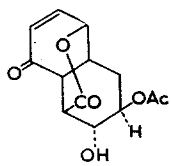


XXVIII

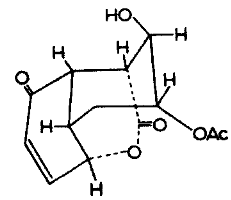
known that the cleavage of cyclohexane oxides proceeds by preference with the formation of axial *trans* diols (cf. XXVII).[10] However, it was clear that the opening of the oxide could be forced to take the alternative desired direction if the molecule of (XIX) could be forced to assume the alternative conformation available to it as a *cis* decalin derivative. Our earlier experience with the lactonization of the simple hydroxy acid (XII) had shown us how this conformational change could be realized, and we next converted the oxide (XIX) into the corresponding lactone (XXVIII), by treatment with acetic anhydride and sodium acetate in benzene. We could now be

[10] D. H. R. Barton and R. C. Cookson *Quart. Rev. Chem. Soc.* **10**, 67 (1956).

confident that the hydroxy acetate which we obtained from the oxide lactone by the action of boiling acetic acid had the desired structure (XXIX ≡ XXX). Indeed, in



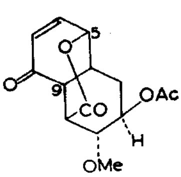
XXIX



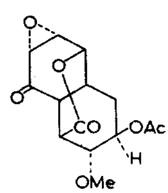
XXX

the latter, *we had in hand for the first time an intermediate in which the problem presented by the stereochemistry of Ring E of reserpine was solved.* Further, the hydroxy acetate possesses only one active hydrogen atom, and further progress toward an appropriate reserpine intermediate was readily achieved through conversion to the corresponding methyl ether (XXXI) by treatment with silver oxide and methyl iodide.*

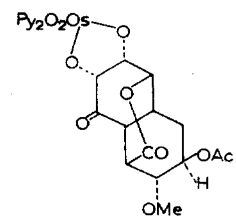
The further elaboration of the methoxy acetate (XXXI) in the direction of an intermediate of the desired general type (III) required the removal of the oxygen atom at C.8, or the interpolation of a new methylene group between C.8 and C.9. No



XXXI



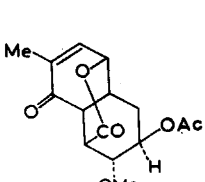
XXXII



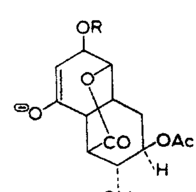
XXXIII

doubt one or the other of these objectives could have been realized, but very favorable developments in another direction supervened at this point, and this series was not carried beyond the oxide (XXXII) and the glycol osmate (XXXIII) prepared from

* The preparation of pure samples of the methoxy acetate (XXXI) was often attended by considerable difficulty. Careful chromatography of the crude product showed that it was contaminated with a homolog for which the structure (iii) is proposed (λ_{max} 234 mμ, as contrasted with λ_{max} 222 mμ for (XXXI)). The details of the course followed in the formation of (iii) have not been established, but it may be suggested that addition of an anion (perhaps MeO^- or AgO^-) to the conjugated double bond gives (iv), which is then



iii



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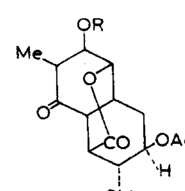


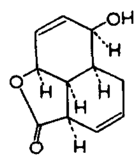
v

discharged by C-alkylation. Subsequent loss of ROH from the resulting (v), with formation of the observed product, would be unexceptional.

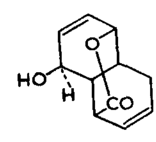
It may be noted that steric factors prohibit direct enolization of (XXXI), by proton migration from *either* C.5 or C.9.

the unsaturated ketone by treatment with alkaline hydrogen peroxide, and osmium tetroxide in pyridine respectively.

While the studies of the six-membered lactone intermediates just described were in progress, we were at the same time investigating the opportunities presented by a series of five-membered lactones, of which (XXXIV) may serve as the prototype.

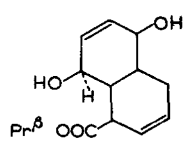


XXXIV

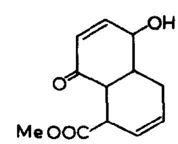


XXXV

This substance was first encountered as the product of the reduction of the simple six-membered lactone (XIII) by aluminium *iso*propoxide in *iso*propanol. That it possessed the structure (XXXIV) rather than that of the proximate reduction product (XXXV) was clearly apparent from the presence in its infrared spectrum of a band at 5·68 μ. Since direct translactonization by attack of the hydroxyl group of (XXXV) upon the lactone carbonyl group is sterically improbable, it was necessary to presume that the lactone ring had first been cleaved by *iso*propanol with formation of an ester (XXXVI), from which the product (XXXIV) could be formed without difficulty.



XXXVI

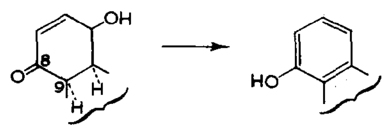


XXXVII

This view received support when it was found that the ester (XXXVII), prepared from the corresponding acid (XII) by the action of diazomethane in dioxane* was, like the lactone (XIII), converted smoothly into (XXXIV) by aluminium *iso*propoxide in *iso*propanol. Finally, the five-membered lactone was found to be most simply preparable by the direct reduction of the ester adduct (IV : R = Me).

The hydroxy lactone (XXXIV) was readily oxidizable by chromic acid in acetic

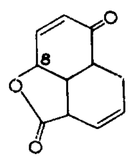
* Like the adducts (IV), though less so, our compounds containing the system (vi) were susceptible to aromatization in the presence of strong acids. When an attempt was made to prepare the ester (XXXVII)



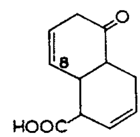
vi vii

by acid-catalyzed esterification of the corresponding acid, crude mixtures were obtained whose ultraviolet and infrared absorption was clearly indicative of the presence of substances containing the chromophore (vii). It is likely that the aromatization reaction involves prior enolization of the C.8 carbonyl group towards C.9; our qualitative observations suggest that substances such as the lactone (XXVIII) in which such enolization is sterically prohibited, are more resistant to aromatization than the enolizable analogues.

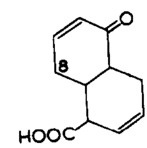
acid to the corresponding keto lactone (XXXVIII), which was found to be subject to remarkably facile reductive cleavage by zinc and acetic acid, with formation of the β,γ-unsaturated keto acid (XXXIX).* The latter was readily converted to



XXXVIII



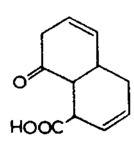
XXXIX



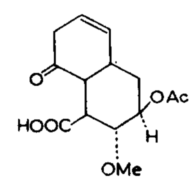
XL

the corresponding conjugated isomer (XL) when it was warmed with potassium acetate in alcohol. Clearly, these developments suggested a very simple possibility for the removal of the unwanted oxygen atom at C.8 in our intermediates, *provided that a representative of the five-membered lactone series suitably oxygenated at* C.2 *and* C.3 *could be found.* Experiments on the direct oxidation of the $\Delta^{2,3}$ double bond of the keto lactone (XXXVIII) were not promising since, as in the earlier studies with the six-membered lactone (XIII), perbenzoic acid did not differentiate satisfactorily between the two oxidizable portions of the molecule.† Thus, the reagent was consumed slowly, an integral number of moles of oxidant was not consumed,

* The α,β-unsaturated ketones of the six-membered lactone series, e.g., (XIII) and (XXXI), were also very readily reduced by zinc and acetic acid, with the formation of (viii) and (ix), respectively.

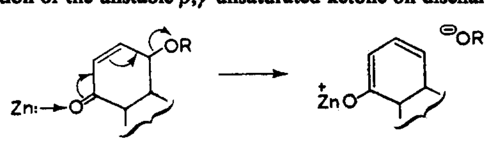


viii



ix

We suggest that the process involves attack of zinc on the oxygen atom of the ketonic carbonyl group (x, arrows).[11] The formation of the unstable β,γ-unsaturated ketone on discharge of the resulting complex



x xi

enolate (xi), *under essentially irreversible conditions,* is expected.

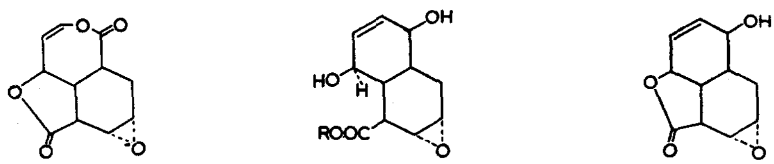
† As in the case of the six-membered lactone (XIII), (*vide supra*), the sluggishness of the $\Delta^{2,3}$ bond of (XXXVIII) is attributed to electron release from that center to a non-conjugated carbonyl group. The five-membered lactone may exist in one of two conformations; in view of the presence of three trigonal atoms in one ring, a decision in respect to the relative stabilities of the two conformational isomers is difficult, but in any event, in one of them, the lactone carbonyl group is axially oriented with respect to the $\Delta^{2,3}$-bond, as in (XIII), while in the other, the geometry is very favorable for interaction *between the* $\Delta^{2,3}$ *bond and the* C.5 *carbonyl group.*

It is worthy of note that the five-membered lactone (XXXVIII) further resembled the six-membered analogue (XIII) in that it was attacked at the unconjugated $\Delta^{2,3}$ double bond by iodine and silver acetate in acetic acid, with formation of the corresponding iodoacetate.

[11] R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler and W. M. McLamore *J. Amer. Chem. Soc.* **74**, 4225 (1952).

and the sole isolable product was a substance whose characteristic physical properties indicated clearly that it possessed the structure (XLI).

In these circumstances, it was natural to consider whether the oxide lactone (XXVIII), which was an important intermediate in our earlier series, could be converted into a representative of the five-membered lactone series through reduction



XLI XLII XLIII

by aluminium *iso*propoxide in *iso*propanol. We anticipated that the lactone would first be converted into an hydroxy ester of the type (XLII : R = Pr^{β}), that further change to an hydroxy lactone (XLIII) would then result, and were cognizant of the possibility that the latter might well be converted into an hydroxy ether (XLIV).

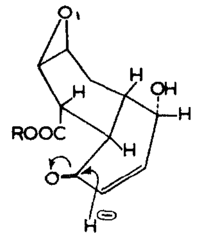
XLIV XLV

For aluminium *iso*propoxide can function as an acidic reagent, capable of labilizing the oxide ring for intramolecular attack by a sterically favorably disposed hydroxyl group (cf. XLV, arrow). In the event, all of these changes did in fact occur, and yet another. The major product of the reaction was the unsaturated ether (XLVI). Clearly, the lactone carbonyl group of the presumed intermediate (XLIV) activates

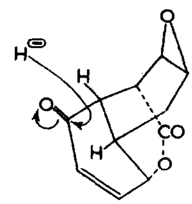
XLVI XLVII

the adjacent methine hydrogen, and permits a ready β elimination of the hydroxyl group. It may be noted that as in the simpler series, the ester (XLVII), prepared from the corresponding acid (XIX) by the action of diazomethane in dioxane, was likewise converted into the unsaturated ether (XLVI) on aluminium *iso*propoxide reduction.

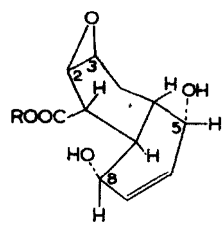
We turn now to a discussion of the stereochemistry of the formation of the unsaturated ether (XLVI), and of the five-membered lactone series in general. First, it is clear that the reduction of the carbonyl group at C.8 in either the ester (XLVII), or the lactone (XXVIII), will involve addition at the convex face of the molecule, since in both compounds access to the carbonyl group at the concave face is very severely obstructed (cf. XLVIII and XLIX). Secondly, the preferred conformation (L) of



XLVIII

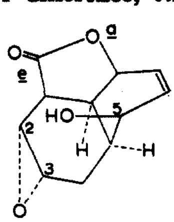


XLIX

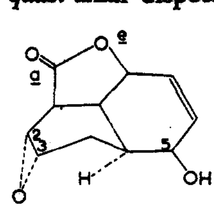


L

the dihydroxy ester (XLII) which must be assumed as an intermediate in the processes leading to (XLVI) does not permit a concerted oxide opening with formation of the required 3,5 ether linkage. Indeed, cyclic ether formation at the ester stage should lead to a 2,8 oxide ring.* These considerations led us to conclude that *the formation of the 3,5 oxide bridge follows establishment of the five-membered lactone ring*. For the lactone oxide (XLIII), two alternative conformations, (LI) and (LII), are available, whose major difference, *vis-a-vis* energy, lies in the *quasi*-axial disposition of the



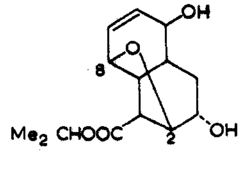
LI



LII

hydroxyl group at C.5 in one, and the *quasi*-equatorial orientation of the same group

* In the light of the above discussion, a dihydroxy ester $C_{14}H_{20}O_5$, which is a major by-product of the

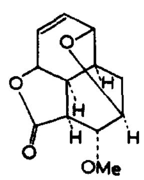


xii

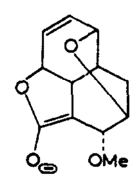
reaction, may well have the structure (xii).

in the other. Consequently, (LII), in which 3,5 oxide bridge formation is impossible, is undoubtedly the predominant species. However, the cleavage of the 2,3 oxide ring involves an increase in electron deficiency at C.2 and C.3, and factors similar to those which render the $\Delta^{2,3}$ double bond of the lactone (XX), *with an adjacent axial carbonyl group*, relatively inert to cationoid oxidants (*vide supra*) will oppose the opening of the ethylene oxide ring of (LII), as compared with that of (LI), whose adjacent carbonyl group is equatorial. The extent to which the concerted reaction occurs indicates that the greater reactivity of (LI) more than compensates for the position of the isomer as minor component in the conformational equilibrium.

The presence in the unsaturated ether (XLVI) of a double bond conjugated with a carbonyl group now suggested a new and simple possibility for the introduction of the required methoxyl group at C.2. When (XLVI) was treated with sodium methoxide in methanol, it was smoothly transformed into the methoxy ether (LIII). The

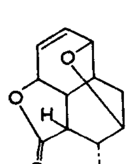


LIII

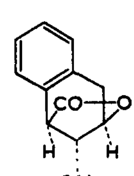


LIV

stereochemical factors attendant upon this change require comment. There was no doubt that methoxide ion would attack the molecule at the convex face, since the hindrance to access from the alternative direction which is present in all *cis* decalin derivatives was in this case rendered even more formidable by the 3,5 oxide bridge. On the other hand, discharge of the resulting anion (LIV) by a proton could *a priori* occur to give either of two isomers. Since the reaction was carried out under conditions which would in all likelihood lead to equilibration, with formation of the more stable of the two isomers, it was necessary to attempt to estimate whether the desired lactone (LIII), or the isomer (LV) would be more stable. The study of models pointed very strongly in one direction, but did not permit a conclusion of the rigorous sort which could be made, for example, in the case of the lactone (XIII). Thus, in the lactone (LIII) Ring E must assume the boat form. Further, it was possible, albeit with much strain, to construct models of the lactone (LV) with both carbocyclic rings in the chair conformation. Consequently, it was desirable to call upon generalized



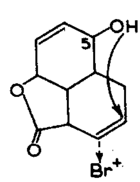
LV



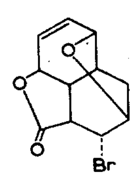
LVI

experience, which indicates that five-membered lactone rings fused to a six-membered ring are in all simple cases far more stable when the ring fusion is *cis* than when it is *trans*. Since our lactone was a very stable one, and we could discern in its molecule no special factors which could confer special stability on a *trans* fused bicyclic lactone system, we were confident that the substance had the desired structure (LIII). This conclusion was confirmed experimentally when it was found that the methoxy lactone was converted by stannic chloride in acetyl chloride to a simple aromatic methoxy lactone of the structure (LVI); clearly the formation of the new five-membered lactone ring of (LVI) requires that the ether oxygen atom and the lactone carbonyl group of (LIII) be on the same side of the molecule.

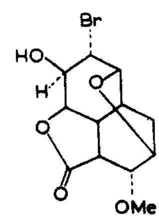
In the methoxy ether (LIII) we now had a second, and relatively readily available intermediate containing all five of the asymmetric carbon atoms of Ring E of reserpine, properly oriented. Upon finding that the carbon-carbon double bond of the ether was markedly resistant to attack by bromine, we now foresaw the possibility of preparing that intermediate by a process even simpler than that just described. The considerations advanced above suggested that just as a 2,3 oxide in the five-membered lactone series was susceptible to concerted cleavage, so a double bond at that position should be susceptible to attack by an electron-deficient reagent with concerted intramolecular release of the electron deficiency in the resulting intermediate by the hydroxyl group at C.5 (cf. LVII, arrows), and indeed, when the simple doubly unsaturated lactone (XXXIV) was treated with bromine, preferably in an inert solvent, but even in methanol solution, the bromo lactone (LVIII) was produced. Not surprisingly, when the latter was treated with sodium methoxide in methanol, dehydrobromination occurred readily, and methanol was added to the double bond of the resulting conjugated lactone (XLVI), to give directly the familiar methoxy ether (LIII).



LVII

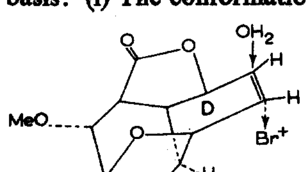


LVIII

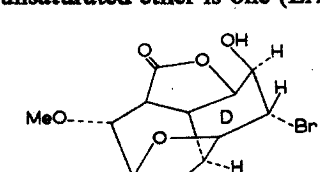


LIX

We next turned our attention to modification of the upper ring of the intermediate (LIII). While the double bond in that substance was not attacked by bromine in chloroform or acetic acid at room temperature, aqueous N-bromosuccinimide in the presence of sulfuric acid at 80° readily converted the unsaturated ether to the bromohydrin (LIX). The structure of the bromohydrin was assigned on the following basis: (i) The conformation of the unsaturated ether is one (LX) in which

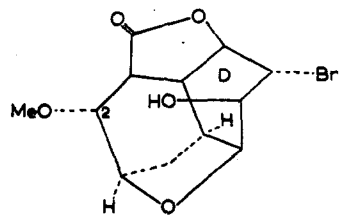


LX



LXI

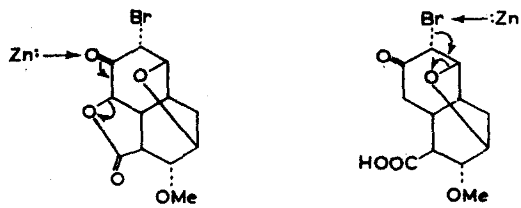
the unsaturated ring (D) assumes the *quasi*-chair form and the other ring a (slightly distorted) boat form. (ii) Attack upon the molecule is initiated at the convex face by positive bromine. (iii) Therefore, the most readily accessible transition state for hypobromous acid addition is one which leads directly (cf. LX, arrows) to the di-axial *trans*-bromohydrin (LXI). The only possible competitor would be a transition state related to a bromohydrin (LXII), in which Ring D is converted to a boat conformation. In addition to the usual factors which render boat-like species energetically unfavorable relative to alternative chair forms, it may be noted that in the case at



LXII

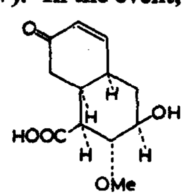
hand, the methine hydrogen atom at C.2 would offer special obstruction to the processes necessary for the formation of (LXII).

The bromohydrin (LIX) was smoothly oxidized to the corresponding ketone (LXIII) by means of chromic acid in acetic acid. We now hoped that the attack of



LXIII LXIV

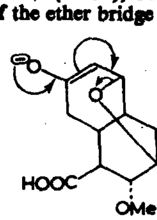
a metallic reducing agent upon (LXIII) would bring about reductive cleavage of the carbon-oxygen bond at C.8 (cf. LXIII, arrows),* as well as removal of the bromine atom and elimination of the 3,5 ether bridge (cf. LXIV, arrows),† with formation of the unsaturated keto acid (LXV). In the event, when the bromo ketone was treated



LXV

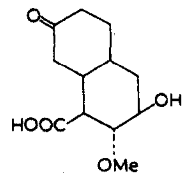
* The process involved here is of course very similar to that involved in the reductive cleavage of our γ-oxygenated α,β-unsaturated ketones (cf. footnote p. 10).

