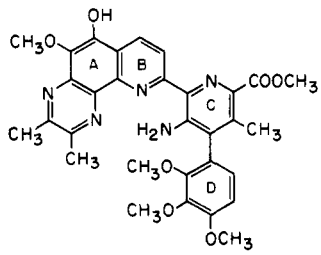
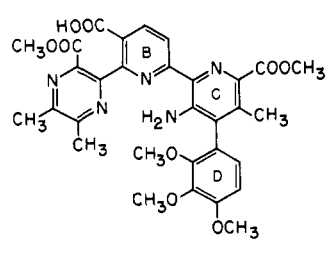
carboxylated very readily to pyridine-2,5-dicarboxylic acid, m.p. 256–258°,[9] identical with an authentic sample. When the product from hydrogenation of streptonigrinic acid (IV, R = H) over reduced platinum oxide in aqueous ethanolic hydrochloric acid was oxidized with alkaline permanganate, a crude acidic material was obtained from which, by distillation from soda lime, 3-amino-5-methylpyridine [mol. wt. 108; n.m.r. spectrum 7.83 τ (CH_3), 5.90 τ (NH_2), 3.20 τ (H at C-4), 2.08 τ (H at C-2); ultraviolet spectrum: 234, 300 mμ (MeOH)] was produced. Since streptonigrinic acid must contain two *adjacent* carboxyl groups (originating from destruction of a quinonoid ring) and two *adjacent* hydrogen atoms [n.m.r. spectrum of the ester (IV, R = CH_3): quartet, 1.06, 1.22, 1.64, 1.80 τ, the further degradations just detailed complete the proof of the structure (IV, R = H)].

When O-methylstreptonigric acid (III, R = H, R′ = CH_3), m.p. 205–207°, obtained by alkaline hydrolysis of the ester (III, R = R′ = CH_3), was oxidized by hot alkaline permanganate, 2,3,4-trimethoxybenzoic acid, m.p. 98–99°,[10] identical with an authentic sample, was obtained. The ester (III, R = R′ = CH_3) was converted by nitric acid–ether to the benzofuran derivative (VI), $C_{25}H_{22}O_9N_2$ (mol. wt. 494), m.p. 186–187°, whose formation demonstrates the contiguous positions of the amino and trimethoxyphenyl substituents. Further, the analogous O-trideuteriomethyl compound (III, R = CH_3, R′ = CD_3) *was converted by the same reagents to the identical benzofuran* (mol. wt. 494). The phenolic hydroxyl group of streptonigrin must therefore be in the 2 position of the phenyl ring D, and these facts complete the proof of the structure (III, R = R′ = H) for streptonigric acid.

It remains to choose among 12 possible nontautomeric arrangements of the quinonoid ring A. Streptonigrin cannot be a hydroxyquinonimine, since it gave a *non-acidic* derivative, $C_{27}H_{26}O_8N_4$ (mol. wt. 534), m.p. 230–232°, containing only *two* new O-methyl groups, even on long-continued treatment with dimethyl sulfate, acetone, and potassium carbonate. This dimethylstreptonigrin reacted readily with hydroxylamine to give a substance, m.p. 202–204°, which was reduced by sodium dithionite in aqueous alcohol to an easily oxidizable diamino compound. The latter was condensed with diacetyl to give the quinoxaline (VII), m.p. 260–262°, which was oxidized by potassium per-



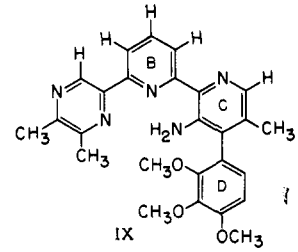
VII



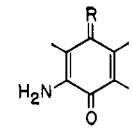
VIII

manganate in hot pyridine to the acid (VIII), m.p. 160–162° dec. [methyl ester, $C_{32}H_{33}O_9N_5$ (mol. wt. 631), m.p. 260–262°]. Hydrolysis with aqueous alcoholic potassium hydroxide gave the corresponding triacid, m.p. 193–195° dec., which was decarboxylated at 250° to the compound IX, $C_{26}H_{25}O_3N_5$ (mol. wt. 457), m.p. 192–194°. The nuclear magnetic resonance spectrum of IX possesses sharp singlets at 0.93 τ (H at C-2 in pyrazine ring), 1.98 (H at C-6 in pyridine ring C), and a typical ABC pattern ($J_{AB} \sim 2$ c.p.s., $J_{AC} = J_{BC} \sim 8$ c.p.s.)—1.35 + 1.38; 1.47 + 1.50; 1.72 +

