[CONTRIBUTION FROM THE SQUIBB INSTITUTE FOR MEDICAL RESEARCH]

8,9-Seco Derivatives of Triacetyldihydroveratramine[1]

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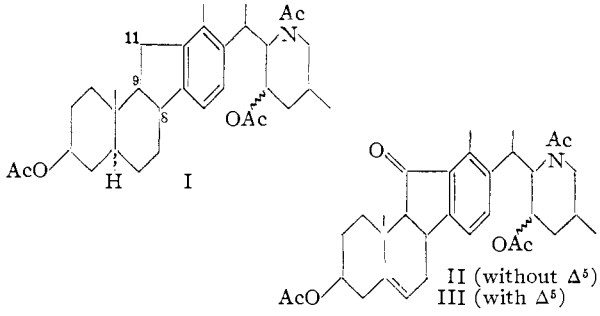
The main product formed in the chromic acid oxidation of triacetyldihydroveratramine (I) is not the previously reported[3] 11-keto derivative II but a compound carrying two new oxygen functions in the B/C ring moiety. It differs from II by its instability to acid and alkali, which cause it to rearrange to α-naphthol derivatives of type VIII. From this behavior, its spectral and other properties, and those of its reduction products V and X, it is deduced that the oxidation product is a ketoxide in which rings B and C are consolidated into a 9-membered ring (IV). While conclusive proof for the location of the two new functional groups within this ring is lacking, the 8,9-*seco*-8-keto-9,11-oxido structure (A) is proposed as the best expression presently available.

Four years ago we reported in a preliminary communication[2] that we had succeeded in linking veratramine structurally with jervine by establishing the identity of an unreactive ketone which Tamm and Wintersteiner[3] had obtained by chromic acid oxidation of triacetyldihydroveratramine (I) with the 5,6-dihydro derivative II of the indanone III, an acetolysis product of O,N-diacetyljervine.[4] When, in the course of this work,[2] the oxidation of I was repeated on a larger scale, we encountered



in addition to II another crystalline compound (IV) which is actually the main neutral product formed in this reaction (yield 20–30%) but had been missed in the earlier investigation[3] for reasons which will become apparent further below. An inquiry into the nature of this substance seemed in order, the more so as some of its properties, particularly its instability to strong acids and bases, could not be readily interpreted at that time in terms of the new veratramine formula proposed by us.[3]

The analysis of the new oxidation product (m.p. 225–225.5°, $[a]_D$ +50°) fitted best the formula $C_{33}H_{45}O_7N$ (I, −2H +2O). The infrared spectrum exhibited in addition to the bands at 5.78 and 6.11 μ originating in the O- and N-acetyl groups of I, a strong new maximum at 5.88 μ, present also in the spectra of the indanones II and III and hence apparently attributable to a ketonic carbonyl vicinal to the benzene ring. The ultraviolet absorption curve (Fig. 1, curve 2), however, was far less characteristic than that of II (Fig. 1, curve 1) in that it showed merely gradually rising extinction below 350 mμ with a plateau between 245 and 255 mμ (ε ~ 3000) and a slight shoulder at 320 mμ (ε 25) as the only distinctive features. That the keto group in question is masked or severely hindered was indicated by its lack of reactivity toward semicarbazide and 2,4-dinitrophenylhydrazine. Treatment with hydroxylamine afforded in poor yield a monoxime, m.p. 263–266°; however, the analytical composition (IV + NH_2-OH) and ultraviolet spectrum (λ_{max} 265 mμ, log ε 4.19) of this derivative clearly showed that a structural change had occurred in its formation (see below). Moreover, IV proved to be completely resistant to catalytic hydrogenation (PtO_2, acetic acid) and was recovered unchanged after treatment with an enolizing agent, isopropenyl acetate. An aldehydic carbonyl was excluded by the negative Schiff test and the fact that IV was not affected by prolonged contact at room temperature with permanganate in acetone or with a large excess of chromium trioxide in acetic acid. It was also inert to periodic acid and perbenzoic acid. As was to be expected from the absence of a band in the 3.0μ region of the infrared spectrum, no change occurred on treatment with acetic anhydride and pyridine.

Definite chemical evidence for the presence of a keto group came to hand with the finding that IV could be reduced with zinc and aqueous acetic acid to an alcohol $C_{33}H_{47}O_7N$ (m.p. 202–205°, $[a]_D$ +28°), which reverted to IV on oxidation with chromic acid. The infrared spectrum of this "zinc reduction product" (V) confirmed the replacement of the carbonyl giving rise to the 5.88 μ band by a hydroxyl group (band at 3.03 μ), while the ultraviolet spectrum (Fig. 1, curve 3) which was indistinguishable from that of veratramine and of I, made it clear that the chromophore in IV must be an acetophenone-like grouping in which resonance is severely restricted by steric factors. The new secondary hydroxyl group in V, like the keto group in IV, proved to be sterically hindered, as it could be acetylated only with the aid of boron trifluoride. The resulting tetraacetate VI (m.p. 153–156°, $[a]_D$ +58.5°), as well as the parent triacetate V, on hydrolysis with alkali afforded an N-acetate VII which could be obtained only in the form of a monohydrate. The additional mole of water was not chemically bound, as VII reverted to the triacetate V on acetylation with acetic anhydride and pyridine. Significantly, the infrared spectrum of VII was devoid of bands in the 6.0 μ region, except for that (at 6.21 μ) originating in the N-acetyl group, showing that the second new

(1) Part of thesis submitted by N. L. Hosansky in May, 1953, to the Graduate Faculty of Rutgers University in partial fulfillment of the requirements for the Ph.D. degree.

(2) O. Wintersteiner and N. L. Hosansky, THIS JOURNAL, **74**, 4474 (1952).

(3) Ch. Tamm and O. Wintersteiner, *ibid.*, **74**, 3842 (1952 .

(4) O. Wintersteiner and M. Moore, *ibid.*, **75**, 4938 (1953).

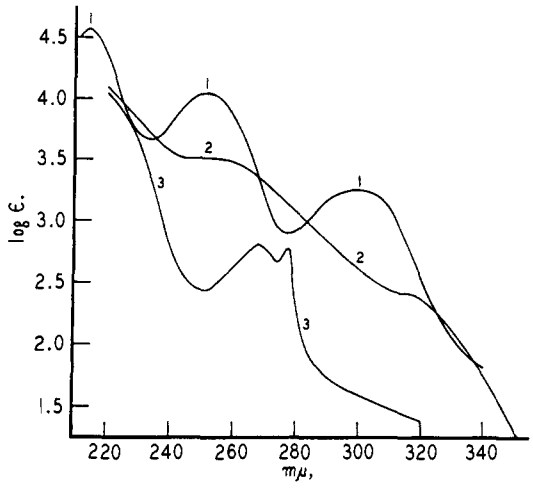


Fig. 1.—Curve 1, triacetyl-11-ketodihydroveratramine (II); curve 2, oxidation product IV; curve 3, zinc reduction product V.

oxygen function in IV and V could not be ketonic.

As follows from the reversible reaction V ⇆ VII, the zinc reduction product is stable to caustic alkali. However, this is not true of the original oxidation product, IV. This compound undergoes a rapid, irreversible change on treatment with strong bases (or acids) and even when brought in contact with activated surfaces. We became aware of the latter fact when, after the isolation of IV (by direct crystallization), a crystalline but slightly impure mother liquor fraction was subjected to chromatography on (sulfuric acid-washed and reactivated) alumina. The eluted fractions all resisted crystallization and their ultraviolet characteristics were quite unlike those of IV (maxima at 240 and 328 mμ and a broad band in the 285–300 mμ region). This explained why in the original experiments,[3] in which the total neutral fraction had been chromatographed, IV was not encountered.[5] From a study of the spectral changes produced in alcoholic solutions of IV by the addition of potassium hydroxide or hydrochloric acid it became evident that the entity in question was a naphthol. The preparative experiment with alkali yielded an N-acetate $C_{29}H_{39}O_4N$ (VIII), the properties of which confirmed this conclusion. In the infrared spectrum the carbonyl band at 5.88 μ had disappeared, and hydroxyl absorption (3.16 μ) was now in evidence. The ultraviolet spectrum in ethanol or ethanolic hydrochloric acid showed the characteristic already mentioned (Fig. 2, curve 1); potassium hydroxide produced the expected shifts (Fig. 2, curve 2). Spectra of this type are typical for α- rather than β-naphthols.[6] Although VIII failed to react with ferric chloride, it formed a deep red azo dye when coupled with diazotized sulfanilic acid, indicating the presence of a replacable hydrogen atom *ortho* or *para* to the naphtholic hydroxyl.

