[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, CIBA PHARMACEUTICAL PRODUCTS, INC.]

Investigations in Heterocycles. IX. Resonance Effects in Pyrazolin-5-ones and Related Compounds

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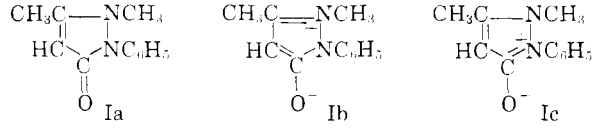
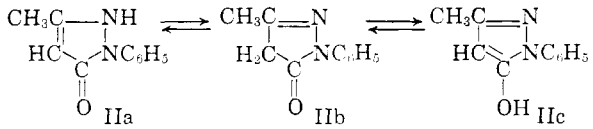
The spectral properties of tetrahydroindazolone, structurally related to pyrazolin-5-one, suggest that this type of compound exists predominantly in the dipolar or zwitterion form. The predominance of this structure was demonstrated by several chemical transformations.

Since the discovery of antipyrine by Knorr,[1] the structural features of the compound have occasioned some controversy. Structure Ia, first advanced by Knorr, failed to account for all the properties of the compound



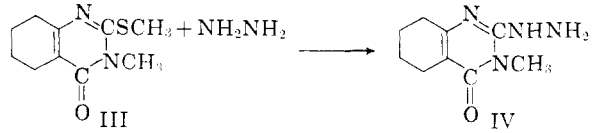
Ia Ib Ic

leading to the suggestion Ib by Brown[2] and coworkers and Veibel,[3] *et al.*, on the basis of dipole measurements. The latter group suggested that the true structure of antipyrine is a resonance hybrid of all of these forms with Ib accounting for approximately 30–35% and Ic contributing to only a limited degree. On the other hand, Kitamura[4] suggested Ic to be the correct structure on the basis of some ambiguous methylation experiments. Finally, the use of ultraviolet absorption spectra[5] led to the proposal that 1-phenyl-3-methyl-pyrazolin-5-one (II) exists as a mixture of the three most probable tautomeric structures IIa–IIc.



IIa IIb IIc

Our interest in this unresolved problem resulted from the finding that 2-methylmercapto-3-methyl-5,6,7,8-tetrahydroquinazolin-4-one (III)



III IV

reacts under reflux with hydrazine in alcohol to give the desired hydrazine derivative IV in low yields. On working up the reaction mixture a crystalline substance $C_7H_{10}N_2O$ was isolated, m.p. 298–300°. The ultraviolet absorption spectrum showed a maximum at 248 mμ. The infrared spectrum revealed a band at 3064 cm.$^{-1}$, the region of bonded NH, strong absorption at 2700 to 2200 cm.$^{-1}$ and moderate absorption at 1613 cm.$^{-1}$ (see Table I). The empirical formulation and some of the spectral data indicated that the compound could be 4,5,6,7-tetrahydro-3(1)-indazolone (IX) which was synthesized readily by condensing ethyl 2-oxocyclohexanecarboxylate (VI) with hydrazine. The product was found to be

TABLE I

INFRARED ABSORPTION DATA[a]

	N–H, cm.$^{-1}$	$-N^+$, cm.$^{-1}$	C=N C=O or C—O$^-$, cm.$^{-1}$
A. 5-Pyrazolones			
3,4-Dimethyl-2-phenyl-pyrazolin-5-one (Ia)	3100	None	1665vs 1600m 1592m
3-Trifluoromethylpyrazolin-5-one	3288	2500 2380	1750m 1607s 1512ms
1-Methyl-3-trifluoromethylpyrazolin-5-one		2600 2475	1590s 1515ms
1-Phenyl-3-trifluoromethylpyrazolin-5-one	3120	2710 2600 2500 2400	1750w 1600ms 1572s 1500ms
VIII			1700s 1622m
IX[b]	3064	2700–2200s Peak at 2640	1613s 1588vs 1545ms
X[b]	3040	2800–2500s	1640s 1613vs 1595vs 1510s
XII[c]		None	1670s 1600s
XIII	3165 3062	None	1695 1611
XVII[b]	3098	2700–2200s	1605vs 1535s
2-*n*-Butyl-4,5,6,7-tetrahydro-3(1)-indazolone		2634	1600w 1530s 1510s
3a-β-Diethylaminoethyl-4,5,6,7-tetrahydro-3(1)-indazolone hydrobromide	3172	2470s 2654s 2744s	1694 1624
XIV	3190 3055	None	1689 1624

