admixture with an authentic sample of *p*-phenylphenacyl *n*-tridecanoate, m.p. 86.6–87°.

Isomycomycin Methyl Ester.—Isomycomycin (900 mg.) dissolved in 100 ml. of ether was treated with an excess of ethereal diazomethane. The solution was evaporated to dryness and the residual solid was recrystallized from hexane to yield 800 mg. of the methyl ester of isomycomycin, m.p. 69–70°.

Anal. Calcd. for $C_{14}H_{12}O_2$: C, 79.24; H, 5.66; CH_3O, 14.62. Found: C, 79.23; H, 5.71; CH_3O, 14.01.

See Table I and Figs. 1 and 3 for light absorption data.

Hydrogenation of isomycomycin methyl ester (110 mg., 0.52 millimole) in 10 ml. of ethyl acetate over 200 mg. of previously reduced platinum oxide catalyst at atmospheric pressure required 93 ml. of hydrogen (S.T.P.) equivalent to 4.11 millimoles or 7.9 moles per mole of ester. The infrared spectrum of the reduction product was indistinguishable from that of methyl *n*-tridecanoate.

Maleic Anhydride Adduct of Isomycomycin Methyl Ester.—Milliequivalent portions of isomycomycin methyl ester (212 mg.) and maleic anhydride (98 mg.) were mixed and heated at 69–72° for 40 minutes in a sealed tube. Unreacted materials were extracted with ether leaving a white, crystalline residue (125 mg.), m.p. 165–170° (dec.). Recrystallization from acetone–hexane yielded crystalline plates, m.p. 177–178° (dec.). See Table I and Figs. 1 and 2 for light absorption properties.

Anal. Calcd. for $C_{18}H_{14}O_5$: C, 69.67; H, 4.55; CH_3O, 10.00. Found: C, 69.59; H, 4.64; CH_3O, 10.89.

The same product was isolated in comparable yield using a fourfold excess of maleic anhydride.

Hydrogenation of Maleic Anhydride Adduct of Isomycomycin Methyl Ester.—The maleic anhydride adduct of isomycomycin methyl ester (145 mg., 0.47 millimole) dissolved in 15 ml. of ethyl acetate was hydrogenated at atmospheric pressure and 27° over 100 mg. of previously reduced Adams platinum oxide catalyst. The compound consumed 76 ml. of hydrogen (S.T.P.) equivalent to 3.4 millimoles or 7.2 moles per mole of adduct. The catalyst was removed by filtration and the filtrate evaporated *in vacuo*. A colorless oil remained which was evaporatively distilled at approximately 1 mm. pressure and 160° block temperature. The distillate, $n^{25}D$ 1.4780, was too viscous for a precise density determination.

Anal. Calcd. for $C_{15}H_{28}O_3$: C, 66.64; H, 8.70. Found: C, 66.86; H, 8.73.

Acknowledgments.—The authors wish to express deep appreciation to Dr. Wilbur A. Lazier for his active interest in the investigation. We are indebted to Dr. John Means and Mr. Glenn B. Hess for the analytical and spectral data.

BROOKLYN 6, N. Y.

[CONTRIBUTION FROM THE SQUIBB INSTITUTE FOR MEDICAL RESEARCH]

The Structure of Veratramine

BY CH. TAMM[1] AND O. WINTERSTEINER

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Chemical proof for the existence in veratramine of a preformed benzeneoid ring has been adduced by the conversion of triacetyldihydroveratramine to an aromatic nitro derivative. N-Acetylveratramine on Oppenauer oxidation yielded an α,β-unsaturated monoketone which is undoubtedly a Δ^4-3-ketone, thus confirming the conclusion reached by Jacobs and Sato[5] regarding the 5,6-position of the double bond from the corresponding experiment on the free base. Chromic acid oxidation of triacetyldihydroveratramine afforded a compound to which the indanone structure VI is assigned in consideration of the identity of its ultraviolet absorption spectrum with that of the jervine derivative V. Accordingly the perhydrobenzfluorene structure III is proposed for veratramine. Several other new derivatives of the alkaloid are described and formulated on this basis.

Our knowledge of the chemistry of the secondary base veratramine, $C_{27}H_{39}O_2N$, which was first isolated by Saito[2] from *Veratrum grandifolium* Loes. fil., is largely based on the recent studies of Jacobs and his collaborators[3–5] who secured it from the domestic species *Veratrum viride* Aiton. Both oxygen atoms are present as acylable hydroxyl groups.[3] Veratramine contains a benzenoid ring, as evidenced by its ultraviolet absorption spectrum,[3] which resembles that of neoergosterol, and furthermore an ethylenic bond demonstrable by catalytic hydrogenation.[2,3] On selenium dehydrogenation[4] the alkaloid yielded a basic fragment C_6H_7ON later identified by synthesis as 3-methyl-5-hydroxypyridine,[5] and in the neutral fraction a hydrocarbon $C_{22}H_{20}$ indistinguishable from one obtained in the same reaction from the closely related secondary base jervine, the main alkaloid of *Veratrum viride*,[6] and believed to be either a homolog of 1,2-benzfluorene[6] or of chrysene.[4]

In 1949 Jacobs and Sato[4] proposed, on the basis of the facts then available, structure I for veratramine. This formula became untenable when it was found more recently[5] that veratramine could be converted by Oppenauer oxidation to an amorphous ketonic base (λ_{max}^{alc} 230 mμ, log ε 4.3) which was crystallizable as the hydrochloride and yielded an amorphous monoxime. This compound is undoubtedly Δ^4-veratramin-3-one, as the allylic alcohol obtained from it by Meerwein–Ponndorf reduction gave a positive Rosenheim test. It is thus clear that the double bond occupies the 5,6-position (4,5 being excluded by other evidence), and formula I was accordingly abandoned in favor of the perhydrochrysene structure, II, in which ring D is aromatic. The latter postulate derives its support from the fact already mentioned that veratramine on selenium dehydrogenation yielded its nitrogenous ring as 3-methyl-5-hydroxypyridine, whereas all other veratrum alkaloids gave rise in this reaction to pyridine derivatives carrying in position 6 an ethyl group representing carbon atoms 20 and 21 of the skeleton (*i.e.*, 3-methyl-6-ethylpyridine, and in the case of jervine, 3-methyl-5-hydroxy-6-ethylpyridine). It is reasoned that attachment, in veratramine, of the side chain to the aromatic nucleus would result in scission of the

(1) Research Fellow 1949-1950, Schweizerische Stiftung für Stipendien auf dem Gebiete der Chemie.

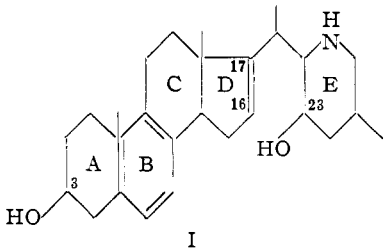
(2) K. Saito, *Bull. Chem. Soc. Japan*, **15**, 22 (1940).

(3) W. A. Jacobs and L. C. Craig, *J. Biol. Chem.*, **160**, 555 (1945).

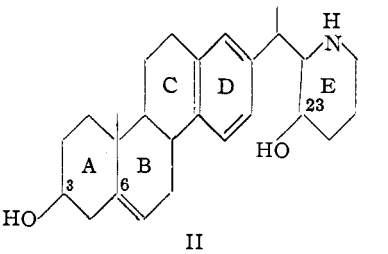
(4) W. A. Jacobs and Y. Sato, *ibid.*, **181**, 55 (1949).

(5) W. A. Jacobs and Y. Sato, *ibid.*, **191**, 71 (1951).

