

*Anal.* Calcd. for  $C_{20}H_{30}O_2$ : C, 79.42; H, 9.99. Found: C, 79.52; H, 10.25.

### Summary

Pure dehydroabiatic acid can be prepared very conveniently by the previous process but starting with Steele's abiatic acid. The Friedel and Crafts reaction of the ester with acetyl chloride gives chiefly the 6-acetyl derivative, but this is accompanied by a small amount of the 8-isomer with which it forms a stable molecular compound resolvable by preferential reaction with hydroxylamine.

The oxime of methyl 6-aminodehydroabietate rearranges smoothly on treatment with hydrogen chloride in acetic acid-anhydride and gives chiefly the acetylamine derivative, along with a small amount of the isomeric methyl amide. After

suitable hydrolysis, derivatives of these substances can be separated efficiently and pure 6-aminodehydroabiatic acid and its ester can be obtained by this route in good yield.

By hydrogenation over copper chromite catalyst methyl dehydroabietate and its 6-amino derivative can be converted smoothly to the carbinols. The amino alcohol on methylation with methyl iodide-silver oxide gives 6-dimethylamino-dehydroabietinol methyl ether, which is being tested for possible morphine-like actions. The phenols methyl 6-hydroxydehydroabietate and 6-hydroxydehydroabietinol were prepared from the amines by the diazo reaction; the latter substance has some of the structural features of oestradiol.

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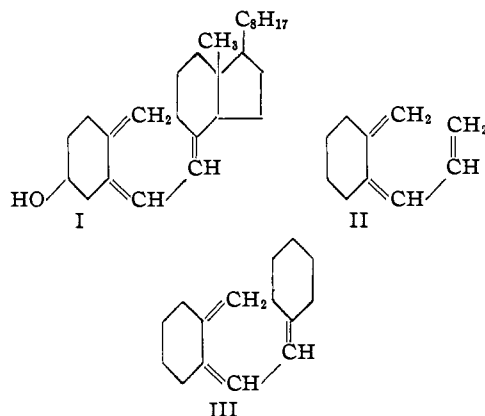
## Studies in the Synthesis of the Antirachitic Vitamins. I. The Synthesis of 3-[2'-Methylenecyclohexylidene-1']-propene-1

BY NICHOLAS A. MILAS AND W. LYSLE ALDERSON, JR.

Although the structure of the antirachitic vitamins has been fairly well elucidated, ultimate proof is lacking because they have not yet been synthesized from simple substances. Some time ago we undertook the problem of synthesis, but in view of its complexity we decided first to synthesize the most unstable portion of the vitamin molecule, then to build the other parts together with the necessary functional groups around this portion. The most unstable portion of an antirachitic vitamin, represented by structure I, is that which includes the three conjugated double bonds. This is known to be responsible for the characteristic spectrum of the vitamin and, together with the hydroxyl group and the side chain,<sup>1</sup> contributes to its antirachitic action.

Two of the simplest configurations which represent this portion of the antirachitic molecule are indicated by structures II and III. After a number of attempts on various reactions which would lead to the synthesis of II and III, we have found that in the case of II the reactions outlined by the equations below led to the expected product in fairly good yields. In view of similar work

(1) Milas and Milone, unpublished work which indicates that the side chain of the antirachitic vitamins plays an important role.