[a] The spectral data recorded were obtained by a recording Perkin–Elmer infrared spectrometer, model 21. All samples were mulled in Nujol. [b] W. Dieckmann, *Ann.*, **317**, 102 (1901). [c] J. Lee and W. G. Christiansen, *J. Am. Pharm. Assoc.*, **25**, 691 (1936).

(1) J. Knorr, *Ann.*, **238**, 137 (1887).

(2) R. D. Brown, A. A. Hukins, R. J. W. Le Fevre, J. Northcott and I. R. Wilson, *J. Chem. Soc.*, 2812 (1949).

(3) S. Veibel, K. Eggerson and S. C. Linholt, *Acta Chem. Scand.*, **8**, 768 (1954).

(4) R. Kitamura, *J. Pharm. Soc. Japan*, **60**, 45 (1940).

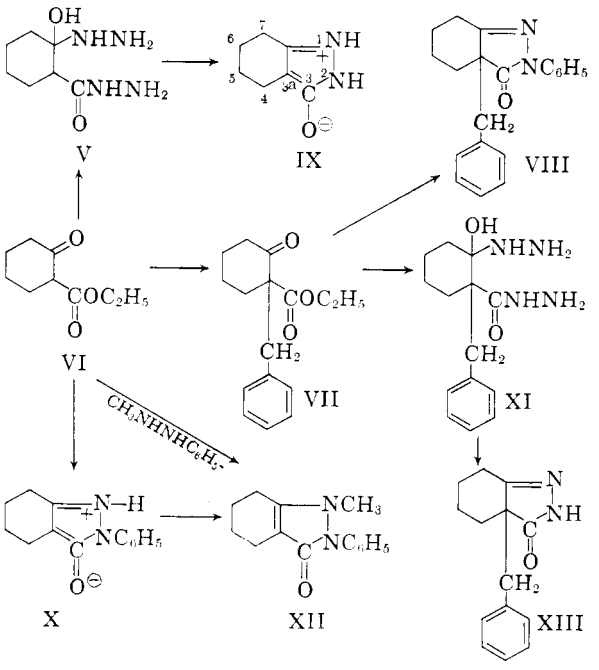
(5) D. Biguard and P. Grammaticakis, *Bull. Soc. Chim. France*, **8**, 246 (1941).

identical with the compound in question including the strong absorption in the infrared at 2700 to 2200 cm.$^{-1}$.

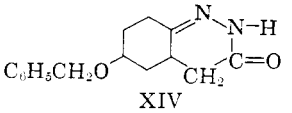
It has been amply demonstrated[6] that such strong absorption bands are associated with acid salts or zwitterionic type compounds. Thus, it appeared that infrared data, which heretofore had not been used to advantage in this series, might be of some help in elucidating some of the structural details of this class of heterocycle. In Scheme I are outlined some of the reactions that were carried out in this study.

Ethyl 1 - benzyl - 2 - oxocyclohexanecarboxylate (VII) was condensed first with hydrazine to yield XIII. If the enol or zwitterion form suggested by the aforementioned authors were present, then the strong absorption bands at 2700 to 2200 cm.$^{-1}$ should still prevail. This was not found to be the case, showing that the electron displacement does not occur through the amide nitrogen. A strong cyclic amido band is present at 1689 to 1700 cm.$^{-1}$ and the C–N band is found at 1611–1624 cm.$^{-1}$ and is of medium strength. Corroboration of these initial conclusions was obtained by the study of the infrared spectrum of XIV.

