acids,[10,1] were being developed, several completely general systems for the naming of substances with more than one asymmetric center were put forward. Of these, that of Cahn and Ingold,[11] although it has occasionally been used in the literature, was not found to be completely acceptable. The use of the carbohydrate prefixes in the special field of amino acids was considered, but appeared to be inapplicable since at that time the committee working on the carbohydrate rules restricted the use of these prefixes to the names of substances containing adjacent asymmetric centers. However, a recent draft of the rules of carbohydrate nomenclature does not make this restriction. Accordingly, the prefixes may now be applied even when one or more methylene groups separate the asymmetric centers. It thus becomes possible to use these prefixes in naming amino acids such as hydroxyproline and hydroxylysine.

When the carbohydrate prefixes are so used, it is essential to specify with great care the significance of the capital letter prefix. In carbohydrate nomenclature, this prefix denotes the configuration of the highest numbered asymmetric center. In amino acid nomenclature, it denotes the configuration of the α-amino group, that is, the *lowest* numbered asymmetric center. Accordingly, the subscript s (for serine) to the L or D prefix must invariably be shown when naming amino acids with carbohydrate prefixes since without the subscript the center to which the capital letter prefix applies is left uncertain. The prefix is placed immediately before the trivial name of the parent amino acid since it refers only to the configuration of the α-carbon atom in the parent acid however substituted elsewhere.

Although the use of the carbohydrate prefixes is restricted under the rules of carbohydrate nomenclature to the naming of substances which contain asymmetric centers in which hydroxyl, methoxyl, acetoxyl, or amino groups occur, the use of the capital letter prefixes to denote configuration has been extended in recent years to other classes of substances in which configurational relationships have been established. This is notably the case for a number of substances that contain branched hydrocarbon chains. Inasmuch as the methyl group of isoleucine has been shown by Trommel and Bijvoet[3] to be in the *cis* position to the amino group, it is possible to suggest specific names with carbohydrate prefixes for the diastereomers of this substance. The extention of the rule to the naming of homologs and analogs of established configuration may require the development of a convention for the precedence of radicals.

It is not proposed that names devised under this Rule should replace the commonly used names for these amino acids. The Rule has been suggested to meet the situation where exact definition of the configurational relationships has become essential as, for example, in papers that deal with such relationships. Furthermore, as more and more complex amino acids are found in nature or are prepared in the laboratory, it is obvious that substances will be encountered which approach ever closer in structure to the acids derived from the amino sugars. At some level of complexity it will be necessary to draw the line between the use of a nomenclature based upon the rules for naming amino acids and the rules for naming carbohydrate derivatives. This point has been dealt with by Rule AA-3.2 of the Definitive Rules for the Nomenclature of Natural Amino Acids and Related Substances[1] and was also discussed in the Comment on the rules for amino acid nomenclature published in 1952.[10] It was there stated that such substances as mannosaminic acid should be named according to the custom in carbohydrate nomenclature, for example D_g-mannosaminic acid (2-amino-2-deoxy-D_g-mannonic acid), the subscript g (for glyceraldehyde) being written when any possibility occurs of confusion between the meaning of the capital letter prefix as used in carbohydrate nomenclature and in amino acid nomenclature. It is obvious that good judgment must be employed in applying Rule AA-11 for the naming of complex amino acids.

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(10) *Chem. Eng. News*, **30**, 4522 (1952).
(11) R. S. Cahn and C. K. Ingold, *J. Chem. Soc.*, 612 (1951).

The Structure of Isojervine[1]

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Received September 7, 1962

When the veratrum alkaloid jervine is allowed to react with ethanolic hydrochloric acid, it is isomerized into isojervine. This new isomer possesses structure II resulting from the opening of the 17,23-oxide with concomitant migration of the 13,17a-double bond to the 17,17a-position and the introduction of a new double bond at the 8,9-position. The ultraviolet spectral features of this new isomer are analogous to those found with 2,5-dihydroacetophenone.

In the course of the elucidation of the structure of the veratrum alkaloid jervine (I), particular attention was paid to the transformations induced by acids. Depending on the conditions employed, a variety of products were isolated[2-4] and the structures of most of the transformations products were established. It is of interest to note, however, that the first acid transformation product ever reported in this series has received little attention and its structure has not been determined.