† This reaction may be direct, as implied in (LXIV), but it could well involve prior reduction of the α-bromine atom, followed by elimination of the ether bridge in the resulting enolate (xiii).



xiii

for a very short time with zinc in aqueous acetic acid, acidic products were obtained, whose ultraviolet absorption indicated clearly that the desired unsaturated ketone was present, but it was also apparent from the intensity of the absorption that substantial

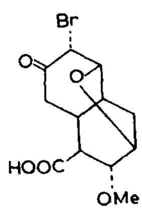


LXVI

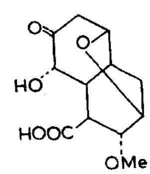
over-reduction to the saturated keto acid (LXVI) had occurred. On the other hand, when zinc and glacial acetic acid was used, the desired unsaturated keto acid was formed very smoothly.*,†

* We attribute the marked difference between the results obtained with glacial and aqueous acetic acid to the possibility that the processes leading to (LXV) utilize only zinc metal, while the reduction of (LXV) to (LXVI) involves nascent hydrogen, generated from the action of acetic acid upon zinc. It is a fact that glacial acetic acid attacks zinc very much less rapidly than the wet acid.

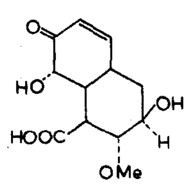
The use of other solvents than acetic acid was not successful, probably because the acid is needed to keep the zinc surface fresh, by dissolution of zinc salts formed as reaction proceeds. When the reaction was attempted in dioxane solution, containing small amounts of acetic acid and water, and the resulting acidic material was allowed to stand for some time in sodium carbonate solution, a substance of the probable structure (xvi) was formed. This compound may have resulted from reductive cleavage of (LXIII) to (xiv), followed by hydrolytic rearrangement of the α-bromine atom (xiv → xv)[13] and elimination of the 3,5 oxide bridge.



xiv

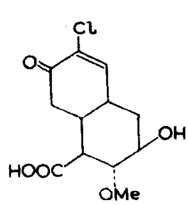


xv



xvi

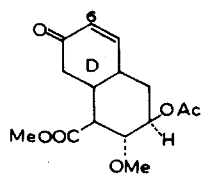
† In another series of experiments, the *chloro*hydrin corresponding to (LIX) was prepared from (LIII) by the action of hot aqueous hypochlorous acid, oxidized to the corresponding ketone, and reduced with zinc and acetic acid. The series offered no advantage, and the only point of special interest which emerged was that a by-product of zinc reduction was obtained, whose properties showed that it possessed the structure (xvii).



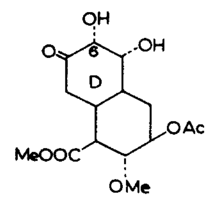
xvii

[13] L. F. Fieser and M. A. Romero *J. Amer. Chem. Soc.* 75, 4717 (1953).

With the obtention of (LXV) our primary objective of preparing an intermediate of the general type (III) was completed. After conversion of the unsaturated keto acid to (LXVII) by esterification and acetylation, we were ready to effect cleavage of Ring D, with the ejection of C.6. Although ring cleavage could no doubt have been

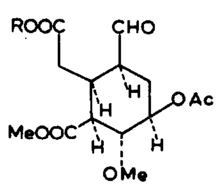


LXVII

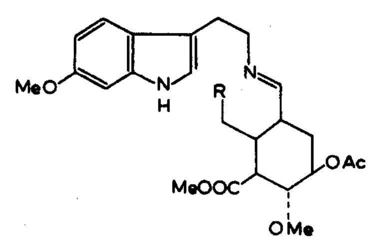


LXVIII

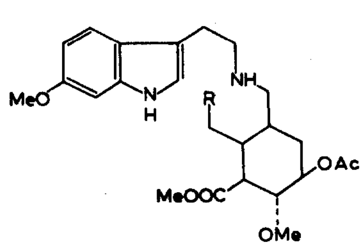
brought about directly through the use of one of a number of oxidizing agents, we chose to proceed with circumspection, and converted the unsaturated ketone first into the diol (LXVIII), through reaction with aqueous osmium tetroxide, followed



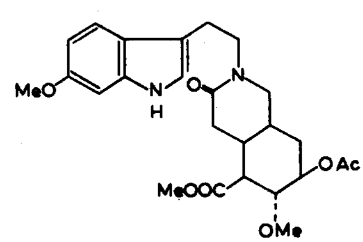
LXIX



LXX



LXXI

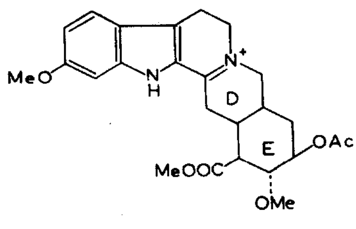


LXXII

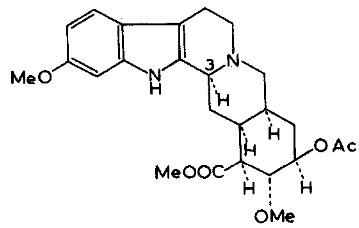
by decomposition of the intermediary osmate ester with sodium chlorate. The diol was then transformed directly in high yield, without isolation of the labile intermediates (LXIX : R = H),* (LXIX : R = Me), (LXX : R = COOMe), and (LXXI : R = COOMe), to the lactam (LXXII), through successive treatments with aqueous

* It may be noted that the aldehyde group is adjacent to an asymmetric center, but is equatorial, and consequently configurationally stable.

periodic acid and ethereal diazomethane, condensation* with 6-methoxytryptamine† in benzene, and reduction with sodium borohydride in methanol. When the lactam



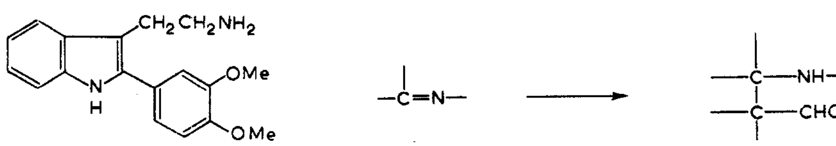
LXXIII



LXXIV

was treated with boiling phosphorus oxychloride, it was smoothly converted into the quaternary cation (LXXIII), which was reduced directly with aqueous methanolic

* Infrared spectrophotometric studies of this smooth, rapid, spontaneous condensation demonstrated that the Schiff base (LXX), and simpler analogs, which were easily detectable by their weak, sharp absorption band at 6·0 μ, disappeared slowly from the solution, *particularly in the presence of excess aldehyde*. That the further reaction did not involve cyclization to the free α position of the indole nucleus was shown by the fact that precisely similar phenomena were observed in the condensation of the substituted tryptamine derivative (xviii) with aldehydes. Quite possibly the secondary reaction involves addition of the α-carbon atom of the aldehyde to the carbon-nitrogen double bond (xix → xx).

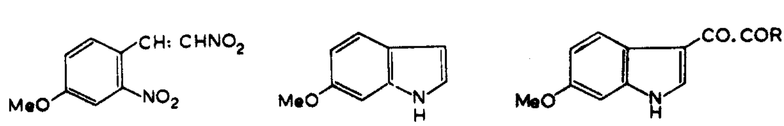


xviii xix xx

† 6-Methoxytryptamine has been prepared previously by Akabori and Saito.[13] We have prepared the base by a new synthesis: 2-Nitroanisidine (xxi) was diazotized and converted by treatment with formaldoxime to 2-nitroanisaldoxime (xxii). The corresponding aldehyde, obtained from (xxii) by steam distillation

xxi xxii

from acid solution, was condensed with nitromethane, and the resulting ω-nitrostyrene (xxiii) was reduced,

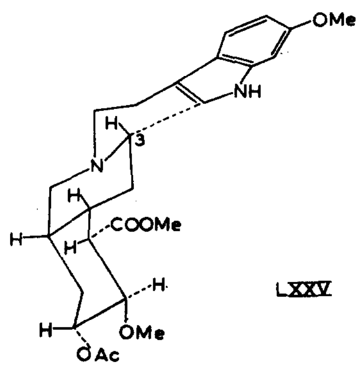


xxiii xxiv xxv

by hydrogen in the presence of palladized charcoal, to 6-methoxyindole (xxiv). Condensation of the latter with oxalyl chloride[14] gave (xxv : R = Cl), which was converted by aqueous ammonia to the amide (xxv : R = NH_2), and reduced to the desired 6-methoxytryptamine by lithium aluminium hydride in boiling tetrahydrofuran.

[13] S. Akabori and K. Saito *Ber. Dtsch. Chem. Ges.* **63**, 2245 (1930).
[14] Cf. M. E. Specter and W. C. Anthony *J. Amer. Chem. Soc.* **76**, 6208 (1954).

sodium borohydride to *dl* methyl-O-acetyl-*iso*reserpate (LXXIV).* It will be noted that that product is the expected one, whether the stereochemical sense of the reaction is subject to steric or thermodynamic control. Thus, attack at the convex face of the D/E ring system will place the newly added hydrogen atom at C.3 on the same side of the molecule as the bridgehead hydrogen atoms. Further, of the two possible isomers which might be formed on the creation of a new asymmetric center at C.3, (LXXIV) is the one in which all of the large groups attached to the D/E ring skeleton are equatorially disposed (cf. LXXV).



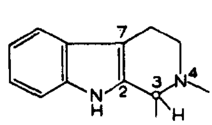
LXXV

Only one major task now remained—to effect inversion at the newly created asymmetric center, C.3. It was well known that a reaction path was available for isomerization at a center so located, through treatment with acid,† but it was clear

* We were first able to ascertain that the synthetic ester in fact possessed the structure (LXXIV) through comparison of its infrared spectrum with that of a sample of *l* methyl-O-acetyl-*iso*reserpate, prepared from reserpine.[15] Further, the racemic ester was readily resolved, using di-*p*-toluyl *l* tartaric acid, and the resulting synthetic *laevo*rotatory ester was found to be identical in all respects with material from natural sources.

The availability of *l* methyl-O-acetyl-*iso*reserpate from natural sources was also of much value in that it permitted us to pilot the experiments described in the sequel with relatively accessible optically active intermediates, at a time when the corresponding racemic synthetic compounds were in short supply.

† The fact that inversions at C.3 in tetrahydrocarbolines (xxvi) can be brought about by vigorous treatment with acids is well established, though the mechanism of the changes involved is not clear. One possibility is that the indole ring is reversibly protonated at C.7, and that the resulting cation is reversibly deprotonated at C.3 (xxvi ⇄ xxvii ⇄ xxviii). Alternatively, Wenkert and Liu[4b] have suggested the reversible change



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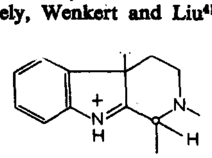

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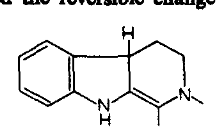

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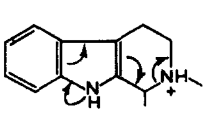

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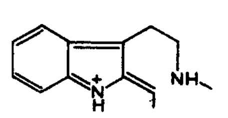

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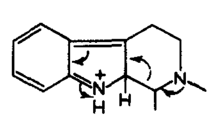

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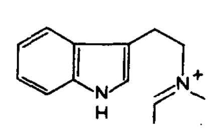
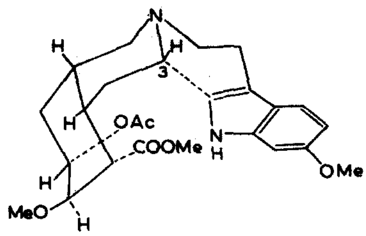


xxxii

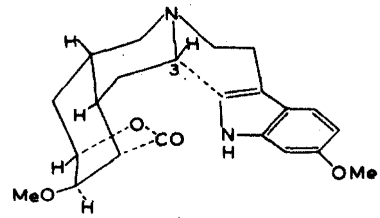
(xxix ⇄ xxx). Still another possibility lies in protonation at C.2, to give (xxxi), followed by reversible ring cleavage to (xxxii).

[15] H. B. MacPhillamy, C. F. Huebner, E. Schlittler, A. F. St. André and P. R. Ulshafer *J. Amer. Chem. Soc.* 77, 4335 (1955).

that it would not be operative in the case at hand, since C.3 in (LXXIV ≡ LXXV) is configurationally stable. However, if the molecular framework of (LXXV) could be forced to assume the alternative conformation (LXXVI), available to it in virtue of

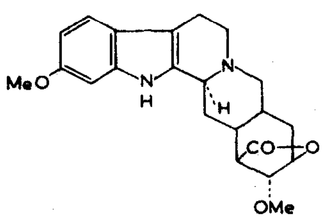


LXXVI

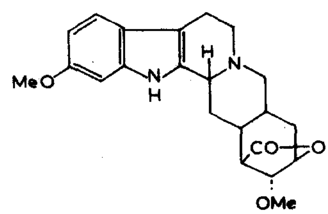


LXXVII

the *cis* locking of Rings D and E, the large indole group at C.3 would be axial, and that center should then be susceptible to inversion. Our experience with our bicyclic intermediates was clearly suggestive of the manner in which such a conformational change to a normally unfavorable state could be brought about, and we set about to prepare the lactone (LXXVII) of *iso*reserpic acid. The ester (LXXIV) was

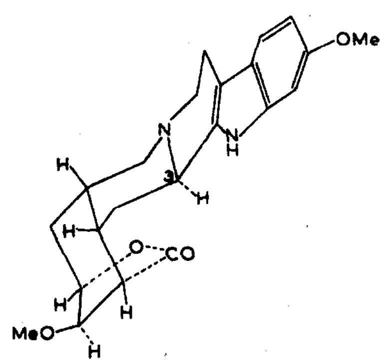


LXXVIII



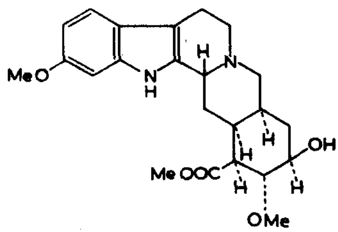
LXXIX

hydrolyzed with methanolic potash, and the resulting hydroxy acid was converted to the desired *dl* *iso*reserpic acid lactone (LXXVII ≡ LXXVIII) by treatment with N,N'-*dicyclo*hexylcarbodiimide in pyridine, or less efficiently by a single molar proportion of acetic anhydride in hot xylene. Further, as expected on the basis of the argument set out above, the lactone (LXXVIII) was substantially quantitatively

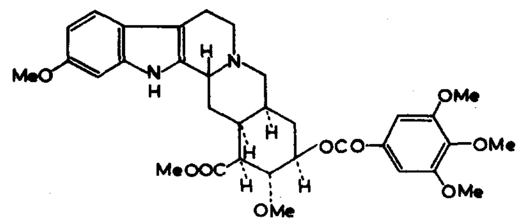


LXXX

isomerized by pivalic acid* in boiling xylene to *dl* reserpic acid lactone (LXXIX ≡ LXXX). Following known reactions[35] in the natural series, the latter was converted by methanolysis to *dl* methyl reserpate (LXXXI), and thence, by treatment with 3,4,5-trimethoxybenzoyl chloride in pyridine, to *dl* reserpine (LXXXII ≡ II).



LXXXI



LXXXII

The racemic reserpine thus obtained was readily resolved by taking advantage of the high crystallinity and low solubility, in methanol, of *l* reserpine *d* camphor-10-sulfonate. The infrared and ultraviolet spectra of the synthetic *l* reserpine were identical in all respects with those of the natural alkaloid. Other properties of the synthetic and natural bases are summarized in Table 1.

TABLE 1

	M.p. (vac.)	$[\alpha]_D^{27°}$ ($CHCl_3$, $c = 1{\cdot}08$)
dl reserpine	260·0–262·0° (*dec.*)	
l reserpine (synthetic)	286·5–288·5° (*dec.*)*	− 120°
l reserpine (natural)	284·0–285·0° (*dec.*)*	− 118°

* Mixture m.p. 285·5–286·5° (*dec.*)

EXPERIMENTAL

Melting points, unless otherwise stated, were determined on a micro hot-stage. Those marked "(vac.)" were taken in evacuated Pyrex capillary tubes; the melting points observed for reserpine, and many related substances, are higher, sharper, and more reproducible, when observed *in vacuo*, than when taken on the hot-stage, or in open-ended capillaries. Ultraviolet spectra were measured in ethanol solution.

Infrared measurements were used for control purposes throughout this investigation, and spectra of all pure substances prepared were determined. Spectra are ordinarily recorded here only for substances in the main line of the synthesis. In each case, the abscissa is plotted in *wave lengths* (2–12 μ), and the ordinate in *percentage transmission* (0–100 per cent). For other substances, pertinent features of the spectra are described textually where desirable.

* Acetic acid, and occasionally mineral acids, have ordinarily been used in bringing about similar isomerizations. We chose pivalic acid, first in order to have a catalyst with boiling point close to that of our solvent, but mainly to suppress side reactions involving cleavage at N^b (→ —N—COR) and opening of the lactone ring (→ —O—COR). All such reactions involve reaction at the carbonyl group of the acid catalyst, and will be relatively difficult with the highly hindered carbonyl function of pivalic acid.

Synthesis of 6-methoxytryptamine

2-*Nitroanisaldehyde*. The following solution of formaldoxime (10 per cent) was prepared. Paraformaldehyde (69 g) and hydroxylamine hydrochloride (158 g) were heated with water (1020 cm^3) until a clear solution was obtained. Sodium acetate (306 g) was then added, and the reaction mixture was kept under gentle reflux for 15–20 min. The solution was cooled to 10° and 6 g of sodium sulfate, 37·5 g of copper sulfate and a solution of 990 g of sodium acetate in 1080 cm^3 of water were added. To this solution of formaldoxime, in a 12 l. three-necked flask, was added an ice-cold solution of 2-nitro-4-methoxybenzene diazonium chloride which had been prepared in advance, as follows. 2-Nitroanisidine (252 g) was suspended with stirring in a mixture of concentrated hydrochloric acid (342 cm^3), water (300 cm^3), and ice (600 g). A solution of sodium nitrite (105 g) in water (150 cm^3) was added slowly at 0–5°. The dark-red solution was filtered through glass wool, and a solution of sodium acetate (185 g) in water (310 cm^3) was added until the mixture was neutral to Congo paper. This solution of 2-nitro-4-methoxybenzene diazonium chloride was added below the surface of the formaldoxime solution, with vigorous stirring. The oxime of 2-nitroanisaldehyde was precipitated as a dark-brown tar which slowly coalesced into one large lump. The nitrogen liberated during the reaction tended to cause heavy foaming. Stirring was continued for 1 hr after the addition was complete. The mixture was then acidified to Congo with concentrated hydrochloric acid. The supernatant liquor was decanted from the tarry oxime, to which ferric ammonium sulfate (1800 g) and water (3 l.) were added. This mixture was heated under reflux for 40 min, and then distilled with steam. The 2-nitroanisaldehyde separated from the distillate on cooling. The first fraction of distillate usually contained a considerable amount of *m*-nitroanisol (orange-yellow, m.p. 38°), which was separated from the desired aldehyde via bisulfite treatment. The steam distillation was continued until no more aldehyde separated from the distillate. The aldehyde was then collected, washed with water, and dried. One hundred and seventy grams of 2-nitroanisaldehyde, m.p. 95–96°, were obtained. For analysis the aldehyde was recrystallized four times from chloroform/petroleum ether, m.p. 95·5–96°.

Anal. Calcd. for $C_8H_7O_4N$: C, 53·04; H, 3·90; N, 7·73. Found: C, 53·30; H, 4·19; N, 7·68.

The 2,4-*dinitrophenylhydrazone*, crystallized once from glacial acetic acid/ethanol (2 : 1) and three times from nitrobenzene, melted at 222–223°.

Anal. Calcd. for $C_{14}H_{11}O_7N$: C, 46·54; H, 3·07; N, 19·39. Found: C, 46·80; H, 3·08; N, 19·63.

2,*β*-*Dinitro-4-methoxystyrene*. A mixture of 2-nitroanisaldehyde (10 g), nitromethane (10 cm^3), ammonium acetate (4 g) and glacial acetic acid (40 cm^3) was heated under reflux in an atmosphere of nitrogen for 2 hr. The hot dark-red solution was slowly poured into 200 cm^3 of ice water with vigorous stirring. The styrene was precipitated as an oily brown material which slowly solidified. The mixture was stirred for 3 hr and then filtered. When the filter cake was washed well with water and dried *in vacuo*, 11 g of amorphous brown crude styrene were obtained. The material was dissolved in chloroform, washed once with saturated sodium bisulfite solution, twice with saturated brine, and dried over anhydrous sodium sulfate. It was then heated under reflux for a few minutes with Norite and filtered through Celite. The filtrate was concentrated to a small volume and petroleum ether was added to bring about crystallization of the product. After 2 hr at room temperature, 8 g of 2,β-dinitro-4-methoxystyrene, m.p. 103°, was collected. For analysis the substance was recrystallized four times from chloroform/petroleum ether, appearing as beautiful long yellow needles, m. p. 103–104°.

Anal. Calcd. for $C_9H_8O_5N_2$: C, 48·22; H, 3·60; N, 12·50. Found: C, 48·30; H, 3·59; N, 12·53.