SCHEME I



Resonance stabilization in such a structure is ruled out accounting for the absence of the 2700 to



XIV

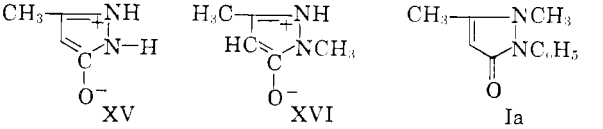
2200 cm.$^{-1}$ bands. The amide band is present at 1689 cm.$^{-1}$ and a band of medium strength appears at 1620 cm.$^{-1}$ for C=N vibration.

On the other hand, 2-phenyl-4,5,6,7-tetrahydro-3(1)-indazolone (X) does give a strong band at 2700 to 2200 cm.$^{-1}$. The conversion of X to 1 - methyl - 2 - phenyl - 4,5,6,7, - tetrahydro - 3(1)-indazolone (XII) through methylation with dimethyl sulfate (see reference *c* in Table I) resulted in a compound completely devoid of absorption in this region of the infrared. Compound XII was synthesized unambiguously by condensing symmetrical methylphenylhydrazine with ethyl 2-oxocyclohexanecarboxylate. Finally, conversion of VII to VIII gave a compound which again did not exhibit absorption bands at 2700 to 2200 cm.$^{-1}$.

In summary then, these results show that substitution at carbon 3a in the tetrahydro-3(1)-indazolone system insulates the electrophilic carbonyl group from the basic nitrogen (N′), thus inhibiting electron displacement and the formation of a zwitterion. When the basic nitrogen is substituted (*e.g.*, XII) the amide form is favored over the dipolar structure. The infrared spectra of all such compounds then are devoid of absorption bands at 2700 to 2200 cm.$^{-1}$. The data outlined in Table I on pyrazolin-5-ones and tetrahydro-3(1)-indazolones lend support to this conclusion. Consequently, infrared spectroscopy serves as a useful tool in approximating whether one or more canonical species contribute more significantly to the true structure of these heterocyclic compounds in the solid state.

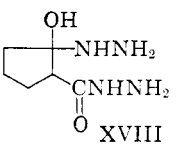
Therefore, the true structure of 4,5,6,7,-tetrahydro-3(1)-indazolone more closely approximates IX. Further support for this conclusion is had by the strong broad and sometimes split absorption bands at 1600 to 1620 cm.$^{-1}$. Although it is known[7] that the C=N$^+$H group absorption appears at 1660 to 1680 cm.$^{-1}$, the resulting shift to the longer wave length in our series is explicable by the zwitterion. The amidocarbonyl group whose double bond character has been reduced by the dipolar structure is also expected to absorb at 1600 to 1620 cm.$^{-1}$, thus accounting for the broadness of the absorption band in this area.

We have also found that 3-methylpyrazolin-5-one (XV) and 1,3-dimethylpyrazolin-5-one (XVI) give strong absorption bands at 2700 to 2400 cm.$^{-1}$, whereas these bands are absent in the spectrum of antipyrine (Ia). Thus, the predominating structure of these compounds can be written as



XV XVI Ia

In correlating these results with other cycloalkeno derivatives, it was observed that ethyl 2-oxocyclopentanecarboxylate reacted with hydrazine only with difficulty to give 3a,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-one (XVII). A close examination of the mother liquors led to the isolation of 2-hydrazino-2-hydroxycyclopentanecarbo-



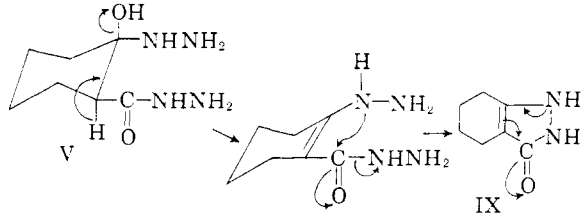
XVIII

(6) B. Witkop, THIS JOURNAL, **78**, 2873 (1956).