In 1944, Jacobs and Craig[5] reported that when jervine was allowed to react with ethanolic hydrochloric acid, it was transformed into an isomeric substance

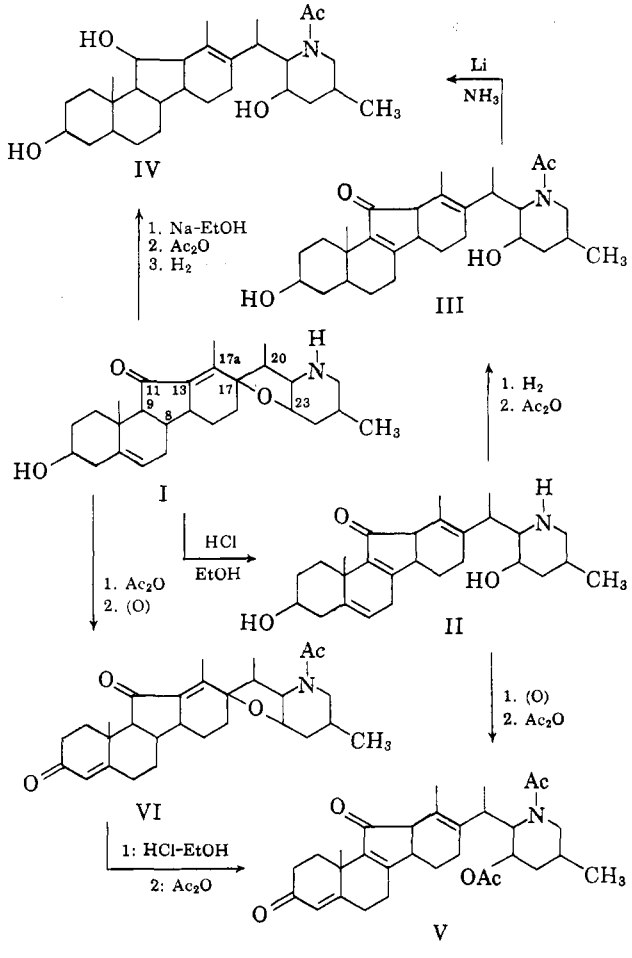
(1) This work was supported in part by the National Science Foundation, grant no. G-14526.
(2) O. Wintersteiner and M. Moore, *J. Am. Chem. Soc.*, **75**, 4938 (1953).
(3) J. Fried and A. Klingsberg, *ibid.*, **75**, 4929 (1953).
(4) O. Wintersteiner and M. Moore, *ibid.*, **78**, 6193 (1956).
(5) W. A. Jacobs and L. C. Craig, *J. Biol. Chem.*, **155**, 565 (1944).

which they called isojervine (II). This new isomer possesses an ultraviolet spectrum exhibiting only strong end absorption with an inflection at 250 mμ (ε 3500) and a low intensity maximum at 333 mμ (ε 200) and the material upon reaction with acetic anhydride yields a triacetate (di-O,N). In contrast, jervine has a well defined peak at 252 mμ (ε 14,000) and a less intense peak at 360 mμ (ε 70), characteristic of the 13,17a-ene-11-one system and upon reaction with acetic anhydride gives a diacetate (O,N). The possibility that the new acetylable hydroxyl group in isojervine arose from the opening of the 17,23-oxide bridge in jervine gained support from the fact that both I and II upon dehydrogenation yielded 2-ethyl-5-methyl-3-hydroxypyridine.[6] Such a ring opening requires the introduction of a new olefinic double bond or its equivalent, but no information is afforded as to the degree or types of unsaturation in isojervine. To date, three structures have been postulated for isojervine on the basis of the existing information. First, Jacobs and Sato[6] postulated the isomerization conditions might have aromatized ring B. Second, Wintersteiner[7] proposed that rings C and D could have changed size or that a cyclopropane ring may be present. The final suggestion for isojervine was that a new carbon–carbon double bond could have been introduced at position 17,20 to form a conjugated dienone.[8] However, on the basis of the ultraviolet spectral characteristics reported above, all three structures would, at best, need to be considered only tentatively. Furthermore, the dramatic change in the ultraviolet spectrum in going from jervine to isojervine made the latter material worthy of further study.

As mentioned earlier, isojervine readily formed a triacetate (di-O,N). On acid-catalyzed hydrolysis, this material was transformed into an O,N-diacetate; with basic saponification, the triacetate was converted back to the N-acetate. This selective removal of the O-acetyl groups indicated that the two hydroxyls differ in steric surroundings and it would appear that the more readily removed ester should be the one associated with the original C-3 hydroxyl group. In performing the basic saponification, great care had to be taken to exclude all oxygen, since otherwise the product underwent isomerization.