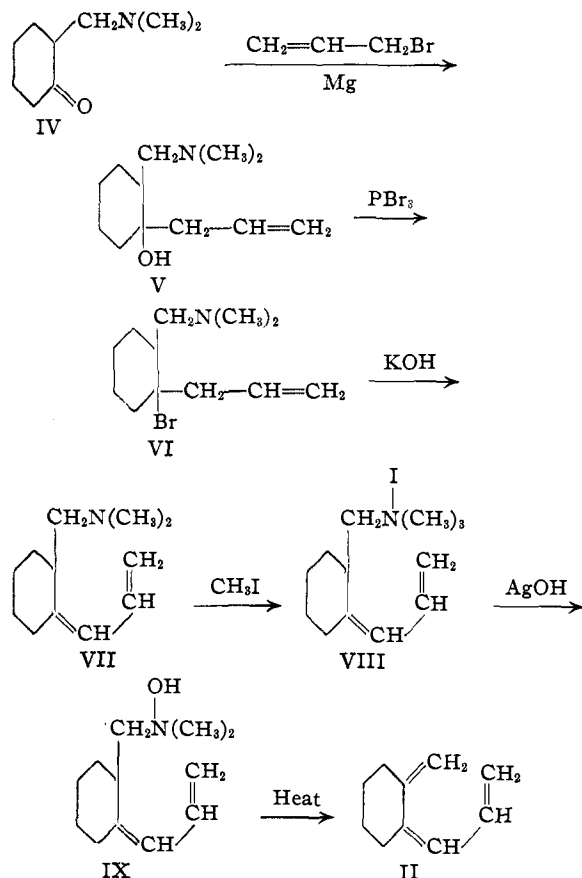


undertaken in other laboratories,<sup>2,3</sup> we are publishing at present the synthesis of II which will be followed shortly by that of III and other portions of the antirachitic molecule.

The ultraviolet absorption spectra of II and VII have been plotted side by side in Fig. 1. It may be seen readily that the amine VII absorbs rather strongly in the region of 236  $m\mu$ . Its extinction coefficient has been calculated to be 10,500, which is of the right order of magnitude

(2) Aldersley and Burkhart, *J. Chem. Soc.*, 545 (1938).

(3) Dimroth, *Ber.*, **71**, 1333, 1346 (1938); Dimroth and Jonsson, *ibid.*, **71**, 2658 (1938).



for substances of this type having two conjugated double bonds. The triene II has a very prominent band with a maximum at  $255 \text{ m}\mu$  which is slightly displaced toward the short ultraviolet as compared with the important maximum of calciferol at  $265 \text{ m}\mu$ . However, its molecular extinction coefficient agrees remarkably well with that of calciferol, vitamin  $\text{D}_3$  and vitamin  $\text{D}_4$  as shown in Table I.

TABLE I  
THE MOLECULAR EXTINCTION COEFFICIENT,  $\epsilon$ , OF THE  
ANTIRACHITIC VITAMINS

Calciferol <sup>4</sup> (Vitamin $\text{D}_2$ ) <sup>5</sup>	19,200 (18,200)
Vitamin $\text{D}_3$ <sup>5</sup>	19,200
Vitamin $\text{D}_4$ <sup>5</sup>	18,700
Triene II	19,000

### Experimental Part

**2-Dimethylaminomethyl Cyclohexanone-1 (IV).**—In the preparation of this ketone the procedure of Mannich and Braun<sup>6</sup> was followed. A mixture of 49 g. of cyclohexanone

(4) Morton, "Absorption Spectra of Vitamins and Hormones," Adam Hilger, Ltd., London, 1935, p. 11.

(5) Brockmann and Busse, *Naturwissenschaften*, **26**, 122 (1938); *Z. physiol. Chem.*, **256**, 252 (1938).

(6) Mannich and Braun, *Ber.*, **53**, 1875 (1920).

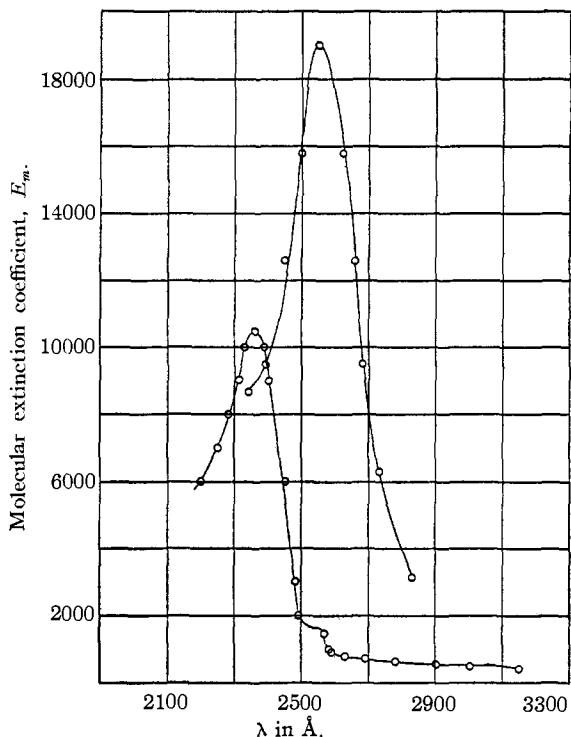


Fig. 1.—The absorption spectra of II and VII.

