Anal. Calcd. for $C_9H_{11}BrClNO_4$: C, 34.58; H, 3.55. Found: C, 34.82; H, 3.52.

2-Chloroveratraldehyde (XI).—A solution of 83 g. of 3-chloro-4-chloromethylveratrole and 60 g. of hexamethylenetetramine in 400 ml. of chloroform was refluxed for three hours, cooled, and the precipitated colorless salt (127 g., 93%) filtered and washed with chloroform. It then was refluxed with 400 ml. of 50% acetic acid for seven hours, the solution was stirred into 800 ml. of ice-water, the aldehyde was filtered and washed with water. The dried material weighed 48 g. (64%). Recrystallization from petroleum ether gave colorless needles, m.p. 70.5–72°.

Anal. Calcd. for $C_9H_9ClO_3$: C, 53.88; H, 4.52. Found: C, 53.83; H, 4.50.

1-(2-Chloro-3,4-dimethoxyphenyl)-2-nitroethanol (XII).—A stirred solution of 10 g. of 2-chloroveratraldehyde and 3.5 g. of nitromethane in 90 ml. of ethanol was cooled to 0°, and a solution of 2.8 g. of potassium hydroxide in 4 ml. of water and 7 ml. of ethanol was added dropwise to the resulting suspension at 0°. The suspension cleared as the first drops of base were added, but the sodium salt of the nitro alcohol soon precipitated. It was filtered after 30 minutes, washed with ethanol and ether, dissolved in 75 ml. of water and, at 0°, added dropwise and with stirring to 45 ml. of 50% acetic acid. The nitro alcohol was precipitated with 170 ml. of water, dried and recrystallized from benzene-petroleum ether. The pale yellow needles, m.p. 111–113°, weighed 7.6 g. (58%).

Anal. Calcd. for $C_{10}H_{12}ClNO_5$: C, 45.89; H, 4.62. Found: C, 46.06; H, 4.56.

1-(2-Chloro-3,4-dimethoxyphenyl)-2-aminoethanol (XIII).—(a) A stirred solution of 3 g. of 1-(2-chloro-3,4-dimethoxyphenyl)-2-nitroethanol in 190 ml. of ether was reduced with 3.6 g. of lithium aluminum hydride under reflux for 30 hours. Water was added dropwise until a granular precipitate had formed, the ether layer was decanted, dried, and treated with hydrogen chloride. Filtration of the precipitate gave 1.8 g. (59%) of hydrochloride as colorless leaflets which were recrystallized from ethanol–ether, m.p. 220–221° dec.

Anal. Calcd. for $C_{10}H_{15}Cl_2NO_3$: C, 44.79; H, 5.64. Found: C, 44.87; H, 5.50.

(b) A mixture of 2 g. of the nitro alcohol, 2.3 g. of 30-mesh zinc dust, 15 ml. of ethanol and 25 ml. of 30% sulfuric acid was stirred at 50–60° for four hours. The clear solution was extracted with ether, made strongly alkaline with sodium hydroxide, and the supernatant liquid was decanted from the inorganic precipitate. Both this solid and the alkaline solution were extracted repeatedly with ether, the combined ether extracts were dried, and the hydrochloride of the amino alcohol precipitated with hydrogen chloride. It weighed 0.8 g. (39%) and after recrystallization from ethanol–ether did not depress the melting point of a sample prepared by method (a).

Anal. Found: C, 44.79; H, 5.52.

Demethylation of 2-Chloroveratraldehyde.—A mixture of 3 g. of 2-chloroveratraldehyde and 20 ml. of 48% hydrobromic acid was refluxed for 20 minutes, cooled and filtered. Recrystallization of the product from ethanol with the aid of carbon gave 1.5 g. (54%) of colorless needles, m.p. 208–209°.

Anal. Calcd. for $C_8H_7ClO_3$: C, 51.49; H, 3.78. Found: C, 51.26; H, 3.83.

The product was soluble in 5% sodium hydroxide solution and essentially insoluble in water and in 5% sodium bicarbonate solution. It gave the Schiff aldehyde test, and a green color with ferric chloride.

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[CONTRIBUTION FROM THE SQUIBB INSTITUTE FOR MEDICAL RESEARCH]

Jervine. VIII. Δ^{13}-Jervine, a New Double Bond Isomer of Jervine

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Jervine (I) is transformed by prolonged treatment with hydrogen and palladium black in aqueous acetic acid into a double bond isomer, Δ^{13}-jervine (II). Δ^{13}-Jervine is far more stable toward acidic reagents than jervine, but, in contradistinction to the latter, is attacked by strong alkali with the formation of yet another isomer to which the dienone structure V is ascribed. This assignment rests mainly on the fact that the diketone XII obtained by Oppenauer oxidation of the N-acetate of V shows the same ultraviolet absorption spectrum as V, while the spectrum of the corresponding diketone XI from Δ^{13}-jervine N-acetate reveals the presence of a new α,β-unsaturated ketone chromophore. Various observations indicate that the formation of XI is accompanied by inversion of the configuration of carbon atom 8.

