6.59). Treatment of IVa with potassium hydroxide in methanol followed by acetylation yielded 11β,12β-oxido-Δ^4-pregnene-21-ol-3,20-dione acetate (III), m.p. 172–173°; $[\alpha]^{CHCl_3}D$ +192°; $\lambda_{max.}^{CH_3OH}$ 238.5 mμ (17,400); $\lambda_{max.}^{Nujol}$ 5.72, 5.80, 5.99, 6.17 μ (C, 71.68; H, 7.70). Reaction of the 11β,12β-oxide III with hydrogen chloride in organic solvents[4b] produced 12α-chlorocorticosterone acetate, IVb (R = CH_3CO), m.p. 228–233°; $[\alpha]^{CHCl_3}D$ +179°; $\lambda_{max.}^{CH_3OH}$ 240 mμ (15,600); $\lambda_{max.}^{Nujol}$ 2.87, 5.70, 5.80, 6.01, 6.15 μ. (C, 64.76; H, 7.27; Cl, 8.61). Similar treatment of III with hydrogen fluoride afforded 12α-fluorocorticosterone acetate, IVc (R = CH_3CO), m.p. 197–200°; $[\alpha]^{CHCl_3}D$ +209°; $\lambda_{max.}^{CH_3OH}$ 240.5 mμ (16,600); $\lambda_{max.}^{Nujol}$ 3.02, 5.70, 5.78, 6.06, 6.15 μ (C, 68.21; H, 7.67; F, 4.72). 12α-Fluoro-11-dehydrocorticosterone acetate, IVe (R = CH_3CO), m.p. 177–180°; $\lambda_{max.}^{CH_3OH}$ 237 mμ (15,800); $\lambda_{max.}^{Nujol}$ 5.75, 5.81, 5.88, 6.01, 6.20 μ; (C, 68.35; H, 7.45) was obtained from IVc (R = CH_3CO) by oxidation with sodium dichromate in acetic acid. Microbial dehydrogenation of IVc (R = CH_3CO) at positions 1:2 utilizing *Bacillus sphaericus*[5] produced 1-dehydro-12α-fluorocorticosterone, IVd (R = H) isolated, after acetylation, as its 21-acetate IVd (R = CH_3CO), m.p. 218–222°; $\lambda_{max.}^{CH_3OH}$ 242 mμ (15,700); $\lambda_{max.}^{Nujol}$ 3.08, 5.72, 5.78, 6.03, 6.18, 6.23, 11.10 μ; (C, 68.14; H, 7.11). Hydrolytic fission of the oxide III with perchloric acid[6] produced 12α-hydroxycorticosterone IVf (R = H), m.p. 208–212°; $[\alpha]^{CHCl_3}D$ +194°; $\lambda_{max.}^{CH_3OH}$ 241 mμ (15,900); $\lambda_{max.}^{Nujol}$ 2.90–3.02, 5.84, 6.08, 6.18 μ; (C, 69.97; H, 8.47) which gave, after acetylation and subsequent oxidation with chromic acid, 12α-acetoxy-11-dehydrocorticosterone acetate, II, m.p. 170–172°; $\lambda_{max.}^{CH_3OH}$ 238 (16,000); $\lambda_{max.}^{Nujol}$ 5.71, 5.80, 5.97, 6.12 μ; (C, 67.29; H, 7.06).

The 12α-fluoro analogs exhibit the same enhanced glucocorticoid activity relative to cortisone acetate as do the corresponding 9α-fluoro isomers but exhibit a somewhat lower mineralocorticoid activity than the latter.[7]

(5) T. H. Stoudt, W. J. McAleer, J. M. Chemerda, M. A. Koslowski, R. F. Hirschmann, V. Marlatt and R. Miller, *Arch. Biochem. Biophys.*, **59**, 304 (1955). We are indebted to Dr. Stoudt of these laboratories for his aid in this procedure.

