Intermediates in the Synthesis of Xanthophyll and Zeaxanthin

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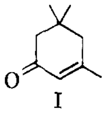
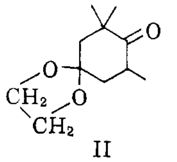
Several reactions are described in the attempted preparation of substituted trimethylcyclohexenones which could be used in the synthesis of Xanthophyll and Zeaxanthin. The synthesis of ethyl 2,6,6-trimethyl-4-keto-2-cyclohexenecarboxylate (VIII) is described. VIII could serve as a suitable starting material for the preparation of the desired carotenoids.

In a recent patent[2] the synthesis of zeaxanthin was described. The method utilized isophorone (I) which was converted to 2,6,6-trimethyl-4-ethylenedioxy-1-cyclohexanone (II) by a series of reactions and was then further utilized in the synthesis of zeaxanthin.



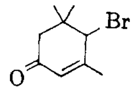
I



II

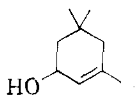
This manuscript describes a more conveniently prepared intermediate for the synthesis of this and related carotenoids.

The search for this intermediate was begun with the preparation of 4-bromo-3 5,5-trimethyl-2-cyclohexenone (III) by a known procedure[3]; several attempts to reduce the ketone however gave unsatisfactory results.



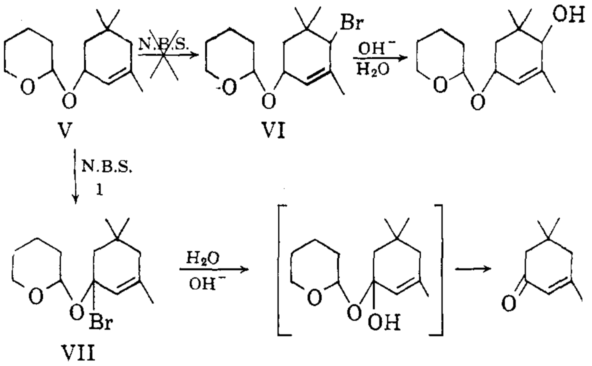
III

Because of this it was thought desirable to reduce isophorone before attempting any further reactions. The reduction of isophorone gave 3,5,5-trimethyl-2-cyclohexenol IV in good conversion. The reaction of IV with N-bromosuccinimide was not successful, however, giving tars in an ether medium and an uncontrolled reaction in carbon tetrachloride.



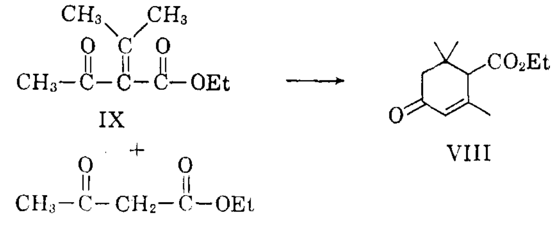
IV

The pyranylate V was prepared from IV by a procedure described in the Experimental of this paper. The ether (V) when treated with N-bromosuccinimide gave a bromine-containing liquid which decomposed upon standing, even when sealed under a nitrogen atmosphere. Hydrolysis of this material in the presence of mild base led to the formation of isophorone. This unexpected result shows that compound VII was probably formed.



Because of the difficulties encountered in the attempted direct substitution of isophorone, a different approach was sought.

Merling and Welde[4] and Knoevenagel[5] reported the preparation of ethyl 2,6,6-trimethyl-4-keto-2-cyclohexenecarboxylate (VIII) from the condensation of acetoacetic ester with 2-isopropylidene acetoacetate (IX).



This cyclohexenone derivative would be a suitable starting material for the preparation of zeaxanthin and related carotenoids, if readily available. IX was first prepared by Pauly[6] and later by Merling and Welde[7] by procedures requiring two weeks and yielding only 5–10% of product. The subsequent reaction of IX to give VIII is also a long and involved procedure.[4,5,8]

Acetone and acetoacetic ester were found to react directly giving VIII in the presence of boron trifluoride etherate in yields of *ca.* 40%.[9] Further

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(1) Present address: Merck and Co., Inc., Danville, Pennsylvania.

