determined by hydroxamate formation and radioactivity. The purity of the thiophenylmalonic ester was 98% as determined by measuring the extinction at 237 mμ ($E = 8.4 \times 10^3$) in ethanol and the yield of hydroxamic acid. The thiophenylmalonate was concentrated under reduced pressure and a slight excess was added slowly with shaking to a solution of 10 μM. of coenzyme A in 0.1 *M* bicarbonate buffer at *p*H 8.0. Nitrogen was bubbled through the mixture at 0° for 3 hours. The mixture was then acidified and extracted several times with ether. In the aqueous phase 7.5 μM. of malonyl-CoA was obtained which had an hydroxamate:adenine ratio of 0.66. The aqueous phase was then lyophilized or frozen. The aqueous phase which contained some unreacted CoA could be purified by paper chromatography in 0.1 *M* potassium acetate at *p*H 4.5:ethanol 1:1 at 4°. The eluted material was 96% pure based on the ratio of hydroxamic acid to adenine. The yield was 4.5 μM. of malonyl coenzyme A. Chromatography of the hydroxamic acid derivatives obtained from malonyl CoA yielded R_f values of 0.36 in water-saturated 1-butanol[6] and 0.5 in pyridine:2-butanol:water (1:1:1).[7] The over-all yield in respect to malonic acid-C^{14} was 18–27%.

When malonyl-C^{14} CoA was incubated with an enzyme system which synthesized fatty acids from malonyl CoA and acetyl CoA, radioactivity was incorporated into palmitic acid in good yield. Methylmalonyl CoA also has been prepared satisfactorily by this procedure.

(6) O. Hayaishi, *J. Biol. Chem.*, **215**, 125 (1955).
(7) P. R. Vagelos, THIS JOURNAL, **81**, 4119 (1959).

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RECEIVED APRIL 18, 1960

THE PHOTOLYSIS OF ORGANIC NITRITES. I. 18-NITRILOPROGESTERONE: CORRELATION WITH CONESSINE

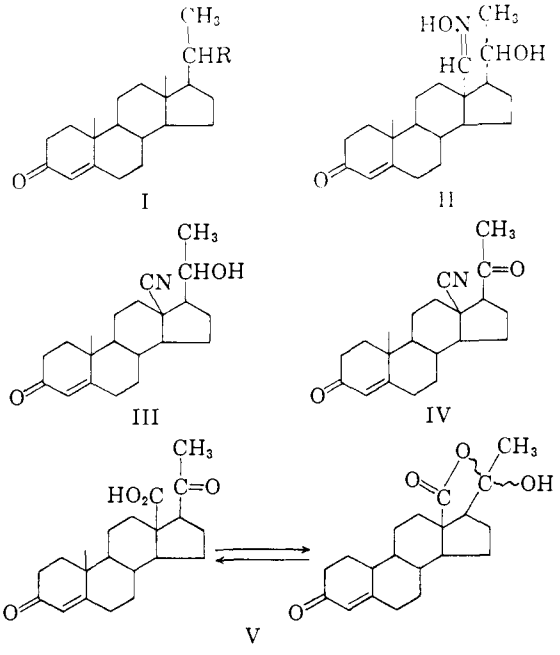
Sir:

The discovery that it is possible to effect specific intramolecular hydrogen abstraction by the photolysis of a strategically located nitrite ester grouping already has led to a simple synthesis of the potent cortical steroid aldosterone.[1] This general method opened the way to analogous syntheses of a variety of steroidal structures heretofore not easily accessible. We wish to describe here the synthesis of 18-nitriloprogesterone (IV).

20β-Hydroxy-4-pregnene-3-one (I, R = β-OH) in pyridine, upon treatment with nitrosyl chloride, gave the corresponding nitrite ester (I, R = β-ONO; m.p. 153–157°; $[\alpha]^{23}D$ + 92.3 ($CHCl_3$); ϵ_{241}^{MeOH} = 17,590; λ^{Nujol} at 5.98, 6.18, 6.25 and 10.88 μ; found: C, 72.94; H, 9.01; N, 4.26), which, upon irradiation in benzene,[2] gave a mixture of at least seven substances (paper chromatography).

(1) D. H. R. Barton, J. M. Beaton, L. E. Geller and M. M. Pechet, THIS JOURNAL, **82**, 2640 (1960); D. H. R. Barton and J. M. Beaton, *ibid.*, **82**, 2641 (1960). The Schering group is grateful to those authors for communicating their experimental results prior to publication. Schering's activities in this field are a direct extension of this information.

(2) We wish to thank Mr. Robert Armswood for his assistance with the photolysis reactions.