It had been reported by earlier workers[9] that isojervine was resistant to hydrogenation in ethanol. However, if the material is first recrystallized from ethanol, it can be readily hydrogenated in this solvent to form a dihydro derivative (III). The dihydroisojervine had a maximum in the ultraviolet at 238 mμ (ε 9000) and such an absorption indicated the presence of an α,β-unsaturated ketone in dihydroisojervine. Furthermore, the position of the maximum clearly indicated that the unsaturated ketone was different from that originally present in jervine (λ_{max} 252 mμ).

Dihydroisojervine triacetate (III, di-O,N triacetate) upon reduction with lithium and ammonia in the presence of methanol yielded N-acetyltetrahydroisojervinol (IV). This same material was obtained directly from jervine *via* the well known α-dihydrojervine[9,10] which is a jervanedienetriol formed by the action of sodium and ethanol on jervine. Hydrogenation of the Δ⁵-double bond in the N-acetyl derivative yielded N-acetyltetrahydroisojervinol. This result clearly established that isojervine possesses the carbon skeleton of jervine but with the ether bridge open. The placement of the unsaturated centers in the nucleus is not supplied by this correlation evidence.



The formation of N-acetyltetrahydroisojervinol (IV), a compound which contains only one double bond, by first hydrogenation of one unsaturated center and then by chemical reduction of a second unsaturated center, showed that in isojervine there were three unsaturated centers. To make certain that all three unsaturated centers were olefinic double bonds and that no cyclopropane ring was present which could have undergone hydrogenolysis, isojervine triacetate was allowed to react with perbenzoic acid. A diepoxide was obtained which still retained the ultraviolet maximum at 238 mμ; under prolonged reaction, a total of 2.45 moles of peracid was consumed by II. These results established the presence of three olefinic double bonds, one of which was conjugated with the ring-C carbonyl group. The n.m.r. spectrum of II showed that only one vinyl proton (4.57 τ) was present and this sole trisubstituted bond most likely was the Δ⁵-bond of the original jervine nucleus.

The presence of the 3β-hydroxy-Δ⁵-ene system in isojervine was established by Oppenauer oxidation of the N-acetylisojervine followed by acetylation to Δ⁴-iso-

(6) W. A. Jacobs, L. C. Craig, and G. I. Lavin, *J. Biol. Chem.*, **141**, 51 (1941); W. A. Jacobs and Y. Sato, *ibid.*, **181**, 55 (1949).

(7) O. Wintersteiner, "Festschrift," Authur Stoll, Birkhauser, Basel, 1957, p. 166.

(8) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p. 872.

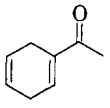
(9) W. A. Jacobs and C. F. Huebner, *J. Biol. Chem.*, **170**, 635 (1947).

(10) B. M. Iselin, M. Moore, and O. Wintersteiner, *J. Am. Chem. Soc.* **78**, 403 (1956), footnote 4.

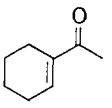
jervone diacetate (V). This same material was obtained from N-acetyl-Δ^4-jervone (VI)[9] by treatment with ethanolic hydrochloric acid (isojervine formation conditions) followed by acetylation with acetic anhydride. The ability to transform N-acetyl-Δ^4-jervone into an isojervine type of molecule showed that the Δ^5-double bond present in jervine was also present in isojervine and that it was not involved in the acid-catalyzed rearrangement.

Hydrogenation of Δ^4-isojervone diacetate yielded a dihydro derivative (VII) which also possessed a maximum at 238 mμ. If the ultraviolet spectrum of cholestenone is subtracted from the spectrum of V, a residual maximum is found at 238 mμ, thus showing the presence of two separate chromophores in Δ^4-isojervone diacetate. The finding of the same ultraviolet spectrum in VII as well as in the dihydro derivative obtained by hydrogenation of isojervine indicated that reduction of the Δ^5-ene system in V had occurred and the material was a 5,6-dihydro derivative.

Of the two remaining tetrasubstituted double bonds, one must be conjugated with the carbonyl group in ring C and thus located at the 8:9-, the 13:14-, or the original 13:17a-position. The shift of the ultraviolet spectrum from 252 mμ in jervine to 238 mμ in isojervine diepoxide, 5,6-dihydroisojervine, and in Δ^4-isojervone showed that the conjugated double bond must occupy a position in isojervine which is different from that in jervine. The hypsochromic shift of 14 mμ is too large to be accommodated by only a change from an *exo* to an *endo* cyclic position, but this feature in conjunction with the migration of the double bond into a five-membered ring to form a cyclopentenone, as would be found by a shift to the 8:9- or 13:14-position, could account for the shift. Since the maximum does not appear at the normal position of 238 mμ until the 5,6-double bond is removed, it is imperative that the enone system in isojervine be associated in some way with the 5,6-position. The hypsochromic shift of the maximum in shifting from 250 mμ to 238 mμ and the intensification of the maximum from 3600 to 9000 in going from isojervine to its 5,6-dihydro derivative has an analogy in the 2,5-dihydroacetophenone (VIII) to acetylcyclohexene (IX) transformation. The maximum of VIII