(9) W. A. Jacobs and L. C. Craig, *J. Biol. Chem.*, **124**, 659 (1938).
(10) N. Rabjohn and A. Mendel, *J. Org. Chem.*, **21**, 218 (1956).



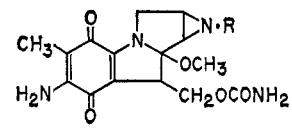
IX



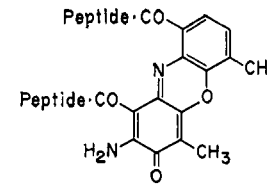
X

1.75; 1.85 + 1.88; 1.98 + 2.11 + 2.23[11]—for the three *adjacent* hydrogen atoms in the pyridine ring B. These observations complete the proof of the full structure I for streptonigrin.

The presence of the common structural unit X in the otherwise very differently constituted molecules of streptonigrin, mitomycin C (XI, R = H)[12] and porfiromycin (XI, R = CH_3),[12] and the actinomycins (XII),[13] taken with the observed loss of activity concomitant with replacement of the primary amino



XI



XII

group, is strongly suggestive of an intimate relationship between the aminoquinone structure X and the marked anticancer activity of all of these substances.[14]

Acknowledgment.—We wish to acknowledge the cooperation of Drs. James A. McCloskey, P. Bommer, Claude Wintner, and R. L. Wagner in making many physical measurements, to express appreciation to the National Institutes of Health for generous support, and to thank Mr. John L. Davenport for his unfailing interest and encouragement.

(11) *Cf.* spectra 3D-14 and 3E-14 in K. B. Wiberg and B. J. Nist, "The Interpretation of NMR Spectra," W. A. Benjamin, Inc., New York, N. Y., 1962, pp. 184, 246.
(12) *Cf.* J. S. Webb, *et al.*, *J. Am. Chem. Soc.*, **84**, 3185, 3187 (1962).
(13) *Cf.* H. Brockmann, *Fortschr. Chem. Org. Naturstoffe*, **18**, 1 (1960).
(14) *Cf.* L. D. Hamilton, W. Fuller, and E. Reich, *Nature*, **198**, 538 (1963).

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RECEIVED JULY 10, 1963

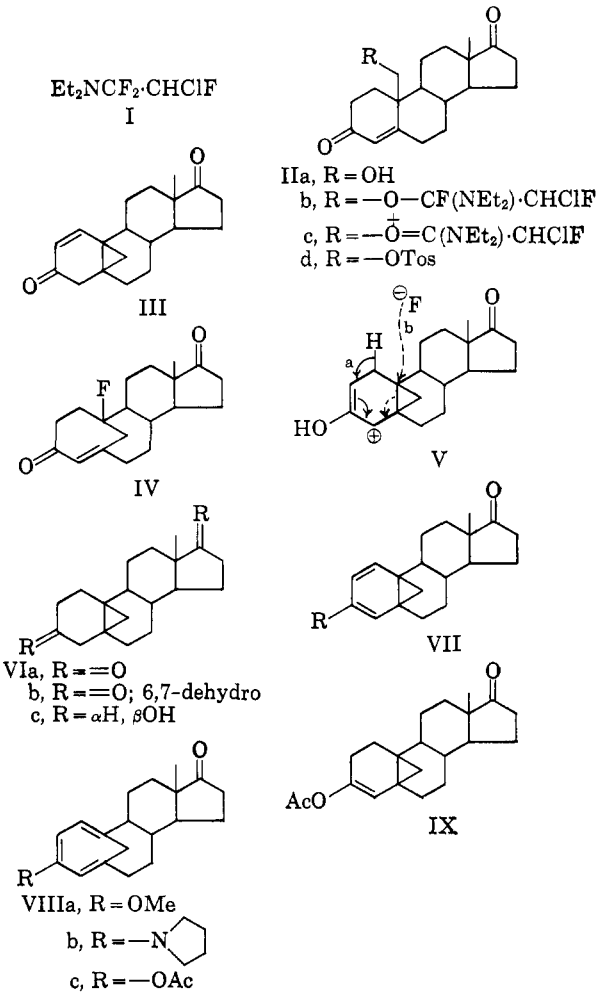
Studies of the Cycloheptatriene–Norcaradiene Isomerism in Some Novel Steroids

