topic enrichment of the alcohol (30% excess C^{13}) suggests that detection of C^{13} in carbon-4 would have been achieved, had mechanism (1) occurred to the extent of 20% or more.

The above arguments lead to the conclusion that under strong acid conditions carbonium ion rearrangements of the neopentyl system do not occur mainly *via* protonated cyclopropanes.[5]

(5) Since our interests when we started this work were not centered around the intermediacy of protonated cyclopropanes in carbonium ion rearrangements, no attempt was made to identify any product of cyclopropane skeleton. We wish to emphasize that our arguments do not necessarily apply to reactions done under basic conditions,[1a] nor do they exclude protonated cyclopropanes as intermediates in the formation of cyclopropane compounds.[1b] In addition we wish to point out that the work of J. D. Roberts and J. A. Yancy, THIS JOURNAL, **77**, 5558 (1955), on the reaction of 2,3,3-trimethyl-2-butanol-1-C^{14} with concentrated hydrochloric acid also excludes any protonated cyclopropane intermediates prior to formation of classical carbonium ions, or before reaction of classical carbonium ions with chloride ions.

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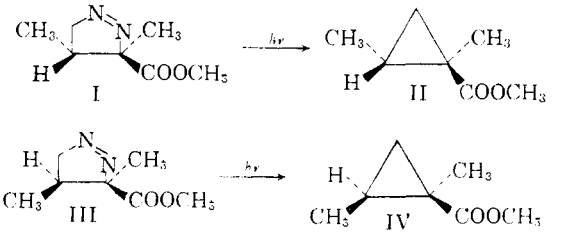
RECEIVED AUGUST 10, 1960

LIGHT-INDUCED DECOMPOSITION OF PYRAZOLINES. AN IMPROVED ENTRY INTO THE CYCLOPROPANE SERIES

Sir:

Thermal decomposition of pyrazolines is a well-known route to cyclopropanes.[1,2,3,4] The synthetic value of the reaction is reduced considerably, however, by the extensive formation of olefinic products,[2,3,4,5,6] by a lack of stereospecificity,[5] and often by extensive tar formation.[2] We now wish to report that light-induced decomposition of stereoisomeric pyrazolines has led to the formation of cyclopropanes stereospecifically, and without olefin formation.

When 3-carbomethoxy-*cis*-3,4-dimethyl-1-pyrazoline (I), prepared by treatment of methyl tiglate with diazomethane,[5,7] was irradiated with a sunlamp at *ca.* 15°, the sole product (by gas-liquid chromatographic analysis) was methyl *cis*-1,2-dimethylcyclopropane - 1 - carboxylate (II), $n^{25}D$ 1.4289 [*Anal.* Found: C, 65.26; H, 9.44].



Irradiation at *ca.* 30–35° of 3-carbomethoxy-*trans*-3,4-dimethyl-1-pyrazoline (III),[5] prepared from methyl angelate and diazomethane, gave a mixture of esters which gas chromatographic analysis showed to consist of 87% methyl *trans*-1,2-dimethylcyclopropane - 1 - carboxylate (IV), $n^{25}D$ 1.4218 [*Anal.* Found: C, 65.86; H, 9.50], 2% II, 7% methyl 2,3-dimethyl-2-butenoate (V) (identified by infrared spectrum and gas chromatographic retention time identical with those of an authentic sample), and 4% methyl angelate (identified in the same manner as V). At 33–35° irradiation of I gave a mixture of esters found by gas chromatography to consist of 73% II, 3% V, and 20% methyl tiglate (identified in the same manner as V). The methyl angelate and methyl tiglate formed in these irradiations resulted from the apparent reversal of pyrazoline formation, a reaction which has not been previously observed.

The structures of the products were established as cyclopropanes by their infrared, ultraviolet, and n.m.r. spectra. The infrared spectra of II and IV (in carbon tetrachloride) contain no olefinic bands in the 1700–1600 or 950–880 cm.$^{-1}$ regions,[8] while their ultraviolet spectra show only weak end absorption (ϵ *ca.* 200). Olefinic hydrogen peaks are absent from their n.m.r. spectra, while cyclopropane hydrogens appear in the region τ[9] = 8.6–9.8.[10]

Steric assignments of II and IV were made on the basis of (a) competitive saponification of a mixture of II and IV in which the less hindered ester moiety of II was hydrolyzed more rapidly than that of IV, and (b) their formation from pyrazolines, in which stereospecific inversion is considered to be unlikely.