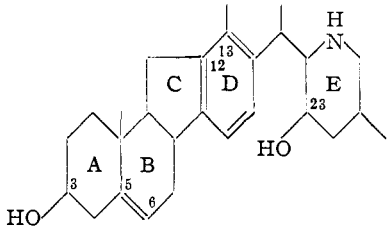
(6) W. A. Jacobs, L. C. Craig and G. I. Lavin, *ibid.*, **141**, 51 (1941).



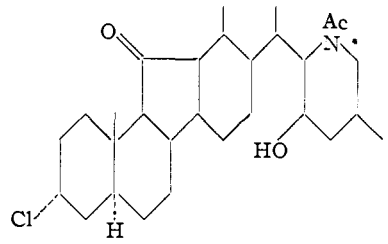
I



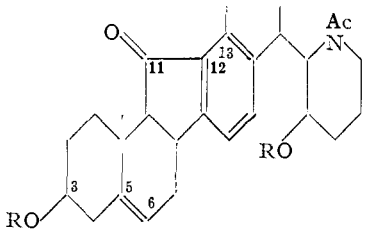
II



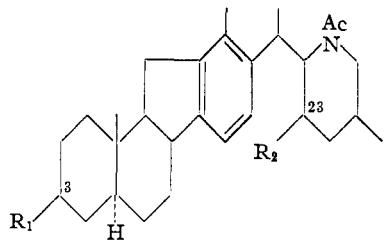
III



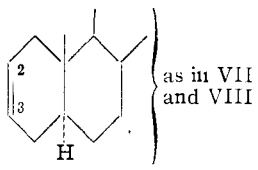
IV



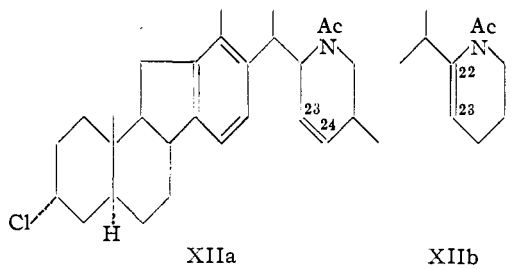
Va, R = Ac
Vb, R = H
VI, 5,6-Dihydro derivative of Va



VII, R_1 = $OSO_2C_7H_7$, R_2 = OH
VIII, R_1 = $OSO_2C_7H_7$, R_2 = OAc
XI, R_1 = H, R_2 = OAc

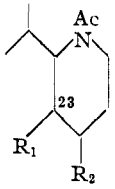


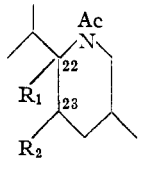
IX, R_2 = OAc
X, R_2 = OH



XIIa

XIIb

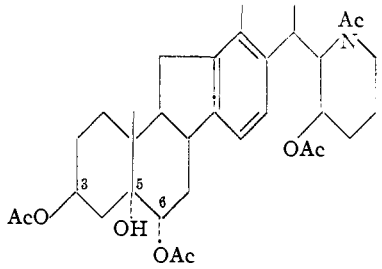




XIII R_1 = R_2 = H
XIVa R_1 = R_2 = OAc

XIVb, R_1 = R_2 = OAc

Tetracyclic portion as in XIIa



XV

chain between carbon atoms 20 and 22 rather than at the usual site 17–20.

The work reported in this paper was started late in 1949 and completed in 1950, and hence was in part concerned with testing the validity of formula I. It soon brought forth a number of facts incompatible with this structure and pointing toward rings C or D as the site of the aromatic nucleus. Later, guided by structural concepts which had meanwhile emerged from simultaneous studies in this Laboratory on jervine[7] we were led to adopt yet another formula (III) which differs from II in that ring C is 5- instead of 6-membered. We shall first present those of our findings which are directly related to that structure. and then describe and discuss on this basis the remainder of the work.

As mentioned, the postulate that veratramine contains a benzenoid ring has rested up to now mainly on its ultraviolet absorption characteristics (λ_{max}^{alc} 268 mμ, log ϵ 2.8).[3] Feeling the need for more substantial evidence on this point we have converted the hitherto undescribed triacetyldihydroveratramine (m.p. 189.5–190.5°, $[\alpha]^{24}D$ +84°) by nitration with fuming nitric acid in acetic acid–acetic anhydride at 0° to a crystalline compound (m.p. 238–239°, $[\alpha]^{24}D$ −263°), which according to the analysis and the ultraviolet (Fig. 1, curve 1) and infrared data is undoubtedly a mononitro derivative of the starting material. Moreover, catalytic reduction of this compound afforded an amorphous base which after diazotization coupled with β-naphthol to a deep-red azo dye. The ultraviolet characteristics of this product (Fig. 1, curves 2 and 3) were also those of an aromatic amine. There can then be no doubt regarding the presence in veratramine of a preformed benzenoid ring.

The lack of success experienced by Jacobs and Sato in their earlier attempt to secure a ketone from veratramine by the use of the Oppenauer method had prompted us to apply this reaction to N-acetylveratramine instead of to the free base. A prolonged reaction period and the use of Girard reagent proved essential for obtaining the oxidation product (m.p. 249–251°, $[\alpha]D$ +124°) in pure form. It was characterized as a monoketone by the preparation of a monoxime and a mono-2,4-dinitrophenylhydrazone, both crystalline compounds, while the monosemicarbazone was amorphous. The absorption curves for the ketone, the oxime and the semicarbazone are given in Fig. 2. It will be noted that in the spectra of the parent ketone and the oxime the maximum is shifted from the position characteristic for steroidal Δ^4-3-ketones and their

(7) J. Fried, O. Wintersteiner, M. Moore, B. M. Iselin and A. Klingsberg, THIS JOURNAL, 73, 2970 (1951).

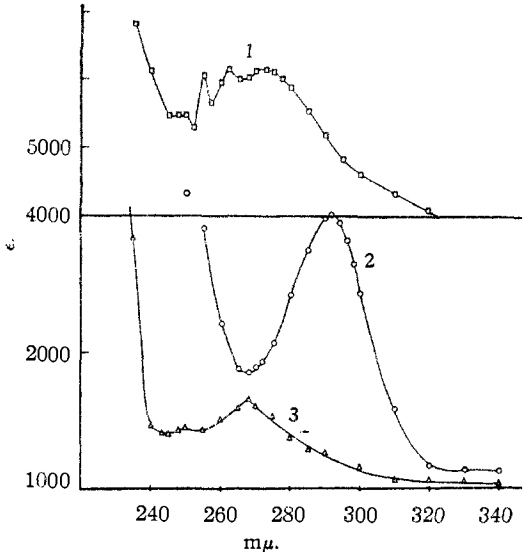


Fig. 1.—Absorption spectra of: 1, nitro derivative of triacetyldihydroveratramine (ethanol); 2, amine from 1 (ethanol); 3, amine from 1 (3.5% ethanolic HCl).