Column chromatography furnished, in addition to small amounts of progesterone and starting 20β-ol (I), some 15% of 20β-hydroxy-18-oximino-4-pregnen-3-one (II, 20β-OH; m.p. 242–243°; $[\alpha]^{24}D$ + 154.2; ϵ_{241}^{MeOH} = 16,800; λ^{Nujol} at 2.85, 3.14, 6.05, 6.18 and 10.75 μ; found: 73.01; H, 9.34; N, 4.29). On the other hand, a like series of reactions with the 20α-hydroxy-4-pregnen-3-one (I, R = α-OH), via the nitrite (I, R = α-ONO; m.p. 192–198°; $[\alpha]^{23}D$ + 103.9; ϵ_{240}^{MeOH} = 19,000; λ^{Nujol} at 6.00, 6.14, 6.20, 6.29, and 12.78 μ; found: N, 4.21), gave the oxime (II, 20α-OH; m.p. 184–186°, $[\alpha]^{24}D$ + 148.8, ϵ_{241}^{MeOH} = 17,300, λ^{Nujol} at 2.95, 3.10, 6.04 and 6.19 μ; found: C, 73.18; H, 8.86; H, 4.03) in 60% yield by direct crystallization from the photolysis mixture. This difference in yield is believed to reflect the more favorable conformation of the active intermediate in the 20α-series *vis-à-vis* the angular methyl group.[3]

Both oximes were converted to a common derivative by destroying assymetry at C-20: the "α-oxime" (II, 20α-OH) was smoothly dehydrated to 20α-hydroxy-18-nitrilo-4-pregnen-3-one (III, 20α-OH; m.p. 237–241°; $[\alpha]^{24}D$ +136.2; ϵ_{239}^{MeOH} = 16,400, λ^{Nujol} at 2.97, 4.46; 6.01 and 6.6 μ; found: C, 76.99; H, 8.70; N, 4.31) by hot pyridine–acetic anhydride and then alkaline hydrolysis. In the same manner, conversion of the "β-oxime" (II, 20β-OH) gave the isomer (III, 20β-OH; m.p. 166–168°; $[\alpha]D$ + 115.9; $\epsilon_{239.5}^{MeOH}$ = 17,000; λ^{Nujol} at 2.88, 4.46, 5.99 and 6.17 μ; found: C, 76.80; H, 8.75; N, 4.30). Both of these were oxidized with chromic acid to 18-nitrilo-4-pregnene-3,20-dione (IV, 18-nitriloprogesterone, m.p. 138–140°; [α] + 137.1; ϵ_{239}^{MeOH} = 16,700; λ^{Nujol} at 4.48, 5.82, 6.02 and 6.18 μ; found: C, 77.31; H, 7.96; N, 4.51).

(3) In a very recent communication; a group of French workers have found a similar stereo-dependency in the attack on the angular methyl group mediated by lead tetraacetate; *vide* L. Velluz, G. Muller, R. Bardoneschi and A. Poittevin, *Compt. rend.*, 725 (1960).

Structure proof was provided by converting IV to 3,20-diketo-4-pregnen-18-oic acid (V) by hydrolysis in 60% sulfuric acid. A base-soluble product thus obtained was identical in melting point, paper-chromatographic migration rate and infrared spectrum with a genuine sample obtained from conessine.[4]

(4) R. Pappo, THIS JOURNAL, **81**, 1011 (1959). We wish to thank Dr. Pappo for his kindness in providing us with the comparison sample.

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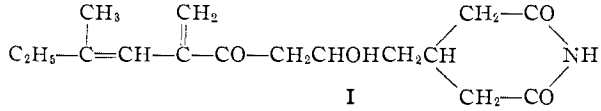
RECEIVED APRIL 29, 1960

STRUCTURE OF THE ANTIBIOTIC STREPTIMIDONE

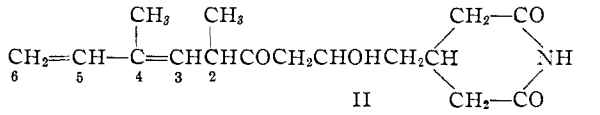
Sir:

Recently structure I was proposed for a new



I

Streptomyces antibiotic, streptimidone.[1] It appeared to us that certain of the recorded properties, in particular the base-catalyzed conversion of the existing chromophore to a 2,4-dienone system, could be better interpreted in terms of an alternative, II. We have now found that, by employing



II

nuclear magnetic resonance data, a clear decision in favor of the latter possibility can be made.

