be entirely justifiable, it is thought, in the case of extremely gifted young men, who could then perform their service in the various laboratories, research divisions, arsenals, and other technical agencies of the armed forces. In addition to a wise policy of deferment, the encouragement and development of youthful scientific talent under the circumstances which would be produced by universal compulsory military training make necessary a policy of strengthening scientific training both before and during the term of service. To this end, added efforts should be made in the field of secondary education to teach the better students as much mathematics and physical science as possible; and young men in military service should be given every encouragement, including the payment by government of the necessary fees, to extend their formal education by pursuing correspondence courses, including courses at college level. The report therefore recommends that:

(5) If universal military service is adopted, in the field of secondary education particular attention should be paid to increasing the efficiency and quantity of instruction given in mathematics and physical science to the students of better than average ability.

(6) The armed forces should encourage young men to continue their education during military service by taking correspondence work through regular school channels, and should pay the costs of such study if a man carries it through diligently.

Technical Papers

Synthesis of Biologically Active Vitamin A Substances[1]

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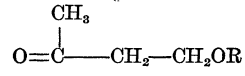
Massachusetts Institute of Technology

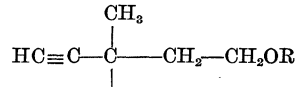
The structure of vitamin A was definitely established from degradation and other experiments as far back as 1931 by Karrer (*4*) and was later confirmed by Heilbron (*2*) and others. On the basis of this knowledge, several synthetic methods, claiming the synthesis of vitamin A itself and some of its derivatives, have been published in various countries during the last decade. Of these, only one—that published in Germany in 1937 by Kuhn and Morris (*6*)—claims to have produced a biologically active product. Subsequent attempts to reproduce this synthesis in other countries (*5*) as well as in Germany (*8*) have been entirely unsuccessful.

The German method was one of the first we investigated, but our failure to obtain one of the key intermediates, β-ionylidene acetaldehyde, forced us to abandon this method early in 1940. Since then, we have investigated several alternative syntheses (*7*). In one of these syntheses, which led to biologically active vitamin A substances, the aldehyde (I), originally prepared by Ishikawa and Matsuura (*3*) from β-ionone and ethyl chloroacetate, was condensed with lithium acetylide in liquid ammonia at −60 to −70° C. to give the acetylene carbinol (II) in about 65 to 70 per cent yields. A condensation of this product, via the Grignard reaction, with the ketone (III), in which R may be either an alkyl or an acyl group



(III)

depending upon whether an ether or an ester of vitamin A is wanted, produced the acetylene glycol (IV) in about 70 to 80 per cent yields. The acetylene glycol ethers have also been synthesized in higher yields by condensing, again via the Grignard reaction, 3-methyl 3-hydroxy 5-alkoxy pentyne-1 (V) with the aldehyde (I). Unfortunately, the corresponding acetylene glycol esters cannot be obtained easily by this reaction. In the next step of the synthesis, the

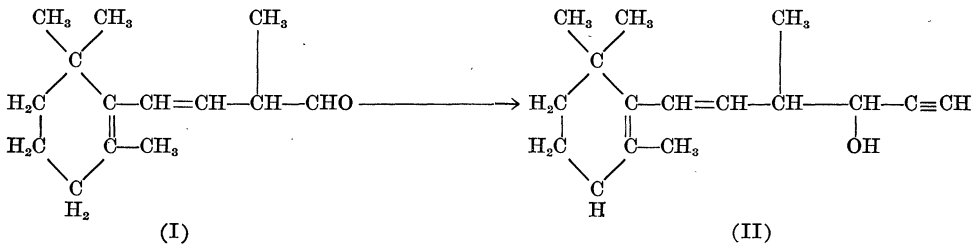


(V)

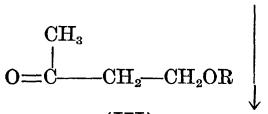
acetylene glycol was dehydrated, using *p*-toluene sulfonic acid as the dehydrating agent, to produce the polyvinyl acetylene (VI), which, when selectively hydrogenated, yielded biologically active ethers or esters of vitamin A (VII), depending upon whether R was an alkyl or an acyl group.

[1] Presented in part before the North Jersey Section of the American Chemical Society, 9 April 1945; the AAAS-Gibson Island Conferences, 23 July 1945; and in a Vitamin A Symposium sponsored by the Northeastern Section of the American Chemical Society, 10 January 1946.

[2] The author takes this opportunity to gratefully acknowledge the assistance of (Miss) M. A. Campbell, R. O. Edgerton, (Mrs.) J. Gladding, F. X. Grossi, J. N. Ingraham, S. W. Lee, (Mrs.) A. R. Lowry, N. S. MacDonald, (Miss) S. Z. Paul, (Mrs.) R. Pitt, J. T. Plati, E. Sakal, (Miss) Z. Weiss, H. C. Wohlers, and H. F. Wright.