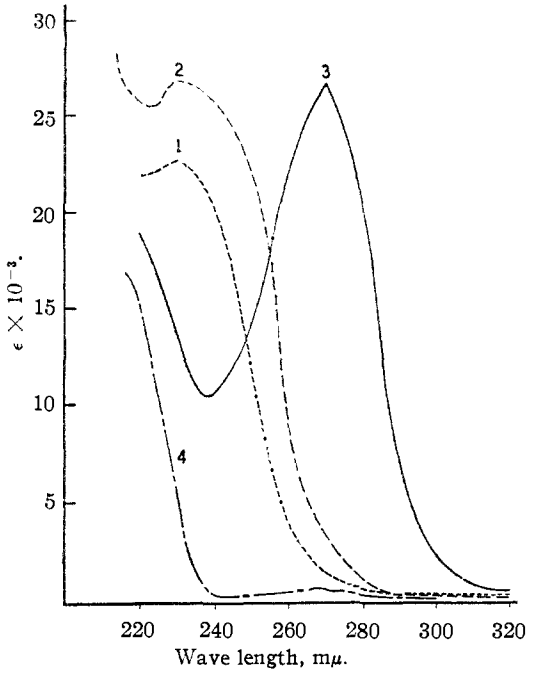


Fig. 2.—Absorption spectra (ethanol) of: 1, N-acetyl-Δ^4-veratramin-3-one; 2, oxime of 1; 3, semicarbazone of 1; 4, N-acetylveratramine.

oximes (238–240 mμ), to a lower wave length (230 mμ), and also that the molecular extinction coefficients in both cases exceed the usual values (*cf.* Δ^4-cholestenone: 17,000; Δ^4-cholestenone oxime,[8] 24,000). This is not an anomaly, but a consequence of the fact that the benzene chromophor of veratramine strongly contributes to absorption in the region below 240 mμ (curve 4, Fig. 2). Indeed the curves obtained by summation of those of the pairs cholestenone–veratramine, and cholestenone oxime–veratramine, show near-coincidence with curves 1 and 2, respectively, in Fig. 2. In the case of the semicarbazone (curve 3) the marked red shift accompanying the conversion of an α,β-unsaturated ketone into its semicarbazone is clearly in evidence. Finally the curve of the dinitrophenylhydrazone (not shown) exhibits a strong band at 390 mμ (ε 35,000), a property characteristic for the dinitrophenylhydrazones of Δ^4-unsaturated 3-ketones.[9] Our findings thus completely parallel those of Jacobs and Sato and confirm their conclusion regarding the 5,6-position of the double bond. It is worth noting that the 23-hydroxyl group resisted oxidation in the free base as well as in the N-acetyl derivative. The 23-acetate of N-acetyl-Δ^4-veratramin-3-one, prepared by acetylation with acetic anhydride in pyridine, could not be obtained in crystalline form.

Jacobs and Sato[5] oxidized dihydroveratramine with chromic acid and obtained dihydroveratramine-3,23-dione as well as the monoketone, dihydroveratramin-3-one. That the keto group in the latter was in position 3 was deduced from the molecular rotation change +108°, which is not too divergent from the average value for the oxidation of 3-stanols to 3-stanones, +73°.[10] In our hands application of the same reaction to N-acetyldihydroveratramine (m.p. 220–223°, $[\alpha]^{26}D$ +81°) yielded the corresponding N-acetylated ketones, N-acetyldihydroveratramine-3,23-dione (m.p. 264–267°, $[\alpha]D$ − 13°) and N-acetyldihydroveratramin-3-one (m.p. 186–188°, $[\alpha]D$ +100°; Jacobs and Sato[4]: m.p. 191–194° for derivative prepared from the free base with boiling acetic anhydride). In this case $\Delta[M]D$ for the oxidation to the 3-monoketone (+84°) is in good agreement with the normal value and with that observed for the analogous transformation in the jervine series.[11] $\Delta[M]_D^{\text{ketone}}$ in respect to the 23-hydroxyl is highly negative, namely, −509°. A similar though less pronounced rotation change toward the negative side (−298°) accompanies the oxidation of this group in a compound derived from tetrahydrojervine to which formula IV has been assigned.[12]

The ultraviolet absorption spectra of the two ketones derived from N-acetyldihydroveratramine are likewise of interest in this connection. While the band at 268 mμ characteristic for the benzene chromophor is, of course, in evidence in both, the spectrum of the diketone shows a second distinct maximum at 304 mμ (ε 230) which is absent in that of the 3-monoketone. This band originates in the 23-keto group, since it is also exhibited by the 11,23-diketone obtained by chromic acid oxidation of the tetrahydrojervine derivative IV, as well as by the dihydroveratramin-3,23-dione of Jacobs

(8) M. Mohler, *Helv. Chim. Acta*, **20**, 289 (1947).
(9) C. Djerassi and E. Ryan, THIS JOURNAL, **71**, 1000 (1949).
(10) D. H. R. Barton, *J. Chem. Soc.*, 813 (1945).

(11) For instance $\Delta[M]D$ (N-acetyltetrahydrojerv-3-one − N-acetyltetrahydrojervine) = +75° (O. Wintersteiner and M. Moore, to be published).

(12) O. Wintersteiner, B. M. Iselin and M. Moore, Abstracts, XIIth Internatl. Congress of Chemistry, New York, N. Y., 1951, p. 292. It should be pointed out, however, that the contribution of the 23-keto group to rotation tends to be highly negative only when the basic group is acylated; thus in the case of the basic diketone prepared by Jacobs and Sato $\Delta[M]D$ (dihydroveratramin-3,23-dione − dihydroveratramine) is +122°, and the change coincident to the oxidation of the 23-hydroxyl group consequently +122° − (+108°) = +14°, as compared with the value −509° computed above from the data in the N-acetylated series.

and Sato, except that in the latter case its intensity is markedly less (ϵ about 100).[5] Such high extinction coefficients are not usually encountered with bands arising in unconjugated keto groups. In contrast, the band due to the 3-keto group in N-acetyldihydroveratramin-3-one is so low that it is obscured, except for a slight inflection at 300 mμ, ϵ about 30, by the absorption of the benzene chromophor extending into that region (*cf.* cholestanone, λ_{max} 280 mμ, ϵ 20).

The argument put forward by Jacobs and Sato for the benzenoid nature of ring D has been already mentioned. Our own evidence in support of this feature of formulas II and III derives from the following observations: Triacetyldihydroveratramine on treatment with chromium trioxide at room temperature yielded among other products a compound m.p. 241–245°, $[\alpha]^{26}D$ +59°, the analysis and infrared spectrum of which indicated the presence of a new keto group. That this keto group adjoins the aromatic ring is evident from the ultraviolet absorption characteristics (λ^{alc}_{max} 251 mμ, ϵ 10,700; 300 mμ, ϵ 2000) which are similar to those of α-tetralones and α-indanones. Moreover, the spectrum was identical with that of a recently reported acetolysis product of jervine[7,12] for which the indanone structure Va has been proposed.[13] Significantly the keto group in the compound m.p. 245° obtained by chromic acid oxidation of triacetyldihydroveratramine is inert toward keto reagents, as is the indanone carbonyl in Va. This adds considerable strength to the supposition that the two products contain the same chromophoric group. For the structural identity of the side chain in the two products speaks, *inter alia*, the fact that the 23-hydroxyl group in Vb, the hydrolysis product of Va, resists attack in the Oppenauer oxidation, as it does in N-acetylveratramine. It would then appear that the ketone m.p. 245° from triacetyldehydroveratramine corresponds structurally, though perhaps not sterically, to the 5,6-dihydro derivative VI of Va, and hence that veratramine itself is III. Needless to say this formulation should be regarded as provisional till the suggested relationship between the oxidation product from triacetyldihydroveratramine and the jervine derivative Va is substantiated experimentally,[14] and rigid proof for the postulate that ring C is 5-membered has been adduced. Should such a structural correlation be achieved, it would largely remove the objection that V may not reflect the original structure of jervine because it arises from the latter in an acid-catalyzed reaction in which a rearrangement of the carbon skeleton may well take place. It hardly needs to be pointed out that in the case of the dihydroveratramine derivative the oxidative introduction of a keto group next to a preformed benzene ring is not likely to involve a change in the carbon skeleton, and that the possibility of a rearrangement in the procedures used for the isolation of veratramine from the plant source is equally remote.

