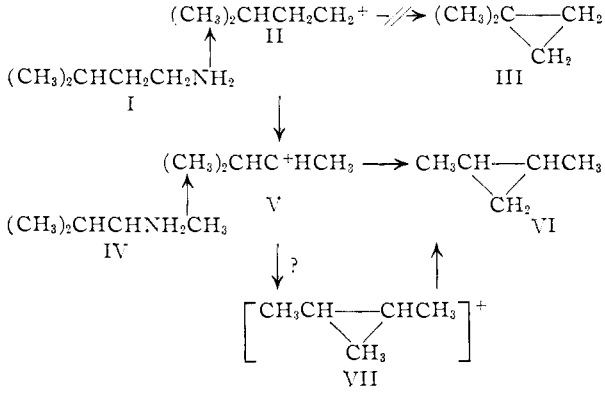
dation and infrared spectra.[4] In the original hydrocarbon fraction, the *cis* isomer is present to the extent of 5.6%, and the *trans*, to the extent of 10.1%. This is the first time that the formation of a cyclopropane from the deamination of a saturated amine (IV → VI) has been reported.

It seemed possible that similar cyclizations might be observable in other systems. For instance, the 3-methyl-2-butyl cation (V) could be formed by hydrogen migration in the isoamyl cation (II), which in turn could be generated by the deamination of isoamylamine (thus, I → II → V). If the 3-methyl-2-butyl cation were implicated in the formation of 1,2-dimethylcyclopropane from the deamination of IV, then the 3-methyl-2-butyl cation formed by this alternative path from isoamylamine might also yield 1,2-dimethylcyclopropane (I → VI). On the other hand, the deamination of isoamylamine might produce 1,1-dimethylcyclopropane (I → III).

Experimentally, the deamination of isoamylamine gave a hydrocarbon fraction which contained 0.5% *cis*-1,2-dimethylcyclopropane and 1% *trans*-isomer, as determined by the procedures outlined above for the deamination of 3-methyl-2-aminobutane.[5] No 1,1-dimethylcyclopropane was detected in the deamination of isoamylamine and no cyclopropanes at all were detected in either the deamination of neopentylamine or in the acetolysis of 3-methyl-2-butyl *p*-toluenesulfonate.[3,6]



It is interesting to speculate on the mode of formation of these cyclopropanes. At least two possible explanations come to mind. First, a carbene-type mechanism may be involved, related to the "intramolecular insertion" reaction of diazoalkanes, recently described by Friedman and Shechter.[7] However, the conditions of the deamination reaction (acetic acid) do not appear favorable to the formation of a diazoalkane from an alkyldiazonium ion. The present observations on the behavior of isoamylamine and neopentylamine are also not readily accommodated in such a mechanism.[8]

A second explanation is that a discrete bridged methylcarbonium ion (VII) is produced and that this ion then loses a proton to yield the cyclopropanes.[9] Attempts at interpreting the results with isoamylamine and neopentylamine in terms of this mechanism also lead to difficulties, but they do not appear insurmountable. In any event, the present results and future experiments suggested by them should prove illuminating in the study of the nature of the intermediates in the amine–nitrous acid reaction.

The author thanks Dr. A. Kropf for helpful discussions.

(4) Infrared spectra were run at the University of Massachusetts, by kind permission of Dr. L. Carpino.

(5) The *cis*/*trans* ratio is about 1:2 for both isoamylamine and 3-methyl-2-aminobutane.

(6) It is estimated that 0.1% would have been detected in the present experiments.

(7) L. Friedman and H. Shechter, THIS JOURNAL, **81**, 5512 (1959).

(8) Decomposition of 2,2-dimethylpropanal tosylhydrazone (analogous to neopentylamine) gives a hydrocarbon fraction that is mainly 1,1-dimethylcyclopropane (ref. 7).

(9) D. J. Cram and J. E. McCarty, THIS JOURNAL, **79**, 2866 (1957), recently have discussed the question of bridged methylcarbonium ions.