Acknowledgment.—This investigation was supported in part by a grant (No. RG-5883) from the Division of Research Grants, National Institutes of Health.

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(2) K. von Auwers and F. König, *Ann.*, **496**, 252 (1932).
(3) D. E. McGreer, *J. Org. Chem.*, **25**, 852 (1960).
(4) W. M. Jones, THIS JOURNAL, **82**, 3136 (1960), and preceding papers.
(5) K. L. Rinehart, Jr., and T. V. Van Auken, paper in preparation.
(6) H. L. Slates and N. L. Wender, THIS JOURNAL, **81**, 5472 (1959).
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(8) L. J. Bellamy, "Infrared-red Spectra of Complex Molecules," 2nd ed., John Wiley and Sons, New York, N. Y., 1958.
(9) G. V. D. Tiers, *J. Phys. Chem.*, **62**, 1151 (1958).
(10) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, New York, N. Y., 1959.
(11) Lubrizol Fellow, 1959–1960.

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RECEIVED AUGUST 22, 1960

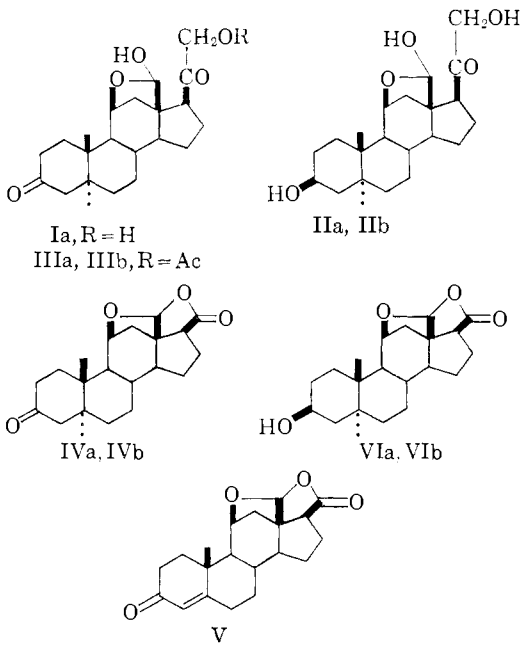
THE METABOLISM OF ALDOSTERONE: ISOLATION AND CHARACTERIZATION OF TWO NEW METABOLITES[1]

Sir:

In this report we describe the isolation of two new metabolites of *d*-aldosterone, 5α-(4,5)-dihydroaldosterone (Ia) and 3βOH,5α-(4,5)-tetrahydroaldosterone (IIa), from the incubate of *d*-aldosterone with rat liver homogenates. In addition, the synthetic preparation of 5α-(4,5)-dihydroaldosterone 21-acetate (IIIb), 3βOH,5α-(4,5)-tetrahydroaldosterone (IIb), the 3-keto etiolactone (IVb), and the 3-hydroxy etiolactone (VIb) are recorded. Romani, *et al.*,[2] have suggested the formation of

(1) This work was supported in part by a grant (P. H. S. A-1156) from the National Institute of Arthritis and Metabolic Diseases of the National Institutes of Health, Education and Welfare.

(2) J. D. Romani, C. Bessard, J. Sosa-Castellanos and A. Keller, *Ann. Endocrinol.*, **20**, 209 (1959).



a tetrahydro derivative during incubation of *dl*-aldosterone with rat liver homogenates. Ulick and Lieberman[3] have reported the isolation from human urine of a $C_{21}O_5$ pregnane derivative possessing hydroxyl groups at C_3, C_{18} and C_{21}, and two carbonyl groups, one at C_{20}; however, definite characterization and assignment of structure was not possible.