Sir:

We recently reported the reactions of steroidal alcohols with diethyl-[2-chloro-1,1,2-trifluoroethyl]-amine (I).[2] We have since examined closely the reactions of the fluoramine I with 19-hydroxyandrost-4-ene-3,17-dione (IIa).[3]

(1) This communication constitutes "Steroids CCXXXIX and Spectra and Stereochemistry VIII"; for "Steroids CCXXXVIII and Spectra and Stereochemistry VII," see A. D. Cross and I. T. Harrison, *J. Am. Chem. Soc.*, forthcoming publication.
(2) L. H. Knox, E. Velarde, S. Berger, D. Cuadriello, and A. D. Cross, *Tetrahedron Letters*, 1213 (1962).
(3) A. S. Meyer, *Experientia*, **11**, 99 (1955).

When a solution of the alcohol IIa and an excess of the amine I in dry acetonitrile was heated under reflux for 30 min. there were obtained 5β,19-cycloandrost-1-ene-3,17-dione (III) (47%), m.p. 173–175°, $[\alpha]_D$ +253°; λ_{max} 270–272 mμ (log ε 3.80); γ_{max} 3040, 1742, 1665, 1615, and 670 cm.$^{-1}$,[4] and the previously reported[2] 10β-fluoro-5,10-seco-5β-19-cycloandrost-4-ene-



3,17-dione (IV) (38%). In the n.m.r. spectrum[5] of III an AB quartet[6] at 340.0, 350.0, 432.1, and 442.1 c.p.s., J_{HH} 10.0 c.p.s., unsplit by further coupling, was indicative of C—CH=CH—CO, with the carbon γ to carbonyl bearing no hydrogens. Another two-proton quartet at 136.6, 155.1, 165.0, and 183.6 c.p.s., J_{HH} 18.5 c.p.s., was reminiscent of the C_4-methylene protons in 5β-substituted-3-ketones.[7] Doublets, at 21.9 and 70.6 c.p.s., J_{HH} 4.2 c.p.s., were assigned to two *geminal* methylene protons of an otherwise fully substituted cyclopropane ring.[8] Compounds III and IV presumably are formed by the mechanism: I + IIa → IIb → IIc → V → III (pathway a) or IV (pathway b), the incipient primary carbonium ion at C–19 undergoing an internal cyclization to the cation V.[9–11]

Catalytic hydrogenation of the enone III furnished the dione VIa, m.p. 136–137°, $[\alpha]_D$ +112°, indistinguishable from an authentic sample prepared by hydrogenation of the 6-dehydro derivative VIb.[12]

The tosylate IId with lithium in liquid ammonia[13] gave the diol VIc, m.p. 155–157°, $[\alpha]_D$ +56°, further oxidized to the dione VIa.