Acetylation in pyridine converted VIII to a tetraacetate $C_{33}H_{45}O_7N$ (IX), the infrared spectrum of which exhibited in addition to the normal O-acetyl and N-acetyl bands, one at 5.68 (phenolic acetyl).[7] The ultraviolet spectrum of IX showed the expected hypsochromic displacement of the two high maxima of VIII.[8] The tetraacetate was also obtained by two other routes: (1) treatment of the oxidation product IV with hydrochloric acid in methanol and acetylation of the resulting amorphous product, and (2) from IV directly by acetylation with acetic anhydride—acetic acid in the presence of boron trifluoride.

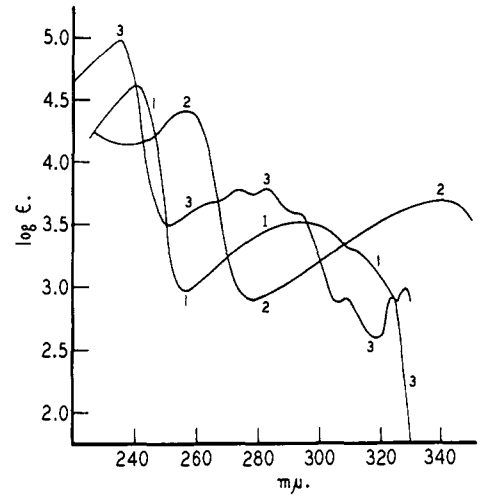


Fig. 2.—Curve 1, naphthol N-acetate VIII in ethanol; curve 2, naphthol N-acetate VIII in methanolic KOH; curve 3, naphthalene N-acetate XIII.

It is obvious from the above facts that the naphthol N-acetate VIII and its tetraacetate IX must be formulated either as shown below or as the isomer with the naphtholic hydroxyl attached to carbon atom 11. (For reasons to be given later we prefer the 8-hydroxy structure.) At any rate, it was clear at this point that the two oxygen atoms introduced in the formation of IV had to be accommodated in a moiety comprising C-8, C-9, C-11 and perhaps also C-7. Furthermore, it was now possible to define precisely the oxidation state of IV which had hitherto rested merely on the analytical data, particularly the hydrogen values, for IV and V and the latter's derivatives. Since the yield of the naphthol from IV exceeded 50% and the reaction was found to proceed just as well in the absence of oxygen, dismutation or autoxidation is not involved, *i.e.*, the oxidation state of VIII is also that of IV. Now, VIII must obviously be tetracyclic (counting for this purpose only the rings of the nucleus) and if this were true also for IV, its second new oxygen function would have to be hydroxylic; if, on the other hand, IV possesses a tricyclic 8,9-*seco* structure, then the oxygen atom would be

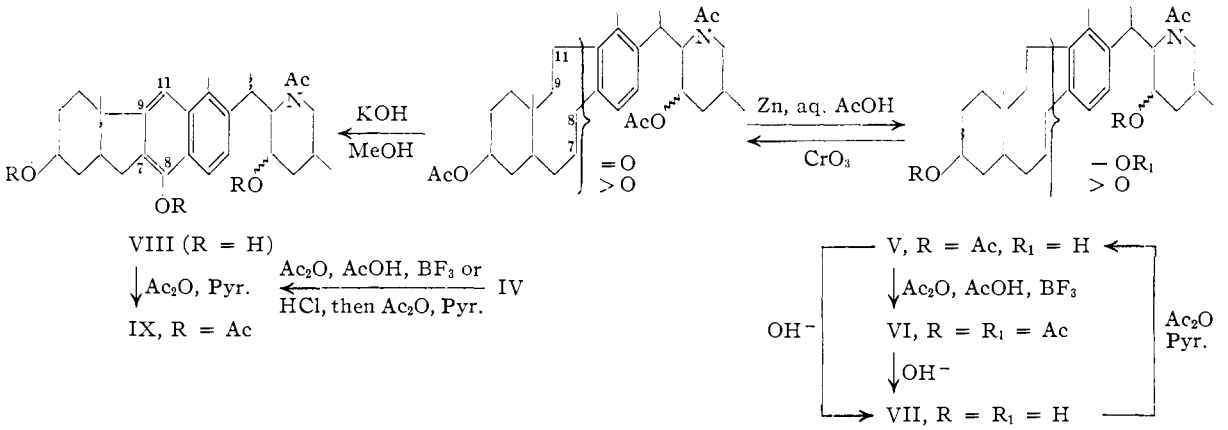
(5) Even contact with soft glass at elevated temperature will catalyze this reaction. Thus, while pure IV in a Pyrex capillary melts at 225–225.5°, and the colorless melt exhibits the original ultraviolet characteristics, when a soft glass capillary was used the compound liquified at 204–207°, forming a bright red melt the spectrum of which was similar to that of the chromatographed material.

(6) W. Cocker, B. E. Cross, A. K. Fateen, C. Lipman, E. R. Stuart, W. H. Thompson and D. R. A. Whyte, *J. Chem. Soc.*, 1781 (1950).

(7) R. N. Jones, P. Humphries and K. Dobriner, THIS JOURNAL, **72**, 956 (1950).

(8) The curve was almost identical with that of the naphthalene XIII described further below, clearly demonstrating the resonance-restricting effect of acetylation (*cf.* C. Daglish, *ibid.*, **72**, 4859 (1950)).

either ketonic or oxidic. Of these three possibilities, the first and second are excluded, respectively, by the absence of a hydroxyl band in the infrared spectrum of IV and of a ketone band in that of the N-acetate VII of the zinc reduction product V. On this basis IV may now be written as a tricyclic 8,9-*seco* ketoxide and V as the corresponding oxido alcohol, with the location of the new functional groups in the 9-membered ring left undefined, as shown below.



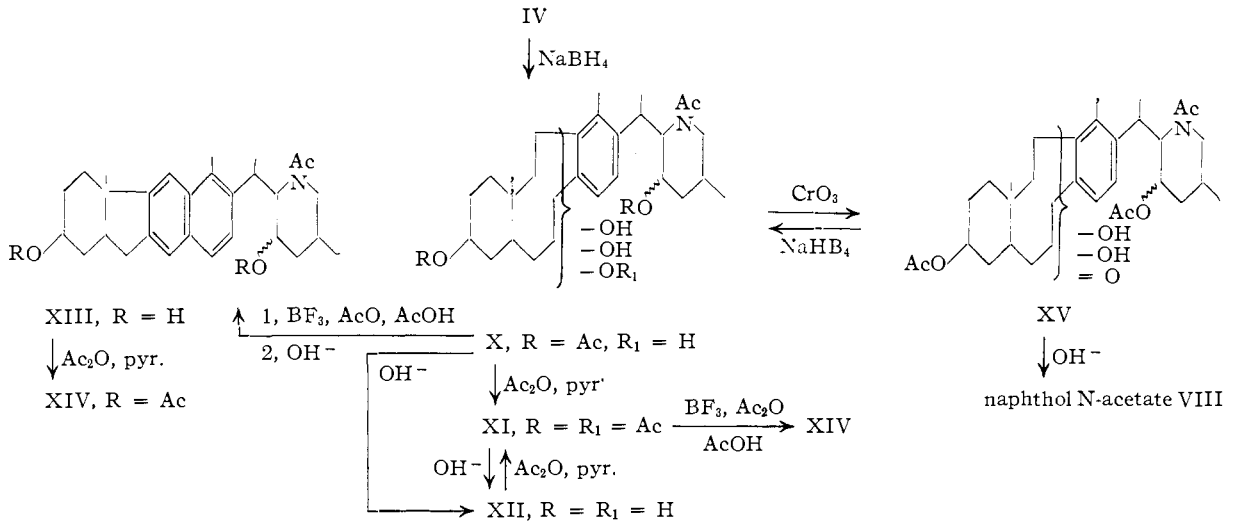
In searching for reactions of IV and V which would substantiate these structures, we found that IV could be reduced with sodium borohydride in methanol to a compound (X) which had the elementary composition $C_{33}H_{49}O_8N$ (IV + 2H + H_2O), suggesting that besides reduction of the keto group hydrolytic opening of the presumed oxide ring had occurred. As with the zinc reduction product V, the ultraviolet and infrared data disclosed only the disappearance of the ketonic carbonyl and the emergence of one or more hydroxyl functions. On acetylation with acetic anhydride in pyridine, this "sodium borohydride reduction product" formed a tetraacetate $C_{35}H_{51}O_9N$ (XI); thus only one of the 3 new hydroxyl groups indicated by the analysis of X had been acetylated. Treatment of either X or XI with methanolic potassium hydroxide yielded a product which could not be obtained in crystalline form, but was shown by analysis and the infrared data (only N-acetyl band at 6.19 μ in carbonyl region) to be the expected pentahydroxy N-acetate XII. On acetylation in pyridine it reverted to the tetraacetate XI.

