Attempts at hydrolysis of VII in dilute hydrochloric acid were unsuccessful; only the unchanged dioxino compound was recovered. Treating with fuming hydrochloric acid caused the formation of a tar from which nothing could be extracted.

8-Nitro-5-hydroxymethyl-6-quinolinol Diacetate (IX).—A solution of 1.16 g. (0.005 mole) of VII in 10 ml. of acetic anhydride, 15 ml. of acetic acid, and 5 ml. of concentrated sulfuric acid was allowed to stand at room temperature for seven days. It was then poured into 200 ml. of water and stirred to hydrolyze the excess anhydride. The precipitate of light yellow needles was filtered and washed, giving 1.15 g. (76%) of pure IX, m. p. 173–173.5. Recrystallization from benzene did not raise the melting point.

Anal. Calcd. for $C_{14}H_{12}N_2O_6$: N, 9.21. Found: N, 9.33.

8-Nitro-5-hydroxymethyl-6-quinolinol (X).—The diacetate, IX, (3.04 g., 0.01 mole) was dissolved in 50 ml. of absolute alcohol containing 0.46 g. (0.02 mole) of sodium. After one and one-half hours the solution was poured into 120 ml. of water and allowed to stand for several hours after neutralization to allow complete precipitation of X. After drying the solid, it was dissolved in benzene, filtered and the benzene solution was concentrated in vacuum at a low temperature to a small volume and diluted with an equal volume of ligroin (b. p. 75–85°). A yield of 1.4 g. (62%) of yellow crystals melting at 97–99° was obtained.

Anal. Calcd. for $C_{10}H_8N_2O_4$: N, 12.83. Found: N, 12.72.

The substance is quite unstable; after standing for several days, the odor of formaldehyde was very noticeable and the material became a dark red color. The main product of decomposition is presumably 5,5′-methylene-bis-8-nitro-6-quinolinol, XI, which can be separated due to its insolubility in benzene. The same substance was obtained when either IX or X was boiled with a dilute aqueous solution of potassium carbonate. A strong odor of formaldehyde was evident. When the solution was neutralized with acetic acid, a quantitative yield of a light brown solid was obtained; the substance showed no indication of melting at 320°.

Oxidation of VII.—To a solution of 1.16 g. (0.005 mole) of VII in 10 ml. of acetic acid was added, at a temperature of 25–30°, a solution of 1.3 g. of chromic anhydride in 10 ml. of acetic acid. The solution became dark green immediately and after five minutes was poured into 200 ml. of water. The resulting precipitate was filtered off and washed with water. A yield of 0.80 g. (65%) of the substance was obtained as short white needles which melted at 219–220°.

Anal. Calcd. for $C_{11}H_6N_2O_5$: N, 11.38. Found: N, 11.33.

The oxidation product was insoluble in cold sodium carbonate solution but dissolved readily on heating. Neutralization precipitated an acidic compound, m. p. 194–195°. The structure of this acid has not been proven as yet but is probably that represented by XIII.

5,5′-Methylene-bis-8-acetamido-6-methoxyquinoline.—A solution of 10.8 g. (0.05 mole) of 8-acetamido-6-methoxyquinoline in 20 ml. of cold concentrated sulfuric acid was treated with 2 ml. (0.025 mole) of formalin and allowed to stand for nine days. The reaction mixture was poured into ice-water, neutralized and the light colored solid removed by filtration. The dried solid weighed 11.5 g. (100%). The substance was recrystallized from boiling xylene as white needles. The recovery was nearly quantitative; m. p. 298–299°.

Anal. Calcd. for $C_{25}H_{24}N_4O_4$: N, 12.79. Found: N, 12.50.

Summary

The condensation of 6-methoxyquinoline with formaldehyde in sulfuric acid solution gave 5,5′-methylene-bis-6-methoxyquinoline, while condensation of 6-quinolinol and 8-nitro-6-quinolinol with formaldehyde in sulfuric acid gave dioxino(5,4-f)-quinoline and 6-nitrodioxino(5,4-f)quinoline, respectively. Treatment of the dioxino compounds in acetic anhydride–sulfuric acid mixture gave the diacetates of 5-hydroxymethyl-6-quinolinol and 8-nitro-5-hydroxymethyl-6-quinolinol. These latter substances converted readily to the corresponding diquinolylmethanes.