Eucarvone is known to undergo chemical transformations leading to carenone derivatives related to the enone III, but enol esters of eucarvone, which can exhibit cycloheptatriene–norcaradiene equilibria, have been shown to exist completely in the monocyclic form.[14–18] Molecular models[19] suggested that enolic derivatives of III might be less strained in the norcaradiene form VII than as the cycloheptatriene VIII. The enone III was converted (methanol-*p*-toluenesulfonic acid) to the enol ether VIIIa, m.p. 135–136°, $[\alpha]_D$ +246°, λ_{max} 256–258 mμ (log ε 3.76), ν_{max} 1742, 1630, 1600, 1515, 1164, 853, 702, 737, and 710 cm.$^{-1}$. Treatment of VIIIa with aqueous acid regenerated the enone III. With pyrrolidine and *p*-toluenesulfonic acid in benzene the enone III gave the enamine VIIIb, m.p. 203–205°, $[\alpha]_D$ +242°, λ_{max} 222 mμ (log ε 4.13), 282–284 mμ (log ε 3.91). The enol acetate VIIIc, m.p. 164–165°, $[\alpha]_D$ +202, λ_{max} 256–258 mμ (log ε 3.78), was prepared from the enone III with acetic anhydride, acetic acid, and *p*-toluenesulfonic acid. Catalytic hydrogenation of the cycloheptatrienyl acetate VIIIc furnished the norcarenyl acetate IX, m.p. 127–129°, $[\alpha]_D$ +102°, hydrolyzable to the ketone VIa.

N.m.r. spectra of the derivatives VIIIa–c have been obtained for polar and nonpolar solvents (including carbon tetrachloride and pyridine) and in *all* cases indicated the cycloheptatriene structure VIII with no detectable norcaradiene tautomer VII. The methyl ether VIIIa in deuteriochloroform showed methylene bridge proton resonances shifted downfield to 63.8 and 188.0 c.p.s., J_{HH} 10.0 c.p.s. The high value of J is incompatible with the continued presence of the cyclopropane protons.[20–22] However, this J value and the sub-

(4) Melting points are uncorrected. Optical rotations were determined for *ca.* 0.3% chloroform solutions, ultraviolet spectra were measured on ethanol solutions, and infrared spectra were obtained using potassium bromide disks. Satisfactory analyses were obtained for all new compounds.

(5) N.m.r. spectra were measured for 5–8% w./v. solutions of the steroid in deuteriochloroform containing tetramethylsilane (TMS) as an internal reference (0.0 c.p.s.). Chemical shifts, quoted as c.p.s. downfield from the TMS reference, are accurate to ±1 c.p.s., and coupling constants, J, expressed as c.p.s., are accurate to ±0.5 c.p.s. A. D. C. thanks the Universidad Nacional Autonoma de México and the University of Texas, Austin, for time on Varian A-60 spectrometers.

(6) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High-resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, p. 119.

(7) See footnote 1 for data on 5β-cyano-3-ketones.

(8) Earlier,[2] an n.m.r. study at high concentration was reported of an apparently homogeneous specimen of IV. The observation of a doublet at 22 c.p.s. was used in the structural assignment.[2] We became aware subsequently that this specimen was an approximately 50:50 mixture of III and IV, and that the doublet was in fact due to III.

(9) An analogous internal cyclization mechanism involving a primary radical at C-19 has been postulated.[10]

(10) D. H. R. Barton and J. M. Beaton, *J. Am. Chem. Soc.*, **84**, 199 (1962); **83**, 4083 (1961).

(11) This mechanism is preferred to that suggested earlier.[2]

(12) J. J. Bonet, H. Wehrli, and K. Schaffner, *Helv. Chim. Acta*, **45**, 2615 (1962); O. Halpern, unpublished results. We thank Drs. Schaffner and Halpern for authentic samples of VIa.

(13) *Cf.* G. Stork and J. Tsuji, *J. Am. Chem. Soc.*, **83**, 2783 (1961).

(14) E. J. Corey and H. J. Burke, *ibid.*, **76**, 5257 (1954); **78**, 174 (1956).

(15) E. J. Corey, H. J. Burke, and W. A. Remers, *ibid.*, **77**, 4941 (1955); **78**, 180 (1956).

(16) An enol ether from eucarvone existing as the norcaradiene tautomer was recently claimed,[17] but subsequently disproved.[18]

(17) K. Conrow, *J. Am. Chem. Soc.*, **82**, 5504 (1960).