6-Methoxyindole. 2,β-Dinitro-4-methoxystyrene (25 g) was dissolved in ethyl acetate (281 cm^3). To this solution, 31 cm^3 of ethanol, 35 cm^3 of glacial acetic acid and 2·5 g of palladium/charcoal(10 per cent) were added. The mixture was reduced with hydrogen under a pressure of 50 lb/in^2. The consumption of hydrogen was very rapid, and the reaction strongly exothermic. When the reduction was complete, the mixture was filtered through Celite. The filtrate was added with stirring to a mixture of ether and saturated sodium bicarbonate solution. The two phases were separated, and the ether phase was extracted several times with water to remove ethanol, acetic acid and ammonium acetate. The ether solution was then dried over anhydrous sodium carbonate, and concentrated to approximately 30 cm^3. When petroleum ether was added to the concentrate, crude 6-methoxyindole was precipitated as a brown crystalline mass which was collected after 2 hr (11 g). The crude indole was dissolved in ether, and the ethereal solution was filtered through a column of 75 g of basic aluminium oxide (Merck, activity I). The filtrate was concentrated to a very small volume and petroleum ether was added. Pure, almost colorless 6-methoxyindole (9 g), m.p. 91°, crystallized readily. For analysis the substance was recrystallized three times from petroleum ether, m.p. 91–92°.

Anal. Calcd. for C_9H_9ON: C, 73·45; H, 6·16; N, 9·52. Found: C, 73·53; H, 6·34; N, 9·51.

Ultraviolet spectrum: $\lambda\lambda_{max}$ 220 mμ (ε 29,100), 267 mμ (ε 4100), 292 mμ (ε 5370).

β-6-Methoxyindolyl-glyoxylic acid chloride. 6-Methoxyindole (20 g) was dissolved in anhydrous ether (400 cm^3) with shaking. Oxalyl chloride (20 cm^3) was gradually added at 0°. The bright-red product crystallized readily. After 30 min at 0°, it was collected and washed liberally with ether. Twenty-nine grams (90 per cent) of the chloride, m.p. 125–128° (dec.) $\rightarrow$ 150–165°, were obtained.

Anal. Calcd. for $C_{11}H_8O_3NCl$: Cl, 14·90. Found: Cl, 14·36.

β-6-Methoxyindolyl-glyoxylic acid amide. β-6-Methoxyindolyl-glyoxylic acid chloride (29 g) was added gradually with vigorous stirring to 500 cm^3 of concentrated aqueous ammonia. Reaction took place instantaneously with formation of the yellow amide. After the addition was complete, stirring was continued for 30 min at 40–50°. The mixture was then cooled to 10–20°, and the product was collected (24 g, 90 per cent). For analysis the amide was crystallized four times from tetrahydrofuran/ether m.p. 258–259°.

Anal. Calcd. for $C_{11}H_{10}O_3N_2$: C, 60·54; H, 4·62; N, 12·84. Found: C, 60·54; H, 4·66; N, 12·82.

6-Methoxytryptamine. β-6-Methoxyindolyl-glyoxylic acid amide (20 g), dried in high vacuum, was dissolved in 600 cm^3 of anhydrous tetrahydrofuran under gentle reflux in a 3 l. three-necked flask equipped with stirrer, reflux condenser, and dropping funnel. The entire reaction was carried out in an atmosphere of nitrogen. To the solution of the amide, fresh lithium aluminium hydride (20 g) slurried in 400 cm^3 of anhydrous tetrahydrofuran was added carefully in small portions. The orange-red mixture was kept under gentle reflux overnight. The reaction vessel was then cooled in ice, and 1 kg of methylene chloride was added. Excess lithium aluminium hydride was destroyed with wet tetrahydrofuran. Water was then added until the precipitated hydroxides formed large lumps. The mixture was filtered through Celite and the filter cake was washed with 1 kg of methylene chloride. The filtrate was extracted with a total of 1·4 l of 10 per cent aqueous acetic acid, in four portions. The acetic acid extract was concentrated somewhat *in vacuo* to remove organic solvents. It was then refluxed for 5 min with Norite, under nitrogen, filtered through Celite directly onto ice, made alkaline with sodium hydroxide, and extracted several times with methylene chloride. The methylene chloride extract was washed twice with saturated brine and dried over anhydrous potassium carbonate. When the solvent was removed, 11 g (63 per cent) of crude crystalline 6-methoxytryptamine were obtained. For purification, the base was dissolved in a small amount of methanol and brought to boil. The boiling methanol was then gradually displaced by hot benzene. When the mixture was cooled, the pure 6-methoxytryptamine crystallized in beautiful silky, almost colorless, needles, m.p. 142°. For analysis the base was crystallized three times from aqueous methanol, m.p. 140–141°.

Anal. Calcd. for $C_{11}H_{14}ON_2$: C, 69·44; H, 7·42; N, 14·73. Found: C, 69·24; H, 7·56; N, 14·80.

Ultraviolet spectrum: $\lambda\lambda_{max}$ 224 mμ (ε 33,300), 274 mμ (ε 4620), 293 mμ (ε 5580).

The corresponding *hydrochloride*, twice crystallized from ethanol/ether, melted at 221–223°.

Anal. Calcd. for $C_{11}H_{14}ON_2 \cdot HCl$: C, 58·27; H, 6·67; N, 12·35; Cl, 15·64. Found: C, 58·27; H, 6·91; N, 12·32; Cl, 15·47.

Preparation and characterization of the adducts (IV)

Cis-5, 8-*diketo*-1,4,5,8,9,10-*hexahydronaphthalene*-1-*carboxylic acid* (IV: R = H). Vinylacrylic acid is a sensitive substance, whose isolation in a pure state is attended by severe losses. Further, the pure acid cannot be kept more than a short time before serious decomposition sets in. In these circumstances, we found it convenient to use a freshly prepared crude solution of vinylacrylic acid for the addition reaction with quinone. It should be mentioned, however, that reactions on a small scale, using pure, isolated, vinylacrylic acid, gave the adduct (IV) in yields comparable with or rather better than that described below. The following procedure for the preparation of the vinylacrylic acid solution is patterned after that of Kohler and Butler.[16]

The condensation of malonic acid with acrolein was carried out in three identical separate batches. In each, 2000 g of malonic acid were added to 4·5 l. of pyridine (technical, containing 0·5 per cent of water) with vigorous stirring. After about 40 min the major part of the malonic acid had dissolved. The mixture was then cooled to 10° in an ice-cold bath, and 1333 g of acrolein were added at such a rate that the temperature did not exceed 12°. The addition was complete in about 90 min; stirring was then continued for 3 hr at 0° and subsequently for 5 hr at 35–40°. (The reaction mixture is very viscous at 0° and becomes fairly mobile at 35–40°.) At the end of the stirring period, the three batches were combined and slowly added to 13 l. of a 50

[16] E. P. Kohler and F. R. Butler *J. Amer. Chem. Soc.* **48**, 1041 (1926). Cf. also O. Doebner *Ber. Dtsch. Chem. Ges.* **35**, 1137 (1902); K. Alder and W. Vogt *Liebigs Ann.* **570**, 196 (1950).

per cent (v/v) aqueous solution of sulfuric acid at −5°, with stirring, and at such a rate that the temperature did not exceed 15–20°. The mixture, which was acidic to Congo, was filtered through Celite. The clear yellow filtrate was extracted six times with ether (three times with 7 gal and three times with 3 gal each). The ether extracts were twice washed quickly with water, dried over anhydrous sodium sulfate, and concentrated to 3 gal. Six gallons of benzene were then added, and the mixture was again concentrated to 3 gal.

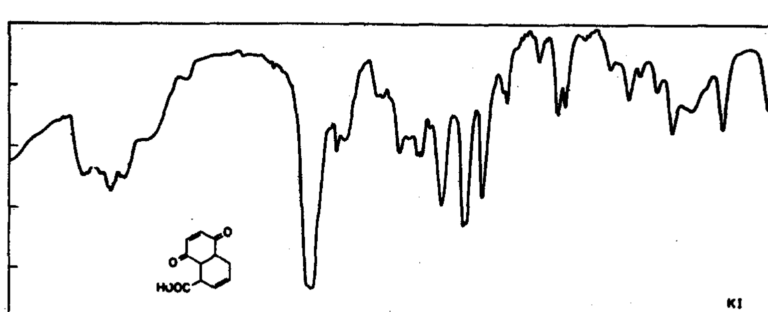
Three and one-half kilograms of quinone (Eastman Kodak Practical, recrystallized by Soxhlet extraction with octane; if large crystals of quinone are present, the material should be ground before use), dissolved in 2 gal of benzene, were added to the above benzene solution of vinylacrylic acid. The mixture was heated under reflux for 3 hr, and then filtered hot (*c.* 45–50°). The filter cake comprised 2·3 kg of grey crude adduct. The benzene mother liquors were concentrated at normal pressure to *c.* 1·5 gal and again filtered hot. This second filtration gave a further 700 g of adduct, black in color. The filtrate was discarded. The combined fractions of crude adduct (3 kg) were dissolved under reflux in a mixture of 30 l. of pure acetone and 30 l. of pure methanol. Norite (450 g) was added to the clear, dark-red, solution, and the mixture was kept under reflux for 10 min. It was then filtered hot and under pressure through a large-diameter filter, pre-coated with Celite. During filtration, the solution was kept at about 50°. The filtrate was cooled to 10–15°, and 70 l. of pentane were added gradually, with stirring. The adduct crystallized readily in almost colorless small prisms. The mixture was stirred at 10–15° for 3 hr and then filtered. The filter cake was washed with acetone/pentane (1 : 2) until it did not darken on exposure to air. The product was then washed with pentane, and air dried. Yield: 2 kg, m.p. 215–225°.

The adduct could be recrystallized readily by addition of pentane to its solutions in acetone, ethyl acetate, chloroform, or acetone/methanol mixtures, or from tetrahydrofuran/ether. After two crystallizations from the latter solvent, the air-dried material had m.p. 223–229°. Although no sharp-melting sample of the adduct was ever obtained, a fourteen-plate counter-current distribution of once-crystallized material, m.p. 215–225°, using 70 per cent aqueous methanol versus chloroform/ethyl acetate (1 : 18) revealed no significant amount of any contaminating substance.

For analysis the adduct was twice crystallized from water, m.p. 215–225°.

Anal. Calcd. for $C_{11}H_{10}O_4$: C, 64·07; H, 4·89. Found: C, 63·91: H, 5·00

Ultraviolet spectrum: λ_{max} 224 mμ (ε 11,300) and 355 mμ (ε 71).

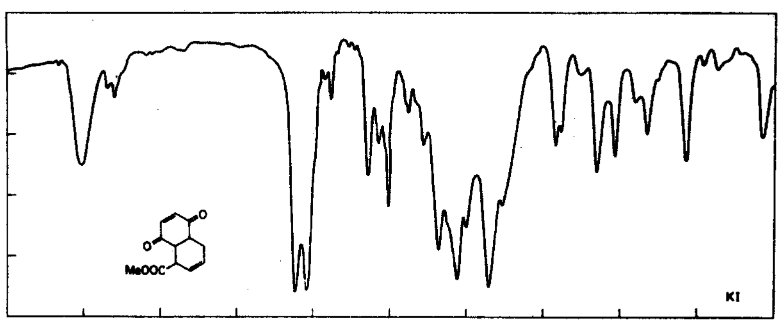


The *methyl ester* (IV : R = H) was prepared either by methylation of the acid adduct (IV : R = H) with diazomethane, or by reaction of quinone with methyl vinylacrylate. Neither of these methods was investigated extensively with a view to determining optimum conditions.

Method (a). Two grams of the adduct (IV : R = H) were dissolved in 50 cm³ of methylcellosolve and treated on 0–5° with 1·2 moles of ethereal diazomethane solution. The reaction mixture was allowed to stand for 15 min at 0° and then for 2 hr at room temperature. It was then evaporated to dryness *in vacuo*. When the residue was extracted several times with boiling ether, 300 mg of crystalline starting material remained undissolved. The combined ethereal extracts were shaken with ice-cold sodium bicarbonate solution, dried with sodium sulfate, and taken to dryness *in vacuo*. When the residue was crystallized from ether, 910 mg of thick glassy prisms of the desired ester, m.p. 103–104°, were obtained. For analysis this material was dried for 5 hr at 60° in high vacuum.

Anal. Calcd. for $C_{12}H_{12}O_4$: C, 65·44; H, 5·59. Found: C, 65·07; H, 5·57.

Ultraviolet spectrum: λ_{max} 223 mμ (ε 10,670).



When the mother liquors from the above preparation were allowed to stand, a considerable amount of crystalline material separated. When this was washed with benzene and crystallized from methanol, it had m.p. 168–170°, and was shown to be the aromatic ester (VI) (see below).

Method (b). Methyl vinylacrylate, b.p. 57–58°/25 mm (n_D^{25} 1·4797), was prepared by esterification of crude vinylacrylic acid, obtained by evaporation of the benzene concentrate, whose preparation is described above, by boiling in methanol containing sulfuric acid for 3 hr. A sample of the ester so obtained (63 g) was heated under reflux for 10 hr with 70 g of quinone in 200 cm³ of benzene. The reaction mixture was then shaken successively with aqueous sodium bisulfite and dilute aqueous potassium hydroxide. During the last of these separations, 34 g of a colorless solid, m.p. 120–125°, separated, which was crystallized from acetone/ether, m.p. 125–126°. This substance was shown to be a molecular compound of the desired adduct ester (IV: R = Me) with hydroquinone.

Anal. Calcd. for $C_{12}H_{12}O_4 \cdot C_6H_6O_2$: C, 65·44; H, 5·50; OMe, 9·4. Found: C, 65·24; H, 5·63; OMe, 10·58.

The ultraviolet and infrared spectra of the substance were composites of those of hydroquinone and the ester (IV: R = Me). When the material was dissolved in methylene chloride and shaken with ice-cold dilute aqueous potassium hydroxide, the ester (IV: R = Me) was recovered from the methylene chloride phase. This procedure for the separation of the components was attended by considerable loss, and undoubtedly does not represent the best method for recovering the desired ester from the molecular complex.

The filtrate from the separation of the molecular compound was further washed with dilute aqueous potash, then with water, dried over sodium sulfate, and evaporated. When the residue was dissolved in benzene and allowed to stand, 13 g of the aromatic ester (VI), m.p. 170–172°, separated. After removal of this material, the filtrate was concentrated *in vacuo*, dissolved in ether, and seeded with a specimen of the ester (IV: R = Me). Overnight, 10·2 g of the ester (IV: R = Me), m.p. 98–103°, separated.

5,8-*Dihydroxy*-1,4-*dihydronaphthoic acid methyl ester* (VI). The adduct (IV: R = H) (500 mg) was suspended in 4 cm^3 of methanol. The reaction mixture was saturated with hydrogen chloride at 0°, and allowed to stand overnight. The solution was then taken to dryness *in vacuo*, and the residue crystallized by trituration with ether. Recrystallization from methanol/ether gave colorless needles, m.p. 168–170°.

Anal. Calcd. for $C_{12}H_{12}O_4$: C, 65·44; H, 5·50. Found: C, 65·09; H, 5·66.

Ultraviolet spectrum: λ_{max} 210 mμ (ε 7090) and λ_{max} 294 mμ (ε 3710).

The infrared spectrum ($CHCl_3$) displayed sharp phenolic hydroxyl absorption at 3·00 μ, and an ester band at 5·83 μ.

5,8-*Diketo*-1,4,5,6,7,8,9,10-*octahydronaphthoic acid.* When the adduct (IV: R = H) was reduced with zinc and acetic acid, the conjugated double bond ($\Delta^{6,7}$) was reduced. The adduct (IV: R = H) (2 g) was dissolved in a mixture of 40 cm^3 of acetic acid and 20 cm^3 of water. Four grams of zinc dust were added with stirring over a period of 10 min, and the stirring was continued for a further 15 min. The zinc was then removed by filtration, and the filtrate was concentrated *in vacuo* to about 4 cm^3. The material which separated was dissolved in chloroform, filtered from some insoluble matter, and concentrated to dryness. Crystallization from chloroform gave 860 mg of crystalline solid, m.p. 154·5–158°. After recrystallization from acetone, the melting point was 159–160°, and was not elevated by further recrystallization.

Anal. Calcd. for $C_{11}H_{12}O_4$: C, 63·45; H, 5·81. Found: C, 63·03; H, 5·95.

This compound showed no high intensity absorption in the ultraviolet above 210 mμ.

The infrared spectrum ($CHCl_3$) in the carbonyl region possessed only a single rather broad band (λ_{max} 5·85 μ).

Acetylation of the adduct (IV: R = H). The adduct (IV: R = H) (100 mg) was dissolved in 6 cm^3 of a solution of acetic anhydride containing 3 per cent of acetyl chloride, and allowed to stand at room temperature for 7 hr. The reaction mixture was then taken to dryness *in vacuo* at 70°. The crystalline residue was washed thrice with cold ethanol and recrystallized three times from acetone/ethanol. Thirty-five milligrams of the *mixed anhydride* (XI) were obtained as fine colorless needles, m.p. 120–122°. For analysis, the material was dried for 6 hr at 60° in high vacuum.

Anal. Calcd. for $C_{13}H_{12}O_5$: C, 62·90; H, 4·87. Found: C, 62·79; H, 5·18.

Ultraviolet spectrum: λ_{max} 224 mμ (ε 8970).

The infrared spectrum ($CHCl_3$) possessed bands at 5·48, 5·68 and 5·90 μ.

Oxidation of the ester adduct (IV: R = Me) *by perbenzoic acid.* The ester adduct (IV: R = Me) (440 mg) was dissolved in 4 cm³ of benzene and treated with 4 cm³ of a 0·63 M solution of perbenzoic acid in benzene. After it had stood for 20 hr at room temperature, the reaction mixture was shaken successively with dilute aqueous sodium iodide, sodium thiosulfate, acetic acid, and sodium bicarbonate. It was then dried over sodium sulfate and concentrated *in vacuo*. When the residue was twice crystallized from benzene/ether, 244 mg of the *oxide* (VII), m.p. 136–139°, were obtained as colorless needles. For analysis, the substance was crystallized further from chloroform/ether (m.p. 140–141°) and dried at 60° in high vacuum for 5 hr.

Anal. Calcd. for $C_{12}H_{12}O_5$: C, 61·01; H, 5·12. Found: C, 61·06; H, 5·25.

Ultraviolet spectrum: λ_{max} 221 mμ (ε 10,380).

The infrared spectrum ($CHCl_3$) possessed bands at 5·73 and 5·90 μ.

Hydroxylation of the oxide (VII). The oxide (VII) (600 mg) was treated with 50 cm³ of a solution prepared by shaking 3 cm³ of perhydrol (30 per cent) with 100 cm³ of ether and drying with sodium sulfate. After addition of 20 cm³ of benzene to bring the oxide into solution, 50 mg of osmium tetroxide in 5 cm³ of ether were added. After standing for 37 hr at room temperature, the solution had deposited well-formed crystals which were removed by filtration and washed with ether. When the mother liquor was taken to dryness *in vacuo* and the residue triturated with acetone, further crystalline material was obtained (total, 335 mg). After three recrystallizations from acetone, the diol (VIII) was obtained as elongated colorless prisms, m.p. 159–161° (*dec.*); it was dried for analysis for several hours at 80° in high vacuum.

Anal. Calcd. for $C_{12}H_{14}O_7$: C, 53·33; H, 5·22. Found: C, 53·61; H, 5·53.

This compound showed no intense ultraviolet absorption above 210 mμ.

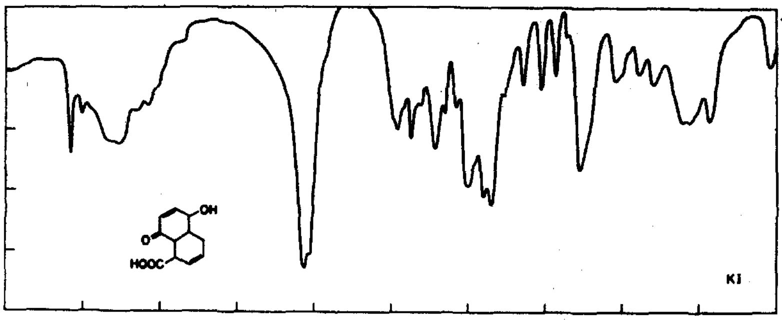
The infrared spectrum (KI) possessed bands at 2·95, 5·75 and 5·80 μ.