(b. p.  $155\text{--}156^\circ$ ), 9 g. of 39% formaldehyde solution (Merck) and 9 g. of dimethylamine hydrochloride was heated slowly over a free flame until refluxing commenced. The flame was then removed as the heat evolved by the reaction was sufficient to cause vigorous refluxing which subsided after about two minutes. After the reaction product was allowed to cool to room temperature, it was shaken with 50 cc. of water, the aqueous layer extracted several times with ether to remove any unconverted cyclohexanone, made alkaline with potassium hydroxide and the liberated amine extracted with ether, the ethereal solution dried over anhydrous sodium sulfate, filtered and the ether removed under reduced pressure. Finally, the amine was fractionally distilled and the fraction, 10 g., boiling at  $91\text{--}92^\circ$  (7 mm.) collected. The b. p. of this was redetermined at 13 mm. and found to be  $97\text{--}100^\circ$ . Mannich and Braun<sup>6</sup> report the b. p. of 2-dimethylaminomethylcyclohexanone-1 to be about  $100^\circ$  (13 mm.).

**2-Dimethylaminomethyl 1-Allylcyclohexanol-1 (V).**—A solution of 41.5 g. of 2-dimethylaminomethyl-cyclohexanone-1 in 100 cc. of anhydrous ether was added over a period of four hours to an efficiently stirred solution of allylmagnesium bromide<sup>7</sup> in 500 cc. of dry ether. A white precipitate was formed which remained insoluble in ether. After all the ketone had been added, stirring was continued for twelve hours, then the mixture was poured on ice which was mixed with ammonium chloride to decompose the addition product. The ether layer was separated, dried over anhydrous sodium sulfate, filtered, the ether removed under reduced pressure, the residue fractionated,

(7) (a) Gilman and McGlumphy, *Bull. soc. chim.*, **43**, 1825 (1928);

(b) Milas and McAlevy, *This Journal*, **57**, 581 (1935).

and the fraction boiling at 112–117° (5 mm.) collected; yield 34.3 g. This substance was a colorless oil with a rather unpleasant odor.

Inasmuch as it was nearly impossible to obtain this alcohol free from the diene, the dehydrated alcohol, and in order to identify it definitely, it was decided to prepare the acetate. Three grams of the dimethylamino alcohol was refluxed with 6 g. of acetic anhydride for one and a half hours. The product was then poured on cracked ice, neutralized with dilute potassium hydroxide, the resulting mixture extracted several times with ether and the ether extracts dried over anhydrous sodium sulfate, filtered and the ether removed in vacuum. The residue was then fractionated and the fraction, 1.8 g., boiling at 129–130° (9 mm.) collected and analyzed.

*Anal.* Calcd. for  $C_{14}H_{25}O_2N$ : N, 5.85. Found: N, 5.8, 5.9.

The acetate is a colorless viscous oil of a sharp, rather pleasant odor, having the physical constants:  $d^{25}_4$  0.9596;  $n^{25}_D$  1.4740. When exposed to air for long periods of time, it turns brown.

**3 - [2' - Dimethylaminomethylcyclohexylidene - 1']-propene-1(VII).**—Potassium acid sulfate, phenyl isocyanate, oxalic acid, phthalic anhydride, methylmagnesium iodide and the xanthate method of Tschugaeff were used for the dehydration of 2-dimethylaminomethyl-1-allylcyclohexanol-1. All gave varying yields of the dehydrated amine, but it was found that a purer product could be obtained in higher yields by first converting the alcohol into the bromide and eliminating hydrogen bromide with solid potassium hydroxide.<sup>7b</sup> Although the use of potassium acid sulfate led to satisfactory yields of a dehydrated product, its b. p. of 100–103° (9 mm.) was considerably lower than that produced by the use of the other reagents. This was probably the undesirable product in which the double bond migrated into the ring, a reaction which Wallach<sup>8</sup> has shown to take place readily with similar compounds under the influence of acid reagents.

**2-Dimethylaminomethyl-1-allylcyclohexyl Bromide-1 (VI).**—In view of its high instability this bromide was not isolated but was prepared as follows. Two grams of freshly distilled phosphorus tribromide dissolved in 5 cc. of anhydrous benzene was added slowly to a vigorously stirred and well cooled solution of 3 g. of the dimethylaminocarbonyl dissolved in 10 cc. of dry benzene. The temperature of the reaction mixture while the bromide was added was never allowed to exceed +5°. After all of the bromide had been added, the reaction mixture was stirred at room temperature for six hours longer, whereby the phosphorous acid salt of the amine began to crystallize. To this mixture was then added 6 g. of finely powdered solid potassium hydroxide and the mixture distilled under reduced pressure using an oil-bath. After the benzene distilled over, the oil-bath was heated rapidly to 175°, whereupon the salt of the dimethylamino bromide began to decompose and 2 g. of the crude dimethylaminodiene distilled over at 116–126°. When 2 g. of this amine was fractionated from finely divided sodium, 1.8 g. of pure product was obtained boiling at 126.5–128° (10 mm.).