VIII



IX

is at 245 mμ (ϵ 4000) while IX has a maximum at the predicted position of 232 mμ (ϵ 12,500). This effect of a nonconjugated double bond has been attributed to a nonclassical interaction in the excited electronic state of VIII in which the electrons of the nonconjugated double bond are involved.[11] A similar interaction in isojervine is only possible if the double bond conjugated with the carbonyl group is located at the 8,9-position. In line with this location of the double bond was the formation of 7-ketoisojervine triacetate by oxidation of the triacetate of isojervine. The product possessed a triple maximum in the ultraviolet at 235, 270, and 325 mμ. A similar $\Delta^{5,8(9)}$-7,11-dienedione chromophore in the tetracyclic triterpenes[12] is known to absorb at 275 mμ.

The remaining tetrasubstituted double bond must be located at the 17,17a- or 17,20-position since in the n.m.r. spectrum of isojervine there is an absorption band at 8.16 τ which is due to a methyl group on a double bond. The 17,17a-position is favored as the most likely site based on mechanistic considerations pertaining to the formation of both α-dihydrojervinol and isojervine.[13] With such a location of a bond it is quite surprising that isojervine is stable to acid, since it might be expected that the 17,17a-double bond would desire to move into conjugation with the C-11 carbonyl group. However, Dreiding models indicate that a 8,9:13,17a dienone system is more strained than the related 8,9:17,17a system and such strain may well inhibit bond migration.

In this discussion of the chemistry of isojervine and its tetrahydro derivative, no attempt has been made to depict the stereochemistry of the various asymmetric centers associated with ring C, since it has previously been shown[14] that in the related B-norsteroid system the usual conformational concepts fail to hold.

Experimental

The melting points were taken on a Köfler block and are uncorrected. The rotational measurements, unless otherwise stated, were taken in chloroform solution in a 1-dm. tube. The ultraviolet spectra were measured in methanol or ethanol unless otherwise stated. N.m.r. measurements were taken in deuteriochloroform using tetramethylsilane as an internal standard. Woelm neutral alumina (activity I) was used for chromatography. The microanalyses were performed by the Microanalytical Laboratory, Department of Chemistry, University of California.

Isojervine (II). Method 1.—A mixture of 150 g. (0.357 mole) of jervine, 5.5 l. of ethanol, 4.0 l. of water, and 410 ml. of concentrated hydrochloric acid was heated under reflux for 24 hr. The solution was cooled at 0° for 12 hr. and then filtered to remove any recovered jervine hydrochloride. The filtrate was evaporated under reduced pressure to a volume of 4 l., extracted with chloroform (10 × 500 ml.), and the combined extracts filtered through anhydrous magnesium sulfate. The dried chloroform solution was made basic with gaseous ammonia and concentrated to yield crystalline isojervine, yield 102 g. (68%, m.p. 120–125°.

Occasionally, a precipitate of isojervine hydrochloride was formed during the extraction. This solid was filtered, dissolved in hot aqueous methanol, the solution made basic with ammonia, and cooled to afford isojervine.

Method 2.—It was found that a similar product in equivalent yield was obtained by omitting the ethanol and refluxing the aqueous acid suspension until all the jervine had dissolved, m.p. 124–126°, $[\alpha]_D$ −32.5° (*c* 1.0, EtOH).

Isojervine Hydrochloride.—A portion of the isojervine hydrochloride formed in the extracts of method 1 was recrystallized from ethanol to give white needles, m.p. 240.0–242.0° dec., infrared maxima, 2.92, 5.9, 5.95, and 6.10 μ (KBr).

Anal. Calcd. for $C_{27}H_{40}O_3NCl$ (462.06): C, 70.18; H, 8.79; N, 3.03; Cl, 7.67. Found: C, 70.05; H, 8.80; N, 3.23; Cl, 7.58.

N-Acetylisojervine.—A mixture of 0.5 g. (1.18 mmoles) of isojervine (from benzene after filtration of hot solution through Florex XXS) and 5 ml. of acetic anhydride was heated on a steam bath until solution was complete. The solution was poured into

(11) E. R. H. Jones, G. H. Mansfield, and M. C. Whiting, *J. Chem. Soc.*, 4073 (1956).

