THE STEREOCHEMISTRY OF THE DECOMPOSITION OF 2-PYRAZOLINES

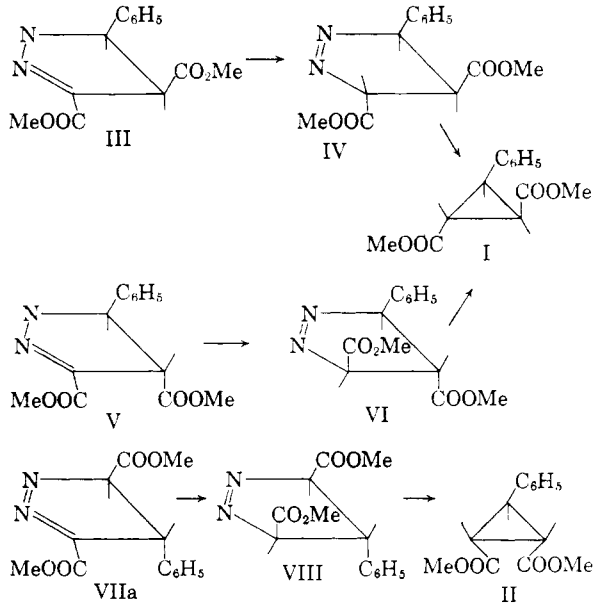
Sir:

We wish to report here the thermal decomposition of the two stereoisomeric 3,4-dicarbomethoxy-5-phenyl-2-pyrazolines (III and V) to give as their exclusive cyclopropane product 1,2-dicarbomethoxy-3-phenylcyclopropane, in which the carboalkoxy groups are *trans* (I). This is to be compared with the observation that the thermal decomposition of 3,5-dicarbomethoxy-4-phenyl-2-pyrazoline (VII) gives as its exclusive cyclopropane product the geometrical isomer of I (II).[1]

These results represent, to the best of our knowledge, the first clear-cut example of a thermal decomposition of a 2-pyrazoline in which the configuration of the predominant cyclopropane product cannot be explained in terms of its relative stability.[2]

These observations can be rationalized, however, if it is assumed that the decomposition of a 2-pyrazoline proceeds *via* tautomerization to the favored 1-pyrazoline and then stereospecific loss of nitrogen.[3]

Thus, tautomerization of III and V would lead to IV and VI, respectively. Stereospecific decomposition[3] of both IV and VI would give the observed *trans* product I. On the other hand, if it is assumed that the configuration of Buchner's pyrazoline is that pictured in VII-a, tautomerization would lead to VIII which, upon decomposition, would give II.



Pyrazolines III (m.p. 132°, calcd. for $C_{13}H_{14}N_2O_4$: C, 59.53; H, 5.38; N, 10.69. Found: 59.74; 5.38; 10.75) and V, (an uncrystallizable oil), synthesized by the reaction of phenyldiazomethane with dimethyl fumarate, exhibited the anticipated infrared absorptions (III, 3.01 and 6.38 microns; V, 2.98 and 6.43 microns).

(1) E. Buchner and H. Dessauer, *Ber.*, **25**, 1147 (1892).

(2) T. L. Jacobs in R. C. Elderfield, "Heterocyclic Compounds," John Wiley and Sons, Inc., New York, N. Y., Vol. 5. 1957, p. 80.

(3) K. von Auwers and F. Konig, *Ann.*, **496**, 27, 252 (1932).

Thermal decomposition of each of these materials gave oily solids whose infrared spectra showed no detectable amount (less than 10%) of the *cis*-isomer II. Recrystallization from hexane gave I (m.p. 83°, calcd. for $C_{13}H_{14}O_4$: C, 66.65; H, 6.02. Found: C, 66.59; H, 5.85; configuration proved by resolution) and an olefin.