The other new derivatives of veratramine prepared by us may now be described and formulated on the basis of III.

Tosylation in pyridine of N-acetyldihydroveratramine afforded the 3-monotosylate VII, m.p. 167.5–168.5°, $[\alpha]^{25}D$ +53°, which was acetylated with acetic anhydride and pyridine to the expected 3-tosylate-23,N-diacetate VIII, m.p. 168–169°, $[\alpha]^{22}D$ +74°. On the other hand, treatment of VII with boiling acetic anhydride resulted in the elimination of the tosyloxy group, and thus lead to the formation of an unsaturated 23,N-diacetate, m.p. 208–210°, $[\alpha]D$ +109°, which is tentatively written as the Δ^2-ethylenic derivative IX. On hydrolysis with alkali this compound gave the N-monoacetate X, m.p. 224–226°, $[\alpha]^{24}D$ +108°, while catalytic reduction with palladium in dioxane afforded the saturated 23,N-diacetate XI, m.p. 204–205°, $[\alpha]^{24}D$ +99°. The contribution of the double bond in IX, *i.e.*, $\Delta[M]D$ (IX–XI) is +47°, which agrees neither with the value calculated for the 2,3-double bond in Δ^2-cholestene (+152°)[15] nor with that for the 3,4-double bond in Δ^3-cholestene[16,17] (+140°). The only explanation which can be offered at present for the anomalous value observed is the possible inductive influence exerted by the abnormal portion of the skeleton.

When N-acetyldihydroveratramine was treated with phosphorus oxychloride in pyridine, only one of the hydroxyl groups was eliminated with double bond formation, while the other was replaced by chlorine. Since the hydroxyl group in 7α-benzoxycholestan-3β-ol behaves in the latter fashion, the reaction being accompanied by Walden inversion,[18] it seems likely that the product in question (m.p. 205–206°, $[\alpha]^{25}D$ +178°) is a 3α-chloride in which the double bond occupies either the 22,23- or 23,24-position (XII a or b). On catalytic hydrogenation with platinum oxide in acetic acid it formed the

(13) While it would lead too far to recount here all the facts supporting this structure, the following two points are pertinent to the present problem: (1) One of the double bonds entering in the formation of the aromatic ring arises by opening of the oxygen bridge linking ring D with the nitrogenous side chain ring. Therefore, lest a profound rearrangement of the ring skeleton has occurred in the acetolysis reaction (which is carried out at room temperature) it must be ring D which has undergone aromatization. (2) The indanone carbonyl in V must represent the original unreactive keto group in jervine, since it is inert toward ketone reagents. This should not be the case if its site were position 12 in a 6-membered ring C belonging to a perhydrochrysene system such as II. Thus the keto group in the analogous α-tetralone grouping of 6-ketoestradiol (B. Longwell and O. Wintersteiner, *J. Biol. Chem.*, **133**, 219 (1940)) shows normal reactivity. In the indanone structure V, on the other hand, the keto group would be subject to the hindering effect of the methyl group at C_{13} and possibly also the one we have assigned position 13. It was mainly this consideration which has led to the adoption of the unorthodox perhydrobenzfluorene structure, in preference to the *a priori* more reasonable perhydrochrysene structure, for this and another acetolysis product derived from jervine.[7]

(14) This problem is being investigated by Mr. N. Hosansky in this Laboratory. Catalytic reduction of Va followed by treatment with chromic acid (to reconstitute the keto group which is in part reduced simultaneously with the double bond) yielded a product, m.p. 214–217°, exhibiting the same specific rotation and ultraviolet spectrum as the ketone, m.p. 245°. While the bands in the double bond region of the infrared spectra were likewise identical, significant differences were in evidence in the molecular vibration region. It remains to be seen whether the observed discrepancies are actually due to non-identity or merely referable to inhomogeneity of one or the other of these products.

(15) D. H. R. Barton and W. Klyne, *Chemistry and Industry*, 755 (1948).

(16) G. Lardelli and O. Jeger, *Helv. Chim. Acta*, **32**, 1817 (1949).

(17) M. Schmid and K. Kägi, *ibid.*, **33**, 1582 (1950).

(18) O. Wintersteiner and M. Moore, THIS JOURNAL, **72**, 1923 (1950).

dihydro derivative XIII (m.p. 178.5–180°, $[\alpha]^{26}D$ +65°). The molecular rotation increment for the double bond in XII, $\Delta[M]D$ (XII–XIII) has the unusually high positive value of +541°. To gain insight into the location of the double bond, XII was hydroxylated by means of osmium tetroxide. The resulting glycol was amorphous, but subsequent acetylation led to a crystalline compound m.p. 210–211°, $[\alpha]^{23}D$ +74°, which analytically appeared to be an O-diacetate, and hence could be derived from a 23,24-*cis*-glycol (XIVa). This is also in accord with the fact that the amorphous glycol consumed one mole of periodic acid under conditions under which only *disecondary cis*-glycol groupings located in a ring are attacked. Nevertheless, these observations do not *a priori* exclude the 22,23-position of the double bond (XIIb) and of the glycolic group (XIVb) because a hydroxyl group at C_{22}, being ketalic in nature, may show greater reactivity toward acylating and oxidizing reagents than a tertiary hydroxyl group proper. Moreover, the possibility that the dehydration of the 23-hydroxyl group is accompanied by other, more profound changes in that part of the molecule cannot be entirely discounted.

There is further to be mentioned the tetraacetate XV (5α,6α-dihydroxydihydroveratramine 3,6,23,N-tetraacetate, m.p. 156–157°, $[\alpha]^{23}D$ +81°) which resulted from the hydroxylation of triacetylveratramine with osmium tetroxide and subsequent acetylation. Jacobs and Sato[5] have described an isomer of this compound which should differ from it, according to the mode of its formation (hydrolysis of the α- or β-5,6-oxide and acetylation) only by epimerism at carbon atom 6. The amorphous glycol from which XV was obtained by acetylation was practically inert toward periodic acid, as is the comparable cholestane-3β,5α,6α-triol.[18] The molecular rotation difference $\Delta[M]D$ (XV-triacetyldihydroveratramine), *i.e.*, the change incident to the insertion in the latter compound of a 5α-hydroxyl group and a 6α-acetoxy group, is 388° − 355° = +33°, which, all things considered, is reasonably close to the value 62°[19] − 60° = +2° for $\Delta[M]D$ (cholestane-3β,5α,6α-triol 3,6-diacetate − cholestan-3β-ol acetate).

Finally there is described in the experimental part the hitherto unreported N-nitrosoveratramine, which was needed for comparison of its ultraviolet and infrared absorption characteristics with those of the nitro derivative mentioned earlier.

Experimental

The melting points were taken in the capillary and are corrected for stem exposure. The rotation measurements were taken in a 1-dm. semi-micro tube. The solvent was chloroform unless indicated otherwise. The infrared spectra were determined in nujol suspension in a Perkin–Elmer Model 12-B spectrophotometer. The analytical samples were dried 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 hours.

The veratramine used as the starting product in this work melted at 206–207° (lit.[2] 204–207°) and showed $[\alpha]^{25}D$ −71 ± 1° (*c* 1.21), −70 ± 1° (*c* 1.56 in methanol) (lit. −71.8°,[3] −69°,[2] respectively); λ_{max}^{alc} 268 mμ (575). It was reduced catalytically (PtO_2) in acetic acid to dihydroveratramine, m.p. 192.5–194°, $[\alpha]^{25}D$ +26 ± 1° (*c* 1.26); lit. m.p. 198–200°,[3] $[\alpha]^{27}D$ +27.4°.[4]

Triacetyldihydroveratramine was prepared from dihydroveratramine by treatment with boiling acetic anhydride (90 min. refluxing) and after removal of the reagent was isolated in the usual way by chloroform extraction. It formed clusters of fine needles from ether–pentane, m.p. 189.5–190.5°, $[\alpha]^{24}D$ +84 ±2° (*c* 0.87); λ_{max}^{alc} 269 mμ (600).