In the expectation that one or both of the unreactive hydroxyl groups in X would be amenable to acetylation under more stringent conditions, the triacetate was treated with the boron trifluoride-containing acetylation mixture. The resulting product was amorphous, but on alkaline hydrolysis it afforded a crystalline substance, the composition $C_{29}H_{39}O_3N$ of which showed that the three "new" hydroxyl groups of X had all been eliminated. That dehydration had occurred already during the acetylation step was evident from the fact that the crystalline hydrolysis product and its amorphous precursor exhibited identical ultraviolet absorption. The absorption curve (Fig. 2, curve 3) strongly resembled that of the naphthol tetraacetate IX; almost identical characteristics have been reported for 2,3,5-trimethylnaphthalene.[9] There can be no doubt then that this compound is the naphthalene XIII. Here again the formation, consequent to the elimination of three hydroxyl groups, of a tetracyclic product with only two new double bonds calls for a tricyclic precursor in which the central rings of veratramine are consolidated into a nine-membered ring.

Acetylation of the naphthalene N-acetate XIII in pyridine gave an amorphous triacetate XIV. A product exhibiting substantially the same rotation and spectral properties was obtained when the tetraacetate XI of the sodium borohydride reduction product was treated with the boron trifluoride-containing acetylation mixture. Esterification of the reactive hydroxyl group among the three present in the B/C moiety does therefore not prevent the transannular reaction leading to the naphthalenic system.

Since on the basis of IV one could expect the sodium borohydride reduction product X to contain a 1,2-glycol grouping, it was surprising to find it inert toward periodate and lead tetraacetate. That two of the three "new" hydroxyl groups of X are not readily attacked by oxidizing agents was also indicated by the fact that on oxidation with a limited amount of chromium trioxide (2.5 equivalents) it afforded in 35% yield a monoketone $C_{33}H_{47}O_8N$ (XV) which reverted to X on reduction with sodium borohydride. Although λ_{max} 265 mμ in the ultraviolet spectrum of XV (Fig. 3, curve 1) is unusually high for an acetophenone-type chromophore (compare with II, Fig. 1), the high shoulder at 295 mμ (ϵ 2000) and the appearance in the infrared spectrum of a band at 6.03 μ permits of no other interpretation but that the keto group is vicinal to the benzene ring. That it must also occupy the same position as that in the original oxido ketone IV derives from the following lines of evidence: (1) its oxime was identical, except for a slight discrepancy in the melting point, with that obtained from IV (λ_{max} 265 mμ); (2) treatment with methanolic potassium hydroxide at room temperature converted the monoketone in 60% yield to a naphthol identical with that (VIII) formed under the same conditions from IV; (3) the monoketone was found to be identical with a substance showing

(9) R. A. Morton and A. J. A. de Gouveia, *J. Chem. Soc.*, 911 (1934).



the same constants which Tamm and Wintersteiner[3] had encountered in small amounts among the oxidation products of triacetyldihydroveratramine and must have arisen in that case by hydrolysis of the oxide ring of the main oxidation product IV. Furthermore, since the ketone XV was recovered unchanged on acetylation with acetic anhydride and pyridine, it must be the acylable hydroxyl in X which has undergone oxidation. Whether the resistance to acetylation under mild conditions shown by the hydroxyl group of V, which must occupy the same site, is due to epimerism or to differences in the conformation of the 9-membered ring in II and X cannot be decided at present.

Although XV failed to react with periodic acid, it consumed 1.3 moles of lead tetraacetate. Since any 1,2-glycol or ketol grouping present would necessarily have to be vicinal to the benzene ring, cleavage of such a system should result in an alteration of the ultraviolet characteristics. However, the spectrum of the recovered material was essentially the same as that of XV. In all likelihood the reagent had been consumed in an atypical reaction such as acetoxylation of an activated methylene group.[10]

Surprisingly, oxidation of the tetraacetate XI with chromic acid under the condition employed with X gave a much larger proportion of acids than X. With a larger excess of oxidant (10 equivalents of O) 65% of the material oxidized was converted into acids. The investigation of these products, one of which was obtained in form of a crystalline methyl ester, could not be carried to a conclusive stage and will have to be the subject of a future report.

While the formation and properties of the sodium borohydride reduction product provided reasonably good support for the ketoxide structure of its progenitor IV, means were sought for demonstrating more conclusively the oxidic nature of the second new oxygen function. Clearly the zinc reduction product V was more suitable for this purpose than IV as it appeared to be less prone than the latter to enter acid-catalyzed transannular reactions (as indicated, for instance, by the difference in their behavior in the boron trifluoride-catalyzed acetylation). Of the procedures studied, only the reaction of the tetraacetate VI with 1.5 moles of hydrobromic acid in acetic acid solution (room temperature, one hour), followed by alkaline hydrolysis, afforded a crystalline product. This substance was yellow and free of bromine. Its composition $C_{29}H_{39}O_3N$ showed that, aside from the loss of the 3- and 23-acetyl groups, one molecule each of water and acetic acid had been eliminated in the over-all reaction from VI. On the premise that the latter contains an oxidic linkage, this would correspond to the formation of three new double bonds, or of two double bonds and a carbon–carbon linkage in a transannular reaction. The ultraviolet absorption spectrum (Fig. 3,

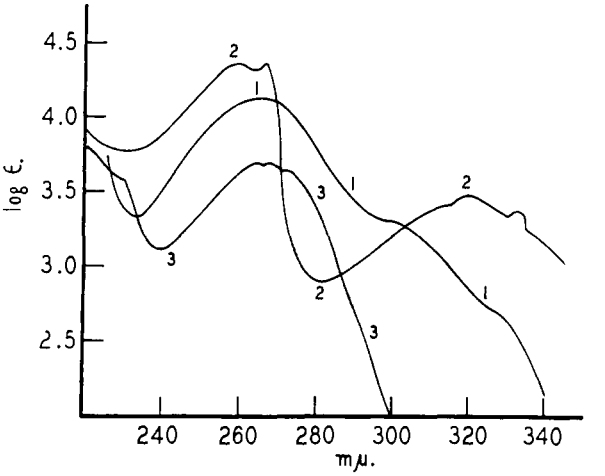


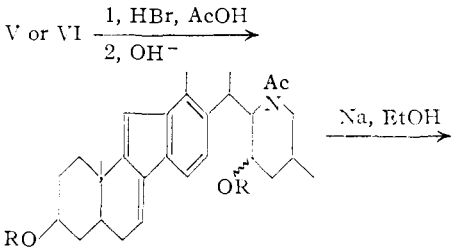
Fig. 3.—Curve 1, ketone XV; curve 2, benzofulvene XVI; curve 3, indene XVIII.

curve 2) was very similar to that reported for isopropylidene-indene ($\lambda_{max}^{heptane}$ 261 mμ (4.41), 308 mμ (3.80), 320 mμ (3.92), sh. 342 mμ (3.22)[11]) and this persuaded us that we were dealing with the

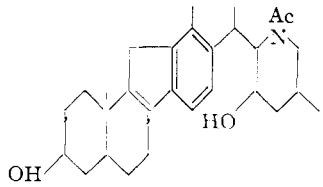
(10) R. Criegee, "Newer Methods of Preparative Organic Chemistry," Interscience Publishers, Inc., New York, N. Y., 1948, p. 8.