(18) W. von E. Doering and M. R. Willcott, *Tetrahedron Letters*, **15**, 663 (1962).

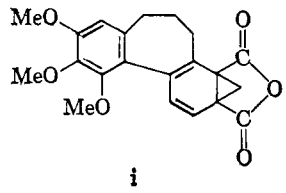
(19) A. S. Dreiding, *Helv. Chim. Acta*, **42**, 1339 (1959).

(20) H. M. Hutton and I. Schaefer, *Can. J. Chem.*, **41**, 684 (1963), find geminal couplings of cyclopropyl protons to be greatest when highly polar cyclopropyl substituents are present.

(21) For six 5,10-methylene steroids J = 4.8–6.1 c.p.s. for this geminal coupling: A. D. Cross, unpublished observations.

(22) J. Schreiber, W. Leimgruber, M. Pesaro, P. Schudel, T. Threlfall, and A. Eschenmoser, *Helv. Chim. Acta*, **44**, 540 (1961), have described a norcaradiene (i) with *geminal* cyclopropyl protons appearing in the n.m.r. spectrum as doublets, at 62 c.p.s. (8.97 τ) and 145 c.p.s. (7.58 τ), J = 4.5 c.p.s. The similarity of these chemical shift values to those of the enol derivatives (*vide supra*) does not, however, permit structural correlations to be made. Powerful extra long-range shielding, or deshielding, of *both geminal* protons due to the anhydride operates in i but is absent in VII and VIII. J-values constitute a sounder basis for comparisons.

stantial downfield shift of one resonance are in accord with structure VIIIa where the methylene is doubly allylic. From models[19] it is apparent that the methylene proton resonating at 63.8 c.p.s. is shielded by the 2,3-double bond in VIIIa where ring A cannot be planar.



i

That the enol derivatives are represented structurally by VIIIa–c, and are not resonance hybrids of which structures VII and VIII represent contributing forms, is further evidenced by the consistency of J values (10 c.p.s.) for the geminal cyclopropyl protons in VIIIc, *irrespective* of the solvent polarity.

The action of the fluoramine on other tetracyclic and bicyclic alcohols will be the subject of future communications.

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RECEIVED MAY 13, 1963

BOOK REVIEWS

Traité de Biochimie Générale. Tome II. Les Agents des Synthèses et des Dégradations Biochimiques. Premier Fascicule. Vitamines, Oligoeléments, Hormones. By M. JAVILLIER, M. POLONOVSKI, M. FLORKIN, P. BOULANGER, M. LEMOIGNE, J. ROCHE, and R. WURMSER. Masson et Cie, 120, Boulevard Saint-Germain, Paris VI, France. 1962. 700 pp. 17.5 × 25.5 cm. Price, broché, 140 NF.; cartonné toile, 155 NF.

This is the third volume of a series of six, comprising this "Traité de Biochimie Générale." The first two volumes dealt with the chemical composition of organisms and appeared in 1959. The present third volume is the first of two parts covering the agents of biochemical syntheses and degradations and is limited to vitamins, trace-elements, and hormones, while the second part, which will appear shortly, will cover enzymes. Volumes 5 and 6 will discuss the biochemical processes and their coordinations, and are expected some time in 1963.

Part I deals with Vitamins. The first chapter covers vitamins A_1 and A_2 and represents a very good summary of the state of our knowledge in this field. Chapter II presents vitamins D in the same comprehensive way. Chapter III describes vitamins R (tocopherols) while Chapter IV covers the vitamins K.

The first 130 pages are therefore devoted only to the fat-soluble vitamins. Pages 131–372 discuss the water-soluble vitamins. Here again, a chapter is reserved for each kind, including vitamin B_1 (thiamine), vitamin B_2 (riboflavin), vitamin PP (niacinamide), vitamin B_6 (pyridoxine, biotine, pentothenic acid, inositol, thioctic and lipoic acid, folic acid), vitamin B_{12}, vitamin C or ascorbic acid, and vitamin P.