Preparation of the dihydro adduct (XII). *The six-membered lactone series*

Cis-5-*hydroxy*-8-*keto*-1,4,5,8,9,10-*hexahydronaphthoic acid* (XII). Three hundred grams of the adduct (IV: R = H) were slurried with 2000 cm³ of water, and cooled in an ice bath. One hundred and twenty-three grams of sodium bicarbonate dissolved in 2000 cm³ of water were then added slowly. A thin layer of ethyl acetate was maintained on top of the reaction mixture to prevent foaming. When nearly all of the adduct had dissolved, 35 g of sodium borohydride, dissolved in water, were added in portions, and the mixture was then stirred for 15 min. Ethyl acetate (1000 cm³) was then added, and the solution was acidified to Congo with 20 per cent aqueous sulfuric acid. The acidic solution was seeded with a sample of the dihydro derivative (XII) and stirred at 0° for another 30 min. The product which separated was removed and washed with *c.* 2000 cm³ of water. After having been dried, this crude material weighed 220 g. Ethyl acetate (500 cm³) was then added to the mother liquors, and the two phases were separated. The dark-colored organic phase was discarded, and the remaining aqueous liquor was extracted three times with ethyl acetate. The combined extracts were washed twice with saturated sodium chloride solution, and dried over anhydrous sodium sulfate. When the extract was concentrated and treated with ether, a further 20 g of the dihydro adduct separated. Total yield: 240 g (80 per cent). For analysis the dihydro derivative was crystallized three times from aqueous methanol, m.p. 179–180°.

Anal. Calcd. for $C_{11}H_{12}O_4$: C, 63·45; H, 5·81. Found: C, 63·47; H, 6·08.

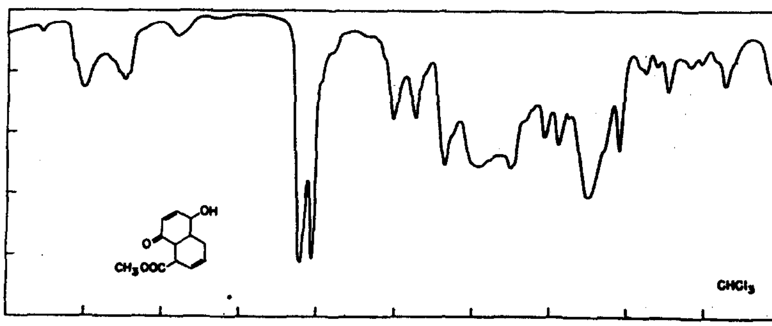
The ultraviolet spectrum of (XII) showed only end absorption ($\varepsilon_{215 m\mu}$ 5000).



The corresponding *methyl ester* (XXXVII) was prepared by the action of diazomethane upon (XII). The latter (5 g) was dissolved in 50 cm^3 of anhydrous dioxane. One mole of diazomethane in ether was added at 0°, and the solvents were removed *in vacuo*; the temperature was not allowed to rise above 30°. When only a small amount of dioxane was left, ether was added, and 3·5 g of the ester (XXXVII) crystallized readily on scratching. For analysis the ester was recrystallized four times from acetone/ether, m.p. 93–94°.

Anal. Calcd. for $C_{12}H_{14}O_4$: C, 64·85; H, 6·35. Found: C, 64·57; H, 6·48.

Ultraviolet spectrum: λ_{max} 215 mμ (ε 7200).



When attempts were made to effect esterification of (XII) with methanol in the presence of acid catalysts, even under very mild conditions, non-crystalline products were obtained, whose ultraviolet spectra indicated clearly that aromatization had occurred to a considerable extent.

Cis-*5-hydroxy-8-ketodecahydronaphthoic acid* (XIV). The dihydro derivative (XII) (5 g), dissolved in 250 cm^3 of glacial acetic acid, was shaken under hydrogen in the presence of 0·25 g of pre-reduced palladium-barium sulfate catalyst. In 2 hr 2 moles of hydrogen had been absorbed, and the consumption of hydrogen had ceased. When the residue, after removal of catalyst and solvent, was crystallized from ethyl acetate/ether, 4·7 g of crystalline hydroxy acid (XIV), m.p. 147–149°, were obtained. The analytical sample, obtained by crystallization from acetone/ether, had m.p. 153–155°.

Anal. Calcd. for $C_{11}H_{16}O_4$: C, 62·25; H, 7·60. Found: C, 62·08; H, 7·54.

No high intensity ultraviolet absorption above 210 mμ was observed.

The corresponding *methyl ester* was obtained by treatment of (XIV) with diazomethane. The ketohydroxy acid (XIV) (4·5 g) was dissolved in 200 cm^3 of absolute dioxane. The solution was cooled to 15°, and 60 cm^3 of ethereal 1·9 per cent diazomethane solution were added. The solvent was then removed *in vacuo* at 40°. When the residual oil was crystallized from ether acetate/ether, 4·2 g of the ester, m.p. 115–118°, were obtained. Further crystallization from acetone/ether raised the melting point to 125–126°. This substance was converted into an *acetyl derivative*. The ester (4 g) was dissolved in absolute pyridine (20 cm^3) and acetic anhydride (15 cm^3). The reaction mixture was allowed to stand at room temperature for 15 hr, and then concentrated to dryness *in vacuo*. The residue was dissolved in chloroform/ether (1 : 3) and washed twice with 2 N hydrochloric acid, twice with aqueous sodium bicarbonate and finally with saturated sodium chloride solution. The dried solvent was evaporated *in vacuo*, and the residue crystallized from ethyl acetate/ether. The *acetyl derivative* (4 g, 85 per cent), was obtained as colorless prisms, m.p. 128–129°, raised to 129–130° by further crystallization from acetone/ether.

Anal. Calcd. for $C_{14}H_{20}O_6$: C, 62·67; H, 7·51. Found: C, 62·93; H, 7·49.

The saturated lactone (XV). The hexahydro derivative (XIV) (1 g), sodium acetate (0·2 g), acetic anhydride (1 cm^3) and benzene (20 cm^3) were heated under reflux in an atmosphere of nitrogen for 2 hr. The cooled solution was taken up in chloroform, washed twice with saturated sodium bicarbonate, and then with water. After the extract had been dried over sodium sulfate and evaporated, the residue was crystallized from acetone/ether: 585 mg (64 per cent), m.p. 123–125°. For analysis the lactone was recrystallized from acetone/ether, m.p. 127–128°.

Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68·02; H, 7·27. Found: C, 67·41; H, 6·95.

The infrared spectrum of the saturated lactone in chloroform solution possessed a complex, not quite completely resolved, band in the carbonyl region. A potassium iodide spectrum, however, showed two clearly resolved bands at 5·80 and 5·85 μ.

The 2,4-*dinitrophenylhydrazone* of the saturated lactone, crystallized from dichloromethane/methanol, had m.p. 246–248°. Its infrared spectrum possessed a single sharp band in the carbonyl region, at 5·79 μ.

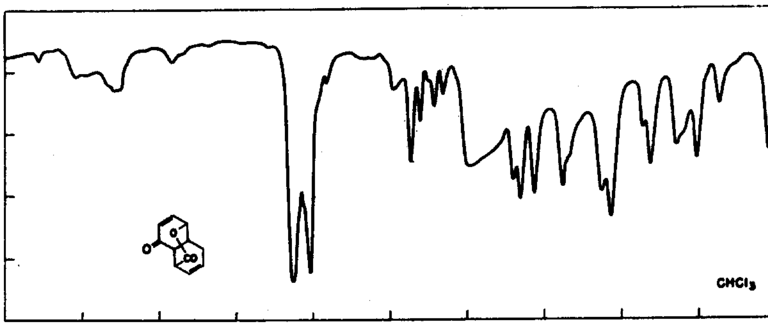
An alternative method of preparing the saturated keto lactone (XV) is described below.

Preparation of the transannular six-membered lactone (XIII). A mixture of 200 g of the dihydro derivative (XII), 200 cm^3 of acetic anhydride, 40 g of anhydrous sodium acetate, and 4000 cm^3 of benzene was heated under reflux with vigorous stirring. The insoluble dihydro derivative dissolved slowly; in about 15 min the reaction mixture was a clear yellow solution containing some undissolved sodium acetate. After the mixture had been heated for 1 hr, it was cooled in an ice bath, and 2000 cm^3 of ethyl acetate and some ice-cold water were added with stirring. The phases were separated, and the organic phase was extracted once with ice-cold sodium bicarbonate. The combined aqueous phases were back-washed with ethyl acetate. The ethyl acetate solutions were combined, washed twice with saturated sodium chloride solution, and dried over sodium sulfate. When the solvent was concentrated to a small volume, crystallization of the lactone (XIII) commenced. Ether was added, and the mixture was kept in the cold for a few hours. The crystalline product was cooled and washed well with ethyl acetate/ether, and subsequently with ether alone: 111 g. From the mother liquors, another 10 g of the lactone were recovered. Total yield: 121 g (66 per cent). For analysis, the lactone was crystallized once from acetone.

Anal. Calcd. for $C_{11}H_{10}O_3$: C, 69·46; H, 5·30. Found: C, 69·41; H, 5·29.

Ultraviolet spectrum: λ_{max} 220 mμ (ε 9200).

The infrared spectrum of the lactone in chloroform solution possessed bands at 5·74 and 5·96 μ.



Hydrogenation of (XIII) gave the saturated lactone (XV), whose preparation by an alternative method is described above. The keto lactone (XIII) (1·27 g) dissolved in dry dioxane (20 cm^3) was shaken under hydrogen in the presence of a pre-reduced palladium-barium sulfate catalyst (300 mg). In 2 hr 30 min 2 moles of hydrogen had been absorbed and the absorption ceased. The residue, after removal of catalyst, and concentration *in vacuo*, was crystallized from ether, and gave 1·05 g (82 per cent) of the saturated keto lactone (XV), m.p. 126–127°, identical with the material described above.

Bromination of the unsaturated keto lactone (XIII). The lactone (XIII) (190 mg) was dissolved in 5 cm^3 of glacial acetic acid. A solution of bromine in acetic acid (2·9 g bromine in 25 cm^3 glacial acetic acid) was added drop-wise with cooling and stirring until the reaction mixture remained slightly yellow. The excess of bromine was destroyed with a few drops of 1 N sodium thiosulfate solution, and the solvent was evaporated *in vacuo* at 40°. The residual oil was dissolved in ethyl acetate and the organic layer was washed with saturated sodium bicarbonate and water. The dried extract was evaporated *in vacuo* at 40°, and the residue crystallized from ether. The bromolactone (i) (268 mg) was obtained as colorless prisms, m.p. 156–162°. For analysis the bromo derivative was recrystallized from acetone/ether, m.p. 167–168°.

Anal. Calcd. for $C_{11}H_9O_3Br$: C, 49·10; H, 3·37; Br, 29·70. Found: C, 49·06; H, 3·14; Br, 29·81.

Ultraviolet spectrum: λ_{max} 253 mμ (ε 4250).

The infrared spectrum of the bromolactone in chloroform possesses bands at 5·72 and 5·91 μ. In solid potassium iodide the lower wavelength band is displaced to 5·78 μ.

Preparation of the iodoacetate (ii). To a well-stirred suspension of the unsaturated keto lactone (XIII) (3·8 g) and silver acetate (3·4 g) in glacial acetic acid (100 cm^3), finely powdered iodine (5 g) was added. After the mixture had been stirred for 2 hr 30 min, a further 100 mg of silver acetate was added to destroy excess iodine. The mixture was then filtered through Celite, and the filtrate was evaporated *in vacuo*. The residue solidified, and was recrystallized from dichloromethane to give 3·2 g of slightly yellow *iodoacetate* (ii), m.p. 185–186° (*dec.*). For analysis the substance was recrystallized from dichloromethane/ether, and was obtained as colorless prisms, m.p. 186° (*dec.*).

Anal. Calcd. for $C_{13}H_{13}O_5I$: C, 41·40; H, 3·49; I, 33·70. Found: C, 41·02; H, 3·65; I, 33·94.

Ultraviolet spectrum: λ_{max} 222 mμ (ε 4000).

Zinc reduction of the lactone (XIII): Cis-8-*keto*-1,4,7,8,9,10-*hexahydronaphthoic acid* (viii). The lactone (XIII) (1 g) was dissolved in 10 cm³ of warm glacial acetic acid. The solution was cooled to room temperature, and 3·25 cm³ of water were added. Zinc dust (2 g) was added with vigorous stirring, and the mixture was then stirred further for 10 min. The zinc was removed by filtration, and the filter cake was washed with aqueous acetic acid of the concentration used for the reaction. The filtrate was then poured into a large amount of ethyl acetate. The ethyl acetate solution, from which considerable zinc acetate had separated, was washed twice with water and once with saturated sodium chloride solution, and then dried over sodium sulfate. When the solvent was removed *in vacuo*, the residue crystallized readily, and after recrystallization from ethyl acetate, 1 g of the keto acid (viii), m.p. 155–158°, was obtained. For analysis the acid was recrystallized three times from ethyl acetate, m.p. 154–156°.

Anal. Calcd. for $C_{11}H_{12}O_3$: C, 68·73; H, 6·29. Found: C, 68·93; H, 6·47.

The corresponding *methyl ester* was formed when the keto acid (viii) (1 g) was dissolved in a small amount of methanol, and the cooled solution (5°) was treated with excess ethereal diazomethane. The ester crystallized readily after the solvents were removed *in vacuo* and ether was added. For analysis the ester was recrystallized three times from ether containing a small amount of petroleum ether, m.p. 68·5–69°.

Anal. Calcd. for $C_{12}H_{14}O_3$: C, 69·88; H, 6·84. Found: C, 69·94; H, 6·98.

Ultraviolet spectrum: weak end absorption ($\varepsilon_{215m\mu}$ 506).

The infrared spectrum possessed a poorly resolved complex band in the carbonyl region, with indications of maxima at 5·78 and 5·84 μ.

The ester was transformed into a corresponding *ethylene thioketal*: The ester (1·1 g) was dissolved in glacial acetic acid (5 cm³). Ethanedithiol (0·7 cm³) and freshly distilled boron trifluoride etherate (0·7 cm³) were added, and the solution was kept at room temperature for 1 hr 45 min. The reaction mixture was then poured into a large amount of ice-cold ethyl acetate. The solution was then washed twice with ice-cold sodium bicarbonate, once with saturated sodium chloride solution, and dried over magnesium sulfate. When the solvent was removed, 1·5 g of a yellowish oil remained. This residue was filtered through a short column of neutral alumina (Woelm, activity I) in methylene chloride/benzene (1 : 1). The first two 20 cm³ fractions of the eluate gave 550 mg and 260 mg respectively of almost entirely crystalline thioketal. The first fraction was distilled in high vacuum (125–135° air-bath temperature) and subsequently recrystallized three times from ether containing a little petroleum ether, m.p. 118–118·5°.

Anal. Calcd. for $C_{14}H_{18}O_2S_2$: C, 59·54; H, 6·42; S, 22·75. Found: C, 59·42; H, 6·47; S, 23·25.

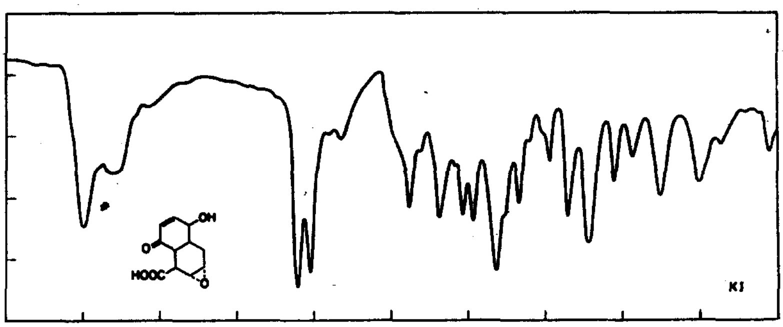
Ultraviolet spectrum: no absorption.

Perbenzoic acid oxidation of the dihydro derivative (XII): Cis-2,3-*oxido*-5-*hydroxy*-8-*keto*-1,2,3,4,5,8,9,10-*octahydronaphthoic acid* (XIX). The dihydro derivative (XII)

(35 g, 0·168 mole) was dissolved (by warming) in 300 cm³ of dioxane. To the cooled solution, 320 cm³ of 0·605 M perbenzoic acid in benzene (0·194 mole) were added. The resulting mixture, which became warm, was allowed to stand at room temperature for 25 hr. When the solvent was removed *in vacuo*, and the residue was treated with ethyl acetate, the product crystallized. After the residue had been triturated with ethyl acetate in ether, 26 g of colorless oxide, m.p. 156–160°, was collected. Concentration of the mother liquors afforded a further 4 g of product, m.p. 150–156°: the total yield of the crude oxide (XIX) was 80 per cent. For analysis the material was crystallized from ethyl acetate to give colorless prisms, m.p. 160–161°.

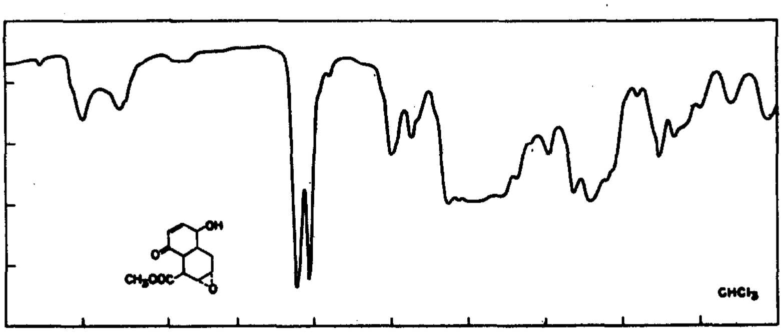
Anal. Calcd. for $C_{11}H_{12}O_5$: C, 58·92; H, 5·40. Found: C, 58·86; H, 5·64.

Ultraviolet spectrum: λ_{max} 223 mμ (ε 5800).



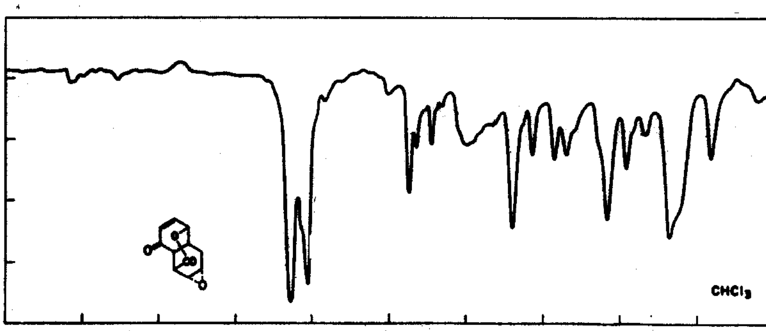
The corresponding *methyl ester* (XLVII) was obtained by the action of diazomethane upon the acid (XIX). The latter (20 g) was dissolved in 200 cm³ of warm anhydrous dioxane. The solution was cooled to 5° and treated with 1 mole of diazomethane in ether. The solvents were immediately concentrated, first at atmospheric, and later at reduced pressure, to about 50 cm³. After most of the ether had been removed, the temperature was kept below 30°. When ether was added to the concentrated dioxane solution, crystallization set in immediately. After the mixture had been kept at 0° for 3 hr, 19 g of the ester (XLVII), m.p. 130–131°, were collected. Another gram of the ester was recovered from the mother liquors. Total yield: 20 g (95 per cent). For analysis the ester was recrystallized twice from acetone/petroleum ether and dried 6 hr at 60° in high vacuum, m.p. 132°.

Anal. Calcd. for $C_{12}H_{14}O_5$: C, 60·50; H, 5·92. Found: C, 60·46; H, 6·12.



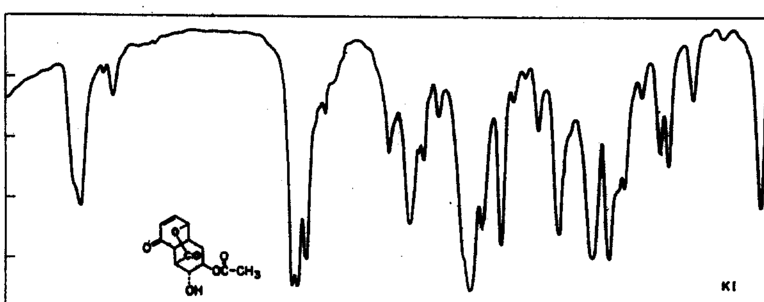
Lactonization of the hydroxy acid (XIX): *The oxido lactone* (XXVIII). A mixture of the oxido acid (XIX) (15·4 g), sodium acetate (3·1 g), acetic anhydride (15·5 cm³) and benzene (300 cm^3) was heated under reflux for 4 hr. The reaction mixture was then cooled, ethyl acetate (300 cm^3) and some chipped ice were added, and the resulting mixture was washed with cold 5 per cent sodium bicarbonate solution. The two phases were filtered together to remove a small amount of polymeric material which hindered separation, and the bicarbonate layer was washed twice with ethyl acetate and once with chloroform. The combined organic phases were dried over sodium sulfate and evaporated to yield an oil which slowly solidified. This product was triturated with ethyl acetate and filtered to yield 5·8 g (41 per cent) of the lactone (XXVIII), m.p. 172–177°. For analysis the lactone was crystallized from acetone to give colorless prisms, m.p. 177–177·5°.

Anal. Calcd. for $C_{11}H_{10}O_4$: C, 64·07; H, 4·89. Found: C, 64·13; H, 4·95.
Ultraviolet spectrum: λ_{max} 219 mμ (ε 6160).