(I) (II)



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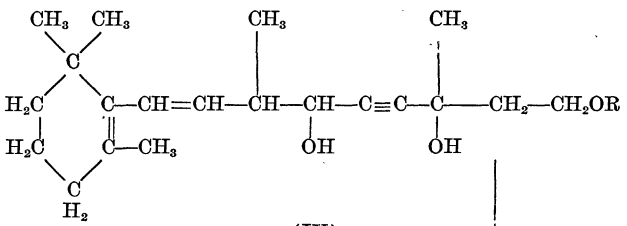

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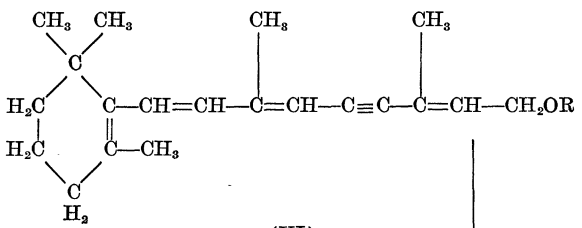

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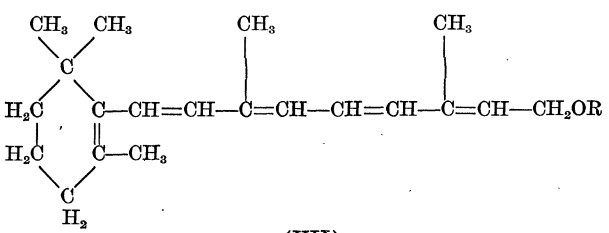
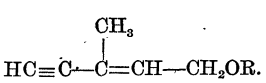


(VII)

The final products were also synthesized by following a slightly different set of reactions. The acetylene glycol (IV) was first selectively hydrogenated to an olefinic glycol (VIII), which was then converted to the dichloride (IX), and the latter dehydrochlorinated with alcoholic potash to the corresponding ethers of vitamin A when R was an alkyl group and to the vitamin A alcohol itself when R was an acyl group.

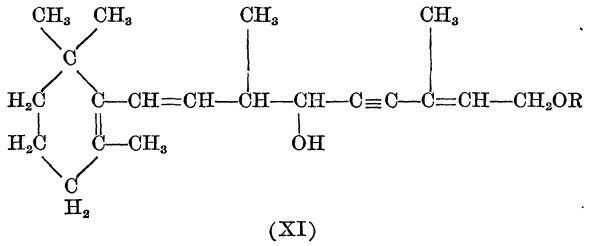
In order to obtain additional data on the synthetic ethers of vitamin A and to avoid going through the acetylene glycol (IV), a third, slightly different method was developed. The acetylene carbinol (V) was first dehydrated to produce 3-methyl 5-alkoxy vinyl acetylene (X),



(X)

When this was condensed, via the Grignard reaction, with the aldehyde (I), the acetylene carbinol (XI)

was produced in very good yields. This carbinol was easily dehydrated to the polyvinyl acetylene (VI),



(XI)

from which the vitamin A ethers were obtained by selective hydrogenation. The acetylene carbinol (XI) has also been selectively hydrogenated to the corresponding polyene carbinol (XII), which was advantageously dehydrated to give good yields of vitamin A ethers.

The final products produced by the three synthetic routes outlined above are identical whenever R is the same. Ultimate analysis, unsaturation, and molecular weight determinations agreed well with the expected values for the structural formula (VI). The absorption spectrum in the ultra-violet has a well-defined maximum similar to that observed for the corresponding natural vitamin A substances, except that it is slightly displaced towards the ultraviolet region by about 30 to 50 A. The synthetic ethers of vitamin A give a purplish blue color with antimony trichloride which exhibits both the 6,200-A. and the 5,800-A. bands characteristic of natural vitamin A. The vitamin A esters and the alcohol itself give a deep blue color exhibiting the same bands.

Biologically, all the synthetic products which are represented by the final structure (VI) have been found active by Prof. Harris, of the Nutritional Laboratories of this Institute. Furthermore, the biological effect on rats has been found to be identical with that produced by cod-liver oil. The potency, however, was much lower than that generally accepted for the purest sample of natural crystalline vitamin A (3,500,000 U.S.P. vitamin A units per gram). For the synthetic vitamin A methyl ether, for example, Prof. Harris reported indications of activity in the order of 500,000 to 1,000,000 U.S.P. vitamin A units per gram and reproducible activity of the order of 50,000 to 100,000 U.S.P. units per gram. Several other laboratories have tested our synthetic products and confirmed, within certain limits of variation, the lower potencies reported by Prof. Harris. Although the potency of the synthetic products is much lower than that of the purest natural crystalline vitamin A, the biological activity cannot be disputed and, if compared to commercial products, it is of the order of 50 to 100 times that of ordinary cod-liver oil, one of the chief sources of vitamin A.

If the biological potency of the synthetic products is much lower than that of the corresponding natural products, one can raise the question whether they are identical. We have devoted a considerable amount of our time in an attempt to answer this question. Our most recent results seem to indicate that the synthetic products are mixtures of stereoisomers of the *cis-* and *trans-* type, exceedingly difficult to separate and some of which are probably completely devoid of biological activity. This is not surprising, for even the natural vitamin A, when first isolated by Karrer (1931), presumably in a chemically "pure" form, had a considerably lower potency than the crystalline vitamin A recently prepared by Baxter and Robson (*1*). Was Karrer's sample a mixture of stereoisomeric forms, some of which were biologically inactive? This question cannot be answered until the stereochemical configuration of vitamin A is known. Merely speculating from analogies with certain carotenoids may lead to a false conclusion. Some organic chemists are unwilling to admit that *cis-* and *trans-*isomerism is even present in molecules which have more than three double bonds in conjugation. Work along these lines is exceedingly difficult and time-consuming, but it is quite essential because of its connection to the important problem of specificity of vitamin A.

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Treatment of Severe Erythroblastosis by Simultaneous Removal and Replacement of the Blood of the Newborn Infant[1]

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Although considerable information has been accumulated concerning the mechanisms involved in the causation of erythroblastosis fetalis, the established treatment by repeated transfusions of Rh– blood has thus far not been entirely successful. Many babies with erythroblastosis have died of the disease, though no evidence of severe anemia existed. A fac-

[1] Preliminary report from the Laboratories of the Queens General Hospital, Jamaica, Long Island, and from the Department of Hematology, Jewish Memorial Hospital, New York City.