(2) O. Isler, M. Montavon, and R. Ruegg, U. S. Patent 2,917,539, December 15, 1959.

(3) J. B. Edgar, S. H. Harper, and M. A. Kazi, *J. Chem. Soc.*, 1083 (1957).

(4) G. Merling and R. Welde, *Ann.*, **366**, 141 (1909).

(5) E. Knoevenagel, *ibid.*, **297**, 185 (1897).

(6) H. Pauly, *Ber.*, **30**, 482 (1897).

(7) G. Merling and R. Welde, *ibid.*, **30**, 136 (1897).

(8) Meister Lucius & Bruning, German Patent 148,080, January, 1904.

(9) The yields are based upon the assumption that one mole of acetoacetic ester yields one mole of VIII.

investigation of this reaction showed that VIII could be prepared in almost equal yields by treating mesityl oxide and acetoacetic ester.

The facile preparation of compound VIII by these methods should make possible the preparation of the desired carotenoids by any one of several reaction paths.

Experimental

Prepration of 3,5,5-Trimethyl-2-cyclohexenol (IV). Reduction of Isophorone.—A three-necked 2-l. flask containing a stirrer, dropping funnel, and condenser was charged with 26.6 g. of lithium aluminum hydride in 500 cc. of ether. Isophorone (276 g., 2 moles) in 500 cc. of ether was added over a 3-hr. period and the mixture was stirred for 4 additional hours. Water (200 cc.) was then carefully added to the resulting mixture and after filtration the precipitated gel was washed with ether. The combined ether layers were concentrated *in vacuo*, dried over magnesium sulfate, filtered, and distilled. The fraction, b.p. 54–56° (1 mm.), n^{26}_{D} 1.4693, was collected and weighed 234 g. (1.67 moles). The m.p. of the *p*-nitrobenzoate was 70–71° (uncor.); lit.,[10] b.p. 69° (5 mm.), n^{20}_{D} 1.4717, m.p. *p*-nitrobenzoate 68.5–69.5.

Pyranylation of 3,5,5-Trimethylcyclohex-2-eneol.—A 1-l. three-necked flask containing a stirrer, addition funnel, and thermometer was charged with 193 g. (2.3 moles) of dihydropyran (Quaker Oats Chemical Co.) and surrounded by aluminum foil so as to exclude light. Toluenesulfonic acid (*ca.* 0.1 g., two recrystallizations from chloroform m.p. 104–105°) was added and 158.5 g. (1.13 moles) of the alcohol (IV) was slowly added to the stirred solution over 2.5 hr. so as to maintain a temperature of 40–45°. The resulting solution was stirred for an additional 2.5 hr., neutralized with 5 g. of powdered potassium carbonate, filtered, concentrated *in vacuo* under a nitrogen atmosphere, and distilled under nitrogen giving 178 g. of a clear liquid b.p. 91–97° (1–2.5 mm.), n^{24}_{D} 1.4700–1.4734. This was redistilled giving 107 g. of a liquid b.p. 78–80° (0.7 mm.), 108–109° (4 mm.); n^{25}_{D} 1.4720. The infrared spectrum of the pure pyranylate showed no bands below 3000 cm.$^{-1}$ (OH) and no bands between 2500–1700 cm.$^{-1}$ (ester and ketone impurities) but showed strong bands at 1195, 1126, 1109, and 1073 cm.$^{-1}$.

Anal. Calcd. for $C_{14}H_{24}O_2$: C, 75.0; H, 10.72. Found: C, 75.00; H, 10.73.