*Anal.* Calcd. for  $C_{12}H_{21}N$ : N, 7. Found: N, 7.6, 7.5.

(8) Wallach, *Ann.*, **360**, 29 (190 ).

This amine is a colorless liquid, with a sharp but not unpleasant odor, having the following physical constants:  $d^{25}_6$  0.8776;  $n^{25}_D$  1.4909,  $n^{25}_D$  1.4910; *MR*, calcd. for  $C_{12}H_{21}N$ , 2F, 58.43, found, 59.03; exaltation, 0.6. That the two double bonds in this amine are conjugated is shown by the presence of an exaltation and also by its absorption spectrum shown in Fig. 1 (VII). This was determined in pure ethyl alcohol and found to have a prominent band in the ultraviolet region with a maximum at 236  $m\mu$ . The molecular extinction coefficient was calculated to be 10,500, a value which is of the same order of magnitude as that calculated for substances of this type having two conjugated double bonds.

**3 - [2' - Methylene - cyclohexylidene-1']-propene - 1(II).**—Three grams of the dimethylaminodiene was converted into the methylammonium iodide by allowing it to react for twenty-four hours at room temperature with excess methyl iodide. The white solid formed was dissolved in water and converted into the methylammonium hydroxide by shaking the aqueous solution for three hours with twice the theoretical amount of freshly precipitated silver oxide. The mixture was then filtered and the filtrate concentrated under reduced pressure in an atmosphere of nitrogen using an oil-bath. After most of the water had been removed, the pressure was reduced to 5 mm. and the temperature of the oil-bath slowly raised to 60° at which temperature the ammonium base began to decompose with considerable foaming. One gram of a pleasant smelling product distilled over. This was taken up in ether and the ethereal solution washed several times with a solution of 50% acetic acid followed by a concentrated solution of sodium bicarbonate, dried over anhydrous sodium sulfate, filtered, the filtrate fractionated under reduced pressure in an atmosphere of nitrogen and the fraction, 0.8 g., boiling at 62–63° (7 mm.) collected and analyzed.

*Anal.* Calcd. for  $C_{10}H_{14}$ : C, 89.5; H, 10.5. Found: C, 89.5, 89.4; H, 10.9, 10.5.

The triene is a colorless liquid, with a very characteristic terpene-like odor, having the physical constants:  $d^{27}_{27}$  0.8744;  $n^{25}_D$  1.5281,  $n^{25}_D$  1.5255,  $n^{27}_D$  1.5224; *MR*, calcd. for  $C_{10}H_{14}$ , 3F, 43.57, found, 46.82; exaltation, 3.24. It is highly reactive and when allowed to remain in contact with oxygen it polymerizes rapidly into a white solid. When hydrogenated in ethyl alcohol using platinum oxide as the catalyst, it was found to absorb 2.98 and 3.3 moles of hydrogen as against the theoretical value of 3 showing the presence of three double bonds.

The ultraviolet absorption spectrum of the triene was then determined in pure ethyl alcohol and the results plotted in Fig. 1 (II). This shows a prominent band with a maximum at 255  $m\mu$  and a molecular extinction coefficient of 19,000, a value which is of the right order of magnitude for systems containing three conjugated double bonds one of which is joined to an exomethylene group.

That this triene had not cyclized to form one of the hexahydronaphthalenes is further shown by the work of Morton and de Gouveia<sup>9</sup> and of Huber.<sup>10</sup> These investigators have found that the hexahydronaphthalenes absorb in the region 234–239  $m\mu$  and show practically no exaltation.

(9) Morton and de Gouveia, *J. Chem. Soc.*, 916 (1934).

(10) Huber, *Ber.*, **71**, 729 (1938).

The authors are indebted to Dr. Robert Heggie for valuable suggestions and aid in the spectroscopic measurements. This is the first article of a program of research on the synthesis of vitamins A and D, support of which is derived through contributions from Abbott Laboratories, Eli Lilly and Company, Merck and Co., Inc., Parke, Davis and Company, and the United Drug Company, such contributions being made through the Research Corporation of New York.