(6) R. P. Graber, C. S. Snoddy, Jr., and N. L. Wendler, *Chem. & Ind.*, 57 (1956).

(7) The physiological activities were determined by Drs. C. A. Winter, C. C. Porter and H. Stoerk of the Merck Institute for Therapeutic Research and will be published in detail elsewhere.

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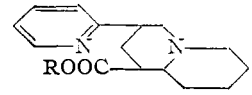
TOTAL SYNTHESIS OF OXYGENATED TETRACYCLIC LUPIN ALKALOIDS

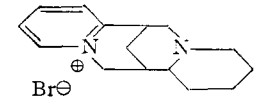
Sir:

Serving as integral units in the gradation of lupin alkaloids, the *oxygenated tetracyclic bases* (I) are flanked on the one side by cytisine and its N-alkyl derivatives (II), and on the other, by the tetracyclic oxygen-free members (III), of which sparteine is a familiar example. In recent times, members of the groups II and III have been attained through total synthesis[1]; however, the bases belonging to type (I) have been heretofore accessible only from the natural sources. Various representatives of the last class can now be produced in the laboratory, as the steps detailed below demonstrate.

Heating an aqueous alcoholic solution of 2-(α-pyridyl-allylmalonic acid[1f] and Δ^1-piperideine (as the α-trimer[2]) resulted in—as a consequence of a decarboxylative Mannich reaction accompanied by cyclization[1f]—complete assemblage of the required carbon–nitrogen skeleton, the 3-α-pyridylquinolizidine-1-carboxylic acid (IV, R = H) being isolated and purified as the ethyl ester (IV, R = C_2H_5), b.p. 155–167° (0.4 mm.) (Found: C, 70.77; H, 8.16). Subsequent to the subjection of the ester

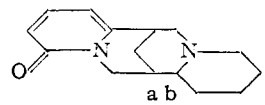


IV

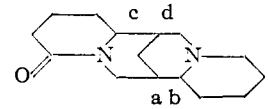


VI

to epimerization conditions (absolute ethanolic sodium ethoxide), the redistilled material was reduced with lithium aluminum hydride to the corresponding carbinol (V), b.p. 180–187° (0.3 mm.) (Found: C, 72.62; H, 8.99).[3] Conversion of V to the bromide, accomplished by means of 48% hydrobromic acid, was followed immediately by cyclization in benzene to the quaternary bromide VI, m.p. 214–216° (Found: C, 58.35; H, 7.06). Oxidation with alkaline ferricyanide led to the pyridone (VII), b.p. 170–175° (0.1 mm.), which remained a viscous oil at room temperature. The



VII



VIII

synthetic product was purified and characterized as a perchlorate (VIIa), m.p. 315°, (Found: C, 52.29; H, 6.12); and the free base, obtained from the pure salt VIIa and then distilled, exhibited a complex infrared spectrum which was identical in every detail with that of 1-*anagyrine* (VII-a,b-*trans*), the liquid[4] specimen being obtained in a comparable fashion from its pure perchlorate, m.p. 315°.[5]

The *lupanine* structure VIII (a,b-*trans*-c,d-*cis*) common (as the *d*-, *l*- or *dl*-form) to a variety of *Cytisus*, *Lupinus* and *Podalyria* genera, falls within the scope of the above synthesis, since Ing[6] has reduced anagyrine to lupanine. *Trilupine*, an alka-

(1) (a) N. J. Leonard and R. E. Beyler, THIS JOURNAL, **70**, 2299 (1948); (b) G. R. Clemo, R. Raper and W. S. Short, *Nature*, **162**, 268 (1948); (c) F. Sorm and B. Keil, *Collection Czechoslov. Chem. Commun.*, **13**, 544 (1948); (d) F. Galinovsky and G. Kainz, *Monatsh.*, **80**, 112 (1949); (e) M. Carmack, B. Douglas, E. W. Martin and H. Suss, THIS JOURNAL, **77**, 4435 (1955); (f) E. E. van Tamelen and J. S. Baran, *ibid.*, **77**, 4944 (1955); (g) F. Bohlmann, A. Englisch, N. Ottawa, H. Sander and W. Weise, *Angew. Chem.*, **67**, 708 (1955).