Reaction of Pyranylate (VI) with N-Bromosuccinimide and Hydrolysis of Reaction Product. a.—A dry three-necked 1-l. flask containing a stirrer, thermometer and condenser was changed with 84.7 g. of the pyranylated alcohol (VI) and 68 g. of N-bromosuccinimide in 250 cc. of petroleum ether (30–60°). The flask was carefully heated until the reaction became exothermic (42°) and the source of heat was removed. This procedure was repeated several times over a 45-min. interval keeping the temperature below 45°. The reaction mixture was then filtered (the resulting precipitate floated on carbon tetrachloride and gave a negative starch–iodide test) and the filtrate was concentrated *in vacuo* under a nitrogen atmosphere. It was noted that the filtrate decomposed upon standing even on ice under nitrogen but appeared to be stable in an ether solution. The concentrated reaction product could not be made to react with β-naphthol[11] or undergo a Grignard reaction. Distillation of an aliquot of this material gave a liquid b.p. 74° (1 mm.), n^{25}_{D} 1.5224 (A) which decomposed upon standing and whose microanalysis could not readily be determined. The analytical value for this material was closer to that of the halogenated cyclohexeneol than the halogenated pyranylate. The infrared spectrum showed an absorption characteristic of the hydroxyl group (3390 cm.$^{-1}$).[12]

b. Hydrolysis.—An aliquot (55.4 g.) of the N-bromosuccinimide reaction concentrate was stirred and heated with 20 g. of sodium carbonate in 50 cc. of water at *ca.* 60° for 17 hr. The reaction mixture was filtered, washed with ether, and the water layer was extracted with ether. The combined ether layers were dried over sodium hydroxide, filtered, and concentrated *in vacuo*. The resulting concentrate (36 g.) was distilled *in vacuo* giving isophorone (8 g.) and 13 g. of unchanged bromo compound similar to (A). In addition to these products, dihydropyran and tarry material were also obtained. The isophorone was identified by its infrared spectrum and by a mixed melting point of its 2,4-dinitrophenylhydrazone derivative with a 2,4-dinitrophenylhydrazone prepared from commercial isophorone.

Preparation of Ethyl 2,6,6-Trimethyl-4-keto-2-cyclohexenecarboxylate (VIII). a. Acetone and Acetoacetic Ester.—A 1-l. Erlenmeyer flask was surrounded by ice and 134 g. (1 mole) of commercial acetoacetic ester, 116 g. (2 moles) of acetone, and 290 g. (2 moles) of boron trifluoride etherate solution (Eastman, practical) were added and mixed. The resulting solution was allowed to stand on ice with intermittent shaking for 1 hr. and then transferred to a refrigerator (0–5°) for 3 days. The reaction mixture was then poured over cracked ice (*ca.* 500 cc.) and carefully neutralized with *ca.* 200 g. of sodium carbonate. The organic layer was separated and the water layer was extracted twice with ether. The combined organic layers were dried over potassium carbonate, concentrated *in vacuo* and distilled. A total of 59 g. (0.28 mole) of ester VIII was obtained. The boiling point of the material was 115–117° (2.3 mm.), n^{23}_{D} 1.4783–1.4790. In addition to VIII at least 39 g. of unchanged acetoacetic ester (0.29 mole) was also obtained; lit.,[4] for VIII, b.p. 111–113° (3.5 mm.).

Anal. Calcd. for $C_{12}H_{18}O_3$: C, 68.60; H, 8.57. Found: C, 68.85; H, 8.75.

b. Mesityl Oxide and Acetoacetic Ester.—Acetoacetic ester (130 g., 1 mole), mesityl oxide (100 g., 1 mole), and boron trifluoride etherate (145 g., 1 mole) were treated as described in the previous experiment and were allowed to stand in a refrigerator at 0–5° for 2.5 days. The reaction mixture was quenched with cracked ice and carefully treated with 110 g. of sodium carbonate. The resulting layers were separated and treated as before. Distillation gave 57 g. (0.27 mole) of VIII and led to the recovery of 35 g. (0.27 mole) of acetoacetic ester.

Acknowledgment.—The author is indebted to Dr. V. B. Fish of Lehigh University for the microanalysis, to Dr. R. T. Schenck for suggesting this problem, and to Dr. P. von Ostwalden for his helpful discussions.

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(10) M. S. Kharasch and P. O. Tawney, *Chem. Abstr.*, **35**, 7367 (1941).

(11) R. L. Shriner and R. C. Fuson, "Identification of Organic Compounds," John Wiley & Sons, Inc., New York, N. Y., 3rd ed., 1951, p. 193.

(12) It is probable that the alcohol was liberated during the course of the distillation since dihydropyran was found to be present in the "Dry Ice" trap.