Anal. Calcd. for $C_{33}H_{47}O_5N$ (537.7): C, 73.71; H, 8.80; $2COCH_3$, 16.0; $3COCH_3$, 24.0. Found: C, 73.65; H, 8.48; $COCH_3$, 17.1.

It is our experience that in many veratramine and jervine derivatives the N-acetyl group is not, or only in part, demonstrable by the Kuhn–Roth procedure.

N-Acetyldihydroveratramine (a).—A solution of triacetyldihydroveratramine (505 mg.) in 2 *N* ethanolic potassium hydroxide (15 cc.) was boiled under reflux for 2 hours. The product, isolated in the usual way by chloroform extraction, was recrystallized several times from aqueous ethanol, from which it formed leaflets melting at 220–223°, $[\alpha]^{26}D$ +81 ± 2° (*c* 1.39).

Anal. Calcd. for $C_{29}H_{43}O_3$ (435.6): C, 76.78; H, 9.55. Found: C, 76.79; H, 9.56.

(b).—N-Acetylveratramine[2,4] (2.5 g.) was dissolved in pure acetic acid (20 cc.) and hydrogenated in the presence of platinum oxide catalyst (310 mg.). After the uptake of one molar equivalent of hydrogen (4.5 hours) the filtered solution was brought to a sirup *in vacuo*, and the product isolated by chloroform extraction. Once recrystallized from aqueous ethanol (1.91 g.) it melted at 215–218°. Further recrystallization afforded material identical by melting point and rotation with that obtained by procedure (a).

Attempts to secure the compound by direct N-acetylation of the base in methanol with either 1.5 equivalents or a large excess of acetic anhydride (4 and 20 hours, respectively, r.t.) resulted in the quantitative recovery of the starting material.

Digitonin Precipitability of Veratramine and Dihydroveratramine.—We wish to record here the incidental observation that the free bases yield a voluminous crystalline precipitate within an hour after the addition of a 1% digitonin solution in 80% ethanol to their ethanolic solution, whereas the respective N-acetates failed to react under these conditions even on prolonged standing.

Nitration of Triacetyldihydroveratramine.—Fuming nitric acid (1.5 d., 2 cc.) was slowly added with stirring to an ice-cold mixture of acetic anhydride (5 cc.) and glacial acetic acid (3 cc.). The nitration mixture was cooled to −10° and this temperature maintained while triacetyldihydroveratramine (988 mg.) was added with stirring in small portions during the course of one hour, care being taken that the added material had completely dissolved before the addition of the next portion. After stirring had been continued at −10° for 15 minutes the yellow mixture was poured into ice-cold water (60 cc.) containing sodium carbonate (7 g.). The resulting precipitate was taken into benzene, and the extract was washed consecutively with ice-water, cold 1 *N* sodium bicarbonate solution, and again ice-water. The residue from the dried and evaporated benzene phase (977 mg.) crystallized from methanol in long, slightly yellow needles (300 mg.). After repeated recrystallization from methanol the product melted at 238–239°; $[\alpha]^{24}D$ −263 ± 2° (*c* 1.25). It was insoluble in 10% aqueous sodium hydroxide. The ultraviolet absorption curve is given in Fig. 1.

Anal. Calcd. for $C_{33}H_{46}O_7N_2$ (582.7): C, 68.02; H, 7.96; N, 4.80; $3COCH_3$, 22.1. Found: C, 68.84, 68.61; H, 8.33, 7.58; N, 5.08; $COCH_3$, 22.8.

The nitro derivative (270 mg.) on catalytic hydrogenation with platinum oxide (150 mg.) in acetic acid (uptake 3 molar equivalents in 95 min.) yielded an amorphous product (233 mg.) which was readily soluble in concentrated hydrochloric acid. After diazotization in concentrated hydrochloric acid–acetic acid (1:1) it coupled with β-naphthol in alkaline solution with the formation of a deep-red azo dye. For the ultraviolet data see Fig. 1, curves 2 and 3 (*cf.* aniline in 10^{-3} *N* NaOH: λ_{max} 281 mμ (1350); in 10^{-2} *N* HCl: fine structure as with benzene[20]).

(19) No rotation data in literature. We found $[\alpha]^{25}D$ +12.4° (*c* 0.95, in chloroform).

(20) G. Kortüm, *Z. physik. Chem.*, **42B**, 39 (1939).

N-Acetyl-Δ^4-veratramine-3-one.—Aluminum *t*-butylate (4.0 g.) dissolved in dry benzene (40 cc.) was added to a solution of N-acetylveratramine (1.0 g.) in dry acetone (20 cc.), and the turbid mixture was boiled under reflux for 23 hours. After cooling 1 *N* sulfuric acid (48 cc.) was added dropwise to dissolve the precipitate. The clear solution was extracted with benzene (3 × 150 cc.). The benzene extract was washed with bicarbonate solution and water, dried and evaporated. The partly crystalline residue was freed from small amounts of oily impurities derived from the acetone by washing with hexane, and then weighed 1.00 g. It was dissolved together with 1.0 g. of Girard Reagent T in absolute ethanol (20 cc.) and acetic acid (2.0 cc.). The solution was boiled for one hour, and after cooling poured into ice-water containing potassium hydroxide sufficient to neutralize 90% of the acetic acid. After extraction of the non-ketonic material with ether (3 × 150 cc.) the aqueous phase was acidified with hydrochloric acid to *p*H 1 and allowed to stand at room temperature overnight. The crystalline product which had precipitated was filtered off, washed with water, dried (551 mg.) and recrystallized repeatedly from 50% aqueous acetone. The pure ketone melted at 249–251° (dec.) and showed $[\alpha]^{26}D$ +124 ± 2° (*c* 0.796); ultraviolet, Fig. 2, curve 1. The infrared spectrum exhibited bands at 2.88 μ (−OH) and 6.11 μ (broad, unsatd. ketone + N-acetyl).

The samples for the physical measurements and for the analysis were dried at 110° (1 mm.) for five hours (1–2% weight loss).

Anal. Calcd. for $C_{29}H_{39}O_3N$ (449.6): C, 77.47; H, 8.74. Found: C, 77.34; H, 8.54.

The oxime was prepared by boiling under reflux a solution of the ketone (57 mg.) and hydroxylamine hydrochloride (69.5 mg.) in absolute alcohol (4 cc.) and pyridine (0.3 cc.) for 5 hours. The crude crystalline product (54 mg.) was repeatedly recrystallized from aqueous ethanol; leaflets m.p. 262–264°; ultraviolet, Fig. 2, curve 2.

Anal. Calcd. for $C_{29}H_{40}O_3N_2$ (469.6): C, 74.69; H, 8.68; N, 6.02. Found: C, 75.50; H, 9.16; N, 5.69.

The semicarbazone, prepared in the usual way (semicarbazide acetate in ethanol, refluxed one hour), could be obtained in amorphous, analytically impure form only. Calcd. for $C_{30}H_{62}O_3N_4$ (506.7): N, 11.06. Found: N, 9.61; ultraviolet: Fig. 2, curve 3.