BLOOMINGTON, INDIANA RECEIVED JUNE 18, 1948

[CONTRIBUTION FROM THE DIVISION OF CHEMISTRY, LABORATORIES OF THE MOUNT SINAI HOSPITAL]

Analogs of Vitamin A[1]

BY HARRY SOBOTKA AND J. D. CHANLEY

The preparation of vitamin A from β-ionone has recently been described by Arens and Van Dorp[2] and by Isler, Huber, Ronco and Kofler.[3] These accomplished syntheses as well as all other reported efforts[4–8] in the direction of vitamin A alcohol and its methyl ether have been based on β-ionone as starting material, because this substance, derived from the naturally occurring citral, contains 13 of the 20 carbon atoms of axerophthol in properly assembled form.

The following considerations suggested to us the idea to attack the synthesis of vitamin A from simpler starting materials:[9] the supply of lemon grass oil, the primary source of β-ionone, from tropical regions had become precarious during the war. In a series of studies[10] the tendency of isomerization of the β-cyclogeranyl ring was demonstrated under certain conditions, likely to

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[1] The work described in this report was initiated under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the Mount Sinai Hospital. Part of the material described is contained in classified progress reports to OSRD, dated December 24, 1943, February 25 and April 17, 1944.

[2] Arens and Van Dorp, *Nature*, **160**, 189 (1947); *cf. Rec. trav. chim.*, **65**, 338 (1946).

[3] Isler, Huber, Ronco and Kofler, *Helv. Chim. Acta*, **30**, 1911, (1947); *cf.* Festchrift f. E. Barell, p. 31 (Bale, 1946).

[4] Kuhn and Morris, *Ber.*, **70**, 853 (1937).

[5] Kipping and Wild, *Chem. and Ind.*, **58**, 802 (1939).

[6] Milas, U. S. Patents 2,369,156–168; 2,382,085–086 (1945).

[7] Oroshnik, THIS JOURNAL, **67**, 1627 (1945).

[8] Heilbron and co-workers whose numerous important contributions to this subject are summarized in *J. Chem. Soc.*, 386 (1948); *cf. ibid.*, 727 (1942).

[9] Sobotka, Progress Reports 1942–1944, Final Report 1944 to OSRD, distributed by Office of Production Board, Nos. 77, 214–215 (1947).

[10] Sobotka, Bloch and Glick, THIS JOURNAL, **65**, 1961; Sobotka, Cahnmann, Feldbau and Rosen, *ibid.*, **65**, 2061 (1943); Sobotka, Darby, Glick and Bloch, *ibid.*, **67**, 403 (1945); Sobotka and Bloch, *Chem. Revs.*, **34**, 435 (1944).

be encountered in the course of syntheses with β-ionone. Recent work by Young[11] has shown that these shifts of double bonds are avoidable. There persists the incentive to achieve a total synthesis of vitamin A, not only as an intellectual challenge, but also because a total synthesis will offer opportunities to compare the biological effects of vitamin A itself with those of homologs, containing a modified cyclic moiety, and also to introduce isotopic carbon atoms in various definite positions to trace the metabolic fate of the vitamin.

In a series of classified reports on an investigation, carried out under a contract with the Office of Scientific Research and Development,[9] one of us, together with Dr. H. J. Cahnmann, described the preparation of 1-ethynyl-2,2,6-trimethyl-1-cyclohexanol and outlined its use as starting material in the total synthesis of vitamin A. The properties and reactions of this compound will be described separately. In order to study the various alternatives for building the side-chain, a series of model experiments were performed, starting from the simpler homolog 1-ethynylcyclohexanol (I). Since similar work is mentioned[12] and very recently reported,[13] we wish to describe these studies which have resulted in the synthesis of the methyl ether of trisnor-bisdehydro-vitamin A (XV) and of a lower homolog in the same series (V). In the course of this investigation, we have also prepared 1-(1′-cyclohexenyl)-1-butyn-3-one (III), 3,4-epoxy-1-(1′-cyclohexenyl)-3-methyl-1-butyne (IX), and two isomeric 1-(1′-cyclohexenyl)-3-methyl-1-hexynols (VI and X).