Synthetic *d*-aldosterone 21-acetate, m.p. 195.5–201°, $[\alpha]D + 130°$,[4] was incubated with a homogenate of rat liver, enzymatically reduced TPNH and a TPNH generating system[5] for three hours at 37° under nitrogen. The incubate was extracted with organic solvents, and the extracts were chromatographed on paper using a new paper chromatography system of aqueous diethylacetamide.[6]

Compound Ia migrated with an $R_E = 0.60$[7] and gave positive color tests with blue tetrazolium chloride,[8] with $SbCl_3$[9] and with Zimmermann's dinitrobenzene reagent.[10] There was no absorption in the ultraviolet. Compound IIa migrated with an $R_E = 0.21$ and gave positive color tests with blue tetrazolium chloride and with $SbCl_3$, a negative test with Zimmermann's reagent, and no absorption in the ultraviolet. These compounds were eluted from paper chromatograms and further purified by chromatography over Al_2O_3. Compound Ia was crystallized from $CHCl_3$–Et_2O, m.p. (needles) 154–156°, $[\alpha]^{23}D + 53°$ ($CHCl_3$, $C = 0.362$), $\nu_{max}^{CHCl_3}$ 3700, 3500, 1710, 1060, 982, 965, 911 cm.$^{-1}$. Compound IIa was purified by formation of the digitonide, $[\alpha]^{22}D + 48°$ ($CHCl_3$, $C = 0.165$). Compound Ia was acetylated with Ac_2O in pyridine and gave after crystallization from moist CH_3OH the monoacetate (IIIa), m.p. (needles) 173–174°. $R_{aldosterone\ 21\text{-}acetate} = 2.15$; $\nu_{max}^{CHCl_3}$ 3700, 3500, 1745, 1710, 1135, 1100, 995, 980, 903 cm.$^{-1}$. For comparison, the dihydroaldosterone 21-acetate (IIIb) was prepared by reduction of synthetic *d*-aldosterone 21-acetate over PtO_2 in neutral solution, m.p. (needles) (analytical sample) 176–184°, mixed m.p. with IIIa 174–184°, $[\alpha]^{24}D$ 51 ± 3° ($CHCl_3$, $C = 0.652$), $\nu_{max}^{CHCl_3}$ 3700, 3500, 1745, 1710, 1135, 1100, 995, 980, 903 cm.$^{-1}$. (*Anal.* Calcd. for $C_{23}H_{32}O_6$: C, 68.29; H, 7.94. Found: C, 68.20; H, 7.54.) $R_{aldosterone\ 21\text{-}acetate} = 2.0$. Compounds IIIa and IIIb were identical. The dihydroaldosterone (Ia) was oxidized with $NaIO_4$ to the 3-ketoetiolactone (IVa), m.p. (prisms from moist EtOH) 264–275°, $\nu_{max}^{CHCl_3}$ 1780, 1710, 1135, 1095, 965–995 (multiple), 910 cm.$^{-1}$.

Synthetic *d*-aldosterone was oxidized with $NaIO_4$ to the etiolactone (V), m.p. 323–326°, $\nu_{max}^{CHCl_3}$ 1780, 1670, 1618, 1115, 1100, 1080, 1060, 980, 960, 910 cm.$^{-1}$. (Although the reported m.p. for V is 308–313°,[11] the infrared spectra are identical.) The etiolactone (V) was reduced over PtO_2 in acidic solution to the 3-ketoetiolactone (IVb), m.p. (prisms from moist acetone) 282–295°, (needles from moist EtOH) (analytical sample) 278–285°, mixed m.p. with IVa 265–282°, $[\alpha]^{23}D$ 24 ± 4° ($CHCl_3$, $C = 0.45$), (*Anal.* Calcd. for $C_{20}H_{26}O_4$: C, 72.70; H, 7.93. Found: C, 72.48; H, 7.82.); and the 3-hydroxyetiolactone compound (VIb), purified by formation of the digitonide, m.p. (prisms from moist acetone) 230–235°. Compounds IVa and IVb were identical. Compound VIb was oxidized with chromic acid in pyridine solution to Compound IVb. Since the 3-acetate of Compound VIb previously had been shown to be of the 5αH series,[11] the configuration of IVa and IVb at 5 is thus determined. The structure of Compound Ia is established by direct comparison with synthetically prepared 5α-(4,5)-dihydroaldosterone and, further, by conversion to the 3-ketoetiolactone (IVa) and direct comparison with the synthetically prepared 3-ketoetiolactone (IVb).