(7) N. J. Leonard and V. W. Gash, *ibid.*, **76**, 2781 (1954).

hydrazide (XVIII) in 50% yield. Because of mechanistic implications, it was important to determine whether its analog were isolatable in the cyclohexane series. Compounds V and XI (see Scheme I) were indeed obtained although in small amounts. Moreover, it was found that greater amounts of V and XI could be obtained if the reaction were run in boiling ethyl alcohol. These intermediates were in turn converted to the corresponding tetrahydroindazolones by heating to melting.

The isolation of these intermediates indicates that compound XI undergoes dehydration to form the hydrazone which in turn undergoes cyclization. However, compound V is more likely to follow an alternate course. Assuming Barton's[8] rule that



bulkier groups are more favored in the equatorial conformation, then V can readily undergo *trans* elimination of water to give IX. Electronic displacement to the electrophilic carbonyl is then more likely than the proton shift necessary if the hydrazone were formed.

Thus, it would appear that substitution at C_1 of 2-oxocyclohexane-carboxylate merely alters the path of dehydration leading to the heterocyclic compound. However, that position 3a is not the source of the proton in IX and X cannot be established unequivocally at this time.

Acknowledgments.—The authors take this opportunity to thank Dr. E. Schlittler for his interest and encouragement. We are indebted to Mr. George Robertson, Miss Pat Gallant and Mrs. Louise Porter for the micro analyses and Mr. Herbert Behrens for the infrared data.

Experimental[9]

4,5,6,7-Tetrahydro-3(1)-indazolone. From 2-Hydrazino-3-methyl-5,6,7,8-tetrahydro-quinazolin-4-one (III).[10]—Six grams of III was heated under reflux with 15 ml. of hydrazine hydrate dissolved in 25 ml. of ethyl alcohol for 4 hours. Methyl mercaptan was evolved. The solution was chilled and acidified with glacial acetic acid. The precipitate which was obtained was recrystallized from ethyl alcohol to give 1.2 g. of pure substance, m.p. 298–300°.

Anal. Calcd. for $C_7H_{10}N_2O$: C, 60.84; H, 7.29; N, 20.28. Found: C, 60.88; H, 7.25; N, 20.28.

This material was identical with that obtained through condensation of ethyl 2-oxocyclohexanecarboxylate with hydrazine hydrate according to the conditions outlined by W. Dieckmann. Mixture melting point gave no depression.

2-Hydrazino-2-hydroxycyclopentanecarbohydrazide (XV-III).—A mixture of 5.25 g. (0.03 mole) of ethyl 2-oxocyclopentanecarboxylate and 15 ml. of hydrazine hydrate was heated at 125° for 3 hours. On chilling, 1.2 g. of crystals, m.p. 180–184°, was obtained. These were recrystallized from ethyl alcohol to give 1.0 g. of product, m.p. 184–185°. This compound only exhibited end absorption in the ultraviolet. The infrared spectrum showed a strong band at 1640 cm.$^{-1}$ (amide) but no absorption band at 1600–1610 cm.$^{-1}$, the region for C=N.

Anal. Calcd. for $C_6H_{14}N_4O_2$: C, 41.41; H, 8.11; N, 32.20. Found: C, 41.22; H, 8.10; N, 32.41.

2-Hydrazino-2-hydroxycyclohexanecarbohydrazide (V).—A solution of 3.4 g. (0.02 mole) of ethyl 2-oxycyclohexanecarboxylate, 10 ml. of hydrazine hydrate and 30 ml. of ethyl alcohol was refluxed for 2 hours. On cooling, 4,5,6,7-tetrahydro-3(1)-indazalone was filtered off. The alcohol was removed *in vacuo* from the mother liquor and the resulting oil was allowed to stand for several days at room temperature. A small amount of crystals (0.1 g.) separated which were collected and washed with a small amount of ethyl alcohol. The substance, m.p. 196–198°, was submitted for analysis without further purification. This compound also exhibited only end absorption in the ultraviolet. When compounds V or XVIII were heated to melting, they were converted to the corresponding heterocyclic compound.