Ethynylcyclohexanol (I) was dehydrated over an alumina catalyst to 1-ethynylcyclohexene (II). The Grignard compound, prepared from this hydrocarbon, was treated with chloroacetone to yield the chlorohydrin (VIII) which, in turn, was dehydrohalogenated to the epoxide (IX). The latter was condensed with the Grignard compound of the methyl ether of β-ethynylcrotonalcohol to yield the monomethyl ether of the glycol (XIII). In order to confirm the secondary nature of the hydroxyl group, anticipated from this condensation,[14] the oxide was condensed in a model experiment with ethylmagnesium bromide to yield a carbinol (X) which gave a phenylurethan and whose completely saturated derivative (XI) could be oxidized to a ketone (XII). This carbinol differed from the isomeric carbinol (VI), obtained by condensation of 1-ethynylcyclohexene with 2-pentanone; this tertiary alcohol gave no phenyl urethan and its perhydrogenation product was not oxidizable by dichromate.

The methyl ether of the *prim.-sec.*-glycol, containing the complete side-chain of vitamin A, was converted into the monobromide (XIV). This, on dehydrohalogenation, yielded compound XV which proved to be highly sensitive to atmospheric oxygen. It contains a novel conjugated system of alternating double and triple bonds. The relatively low $\epsilon_{\text{max.}}$ of 22,000 and the $\lambda_{\text{max.}}$ of 315 mμ, as compared with $\epsilon_{\text{max.}} = 49{,}800$ and $\lambda_{\text{max.}} = 326$ mμ for the methyl ether of vitamin A[15] might be interpreted by a conjugated system of but four unsaturated bonds with the fifth bond shifted into the α-ionone position. The similar values ($\epsilon_{\text{max.}} = 29{,}000$, $\lambda_{\text{max.}} = 316$ mμ) for the methyl ether of 1-(2′,2′,6′-trimethyl-5′-cyclohexenyl)-3-methyl-1,3,7-decatrien-5-yn-9-ol[16] would support this formulation. However, the absence of a methyl group in position 6′ in our case and the presence of two acetylenic bonds, known to lower the extinction,[17] may account for the values observed in compound XV as formulated.

The Grignard compound of 1-ethynylcyclohexene yielded upon condensation with acetic anhydride the acetylenic ketone C_6H_9–C≡C–CO–CH_3 (III).[18]

The same Grignard compound was condensed with butanolone to give the acetylene analog, lacking the three methyl groups in the ring of β-ionylideneethanol, the lower isoprenolog of vitamin A. In order to protect the primary alcohol group of the 1-butanol-3-one during this condensation by a group which could be removed by mild acid, we prepared the trityl ether of butanolone (IV) with the assistance of Dr. Gerda Gernsheim Mayer.[19] Acid hydrolysis of the resulting trityl ether yielded the extremely unstable alcohol V by simultaneous dehydration.

Experimental

All reactions were carried out under nitrogen. The ultraviolet absorption spectra were obtained with a Beckman spectrophotometer Model DU, using 95% ethanol as solvent. We are indebted for the microanalyses to Dr. Gertrude Oppenheimer, Microchemical Laboratory, California Institute of Technology, Pasadena, Calif.

1-Ethynylcyclohexanol (I) was prepared according to Campbell and co-workers[20,21]; b. p. 72.5–73° (11 mm.), m. p. 28–30°, n^{25}D 1.4810.

1-Ethynylcyclohexene (II).—Ethynylcyclohexanol was dehydrated in 1 mol. batches by passing it in a current of nitrogen over a period of two to three hours at 15 mm. pressure over an activated aluminum oxide catalyst in a horizontal tube, 76 cm. long and 2.0 cm. inside diameter. A temperature of 190–200° was found to be most favor-

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[11] Young and Linden, This Journal, **69**, 2042 (1947); *cf.* Young and co-workers, *ibid.*, **66**, 520, 2130 (1944). But see also Ref. 16.

[12] Milas, Grossi, Penner and Kahn, This Journal, **70**, 1292 (1948).

[13] Milas, *et al.*, *ibid.*, **70**, 1584, 1597, 1829 (1948).

[14] Norton and Hass, This Journal, **58**, 2148 (1936).

[15] Hanze, Conger, Wise and Weisblat, This Journal, **70**, 1253 (1948).

[16] Cymerman, Heilbron, Jones and Lacey, *J. Chem. Soc.*, 500 (1946).