In early attempts to improve on existing methods for the preparation of tetrahydrojervine[2,3] we essayed the catalytic reduction of jervine (later assigned structure I[4–6]) in 10% aqueous acetic acid solution with palladium black as the catalyst. The reaction proceeded rather sluggishly and came to a standstill after several days of shaking with an uptake of only 1.3 to 1.5 moles of hydrogen. The crude product still exhibited jervine-like ultraviolet absorption, but it was noted that the main maximum at 250 mμ had shifted to a somewhat lower wave length (around 245 mμ). The entity responsible for this absorption, isolated from the mixture in about 20% yield, had the composition $C_{27}H_{39}O_3N$, *i.e.*, that of jervine, but markedly differed from the native alkaloid in its physical properties (m.p. 269–271°, $[\alpha]^{22}\mathrm{D}$ −50°, $\lambda_{\max}^{\mathrm{alc}}$ 245 mμ (8,300) and 320 mμ (37)). The change in the α,β-unsaturated ketone chromophore was also evident in the infrared spectrum, the C=O and C=C bands in the double bond stretching vibration region appearing at 5.94 and 6.12 μ, respectively, rather than at the positions characteristic for jervine (5.88, 6.16). It is interesting that these are also the positions occupied by these bands in the spectrum of *isojervine* (m.p. 114–116°), an isomer of an as yet undetermined structure which Jacobs and Craig[7] had obtained by treatment of jervine with methanolic hydrogen chloride.

The new isomer, like jervine, formed an O,N-diacetate (m.p. 189–192°, $[\alpha]^{23}\mathrm{D}$ −18°), which on mild alkaline hydrolysis yielded the N-acetate (m.p. 240–242°, $[\alpha]^{24}\mathrm{D}$ −41°), also obtainable directly from the free base by selective N-acetylation. Hydrogenation in acetic acid yielded a difficultly separable and ill-reproducible mixture of tetrahy-

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(1) Ciba Research Laboratories, Basel, Switzerland.

(2) W. A. Jacobs and L. C. Craig, *J. Biol. Chem.*, **148**, 57 (1943).

(3) W. A. Jacobs and C. F. Huebner, *ibid.*, **170**, 635 (1947).

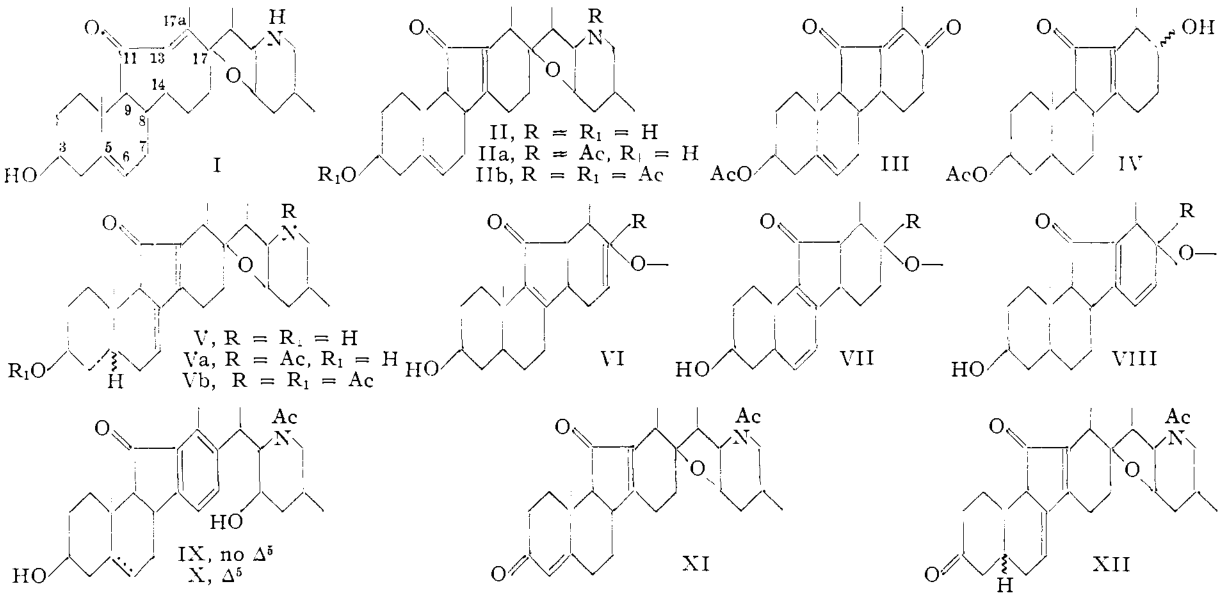
(4) J. Fried, O. Wintersteiner, M. Moore, B. Iselin and A. Klingsberg, THIS JOURNAL, **73**, 2970 (1951).

(5) J. Fried and A. Klingsberg, *ibid.*, **75**, 4929 (1953).

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

(7) W. A. Jacobs and L. C. Craig, *J. Biol. Chem.*, **155**, 565 (1944).

CHART I



drojervine isomers which will require further study. In our experience jervine in the same reaction[2] likewise gives rise to a mixture of products from which only small amounts of "normal" tetrahydrojervine[3] can be isolated.

On the basis of these facts and others to be discussed presently we attribute to the new isomer and its N- and diacetates structures II, IIa and IIb, respectively and propose for it the trivial name Δ^{13}-jervine. It is assumed that under the influence of the palladium catalyst the 13,17a-double bond migrates into the doubly endocyclic 13,14-position where it is resistant to palladium (but not to platinum oxide) catalyzed hydrogenation.[8] The same interpretation has been adopted by Fried and Klingsberg[5] to explain the formation of a substance IV with similar ultraviolet characteristics ($\lambda_{\max}$ 243 mμ (9,000), 318 mμ (45)) in the palladium-catalyzed hydrogenation of etiojerva-5,13(17a)-dien-3β-ol-11,17-dione 3-acetate (III). The ultraviolet spectra of two compounds having the same chromophore as II have been reported by Braude and Coles.[9] These are 4,5,6,7-tetrahydroindanone and its 3-methyl homolog ($\lambda_{\max}^{\text{alc}}$ 237 mμ (12,500), 300 mμ (50)), and 1,2,3,4,5,6,7,8,(*cis?*) - 10,11 - decahydrofluoren-9-one ($\lambda_{\max}^{\text{alc}}$ 240 mμ (12,500), 304 mμ (70)). The bathochromic displacement of the main maximum of II from its location in the spectrum of the decahydrofluorenone may have its cause in steric factors operative in II.