Cleavage of the oxide (XXVIII): *The hydroxy acetate* (XXIX). The oxide (XXVIII) (5·2 g), trifluoroacetic acid (5·2 cm^3), and glacial acetic acid (390 cm^3) were heated under reflux for 2 hr. The solvent was then evaporated *in vacuo* to give a solid residue which, when washed with acetone, gave 1·93 g of colorless crystalline material, m.p. 224–226°. The acetone wash liquor was concentrated and treated with ether to give a second crop, 2·66 g, which was crystallized from acetone/benzene to yield 1·85 g of product, m.p. 229–231°. The analytical sample of the hydroxy acetate (XXIX), obtained by recrystallization from acetone/benzene, had m.p. 232–233°.

Anal. Calcd. for $C_{13}H_{14}O_6$: C, 58·64; H, 5·30. Found: C, 58·87; H, 5·48.
Ultraviolet spectrum: λ_{max} 223 mμ (ε 6600).

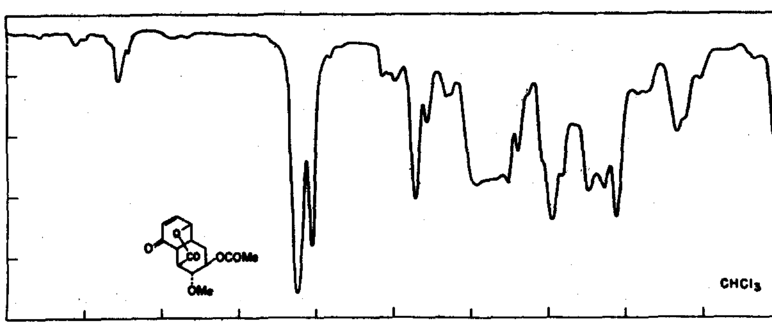


When the oxido acid (XIX) was treated with acetic acid containing trifluoroacetic acid under conditions identical with those just described, no pure product could be isolated, but the ultraviolet and infrared spectra of the crude materials obtained indicated clearly that aromatization had occurred to a considerable extent (cf. footnote p. 9).

Methylation of the hydroxy acetate (XXIX): *The methoxy acetate* (XXXI). The hydroxy acetate (XXIX) (1·29 g), dissolved in 52 cm^3 of dioxane, was treated with 39 cm^3 of methyl iodide, 20 g of freshly prepared silver oxide and 20 g of anhydrous sodium sulfate. This mixture was heated under reflux, with stirring, for 1 hr, and then filtered through a sintered glass plate. After the filtrate had been taken to dryness *in vacuo*, the residue was dissolved in ethyl acetate and filtered through 15 g of neutral aluminium oxide (activity II/III). When the eluate was concentrated to a small volume and treated with some drops of ether, 557 mg (41 per cent) of methoxy acetate (XXXI), m.p. 162–165°, separated. For analysis the compound was crystallized from ethyl acetate/ether, to give heavy glassy prisms, m.p. 167–169°, which were dried at 70° in high vacuum for several hours.

Anal. Calcd. for $C_{14}H_{16}O_6$: C, 59·99; H, 5·75; OMe, 11·07. Found: C, 60·08; H, 6·02; OMe, 11·03.

Ultraviolet spectrum: λ_{max} 222 mμ (ε 5880).



From the mother liquors, after separation of the methoxy acetate (XXXI), the *C-methylated compound* (iii) was isolated by careful chromatography on aluminium oxide (activity II/III). The substance was eluted in the early fractions of the chromatogram, using benzene containing 20 per cent of ethyl acetate. The material in these fractions had m.p. 144–145°. Further crystallization from acetone gave colorless needles, m.p. 152–153°. This substance forms a continuous series of mixed crystals with the methoxy acetate (XXXI). The melting point of a mixture of (XXXI) and (iii) was 136–155°. For analysis, (iii) was dried overnight in high vacuum at 80°.

Anal. Calcd. for $C_{15}H_{18}O_6$: C, 61·21; H, 6·17; OMe, 10·55. Found: C, 61·28; H, 6·35; OMe, 10·88.

Ultraviolet spectrum: λ_{max} 234 mμ (ε 7700).

Hydrogen peroxide oxidation of the methoxy acetate (XXXI): *The oxide* (XXXII). The methoxy acetate (XXXI) (180 mg) in pyridine (7 cm^3) and hydrogen peroxide (1·4 cm^3 of 30 per cent solution) was allowed to stand at room temperature for 18 hr. The reaction mixture was then poured onto ice. The product was extracted with ethyl acetate, and the organic layer washed with dilute hydrochloric acid, saturated sodium bicarbonate solution, and saturated sodium chloride solution. The extract was dried and evaporated, and the colorless oily residue was crystallized from ether to give 62 mg of the oxide (XXXII), m.p. 165–168°. The analytical sample, obtained by recrystallization from acetone/ether, formed plates, m.p. 169–170°.

Anal. Calcd. for $C_{14}H_{18}O_7$: C, 56·75; H, 5·44. Found: C, 56·77; H, 5·58.

Ultraviolet spectrum: no absorption of high intensity above 210 mμ.

Oxidation of the methoxy acetate (XXXI) *by osmium tetroxide*. Osmium tetroxide (82 mg), dissolved in dry benzene (1·25 cm^3), was added to a solution of the methoxy acetate (XXXI) (70 mg) in absolute benzene (2 cm^3) containing pyridine (0·05 cm^3). The mixture was allowed to stand at room temperature for 15 hr. During this time 138 mg (80 per cent) of the osmium complex (XXXIII), m.p. 175–182° (*dec.*), separated as brown prisms. For analysis the material was crystallized from dichloromethane. m.p. 180–190° (*dec.*).

Anal. Calcd. for $C_{34}H_{46}O_{10}N_2Os$: N, 4·04. Found: N, 4·21.

Zinc reduction of the methoxy acetate (XXXI): *The unsaturated acid* (ix). The methoxy acetate (XXXI) (200 mg) was dissolved in acetic acid (2 cm^3) and water (0·65 cm^3). To the cooled, well-stirred, solution, 400 mg of zinc powder were added all at once; the cooling was such as to keep the temperature below 15°. Stirring was continued for 8 min, and the reaction mixture was then poured into 100 cm^3 of ethyl acetate. The solution was then shaken with water and saturated sodium chloride solution, dried over sodium sulfate, and taken to dryness *in vacuo* at 30–50°. The crystalline residue (200 mg) was washed with cold acetone. The fine prisms of (ix) so obtained melted at 165–168°, resolidified in needles, and melted again at 207–215°. For analysis the material was dried in high vacuum at 80° for several hours.

Anal. Calcd. for $C_{14}H_{18}O_6$: C, 59·56; H, 6·43. Found: C, 59·84; H, 6·64.

The infrared spectrum ($CHCl_3$) possessed bands at 5·73 and 5·80 μ.

The above acid (ix) was transformed into its *methyl ester*, and thence into the corresponding *ethylene thioketal*. The acid (ix) (200 mg) was dissolved in 5 cm^3 of methanol, diluted with 5 cm^3 of ether, and treated with an excess of ethereal diazomethane solution at 0°. After 5 min the solution was taken to dryness *in vacuo* and the residue was dissolved in 2 cm^3 of acetic acid. Ethylene dithiol (0·3 cm^3) and boron trifluoride etherate (0·2 cm^3) were added, and the reaction mixture was allowed to stand at room temperature for 1 hr. The solvent was then removed *in vacuo*, the yellowish residue was dissolved in dichloromethane/ether (1 : 1) and shaken with water, sodium bicarbonate solution, and saturated sodium chloride solution. The organic phase was dried with sodium sulfate, and evaporated to dryness. When the yellow residue was distilled in high vacuum, 166 mg of colorless distillate was obtained which was chromatographed on 10 g of neutral alumina (activity II/III). Dichloromethane/benzene (1 : 1) eluted 133 mg of crystalline material. For analysis the *ethylene thioketal* was crystallized twice from ether/petroleum ether, to give colorless prisms, m.p. 112–113°, which were dried in high vacuum for several hours at 80°.

Anal. Calcd. for $C_{17}H_{24}O_5S_2$: C, 54·83; H, 6·50; S, 17·15. Found: C, 55·01; H, 6·55; S, 17·40.

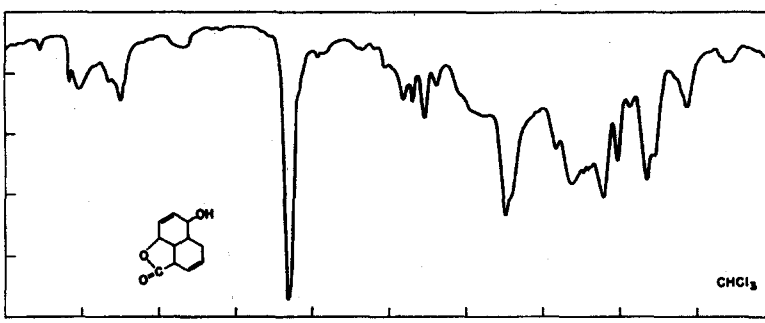
The five-membered lactone series

Preparation of the five-membered lactone (XXXIV). This substance is preparable by aluminium *iso*propoxide reduction of the ester adduct (IV : R = Me), the lactone (XIII), or the hydroxy ester (XXXVII).

Method (a). *From the lactone* (XIII) *or the hydroxy ester* (XXXVII). The lactone (XIII) (5 g), or the ester (XXXVII) (5 g), and freshly distilled aluminium *iso*propoxide (6 g) were added to 80 cm^3 of anhydrous *iso*propanol, in a flask equipped with a stirrer, a Vigreux column, and separatory funnel. The reaction mixture was stirred, and heated at such a rate that slow distillation took place; *iso*propanol was introduced at such a rate as to keep the reaction mixture approximately at constant volume. After the distillation of acetone had ceased (about 45 min), the reaction mixture was kept under gentle reflux for another 45 min. The solvent was then removed *in vacuo*. The foamy residue was dissolved in ethyl acetate (80 cm^3), and the resulting milky solution was cooled to 0° and added to a solution of sodium potassium tartrate (83 g) and sodium bicarbonate (6·3 g) in water (125 cm^3). The mixture was shaken and the two phases were separated. The aqueous phase was extracted three times further with ethyl acetate. The combined ethyl acetate extracts were washed once with ice-cold sodium bicarbonate, once with saturated sodium chloride solution, and dried over sodium sulfate. When the solvent was removed, 4·5 g of a colorless crystalline solid remained. Recrystallization from acetone/ether gave 3·7 g of the hydroxy lactone (XXXIV), m.p. 120–122°. For analysis the lactone was recrystallized once from acetone/ether; prisms, m.p. 122–123°.

Anal. Calcd. for $C_{11}H_{12}O_3$: C, 68·73; H, 6·29. Found: C, 68·79; H, 6·50.

Ultraviolet spectrum: end absorption.



Method (b). *From the ester adduct* (IV : R = Me). The ester adduct (440 mg) and aluminium *iso*propoxide (1·83 g) were dissolved in dry *iso*propanol (8 cm^3). The mixture was boiled gently, and acetone and *iso*propanol were distilled slowly from the reaction mixture through a short column. From time to time *iso*propanol was added to maintain a constant volume. After one hour no more acetone could be detected in the distillate. The reaction mixture was then concentrated under reduced pressure, treated with ice-cold 2 N hydrochloric acid, and extracted with methylene chloride/ether (1 : 3). The organic phase was washed with sodium bicarbonate and saturated sodium chloride solution, and taken to dryness *in vacuo*. The residue was crystallized twice from acetone/ether, to give 230 mg of colorless prisms of the lactone (XXXIV), m.p. 119–120°, identical with the material prepared by method (a).

Oxidation of the lactone (XXXIV): *The ketone* (XXXVIII). To a solution of the hydroxy lactone (XXXIV) (1 g) in acetone (50 cm^3), 1·90 cm^3 of chromic acid oxidation mixture (92 cm^3 concentrated sulfuric acid, 290 cm^3 of water, 106 g chromium trioxide) were added slowly with stirring at room temperature. A slight excess of chromic acid was then destroyed by adding two drops of butanol. The reaction mixture was filtered quickly through a small column of aluminium oxide (activity II/III), and the filtrate was taken to dryness. Crystallization from acetone/ether gave 830 mg of the *ketone* (XXXVIII) as colorless prisms, m.p. 125–126°. For analysis the material was crystallized once again from acetone/ether and dried for several hours at 80° in high vacuum, m.p. 126–128°.

Anal. Calcd. for $C_{11}H_{10}O_3$: C, 69·46; H, 5·30. Found: C, 69·50; H, 5·43.

Ultraviolet spectrum: λ_{max} 216 mμ (ε 8500).

Infrared spectrum ($CHCl_3$): 5·65 and 5·95 μ.

Oxidation of the keto lactone (XXXVIII) *by perbenzoic acid.* To a solution of the keto lactone (XXXVIII) (600 mg, 3·16 mmoles) in dioxane (2 cm^3), 7 cm^3 of a benzene solution of perbenzoic acid (0·575 M) was added. Dioxane was then added to bring the total volume to 10 cm^3. The reaction mixture was allowed to stand at room temperature for 10 hr, during which time a solid separated. When the colorless crystalline material (206 mg, m.p. 185–187·5°) was collected, and recrystallized from ethyl acetate, the *dilactone* (XLI) was obtained as colorless prisms, m.p. 189–193° (*dec.*).

Anal. Calcd. for $C_{11}H_{10}O_5$: C, 59·46; H, 4·54. Found: C, 59·26; H, 4·68.

Ultraviolet spectrum: end absorption ($\varepsilon_{210\,m\mu}$ 5500).

Infrared spectrum (KI): 5·67 μ, 5·70 μ, 6·04 μ (weak).

Action of iodine/silver acetate on the keto lactone (XXXVIII). To a well-stirred suspension of the keto lactone (XXXVIII) (498 mg) and silver acetate (522 mg) in glacial acetic acid (13 cm^3), finely powdered iodine (684 mg) was added all at once. The reaction mixture was stirred for 2 hr 30 min. Silver iodide was removed by filtration through Celite, which was washed three times with hot chloroform. The filtrate was evaporated to dryness *in vacuo* at 40°. The brown residual oil was taken up in chloroform/ethyl acetate (1 : 3) and washed with 0·1 N sodium thiosulfate, saturated sodium bicarbonate solution, and water. When the dried organic layer was evaporated at the water pump, a colorless oil was obtained, which crystallized from acetone/dichloromethane to yield 330 mg of colorless prisms of the *iodo acetate*, m.p. 156–158° (*dec.*). The analytical sample, obtained by recrystallization from a large volume of dichloromethane had m.p. 161–162° (*dec.*).

Anal. Calcd. for $C_{13}H_{13}O_5I$: C, 41·40; H, 3·49; I, 33·70. Found: C, 41·72; H, 3·49; I, 34·07.

Ultraviolet spectrum: end absorption ($\varepsilon_{210\,m\mu}$ 10,000).

Infrared spectrum: 5·64 μ, 5·80 μ, 5·95 μ.

Zinc reduction of the keto lactone (XXXVIII). The keto lactone (XXXVIII) (600 mg) was dissolved in acetic acid (6 cm^3) and water (2·6 cm^3). While the mixture was stirred vigorously, and kept at 15°, zinc powder (1·2 g) was added all at once. After 10 min the reaction mixture was diluted with ethyl acetate, filtered, and the filtrate was washed with dilute hydrochloric acid and saturated aqueous sodium chloride solution. The organic phase was dried with anhydrous sodium sulfate, and taken to dryness *in vacuo*. The residue was taken up in acetone, treated with a small amount of Norite and filtered. When the filtrate was concentrated to a small volume and treated with a few drops of ether, 420 mg of the acid (XXXIX), m.p. 123–127°, separated. For analysis the acid was recrystallized twice from acetone/ether, from which it separated as colorless needles, m.p. 124–127°.

Anal. Calcd. for $C_{11}H_{12}O_3$: C, 68·73; H, 6·29. Found: C, 68·51; H, 6·49.

Infrared spectrum ($CHCl_3$): 5·83 and 5·85 μ.

The above *β,γ-unsaturated keto acid* was isomerized to the conjugated isomer (XL) by potassium acetate in ethanol. The acid (XXXIX) (100 mg), potassium acetate

(100 mg), and absolute ethanol (5 cm³) were heated under reflux in an atmosphere of nitrogen for 3 hr. The solvent was then evaporated *in vacuo* and the residue was taken up in ethyl acetate and water. The organic layer was washed three times with saturated sodium chloride solution, dried, and evaporated *in vacuo*. When the colorless residual oil was crystallized from ether, 60 mg of the acid (XL), m.p. 163–165°, were obtained. The analytical sample, obtained by recrystallization from dichloromethane/ether formed colorless prisms, m.p. 165–166°.

Anal. Calcd. for $C_{11}H_{12}O_3$: C, 68·73; H, 6·29. Found: C, 68·63; H, 6·51.

Ultraviolet spectrum: λ_{max} 223 mμ (ε 7400).

Infrared spectrum ($CHCl_3$): 5·85 μ and 5·97 μ.

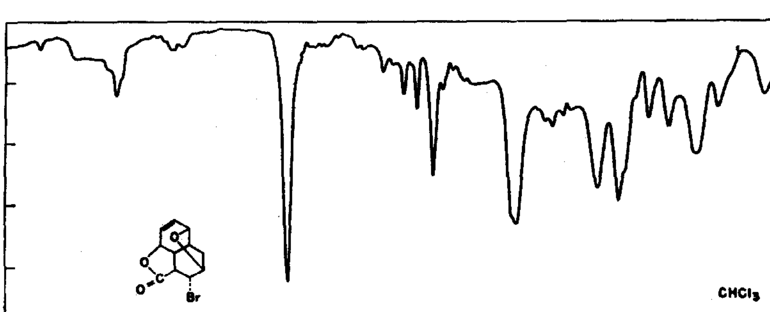
The above acid (XL) was converted to the corresponding *methyl ester* by treatment with excess ethereal diazomethane. Crystallized from acetone/ether, the ester had m.p. 77–78°.

Infrared spectrum ($CHCl_3$): 5·79 and 6·0 μ.

Bromination of the hydroxy lactone (XXXIV): *The bromo lactone* (LVIII). *Method* (a). *In methanol*: The hydroxy lactone (XXXIV) (23 g) in methanol (230 cm³) was treated with a solution of bromine (19·2 g) in methanol (200 cm³). After the mixture had stood at room temperature for 45 min, sufficient solid sodium bicarbonate was added to neutralize the hydrobromic acid, and the solution was then concentrated to approximately 30 cm³. A large volume of methylene chloride was added, and the mixture was washed twice with water, once with sodium bicarbonate solution, once with saturated sodium chloride solution, and the organic phase was dried over anhydrous sodium sulfate. The solvent was then removed *in vacuo*, and the residual yellow oil was taken up in acetone and ether, and allowed to stand in the cold for 24 hr. Fifteen grams of the bromo lactone (LVIII), m.p. 120–124°, separated. For analysis the substance was recrystallized four times from acetone/ether, m.p. 129–130°.

Anal. Calcd. for $C_{11}H_{11}O_3Br$: C, 48·72; H, 4·09; Br, 29·47. Found: C, 48·53; H, 4·21; Br, 29·30.

Ultraviolet spectrum: end absorption.



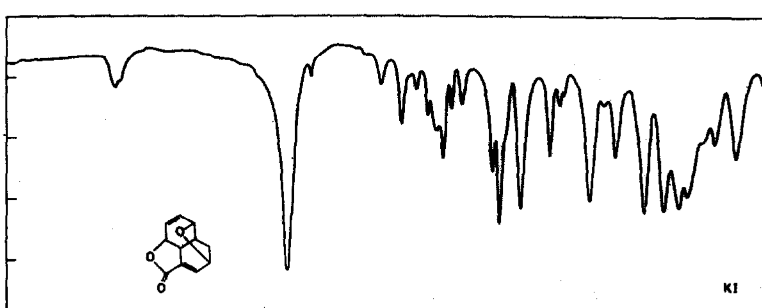
Method (b). *In methylene chloride*. The hydroxy lactone (XXXIV) (20 g) was dissolved in methylene chloride (500 cm³). Bromine (5·4 cm³) was added slowly at room temperature, and the reaction mixture was allowed to stand for 20 min. It was then cooled in an ice-bath and extracted once with aqueous sodium bicarbonate, containing a small amount of sodium thiosulfate, and once with sodium bicarbonate alone. The organic phase was then washed with saturated sodium chloride solution and dried over anhydrous sodium sulfate. The solvent was removed, and the residual yellow oil was taken up in acetone and ether. When the solution was allowed to stand, 21 g of the bromo lactone (LVIII), m.p. 122–125°, separated. This material was sufficiently pure to be converted directly into the methoxy ether (LIII) (see below), in approximately 80 per cent yield. However, it was contaminated with a small amount of a relatively insoluble high-melting substance, which frequently separated first from the acetone/ether solution of the crude product. The high-melting material is a *dibromide*; for analysis it was recrystallized three times from acetone, and had m.p. 175–176°.