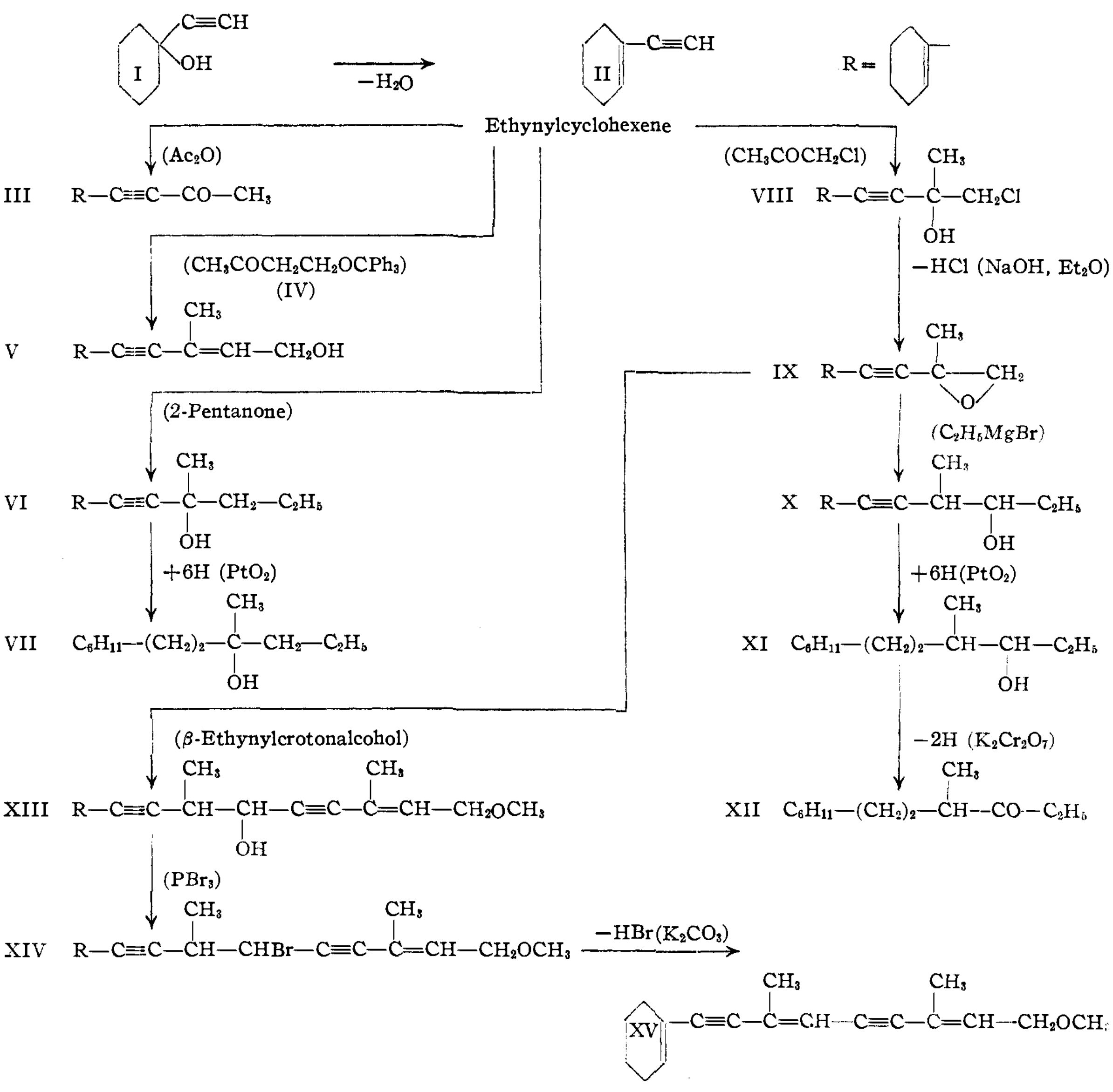
[17] Johnson, "The Chemistry of the Acetylenic Compounds," Vol. I, E. Arnold and Co., New York, N. Y., 1946, pp. 33, 151.

[18] Since the preparation of this paper the review article by Heilbron (ref. 8) has appeared in which reference is made to recent unpublished work on this compound.

[19] This portion of the work was carried out in 1944/45 with the aid of a research grant from the United Hospital Fund to whom we wish to express our thanks and appreciation.

[20] K. Campbell, B. Campbell and Eby, This Journal, **60**, 2282 (1938).