Structure II is supported furthermore by the fact that Δ^{13}-jervine is far less apt than jervine to undergo solvolytic reactions which result in the cleavage of the oxidic linkage attached at C_{17}, and in this respect resembles dihydrojervine and tetrahydrojervine rather than jervine, whose sensitivity to attack at this point is clearly contingent on the activation of the oxidic oxygen by the allylic 13,17a-double bond. Thus Δ^{13}-jervine is not changed by treatment with methanolic hydrogen chloride under conditions which bring about the isomerization of jervine to isojervine (which according to findings, to be reported in a later paper, is unquestionably an "open" derivative), although on prolonged contact with this reagent it is transformed to a new chlorine-containing substance (m.p. 291–293°, $\lambda_{\max}$ 240 mμ) which was not investigated further. Similarly, diacetyl-Δ^{13}-jervine was in part recovered unchanged when it was subjected to the perchloric acid-catalyzed acetolysis procedure which in the case of diacetyljervine affords in facile reaction the crystalline perchlorate of a secondary base formed by migration of the N-acetyl group to a newly established hydroxyl function at C_{17}.[6]

Under strongly alkaline conditions, however, Δ^{13}-jervine is far less stable than jervine. While the latter remains virtually unaltered on prolonged boiling in methanolic potassium hydroxide solution, Δ^{13}-jervine when so treated suffers a slow but profound change, as evidenced by the emergence on the ultraviolet spectrum of a high maximum at 287 mμ. The product accounting for this absorption, isolated in about 10% yield, had m.p. 297–301°, $[\alpha]^{24}\text{D}$ +25°, and proved to be yet another isomer of jervine. The spectral characteristics (single band at 287 mμ with ϵ 10,000, infrared bands at 5.96 and 6.23 μ) suggested a linear dienone chromophore including the original α,β-unsaturated ketone grouping. The N-acetate and the diacetate ($[\alpha]\text{D}$ +58 and +53°, respectively) were both amorphous, but their analyses left no doubt about the presence of the original acylatable groups only. From this it could be inferred that the dienone system had acquired its new terminal ethylenic bond by migration of the 5,6-double bond, an assumption borne out by the result of the Oppenauer oxidation to be described later. Of the four isomeric structures

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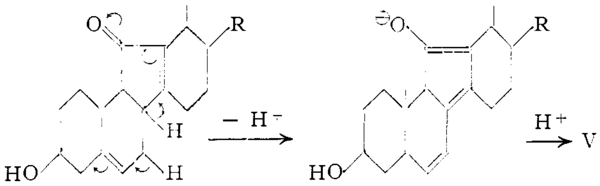
[8] The migration seems to occur to an appreciable extent only in the presence of water and of hydrogen. When the hydrogenation was carried out in glacial acetic acid (H_2-uptake after 70 hours 0.8 mole) about half of the jervine used was recovered as the sole product. The same was true when a solution of jervine in 10% aqueous acetic acid was shaken for 4 days *in air* with palladium black previously saturated with hydrogen (recovery 60%).

[9] E. A. Braude and J. A. Coles, *J. Chem. Soc.*, 1430 (1952).

which conceivably could arise from II in this fashion (V, VI, VII and VIII) we prefer V, because its formation can be envisaged readily as occurring by a proton shift from C_7 to C_5 following the shift in the opposite direction due to enolization of the Δ^{13}-unsaturated 11-ketone grouping



II

Structure VI appears improbable for steric reasons; the cyclopentadienone system seems to be capable of existence only when resonance stabilization is provided by fusion or multiple substitution of the ring with aromatic groups. Structures VII and VIII may be discounted on the grounds that the observed λ_{max} is too low for a homoannular dienone (*cf.* $\Delta^{6,8,22}$-ergostatrien-3β,14-diol-11-one 3-acetate), λ_{max} 308 mμ (6,900)).[10] Moreover, the dienone, like its progenitor, is stable to methanolic hydrogen chloride even on prolonged exposure (68 hours),[11] whereas one would expect the oxidic bridge in VIII, on account of its allylic relationship to the conjugated system, to be cleaved readily by this agent with the establishment of a third double bond in ring D. The end-product of this sequence should be the free base corresponding to the known indanone IX,[12] a substance easily recognizable by its characteristic two peak ultraviolet absorption spectrum. However, the absorption curve of the total crude reaction product from the reaction with methanolic hydrogen chloride gave no indication for the presence of a compound of this type.