(12) W. Voser, M. Montavon, Hs. H. Günthard, O. Jeger, and L. Ruzicka, *Helv. Chim. Acta*, **33**, 1893 (1950).

(13) Dr. O. Wintersteiner of the Squibb Institute and Prof. T. Masamune of Hokkaido University, Sapporo, Japan, have informed us that they also have established the same structure for isojervine. Their results have now been published in *Tetrahedron Letters*, 795 (1962) and *Bull. Chem. Soc. Japan*, **35**, 1749 (1962), respectively. After submission of this manuscript, R. Ikan and H. Conroy [*Proc. Israel Chem. Soc.*, **11A**, 33 (1962)] also postulated a similar formula.

(14) W. G. Dauben, *Bull. soc. chim. France*, 1338 (1960).

water and an oil separated which crystallized upon standing. The solid was recrystallized twice from acetone–ligroin, yield 250 mg. (45%), m.p. 207–208°, $[\alpha]_D$ +47° (*c* 1.74, EtOH), λ_{max} 245 mμ (ε 3550), 330 mμ (ε 160), infrared maxima, 5.93 and 6.13 μ (Nujol). The literature values[9] are m.p. 202–203°, $[\alpha]_D$ +44°.

Isojervine Triacetate (Di-O,N).—A mixture of 3.0 g. (7.05 mmoles) of isojervine and 25 ml. of acetic anhydride was heated under reflux for 1 hr. The solution was poured into water and a semicrystalline mass formed. The solid was filtered, washed with water, and recrystallized twice from benzene–petroleum ether; yield, 2.79 g. (72%), m.p. 190–191°, $[\alpha]_D$ −61° (*c* 1, EtOH), infrared maxima (CS_2), 5.78 5.92, and 6.08 μ, $\lambda_{max}^{heptane}$ 242 mμ (ε 3500), 322 mμ (ε 140), λ_{max}^{MeOH} inflection 245 mμ (ε 3600), 330 mμ (ε 160). The literature value[9] is m.p. 192–193°.

Acid Hydrolysis of Isojervine Triacetate.—A mixture of 180 mg. (0.33 mmole) of isojervine triacetate and 20 ml. of methanol containing 0.4 ml. of concentrated hydrochloric acid was heated under reflux for 3 hr. The reaction mixture was poured into water and the solid which formed immediately was filtered and washed. The light yellow material was recrystallized three times from dilute methanol to yield 49 mg. of isojervine diacetate (O,N), m.p. 261–263°. The mother liquors gave an additional 25 mg. of material, total yield, 74 mg. (45%), $[\alpha]_D$ +43° (*c* 1.3), infrared maxima ($CHCl_3$), 5.82, 5.95, and 6.12 μ, λ_{max} inflection at 245 mμ (ε 3600), 330 mμ (ε 170).

Anal. Calcd. for $C_{31}H_{43}O_5N$ (509.66): C, 73.05; H, 8.50; N, 2.75; acetyl, 16.9. Found: C, 72.85; H, 8.45; N, 2.7; acetyl, 14.7.

Alkaline Saponification of Isojervine Triacetate.—To 180 mg. (0.33 mmole) of isojervine triacetate which had been swept with oxygen-free nitrogen (prepared by passing nitrogen through copper turnings at 300°) for 24 hr. was added 50 ml. of methanol in which 0.2 g. (8.7 mmoles) of sodium had been dissolved in a nitrogen atmosphere and the reaction mixture was refluxed for 90 min. Aqueous hydrochloric acid (1:1) was added until the excess base was neutralized (congo red end point), the solution diluted with water, and the mixture extracted with ether. The ethereal extract was evaporated and the partially crystallized oil was recrystallized twice from acetone–ligroin to yield 50 mg. (33%) of N-acetylisojervine, m.p. 206–207°, no depression upon admixture with authentic sample.

5,6-Dihydroisojervine (III).—A solution of 1.0 g. (2.34 mmoles) of isojervine (recrystallized from dilute ethanol) in ethanol was hydrogenated over 200 mg. of prereduced platinum oxide at atmospheric pressure. The catalyst was filtered, the filtrate concentrated under reduced pressure, and the residue crystallized from ethanol; yield 900 mg. (90%), m.p. 159.0–161.0°, $[\alpha]_D$ −16° (*c* 1, EtOH), infrared a maxima (Nujol), 5.95 and 6.20 μ, λ_{max} 238 mμ (ε 9000).

Anal. Calcd. for $C_{27}H_{41}O_3N$ (427.61): C, 75.83; H, 9.66; N, 3.28; neut. equiv., 427. Found: C, 75.72; H, 9.62; N, 3.35; neut. equiv., 432.