[21] Chanley, *ibid.*, **70**, 244 (1948).



able.[22] The catalyst was prepared from 75 g. of $Al_2(SO_4)_3 \cdot 18H_2O$, dissolved in 350 ml. boiling water and 300 g. aluminum oxide (Alcoa, mesh 8–12) which was added to the boiling solution over a period of three to five minutes. After ten minutes boiling, the mixture was washed thoroughly with running hot water for another ten minutes, filtered and the slightly moist catalyst was then activated at 800° for twelve to fourteen hours. The yield of ethynylcyclohexene was 30–40%, besides an average of 20% of the starting material was recovered; b. p. 38–40° (12 mm.), $n^{20}D$ 1.4955–1.4970, λ max. 223 mμ, ε max. 10,400. After purification through the silver salt, the compound had the same b. p. and $n^{20}D$ 1.4970.[23]

1-(1′-Cyclohexenyl)-1-butyn-3-one (III).—The acetylenic hydrocarbon II was converted into its Grignard compound by adding 26.5 g. (0.25 mole) in ether to the equivalent amount of freshly prepared C_2H_5MgBr. After stirring under reflux for two hours, a precipitate of the Grignard compound settled. At the temperature of −60°, 0.5 mole of acetic anhydride in ether was slowly added. After several hours, the condensation product was decomposed with 45 ml. of saturated ammonium chloride solution. On distillation of the reaction product 5.0 g. of the ketone III was obtained, boiling at 118–119° (12 mm.); $n^{20}D$ 1.5265, λ max. 274 mμ, ε max. 9,500. The compound has a sweet odor and is lachrymatory; it polymerizes on standing.

Anal. Calcd. for $C_{10}H_{12}O$: C, 81.04; H, 8.09. Found: C, 81.10; H, 8.30.

The **semicarbazone**, after repeated recrystallization from 75% ethanol, melted at 132.5–133°. It has a tendency to turn yellow on standing. λ max. 285 mμ, ε max. 14,500.

Anal. Calcd. for $C_{11}H_{15}N_3O$: C, 64.32; H, 7.36; N, 20.47. Found: C, 64.32; H, 7.37; N, 20.43.

2,4-Dinitrophenylhydrazone of III, prepared in glacial acetic acid, m. p. 147–148° (from 95% ethanol).

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[22] The details of the preparation of the catalyst and the conditions, given above for dehydration, have to be strictly observed. Slight variations yielded completely different products among which ethylbenzene was found. The observations on this and on analogous carbinols will be reported separately.

[23] (a) Carothers and co-workers, THIS JOURNAL, **54**, 4074 (1932); U. S. Patent 1,950,441 (1934), report b. p. 40–43° (12 mm.); (b) Vaughn, U. S. Patent 2,197,956 (1937), b. p. 45–50° (15 mm.); (c) Bayer and Co., German Patent 290,558 (1916), report $n^{20}D$ 1.4922; (d) Levina and Levina, *J. Gen. Chem. U. S. S. R.*, **8**, 1776 (1938); *C. A.*, **33**, 4966 (1939), give $n^{20}D$ 1.4978.

Anal. Calcd. for $C_{16}H_{16}N_4O_4$: N, 17.06, for $C_{16}H_{18}N_4O_5$[24]: N, 16.17. Found: N, 16.39.

The **trityl ether of 1-butanol-3-one (IV)** was prepared from 48 g. (0.55 mole) of butanolone, synthesized according to White and Haward,[25] by heating it for two hours on the steam-bath with 144 g. (0.5 mole) of triphenylmethyl chloride, dissolved in 300 ml. of dry pyridine. After standing overnight, 200 ml. of the solvent was removed *in vacuo*, and the solid residue was thoroughly mixed with 100 ml. of ice water, filtered and dried; yield of crude product, 87%. After purification by Soxhlet extraction with petroleum ether and recrystallization from 95% ethanol, the pure product crystallized in polygonal platelets, melting at 90–91°. Its solubility in ethyl ether is much less than indicated by Milas[6] (U. S. patent 2,369,157) who reports no melting point.

Anal. Calcd. for $C_{23}H_{22}O_2$: C, 83.60; H, 6.71. Found: C, 83.67; H, 6.73.