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RECEIVED FEBRUARY 26, 1960

THE SYNTHESIS OF MALONYL-C^{14} COENZYME A

Sir:

Malonyl CoA has been established as one of the key intermediates in the biosynthesis of fatty acids.[1,2] In order to discover the detailed mechanism of the condensation of malonyl CoA with acyl CoA acceptors, it was essential to obtain isotopically labeled malonyl CoA of high purity in good yield. In a recent communication, Vagelos[3] has described a method for the synthesis of malonyl-coenzyme A, based on the preparation of a mixed anhydride of malonic acid. For the preparation of isotopically labeled malonyl CoA, the method of Vagelos seemed uneconomical since the over-all reported yield was of the order of 3.1 to 5.5% in respect to malonic acid. In our laboratory, a synthesis based on the observations of Khorana and co-workers[4] employing dicyclohexylcarbodiimide (DCC) as a condensing agent was used to synthesize the monothiophenyl ester of malonic acid. The latter compound was transesterified with coenzyme A according to the method of Wieland and Rueff.[5]

Experimental.—1 mM. of malonic acid (1-C^{14} or 2-C^{14}) and 1 mM. of thiophenol were dissolved in 5.0 ml. of N,N′-dimethylformamide at 0°. To the mixture was added with stirring over a period of 1 hour 500 mg. of DCC in 5 ml. of N,N′-dimethylformamide. The mixture was stirred for three hours at 0°. After the addition of 10 ml. of water, the stirring was continued for 15 minutes. The mixture was filtered with suction and the precipitate washed with water. The filtrate was made slightly acidic and extracted with several volumes of ether. The ether phase was washed with 0.01 *M* hydrochloric acid and with water. After drying over anhydrous sodium sulfate, the solution was shaken out with activated charcoal and filtered. The yield varied from 400 to 600 micromoles of monothiophenylmalonic ester as

(1) R. O. Brady, *Proc. U. S. Nat. Acad. Sci.*, **44**, 993 (1958).

(2) S. J. Wakil, THIS JOURNAL, **80**, 6465 (1958).

(3) P. R. Vagelos, *J. Biol. Chem.*, **235**, 346 (1960).

(4) H. G. Khorana, W. E. Razzell, P. T. Gilham, G. M. Tener and E. H. Pol, THIS JOURNAL, **79**, 1002 (1957).

(5) T. Wieland and L. Rueff, *Angew. Chem.*, **65**, 186 (1953).

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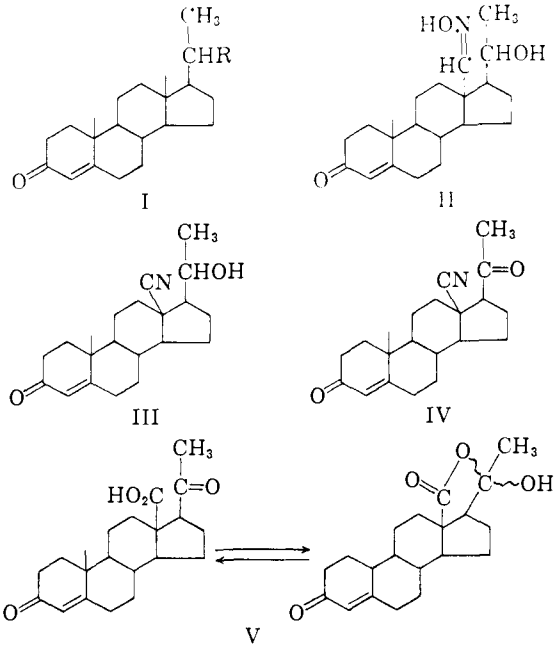
THE PHOTOLYSIS OF ORGANIC NITRITES. I. 18-NITRILOPROGESTERONE: CORRELATION WITH CONESSINE

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).



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).

(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.

(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).