5,6-Dihydroisojervine Triacetate.—A mixture of 130 mg. (0.32 mmole) of 5,6-dihydroisojervine and 10 ml. of acetic anhydride was heated under reflux for 45 min. and the solution processed in the usual manner. The resulting light yellow solid was recrystallized twice from dilute methanol to yield 100 mg. (58%) of product, m.p. 213.5–214.5°, $[\alpha]_D$ +37° (*c* 1, EtOH), infrared maxima (CS_2), 5.80, 5.95, and 6.10 μ, $\lambda_{max}^{heptane}$ 232 mμ (ε 10,500), 321 mμ (ε 130), λ_{max}^{MeOH} 238 mμ (ε 10,750), 330 mμ (ε 145).

Anal. Calcd. for $C_{33}H_{47}O_6N$ (553.71): 71.58; H, 8.56; N, 2.33. Found: C, 71.47; H, 8.15; N, 2.47.

The triacetate also could be prepared in 50% yield by direct hydrogenation of isojervine triacetate in acetic acid.

N-Acetyltetrahydroisojervinol (IV). (a) From 5,6-Dihydroisojervine Triacetate.—Lithium wire (500 mg.) was added to liquid ammonia (100 ml.) and the mixture stirred until all the lithium had dissolved. To the blue solution there was added 1.0 g. (1.8 mmoles) of 5,6-dihydroisojervine triacetate in 25 ml. of dioxane and the solution stirred for 1 hr. Methanol (7 ml.) was added to destroy the blue color and lithium was again added as necessary (several 100-mg. portions) until the blue color persisted for at least 30 min. Ammonium chloride (1 g.) was added in small portions to destroy the unchanged lithium and the solution allowed to stand at room temperature for 12 hr. The residue remaining was extracted with boiling benzene (5 × 50 ml.) and then stirred with benzene for 4 hr. The combined benzene extracts were washed with water until neutral, the solution dried, and the benzene evaporated under reduced pressure. The residual white powder (1 g.) was recrystallized twice from toluene, yield 0.473 g. (55.5%), m.p. 135.5–136.5°, $[\alpha]_D$ −9.8°, infrared maxima (KBr), 2.95 and 6.20 μ, no selective absorption in the ultraviolet.

Anal. Calcd. for $C_{29}H_{47}O_4N$ (473.67): C, 73.53; H, 10.00; N, 2.96. Found: C, 73.67; H, 9.66; N, 3.28.

The product was resistant to oxidation by manganese dioxide showing the absence of an allyl alcohol grouping.

(b) From N-Acetyl-α-dihydrojervinol.—A solution of 200 mg. (0.42 mmole) of N-acetyl-α-dihydrojervinol ($[\alpha]_D$ −43°)[9] in 50 ml. of ethanol was hydrogenated over 200 mg. of platinum oxide at 45 p.s.i. for 12 hr. The catalyst was removed by filtration through Celite, the solvent removed under reduced pressure, and the residual oil crystallized from toluene; yield 0.180 g. (90%), m.p. 135.0–136.5°, no depression upon admixture with product prepared from isojervine. The infrared spectra of the two materials in potassium bromide were identical.

The n.m.r. spectrum of N-acetyl-α-dihydrojervinol had absorption at 4.6 τ (C-6 vinyl H), 7.96 τ (N-acetyl), 8.16 τ (vinyl CH_3), and at 8.99 τ (C-19-methyl). The n.m.r. spectrum of N-acetyltetrahydroisojervinol has maxima at 7.94 τ (N-acetyl), 8.20 τ (vinyl CH_3), and at 9.23 τ (C-19 CH_3). The loss of the vinyl proton absorption at 4.6 τ showed that the 5,6-double bond had been hydrogenated and the shift of the C-19 CH_3 absorption 0.24 p.p.m. is in agreement with this conclusion.

Isojervine Triacetate Diepoxide.—To a solution of 200 mg. (0.36 mmole) of isojervine triacetate in 25 ml. of dry benzene there was added 25 ml. of 0.42 *M* perbenzoic acid solution in benzene. The reaction mixture was allowed to stand at room temperature for 3 hr. and then the excess peracid was decomposed with aqueous acetic acid, sodium iodide, and thiosulfate solution. The benzene layer was separated, washed with sodium bicarbonate solution, water, and dried. The benzene was removed under reduced pressure. The yellow oily residue was triturated with petroleum ether to remove any methyl benzoate remaining from the preparation of the perbenzoic acid, and the resulting oil crystallized from aqueous methanol. The solid was recrystallized two times from the same solvent; yield 50 mg. (24%), m.p. 195.5–196.5°, $[\alpha]_D$ −8° (*c* 3.15), λ_{max} 237 mμ (ε 9050) and 305 mμ (ε 75), infrared maxima, 5.82, 5.95, and 6.14 μ.