To 0.25 mole of 1-cyclohexenylethynylmagnesium bromide, prepared as previously described, was added 80 g. (0.24 mole) of trityl ether of butanolone in 800 ml. of ether with vigorous stirring over a period of five hours. Additional amounts of ether were added to dilute the extremely viscous reaction mixture. Upon decomposition with ammonium chloride, the condensation product was obtained as a viscous mass.

1-(1′-Cyclohexenyl)-3-methyl-1-pentyn-3-en-1-ol (V).—Hydrolysis of one part of the condensation product by shaking for two days under nitrogen with 5 parts of a solution of 5 or 10% (weight/vol.) sulfuric acid in 50% or in absolute ethanol yielded a mixture of products amongst which an ethyl ether of the presumable composition $C_6H_9{-}C{\equiv}C{-}CCH_3(OC_2H_5){-}CH_2CH_2OH$ predominated according to ethoxyl determinations. When dioxane was used as solvent in place of ethanol, polymerization occurred.[26] With the use of 20 % (weight/vol.) sulfuric acid in 50% ethanol, we obtained under the above conditions an oily, semisolid layer of tritanol and a clear solution from which extraction with petroleum ether yielded the dehydrated product V, boiling at 122–124° (3.0 mm.) in 10% yield. This compound polymerizes readily: n^{29}D 1.5458, λ max. 263 mμ, ε max. 13,700; reported[12] λ max. 266.5 mμ ε max. 16,000.

Anal. Calcd. for $C_{12}H_{16}O$: C, 81.77; H, 9.10. Found: C, 81.90; H, 9.32.

4-Chloro-1-(1′-cyclohexenyl)-3-methyl-1-butyn-3-ol (VIII).—One hundred fifteen grams (1.25 mole) of chloroacetone[27] in an equal volume of ether were added slowly to a well stirred suspension of 1.25 moles of cyclohexenylethynylmagnesium bromide; during the addition, the solution became clear and subsequently the reaction product separated as a white solid. After decomposition with ammonium chloride, 167 g. of the chlorohydrin VIII were obtained from the ether layer: b.p. 115–117° (1.7 mm.); 107° (0.35 mm.); n^{24}D 1.5280, λ max. 227 mμ, ε max. 14,500; colorless viscous fluid, slightly yellow on standing.

Anal. Calcd. for $C_{11}H_{15}OCl$: C, 66.48; H, 7.69; Cl, 17.80. Found: C, 65.83; H, 7.45; Cl, 17.50.

1,2-Epoxide of 1-(1′-Cyclohexenyl)-3-methyl-1-butyn-3-ene (IX).—Forty-four grams (1.1 moles) of powdered sodium hydroxide was added slowly to a solution of 169 g. (0.85 mole) of the chlorohydrin VIII in 1 liter of dry ether; the mixture was shaken overnight and refluxed after addition of another 11 g. of sodium hydroxide for five hours. After filtration and distillation, 118 g. (0.73 mole) of the epoxide IX was obtained, boiling at 85° (1.0 mm.); n^{25}D 1.5150, λ max. 230 mμ, ε max. 12,500. Reported[13] λ max. 232mμ, ε max. 20,900. The freshly prepared compound gives no Schiff test for aldehyde.

Anal. Calcd. for $C_{11}H_{14}O$: C, 81.43; H, 8.72. Found: C, 80.93; H, 9.05.

1-(1′-Cyclohexenyl)-3-methyl-1-hexyn-4-ol (X).—Eight and one-tenth grams (0.05 mole) of the epoxide IX, dissolved in ether, was added with stirring to 0.075 mole of ethymagnesium bromide in 25 ml. of ethyl ether at 0°. By working up the reaction mixture as previously described, we obtained 6.0 g. (40% yield) of the carbinol X, boiling at 105–106° (0.85 mm.); n^{25}D 1.5109, λ max. 228.5 mμ, ε max. 13,900.

Anal. Calcd. for $C_{13}H_{20}O$: C, 81.19; H, 10.48. Found: C, 80.83; H, 10.73.

The **α-naphthyl urethan** of this alcohol melted, after many recrystallizations from isopropyl ether, at 130–130.5°.

Anal. Calcd. for $C_{24}H_{27}O_2N$: C, 79.74; H, 7.53. Found: C, 80.07; H, 7.92.

The carbinol X was hydrogenated over platinum oxide catalyst in glacial acetic acid to **1-cyclohexyl-3-methyl-4-hexanol (XI)** of b. p. 107–108° (1.7 mm.) and n^{25}D 1.4650.