Anal. Calcd. for $C_7H_{16}N_4O_2$: C, 44.85; H, 8.52. Found: C, 44.53; H, 8.40.

3a-Benzyl-4,5,6,7-tetrahydro-3(1)-indazolone (XIII).—Fifteen grams (0.057 mole) of ethyl-1-benzyl 2-oxocyclohexanecarboxylate[11] and 45 ml. of hydrazine hydrate were refluxed for 4 hours. After chilling the solution, the precipitate was collected and recrystallized from ethyl alcohol to give 11 g. of fine white needles, m.p. 180–182°, $\lambda_{max}^{C_2H_5OH}$ 245, ϵ 3810.

Anal. Calcd. for $C_{14}H_{16}N_2O$: C, 73.66; H, 7.06; N, 12.27. Found: C, 73.30; H, 7.03; N, 12.26.

The mother liquor was concentrated *in vacuo* to one-half its volume and then chilled overnight. The white powder which separated out of solution was collected on a filter and then recrystallized from ethyl alcohol; yield 1.5 g., m.p. 143–144°. This analyzed for 1-benzyl-2-hydrazino-2-hydroxycyclohexanecarbohydrazide. This compound exhibited only end absorption in the ultraviolet.

Anal. Calcd. for $C_{14}H_{22}N_4O_2$: C, 60.41; H, 7.97; N, 20.13. Found: C, 60.40; H, 7.86; N, 20.03.

3a-Benzyl-2-phenyl-4,5,6,7-tetrahydro-3(1)-indazolone (VIII).—Four grams (0.015 mole) of the ester VII was heated at 125° for 2.5 hours with 1.65 g. (0.015 mole) of phenylhydrazine. At the end of this time, the dark viscous solution was distilled at reduced pressure. The product distilled over at 210–214° (0.6 mm.). This oil after trituration with petroleum ether (b.p. 35–60°) crystallized; yield 1.3 g., m.p. 78–80°.

Anal. Calcd. for $C_{20}H_{20}N_2O$: C, 78.91; H, 6.62; N, 9.21. Found: C, 79.08; H, 6.59; N, 9.01.

3a-β-Diethylaminoethyl-4,5,6,7-tetrahydro-3(1)-indazolone.—Ethyl 1-β-diethylaminoethyl-2-oxocyclohexanecarboxylate[12] (3.5 g.) was refluxed with 10 ml. of hydrazine hydrate for 8 hours. After chilling overnight, a gelatinous mass was obtained. The gel was dissolved in 50 ml. of water and extracted with ether. After drying the extract over anhydrous magnesium sulfate, the solution was filtered and dry hydrogen bromide gas was bubbled into the ether filtrate. The crude hydrobromide salt was collected on a filter and then recrystallized from ethyl alcohol–ethyl acetate (1:1) to yield 1.5 g. of product, m.p. 184–185°.

Anal. Calcd. for $C_{13}H_{24}BrN_3O$: C, 49.06; H, 7.61; N, 13.21. Found: C, 48.89; H, 7.54; N, 13.24.

2-n-Butyl-4,5,6,7-tetrahydro-3(1)-indazolone.—To 50 ml. of dry toluene there was added 3.75 g. (0.027 mole) of 4,5,6,7-tetrahydro-3(1)-indazolone and 2.42 g. (0.027 mole) of 55% sodium amide. The mixture was refluxed for 5 hours whereupon an equivalent amount of *n*-butyl bromide was added. After refluxing for an additional 14 hours, the solution was filtered and the filtrate was evaporated to a viscous mass *in vacuo*. The residue crystallized upon standing and was recrystallized from ethyl alcohol to give 1.3 g. of white needles, m.p. 114–115°.

Anal. Calcd. for $C_{11}H_{18}N_2O$: C, 68.01; H, 9.34; N, 14.42. Found: C, 67.76; H, 9.50; N, 14.32.