Decomposition of VII, synthesized by Buchner's method,[1] gave a mixture of the *cis* cyclopropane II and an oil whose infrared spectrum showed no sign of the *trans* isomer, I.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF FLORIDA W. M. JONES
GAINESVILLE, FLORIDA

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16-ALKYLATED CORTICOIDS. III. 16β-METHYL-9α-FLUOROPREDNISOLONE 21-ACETATE

Sirs:

Recent communications[1] have described the preparation of 16α-methyl and 16β-methyl corticoids such as 16α-methyl derivatives of cortisone, hydrocortisone, prednisone, prednisolone, and 9α-fluorohydrocortisone and 9α-fluoroprednisolone, and the 16β-methyl derivatives of cortisone, hydrocortisone, prednisone and prednisolone. All possess enhanced glucocorticoid activity over the non-methylated parent compounds.

We wish to report the first synthesis of a new member of the 16-methyl corticoids, namely, 16β-methyl-9α-fluoroprednisolone 21-acetate (I), which, besides having enhanced glucocorticoid and anti-inflammatory activity in animals and man, is completely devoid of salt and water retaining properties. Thus I is the first reported compound in which the presence of a 16β-substituent has overcome completely the inherent salt and water retaining properties of the parent compound, 9α-fluoroprednisolone.

3α,17α - Dihydroxy - 16β - methylpregnane-11,20-dione is converted to its 20-ethylene ketal ((m.p. 202–208°, $[\alpha]_D$ +55.4° (all rotations in dioxane). *Anal.* Found: C, 70.94; H, 9.32)) by means of ethylene glycol and *p*-toluenesulfonic acid in refluxing benzene. Reduction of the 11-ketone with sodium in *n*-propyl alcohol gives 3α,11α-17α - trihydroxy - 16β - methylpregnan - 20 - one-20-ethylene ketal, m.p. 206–209°, $[\alpha]_D$ +42.5°; *anal.* Found: C, 70.58; H, 10.05. Hydrolysis with aqueous acetic acid produces 3α,11α,17α-trihydroxy - 16β - methylpregnan - 20 - one, m.p. 180–183°, $[\alpha]_D$ +40.7°. *Anal.* Found: C, 72.18; H, 9.72 (3,11-diacetate: m.p. 185–186.5°, $[\alpha]_D$ +37.2°). Bromination at C-21, and then acetoxylation with potassium acetate gives 21-acetoxy - 3α,11α,17α - trihydroxy - 16β -methylpregnan-20-one (3,11,21-triacetate: m.p. 220–226°, $[\alpha]_D$ +76.9°; *anal.* Found: C, 66.48; H,

(1) (a) G. Arth, D. Johnston, J. Fried, W. Spooncer, D. Hoff and L. Sarett, THIS JOURNAL, **80**, 3160 (1958); (b) G. Arth, J. Fried, D. Johnston, D. Hoff, L. Sarett, R. Silber, H. Stoerk and C. Winter, *ibid.*, **80**, 3161 (1958); (c) E. Oliveto, R. Rausser, A. Nussbaum, W. Gebert, E. B. Hershberg, S. Tolksdorf, M. Eisler, P. Perlman and M. Pechet, *ibid.*, **80**, 4428 (1958); (d) E. Oliveto, R. Rausser, L. Weber, A. Nussbaum, W. Gebert, C. Coniglio, E. B. Hershberg, S. Tolksdorf, M. Eisler, P. Perlman and M. Pechet, *ibid.*, **80**, 4431 (1958); (e) D. Taub, R. Hoffsommer, H. Slates and N. Wendler, *ibid.*, **80**, 4335 (1958).