If the two new jervine isomers are represented correctly by II and V, then their N-acetates IIa and Va should yield on Oppenauer oxidation the isomeric diketones XI and XII, respectively. Application of this reaction to IIa followed by treatment with Girard reagent T afforded an amorphous ketonic fraction the ultraviolet spectrum of which (λ_{max} 237 mμ with ϵ 22,400, the shoulder at 245 mμ) left no doubt about the presence of the new α,β-unsaturated ketone chromophore. Surprisingly, this material was more levorotatory (−69°) than IIa (−41°), whereas IIa → XI should be accompanied by a positive rotation change of considerable magnitude ($\Delta[M]_D$ for jervine → Δ^4-jervone +742°). Chromatography on alumina effected separation into two major fractions, A and B, accounting, respectively, for 20 and 43% of the material put on the column. Fraction A, eluted with benzene, was amorphous and dextrorotatory ($[\alpha]_D$ +26°). Fraction B, which was not released from the adsorbent till ether containing 5% of methanol was used as the eluent, contained the levorotatory component ($[\alpha]_D$ −82°). This material, though initially amorphous, eventually could be induced to crystallize, whereupon fraction A as well as most of the intermediate small fractions eluted before fraction B likewise turned crystalline. As could be expected from this behavior, the crystalline products obtained from the dextrorotatory fraction A and the intermediate fractions proved to be identical with the levorotatory substance constituting the bulk of fraction B (m.p. 218–220°, $[\alpha]^{23}_D$ −100°). There can be little doubt from the analytical composition ($C_{29}H_{39}O_4N$), the ultraviolet and infrared data ($\lambda^{\text{alc}}_{\text{max}}$ 237 mμ, (22,800), 315 mμ (149); $\lambda^{\text{Nujol}}_{\text{max}}$ 5.90, 6.03, and the formation of a monoxime (m.p. 236°) that *structurally* this compound is correctly expressed by XI. However, there is good reason to believe that it is not the primary oxidation product, but must have arisen from a dextrorotatory intermediate (*i.e.*, the 3,11-diketone corresponding sterically to II) by inversion of a labile asymmetric center, a change which evidently occurs to a large measure already during the Oppenauer reaction and the work-up procedure. This view is supported by the following observations:

When the dextrorotatory mother liquor material ($[\alpha]_D$ +19° in chloroform) remaining after the removal of the crystalline levorotatory diketone XI from fraction A was dissolved in aqueous ethanol containing a trace of potassium hydroxide, the specific rotation, initially +5.4°, changed rapidly to the negative side to become constant at −52° after 4 hours. Since the crystalline material recovered from the solution was obviously a mixture (m.p. 189–193°, $[\alpha]_D$ −39°), it is probable that an equilibrium is involved. In a similar experiment, in which hydrochloric acid was substituted for the base ($[\alpha]_D$ +8.4°), no mutarotation was observed. Similar observations were made on an amorphous dextrorotatory fraction ($[\alpha]_D$ +20°, λ_{max} 236 mμ[13] representing the total mother liquor material from the crude crystals of the levorotatory diketone (which in this instance was obtained from the ketonic fraction directly without recourse to chromatography, *cf.* Experimental). The dextrorotatory precursor of XI could not be obtained in crystalline form, and attempts to determine the equilibrium point of rotation suffered from lack of reproducibility apparently on account of side reactions. However, from the fact that the levorotatory diketone under the same conditions showed slight but definite mutarotation toward the positive side it would appear that this stereoisomer greatly preponderates at equilibrium.

These findings prompted us to examine the rotation trend of Δ^{13}-jervine itself when exposed to mild alkaline conditions, since it appeared quite possible that the formation of the dienone V was preceded by the steric change postulated above for XI. However, the results provided no clear-cut indication that such was the case. The observed muta-

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[10] G. D. Laubach, E. C. Schreiber, E. J. Agnello, E. N. Lightfoot and K. J. Brunings, This Journal, **75**, 1514 (1953).

[11] Under identical conditions jervine is converted to isojervine in good yield within about 2 hours.

[12] O. Wintersteiner aud N. Hosansky, This Journal, **74**, 4774 (1952).

[13] The position of the maximum in the ultraviolet absorption curve of the levorotatory diketone (237 mμ) does not coincide with that (241 mμ, ϵ 25,000) obtained by superimposition of the curve of Δ^{13}-jervine on that of Δ^4-13,17a-dihydrojervone.[14] Since λ_{max} of the fraction containing the dextrorotatory precursor shows the same displacement, it is clear that the hypsochromic shift is not contingent on the postulated steric change, but must be due to a vicinal effect exerted on the ring A chromophore by the 13,14-double bond.

[14] W. A. Jacobs and Y. Sato, *J. Biol. Chem.*, **157**, 57 (1948).

rotations were quite small, and in the case of the N-acetate IIa in the direction opposite to that expected. That little or none of the dextrorotatory dienone V was formed under these conditions followed from the fact that the ultraviolet spectrum remained essentially unaltered. It would appear then that II represents the stable isomer relative to its C_8- or C_9-epimers (or at least greatly predominates in the equilibrium with the latter in alkaline solution at room temperature), and that the formation of the dienone is not contingent on prior inversion of one of these asymmetric centers.

As regards the site of the postulated epimerization during the oxidation of IIa to XI, it should be recalled that jervine (I), which could enolize only toward C_9, is completely stable to alkali. Furthermore, this is true also of the indanone X,[6] in which the tendency toward enolization in this direction would be, if anything, greater than with I, and in which, moreover, the strain relationships in ring C are probably nearly the same as in II. Unlike II, however, the indanone cannot enolize toward C_8, and since in this case there is no evidence for the occurrence of a steric change at the B/C ring junction on Oppenauer oxidation to the corresponding α,β-unsaturated 3-ketone[5] ($\Delta[\mathrm{M}]_{\mathrm{D}}$ +733°), it seems probable that the formation of XI was accompanied by inversion at C_8 rather than at C_9. On the premise that the B/C ring junction in jervine and in II corresponds sterically to that in normal steroids ($8\beta,9\alpha$)—a postulate supported, *inter alia*, by the occurrence in veratrum plants of tertiary bases possessing a normal steroid nucleus—we tentatively assign the α-configuration to the hydrogen atom at carbon atom 8 in XI. In the scale model the change from the $8\beta,9\alpha$-*trans*- to the $8\alpha,9\alpha$-*cis*-linked ring system produces a marked folding around the 8,9-axis of the formerly essentially flat molecule, and it will have to be assumed that it is this alteration in the geometry of the nucleus which is responsible for the large negative contribution to the molecular rotation of XI reflected in the anomalous negative $\Delta[\mathrm{M}]_{\mathrm{D}}$ accompanying the Oppenauer oxidation of IIa. It might be pointed out in this connection (for whatever bearing it may have on the present case) that the molecular change in passing from 22a-5α-spirostan-3β-ol-11-one[15] to its 8-epimer[16] has a high negative value (−189°).