Anal. Calcd. for $C_{33}H_{45}O_8N$ (583.70): C, 67.90; H, 7.77; N, 2.40. Found: C, 68.12; H, 7.85; N, 2.50.

A quantitative titration of isojervine triacetate with a chloroform solution of perbenzoic acid for 24 hr. showed an uptake of 2.45 moles of perbenzoic acid. A similar titration of 5,6-dihydroisojervine triacetate for 72 hr. consumed 1.55 moles of perbenzoic acid.

Δ⁴-Isojervone Diacetate (V). (a) From N-Acetylisojervine.—To a solution of 800 mg. (1.7 mmoles) of N-acetylisojervine in 20 ml. of dry benzene was added 15 ml. of cyclohexanone and 2 g. of aluminum *t*-butoxide in 15 ml. of dry benzene and the solution heated under reflux for 12 hr. An excess of dilute sulfuric acid was added and the benzene layer separated. The benzene solution was dried and heated under reduced pressure to remove the benzene and most of the cyclohexanone. The yellow residue was dissolved in 10 ml. of acetic anhydride and 10 ml. of pyridine and the solution allowed to stand for 18 hr. at room temperature. Dilute hydrochloric acid was added and the mixture extracted with ether. The combined ether extracts were washed with sodium bicarbonate solution, water, dried, and the solvent removed. The residue was chromatographed on alumina and the ether–methanol (199:1) fractions gave light yellow crystals which were recrystallized from acetone–ligroin; yield 250 mg. (29%), m.p. 210–212°, $[\alpha]_D$ +212° (*c* 2.5), λ_{max} 232 mμ (ε 21,450) and 320 mμ (ε 130), infrared maxima ($CHCl_3$), 5.85, 5.95, 6.03, and 6.11 μ.

Anal. Calcd. for $C_{31}H_{41}O_5N$ (507.65): C, 73.35; H, 8.14; N, 2.76. Found: C, 73.47; H, 8.35; N, 2.87.

(b) From Δ⁴-Jervone (VI).—Δ⁴-Jervone[9] (500 mg., 1.18 mmoles) was treated with aqueous ethanolic hydrochloric acid under the conditions used for the preparation of isojervine. The crude Δ⁴-isojervine was boiled briefly with 10 ml. of acetic anhydride and the resulting N-acetyl-Δ⁴-isojervone was recrystallized from aqueous methanol; yield 75 mg. (16.5%), m.p. 234–236°, $[\alpha]_D$ +190°. The solid was dissolved in acetic anhydride and pyridine, the solution allowed to stand overnight at room temperature, and the product isolated in the usual fashion. The crude material diacetate was recrystallized from acetone–ligroin, m.p. 210–212°, no depression with diacetate prepared from isojervone.

4,5-Dihydroisojervone Diacetate.—To 77 mg. of platinum oxide prereduced in 20 ml. of ethanol was added 231 mg. (0.44 mmole) of Δ^4-isojervone diacetate in 20 ml. of ethanol and the mixture was hydrogenated until one mole equivalent of hydrogen had been adsorbed (10 min.). The catalyst was removed by filtration, the solvent evaporated under reduced pressure, and the yellow oil crystallized from dilute methanol. The material was recrystallized first from the same solvent and then from dilute acetone; yield 150 mg. (67%), m.p. 202.5–204.0°, $[\alpha]_D$ +71° (*c* 2.25).

Anal. Calcd. for $C_{31}H_{43}O_5N$ (509.66): C, 73.05; H, 8.50. Found: C, 73.25; H, 8.51.

Stereospecific Protonation of 4a-Methyl-1,3,9-triphenyl-4a*H*-fluorene[1]

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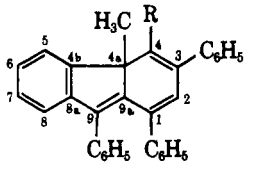
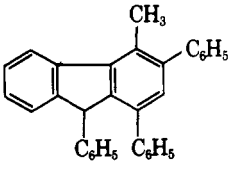
Received October 5, 1962

It is shown that 4a-methyl-1,3,9-triphenyl-4a*H*-fluorene (Ia) forms a carbonium ion in acid media. The protonation is stereospecific and takes place at the 4-position.