The 2,4-dinitrophenylhydrazone was prepared in the usual manner with cold Brady reagent. It was recrystallized by dissolving it in a little chloroform, adding ethanol and concentrating the solution by boiling; small, scarlet-red needles, m.p. 252–255°; λ_{max}^{chlf} 260 mμ (20,500), 390 mμ (35,000); shoulder 290 mμ (11,400), min. 317 mμ (3,400).

Anal. Calcd. for $C_{35}H_{43}O_6N_5$ (629.7): N, 11.12. Found: N, 11.20.

N-Acetyldihydroveratramine-3,23-dione.—To a solution of N-acetyldihydroveratramine (226 mg.) in pure acetic acid (2 cc.) a 2% acetic acid solution of chromium trioxide (3.55 cc., 2.2 atoms of oxygen) was gradually added. After 40 minutes, when most of the oxidant seemed to have been reduced, a few drops of methanol were added, and the solvent was removed *in vacuo*. The residue was dissolved in chloroform and separated into neutral and acidic fractions in the usual way. Only traces of acids were obtained. The neutral fraction, a slightly greenish sirup weighing 227 mg., was dissolved in methanol, and the solution filtered through a bed of charcoal. The filtrate, concentrated to a small volume, on standing deposited crystals (27 mg.) which after 2 recrystallizations from chloroform–methanol melted at 264–267°, and showed $[\alpha]^{25}D$ −13 ± 3° (*c* 0.73), $\lambda_{max}^{alc-chlf}$ 268 mμ (590), 305 mμ (230). The infrared spectrum showed bands at 5.87 μ (ketone) and 6.18 μ (N-acetyl). The analytical sample was dried at 110° (1 mm.) for 3 hours.

Anal. Calcd. for $C_{24}H_{39}O_3N$ (449.6): C, 77.46; H, 8.75. Found: C, 77.68; H, 8.96.

The non-crystallizable material (120 mg.) in the mother liquor from the crude diketone was dissolved in benzene and chromatographed on a column of alumina (3.5 g.). The effluents were collected in 10-cc. portions. Elution was effected with 20 or 30 cc. each of chloroform–benzene 1:99, 2:98, 5:95, 1:9, 1:4, 1:1, then of chloroform, methanol–chloroform 1:99, 2:98 and 5:95. The chloroform–benzene 1:4 and the first of the chloroform–benzene 1:1 fractions afforded acetone-insoluble crystalline material (17 mg.) which after purification was found to be identical with the diketone described above. The remainder of the methanol–chloroform 1:1 eluate (20.5 mg.) likewise yielded crystals, which, however, were readily soluble in acetone and after 2 recrystallizations from acetone–ether melted at 186–188°; N-Acetyldihydroveratramin-3-one, m.p. 186–188°, $[\alpha]^{25}D$ +100 ± 3° (*c* 0.668), λ_{max}^{alc} 270 mμ (550), slight inflection at 300 mμ (27); infrared, bands at 5.86 μ (ketone) and 6.21 μ (N-acetyl).

Anal. Calcd. for $C_{29}H_{41}O_3N$ (451.6): C, 77.12; H, 9.15. Found: C, 77.10; H, 9.35.

From the fractions eluted with chloroform a third crystalline product was isolated which was identified as starting material.

Chromic Acid Oxidation of Triacetyldihydroveratramine; Indanone VI.—A solution of triacetyldihydroveratramine (811 mg.) in acetic acid (80 cc.) was mixed with one containing chromium trioxide (202 mg., 2 atoms of O per mole) in the same solvent (4 cc.). When most of the oxidant had been consumed after 2.5 hours, an additional amount (303 mg.), corresponding to 3 atoms of oxygen per mole, was added. After the solution had stood at room temperature for 48 hours, the remaining slight excess of chromic trioxide was reduced with ethanol, and most of the solvent removed *in vacuo*. The residue was taken up in ether and separated in the usual way into neutral and acidic fractions, which weighed 608 and 159 mg., respectively. The neutral products were dissolved in benzene–hexane 1:4 (10 cc.) and adsorbed on a column of alumina (21 g., 18 × 103 mm.). Elution was effected with benzene (420 cc.), ether–benzene 1:19 (660 cc.), 1:9 (1560 cc.), 1:1 (360 cc.), ether (240 cc.) and methanol–ether 1:99 (180 cc.), the eluates being collected in 60-cc. portions. Only the benzene and ether–benzene 1:1 eluates yielded crystalline material. Repeated recrystallization of the former (86 mg.) from ether afforded needles which melted at 241–245°, after softening and browning at 238°; $[\alpha]^{21}D$ +59 ± 1° (*c* 0.92); λ_{max}^{alc} 251 mμ (10,700), 300 mμ (2100); infrared: bands at 5.75 μ (O-acetyl), 5.87 μ (ketone), 6.08 μ (N-acetyl). (Va: 5.75, 5.88, 6.09 μ).

Anal. Calcd. for $C_{33}H_{45}O_6N$ (551.7): C, 71.83; H, 8.22. Found: C, 72.04; H, 8.31.

The compound did not form an insoluble dinitrophenylhydrazone with Brady reagent, and was recovered unchanged after prolonged refluxing with alcoholic hydroxylamine acetate.

The material remaining in the first mother liquor (50 mg.) was rechromatographed. The benzene–hexane 1:1 and benzene eluates (30 mg.) yielded starting material (m.p. 189.5–192.5°, no depression with authentic sample) while from the ether–benzene 1:19 eluates (19 mg.) an additional amount of the indanone, identified by melting point (240–245°) and ultraviolet spectrum, could be isolated.

The crystalline material in the ether–benzene 1:1 eluates of the original chromatogram was recrystallized twice from acetone–ether, affording 16 mg. of needles m.p. 219–222°, $[\alpha]D$ +31 ± 2° (*c* 0.766). This substance was not further investigated.

3-Tosyl-N-acetyldihydroveratramine (VII).—A solution of N-acetyldihydroveratramine (305 mg.) in dry pyridine (5 cc.), to which toluenesulfonyl chloride (295 mg., 2.5 mole equiv.) had been added, was allowed to stand at room temperature for 48 hours. After decomposition of the excess reagent with water the mixture was extracted several times with ether–chloroform 4:1. The extracts were washed with dilute hydrochloric acid, sodium carbonate solution and water, dried and evaporated. The residue crystallized from acetone–ether (267 mg., m.p. 163–165°). After 2 recrystallizations from the same solvents the compound melted at 167.5–168.5°; $[\alpha]^{25}D$ +53 ± 2° (*c* 1.03).

Anal. Calcd. for $C_{36}H_{49}O_5NS$ (607.8): C, 71.13; H, 8.13; S, 5.27. Found: C, 70.87; H, 8.25; S, 5.58.

3-Tosyl-23,N-diacetyldihydroveratramine (VIII) was prepared from VII (170 mg.) with acetic anhydride (2.0 cc.) and pyridine (2.5 cc.) at room temperature (40 hours). The crude product (187 mg.) was amorphous and hence was adsorbed in benzene–hexane (5:1) on alumina (5.4 g.). Elution was effected with 18-cc. portions of solvent mixtures similar to those employed in the experiment described above under "N-acetylveratramine-3,23-dione." The fractions

eluted with benzene, chloroform–benzene 1:19 and chloroform–benzene 1:10, together 109 mg., yielded from ether–hexane long needles melting in the range 158–160°. The product was recrystallized twice from the same solvents and then melted at 168–169°; $[\alpha]^{22}D$ +74 ± 2°(*c* 1.27). Though the sample for the analysis was dried at 80° (0.1 mm.) for 7 hours, it apparently retained one-half molecule of water.

Anal. Calcd. for $C_{38}H_{51}O_6NS \cdot {}^1/_2H_2O$ (658.9): C, 69.28; H, 7.99; S, 4.87. Found: C, 69.49, 69.24; H, 8.35, 8.31; S, 4.92.

