THE STEREOCHEMISTRY OF THE DECOMPOSITION OF 2-PYRAZOLINES

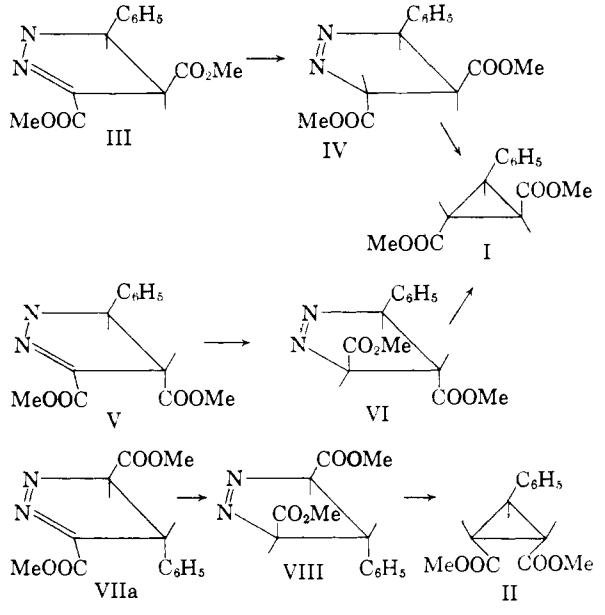
Sir:

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.

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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).