There is even an appendix on "Pteridines" in which the subject is treated in much the same way as a regular chapter on the more clearly defined vitamins. While no attempt is made to exhaust any of these subjects in depth, a great amount of effort is made throughout the book to cover at least adequately every subject which could be considered as coming under the official heading, "Vitamins."

Part II of the book, which in fact covers only 55 pages, describes the trace elements. The treatment here is quite different. Most of this part concerns the experimental determination of these trace elements in green plants, in animals, and in various organisms, while only a few pages are devoted to general and more specific roles played by these elements in the life processes.

The third part, pages 439–637, describes hormones in four chapters and the first one deals with phyto hormones like the gibberrelins. Chapter II, in two parts, discusses the hormones of the vertebrates, the first part covering the peptide hormones and the second part the hormones which are derived from amino acids, such as serotinin, adrenalin, thyroxine, etc. Chapter III discusses the sterol hormones while Chapter IV, the last and shortest of the book, describes the hormones of the arthropodes.

After spending so much time to cover so adequately the vitamins, one has the feeling that no attempt was made to cover as adequately the fields on trace elements and on hormones. This is especially true of the hormones where the amount of knowledge available today is very large indeed, but the coverage is sparse, resulting in a feeling of improper balance between the three parts of the book. One would like to see a much more thorough treatment of the peptide hormones. It is true, however, that the volume to come covering enzymes will deal with subjects which are closely related to peptide hormones. However, in the steroid hormone field, one would expect to see at least a brief mention of some of the highly potent corticoid and progestational hormones used in therapy today, even if these are mostly synthetic steroids. The very fact that they are generally more potent than the naturally occurring steroids and have become so important to the modern treatment of many metabolic diseases would seem to justify their coverage in this book.

However, as is often the case in French textbooks, this one is highly readable, clear, and the presentation is very clear and systematic. The tables of contents make it relatively easy to find what is to be found in the book, although, especially in the hormone field, many valuable data could have been added. Fortunately, there is a good author index and a good subject index which make this book all the more valuable as a source of general reference in the covered fields.

Summarizing, this edition of the "Traité de Biochimie Générale" is still in the very high tradition of the French scientific publishers and certainly has its place between the long comprehensive treatment of the more limited fields and the short but broad coverage of text books.

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Adsorption and Collective Paramagnetism. By PIERCE W. SELWOOD, University of California, Santa Barbara, Calif. Academic Press, Inc., 111 Fifth Avenue, New York 3, N. Y. 1962. ix + 189 pp. 15.5 × 23.5 cm. Price, $7.50.

In the study of heterogeneous catalysis, a variety of experimental techniques has produced a variety of interesting results. In particular, the study of the adsorption of gases has proceeded to such a great extent that it has become a self-sufficient field by itself. In fact, the most successful studies of adsorption often have only a secondary application to catalysis itself; for example, the estimation of surface area by nitrogen adsorption (the BET method) is important to catalysis, but has many applications to systems that are not catalysis, such as carbon blacks.

The problem is that the simple measurement of adsorption gives little information as to the state or chemical nature of the adsorbed species; for that reason collateral studies, such as infrared spectra, electric conductivity, and electron emission potentials have been applied to catalysts in the presence of adsorbed gases.

One of the most successful and promising of these techniques is described at length in this monograph. Relatively small particles, typical of supported catalysts, that would be ferromagnetic in the bulk phase, often exhibit a species of paramagnetism. If a particle contains n atoms of individual moment μ these can produce a total moment $n\mu$ that interacts with similar particles. This particle–particle interaction is not ferromagnetic, as it would be in the bulk phase, because the relatively large distance between particles reduces the interaction energy between them.

Because of complications, notably the heterogeneity in size of the particles, the treatment of systems of this type is not as simple as, say, the paramagnetism of a gas, but the author is able to present a successful treatment of the problem. When this treatment is then applied to the same catalyst, after the chemisorption of a gas such as hydrogen, a powerful tool for the study of catalyst–substrate interaction is provided.

This book is particularly useful in that the complete details of the procedure are elaborated; it gives both the theoretical back-