Compound IIa, the other metabolite isolated, was identical with a sample of tetrahydroaldosterone (IIb) prepared by reduction of synthetic *d*-aldosterone 21-acetate over PtO_2 in acid solution. This compound had m.p. 115–128°, $[\alpha]^{21}D$ 45 ± 6° ($CHCl_3$, $C = 0.291$), $\nu_{max}^{CHCl_3}$ 3700, 3500, 1705 (weak), 1135, 1060, 1025, 998, 960, 904 cm.$^{-1}$.

Compound IIa was oxidized with $NaIO_4$ to the 3-hydroxyetiolactone (VIa) m.p. (needles from moist acetone) 232–238°, $\nu_{max}^{CHCl_3}$ 3700, 1780, 1095, 1085, 1022, 998, 980–965 (multiple), 914,

(3) S. Ulick and S. Lieberman, THIS JOURNAL, **79**, 6567 (1957).

(4) Melting points (uncorrected) were determined on a Kofler type hot stage. Infrared spectra were determined using an Infracord Model 137 Spectrophotometer. Microanalyses were performed by Dr. Alfred Bernhardt, Max Planck Institute, Mulheim, Germany.

(5) "Methods in Enzymology," Edited by S. P. Colowick and N. O. Kaplan, Academic Press, New York, N. Y., 1955, p. 323.

(6) In this report, System No. 7, diethylacetamide:water:isooctane:toluene (1:2:3:3), was used. This is one of a series of aqueous dimethyl- and diethylacetamide systems which have been in use in our laboratory during the past two years. These systems will be described in full in a forthcoming paper.

(7) R_E = distance traveled by sample relative to *E* (cortisone) on paper chromatograms scanned with blue tetrazolium.

(8) K. Savard, *J. Biol. Chem.*, **202**, 457 (1953).

(9) G. M. Shull, J. L. Sardinos and R. C. Nubel, *Arch. Biochem. and Biophys.*, **37**, 186 (1952).

(10) R. B. Burton, A. Zaffaroni and E. H. Keutmann, *J. Biol. Chem.*, **88**, 763 (1951).

(11) S. A. Simpson, J. F. Tait, A. Wettstein, R. Neher, J. V. Euw, O. Schindler and T. Reichstein, *Helv. Chim. Acta*, **37**, 1200 (1954).

890 cm.$^{-1}$, which was identical with VIb, the 3-hydroxyetiolactone prepared from the synthetic etiolactone (V).

The isolation and characterization of 5α-(4,5)-dihydroaldosterone (Ia) and 3βOH,5α-(4,5)-tetrahydroaldosterone (IIa) indicates that the ring A reduced products with A/B *trans* (5α) in configuration are favored.

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RECEIVED AUGUST 4, 1960

THE KETO-ENOL EQUILIBRIUM OF ETHYL ACETOACETATE UNDER HIGH PRESSURE

Sir:

It has been demonstrated in recent years that studies of the effect of pressure on reaction rates in the liquid phase often permit certain conclusions to be drawn regarding the mechanism involved.[1] For instance, reactions are accelerated if they proceed through a transition state that has a greater separation of charge than the reactant(s) and *vice versa*, since the intense electric field of an ion causes local compression of solvent molecules.[2] In the expression $d \ln k/dp = -\Delta V^*/RT$, the volume of activation is negative in such cases. On the other hand, a reaction is decelerated (ΔV^* is positive) if the formation of the transition state depends on homopolar bond breaking and *vice versa*,[3] since the sum of the van der Waals radii of the fragments exceeds that of the reactant.

It appeared that another feature often of interest in mechanistic studies, *i.e.*, formation of a cyclic transition state, could be subject to a pressure effect.[4] A comparison of the densities of straight chain hydrocarbons shows that the molar volume of n-C_mH_{2m+2} exceeds that of n-$C_{m-6}H_{2m-10}$ by 96 ± 1 ml./mole (m ranging from 11 to 17). This difference is a measure of the volume of hexamethylene, —$(CH_2)_6$—. This value is 12 ml./mole *smaller* than the molar volume of cyclohexane (108 ml./mole). Parachor data[5] on ring structures similarly suggest that ring structures have greater volume requirements than straight chains. Presumably the core of such doughnut-like molecules is too small to be accessible to other molecules.