(11) A. Pullman, B. Pullman, E. D. Bergmann, G. Berthier, Y. Hirshberg and Y. Sprinzak, *Bull. soc. chim. France*, 702 (1951).

benzofulvene XVI. This supposition was strengthened by the finding that XVI, though completely inert to hydrogen and platinum oxide in either alcohol or acetic acid solution, could be reduced with a



XVI, R = H
XVII, R = Ac



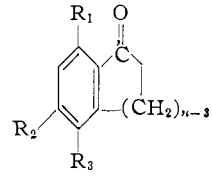
XVIII

large amount of sodium in boiling ethanol to a colorless dihydro- derivative isomeric with N-acetylveratramine, the absorption spectrum of which (Fig. 3, curve 3) was of the same type as that of indene (λ_{max}^{alc} 274 mμ, (4.1)[9]) and 3-methyl-indene (λ_{max} 252 mμ, (3.94)[12]). The bathochromic displacement and higher extinction of the maxima, as well as the absence of fine structure in the 280–300 mμ region, are no doubt referable to the multiple substitution of the chromophore in the reduction product. Of the two possible structures (Δ^{8-9} or Δ^{9-11}-N-acetylisoveratramine) we prefer the former (XVIII), since, with its double bond endocyclic with respect to the 6-membered ring B, it should be the more stable isomer.[13] The Δ^{7}-isomer need not be considered, since styrenes are readily reducible by sodium and alcohol.

That the transannular reaction leading to the reestablishment of the veratramine skeleton is part of a—probably concerted—sequence initiated by the hydrobromic acid rather than an alkali-catalyzed reaction occurring during the subsequent hydrolysis follows from the fact that the absorption spectrum of the intermediate amorphous product was identical with that of XVI. Control measurements showed that within one hour at room temperature 65% of the tetraacetate VI had been converted to this product, which is evidently the triacetate XVII corresponding to XVI. Contrary to expectation, the reaction of the triacetate V (in which the hydroxyl function eliminated in the above sequence is free) with hydrobromic acid proceeded much more sluggishly, but attempts to take advantage of this fact for the isolation of the bromohydrin presumably formed as the primary product were unsuccessful (see Experimental).

Discussion

Further elaboration of the partial structure IV for the oxidation product must start with the consideration that the keto group in this compound (and consequently the hydroxy group in V and the keto group in XV) has been shown to be vicinal to the benzenoid ring. Of the spectral and chemical (α-naphthol formation) evidence adduced on this point, only the ultraviolet spectra of IV and XV need some comment. As regards the lack of specific absorption and the low extinction at 250 mμ of the curve of IV (Fig. 1), it is pertinent to point out that in the 2,3-benzocyclanone (XIX) series ε of the main maximum in the 245–250 mμ region shows a sharp decrease when n becomes 7 and n = 8 is little more than half (7000) that of α-tetralone (12,500).[14] The low intensity maxima in the 280–290 mμ region show a similar trend.[14a,b]



XIX, $R_1 = R_2 = R_3 = H$
XIXa, $n = 7$; $R_1 = R_3 = CH_3$; $R_2 = H$
XIXb, $n = 8$; $R_1 = R_2 = CH_3$; $R_3 = H$

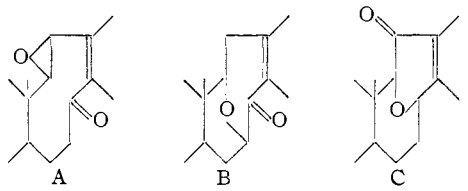
This is ascribed to progressive loss of coplanarity of the conjugated system consequent to the pressure exerted on the carbonyl oxygen by the methylene hydrogens in the interior of the medium sized rings. It stands to reason that this effect would still be more pronounced in a benzocyclononanone derivative. Moreover, it is to be expected that in IV the spatial demands of the additional fused ring A (which would tend to compress the 9-membered ring even further), as well as of the epoxide ring and the axial 19-methyl group, would add to the congestion in the interior of that ring and thus to the twisting-out-of-plane of the ketonic carbonyl Lastly, the dampening of resonance by the alkyl substituents in the aromatic ring D has to be considered. It has been shown[14a] that substitution of the benzene ring in 2,3-benzocycloheptanone (XIX, n = 7) with methyl groups in the 1′- and 4′-positions (XIXa) leads to a marked decrease of ε for λ_{max} ~ 245 mμ (9000 to 4,950), though this is not observed with the corresponding derivatives of α-indanone and α-tetralone. More striking still is the effect on ε of substitution with methyl of the 1′- and 3′-positions in 2,3-benzocycloöctanone (XIXb)[14c] in that the main maximum is replaced, similarly as in IV, by a low plateau at 245 mμ with ε only 2,100. These effects are attributed to resonance dampening mainly by the methyl group R_1 in XIXa and b. While it would appear tempting to allocate on this basis the keto group in IV to position 11, we are reluctant, in the absence of data from models more closely resembling IV, to use this point as a structural argument.

In the ketone XV this steric restraint on resonance must be somehow relieved by the opening of the oxidic ring; indeed the bathochromic displacement of the main maximum to 265 mμ from its usual position around 250 mμ in the benzocyclonones with $n < 8$ indicates that a resonance-enhancing factor, such as a hydroxyl group at the

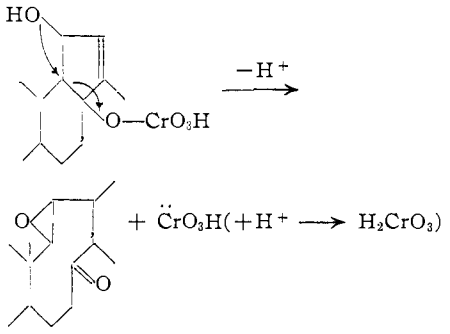
(12) P. Ramart and J. Hoch, *Bull. soc. chim. France*, **5**, 848 (1938).
(13) H. C. Brown, J. H. Brewster and H. Shechter, THIS JOURNAL, **76**, 467 (1954).
(14) (a) G. D. Hedden and W. G. Brown, *ibid.*, **75**, 3744 (1953); (b) R. Huisgen, W. Rapp, I. Hugi, H. Walz and E. Mergenthaler, *Ann.*, **586**, 1 (1954); (c) W. M. Schubert, W. A. Sweeney and M. K. Latourette, THIS JOURNAL, **76**, 5462 (1954).

carbon atom adjoining the keto group or strong hydrogen bonding[15] across the ring, is operative. The position of the carbonyl band in the infrared spectrum of XV (6.05 μ), as compared with those of III and IV (5.88 μ), would accord with the latter explanation (*cf.* α-dipiperitone, 6.10 μ; acetate 5.95 μ).[15]

On the assumption that in IV and its congeners the *seco*-carbon atoms 8 and 9 should both be substituted with oxygen, only three structures A, B and C need to be considered for IV. Of these, C is perhaps the least likely for the reason that the other oxidation product of I, the 11-ketone, III, is com-

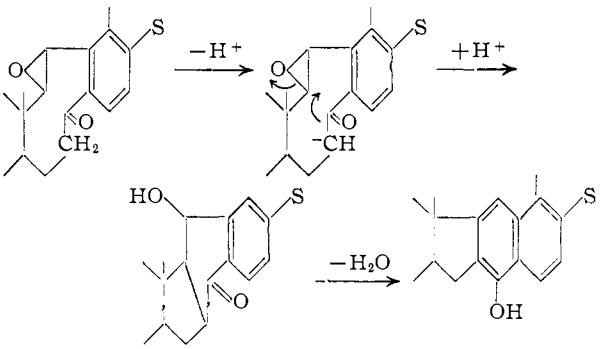


pletely resistant to further attack by chromic acid and hence cannot be a precursor of IV. Moreover, it is difficult to devise a reasonable mechanism for the formation of C either *via* III or a 8,11-dihydroxy derivative of I. Hardly more attractive from this point of view is structure B, unless one assumes that it arises by the lengthy sequence: 8-hydroxy derivative of III → 8,9-ethylene → 8,9-*seco*-diketone → B. The last step would involve a transannular 7 → 9 hydride ion shift consequent to which the carbonium ion at C-7 accepts an electron pair from the C-9 carbonyl oxygen. Although the recent literature on medium size ring compounds records several examples of such shifts across the ring resulting in the formation of "transannular" glycols from 1,2-oxides or from olefins treated with performic acid,[16] there is no precedent for a reaction of the type first mentioned. We are therefore inclined to give preference to A, the formation of which can be pictured to take place by the concerted mechanism shown below.[17]