Anal. Calcd. for $C_{11}H_{12}O_3Br_2$: C, 37·53; H, 3·44; Br, 45·40. Found: C, 38·00; H, 3·34; Br, 45·41.

Preparation of the unsaturated ether (XLVI). To a three-necked flask fitted with an efficient stirrer and a short Vigreux column, 10 g of the oxido lactone (XXVIII), 29·6 g of aluminium *iso*propoxide and 166 cm^3 of anhydrous *iso*propanol were added. The reaction mixture was heated at such a rate that acetone distilled as it was formed. After 3 hr the distillate gave a negative reaction with 2,4-dinitrophenylhydrazine reagent. The reaction mixture was then concentrated to dryness *in vacuo* and the residue was dissolved in 150 cm^3 of ethyl acetate. The mixture was stirred with 300 cm^3 of a saturated Rochelle's salt solution (containing 66 g of sodium potassium tartrate and 5 g of sodium bicarbonate per 100 cm^3 of water). The aqueous solution was extracted three times with ethyl acetate and the combined organic layers were dried over sodium sulfate. When the solvent was removed, an oily residue was obtained, which could be used directly for the preparation of the methoxy lactone (LIII) (see below). In the present experiment, the oil was dissolved in methylene chloride and filtered through deactivated aluminium oxide. The methylene chloride was removed *in vacuo* and the residue was crystallized from ethyl acetate/ether. The unsaturated lactone (XLVI) was obtained in 43 per cent yield as colorless prisms, m.p. 124–126°.

Anal. Calcd. for $C_{11}H_{10}O_3$: C, 69·46; H, 5·30. Found: C, 69·34; H, 5·41.

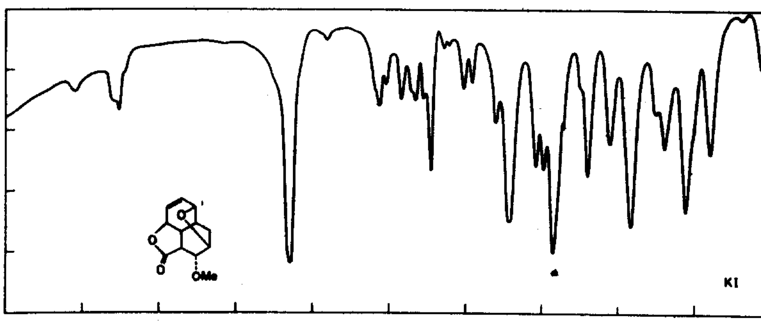
Ultraviolet spectrum: λ_{max} 228 mμ (ε 3140).



Preparation of the methoxy ether (LIII). *Method* (a) The crude oily unsaturated ether (XLVI), whose preparation is described immediately above, was taken up in 260 cm^3 of anhydrous methanol containing 280 mg of sodium methoxide, and allowed to stand at room temperature for 90 min. The reaction mixture was then made acidic with glacial acetic acid and all solvents were removed *in vacuo*. The residue was taken up in methylene chloride, which was washed with water and dried over anhydrous sodium sulfate. The methylene chloride solution was concentrated to about 60 cm^3 and filtered through a short column of aluminium oxide (activity II/III). The column was washed with methylene chloride, and the eluate (about 200 cm^3) was evaporated to give an oil which solidified slowly. Crystallization from a mixture of ethyl acetate (5 cm^3) and ether (5 cm^3) gave 5 g of the *methoxy ether* (LIII) as colorless needles, m.p. 95–98°. For analysis the material was recrystallized from ethyl acetate/ ether, m.p. 103–104°.

Anal. Calcd. for $C_{12}H_{14}O_4$: C, 64·85; H, 6·35; OMe, 13·96. Found: C, 65·11; H, 6·46; OMe, 13·86.

Ultraviolet spectrum: no absorption.



Method (b). Twenty-three grams of oxido ester (XLVII) and freshly distilled aluminium *iso*propoxide (30 g) were dissolved in anhydrous *iso*propanol (400 cm^3). The mixture was stirred, and heated at such a rate that slow distillation through a short Vigreux column took place. During the distillation, *iso*propanol was replaced at such a rate as to maintain the reaction mixture at constant volume. After about 5 hr no acetone could be detected in the distillate (2,4-dinitrophenylhydrazine reagent). After the reduction was complete, the mixture was kept under gentle reflux for a further 2 hr. The solvent was then completely removed *in vacuo*, and the foamy residue was taken up in 375 cm^3 of ethyl acetate. The resulting solution was cooled to 0° and added to a solution of sodium potassium tartrate (410 g) and sodium bicarbonate (31 g) in water (625 cm^3). The mixture was shaken well, and the two phases were separated. The aqueous phase was extracted three times with ethyl acetate. The combined ethyl acetate phases were washed twice with ice-cold sodium bicarbonate, once with saturated sodium chloride solution and dried over anhydrous sodium sulfate. When the solvent was removed *in vacuo*, 21 g of a partially crystalline brown product were obtained. This material was dissolved in the smallest possible amount of dichloromethane and allowed to stand at room temperature for 2 hr; occasionally a considerable amount of crystalline material did not dissolve in the methylene chloride at all. The dichloromethane-insoluble material, and that which separated from the methylene chloride solution on standing, were collected and washed with methylene dichloride. Three grams of this by-product, m.p. 175–176°, which is probably the *dihydroxy ester* (xii), were obtained. For analysis the substance was recrystallized three times from acetone and dried for 12 hr at 80° in high vacuum, m.p. 175–176°.

Anal. Calcd. for $C_{14}H_{20}O_5$: C, 62·67; H, 7·51. Found: C, 62·88; H, 7·65.

Ultraviolet spectrum: no absorption.

Infrared spectrum ($CHCl_3$): single sharp band at 5·81 μ.

The combined filtrates from the above by-product were concentrated and dried in high vacuum. The residue was dissolved in 400 cm³ of anhydrous methanol. One hundred and twenty cm³ of a sodium methoxide solution (made up by dissolving 1 g of sodium in 500 cm³ of anhydrous methanol) were added, and the mixture, which turned brown, was kept at room temperature for 90 min. The solution was then neutralized with glacial acetic acid and the solvents were removed *in vacuo*. The residue was dissolved in methylene chloride, and the solution was washed twice with small amounts of water and then with saturated sodium chloride solution. The dried (anhydrous sodium sulfate) solution was concentrated to small volume and filtered through a short column of neutral aluminium oxide (activity II/III). The eluate was concentrated to a very small volume, and ether was added. Crystallization of the desired *methoxy ether* (LIII) began at once. After the mixture had been kept at 0° for 2 hr, 7·6 g of the methoxy ether (LIII), m.p. 100–102°, were collected. This material was identical with that prepared by method (a) above. After the mother liquors had been treated once again with methoxide, as above, a further 700 mg of the methoxy ether were obtained.

Method (c). The bromo lactone (LVIII), m.p. 122–125°, (see above), (16·5 g) was dissolved in anhydrous methanol (260 cm³). Ninety-five cm³ of a sodium methoxide solution (made up by dissolving 2 g of sodium in 100 cm³ of anhydrous methanol) were added, and the yellow mixture was kept at room temperature for 2 hr 30 min. The reaction mixture was then neutralized with glacial acetic acid, and concentrated *in vacuo* to approximately 10 cm³. Methylene chloride and some ice-cold water were added, and the mixture was shaken. The two phases were separated, and the organic phase was washed once with ice-cold sodium bicarbonate solution, once with saturated sodium chloride solution, and dried over anhydrous sodium sulfate. Removal of the solvents gave a crystalline residue from which 11·3 g of the *methoxy ether* (LIII) were obtained by recrystallization from acetone/ether. The material melted at 100–102°, and was identical with that obtained by methods (a) and (b) above.

Degradation of the methoxy ether (LIII). A, *to the methoxy lactone* (LVI). The methoxy ether (LIII) (60 mg) was dissolved in acetyl chloride (2 cm³). Stannic chloride (0·2 cm³) was added, and the reaction mixture was allowed to stand at room temperature for 15 min. The solvents were then removed *in vacuo*, the residue was taken up in ethyl acetate, and washed with water, sodium bicarbonate solution, and water again. The ethyl acetate solution was dried over sodium sulfate and concentrated to dryness *in vacuo*. The residual oil was distilled, and the first fraction, a colorless oil (b.p. $_{0\cdot08\ mm}$ 110–125°), crystallized. When the material was recrystallized from methylene chloride/ether, 32 mg of the *lactone* (LVI), m.p. 119–122°, were obtained. For analysis the material was crystallized thrice from dichloromethane/ether, m.p. 123–124°.

Anal. Calcd. for $C_{12}H_{12}O_3$: C, 70·57; H, 5·92; OMe, 15·19. Found: C, 70·95; H, 6·17; OMe, 15·26.

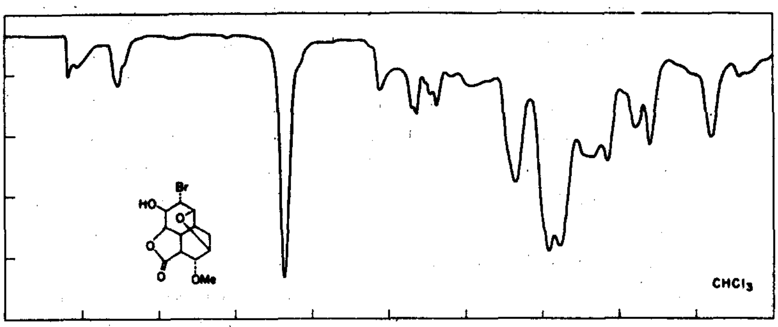
Ultraviolet spectrum: $\lambda\lambda_{max}$ ~253 mμ, ~260 mμ, 266 mμ, 273 mμ ($\varepsilon\varepsilon$ 258, 345, 468, 495).

Infrared spectrum ($CHCl_3$): 5·60 μ.

B, *to α-naphthoic acid*. The methoxy ether (LIII) (80 mg) and freshly sublimed pyridine hydrochloride (400 mg) were sealed together in a highly evacuated Pyrex glass tube, and heated for 5 min at 190–200°. The cooled reaction mixture was dissolved in 2 N hydrochloric acid and extracted with methylene chloride. The organic layer was dried over anhydrous sodium sulfate and evaporated to dryness, leaving 55 mg of colorless crystalline residue. After one recrystallization from methylene chloride, it melted at 152–156°. The material was then partitioned between sodium bicarbonate and ether in the usual way. When the acidic fraction was crystallized from benzene, colorless needles of α-naphthoic acid, m.p. 160–162°, identical with an authentic sample, were obtained, m.m.p. 160–162°. The infrared spectrum of the degradation product and that of an authentic specimen of α-naphthoic acid were identical.

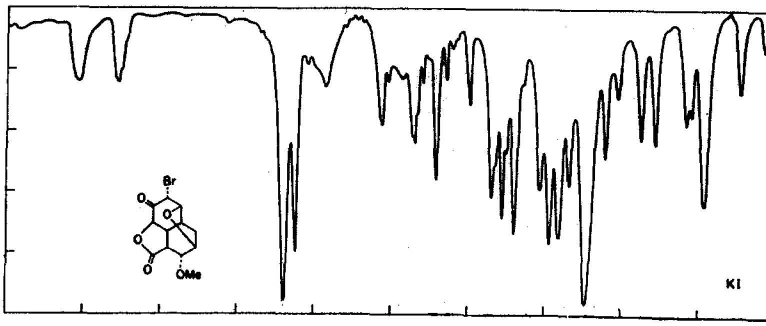
Preparation of the bromohydrin (LIX), *and of the ketone* LXIII). The methoxy ether (LIII) (7 g) was dissolved in water (63 cm³) and 1 N sulfuric acid (12·6 cm³), with stirring, and heating to 80°. To the stirred solution, which was kept between 60–70°, N-bromosuccinimide (5·85 g) was added over a period of 10 min. The reaction mixture was then maintained at 80–90° for 30 min. At the end of that time the potassium iodide-starch test was practically negative. A small quantity of sodium bisulfite was then added to destroy excess N-bromosuccinimide, and the aqueous solution was extracted continuously with methylene dichloride for 4 hr. When the solvent was evaporated, 12·92 g of the crude bromohydrin (LIX) were obtained as a yellow oil. Ordinarily, this crude material was oxidized directly to the corresponding ketone. However, if it was taken up in acetone, crystalline bromohydrin separated. After several further crystallizations from acetone, in order to effect separation from succinimide, the bromohydrin (LIX) was obtained as a colorless solid, m.p. 150–151°.

Anal. Calcd. for $C_{12}H_{15}O_5Br$: C, 45·13; H, 4·74; Br, 25·04. Found: C, 45·24; H, 4·86; Br, 25·13.



The above crude oily bromohydrin (LIX) (12·92 g) was dissolved in 53 cm³. of hot glacial acetic acid. The solution was cooled to room temperature and chromic acid (5·3 g) dissolved in water (2·7 cm³) and acetic acid (27 cm³) was added. The solution became warm, and after 2 min the bromo ketone began to crystallize. The reaction mixture was allowed to stand at room temperature for ten hours. The ketone which had separated (6 g, 60 per cent) was collected and washed with acetic acid and ether. For recrystallization, the crude bromo ketone was extracted with acetone in a Soxhlet apparatus. The pure material crystallized directly from the extractant, and had m.p. 165–167°. For analysis the substance was recrystallized twice from ethyl acetate, m.p. 166–167°.

Anal. Calcd. for $C_{12}H_{13}O_5Br$: C, 45·44; H, 4·13; Br, 25·20. Found C, 45·45; H, 4·32; Br, 25·35.



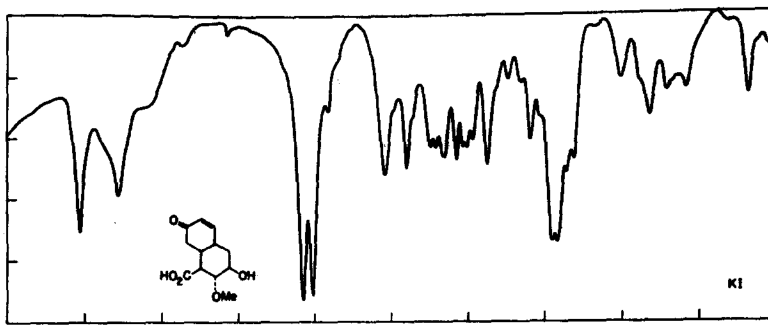
The chloro ketone (LXIII: Br = Cl). The methoxy ether (LIII) (222 mg) dissolved in water (3 cm^3) was stirred at 55–60° over a period of 75 min, while 1·9 cm^3 of a 2·92 per cent solution of hypochlorous acid was added slowly. The aqueous solution was then extracted continuously for 3 hr with methylene chloride. The extract was dried over sodium sulfate, and evaporated, to give 217 mg of a colorless oil which solidified in part. This material was dissolved in acetone (20 cm^3), and 0·38 cm^3 of chromic acid solution (prepared by dissolving 92 g of concentrated sulfuric acid and 106 g of chromic acid in 290 cm^3 of water) were added slowly at room temperature over a period of 1 hr. The excess chromic acid was then destroyed by addition of *iso*propanol, the solvents were removed *in vacuo*, and the residue was taken up in 100 cm^3 of methylene chloride/ether (1 : 3). The solution was washed twice with saturated brine, and once with 5 per cent aqueous sodium bicarbonate. When the solvent was removed *in vacuo*, 178 mg of a foam were obtained from which on trituration with ethyl acetate, 63 mg of colorless crystalline material separated. After one recrystallization from ethyl acetate, 54 mg of chloro ketone were obtained as colorless prisms, m.p. 173–176°(*dec.*).

Infrared spectrum: very similar to that of the corresponding bromo ketone.

Zinc reduction of the bromo ketone (LXIII): *The acid* (LXV). The bromo ketone (LXIII) (1·87 g) was dissolved in hot glacial acetic acid (500 cm^3). The solution was cooled to 17°, zinc dust (7·5 g), previously cooled to 0°, was added all at once, and the mixture was stirred vigorously for 90 sec. The zinc was then immediately removed by rapid filtration through a bed of Celite (previously prepared by suspension in acetic acid, followed by filtration), which was rinsed once with acetone. The filtrate was concentrated to dryness *in vacuo*, the residue was dissolved in 25 cm^3 of water, and made basic with solid sodium bicarbonate. The basic solution was extracted continuously with ether for three hours in order to remove neutral material (34 mg). The aqueous solution was then acidified strongly (Congo), saturated with sodium chloride, and extracted continuously with ether for fourteen hours. During this time 1·03 g of the acid (LXV) separated from the boiling ether. This material had λ_{max} 227 mμ (ε 9750). After the solid was collected by filtration, the filtrate was concentrated to dryness to give a foam which crystallized on trituration with acetone, to yield a further 92 mg of product; total yield 1·12 g (79 per cent). For analysis the acid was crystallized from acetone/ethyl acetate, m.p. 204–206°.

Anal. Calcd. for $C_{12}H_{16}O_5$: C, 59·99; H, 6·71; OMe, 12·92. Found: C, 59·96; H, 6·93; OMe, 12·88.

Ultraviolet spectrum: λ_{max} 227 mμ (ε 10,000).



When aqueous acetic acid was used in the above reduction, the superficial phenomena resembled those just described, but the acid isolated had λ_{max} 227 mμ, with a molecular extinction coefficient of 4000–6000. The desired product (LXV) was clearly contaminated with the corresponding dihydro compound, in which the double bond at $\Delta^{5,6}$ had been saturated. These two substances formed mixed crystals which were separable only with very great difficulty. When the reduction was carried out with acetic acid and aqueous dioxane, the *dihydroxy acid* (xvi) was produced. The bromo ketone (150 mg) was dissolved in 15 cm³ of a dioxane solution, prepared from 94 cm³ of dioxane, 3 cm³ of water and 3 cm³ of acetic acid. Zinc dust (150 mg) was added all at once, and the resulting mixture was stirred vigorously at room temperature for 6 min. The zinc was removed by filtration, the filtrate was concentrated *in vacuo* to approximately 2 cm³, and 25 cm³ of water were added. The solution was made basic with solid sodium bicarbonate and extracted continuously with ether for three hours to remove neutral material (25 mg). The aqueous solution was then acidified and extracted continuously with ether for fourteen hours. The crude product so obtained (109 mg) was triturated with ethyl acetate/ether, and gave 48 mg of the acid (xvi).

Anal. Calcd. for $C_{12}H_{16}O_6$: C, 56·24; H, 6·29; OMe, 12·09. Found: C, 56·22; H, 6·52; OMe, 12·10.

Ultraviolet spectrum: λ_{max} 228 mμ (ε 9000).

Infrared spectrum (KI): 5·80 and 5·96 μ.

For preparation of the corresponding *methyl ester*, the above acid (39 mg) was dissolved in dioxane and treated with excess ethereal diazomethane. The dioxane was removed *in vacuo*, and the residue was triturated with ethyl acetate/ether. Thirty-four milligrams of crystalline, very insoluble, methyl ester were obtained. For analysis the substance was recrystallized from acetone/ether, m.p. 185–186°.

Anal. Calcd. for $C_{13}H_{18}O_6$: C, 57·77; H, 6·71. Found: C, 57·97; H, 6·72.

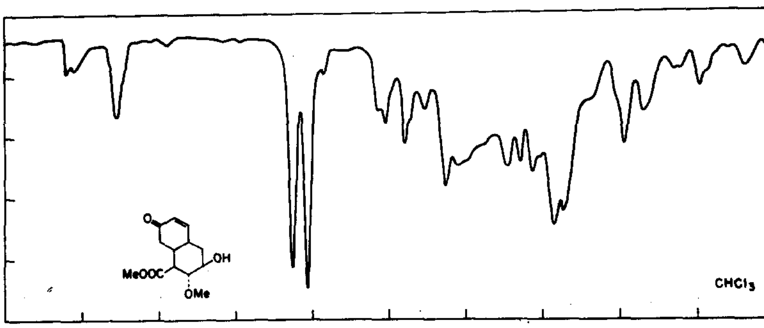
Infrared spectrum (KI): 2·94 μ, 3·04 μ, 5·77 μ, 5·98 μ.

Preparation of the acetoxy ester (LXVII). The hydroxy acid (LXV) (3·7 g) was dissolved in absolute dioxane (150 cm³). The solution was cooled to 10° and 40 cm³ of an ethereal diazomethane solution (1·91 per cent distilled diazomethane in absolute ether) was added slowly. The solvents were then evaporated *in vacuo* at 40°. The residual oil was dissolved in 10 cm³ of acetone, the resulting solution was filtered, and the filtrate was evaporated to dryness *in vacuo*. When the residue was crystallized from acetone/ether, 3·76 g (96 per cent) of the *methyl ester* of the acid (LXV), m.p. 134–136°

were obtained. Four further crystallizations from acetone/ether gave an analytical sample, m.p. 139–140°.