(2) C. Schöpf, A. Komzak, F. Braun and E. Jacobi, *Ann.*, **559**, 1 (1948).

(3) The proportions of diastereoisomers corresponding to structures IV and V were not determined.

(4) A. Partheil and L. Spasski, *Apoth. Zeit.*, **10**, 903 (1895).

(5) L. Marion and S. W. Fenton, *J. Org. Chem.*, **13**, 780 (1948).

(6) H. R. Ing, *J. Chem. Soc.*, 504 (1933).

loid formulated as the di-N-oxide of lupanine, may be regarded similarly, in that it has been secured by calcium peroxide oxidation of the parent amide.[7]

Since *thermopsine* is formulated[8] as a diastereoisomer (VII-a,b-*cis*) of anagyrine, conversion of the latter structure to the former, as an extension of the synthetic plan, was desirable. The epimerization of *dl*-anagyrine was accomplished by mercuric acetate dehydrogenation—leading presumably to the unisolated intermediate imine salt—followed by catalytic reduction (6% palladium-on-strontium carbonate). The final product, after being sublimed at 150–170° (1.0 mm.), melted at 171–172°, and no depression was observed in a mixed melting point determination with this material and *dl*-thermopsine (m.p. 171–173°), obtained by mixing equal parts of *d*- and *l*-thermopsine derived from natural sources. The infrared spectra of the natural and synthetic materials in solution were indistinguishable. In the same vein, it may be mentioned that the rare *Lupinus* alkaloid, *α-isolupanine*, VIII (a,b,c,d-*cis*), had been previously obtained[8] in a like fashion from *d*-lupanine (*vide supra*).

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(7) J. F. Couch, THIS JOURNAL, **59**, 1469 (1937); E. Ochiai, Y. Ito and M. Maruyama, *J. Pharm. Soc. Japan*, **59**, 270, 705 (1939).

(8) L. Marion and N. J. Leonard, *Can. J. Chem.*, **29**, 355 (1951).

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STERIC AND POLAR DISPLACEMENTS OF NUCLEAR SPIN RESONANCES[1]

Sir:

Important advances in structure determination and "fingerprint" identification of chemical compounds are currently being made by nuclear spin resonance (NSR) spectroscopy.[2] The gross features of NSR spectra have been shown to correlate with the electron-withdrawing power of nearby groups in the molecule.[3,4] I wish to report that factors, apparently steric in origin, and quite unrelated to the electronegativities of substituents, are also of considerable importance in determining the positions of NSR lines in fluorocarbon derivatives. The δ*-values reported in Table I are in parts per million, ±1 p.p.m., and refer to the definition $\delta^* = 10^6 (H_{C_4F_8} - H_{obs.})/H_{C_4F_8}$. Positive δ*-values (*i.e.*, less shielding of the fluorine nucleus by its electron cloud) thus indicate greater electron withdrawing power than is shown by the perfluorocyclobutyl group for the NSR spectra. I am indebted to Dr. James N. Shoolery of Varian Associates, Palo Alto, California.

TABLE I

FLUORINE NSR δ*-VALUES (P.P.M.)