Anal. Calcd. for $C_{13}H_{26}O$: C, 78.72; H, 13.21. Found: C, 78.71; H, 13.57.

1-Cyclohexyl-3-methyl-4-hexanone (XII).—One and two-tenths grams of the saturated carbinol XI was oxidized with 8 ml. of an aqueous solution of 0.65 g. potassium bichromate and 0.55 ml. concentrated sulfuric acid in the cold. After heating for one-half hour to 60° the mixture was steam distilled; the distillate was extracted with ether and, on distillation, 0.7 g. of the ketone XII, boiling at 92–94° (1.1 mm.) was obtained; n^{25}D 1.4565. The ketone did not afford a solid semicarbazone or 2,4-dinitrophenylhydrazone.

1-(1′-Cyclohexenyl)-3-methyl-1-hexyn-3-ol (VI) was prepared from 0.17 mole of the Grignard compound of ethynylcyclohexene and the equivalent amount of 2-pentanone in 200 ml. ether at room temperature. Seventeen grams (48% yield) of the carbinol VI was obtained, boiling at 105° (1.2 mm.) and at 96° (0.6 mm.); n^{25}D 1.5015, λ max. 227 mμ, ε max. 13,800.

Anal. Calcd. for $C_{13}H_{20}O$: C, 81.19; H, 10.48. Found: C, 81.85; H, 10.73.

A small amount of a by-product, boiling at 88–90° (1.5 mm.), of n^{25}D 1.5169, λ max. 263 mμ, ε max. 13,900, suggested the occurrence of partial dehydration.

Hydrogenation of carbinol VI in glacial acetic acid with platinum oxide led to **1-cyclohexyl-3-methyl-3-hexanol (VII)**, b. p. 100° (1.1 mm.) n^{25}D 1.4638. Efforts to oxidize this saturated carbinol by the method used for its isomer (X) were of no avail and the starting material was recovered almost quantitatively.

Anal. Calcd. for $C_{13}H_{26}O$: C, 78.72; H, 13.21. Found: C, 78.74; H, 13.58.

9-Methyl Ether of 1-(1′-Cyclohexenyl)-3,7-dimethyl-7-nonen-1,5-diyn-4,9-diol (XIII).—The methyl ether of 3-methyl-2-penten-4-yn-1-ol[16] was prepared according to Isler.[3] It was converted by means of ethylmagnesium bromide into its Grignard compound. To 0.3 mole of the latter in ether was slowly added 48 g. (0.3 mole) of the epoxide IX in ether. After stirring overnight the mixture was decomposed with saturated ammonium chloride solution and worked up in the usual manner. On evaporative distillation (molecular distillation), 10.4 g. of a product was obtained which yielded upon repeated evaporative distillations 7.7 g. (10% yield) of pure material, boiling at 75–80° (0.03 mm.). n^{27}D 1.5318, λ max. 227 mμ, ε max. 25,000.

Anal. Calcd. for $C_{18}H_{24}O_2$: C, 79.39; H, 8.88; OCH_3, 11.38. Found: C, 79.33; H, 8.67; OCH_3, 11.09.

Trisnor-bisdehydro-vitamin A Methyl Ether [9-Methyl ether of 1-(1′-Cyclohexenyl)-3,7-dimethyl-3,7-nonadien-1,5-diyn-9-ol] (XV).—Seven and one-half grams (0.028

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(24) Bowden, Heilbron, Jones and Weedon, *J. Chem. Soc.*, 39 (1946).

(25) White and Haward, *J. Chem. Soc.*, 25 (1943).

(26) Regardless of the concentration of sulfuric acid used for cleavage of the trityl group, the latter was always recovered in the form of its ethyl ether when the reaction was carried out in absolute ethanol, but as tritanol when 50% ethanol was employed.