From the scale model of IV given form A (but omitting the epoxide ring), it appears that there are at least four conformations of the 9-membered ring in which the latter is strain-free, and at the same time the tricyclic ring system is reasonably planar. They all have in common that the carbonyl double bond is bent out of the plane occupied by the aromatic ring by a projected angle approximating 90° (in two forms forward and in the other two backward). They are not readily interconvertible and differ in this respect from the much less rigid models of cyclononanone. This may in part account for the relative or total lack of reactivity of the keto group in IV, the hydroxyl group in V and the two non-acetylatable hydroxyl groups in X, which is in contrast to the behavior of such groups in simple 8-, 9- and 10-membered cycloalkanes. The models show that in the four conformations mentioned there is, generally speaking, marked crowding of the oxygen substituents by carbon-bound hydrogen atoms on the same or the opposite side of the 9-membered ring and in some cases also by the 19-methyl group. Moreover, in order to explain the failure of chromic acid to attack non-acetylatable hydroxyl groups in X (at C-9 and C-11 in the structure corresponding to A), it must be assumed that the hydrogen atoms attached to the carbons carrying these groups are themselves "tucked away" in the interior of the ring.

In view of the wealth of precedent in the recent literature on medium-sized ring compounds for the occurrence of transannular alkylation reactions,[18] it is hardly necessary to argue *in extenso* the feasibility of the transannular reactions leading to the re-establishment of tetracyclic systems in IV or XV → VIII, VI → XVI and X → XIII. That in these cases the primary products thus formed (ketols, diols) should immediately pass by dehydration and double bond shifts into the more stable aromatic or semi-aromatic (XVI) types is only to be expected. For instance, the alkali-catalyzed reaction leading from IV (A) to the naphthol VIII can be readily envisioned as occurring by the sequence



The transannular alkylation step here is entirely analogous to the alkali-catalyzed isomerization of the oxidoketone XX (Treibs' oxidoketone) from caryophyllene to the hydroxy ketone XXI, as formulated by Barton, *et al.*[19]

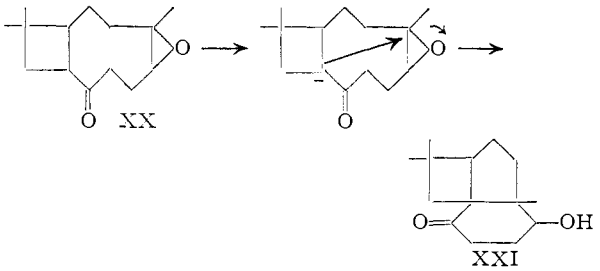
(15) A similar but less pronounced difference between λmax of α-dipiperitone and that of its acetate has been attributed to this cause by W. A. Ayer and W. I. Taylor, *J. Chem. Soc.*, 2227 (1955).

(16) (a) A. C. Cope, S. W. Fenton and C. F. Spencer, THIS JOURNAL, **74**, 5884 (1952); (b) V. Prelog, K. Schenker and W. Kung, *Helv. Chim. Acta*, **36**, 471 (1953), (c) V. Prelog and K. Schenker, *ibid.*, **35**, 2044 (1952).

(17) We are indebted to Prof. D. H. R. Barton for this suggestion (private communication, 1953).

(18) For example: cyclooctane-1,4-dione + NaOH → bicyclo-[3,3,0]-1(5)-octen-2-one (reference 16a); *cis* or *trans*-cyclononane-1,5-diol + CrO_3 → $\Delta^{8,9}$-hydrindene-4-one (reference 16b); 6-tosyloxycyclodecanone + K-*t*-butoxide → bicyclo[5,3,0]decan-2-one; cyclodecane-1,6-diol ditosylate + $C_5H_5N(CH_3)_2$ → 1,9-octalin + 9,10-octalin (A. C. Cope and G. Holzman, THIS JOURNAL, **72**, 3062 (1952)); *trans*-cyclodecene + β-naphthalenesulfonic acid + hydroquinone → *cis*- and *trans*-decalin (A. C. Cope, D. C. McLean and N. A. Nelson, *ibid.*, **77**, 1628 (1955)).

(19) D. H. R. Barton and A. S. Lindsay, *J. Chem. Soc.*, 2988 (1951); D. H. R. Barton, J. Bruun and A. S. Lindsay, *ibid.*, 2210 (1952).



XX

XXI

In conclusion, we believe that the partial formula IV proposed by us for the oxidation product accounts adequately for its properties and reactions. Further oxidative degradation will have to show whether the expansion to IV (A) tentatively proposed by us is tenable.

In the experimental part we also describe the details of the reduction of III to II reported in our preliminary paper.[3]

Experimental[20]

Triacetyl-11-ketodihydroveratramine (II) by Reduction of Triacetyl-11-ketoveratramine (III).[2]—A solution of the indanone III (402 mg., 0.73 mmole), obtained by acetolysis of diacetyljervine, in 95% ethanol (165 ml.) was shaken with hydrogen in the presence of palladium–calcium carbonate catalyst[21] (6.1 g.). Uptake was essentially complete after 6.5 hours (23.7 ml., 1.3 mmoles). The catalyst was filtered off, washed well with warm alcohol and the filtrate was taken to dryness *in vacuo*. The residue was taken up in chloroform, and the solution was washed with dilute hydrochloric acid, water, dried and evaporated. The resulting residue (383 mg.) on several recrystallizations from ether yielded fine needles (84 mg.), m.p. 239.5–243°, $[\alpha]_D$ +39.4° (*c* 0.94).

The material (187 mg.) obtained on evaporation of the mother liquor from the first crystallization showed a somewhat higher $[\alpha]_D$ (+49.6°). It was rehydrogenated as above, whereupon it consumed about 0.5 mmole of hydrogen (assuming that 20% of the material was unreduced III). Isolation as above gave 178 mg. of crystalline material, m.p. 190–204°, $[\alpha]_D$ +52.3°. Several recrystallizations from ether finally afforded substantially pure II, m.p. 238–242.5°, $[\alpha]_D$ +57.5° (*c* 0.76); λ_{max} 251 mμ (4.06), 300 mμ (3.26); infrared: 5.79, 5.89, 6.12 μ.

Anal. Calcd. for $C_{33}H_{45}O_6N$ (551.7): C, 71.83; H, 8.22. Found: C, 71.94; H, 8.26.

There was no depression of the melting point on admixture of a specimen obtained by chromic acid oxidation of triacetyldihydroveratramine (m.p. 241–245°, $[\alpha]_D$ +59°[3]); likewise, the infrared spectra of the two samples was identical in every respect.

N-Acetyl-11-ketodihydroveratramine.[2]—The above reduction product (169 mg.) was dissolved in methanol (8 ml.) and treated with 10% potassium hydroxide in methanol (8 ml.) at room temperature for 24 hr. The pale yellow solution was poured into water and the N-acetate isolated by chloroform extraction (143 mg.). Several crystallizations from ethyl acetate gave needles, m.p. 263–267°, with softening and browning at 261°; $[\alpha]_D$ +68.6° (*c* 0.42); λ_{max} 253 mμ (4.02), 300 mμ (3.27); infrared: 2.91, 6.18 μ.

Anal. Calcd. for $C_{29}H_{41}O_4N$ (467.6): C, 74.46; H, 8.84. Found: C, 74.57; H, 8.64.

A sample of the N-acetate prepared in the same manner from II which had been obtained by oxidation of triacetyldihydroveratramine showed the same melting point and $[\alpha]_D$ +70.7° (*c* 0.91). The infrared spectra of the two specimens were identical.