In this work, the keto–enol equilibrium was studied as an example. If the process of forming a cyclic structure such as the enol form of ethyl acetoacetate[6] does not contribute to the change in molar volume, the equilibrium constant (K keto/enol) should decrease as the pressure is increased, since the molar volume of the group —C(OH)=CH— is smaller than that of the group —$COCH_2$— by about 4.0 ml./mole (estimated from the densities of unsaturated alcohols and isomeric carbonyl compounds); if the internal H-bond is taken into account, this difference would undoubtedly be somewhat greater. If the ring formation has the positive volume requirement described above, the molar volume of the enol form should be *larger* than that of the keto form by about 5 ml./mole. The effect of pressure on this equilibrium was studied by Kabachnik, Yakushkima and Kislyakova,[7] who reported no significant change in K for the pure substance. Since the rate of interconversion is extremely variable (depending on traces of impurities[6]) it appeared desirable to repeat this work. The new data (Table I) show that K in the pure liquid increases with pressure; the molar volume of the enol form exceeds that of the keto form by 1.0–1.5 ml./mole. This would suggest that it may be possible to recognize reactions involving a cyclic transition state by a retarding effect of pressure. An experimental program to test this statement is about to start in this laboratory.

TABLE I

p(atm.)[a]	% enol[b]	K keto/enol	ΔV (ml./mole)[c]
1	7.7	12.0	
			−1.5
1350	7.2	13.0	
			−1.0
2500	7.0	13.2	
			−1.3
3700	6.4	14.6	

[a] The apparatus will be described at a later date. [b] At 25°. Samples of the ester were withdrawn without releasing the pressure, collected in a quartz vessel and analyzed at once in the usual way (K. H. Meyer and P. Kappelmeyer, *Ber.*, **44**, 2718 (1911)). Care was taken to insure the system was at equilibrium and that interconversion during analysis was negligible. [c] Calculated from $(\ln K_p - \ln K_1) = -\Delta V/RT$.

Acknowledgment.—This work was done at the Rohm and Haas Research Laboratories. The author had the benefit of many helpful discussions with Mr. O. H. Loeffler and Drs. C. Huggett and B. Iwanciow.

(1) For an excellent review, see S. D. Hamann, "Physico-Chemical Effects of Pressure," Academic Press, Inc., New York, N. Y., 1957.

(2) H. C. David and S. D. Hamann, *Trans. Far. Soc.*, **50**, 1188 (1952).

(3) A. E. Nicholson and R. G. W. Norrish, *Disc. Far. Soc.*, 97 (1956).

(4) C. Walling and J. Peisach have considered this possibility recently in the dimerization of isoprene to cyclic products (THIS JOURNAL **80**, 5819 (1958)).

(5) S. Sugden, "The Parachor and Valency," Geo. Rutledge & Sons, Ltd., London, 1929.

(6) G. W. Wheland, Ch. XIV, "Advanced Organic Chemistry," 2nd Edition, John Wiley & Sons, Inc., New York, N. Y., 1949.

(7) M. I. Kabachnik, S. E. Yakushkima and N. V. Kislyakova, *Doklady Akad. Nauk., S.S.S.R.*, **96**, 1169 (1954); *cf. C.A.*, **49**, 8815 (1955). The authors stated that the system was allowed 4 hours to reach equilibrium; in this work it was found that at least 20 hours was necessary.

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THE STEREOCHEMISTRY OF JACOBINE

Sir.

Recent investigations[1] have shown all previous structures proposed for jacobine, jaconecic acid and *iso*jaconecic acid to be incorrect. The structures of these compounds are correctly represented by I, II and III, respectively. We wish now to present evidence which permits assignment of stereochemistry to the above compounds, as shown in Ia, IIa and IIIa.

(1) R. B. Bradbury and S. Masamune, THIS JOURNAL, **81**, 5201 (1959), and also see T. A. Geissman, *Aust. J. Chem.*, **12**, 247 (1959).