Since Δ^{13}-jervine, unlike the primary product of the Oppenauer oxidation, does not appear to undergo epimerization at C_8 under mild alkaline conditions, it must be assumed that the 5,6-double bond exerts a stabilizing influence on the *trans*-fused hydrindenone system represented by ring B and C,[17] whereas the exocyclic 4,5-double bond favors the transition to the *cis*-linked $8\alpha,9\alpha$-form.[18]

The ketonic product formed from the dienone N-acetate Va by Oppenauer oxidation and isolated by means of Girard reagent T was amorphous, but had the expected analytical composition $C_{29}H_{39}O_4N$. The identity of its ultraviolet absorption spectrum with that of V confirmed the absence of the 5,6-double bond in the latter. It was slightly more dextrorotatory (+67°) than its precursor (+58°). Chromatography did not change these properties, but yielded in addition a small, highly polar fraction which, to judge from its ultraviolet characteristics ($\lambda_{\max}$ 235 and 292 mμ, with $E^{1\%}_{1\,\mathrm{cm}}$ 177 and 79, respectively), contained a Δ^4-unsaturated 3-ketone, possibly XI. The presence of a new reactive ketone group in the main product is attested by the mode of isolation, the formation of a dinitrophenylhydrazone and oxime, both amorphous, and the appearance in the infrared spectrum of a band at 5.86 μ partly merged with the 5.96 μ band originating in the carbonyl of the dienone system. The oxidation product therefore must be expressed as XII.

Experimental

The melting points were taken in open Pyrex glass capillaries and are corrected for stem exposure. The rotation measurements were carried out in a 1-dm. semi-micro tube, with chloroform as the solvent, unless indicated otherwise. The ultraviolet spectra were measured in a quartz Beckman spectrophotometer, model DU, and those of the more important compounds were later checked in a Cary self-recording instrument. The infrared spectra were determined in nujol suspension in a Perkin–Elmer double beam self-recording instrument, model 21. The analytical samples were dried over phosphorus pentoxide at 110° (1 mm.). The alumina used for chromatography (Harshaw) was washed with dilute sulfuric acid and water, *p*H 4.5, and reactivated by heating at 150° for 48 hours.

Δ^{13}-Jervine (22,26-Imino-17,23-oxido-5,13(14)-jervadien-3β-ol-11-one (II).—A solution of jervine (40 g.) in 10% acetic acid (400 cc.) was shaken in a hydrogen atmosphere in the presence of 5 g. of palladium black. The hydrogen uptake ceased almost completely after shaking for 4 days, the total consumption of hydrogen varying between 1.3 and 1.5 moles per mole of substance in several runs. After removal of the catalyst by filtration, the filtrate was concentrated to 50 cc. *in vacuo*, made alkaline with 5 *N* sodium hydroxide solution while cooling in ice, and thoroughly extracted with chloroform (a large amount of solid material remaining suspended in the aqueous phase was recovered subsequently by filtration and worked up separately, see below). The chloroform extracts were washed with water, dried, evaporated to dryness, and the residual sirup was dissolved in 40 ml. of acetone. On standing, the solution deposited 8.18 g. of the isomer which, after repeated recrystallization from methanol, melted at 269–271°, $[\alpha]^{22}\mathrm{D}$ −50° (*c* 0.89). The ultraviolet spectrum showed two bands at 245 mμ (8,300) and 320 mμ (37), while the infrared spectrum revealed typical maxima at 5.94 and at 6.12 μ.

Anal. Calcd. for $C_{27}H_{39}O_3N$ (425.59): C, 76.18; H, 9.24; N, 3.29. Found: C, 76.03; H, 9.32; N, 3.33.

The chloroform-insoluble product which had remained suspended in the aqueous phase was collected on a filter and thoroughly washed with water. The dried material (17.3 g.), after recrystallization from aqueous methanol, melted at 141–147° and showed $[\alpha]^{25}\mathrm{D}$ +11° (*c* 1.25 in abs. ethanol); $\lambda^{\mathrm{alc}}_{\max}$ 313 mμ (ϵ 160) and end absorption. The substance contained solvent of crystallization (13.2%) which was lost on drying at 110° *in vacuo* (m.p. after drying 123–128°). The analysis was inconclusive except insofar as it indicated a reduced derivative (C, 73.30; H, 9.67; N, 3.19). The melting point and rotation data exclude identity with tetrahydrojervine. The behavior on drying is reminiscent of that of tetrahydroisojervine (to be de-

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[15] C. Djerassi, E. Batres, M. Velasco and G. Rosenkranz, THIS JOURNAL, **74**, 1712 (1952).

[16] C. Djerassi, W. Frick, G. Rosenkranz and F. Sondheimer, *ibid.*, **75**, 3496 (1953).

[17] D. A. H. Taylor (*Chemistry & Industry*, 250 (1954)) has advanced, mainly on the basis of steric considerations, the generalization that Δ^2-*trans*-octalins should be more stable than Δ^1-*trans*-octalins, while the reverse relationship should obtain for Δ^1-*cis*-octalins *versus* Δ^2-*cis*-octalins; *cf.* also A. S. Dreiding, *ibid.*, 1419 (1954).