Chromic Acid Oxidation of Triacetyldihydroveratramine; Oxido Ketone IV.—To a solution of triacetyldihydroveratramine (1.975 g., 3.68 mmoles) in glacial acetic acid (100 ml.), chromium trioxide (493 mg., 2 atoms O per mole) dissolved in several drops of water and acetic acid (8 ml.) was added. After about 2.5 hr., when most of the oxidant had been consumed, an additional amount of chromium trioxide (739 mg., 3 atoms O per mole) in 12 ml. of acetic acid was added. The solution was allowed to stand at room temperature for 48 hr. After addition of a small amount of ethanol, most of the solvent was removed *in vacuo*. The residue was distributed between ether and water and the aqueous layer extracted two more times with ether. The combined ether extracts were washed with dilute potassium carbonate, water, dried over sodium sulfate, filtered and concentrated to a small volume, whereupon crystalline material separated out (519 mg., m.p. 218–221°). Recrystallization from acetone–ether gave the pure product as fine needles (269 mg.); another 100 mg. was obtained from the mother liquors; m.p. 225–225.5°; $[\alpha]_D$ +50.4 ± 1° (*c* 1.00); +123° (*c* 1.01 in pyridine); ultraviolet: plateau 240–255 mμ (3.53), sh. 315 mμ (2.40); infrared: 5.78, 5.88, 6.11 μ.

Anal. Calcd. for $C_{33}H_{45}O_7N$ (567.7): C, 69.81; H, 7.99; N, 2.47; 2 $COCH_3$, 15.16; 3 $COCH_3$, 22.75. Found: C, 70.27, 70.06; H, 8.14, 7.77; N, 2.52; $COCH_3$, 18.4.

The compound did not form an insoluble dinitrophenylhydrazone with Brady reagent. It was recovered unchanged after the following treatments: refluxing with alcoholic semicarbazide acetate for 2 hr.; standing at room temperature with potassium permanganate in acetone, with a large excess of chromium trioxide in acetic acid or with mercuric acetate in acetic acid; refluxing with isopropenyl acetate in the presence of *p*-toluenesulfonic acid for 9.5 hr.

The material from the original mother liquor (1.04 g.) was chromatographed on alumina to yield 96 mg. of starting material (m.p. 189–190.5°, $[\alpha]_D$ +84°) and 53.4 mg. of triacetyl-11-ketodihydroveratramine (m.p. 240.5–242°, $[\alpha]_D$ 58.9°, λ_{max} 252 mμ (4.04); 300 mμ (3.23)).

The acidic fraction recovered from the potassium carbonate washing (523 mg.) did not yield any crystalline products directly or after treatment with diazomethane.

Reaction of IV with Hydroxylamine.—(a) A solution of the ketoxide IV (62 mg.) in methanol (4 ml.) containing hydroxylamine acetate prepared from 42 mg. of hydroxylamine hydrochloride and 70 mg. of potassium acetate was boiled under reflux for 2 hr. Concentration of the cooled solution gave 16 mg. of crystalline material which on recrystallization from acetone–methanol afforded small rods, m.p. 263–266° dec.; λ_{max} 265 mμ (4.19), sh. 303 mμ (3.13).

Anal. Calcd. for $C_{33}H_{48}O_8N_2$ (600.7): C, 65.97; H, 8.05; N, 4.66. Found: C, 65.72; H, 8.67; N, 4.83.

(b) The ketoxide (64 mg.) and hydroxylamine hydrochloride (34 mg.) in pyridine (3 ml.) was heated on the steam-bath for 4 hr. The product obtained by dilution with water (12 mg.) was recrystallized twice from acetone, from which it formed clusters of long rods, m.p. 273–275° dec.; λ_{max} 266 mμ (4.09), sh. 303 mμ (3.03).

Zinc Reduction Product V.—A solution of the ketoxide IV (198 mg.) in acetic acid (10 ml.) and water (10 ml.) was heated in an oil-bath to 80 ± 2°. Zinc dust (1.30 g.) was added in small portions over a 20-minute period and then the reduction was continued for another 50 minutes at this temperature. The excess zinc was filtered off, washed well with chloroform and the filtrate was then concentrated to a small volume. Isolation by extraction with chloroform in the usual manner and crystallization from acetone–ether gave 109.5 mg. (55%) of pure V, m.p. 202–205°, $[\alpha]_D$ +58.1 ± 2° (*c* 0.85); λ_{max} 266 mμ (2.64), 275 mμ (2.55); infrared: 3.03, 5.78, 6.23 μ.

(20) All melting points were taken in the capillary and are corrected for stem exposure. The solvent in the rotation measurements was chloroform unless indicated otherwise; the temperature varied between 21 and 23°. A 1-decimeter polarimeter tube was used which could be filled through a side arm and hence permitted measuring the experimental and solvent blank angles without changing the position of the end-plates between the two readings. The ultraviolet spectra were determined in absolute ethyl alcohol (unless otherwise noted) in a Cary recording spectrophotometer, model 11M. Intensities are expressed as the log of the molecular extinction coefficients, ε; *E*, whenever used, denotes the extinction coefficient $E^{1\%}_{1\,cm.}$. The infrared spectra were determined in Nujol suspension (unless otherwise noted) in a Perkin–Elmer spectrophotometer, model 12B, and in some cases checked on the double beam instrument, model 21. The analytical samples were dried to constant weight over phosphorus pentoxide in a high vacuum at 110° unless indicated otherwise. The alumina used for chromatography (Harshaw) was washed with dilute sulfuric acid and water to *p*H 4.5 and reactivated by heating at 150° for 48 hr.

(21) M. Busch and H. Stove, *Ber.*, **49**, 1063 (1916).

Anal. Calcd. for $C_{33}H_{47}O_7N$ (569.8): C, 69.58; H, 8.32. Found: C, 69.85; H, 8.38.

The compound was recovered unchanged when treated with acetic anhydride in pyridine at room temperature for 17 hr.

The triacetate V (10.2 mg.) was treated in acetic acid (0.62 ml.) with chromium trioxide (1.4 mg., 1.2 atoms O) for 30 minutes at room temperature. After the addition of several drops of alcohol, the solution was poured into water and separated into neutral (9.2 mg.) and acidic fractions. Several crystallizations of the former from acetone–ether afforded 3.0 mg. of needles, m.p. 222.5–223.5°, mixed with authentic IV, 224–225°; ultraviolet: shoulder at 257 mμ (3.46).

Tetraacetate VI from V.—The triacetate V (22.1 mg.) was dissolved in 4 ml. glacial acetic acid and treated with acetic anhydride (0.3 ml.) and boron trifluoride etherate (0.03 ml.) at room temperature overnight. The residue obtained after removal of the solvents *in vacuo* was taken up in chloroform, and the solution was washed with dilute hydrochloric acid, dilute sodium carbonate, water, dried and evaporated. The product recrystallized twice from methanol–water formed platelets (9.6 mg.), m.p. 153–156°, $[\alpha]_D$ +58.5° (*c* 0.75); λ_{max} 267 mμ (2.66), 276 mμ (2.53); infrared: 5.76, 6.12 μ.

Anal. Calcd. for $C_{35}H_{43}O_8N$ (611.8): C, 68.70; H, 8.07. Found: C, 68.75; H, 8.17.

N-Acetate VII from V.—A solution of the triacetate V (101 mg.) in 5% methanolic potassium hydroxide (10 ml.) was allowed to stand at room temperature overnight and then worked up in the usual way by chloroform extraction. The product (66.1 mg.) on recrystallization from ethanol–ether yielded 41.7 mg. of prisms, sintering without completely melting at 164–168°, resolidifying at 179° and then melting at 260.5–263°, $[\alpha]_D$ +39.5° (*c* 0.91); infrared: 2.94, 3.14, 6.21 μ.

Anal. Calcd. for $C_{29}H_{43}O_5N \cdot H_2O$ (503.7): C, 69.10; H, 9.00. Found: C, 69.13; H, 8.94.

The N-acetate VII was also obtained by treating V with sodium methoxide in dry methanol (m.p. 261–262°) or by hydrolysis of the tetraacetate VI with potassium hydroxide in methanol (m.p. 260.5–263°).

Acetylation in pyridine of the N-acetate yielded the triacetate V, m.p. 202–204°.