### Summary

1. A successful synthesis has been accomplished for the triene, 3-[2'-methylene-cyclohexylidene-1']-propene-1, which possesses a conjugated system identical with that present in all antirachitic vitamins.

2. The molecular extinction coefficient of this triene is nearly identical with that reported for the antirachitic vitamins.

3. Work is being continued with the ultimate goal of synthesizing an antirachitic vitamin.

CAMBRIDGE, MASS.

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[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

## Sterols. LXX.\* The Steroid Content of Mares Pregnancy Urine

BY RUSSELL E. MARKER AND EWALD ROHRMANN

In a previous paper<sup>1</sup> from this Laboratory it was pointed out that the ratios of pregnanediol-3( $\alpha$ )-20( $\alpha$ ), *allo*-pregnanediol-3( $\alpha$ )-20( $\alpha$ ) and *allo*-pregnanediol-3( $\beta$ )-20( $\alpha$ ) which occurred in human and cows pregnancy urine and in bulls urine appeared to be constant. The figures reported for mares pregnancy urine were arbitrarily based upon the amount of *allo*-pregnanedione<sup>2</sup> obtained from the oxidation of the total carbinol fraction and from this it was assumed that the observed ratio of the occurrence of the various pregnanediols held for all pregnancy urines. Both pregnanediol-3( $\alpha$ ),20( $\alpha$ )<sup>2</sup> and *allo*-pregnanediol-3( $\beta$ )-20( $\alpha$ )<sup>3</sup> have been isolated while *allo*-pregnanediol-3( $\alpha$ ),20( $\alpha$ ) was assumed to be present from the amount of *allo*-pregnanedione obtained by oxidation of the total carbinol fraction.

Because of the large amount of tar present in mares pregnancy urine the isolation of the pregnanediols by the methods used to work up other urines is extremely difficult and this fact has greatly delayed a quantitative investigation of this urine. Recently we have obtained indications that mares pregnancy urine differs considerably from the other urines studied, especially in regard to the ratio of pregnanediols present. In order to obtain more quantitative information concerning these substances we have undertaken the present investigation of the carbinol fraction from 10,000 gallons of mares pregnancy urine.

(\*) Paper LXIX, Marker and Rohrmann, *THIS JOURNAL*, **61**, 2072 (1939).

(1) Marker, Wittle and Lawson, *ibid.*, **60**, 2931 (1938).

(2) Marker, *et al.*, *ibid.*, **59**, 2297 (1937).

(3) Marker and Rohrmann, *ibid.*, **60**, 1565 (1938).

The results obtained show a remarkable difference between mares pregnancy urine and other urines as is shown in the following table.

APPROXIMATE AMOUNTS INDICATED IN MG. PER GALLON OF URINE

	Pregnane- diol-3( $\alpha$ ), 20( $\alpha$ )	<i>allo</i> - Pregnane- diol-3( $\alpha$ ), 20( $\alpha$ )	<i>allo</i> - Pregnane- diol-3( $\beta$ ), 20( $\alpha$ )
Human pregnancy	50	25	6
Cow pregnancy	25	15	3
Bull	100	50	12
Mare pregnancy	3	2	25

The crude carbinols from 10,000 gallons of hydrolyzed mares pregnancy urine from which the ketones were previously removed with Girard's reagent were separated from the hydrocarbons by means of the half phthalates and the entire carbinol fraction precipitated with an excess of digitonin to separate the steroids epimeric at C-3. The material precipitated by digitonin consisted largely of uranediol-3( $\beta$ ),11<sup>4</sup> and *allo*-pregnanediol-3( $\beta$ ),20( $\alpha$ ) together with a new substance of the composition C<sub>48</sub>H<sub>82</sub>O<sub>3</sub>. This latter substance appears to be a molecular compound of cholesterol and uranediol-3( $\beta$ ),11 since oxidation of the product yielded uranediolone while treatment with acetic anhydride yielded cholesteryl acetate.

The carbinol fraction which did not precipitate with digitonin was oxidized under mild conditions with chromic anhydride and the ketones separated with Girard's reagent. The ketonic material yielded some pregnanediolone and *allo*-pregnanediolone.

(4) Marker, Rohrmann and Wittle, *THIS JOURNAL*, **60**, 1561 (1938).