In earlier papers of this series[2,3] it was shown that the lower-melting hydrocarbon obtained from the polyphosphoric acid-catalyzed condensation of acetophenone is 4a-methyl-1,3,9-triphenyl-4a*H*-fluorene (Ia). It was also established that this hydrocarbon, Ia, is isomerized by hydrogen bromide in glacial acetic acid to 4-methyl-1,3,9-triphenylfluorene (II).



Ia. R = H
b. R = D
c. R = Br



II

Compound Ia is very soluble in strong acids, such as sulfuric acid, trifluoroacetic acid and fluoroboric–acetic acid, giving intense blue-green solutions. The color is due to the presence of a carbonium ion. The hydrocarbon, Ia, can be quantitatively regenerated by the addition of water to solutions of the carbonium ion. The perchlorate, fluoroborate, and bromide have been isolated. The possibility that the color is due to the presence of a free radical was eliminated by the electron-spin resonance spectrum of Ia in concentrated sulfuric acid; no paramagnetism was detected.[4]

With the aid of proton magnetic resonance spectroscopy it was shown that protonation of Ia is a stereospecific process and that attack takes place at the 4-position. The proton magnetic resonance spectrum of Ia in deuteriochloroform (Figure 1) shows an *AB* pattern at τ, 3.33, J = 1.5 c.p.s. and $\delta\nu$ = 3.0 c.p.s. which is due to the vinyl protons at the 2- and 4-positions. The methyl group gives a singlet at τ, 8.31. The aromatic region of the spectrum is very complex, covering a range of 48 c.p.s. (τ, 2.37 to τ, 3.18). The spectrum (Figure 2) of Ia in trifluoroacetic acid, which gives the same spectrum as does the perchlorate salt of Ia in trifluoroacetic acid, shows an *AB* pattern centered at τ, 6.40, J = 18 c.p.s., $\delta\nu$ = 78 c.p.s. This pattern can only be explained in terms of non-equivalent methylene protons.[5] A singlet due to the protons of the methyl group appears at τ, 8.27. The relative intensity of the *AB* pattern to the methyl group absorption is 2:3. The aromatic absorption is shifted to lower field relative to the hydrocarbon, Ia, and it covers a range of 65 c.p.s. (τ, 1.67 to τ, 2.75).

The methylene group formed by the protonation of Ia has been assigned to the 4-position. A methylene group at the 4-position is adjacent to an asymmetric center which causes the methylene protons to be in different chemical environments. These protons are nonequivalent and will appear as an *AB* pattern in the proton magnetic resonance spectrum. If protonation took place at the 2-position, the nonequivalency of the resulting methylene protons in the carbonium ion (IV) would be caused by the asymmetric center three carbon atoms away. It does not seem likely that in such a case the effect would be as great as was observed—*i.e.*, J = 18 c.p.s. and $\delta\nu$ = 78 c.p.s. The absence of any absorption in the vinyl proton region of the proton magnetic resonance spectrum of the carbonium ion is also sig-

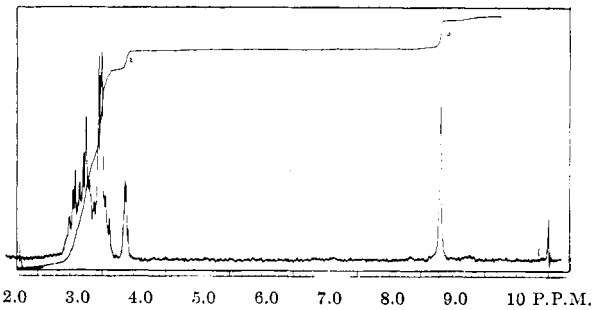


Figure 1

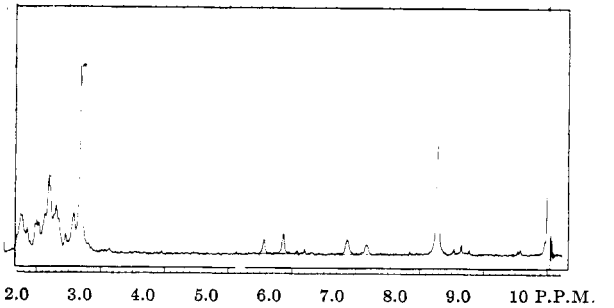


Figure 2

(1) Grateful acknowledgment is made of partial support of this work by a grant from the National Science Foundation (G-6223) and of a Fellowship (1960–1962) to H. W. M. provided by the Phillips Petroleum Company.

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(4) R. W. Bush, thesis, Doctor of Philosophy, University of Illinois, 1960.

(5) L. M. Jackman, "Nuclear Magnetic Resonance Spectroscopy," Pergamon Press, New York, N. Y., 1959, p. 85.