Conversion of IV to Naphthol VIII.—Adsorption of the oxidation product IV (100 mg.) in benzene–hexane (1:1) on alumina followed by elution with benzene–ether 19:1, 9:1 and 1:1 yielded three non-crystallizable fractions differing from each other in rotation ($[\alpha]_D$ +99°, +82° and +66°, respectively) but exhibiting very similar ultraviolet characteristics (λ_{max} (*E*) 240 mμ (1080 to 1343), 285–300 mμ (80), 328 mμ (25–30)), except that in the third fraction the broad band at 285–300 mμ was replaced by one at 260 mμ (*E* 194), possibly due to the presence of an ionized form of the naphthol. The rate of conversion in solution is indicated by the following data: in 1% ethanolic HCl: at 5 minutes, λ_{max} 240, 265, 308 mμ, with *E* 431, 38, 9.7, respectively; at 7.5 hr., λ_{max} 240, 295, 238 mμ, with *E* 887, 99, 21.5, respectively (51% conversion); in 1% methanolic KOH: at 5 minutes, λ_{max} 256 (*E* 316); at 28 hr., λ_{max} 255, 340 mμ, with *E* 895, 145, respectively (90% conversion).

In the preparative experiment the ketoxide IV (220 mg.) was dissolved in methanol (10 ml.) with slight warming and to the cooled solution was added 10% potassium hydroxide in methanol (10 ml.). A pale blue-violet color developed immediately and persisted for about 30 minutes when it faded to a pale yellow-green. After standing overnight the solution was poured into water and extracted with ether before and after acidification with hydrochloric acid. The residues of the two extracts weighed 6 and 227 mg., respectively. The latter product on repeated recrystallization from methanol–water gave 96.0 mg. (53%) of feathery needles, m.p. 207–210°, $[\alpha]_D$ +108° (*c* 0.91), +87° (*c* 0.90 in abs. alc.); λ_{max} 240 mμ (4.91), 288–297 mμ (3.75), 328 mμ (3.26), sh. 313 mμ (3.53); in 1% ethanolic potassium hydroxide: 257 mμ (4.71), 340 mμ (3.95); infrared: 3.16, 6.19 μ.

Anal. Calcd. for $C_{29}H_{39}O_4N$ (465.6): C, 74.78; H, 8.44; N, 3.01; $COCH_3$, 9.24. Found: C, 74.95, 75.13; H, 8.35, 8.64; N, 3.04; $COCH_3$, 3.51.

Addition of diazotized sulfanilic acid to a solution of VIII in 2 *N* sodium hydroxide produced a deep red color.

Tetraacetate IX from VIII.—(a) A solution of the naphthol VIII (35 mg.) in dry pyridine (1 ml.) and acetic anhydride (1 ml.) was allowed to stand overnight at room temperature. The solvents were removed *in vacuo* and the acetate was isolated by chloroform extraction; square plates from methanol–water, m.p. 180.5–183.5°, $[\alpha]_D$ +85° (*c* 0.41); λ_{max} 236 mμ (5.12), 275 mμ (3.83), 285 mμ (3.86), 323 mμ (2.53); infrared: 5.68, 5.79, 6.13 μ.

Anal. Calcd. for $C_{35}H_{45}O_7N$ (591.7): C, 71.03; H, 7.67; 3 $COCH_3$, 21.82; 4 $COCH_3$, 28.97. Found: C, 71.04; H, 7.79; $COCH_3$, 22.1.

(b) A solution of IV (87 mg.) in methanol containing 5% concentrated hydrochloric acid by volume (5 ml.) was allowed to stand overnight. The pale pink solution was poured into water and the white flocculent precipitate extracted with ether. The residue (96 mg.; λ_{max} 240 mμ (*E* 1290), 287 mμ (*E* 105), 328 mμ (*E* 400)), which failed to crystallize, was acetylated in pyridine at room temperature. The acetate was purified by chromatography over alumina to give 28.6 mg. of square plates from methanol–water, m.p. 178–181.5° unchanged by admixture of above preparation.

(c) To a solution of IV (46 mg.), acetic acid (6 ml.), acetic anhydride (0.6 ml.) and boron trifluoride etherate (0.06 ml.) was added. After standing at room temperature overnight the solvents were removed *in vacuo*. The chloroform solution of the residue was washed with water, dilute hydrochloric acid, sodium carbonate solution, and water, dried and evaporated. The product, after removal of some acetone-insoluble material, was obtained from methanol–water as platelets (18.0 mg.), m.p. 182–183°, $[\alpha]_D$ +82° (*c* 0.87); identity with the preparation obtained according to (a) was confirmed by the ultraviolet and infrared spectra.

Sodium Borohydride Reduction Product (X).—The ketoxide IV (9.7 mg., 0.176 mmole) was dissolved in methanol (5 ml.) with slight warming and the solution, after cooling to room temperature, was added dropwise with shaking to one containing sodium borohydride (42.9 mg., 1.13 mmoles) in methanol (4 ml.) over ten minutes. Evolution of gas persisted for 1 hr., after which the reaction mixture was allowed to stand for 4 more hours. The solution was made slightly acidic with 10% acetic acid (no evolution of hydrogen) and then evaporated to dryness *in vacuo*. The residue was taken up in chloroform which was washed with dilute potassium carbonate, water and dried over sodium sulfate. The crystalline chloroform residue (110 mg.) was recrystallized three times from acetone to give needles (57 mg.), m.p. 239–243°, $[\alpha]_D$ +85° (*c* 0.95), λ_{max} 265 mμ (2.53) in ethanol without or with 1% hydrochloric acid; infrared: 3.01, 5.77, 6.08, 6.18 μ (doublet); in chloroform: 2.98, 5.78, 6.10 (sh), 6.15 μ.

Anal. Calcd. for $C_{33}H_{49}O_8N$ (587.7): C, 67.44; H, 8.40; 2 $COCH_3$, 14.65; 3 $COCH_3$, 21.98. Found: C, 67.46, 67.78; H, 8.32, 8.63; $COCH_3$, 14.9.

Tetraacetate XI from X.—The triacetate X (126 mg.) was acetylated with acetic anhydride and pyridine in the usual way. The crude product was recrystallized twice from alcohol–water to give 91 mg. of hexagonal prisms, m.p. 151.5–153.5°, $[\alpha]_D$ +49.4° (*c* 0.89), λ_{max} 265 mμ (2.34); infrared: 2.88, 5.76, 5.88,[22] 6.14 μ.

Anal. Calcd. for $C_{35}H_{51}O_9N$ (629.8): C, 66.73; H, 8.16; 3 $COCH_3$, 20.50; 4 $COCH_3$, 27.33. Found: C, 66.79; H, 8.27; $COCH_3$, 22.6.

N-Acetate XII from X and XI.—A solution of the triacetate X (101 mg.) in 5% methanolic potassium hydroxide X (10 ml.) was allowed to stand at room temperature overnight. It was then poured into water, but no material could be extracted from this solution either before or after acidification. The now acidic aqueous phase, after neutralization with alkali and saturation with carbon dioxide, was lyophilized, and the resulting powder was leached with hot chloroform. The chloroform-soluble material (51 mg.) which failed to crystallize was purified by dissolving in hot ethyl acetate and concentrating to turbidity. The precipitate obtained on cooling was again treated in this manner, m.p. 156–174°, λ_{max} 266 mμ (2.59); infrared: 3.03, 6.19 μ.

(22) This band, the origin of which is unexplained, was invariably present in the Nujol spectrum of XI, although it is lacking in that of X. This point was checked on several different specimens of XI and X. However, it was never observed with chloroform solutions of XI.

Anal. Calcd. for $C_{29}H_{46}O_6N$ (503.7): C, 69.11; H, 9.00. Found: C, 69.85; H, 9.10.

The product obtained by the same procedure from the tetraacetate XI showed similar properties (m.p. 159.5–170°, λ_{max} 265 mμ (2.52)) and identical infrared characteristics.

Anal. Found: C, 69.15; H, 8.71.

Reacetylation in pyridine led back to the tetraacetate XI, m.p. 150–152°, undepressed by an authentic specimen.