[18] This proposition conceivably could be tested by examining the behavior of the Δ^5-3-dioxolane of XI toward alkali at room temperature, on the presumption that this would lead to the re-establishment of the β-configuration at C_8. Hydrolysis with acid then should yield the dextrorotatory form of the diketone corresponding configurationally to Δ^{13}-jervine.

scribed in a later paper) which differs, however, from the above product in its rotation and ultraviolet characteristics.

The O,N-diacetate of Δ^{13}-jervine (IIb) was prepared in the usual manner by acetylation in acetic anhydride and pyridine at room temperature (yield 91%). After recrystallization from acetone–pentane, it melted at 189–192° and showed $[\alpha]^{23}\mathrm{D}$ $-18°$ (*c* 1.20); $\lambda_{\max}^{\text{alc}}$ 243 mμ (8000), 315 mμ (55).

Anal. Calcd. for $C_{31}H_{43}O_5N$ (509.66): C, 73.04; H, 8.53; N, 2.75; 2COCH$_3$, 16.9. Found: C, 73.38; H, 8.70; N, 3.01; COCH$_3$, 17.2.

Acetylation of II by treatment with a slight excess of acetic anhydride in dry methanol (room temp. 5 hours) gave a 56% yield of the **N-acetate IIa** which after recrystallization from acetone–pentane melted at 240–242°, $[\alpha]^{24}\mathrm{D}$ $-41°$ (*c* 1.10); $\lambda_{\max}^{\text{alc}}$ 243 mμ (8400), 320 mμ (33). The slight hypsochromic shift of the main band of II in the spectra of the acetylated derivatives seems to be real.

Anal. Calcd. for $C_{29}H_{41}O_4N$ (467.6): C, 74.47; H, 8.84; COCH$_3$, 9.20. Found: C, 74.41; H, 8.89; COCH$_3$, 9.8, 8.6.

Hydrolysis of the O,N-diacetate by refluxing with 5% methanolic potassium hydroxide for 30 minutes yielded an identical product (m.p. 240°, $[\alpha]^{24}\mathrm{D}$ $-40°$). The ultraviolet spectrum showed no trace of the band at 287 mμ characteristic of the dienone V which is formed from II on more severe treatment with alkali. However, it is likely that some of V or its N-acetate was present in the crude, strongly pigmented reaction product, since the yield of crystalline IIa was only about 30%.

Treatment of Δ^{13}-Jervine with Methanolic Hydrogen Chloride.—A solution of Δ^{13}-jervine (500 mg.) in methanol saturated at 0° with hydrogen chloride gas (10 cc.) was allowed to stand at 0° for one hour (conditions for preparation of isojervine from jervine). The crystalline hydrochloride obtained on removal of the solvent was dissolved in water (in which, unlike jervine hydrochloride, it was readily soluble), converted into the base with potassium bicarbonate, and the latter recovered by chloroform extraction. The chloroform residue (410 mg.) on crystallization from methanol–acetone yielded a product (270 mg.) identified by m.p. (266–270°) rotation ($[\alpha]\mathrm{D}$ $-58°$) and ultraviolet spectrum ($\lambda_{\max}^{\text{alc}}$ 245 mμ, ε 5700) as slightly impure Δ^{13}-jervine. However, the ultraviolet characteristic of the sirupy mother liquor material ($\lambda_{\max}$ 235 mμ, ε 7700) gave evidence of the presence of a new substance not identical with either Δ^{13}-jervine or isojervine.

Under more rigorous conditions (3 hours at room temp. in chloroform solution saturated with hydrogen chloride, then addition of methanol, and HCl gas passed through solution for 2 hours at 0°), Δ^{13}-jervine was converted in about 60% yield to a compound, m.p. 291–293°, which contained organically bound chlorine and showed $\lambda_{\max}^{\text{alc}}$ 240 mμ ($E_{1\,\text{cm}}^{1\%}$ 201).

Attempted Acetolysis of Diacetyl-Δ^{13}-jervine.—Treatment of diacetyl-Δ^{13}-jervine (133 mg.) with the perchloric acid-containing acetolysis mixture previously applied to diacetyljervine[3] (room temp. 2.5 hours) resulted in the formation of a rust-brown amorphous precipitate (152 mg.) which could not be crystallized. It was dissolved in benzene–hexane 1:1 (2 cc.) and chromatographed on sulfuric acid-washed alumina (9 × 51 mm.). After the removal from the column of some amorphous material (34 mg.) with the same solvent mixture a crystalline product (44 mg.) was eluted by benzene which once recrystallized from acetone–pentane melted at 184–186° and was shown to be the starting material by mixed melting point and ultraviolet spectrum. The remainder of the adsorbed material, eluted with more polar solvent mixtures, was amorphous.