3-Trifluoromethylpyrazolin-5-one.—Four grams (0.022 mole) of ethyl trifluoroacetoacetate[13] was added to 1.4 g.

(8) D. H. R. Barton and R. C. Cookson, *Quart. Revs.*, **10**, 44 (1956).

(9) All melting points reported are uncorrected.

(10) G. deStevens, A. Halamandaris, P. Wenk, R. A. Mull and E. Schlittler, *Arch. Biochem. and Biophys.*, **83**, 141 (1959).

(11) J. W. Cook and C. L. Hewett, *J. Chem. Soc.*, 62 (1936).

(12) J. A. Barltrop, *ibid.*, 399 (1947).

(13) This compound was obtained from the Chem-Peninsular Co., Gainesville, Fla.

(0.045 mole) of hydrazine hydrate dissolved in 25 ml. of ethyl alcohol. The solution was refluxed for 2 hours. After removal of the alcohol *in vacuo*, 20 ml. of water was added and the residue and the solution were acidified to *p*H 3 with concentrated hydrochloric acid. On standing, crystals were formed which were collected and recrystallized from ethyl ether–petroleum ether (1:1). The yield of product melting at 210–212° was 2.5 g.

Anal. Calcd. for $C_4H_3F_3N_2O$: C, 31.59; H, 1.99; N, 18.42. Found: C, 31.77; H, 2.10; N, 18.47.

1-Methyl-3-trifluoromethylpyrazolin-5-one.—Methylhydrazine sulfate (5.9 g., 0.041 mole) was dissolved in 10 ml. of water. This solution was neutralized with an equivalent amount of potassium hydroxide whereupon a clear solution was obtained. To this solution there was added 5.0 g. (0.027 mole) of ethyl trifluoroacetoacetate. After the addition of another 10 ml. of water the solution was refluxed for 2 hours. During the reflux period an oil separated out of solution which, on chilling, crystallized. The solid material was collected and, after drying, was recrystallized from ethyl ether–petroleum ether (1:1) to give 1.1 g. of product, m.p. 174–175.5°.

Anal. Calcd. for $C_5H_5F_3N_2O$: C, 36.15; H, 3.04; N, 16.87. Found: C, 36.38; H, 3.28; N, 16.88.

1-Phenyl-3-trifluoromethylpyrazolin-5-one, m.p. 185–187°, was prepared in 75% yield by condensing ethyl trifluoroacetoacetate with phenylhydrazine at 125° for 4 hours. The compound as recrystallized from ethyl alcohol–water mixture.

Anal. Calcd. for $C_{10}H_7F_3N_2O$: C, 52.64; H, 3.09; N, 12.28. Found: C, 52.53; H, 3.19; N, 12.45.

6-Benzyloxy-2,3,4,4a,5,6,7,8-octahydro-3-cinnoline, m.p. 137–138°, was prepared essentially according to the method outlined by Clarke and Lapworth.[14]

Anal. Calcd. for $C_{15}H_{18}N_2O_2$: C, 69.75; H, 7.03; N, 10.58. Found: C, 69.98; H, 7.08; N, 11.10.

(14) R. W. J. Clarke and A. Lapworth, *J. Chem. Soc.*, **89**, 1869 (1906).

SUMMIT, N. J.

[CONTRIBUTION FROM THE BIOLOGICAL AND CHEMICAL RESEARCH DIVISIONS OF G. D. SEARLE AND CO.]