Anal. Calcd. for $C_{13}H_{18}O_5$: C, 61·40; H, 7·14; OMe, 24·38. Found: C, 61·53; H, 7·54; OMe, 24·65.

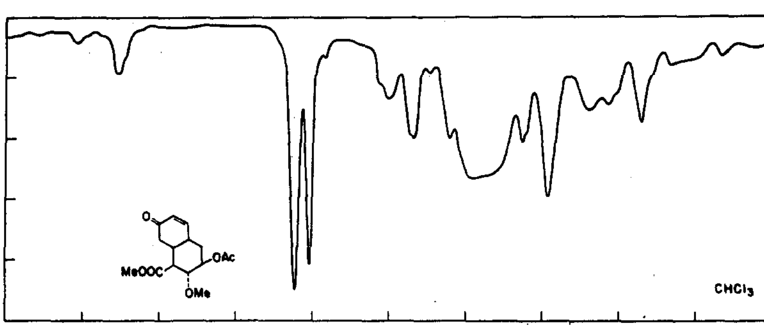
Ultraviolet spectrum: λ_{max} 225 mμ (ε 11,000).



The above *methyl ester* (3·4 g) was dissolved in absolute pyridine (18·5 cm³) and pure acetic anhydride (15 cm³). The reaction mixture was heated for two hours at 80–90° in an atmosphere of nitrogen. The solution was then cooled to room temperature and filtered. The filtrate was concentrated to dryness *in vacuo*, and the residue crystallized from acetone/ether to give 3·65 g (92 per cent) of the acetoxy ester (LXVII), m.p. 135–136°. Recrystallization from acetone/ether gave an analytical sample, m.p. 137–138°.

Anal. Calcd. for $C_{15}H_{20}O_6$: C, 60·80; H, 6·80; OMe, 20·90. Found: C, 60·58; H, 7·00; OMe, 20·43.

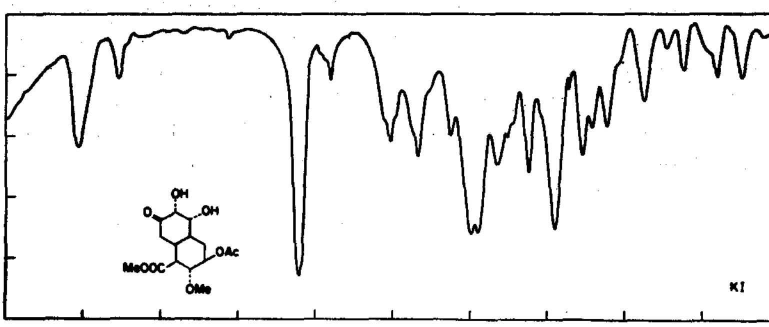
Ultraviolet spectrum: λ_{max} 226 mμ (ε 11,500).



Osmium tetroxide oxidation of the unsaturated ketone (LXVII): *The diol* (LXVIII). The unsaturated ketone (LXVII) (500 mg) was dissolved, with shaking, in a solution of osmium tetroxide (463 mg) in water (50 cm³). The reaction mixture rapidly became very dark blue in color, and was allowed to stand at room temperature under nitrogen for eight hours. The solution was then placed in a separatory funnel in which 25 cm³ of carbon tetrachloride and 4·15 g of sodium chlorate had been placed. When the mixture was shaken vigorously, the blue color rapidly disappeared. The aqueous phase was extracted four times with carbon tetrachloride in order to remove the osmium oxides completely. The aqueous solution was saturated with sodium chloride and then extracted continuously with ether for 8 hr. The ethereal extract was concentrated to a small volume, benzene was added, and the resulting solution was concentrated to dryness *in vacuo*. The residue (568 mg) was crystallized from acetone, and gave 255 mg (46 per cent) of the diol (LXVIII) as colorless needles, m.p. 169–172°. For analysis the material was recrystallized from acetone/ether, m.p. 174–175°.

Anal. Calcd. for $C_{15}H_{22}O_8$: C, 54·54; H, 6·71. Found: C, 54·72; H, 6·82.

Ultraviolet spectrum: no intense absorption above 205 mμ.

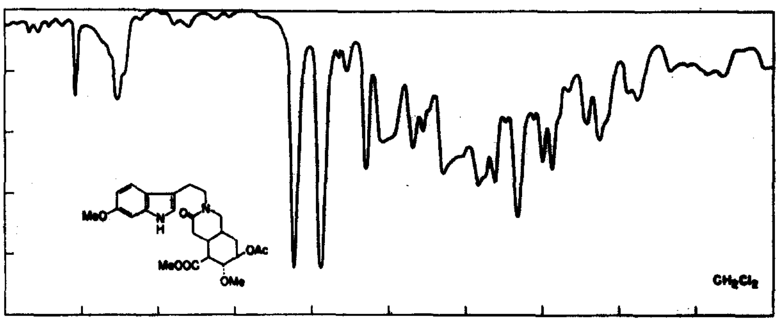


Preparation of the tetracyclic lactam (LXXII)

The lactam (LXXII). The diol (LXVIII) (800 mg) was treated with a solution of 2·3 g of periodic acid hydrate ($HIO_4 \cdot 2H_2O$) in 126 cm³ of water, and allowed to stand in an atmosphere of nitrogen for 20 min at room temperature. The colorless aqueous solution was then shaken five times with 50 cm³ portions of ethyl acetate. The organic layers were combined, washed three times with saturated brine, and dried with a large amount of anhydrous sodium sulfate. The solution was then taken to dryness under reduced pressure in an atmosphere of nitrogen at 40°. The colorless oily residue (LXIX: R = H), which occasionally solidified, was taken up in 80 cm³ of ether and treated at 0° with excess pure ethereal diazomethane. The solution was allowed to stand for 3 min at 0° and was then taken to dryness in a nitrogen atmosphere under reduced pressure at 30°. Seven hundred and ninety-six milligrams of the diester (LXIX: R = Me) were obtained as a slightly yellow oil (infrared spectrum ($CHCl_3$): 3·54 μ, 3·68 μ, 5·77 μ). The diester was taken up in 5 cm³ of benzene and treated with a supersaturated solution of 490 mg of 6-methoxytryptamine (m.p. 142°, see above) in 32 cm³ of benzene. (The hot solution of the amine was cooled quickly to 20°, and used before crystallization set in.) The reaction mixture turned cloudy immediately (separation of water) and was allowed to stand for 3 min at room temperature. It was then evaporated to dryness under reduced pressure under nitrogen at 50°. The yellow oily residual Schiff base (LXX) (infrared spectrum ($CHCl_3$): 2·90 μ, 5·76 μ, 5·99 μ, 6·13 μ) was taken up in 25 cm³ of methanol and treated with 250 mg of solid sodium borohydride. The reaction mixture was allowed to stand for 6 min at room temperature, and was then heated for 4 min on the steam bath. It was then concentrated *in vacuo* to a volume of about 5 cm³ and treated with several drops of acetic acid to destroy excess sodium borohydride. Ethyl acetate (200 cm³) was added, and the mixture was shaken four times with small volumes of 2 N hydrochloric acid. The organic layer was washed with saturated brine, dried with a large amount of anhydrous sodium sulfate, and taken to dryness *in vacuo*. In order to effect remethylation of any ester which had been hydrolyzed, the yellowish oily residue was dissolved in 10 cm³ of dioxane and treated at 10° with an excess of pure ethereal diazomethane.

The reaction mixture was allowed to stand for 3 min at room temperature and was then taken to dryness *in vacuo*. To remove water, the residue was twice boiled for a short time with benzene and concentrated to a small volume. Finally, all of the solvent was removed in high vacuum, and the residual material (1·14 g) was treated with absolute pyridine (15 cm³) and acetic anhydride (10 cm³) and allowed to stand for 12 hr at 30°. The reaction mixture was then taken to dryness *in vacuo*, and the residue was dissolved in chloroform. The chloroform solution was shaken with saturated aqueous sodium bicarbonate, 2 N hydrochloric acid, and saturated brine, and then dried over anhydrous sodium sulfate. It was then concentrated to small volume, and ether was added. The *lactam* (LXXII) (923 mg) (yield 81 per cent, over-all) separated as colorless small prisms, m.p. 237–238°. For analysis the lactam was crystallized once from chloroform/ether and twice from chloroform/benzene, and dried 11 hr at 110° in high vacuum, m.p. (*vac.*) 239–240°.

Anal. Calcd. for $C_{25}H_{32}O_7N_2$: C, 63·54; H, 6·83; N, 5·93. Found: C, 63·18; H, 6·94; N, 5·91.



Model experiments on the formation and stability of Schiff bases from tryptamines. A solution in methylene chloride of 2-anisyltryptamine (0·067 mmoles/cm³) and slightly less than one molecular equivalent of propionaldehyde gave an infrared spectrum (Fig. 1, 5·50–7·00 μ) which was constant after a few minutes, and did not

TABLE 2. 6-METHOXYTRYPTAMINE (0·067 mmole/cm³) + EXCESS EtCHO IN CH_2Cl_2

$T_{6\cdot 12\mu}$ = 20 per cent*

t (min)	$T_{5\cdot 98\mu}$ (per cent)*
0	33
15	42
30	50
45	56
	†

* These intensity values are probably distorted from the true values by the presence of the intense band at 5·78 μ, arising from the excess propionaldehyde.

† In a separate experiment, at different concentrations, the 5·98 μ band was found to have disappeared virtually completely in 3 hr.

change thereafter. With a similar solution of 6-methoxytryptamine and propionaldehyde, a similar, stable, curve (Fig. 2) was observed after a few moments. By contrast, when in each case the experiment was repeated, using an excess of propionaldehyde as compared with the tryptamine, the C═N band at 5·98 μ fell with time (Tables 2 and 3).

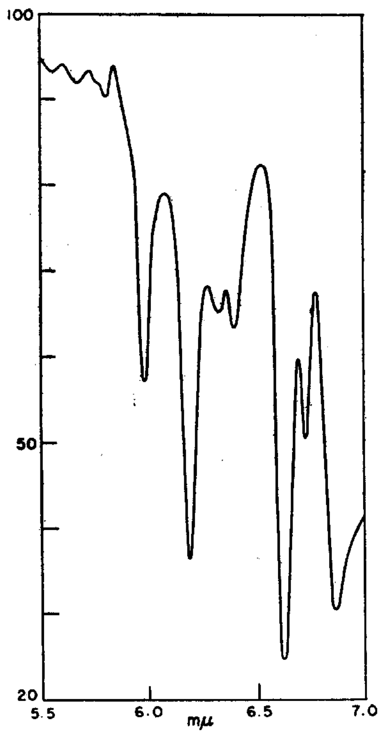


FIG. 1.

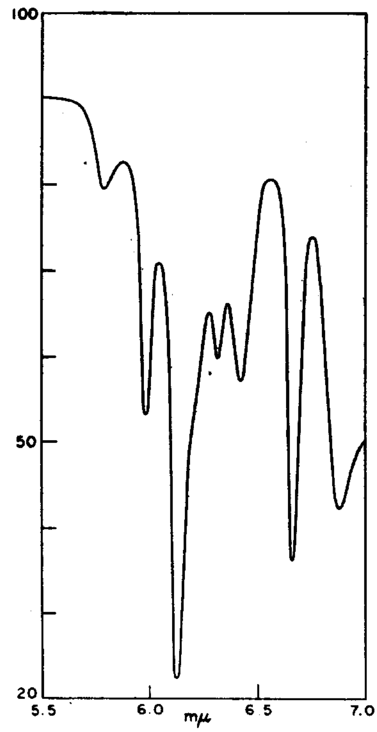


FIG. 2.

TABLE 3. 2-ANISYLTRYPTAMINE (0·067 mmole/cm³) + EXCESS EtCHO IN CH_2Cl_2

$T_{6\cdot 20\mu}$ = 24 per cent*

t (min)	$T_{5\cdot 98\mu}$ (per cent)*
0	32
15	39
30	42
45	44·5
60	46

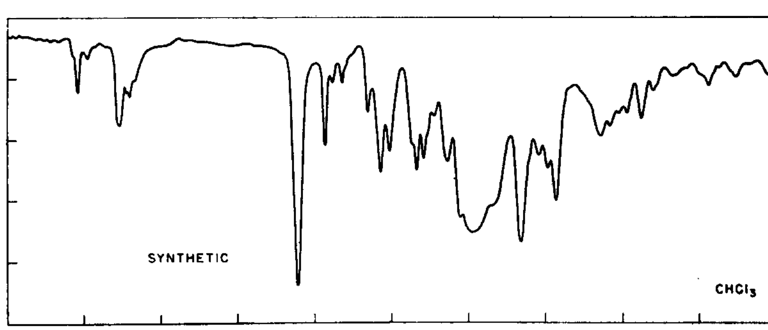
* These intensity values are probably distorted from the true values by the presence of the intense band at 5·78 μ, arising from the excess propionaldehyde.

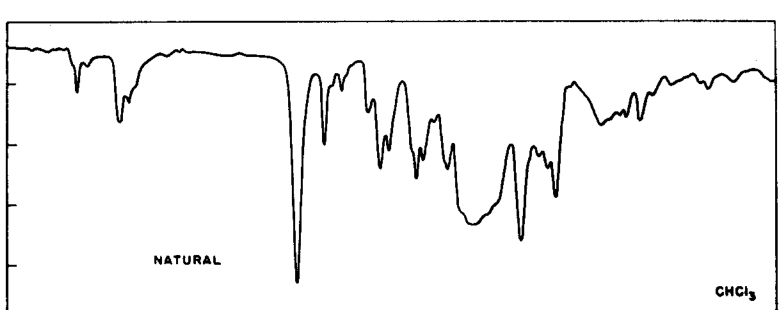
The pentacyclic series

*dl Methyl-O-acetyl-*iso*reserpate* (LXXIV). The well-dried lactam (LXXII) (m.p. 237–238°, 796 mg) was boiled gently for 2 hr in an atmosphere of nitrogen in 20 cm^3 of freshly distilled phosphorus oxychloride. The solution turned green, then yellow, and finally orange. When the solvent was removed *in vacuo* in an atmosphere of nitrogen, a bright-yellow crystalline residue of the *quaternary salt* (LXXIII) was obtained. This material was thoroughly dried in high vacuum, dissolved in 20 cm^3 of 90 per cent methanol, and treated in portions with 210 mg of solid sodium borohydride. The temperature of the reaction mixture was kept below 30° by occasional cooling in an ice-bath. The deep-orange color of the solution disappeared quickly, and the product began to crystallize directly from the reaction mixture in fine needles. After five minutes, 5 cm^3 of water was added, the reaction mixture was cooled to 0°, the crystalline precipitate was collected and washed with water. Recrystallization from acetone/ethanol gave 536 mg of *dl* methyl-O-acetyl-*iso*reserpate (LXXIV), as colorless needles, m.p. (*vac.*) 265–266° (*dec.*). From the mother liquors 71 mg of less pure crystalline material were isolated. For analysis the ester was recrystallized twice from acetone/ethanol. The colorless needles were dried several hours at 110° in high vacuum, m.p. (*vac.*) 267–268° (*dec.*).

Anal. Calcd. for $C_{25}H_{32}O_6N_2$: C, 65·77; H, 7·07; N, 6·14. Found: C, 65·60; H, 7·11; N, 6·17.

The infrared and ultraviolet spectra of the synthetic ester were identical with those of *l* methyl-O-acetyl-*iso*reserpate derived from natural reserpine.[15]





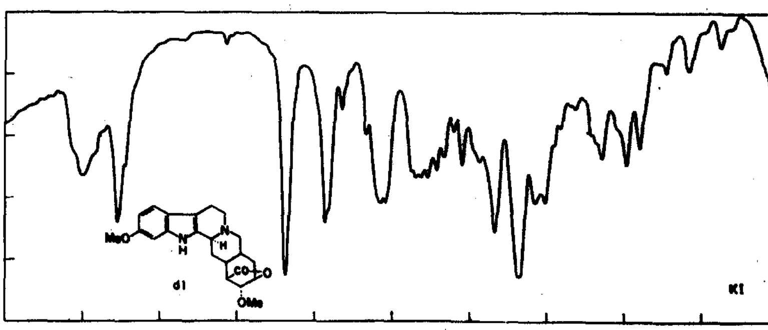
*Resolution of racemic methyl-O-acetyl-*iso*reserpate.* The racemic ester (LXXIV) (300 mg) was dissolved in 9 cm^3 of acetone and treated with a solution of di-*p*-toluyl-*l* tartaric acid (250 mg) in acetone (3 cm³). The solution was concentrated on the steam bath to a volume of 4 cm³. It was then seeded with the di-*p*-toluyl-*l*-tartrate of *l* methyl-O-acetyl-*iso*reserpate, and allowed to crystallize. When the material which separated was recrystallized from methanol/acetone, 120 mg of colorless prisms were obtained. One further crystallization from methanol gave 98 mg of the di-*p*-toluyl-*l*-tartrate of *l* methyl-O-acetyl-*iso*reserpate, m.p. (*vac.*) 153–155° (*dec.*). The mixture melting point (*vac.*) of the synthetic salt, with an authentic specimen of the salt (m.p. (*vac.*) 151–153° (*dec.*)) was 153–155°. Ninety-five milligrams of the synthetic salt were shaken with 5 cm³ of 1 N sodium hydroxide and chloroform. The chloroform extract was washed with saturated brine, dried with sodium sulfate, and taken to dryness *in vacuo*. When the colorless residue was crystallized from acetone/ethanol, 37 mg of colorless needles of synthetic *l* methyl-O-acetyl-*iso*reserpate, m.p. (*vac.*) 287–288° (*dec.*) ($[\alpha]_D^{24}$ — 134°, *c*, 1·04 ($CHCl_3$)) were obtained. The mixture melting point (*vac.*) with *l* methyl-O-acetyl-*iso*reserpate from natural sources (m.p. (*vac.*) 284–285°, $[\alpha]_D^{24}$ — 132°, *c*, 1·04 ($CHCl_3$)) was 285–286° (*dec.*). The mother liquors from the separation of the *l*,*l* salt were decomposed with lye in the above manner. When the resulting free base was treated, as above, with di-*p*-toluyl-*d*-tartaric acid, it gave a salt which was recrystallized and decomposed to give *d* methyl-O-acetyl-*iso*reserpate ($[\alpha]_D^{24}$ + 130°). The infrared spectra ($CHCl_3$) of the synthetic laevorotatory and dextrorotatory bases were identical with that of the racemic base (see above).

dl Iso*reserpic acid hydrochloride*. *dl* Methyl-O-acetyl-*iso*reserpate (2·04 g) was dissolved in absolute methanol (50 cm³) and 40 per cent aqueous potash (15 cm³), and the resulting solution was heated under reflux in an atmosphere of nitrogen for 2 hr. The solution was then cooled, acidified to Congo with concentrated hydrochloric acid, and filtered to remove precipitated potassium chloride. The filtrate was taken to dryness *in vacuo*, the residue was treated with boiling methanol, and again filtered to remove potassium chloride. When the filtrate was concentrated to a small volume, and treated with an equal volume of acetone, 1·37 g of the hydrochloride, m.p. (*vac.*) 265–268° (*dec.*), separated. Concentration of the mother liquors yielded a further 0·63 g of the material, m.p. (*vac.*) 262–264° (*dec.*). For analysis the hydrochloride was recrystallized from methanol/acetone and methanol/water, m.p. (*vac.*) 267–268·5° (*dec.*).

Anal. Calcd. for $C_{22}H_{28}O_5N_2 \cdot HCl \cdot H_2O$: C, 58·07; H, 6·87; N, 6·16; Cl, 7·80. Found: C, 57·82; H, 6·78; N, 6·11; Cl, 9·31.

dl Iso*reserpic acid lactone* (LXXVIII). *dl* *Iso*reserpic acid hydrochloride (127 mg) and N,N′-dicyclohexylcarbodiimide (80 mg) were dissolved in dry pyridine (8 cm³). The resulting solution was heated at 100° in an atmosphere of nitrogen for 2 hr. The pyridine was then removed *in vacuo*, and the lemon-yellow residue was kept in high vacuum for 10 hr to remove the last traces of pyridine. The residue was taken up in 100 cm³ of chloroform, which was extracted four times with 1 N sulfuric acid. The combined acid solutions were washed twice with 10 cm³ portions of chloroform, and then made basic with solid sodium bicarbonate. The basic solution was extracted three times with chloroform, and the extract was dried over solid sodium sulfate. When the solvent was removed *in vacuo*, 120 mg of an oil were obtained which deposited 70 mg (67 per cent) of *dl* *iso*reserpic acid lactone (LXXVIII), m.p. (*vac.*) 233–234° (*dec.*), when it was triturated with ethyl acetate. For analysis the lactone was twice recrystallized from chloroform/ethyl acetate, m.p. (*vac.*) 245–246·5° (*dec.*).