Oxidation of N-Acetyl-Δ^{13}-jervine to Diketone XI (22,26-Imino-17,23-oxido-4,13(14)-jervadiene-3,11-dione N-Acetate.—A solution of N-acetyl-Δ^{13}-jervine (500 mg.) and aluminum *t*-butylate (2 g.) in dry benzene (30 cc.) to which dry acetone (15 cc.) had been added (formation of a gelatinous precipitate) was boiled under reflux for 21 hours. After chilling, ice-cold 1 *N* sulfuric acid (25 cc.) was added, and the aqueous layer was extracted repeatedly with benzene. The combined benzene extracts were washed successively with acid, potassium bicarbonate solution and water, and dried. The yellow sirup obtained on removal of the solvent was subjected to treatment with Girard reagent T (500 mg. in 9 cc. of ethanol–acetic acid 9:1, refluxed 1 hour) and separated into ketonic (410 mg.) and nonketonic (99 mg.) fractions in the usual way, using benzene in both extraction steps. The ketonic material, a yellow glass, showed $[\alpha]^{25}\mathrm{D}$ $-69°$ and $\lambda_{\max}^{\text{alc}}$ 237 mμ (22,400) with a shoulder at 245 mμ. A 250-mg. portion was dissolved in benzene–hexane 1:1 (20 cc.) and adsorbed on a column of sulfuric acid-washed alumina (13 × 58 mm.). Elution was effected with 50-cc. portions of benzene–hexane 1:1 (fractions 1–5, 6 mg.), benzene (fractions 6–14, 96 mg.), benzene–ether 19:1 (fractions 15–18, 13 mg.), benzene–ether 3:1 (fractions 19–22, 29 mg.), ether (fractions 23–25, 9 mg.) and ether–methanol 19:1 (fraction 26, 108 mg., and 27, 4 mg.). All the eluates were at first amorphous. Fractions 6 and 7, containing the bulk (56 mg.) of the material eluted with benzene, were combined (fraction A). This material exhibited dextrorotation ($[\alpha]^{22}\mathrm{D}$ $+26°$). The more strongly polar material in the large fraction 26 needing methanol–ether for elution (fraction B) was levorotatory $[\alpha]^{22}\mathrm{D}$ $-82°$. Analysis after lyophilizing from benzene gave figures in good agreement with those required for the diketone XI.

Anal. Calcd. for $C_{29}H_{39}O_4N$ (465.6): C, 74.80; H, 8.44. Found: C, 74.94; H, 8.13.

After some manipulation crystals were obtained from the remainder of fraction B. The final product, thrice recrystallized from warm ethanol–water 1:3 (48 mg., small rods) melted at 218–220° and showed $[\alpha]^{23}\mathrm{D}$ $-100°$ (*c* 0.788); $\lambda_{\max}^{\text{alc}}$ 237 mμ (22,800), 315 mμ (150); $\lambda_{\max}^{\text{Nujol}}$ 5.90, 6.03 μ.

Anal. Calcd. for $C_{29}H_{39}O_4N$ (465.6): C, 74.80; H, 8.44. Found: C, 74.77; H, 8.44.

The mother liquors yielded additional amounts (23 mg.) of the pure diketone, showing that fraction B was essentially homogeneous.

The oxime, prepared in the usual manner (2 hours reflux), was recrystallized 3 times from aqueous ethanol (very small needles), and then melted at 233–237° after darkening at 223°. The analytical sample was dried to constant weight at 110° (2 mm.) (weight loss 8.3%). To judge from the somewhat low nitrogen value it was contaminated with unreacted XI diketone.

Anal. Calcd. for $C_{29}H_{40}O_4N$ (480.6): N, 5.83. Found: N, 5.09.

After fraction B had given crystals, it was not difficult to induce crystallization also in fraction A as well as in the intermediate benzene–ether 19:1 and 1:1 eluates. The individual fractions in each chromatographic band were combined, and on recrystallization from acetone–ether–pentane yielded the levorotatory diketone XI in varying states of purity. Thus, the remainder of fraction A after combination with the other benzene eluates (total 76 mg.) on 2 recrystallizations gave 20 mg. of crystals, m.p. 210–213° ($[\alpha]\mathrm{D}$ $-96°$; $\lambda_{\max}^{\text{alc}}$ 237 mμ (23,800) and 315 mμ (145), infrared spectrum identical with that of XI from fraction B). The mother liquor from the first recrystallization contained mostly the levorotatory diketone ($[\alpha]\mathrm{D}$ $-66°$), while the material in the mother liquor from the crude crystals (*ca.* 50 mg.) was still dextrorotatory ($+19°$). A weighed portion was dissolved in 50% aqueous ethanol, and a trace of 10% methanolic potassium hydroxide was added. The specific rotation of this solution changed with time as follows: 3 min., $+5.4°$; 1 hour, $-27°$; 4 hours, $-52°$; 3 days, $-51°$. The product recovered by evaporation of the solvent ($[\alpha]\mathrm{D}$ $-39°$ in chf.) was a mixture, as after recrystallization from acetone–ether–pentane it melted at 189–193°. In a subsequent oxidation experiment starting from 605 mg. of IIa, the ketonic fraction (435 mg.) afforded by direct crystallization 261 mg. of crude XI. Attempts to isolate the dextrorotatory precursor of XI in crystalline form from the yellow, resinous mother liquor material ($[\alpha]\mathrm{D}$ $+20°$, $\lambda_{\max}$ 236 mμ, ε 17,600) failed. The chloroform-extractable product obtained on treatment of a small sample of this material with 50% aqueous ethanol containing a trace of potassium hydroxide showed $[\alpha]\mathrm{D}$ $-57°$ in chloroform. However, when the remainder of the dextrorotatory resin was so treated (*p*H 8, initial $[\alpha]\mathrm{D}$ $+9.8°$), the rotation change came to a standstill at $-17°$, and after the *p*H was raised to 10, at $-29°$. The preparative work-up at this point yielded 28 mg. of crystals, m.p. 180–209°, $[\alpha]\mathrm{D}$ $-71°$. Repetition of the *p*H 10 procedure on the mother liquor material ($[\alpha]_D$ −10°) produced no further changes in rotation and crystallizability. Apparently side reactions supervene, particularly at higher *p*H, before equilibrium is reached.