CF_3–CF_2–CF_2–CF_3[5] 55 10	CF_3–CF_2–CF_2–CH_2I[7] 54 10 28
CF_3–CF_2–CF_2–CF_2–CF_2–CF_3[6] 54 10 14 14	CF_3–CF_2–CF_2–$COCl$[7] 55 10 22
CF_3–CF_2–CF_2–CF_2H[6] 54 10 13 7 (0, −2)	CF_3–CF_2–CF_2–CCl_3[7] 55 19 29
HCF_2–CF_2–CF_2–CF_2H[6] 7 (−1, −2)	CF_3–CF_2–CF_2–CF_2–CF_2–CCl_3[7] 55 10 14 20 27
CF_3–CF_2–CF_2–CH_2Cl[7] 54 10 19	CCl_3–CF_2–CF_2–$COCl$[7] (33, 31)
CF_3–CF_2–CF_2–CH_2Br[7] 54 10 22	CCl_3–CF_2–CF_2–CF_2–$COCl$[7] 30 (26, 24)

The NSR line due to CF_3 group provides an internal standard[4] for the compounds bearing it in Table I. It is reasonable to suppose that specific steric and polar effects will no longer be felt by fluorine atoms removed from the varied substituent by three to five carbon atoms. For CF_3CH_2I, $\delta^* = 68$, this is of course not the case. The assignments presented in Table I are my own; they are in every case consistent with the observed relative intensities.

The "apparent electron-withdrawing power" of the substituents X and Y in compounds of the type XCF_2Y (as judged by the NSR δ*-value for the F atoms of the CF_2 group) is in the following order of effectiveness: F ≫ CCl_3, CH_2I > COCl, CH_2Br > CF_2CCl_3, CH_2Cl > C_2F_5, n-C_3F_7 > CF_3 > CF_2H >H. Additional observations made upon perfluoroalkyl chlorides, bromides, and iodides, too numerous for presentation here, lead to the following further evaluations of apparent electron-withdrawing power: I > Br > Cl > F ≫ CF_2I > CF_2Br > CF_2Cl > CF_3.

It appears that the bulkiness of substituents such as I and CCl_3 has the effect of compensating for their lesser electronegativity in producing "electron withdrawal" from nearby CF_2 (and CF_3) groups. Furthermore, these bulky groups still exert strong "electron-withdrawing" effects, even when a CF_2 or CH_2 unit is interposed.

These observations are qualitatively in agreement with the concept of "strained homomorphs,"[8] provided that repulsive steric interaction with neighboring atoms or groups produces a net displacement of electrons away from the fluorine atom, and presumably along the F—C bond. This effect, here entitled "repulsive unshielding," should also be observable in proton NSR spectra.[10] Possible "mechanisms" for non-bonded repulsive interactions have been discussed with reference to potential barriers to internal rotation.[9]

I postulate that net electron displacement away from fluorine (and hydrogen) nuclei may be induced by

(1) The Chemistry of Perfluoro Ethers. IV. Presented in part at the 126th A.C.S. Meeting, New York, 1954; Abstracts, p. 27M.

(2) L. H. Meyer, A. Saika and H. S. Gutowsky, THIS JOURNAL, **75**, 4567 (1953); Corey, *et al.*, *ibid.*, **77**, 4941 (1955). J. N. Shoolery, papers presented at the 124th A.C.S. Meeting, Chicago, 1953, Abstracts, p. 18M, and at the 126th Meeting, New York, 1954, Abstracts, p. 23M; *Anal. Chem.*, **26**, 1400 (1954).

(3) H. S. Gutowsky, *et al.*, THIS JOURNAL, **74**, 4809 (1952).

(4) B. P. Dailey and J. N. Shoolery, *ibid.*, **77**, 3977 (1955).

(5) J. H. Simons, U. S. Patent 2,519,983 (1950).

(6) J. D. LaZerte, L. J. Hals, T. S. Reid and G. H. Smith, THIS JOURNAL, **75**, 4525 (1953).

(7) G. V. D. Tiers, H. A. Brown and T. S. Reid, *ibid.*, **75**, 5978 (1953); G. V. D. Tiers, *ibid.*, **77**, 6703, 6704 (1955).

(8) H. C. Brown, *et al.*, *ibid.*, **75**, 1–24 (1953).

(9) E. A. Mason and M. M. Kreevoy, *ibid.*, **77**, 5808 (1955).