The n.m.r. spectrum[2] of O-acetylstreptimidone[3] displays the following major absorptions, due to hydrogens of the type indicated: (a) −106 (imide); (*b*) *ca.* −25 to +75 (olefinic, and acetoxyl methine); (c) *ca.* +100 to +175 (saturated methine and methylene); (d) +178 and +186 (4- and acetyl methyls), (e) +214 (2-methyl). The hydrogen peak ratio (1:5) of (a) to (b) supports formulation II, but not I. Furthermore, proposal I predicts essentially a simple three peak pattern in region (b), whereas that area features in fact an irregular quadruplet centered at about 0 (one hydrogen), and broadened doublets at about +45 and +62 (four hydrogens). This absorption character corresponds to a superimposition of an "AB" (2- and 3-hydrogens) upon an "ABX" (5- and 6-hydrogens) pattern,[4] and corresponds well to that exhibited by isoprene,[5] a close model for the unsaturated portion of II. Finally, the C-methyl group designated as (e) is split, as required, by the methine hydrogen at position 2; structure I, on the other hand, bears a methyl group in the ethyl unit, and would have given rise to a triplet in (e).

The ultraviolet spectrum (λ_{Max}^{MeOH} 232 and 291 mμ, ϵ 23,100 and 790)[1] and infrared absorption *in solution (inter alia*, 5.8 μ, ketone –CO–; 5.9 μ, imide –CO–; 6.0 (w) and 6.1 (w), diene)[1] are consistent with the revised structure, II. This formula is also compatible with the recorded chemical behavior,[1,6] and has been confirmed by additional chemical findings obtained more recently in the laboratories of the Research Division of Parke, Davis and Company.[7]

(1) R. P. Frohardt, H. W. Dion, Z. L. Jakubowski, A. Ryder, J. C. French and Q. R. Bartz, THIS JOURNAL, **81**, 5500 (1959).

(2) Obtained in $CDCl_3$ solution with a Varian Associates instrument operating at 40 mc. Chemical shifts given in cps. relative to benzene = 0.

(3) We wish to thank Dr. Q. R. Bartz (Parke, Davis and Company) for his coöperation, especially for his kindness in supplying a sample of the derivative used in this investigation.

(4) Pople, Schneider and Bernstein, "High Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., New York, N. Y., 1959, p. 132.

(5) Pople, Schneider and Bernstein, *ibid.*, p. 244.

(6) The positive *m*-phenylenediamine test for an α,β-unsaturated ketone is regarded as due to either prior isomerization of II to a conjugated ketone system, or to dehydration of the aldol moiety.

(7) Re-examination of the ozonolysis of streptimidone has revealed that formaldehyde and pyruvaldehyde are the end products, not formaldehyde and methyl ethyl ketone as reported previously (ref. 1). The latter ketone originated as an impurity in the reagent ethyl acetate (distilled from 2,4-dinitrophenylhydrazine) which was used as a solvent in the isolation procedure (personal communication from H. W. Dion, Parke, Davis and Company).

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RECEIVED APRIL 8, 1960

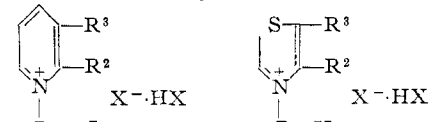
ANTIPARASITIC DRUGS. III. THIAMINE-REVERSIBLE COCCIDIOSTATS

Sir:

We have found that many 1-(2-alkyl-4-amino-5-pyrimidinylmethyl)-alkylpyridinium salts possess marked prophylactic activity in coccidiosis, a protozoan disease of importance in poultry production. Analogous 3-thiazolium compounds are also effective.

The new anticoccidial agents are related structurally to thiamine (II: R^1 and R^2, CH_3, R^3, CH_2CH_2OH) and function by a reversible thiamine inhibition mechanism. These quaternaries, administered in feed, are selectively effective against coccidia of the digestive tract and make possible adequate disease prevention without adverse effect upon the growth of chickens. Another relative of the new coccidiostats is the thiamine antagonist pyrithiamine (neopyrithiamine, I: R^1 and R^2, CH_3, R^3, CH_2CH_2OH).[1]

Compounds of types I and II are made by reaction of 2-alkyl-4-amino-5-pyrimidinylmethyl halide



P is 2-R′-4-amino-5-pyrimidinylmethyl

dihydrohalide with excess pyridine or thiazole base in acetonitrile or other solvents. The synthesis of the 2-methylpyrimidine intermediate has been described by Grewe.[2] Data on typical quaternaries are given in Table I.

(1) A. H. Tracy and R. C. Elderfield, *J. Org. Chem.*, **6**, 54 (1941); A. N. Wilson and S. A. Harris, THIS JOURNAL, **71**, 2231 (1949).

(2) R. Grewe, *Naturwiss.*, **24**, 657 (1936); *Z. physiol. Chem.*, **242**, 89 (1936).