(27) We wish to thank Dr. E. Theimer of Van Ameringen-Haebler Inc. for suggesting the use of this reagent.

mole) of compound XIII reacted with 2.7 g. of phosphorus tribromide (0.03 equiv.) in 80 ml. of dry ether containing 0.56 ml. of pyridine for three hours at −30° and was allowed to stand overnight at room temperature. A spectroscopic examination of the bromide itself and of the two fractions obtained by partition between 95% methanol and petroleum either showed no absorption above 230 mμ even in high concentrations. This shows that no significant amount of spontaneous dehydrobromination had occurred. Seven grams of the crude bromide (XIV), obtained after decomposition of the reaction mixture with water, was dried *in vacuo* and dissolved in 250 ml. of acetone. Upon refluxing of this solution with 40 g. of anhydrous potassium carbonate for twelve hours and filtration, the residue of the acetone solution was taken up in 350 ml. of low boiling petroleum ether (40–60°) and extracted eight times with 35-ml. portions of 95% methanol. Evaporation of the petroleum ether layer yielded 2.44 g. of crude product which was purified by a succession of slow evaporative distillations and chromatographic separations on aluminum oxide. The purified end-product boiled at 48° (10^{-2} mm.); n^{27}D 1.5855 (extrapolated for n^{20}D 1.590), λ max. 315 mμ, ϵ max. 22,000. This compound was very sensitive and unstable on standing.

Anal. Calcd. for $C_{18}H_{22}O$: C, 84.99; H, 8.72; OCH_3, 12.19. Found: C, 82.43; H, 8.88; OCH_3, 11.13.

Acknowledgment.—We wish to thank Mrs. Edith Rosen Kaplan and Miss Bernice Hamerman for their able and painstaking assistance.

Summary

1. The preparation of an analog of vitamin A methyl ether, which differs from it by the absence of three methyl groups on the ring and by containing two triple bonds in the conjugated system, and of the corresponding analog of β-ionylideneethanol, the lower isoprenolog of vitamin A, is described.

2. The preparation of trisnor-dehydro-β-ionone and several other intermediates, especially that of the 3,4-epoxide of 1-cyclohexenyl-3 methyl-1-butyne is reported and the reaction of the latter with ethyl magnesium bromide is discussed.

NEW YORK 29, N. Y. RECEIVED JUNE 8, 1948

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES, GENERAL MILLS, INC.]

Amino Acids. II. A New Synthesis of DL-Lysine[1]

BY DONALD T. WARNER AND OWEN A. MOE

DL-Lysine has been synthesized by the reduction of ethyl α-isonitroso-δ-cyanovalerate,[1a] by reduction and hydrolysis of ethyl α-carbethoxy-α-phthalimido-δ-cyanovalerate,[2] from benzoyl piperidine[3] through the intermediate ϵ-benzoylaminocaproic acid,[4,5] by action of hydrazoic acid[6] upon the proper cyclic ketone,[7] and by a multistep procedure using β-chloropropionaldehyde diethylacetal.[8] The present report describes a new synthesis of DL-lysine which involves γ-acetamido-γ,γ-dicarbethoxybutyraldehyde[9] as the key intermediate. A previous report[10] from this laboratory has demonstrated the usefulness of the phenylhydrazone of this aldehydo compound I in the synthesis of DL-tryptophan and DL-ornithine monohydrochloride.

The addition of liquid hydrogen cyanide to a solution of the aldehydo compound I in benzene yielded the cyanohydrin II. When the reaction mixture was cooled, crude II (m. p. 83.5–85°) was deposited as a white crystalline material in yields of approximately 80%. After recrystallization from benzene, the material was pure and melted at 86.5–87.5°.

However, it was not necessary to isolate the cyanohydrin II as a crystalline material. Either a benzene solution of the cyanohydrin or the crude oily product could be treated directly with acetic anhydride. Presumably, the acetate III was formed which on heating yielded the unsaturated nitrile IV. This was considered a probable course since reduction of the unsaturated nitrile IV in the presence of platinum oxide yielded the diacetamido compound V in approximately 50% yield based on the aldehydo compound I. The structure of V was proved by an unequivocal synthesis involving alkylation of ethyl acetamidomalonate by γ-chlorobutyronitrile followed by the catalytic reduction of the product in the presence of acetic anhydride.

Dehydration of the cyanohydrin, II, with phosphorus oxychloride presumably yielded compound IV directly since it was converted to compound V by reduction in the presence of platinum oxide and acetic anhydride. The pure diacetamido compound, V, was hydrolyzed by the action of acid to DL-lysine dihydrochloride in 77% yield. The over-all yield of DL-lysine dihydrochloride based on the cyanohydrin, II, was approximately 40%. The DL-lysine dihydrochloride was converted to the monohydrochloride and the dibenzoyl derivative in accordance with known procedures.

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