8.28), which on selective oxidation with N-bromoacetamide in aqueous acetone yields 21-acetoxy-11α,17α - dihydroxy - 16β - methylpregnan-3,20-dione, m.p. 187.5–190.5°, $[\alpha]$D +77.9°; *anal.* Found: C, 68.43; H, 8.61. The 1,4-dien-3-one system, is introduced in the usual manner (dibromination at C-2 and C-4 followed by dehydrobromination with dimethylformamide) to give 21-acetoxy - 11α,17α - dihydroxy - 16β -methyl-$\Delta^{1,4}$-pregnadiene-3,20-dione, m.p. 225–228°, $[\alpha]$D +100.0, λ_{max}^{MeOH} 247 mμ (ϵ 16,700). *Anal.* Found: C, 69.35; H. 7.79.

Introduction of the 9α-fluoro-11β-hydroxy group is performed in the usual fashion[2]: the 11α-tosylate is dehydrated to 21-acetoxy-17α-hydroxy-16β-methyl-$\Delta^{1,4,9(11)}$-pregnatriene-3,20-dione, m.p. 205–207°, $[\alpha]$D +140.3°, λ_{max}^{MeOH}, 239 mμ (ϵ 19,300). Addition of HOBr with N-bromosuccinimide followed by closure with potassium acetate to the epoxide gives 9β,11-epoxy-21-acetoxy-17α-hydroxy-$\Delta^{1,4}$-pregnadiene-3,20-dione (m.p. 210–216°, λ_{max}^{MeOH} 249 mμ (ϵ 15,600)) which on treatment with hydrogen fluoride produces 9α-fluoro-16β-methylprednisolone acetate (I), m.p. 196–201°, $[\alpha]$D +107.5°, λ_{max}^{MeOH} 239 mμ (ϵ 25,200); *anal.* Found: C, 66.27; H, 7.51.

The physiological properties of 16β-methyl-9α-fluoroprednisolone acetate in man appear to be quantitatively similar to those of the α-isomer.[1d] The reduction in the number of circulating eosinophiles, the effect on an oral glucose load, the elevation of the fasting blood sugar and the excretion of sodium are responses readily induced by both the 16α- and 16β-methyl isomers.

(2) *Cf.* J. Fried and E. Sabo, THIS JOURNAL, **79**, 1130 (1957).

EUGENE P. OLIVETO
RICHARD RAUSSER
HERSHEL L. HERZOG
E. B. HERSHBERG
S. TOLKSDORF
MILTON EISLER
P. L. PERLMAN
RESEARCH DIVISION
SCHERING CORPORATION
BLOOMFIELD, NEW JERSEY

MASSACHUSETTS GENERAL HOSPITAL
BOSTON, MASSACHUSETTS
M. M. PECHET

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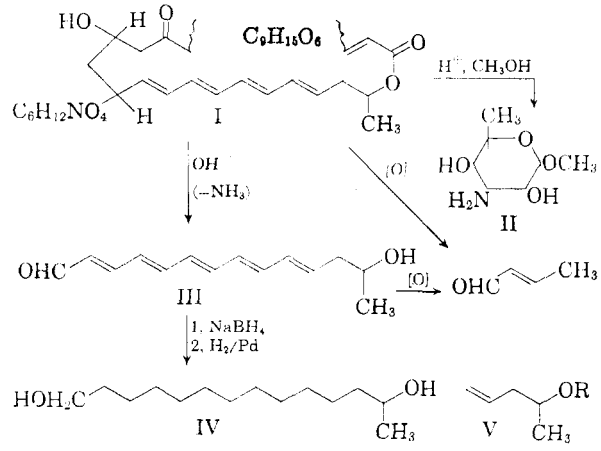
PIMARICIN. I. OXIDATION AND HYDROLYSIS PRODUCTS

Sir:

During investigations on the tetraene antifungal antibiotic pimaricin[1,2,3] we have accumulated evidence for partial structure I for this antibiotic. Pimaricin (calcd. for $C_{34}H_{49}NO_{14}$ (695.74): C, 58.69; H, 7.10; N, 2.01. Found:[4] C, 58.53 ± 0.32; H, 7.32 ± 0.17; N, 2.12 ± 0.14; C-methyl, 1.43, 1.71 methyl groups) gives the usual tests for a primary amino group (Van Slyke), a carboxyl group, and a somewhat hindered keto group. An α,β-unsaturated lactone is present (saponification equivalent: 1 mole of alkali without fission of the molecule, infrared peak at 5.84 μ, shifting to 5.77 μ on hydrogenation of the antibiotic; ultraviolet maximum at 222 mμ, ϵ = 22,400, which disappears on hydrogenation).