Microbiological Transformations. IV. The Oxidation of Dehydroisoandrosterone at C-7

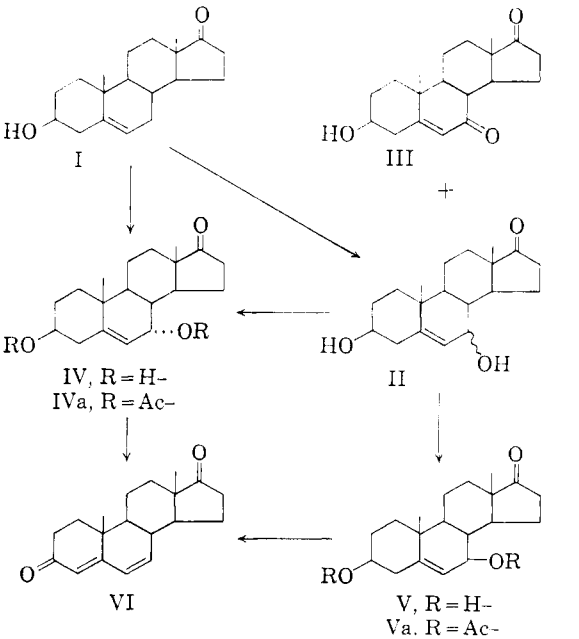
BY R. M. DODSON, R. T. NICHOLSON AND R. D. MUIR

RECEIVED JUNE 15, 1959

The structure and configurations of 7α-hydroxydehydroisoandrosterone and 7β-hydroxydehydroisoandrosterone, obtained by microbiological oxidation of dehydroisoandrosterone, were established. A mixture of these two materials behaves like a molecular compound.

The selective hydroxylation of steroids by microörganisms was first demonstrated by Kramli and Horvath[1] by their conversion of cholesterol to 7-hydroxycholesterol with *Proactinomyces roseus*. More recently Murray and Peterson[2] have demonstrated the 7β-hydroxylation of 3β-hydroxyallopregnan-20-one and 3β-hydroxy-5-pregnen-20-one with *Rh. arrhizus*. The latter compound also was hydroxylated 7β by *Rh. nigricans*.[2] Kahnt and coworkers[3] also have shown the 7β-hydroxylation of a 3β-hydroxyallopregnane with a species of Rhizopus. During our studies on the C-1 hydroxylation of dehydroisoandrosterone,[4] we uncovered a number of organisms which oxidized dehydroisoandrosterone at C-7.

Fermentation of dehydroisoandrosterone (I) by the methods previously described[5] with a species of Rhizopus (M 2045) isolated in our laboratories gave a monohydroxydehydroisoandrosterone (II), m.p. 193–196°, which crystallized readily from acetone and which, in most respects, behaved like a pure compound.[6] Chromatography of the residues from the isolation of II yielded 7-oxodehydroisoandrosterone (III) and 7β-hydroxydehydroisoandrosterone (V), m.p. 215–216°, but no II. Chromatography of II on silica gel yielded a small quantity of V, in the initial fractions eluted with 50% ethyl acetate in benzene, but most of the material was recovered unchanged, m.p. 195–197.5°. A paper chromatography study of II failed to show the presence of more than one compound.



(1) A. Kramli and J. Horvath, *Nature*, **162**, 619 (1948); **163**, 219 (1949).

(2) H. C. Murray and D. H. Peterson, U. S. Patent 2,702,809, Feb. 22, 1955; U. S. Patent 2,703,326, March 1, 1955; U. S. Patent 2,602,769, July 8, 1952; S. H. Epstein, P. D. Meister, H. C. Murray and D. H. Peterson, "Vitamins and Hormones," Vol. XIV, Academic Press, Inc., New York, N. Y., 1956, p. 359.

(3) F. W. Kahnt, Ch. Meystre, R. Neher, E. Vischer and A. Wettstein, *Experientia*, **8**, 422 (1952).

(4) R. M. Dodson, A. H. Goldkamp and R. D. Muir, THIS JOURNAL, **79**, 3921 (1957).

(5) D. H. Peterson, H. C. Murray, S. H. Eppstein, L. M. Reineke, A. Weintraub, P. D. Meister and H. M. Leigh, *ibid.*, **74**, 5933 (1952).

(6) This same material was also separated directly by crystallization from fermentations of dehydroisoandrosterone with two other strains of Rhizopus (M 2052 and M 2051). The identity of these materials was established by comparison of their infrared spectra and by the lack of depression in the m.p.'s of their mixtures.