Dehydro Product IX (23,N-Diacetate).—A solution of the tosylate VII (490 mg.) in acetic anhydride (15 cc.) was boiled under reflux for 90 minutes. The reagent was removed *in vacuo*, and the oily residue dissolved in ether. The ether solution was washed with sodium carbonate solution and water, dried over sodium carbonate, and evaporated. The amorphous residue was dissolved in benzene–hexane 1:4 (10 cc.) and adsorbed on a column of alumina (12 g.). The effluents were collected in 40-cc. portions. Elution was effected with benzene–hexane 1:4 (120 cc.), 1:1 (120 cc.), benzene (160 cc.), and further with benzene containing increasing amounts of ether. Only the benzene eluates crystallized spontaneously (175 mg., m.p. 202–207°). Two recrystallizations from ether–hexane afforded needles m.p. 208–210°, $[\alpha]^{25}D$ +109 ± 2° (*c* 1.01). The compound was free of sulfur, readily decolorized bromine in carbon tetrachloride, but gave a negative Rosenheim reaction. The ultraviolet absorption curve was identical with that of veratramine.

Anal. Calcd. for $C_{31}H_{43}O_3N$ (477.6): C, 77.95; H, 9.07. Found: C, 78.01; H, 9.07.

Dehydro Product X (N-Acetate).—This compound was prepared by heating a solution of the unsaturated diacetate IX (83 mg.) in 2 *N* ethanolic potassium hydroxide solution (5 cc.) for 2 hours at reflux temperature. The product, isolated in the usual manner by chloroform extraction, consisted of fine needles (63 mg., m.p. 223–225°). Twice recrystallized from chloroform–ether–hexane it melted at 224–226° (dec.), $[\alpha]^{24}D$ +108 ± 2° (*c* 1.46).

Anal. Calcd. for $C_{29}H_{41}O_2N$ (435.6): C, 79.97; H, 9.49. Found: C, 79.93; H, 9.33.

3-Desoxydihydroveratramine-23,N-diacetate (XI).—A solution of the unsaturated diacetate IX (61 mg.) in dioxane (4 cc.) was shaken in an hydrogen atmosphere with 5% palladium–charcoal catalyst (76 mg., previously saturated with hydrogen). After 30 minutes uptake ceased with the calculated amount consumed. The residue of the filtered solution crystallized on addition of ether. Two recrystallizations from ether–hexane afforded long needles, m.p. 204–205°, $[\alpha]^{24}D$ +99 ± 2° (*c* 1.03).

Anal. Calcd. for $C_{31}H_{45}O_3N$ (479.7): C, 77.62; H, 9.46. Found: C, 77.56; H, 9.53.

Unsaturated Chloro Compound XII.—Freshly distilled phosphorus oxychloride (12 cc.) was slowly added, with precautions against uptake of moisture, to an ice-cold solution of N-acetyldihydroveratramine (3.0 g.) in pyridine. The mixture became yellow and soon deposited crystals of pyridinium chloride. After all the reagent had been added, the solution was allowed to assume room temperature and to stand for 48 hours. The excess reagent was destroyed by the careful addition of ice, the mixture extracted with chloroform, and the extracts were washed with dilute acid and sodium carbonate and water, dried and evaporated. The brown residue was dissolved in benzene (15 cc.), and the solution passed through a column of alumina (80 g.). The fractions eluted by continued washing with benzene (4 × 250 cc.), and the first chloroform–benzene 1:4 (250 cc.), together 2.63 g., crystallized on wetting with ether. The crystals were collected (1.44 g., m.p. 198–203°) and recrystallized twice from acetone–ether, yielding clusters of fine needles melting at 205–206° (dec.); $[\alpha]^{25}D$ +178 ± 2° (*c* 0.997); λ_{max}^{alc} 269 mμ (510). The analytical sample was dried at 80° (0.01 mm.) for 7 hours.

Anal. Calcd. for $C_{29}H_{40}ONCl$ (454.1): C, 76.70; H, 8.88; Cl, 7.88. Found: C, 76.99, 76.85; H, 9.25, 9.16; Cl, 7.80.

An attempt to effect a dehydrohalogenation of XII by refluxing with *n*-valeric acid in the presence of potassium acetate yielded only intractable tars.

Saturated Chloro Compound XIII.—A solution of XII (113 mg.) in acetic acid (5 cc.) was hydrogenated in the presence of platinum oxide catalyst. Hydrogen uptake was rapid and stopped after 15 minutes. After removal of the catalyst and the solvent the reduced product was taken up in chloroform, which was washed with sodium carbonate solution and water, dried and evaporated. The residue afforded from ether 40 mg. of crystalline material which was purified by crystallization from ether–hexane containing a few drops of acetone, and from ether, m.p. 178.5–180°, $[\alpha]^{25}D$ +65 ± 2° (*c* 1.145).

Anal. Calcd. for $C_{29}H_{42}ONCl$ (456.1): C, 76.36; H, 9.28; Cl, 7.78. Found: C, 76.71; H, 9.48; Cl, 7.47.

Reaction of Unsaturated Chloro Compound XII with Osmium Tetroxide; Triacetate XIV.—To a solution of XII (454 mg.) in dry benzene (20 cc.) were added dry pyridine (0.35 cc.) and osmium tetroxide (328 mg., 1.25 mole equiv.). The mixture was allowed to stand for 44 hours in the dark at room temperature. No crystalline adduct was formed. The dark-brown solution was concentrated *in vacuo* to a small volume, and ethanol (10 cc.) and sodium sulfite (0.9 g.) in water (10 cc.) were added. After 15 minutes boiling the resulting black precipitate was filtered off from the hot solution, removed from the filter and extracted repeatedly with hot ethanol. The combined filtrates were concentrated to a small volume and extracted with chloroform, and the latter was washed with small portions of water, dried and evaporated, leaving an almost colorless, foamy residue (420 mg.) which could not be crystallized. A sample of the amorphous glycol was titrated with periodic acid as described in a previous paper.[19] The mole per mole uptake was 1.00, 1.03 and 1.04 after 1.5, 4.5 and 22 hours, respectively. The remainder of the product (402 mg.) was acetylated with acetic anhydride and pyridine at room temperature. The resulting amorphous product was dissolved in hexane–benzene 3:2 (5 cc.) and chromatographed on a column of alumina in the usual way. The effluent was collected in 50-cc. portions. The above solvent mixture (150 cc.) and hexane–benzene 3:7 (100 cc.) did not elute any material. The fractions subsequently eluted with benzene (250 cc.), ether–benzene 1:9 (100 cc.), together 364 mg., afforded from ether–hexane crystalline material (318 mg., m.p. 210–212°), which on recrystallization from the same solvents formed large leaflets m.p. 210–211° (constant); $[\alpha]^{23}D$ +74 ± 2° (*c* 1.008). The analytical sample was dried at 80° (0.1 mm.) for 20 hours.

Anal. Calcd. for $C_{33}H_{45}O_5NCl$ (572.2): C, 69.27; H, 8.10; Cl, 6.20; 2 O-acetyl, 15.0. Found: C, 69.21; H, 8.09; Cl, 6.58; acetyl, 11.02.