In an attempt to reach the equilibrium point from the side of the levorotatory diketone XI a 7.9-mg. sample of the latter was dissolved in 50% ethanol alkalinized to *p*H 10. The specific rotation, initially −136°, became constant in 5.5 hours at −122°. The crystalline portion of the recovered material (4.4 mg.) consisted of slightly impure XI (m.p. 212-218°, $[\alpha]_D$ −99°).

Isomerization of Δ^{13}-Jervine with Alkali to Dienone V (22,26-Imino-17,23-oxido-7,13(14)-jervadien-3β-ol-11-one).—A solution of Δ^{13}-jervine (8 g.) in 10% methanolic potassium hydroxide (250 cc.) was refluxed for 3 hours. The dark red mixture was concentrated *in vacuo* to about half its volume, diluted with ice-water and extracted with chloroform. The extract was washed with water, dried and freed from the solvent. The crystalline product obtained on addition of acetone to the sirupy residue (1.33 g., m.p. 272–279°) on repeated recrystallization from methanol gave the pure dienone V (needles, 677 mg.) melting at 297–301°, $[\alpha]^{24}D$ +25°, $\lambda_{\max}^{\text{alc}}$ 287 mμ (10,000); $\lambda_{\max}^{\text{Nujol}}$ 3.00, 5.96, 6.23 μ.

Anal. Calcd. for $C_{27}H_{39}O_3N$ (425.6): C, 76.18; H, 9.24; N, 3.29. Found: C, 76.04; H, 9.19; N, 3.24.

For the preparation of the **O,N-diacetate Vb**, the dienone (75 mg.) was acetylated with acetic anhydride and pyridine at room temperature. Since the crude product (90 mg.) showed no tendency to crystallize, it was chromatographed on alumina from benzene–hexane 3:7. The bulk of the material was eluted by benzene–ether mixture 4:1 and 1:1. Addition of ether to the combined solutions of these fractions in acetone gave a gelatinous precipitate which after washing with ether and pentane and drying at 80° for 3 hours melted at 182–188° and showed $[\alpha]^{24}D$ +53° and $\lambda_{\max}^{\text{alc}}$ 287 mμ (10,500).

Anal. Calcd. for $C_{31}H_{43}O_5N$ (509.7): C, 73.04; H, 8.53; 2 $COCH_3$, 16.9. Found: C, 72.95; H, 8.79; $COCH_3$, 15.5.

The likewise amorphous **N-acetate Va** was prepared from V (600 mg.) by N-acetylation with acetic anhydride (0.2 cc.) in dry methanol (20 cc.). The mixture was allowed to stand at room temperature for 4 hours and then worked up in the usual manner. The crude product, which was insoluble in acetone, was purified by dissolving it in methanol and adding ether in excess. The resulting gelatinous precipitate after washing with ether and drying at 110° (0.3 mm.) for 2 hours liquefied at 192–202°; $[\alpha]^{24}D$ +58°, $\lambda_{\max}^{\text{alc}}$ 286 mμ (11,800).

Anal. Calcd. for $C_{29}H_{41}O_4N$ (467.6): C, 74.47; H, 8.84; $COCH_3$, 9.20. Found: C, 74.72; H, 9.04; $COCH_3$, 9.50.

A solution of the free dienone V (50 mg.) in dry methanol saturated with hydrogen chloride at 0° (10 cc.) did not show any change in the ultraviolet spectrum on standing at 5° for 68 hours. The material recovered by evaporation of the solvent, addition of cold potassium bicarbonate solution and chloroform extraction and recrystallization from acetone-methanol (29 mg.) melted at 301–304° and did not depress the melting point of the starting material (m.p. 296–300°).

Oxidation of the Dienone N-Acetate Va to Diketone XII.—The Oppenauer oxidation of Va (510 mg.) and the treatment of the crude product with Girard reagent T was carried out as described above for the N-acetate IIa. The ketonic and non-ketonic fractions, both yellow sirups, weighed 177 and 310 mg., respectively. The ketonic fraction could not be crystallized and was purified by two consecutive precipitations from acetone solution with ether. After drying at 80° (0.3 mm.) the product melted at 160–166°, $[\alpha]^{25}D$ +67°, $\lambda_{\max}^{\text{alc}}$ 286 mμ (9,200).

Anal. Calcd. for $C_{29}H_{39}O_4N$ (465.6): C, 74.80; H, 8.44. Found: C, 74.69; H, 8.64.

The remainder of the product together with the ether–acetone mother liquor material (82 mg.) was dissolved in benzene and chromatographed on a column of alumina (9 × 35 mm.). Most of the material was eluted in the first 3 (20 cc.) benzene eluates (fraction A, 44 mg.). The benzene–ether mixture subsequently used for elution, and ether alone, removed only small amounts, and ether containing 5% of methanol had to be employed to recover the remainder (fraction B, 19 mg.). Neither fraction could be obtained in crystalline form. Fraction A showed the same specific rotation and ultraviolet characteristics as the original product. The infrared spectrum exhibited bands at 5.86–5.92 (doublet) and 6.08 μ. It formed an amorphous yellow 2,4-dinitrophenylhydrazone (m.p. 192–200°) and an amorphous oxime (m.p. 194–215°). Fraction B had $[\alpha]^{23}D$ +46° and $\lambda_{\max}^{\text{alc}}$ 235 mμ ($E_{1\,\text{cm}}^{1\%}$ 177), 292 mμ ($E_{1\,\text{cm}}^{1\%}$ 79). A portion was treated with 0.5% methanolic potassium hydroxide at room temperature for 3 hours and then recovered in the usual way by chloroform extraction. Since the specific rotation of the recovered material was only slightly lower (+38°), the dextrarotatory precursor of XI probably was not present in significant amounts.

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