Refluxing pimaricin with methanolic hydrogen chloride produced the methyl glycoside of the amino sugar mycosamine,[5] identified by mixed melting point and X-ray powder diffraction pattern comparison of the triacetate with authentic methyl mycosaminide triacetate from nystatin.

Hydrogenation of *N-acetyl pimaricin* (m.p. 200°; $[\alpha]^{25}$D + 230°, calcd. for $C_{36}H_{51}NO_{15}$ (737.38): C, 58.60; H, 6.97; N, 1.90. Found: C, 58.86; H, 7.00; N, 1.93) produced *N-acetyldodecahydropimaricin* (m.p. 155–156°; $[\alpha]^{25}$D −67.5°; calcd. for $C_{36}H_{63}NO_{15}$ (748.48): C, 57.66; H, 8.47. Found: C, 57.69; H, 8.64; N, 1.91) which was oxidized by sodium dichromate–sulfuric acid to *sebacic acid*, demonstrating that the tetraene system carried no alkyl substituents.

Acid dichromate oxidation of pimaricin itself yielded crotonaldehyde, suggesting the presence of the grouping V.[6]

Treatment of pimaricin with alkali caused liberation of ammonia, indicating labilization of the glycoside linkage, possibly by beta-elimination.[7] The other isolated product was *13-hydroxy-2,4,6,-8,10-tetradecapentaeneal* (III) [orange crystals, m.p. 124–128°; λ_{max} 375 mμ (MeOH)] whose structure follows from its positive Fehling reaction and sodium borohydride reduction to *1,13-dihydroxy-2,4,6,8,10-tetradecapentaene* (yellow crystals, m.p. 187–188°; $\lambda\lambda_{max}$ 313, 328, 346 mμ). This diol was hydrogenated to 1,13-tetradecanediol (IV) (m.p. 49.0–50.0°; $[\alpha]^{25}$D −6.5°; calcd. for $C_{14}H_{30}O_2$ (230.4): C, 72.98; H, 13.12; C-methyl, (1) 6.5; active hydrogen, 2. Found: C, 72.77; H, 13.15; C-methyl, 5.26; active hydrogen, 1.76) which after hypobromite oxidation, yielded tridecanedioic (brassylic) acid.

(1) A. P. Struyk, *et al.*; *Antibiotics Annual* (1957–1958), 878 (Medical Encyclopedia, Inc., New York, 1958).

(2) Our antibiotic was isolated and identified as pimaricin by comparison of infrared and ultaviolet spectra and paper chromatographic mobilities of the antibiotics (M. Dann, E. J. Backus, R. W. Sharpe, J. H. Mowat, and N. Bohonos, unpublished data) and their N-acetyl derivatives. X-Ray powder diffraction patterns of the antibiotics and their N-acetyl derivatives were compared also. Pimaricin was kindly provided by Dr. J. C. Hoogerheide, Royal Dutch Yeast and Fermentation Industries, Delft.

(3) The registered trademark of the American Cyanamid Company for pimaricin is Myprozine.

(4) Average and average deviation of seventeen analyses.

(5) D. Walters, J. D. Dutcher and O. Wintersteiner, THIS JOURNAL, **79**, 5076 (1957).

(6) Compare D. E. Ames and R. E. Bowman, *J. Chem. Soc.*, 4264 (1955).

(7) F. A. Hochstein and P. P. Regna, THIS JOURNAL, **77**, 3353 (1955).