5α,6α-Dihydroxydihydroveratramine 3,6,23,N-Tetraacetate (XV).—Osmium tetroxide (2.0 g.) and dry pyridine (2.0 cc.) were added to a solution of triacetylveratramine (3.2 g.) in chloroform (5 cc.) and absolute ether (200 cc.). The brown solution was allowed to stand at room temperature in the dark for 48 hours. Without removing the copious dark-brown adduct which had deposited, the mixture was freed from the solvents *in vacuo*, and the residue was worked up as described in the preceding section for the glycol from XII. The resulting colorless product (3.4 g.) could not be obtained in crystalline form. The mole per mole uptake of periodic acid was 0.28, 0.27 and 0.40 after 1.5, 4.5 and 21.5 hours, respectively. A portion (423 mg.) was acetylated with acetic anhydride and pyridine at room temperature. The acetylated product (527 mg.) crystallized in part from ether–hexane (170 mg., m.p. 158–161°). Repeated recrystallization from the same solvents and from ether afforded fine, long needles melting at 156–157°, $[\alpha]^{23}D$ +81 ± 2° (*c* 1.033; λ_{max}^{alc} 268 mμ (520); infrared, bands at 3.08 μ (OH), 5.78 μ (O-acetyl), 6.16 μ (N-acetyl).

Anal. Calcd. for $C_{35}H_{49}O_8N$ (611.7): C, 68.71; H, 8.08; 3 O-acetyl, 21.2. Found: C, 69.01; H, 8.01; acetyl, 21.7.

Chromatographic fractionation of the material remaining in the mother liquors of the crude crystals yielded besides some starting material (benzene eluates) an additional small amount of the tetraacetate (ether–benzene eluates).

N-Nitrosoveratramine.—To a solution of veratramine (845 mg.) in acetic acid (8 cc.), sodium nitrite (1.0 g.) in water (1.6 cc.) was slowly added, causing the gradual deposition of a precipitate. After 15 minutes standing water (25 cc.) was added, and the mixture extracted with chloro-

form. The water-washed and dried extracts on evaporation *in vacuo* left a residue which after two recrystallizations from methanol melted at 212–214° (softening at 207°), $[\alpha]^{24}D$ −27 ± 2° (*c* 1.126); λ_{max}^{alc} 350 mμ (105); shoulder, 240–245 mμ (5800). The infrared spectrum showed bands at 2.85, 3.04 μ (OH) and at 7.31, 7.46 and 11.11μ (NO). The Liebermann reaction for nitrosamines with phenol–sulfuric acid was strongly positive (yellow → deep red → deep blue). It should be mentioned, however, that veratramine itself produces with these reagents a sequence of colors terminating in blue (deep yellow → dirty red → blue → green → blue), except that the latter is far less intense than with the nitroso derivative.

The compound contained solvent of crystallization which could not be completely removed by drying at 110° as prolonged heating led to decomposition. The analytical values obtained on a sample dried at 110° (0.1 mm.) for 3 hours fitted best for a hemihydrate.

Anal. Calcd. for $C_{27}H_{38}O_3N_2 \cdot {}^1/_2H_2O$ (447.6): C, 72.40; H, 8.80; N, 6.27. Found: C, 72.35; H, 8.75; N, 6.42.

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[CONTRIBUTION FROM THE CHEMICAL RESEARCH DIVISION OF SCHERING CORPORATION]

Simultaneous Oxidation and Bromination of 21-Acetoxypregnan-3α,17α-diol-11,20-dione

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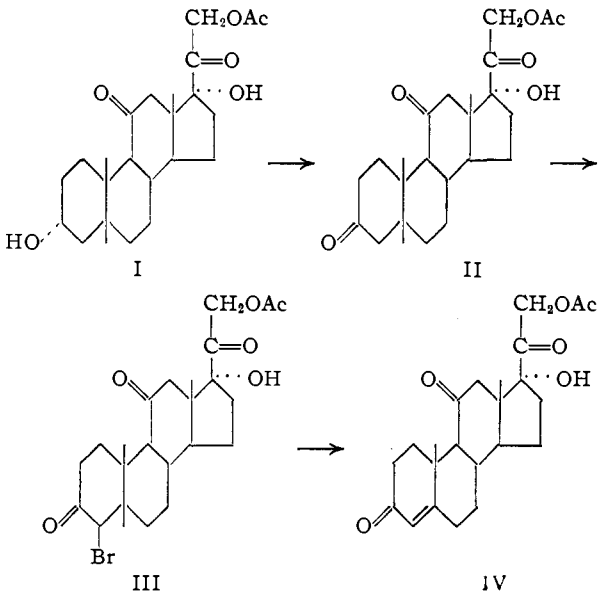
The oxidation of 21-acetoxypregnan-3α,17α-diol-11,20-dione (I) with N-bromosuccinimide in either aqueous acetone, aqueous *t*-butanol or a mixture of *t*-butanol, methylene chloride and pyridine, proceeded normally to the 3-ketone (II). Oxidation in methylene chloride and *t*-butanol solution in the absence of pyridine gave none of II, but instead, a mixture of bromides, 4-bromo-21-acetoxypregnan-17α-ol-3,11,20-trione (III) and 21-bromo-21-acetoxypregnan-17α-ol-3,11,20-trione (V), with the former predominating. The same mixture was obtained from the action of bromine on 21-acetoxypregnan-3α, 17α-diol-11,20-dione (II) dissolved in methylene chloride and *t*-butanol mixture. Some transformations of the 21-bromide (V) are described.

An essential sequence of reactions in one of the alternate syntheses of 11-dehydro-17α-hydroxycorticosterone acetate (cortisone acetate, IV) is the oxidation of 21-acetoxypregnan-3α,17α-diol-11,20-dione (I) to the corresponding 3-ketone, II, followed by bromination at C-4 and finally the introduction of the Δ^4-double bond by the elimination of hydrogen bromide.



I II III IV

Many reagents have been used for the oxidation of a 3α-hydroxyl group to a 3-ketone, among them chromic acid,[1] buffered and unbuffered potassium chromate,[2a] N-bromosuccinimide[3] and N-bromoacetamide.[2] However, no specific directions were available in the literature for the oxidation of I.

We had been privately advised that chromic acid[4] and N-bromoacetamide[5] were satisfactory for the oxidation of I to II. In our hands, the latter reagent gave somewhat better yields, probably because chromic acid is not specific for hydroxyl groups, but will also attack the ketol side-chain. It was important that as clean an oxidation as possible be obtained, for the purity of II is a factor in the success of the bromination step (II to III). The lack of adequate quantities of N-bromoacetamide at the time of this research led us to investigate the action of N-bromosuccinimide on I. Although in only one previous instance[6] had NBS[6] been reported to oxidize a 3α-hydroxy group to the corresponding ketone, we had reason to expect that the similarity of NBA[6] and NBS would allow a substitution of NBS in cases where NBA had been found to be useful. Such proved to be the case and NBS in *t*-butyl alcohol–methylene chloride, in the presence of pyridine, effected a smooth oxidation of I to II. Although the original investigators[7] of NBA had used aqueous *t*-butyl alcohol as the solvent, Sarett[2b] invariably added pyridine to remove the hydrogen bromide formed and to prevent possible attack by the acid on the ketol side-chain. In this particular oxidation, it had been reported[5] that NBA worked equally well either with or without

(1) L. H. Sarett, THIS JOURNAL, 71, 1169, 2443 (1949).

(2) (a) L. F. Fieser and S. Rajagopalan, *ibid.*, 72, 5530 (1950); (b) L. H. Sarett, *ibid.*, 71, 1165 (1949).

(3) L. F. Fieser and S. Rajagopalan, *ibid.*, 73, 118 (1951).

(4) E. C. Kendall, private communication.

(5) T. F. Gallagher, private communication.

(6) NBS = N-bromosuccinimide; NBA = N-bromoacetamide.

(7) H. Reich and T. Reichstein, *Helv. Chim. Acta*, 26, 562 (1943).