Naphthalene XIII.—To a solution of the triacetate X (105.6 mg.) in acetic acid (5 ml.), acetic anhydride (1 ml.) and boron trifluoride etherate (0.1 ml.) were added. After standing at room temperature for 22 hr., the pale yellow solution was poured into ice-water. Extraction with chloroform yielded 117 mg. of a non-crystallizable residue; λ_{max} (*E*) 235 (1646), 273 (105), 282 (105), 309 (16.1), 324 (14.8) mμ. Hydrolysis of this material with 5% potassium hydroxide in methanol afforded a product which crystallized from methanol–water as rectangular prisms (41.6 mg.), m.p. 171.5–173.5°; after drying at 110°, 220.5–222°; $[\alpha]_D$ +126° (*c* 0.87). The mother liquors yielded another 17.1 mg. (total yield 73%), λ_{max} 235 mμ (5.00); 273, 283 mμ (3.80); 310, 324 mμ (2.94); infrared: 3.03, 6.16 μ.

Anal. Calcd. for $C_{29}H_{39}O_3N$ (449.6): C, 77.47; H, 8.74. Found: C, 77.03, 76.94; H, 8.75, 8.50.

Acetylation of XIII in pyridine yielded the amorphous triacetate XIV, $[\alpha]_D$ +127° (*c* 0.94); λ_{max} 235 mμ (5.00), 273, 283 mμ (3.80), 309 mμ (2.96), 323 mμ (2.93).

Anal. Calcd. for $C_{33}H_{43}O_5N$ (533.7): C, 74.26; H, 8.12; 2 $COCH_3$, 16.12. Found: C, 73.61; H, 7.97; $COCH_3$, 15.3.

A product of the same description was obtained when the tetraacetate XI of the sodium borohydride reduction product was treated in acetic acid (2 ml.) with acetic anhydride (0.2 ml.) and boron trifluoride etherate (0.02 ml.) for 17 hr. at room temperature. The material failed to crystallize even after chromatography. The main fraction (23.6 mg.) eluted with benzene showed $[\alpha]_D$ +121° (*c* 0.63); λ_{max} 235 mμ (4.97), 282 mμ (3.78), 309 mμ (2.94), 323 mμ (2.92).

Oxidation of the Sodium Borohydride Product to the Ketone XV.—To the triacetate X (211 mg., 0.358 mmole), dissolved in 2 ml. of glacial acetic acid and cooled to 10–15°, a solution of chromium trioxide (54.8 mg., 2.5 atoms O) in one drop of water and acetic acid (1.5 ml.) was added. After standing at 10–15° for 40 minutes, the mixture was allowed to come to room temperature (75 minutes). After addition of some ethanol, the solution was poured into water and separated into neutral (209 mg.) and acidic (13 mg.) fractions in the usual way. The neutral fraction on repeated crystallization from acetone–ether gave rods (69 mg.), m.p. 220–221.5°, $[\alpha]_D$ +31.2° (*c* 0.99); λ_{max} 265 mμ (4.16), sh. 300 mμ (3.32); in 1% potassium hydroxide in absolute ethanol: λ_{max} (*E*) 257 mμ (90), 340 mμ (111); in 1% hydrochloric acid in absolute ethanol: λ_{max} (E) 239 mμ (1080), 268 mμ (120), 328 mμ (21.8), sh. 312 mμ (50); infrared: 2.90, 5.80, 6.03, 6.18, 6.27 μ.

Anal. Calcd. for $C_{33}H_{47}O_8N$ (585.7): C, 67.67; H, 8.09. Found: C, 67.55; H, 8.12.

The melting point of XV was not depressed by admixture of the substance with m.p. 219–222°, $[\alpha]_D$ +31° encountered by Tamm and Wintersteiner[2] among the chromic acid oxidation products of I. The older specimen exhibited the same ultraviolet characteristics as XV. *Anal.* Found: C, 68.22; H, 7.87.

Treatment of XV (20.8 mg.) with sodium borohydride under the conditions described above gave the triacetate X (9.3 mg.), m.p. 231.5–235°, mixed m.p. 234–238°, $[\alpha]_D$ +82.6° (*c* 0.88), ultraviolet and infrared characteristics identical with those of X.

The ketone was recovered unchanged on treatment with acetic anhydride in pyridine at room temperature. It failed to react with Brady reagent, but when refluxed with hydroxylamine acetate in methanol for 2 hr. gave a monoxime crystallizing in tiny rods from chloroform–methanol; m.p. 256° dec. after softening at 235°; λ_{max} 266 mμ (4.13), sh. 304 mμ (3.11).

Anal. Calcd. for $C_{33}H_{48}O_8N_2$ (600.7): N, 4.66. Found: N, 4.24.

A mixture with the oxime, m.p. 263–266°, derived from IV melted at 255–256° dec.

Hydrolysis of the XV (15.4 mg.) with methanolic potassium hydroxide at room temperature gave the naphthol VIII (7.5 mg.), m.p. 199–202.5°, $[\alpha]_D$ 104° (*c* 0.65), ultraviolet and infrared characteristics identical with those of the sample from IV.

Reaction of VI with Hydrobromic Acid; Benzofulvene XVI.—A mixture containing the tetraacetate VI of the zinc reduction product V (88 mg., 0.15 mmole) and hydrobromic acid (19.8 mg., 0.22 mmole) in acetic acid (2.3 ml.) was allowed to stand at room temperature for 60 minutes and then poured into dilute ice-cold potassium carbonate solution. Extraction with chloroform yielded a yellow gum, which was adsorbed on a column of alumina from benzene solution. The amorphous fractions eluted with benzene (18 mg.) and benzene–ether 19:1 (46 mg.) exhibited similar ultraviolet characteristics (λ_{max} 252, 265, 320, 333 mμ, with *E* 609, 660, 78 and 61, respectively). They were combined and hydrolyzed with 5% methanolic potassium hydroxide at room temperature. The hydrolysis product (44 mg.) was taken up in a few drops of acetone, and ethyl acetate was added in excess. The mother liquor from the resulting amorphous precipitate on concentration yielded crystals which on recrystallization from acetone–ethyl acetate formed rosettes of yellow rods (12 mg.), m.p. 244–248°, $[\alpha]_D$ +31° (*c* 0.71); λ_{max} 257 mμ (4.58), 266 mμ (4.60), 320 mμ (3.64), 333 mμ (3.59), sh. 310 mμ (3.61), 355 mμ (32.0); infrared: 2.93, 6.18 μ.

Anal. Calcd. for $C_{29}H_{39}O_3N$ (449.6): C, 77.46; H, 8.74. Found: C, 76.88; H, 8.69.

The amorphous intermediate product, obviously the triacetate XVII, failed to consume hydrogen in the presence of platinum dioxide in either alcohol or acetic acid but could be reduced to the indene XVIII in the following way: to a boiling solution of XVII (54 mg.) in absolute ethanol (10 ml.), sodium (1 g.) was added in small pieces over a 60-minute period until its color had faded to very pale yellow. Refluxing was continued for another 60 minutes with the addition of ethanol (15 ml.). The solution was cooled, concentrated *in vacuo*, diluted with water and extracted with chloroform. The chloroform solution was washed with dilute hydrochloric acid, water, dried and evaporated. The residue (44 mg.) in benzene was adsorbed on a column of alumina (1.55 g., 10 × 30 mm.). Elution with ether furnished a crystalline fraction (33 mg.) which was repeatedly recrystallized from acetone–water yielding almost white rectangular plates, m.p. 179–181.5°, $[\alpha]_D$ +132.2° (*c* 0.80); λ_{max} 264 mμ (4.18), 267 mμ (4.18).

Anal. Calcd. for $C_{29}H_{41}O_3N$ (451.7): C, 77.12; H, 9.15. Found: C, 77.58; H, 9.04.

Exploratory ultraviolet measurements showed that with the zinc reduction product V (triacetate) the formation of the benzofulvene XVII under the above conditions proceeded much more slowly than with its tetraacetate VI. Thus after 1 hr. only 3% of V had been converted to XVII, after 5 hr. 11%, and only after 72 hr. did the conversion reach 79%. Attempts to utilize this fact for the isolation of intermediates were unsuccessful. Thus V was recovered unchanged when treated in chloroform solution with hydrogen bromide in acetic acid at −18° for 20 minutes, at 0° for 30 minutes or, with the addition of a catalytic amount of boron trifluoride etherate, at 0° for 60 minutes.

This was also true of the tetraacetate VI when it was treated in chloroform solution with hydrogen bromide in acetic acid at +18° for 20 minutes.

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