Anal. Calcd. for $C_{22}H_{26}O_4N_2$: C, 69·09; H, 6·85; N, 7·33. Found: C, 68·98; H, 6·57; N, 7·39.

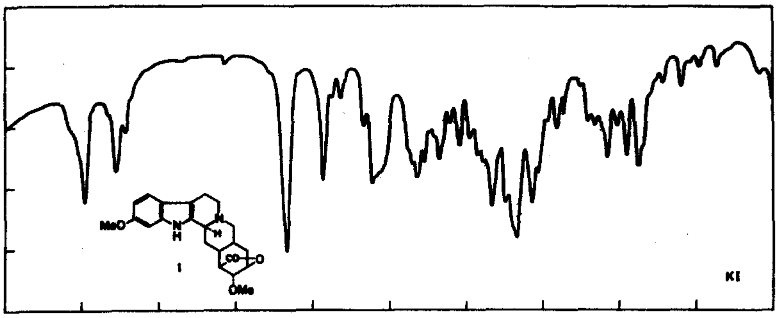


l Iso*reserpic acid hydrochloride.* *l* Methyl-O-acetyl-*iso*reserpate (200 mg) was dissolved in methanol (5 cm³) and 40 per cent aqueous potash (1·5 cm³), and boiled under nitrogen for 2 hr. The resulting solution was acidified to Congo with hydrochloric acid (1 : 1), and filtered from precipitated potassium chloride. The filtrate was concentrated to dryness, boiled with 10 cm³ of anhydrous methanol, and filtered again from potassium chloride. The filtrate was again concentrated to dryness. The residual solid was boiled with 10 cm³ of methanol and 2 cm³ of acetone, and filtered to remove a small amount of insoluble material. The filtrate was concentrated to about 5 cm³, and an equal volume of acetone was added. Colorless needles (131 mg) of the hydrochloride then separated. The mixture was cooled, the product was collected by filtration, the mother liquors were concentrated to about 2 cm³ and diluted with 5 cm³ of acetone to give a further 46 mg of product. The total yield of hydrochloride was 177 mg (92 per cent), m.p. (*vac.*) 273–274° (*dec.*). Further recrystallization from acetone/methanol gave colorless needles, m.p. (*vac.*) 278–279° (*dec.*).

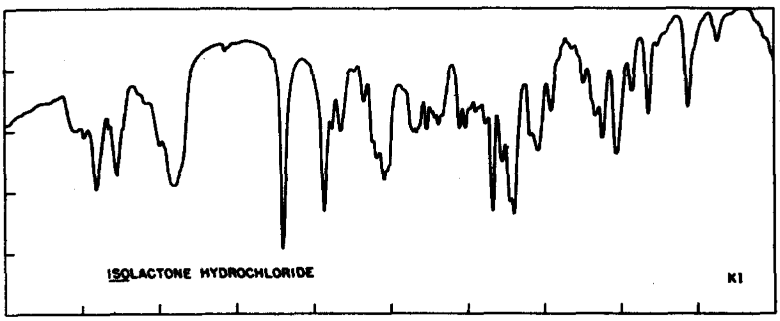
l Iso*reserpic acid lactone*(LXXVIII). *l Iso*reserpic acid hydrochloride (69 mg) and N,N'-dicyclohexylcarbodiimide (40 mg) in dry pyridine (4 cm³) were heated on the steam bath in an atmosphere of nitrogen for 1 hr; a precipitate separated from the reaction mixture. The mixture was allowed to stand at room temperature for 3 hr, and was then concentrated to 2 cm³, cooled, and filtered to give 82 mg of the *hydrochloride* of the *iso*lactone (LXXVIII) (see below), admixed with some di*cyclo*hexylurea. This solid mixture was added to 25 cm³ of chloroform and extracted three times with 1 N sulfuric acid. The combined acid fractions were washed with chloroform and then made basic with solid sodium carbonate. The basic solution was extracted three times with chloroform and the extract was dried over anhydrous sodium sulfate. The oily residue which remained after removal of the solvent crystallized when ethyl acetate was added. The crude product (31 mg) was recrystallized from chloroform/ethyl acetate to give 25 mg (41 per cent) of *l iso*reserpic acid lactone (LXXVIII), m.p. (*vac.*) 222·5–224° (*dec.*) ($[\alpha]_D^{24}$ − 138°, *c*, 1·05 ($CHCl_3$)).

Anal. Calcd. for $C_{22}H_{26}O_4N_2$: C, 69·09; H, 6·85; N, 7·33. Found: C, 69·17; H, 6·59; N, 7·30.

The infrared spectrum ($CHCl_3$) of the *laevo*rotatory *iso*lactone was found to be identical with that of the racemic *iso*lactone, whose preparation is described above.

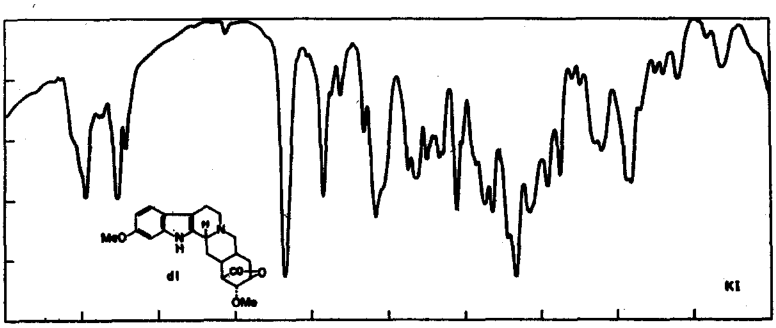


The *laevo*rotatory *iso*lactone forms a chloroform-soluble *hydrochloride*, which crystallizes in colorless needles, m.p. (*vac.*) 285–286° (*dec.*). It is this substance which separates directly from the reaction mixture, above.

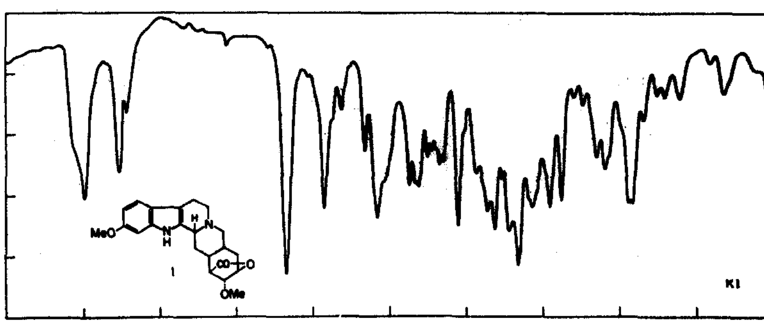


dl Reserpic acid lactone (LXXIX). *dl Iso*reserpic acid lactone (LXXVIII) (200 mg) was dissolved in 8 cm³ of xylene containing 10 volume per cent of pivalic acid, and heated under reflux in an atmosphere of nitrogen for 16 hr. When the reaction mixture was cooled, 179 mg of crystalline material, m.p. (*vac.*) 280–281·5° (*dec.*) separated (perhaps the pivalate of the desired lactone). This material was collected, and the mother liquors were concentrated to yield a further 25 mg of the product. When the combined crystallizates were heated for some time at 140° in high vacuum, in order to effect complete removal of pivalic acid, 148 mg of the crude *lactone* (LXXIX) were obtained. When the lactone was recrystallized from dichloromethane/methanol, it separated as colorless needles, m.p. (*vac.*) 315–317° (*dec.*).

Anal. Calcd. for $C_{22}H_{26}O_4N_2$: C, 69·09; H, 6·85; N, 7·33. Found: C, 69·06; H, 6·86; N, 7·07.



l Reserpic acid lactone (LXXIX). A, *from l isoreserpic acid lactone* (LXXVIII). *l Iso*reserpic acid lactone (52 mg) in 2 cm^3 of xylene containing 10 volume per cent of pivalic acid was heated under reflux in an atmosphere of nitrogen for 13 hr. After some hours of boiling, the product started to crystallize from the boiling solution in long needles. At the end of the reaction time the solution was cooled, and 40 mg of crystalline material which had separated were collected and washed with benzene. The mother liquor was taken to dryness, treated with some drops of acetone, and allowed to crystallize. The combined crystals were dissolved in a small volume of chloroform/methanol (4 : 1), treated with an equal volume of benzene, and concentrated on the steam bath until crystallization commenced. Forty-one milligrams of *l* reserpic acid lactone (LXXIX), m.p. (*vac.*) 319–321° (*dec.*) were obtained as colorless needles. The mixture melting point (*vac.*) with reserpic acid lactone, prepared as described below (m.p. (*vac.*) 325–326° (*dec.*)) was 321–322° (*dec.*). The infrared spectra of the two samples were identical.



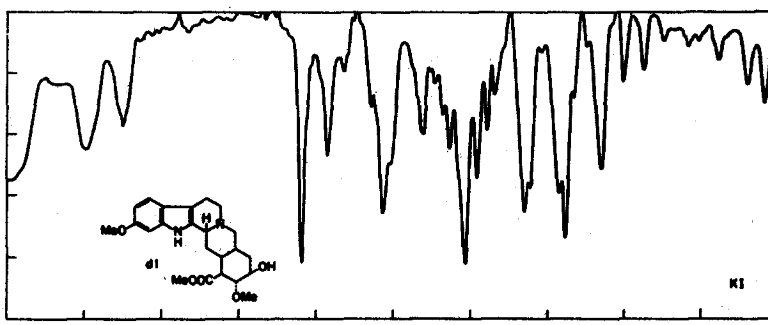
B, *from methyl reserpate* (LXXXI). Aluminium *iso*propoxide (204 mg) was dissolved in xylene (3 cm^3). Methyl reserpate (LXXXI) (55 mg) was added, and the reaction mixture was brought to boil. The ester went into solution readily, and after approximately 5 min, the lactone began to separate as colorless needles. The reaction mixture was heated under reflux for 2 hr. The product which had separated was removed by filtration and washed with xylene and ether; 46 mg (91 per cent) of reserpic acid lactone (LXXIX), m.p. (*vac.*) 325–326° (*dec.*) were obtained.

C, *from methyl-O-acetylreserpate*. Aluminium *iso*propoxide (170 mg) was dissolved in xylene (1·5 cm^3). Methyl-O-acetylreserpate (50 mg) was added, and the reaction mixture was brought to boil. The ester went into solution readily, and after 15 min the lactone began to separate in crystalline form. The reaction was allowed to proceed for 2 hr. The mixture was cooled, and the lactone which had separated was cooled and washed with xylene and ether; 40 mg. (95 per cent) of reserpic acid lactone (LXXIX), m.p. (*vac.*) 326–327° (*dec.*), were obtained as colorless needles.

D, *from reserpine*. Reserpine (4·1 g) was added to a solution of aluminium *iso*propoxide (10·5 g) in xylene (175 cm^3), and the resulting mixture was heated under reflux in an atmosphere of nitrogen. After 1 hr, the addition of a seed of reserpic acid lactone to the boiling solution initiated the separation of the product as colorless needles. After the reaction mixture had been kept under reflux for 5 hr, it was cooled, and 2·22 g (86 per cent) of crude lactone were collected, and washed with benzene and ether. One recrystallization from boiling chloroform gave the lactone (LXXIX) as colorless needles, m.p. (*vac.*) 327–328° (*dec.*).

dl Methyl reserpate (LXXXI). *dl* Reserpic acid lactone (LXXIX) (449 mg) was dissolved in 135 cm^3 of absolute methanol containing 190 mg of sodium methoxide. The resulting solution was heated under reflux in an atmosphere of nitrogen for 90 min. The cooled solution was acidified with 0·5 cm^3 of glacial acetic acid and concentrated to dryness *in vacuo*. The residue was dissolved in methylene dichloride, which was then washed once with water and twice with saturated brine. The organic layer was dried over anhydrous sodium sulfate, and evaporated. When the oily residue was crystallized from methanol/ether, 382 mg of *dl* methyl reserpate (LXXXI), m.p. (*vac.*) 236–237·5° (*dec.*), were obtained. On further crystallization from methanol/ ether, and then from acetone, the melting point (*vac.*) was raised to 241–242° (*dec.*).

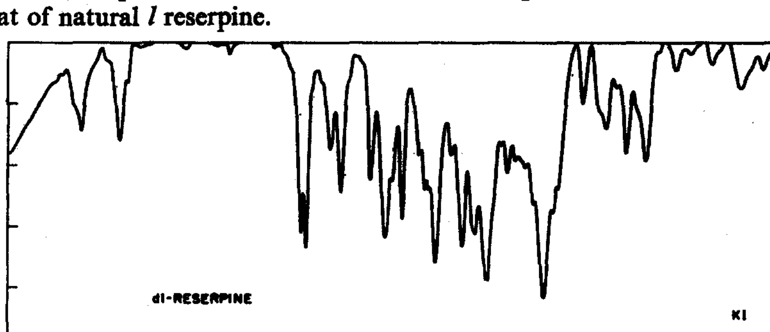
Anal. Calcd. for $C_{23}H_{30}O_5N_2$: C, 66·64; H, 7·30; N, 6·76. Found: C, 66·52; H, 7·36; N, 6·78.

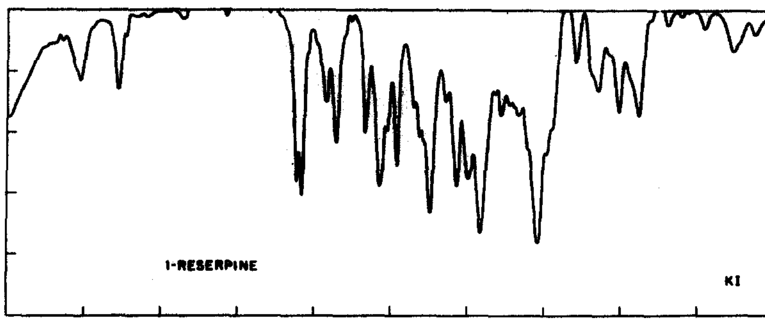


dl Reserpine (LXXXII). *dl* Methyl reserpate (50 mg) and 3,4,5-trimethoxybenzoyl chloride (150 mg, m.p. 80–81°) were dissolved in dry pyridine (1·5 cm^3) and the resulting solution was allowed to stand at room temperature in an atmosphere of nitrogen for four days. The pyridine was then removed *in vacuo* and the residue was dissolved in methylene chloride. The extract was washed twice with cold 1 N sodium carbonate solution, once with saturated brine, dried and evaporated to yield 183 mg of glassy residue. When this material was triturated with methanol/ether, 42 mg of crystalline *racemic reserpine* (LXXXII), m.p. (*vac.*) 258–259·5° (*dec.*) were obtained. For analysis the material was recrystallized twice from acetone/ether, m.p. (*vac.*) 260–262° (*dec.*).

Anal. Calcd. for $C_{30}H_{40}O_9N_2$: C, 65·11; H, 6·62; N, 4·60. Found: C, 65·01; H, 6·65; N, 4·12.

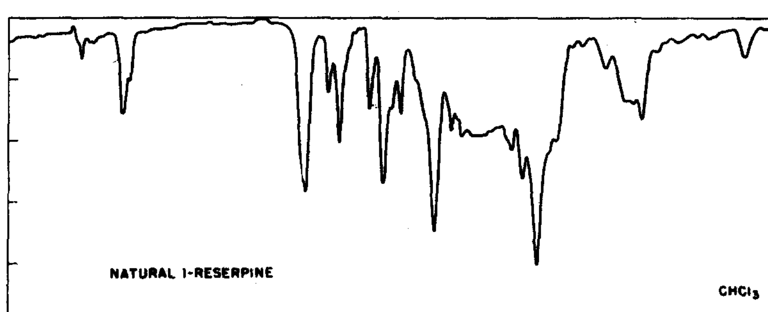
The infrared spectrum (KI!) of the racemic reserpine was found to be identical with that of natural *l* reserpine.

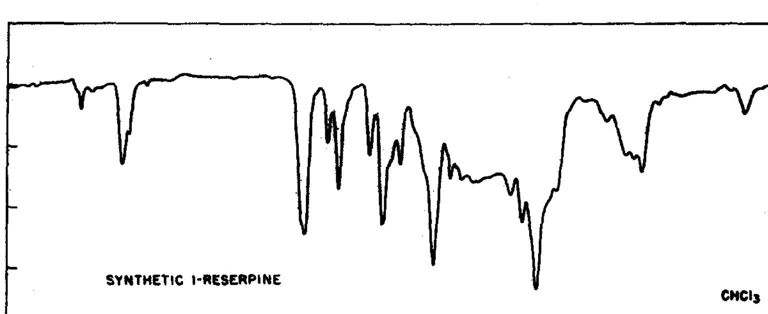


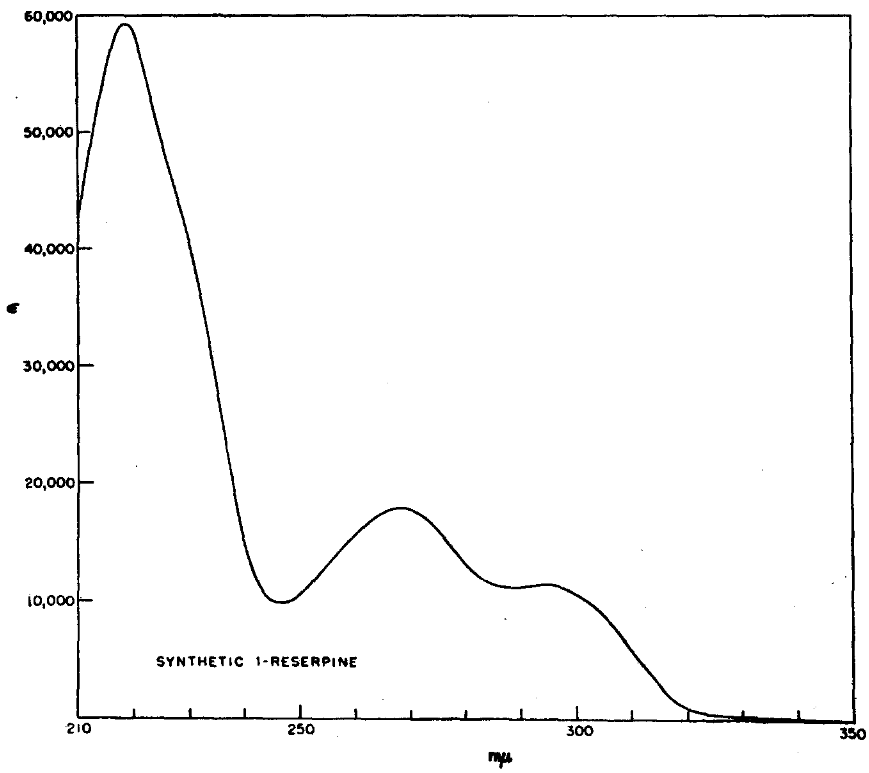


Resolution of racemic reserpine. Racemic reserpine (113 mg, m.p. (*vac.*) 260–262° (*dec.*)) was dissolved in methanol/chloroform (3 : 1). *d* Camphor-10-sulfonic acid (45 mg) was added. The solution was then concentrated on the steam bath to a small volume, and a seed of *l* reserpine-*d*-camphor-10-sulfonate was added. The colorless prisms (57 mg) which separated were recrystallized once from methanol. The beautifully crystalline prisms (52 mg) which separated were partitioned in the usual way between methylene chloride and ice-cold 1 N sodium hydroxide solution. The organic layer was washed with water and saturated brine, dried over anhydrous sodium sulfate, and taken to dryness *in vacuo*. The residue was crystallized twice from methylene chloride/methanol to give 28 mg of synthetic *l* reserpine (LXXXII) as beautiful colorless needles, m.p. (*vac.*) 286–288° (*dec.*) ($[\alpha]_D^{27}$ − 120°; *c*, 1·08 ($CHCl_3$)). The mixture melting point (*vac.*) with natural *l* reserpine (m.p. (*vac.*) 284–285° (*dec.*), $[\alpha]_D^{27}$ − 118°; *c*, 1·08 ($CHCl_3$)) was 285–286° (*dec.*).

The infrared and ultraviolet spectra of the synthetic and natural reserpines were found to be identical in all respects.







The residue obtained by evaporation of the mother liquors from the separation (above) of *l* reserpine-*d*-camphor-10-sulfonate were partitioned in the usual way between methylene chloride and ice-cold 1 N sodium hydroxide. The organic layer was washed with water and saturated brine, and dried over anhydrous sodium sulfate. It was then taken to dryness and the residual base was crystallized three times from methylene chloride. *d* Reserpine (26 mg) (m.p. (*vac.*) 281–284° (*dec.*), $[\alpha]_D^{25} + 117°$; *c*, 0·86 ($CHCl_3$)) was obtained as colorless needles.

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