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Reaction of β-Carotene with N-Bromosuccinimide: The Formation and Conversions of Some Polyene Ketones

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While the dehydrogenation of β-carotene, $C_{40}H_{56}$, with N-bromosuccinimide in CCl_4 solution yielded hydrocarbons, $C_{40}H_{54}$–$C_{40}H_{50}$, the use of commercial, *i.e.*, ethanol-containing, chloroform as a solvent resulted, after dehydrobromination, in the isolation mainly of three ketones, *viz.* 4-keto-3′,4′-dehydro-β-carotene and lesser amounts of 4-keto-β-carotene and 4,4′-diketo-β-carotene. The structural clarification of these ketones is represented in Charts 1–3, and is based on the interrelationship with further carotene derivatives such as 4-keto-4′-hydroxy-β-carotene, 4,4′-dihydroxy- and 4,4′-dimethoxy-β-carotenes, 4-hydroxy-3′,4′-dehydro-β-carotene, some alkoxy compounds, etc. A discussion of spectroscopic effects is given and some assays of vitamin A potencies are mentioned.

As reported earlier,[1–3] a treatment of β-carotene (I), $C_{40}H_{56}$, with N-bromosuccinimide resulted in the formation of a complicated pigment mixture which yielded the following crystalline hydrocarbons: dehydro-β-carotene, $C_{40}H_{54}$ (also termed *retro*-dehydrocarotene)[4]; *retro*-bisdehydrocarotene, $C_{40}H_{52}$; anhydro-eschscholtzxanthin, $C_{40}H_{50}$[5]; 3,4,3′,4′-bisdehydro-β-carotene, $C_{40}H_{52}$ (identical with Inhoffen's total-synthetic product)[4]; and "dehydrocarotene II,"[2] $C_{40}H_{52}$.

Whereas the dehydrogenations mentioned had been carried out in carbon tetrachloride solution, it has now been observed that a markedly different mixture appears, containing mainly oxygenated pigments, when chloroform is used as the solvent. We found that the ethanol present in commercial chloroform is responsible for this phenomenon, since ethanol-free chloroform acts as a medium essentially like carbon tetrachloride. Interestingly, the ethanol content of commercial chloroform, *viz.*, about 1%, represents the optimum alcohol concentration (over the range, 0.1–10%) for the formation of the new products described below. The role of the ethanol is not specific insofar as it can be replaced by methanol or benzyl alcohol without decreasing the yields; phenol and glacial acetic acid are, however, ineffective.

Under the conditions applied (3 moles of NBS per mole carotene), the β-carotene molecule was attacked at much higher rates than in carbon tetrachloride. The bromination phase of the reaction was complete in 30 sec., even at −20°, and the dehydrobromination in 10 min., in contrast to a total of 2–3 hours required in refluxed carbon tetrachloride solution. No unchanged β-carotene was recovered and 60% of the starting material had been converted into a pigment mixture which on chromatographic resolution gave five crystalline compounds (Chart 1). The total yield of all-*trans* crystals amounted to 20–25% of the β-carotene treated. Besides minor quantities of 3,4,3′,4′-bisdehydro-β-carotene (II) and *retro*-bisdehydrocarotene (III), the three ketones IV, V and VI were obtained, V being the main product.

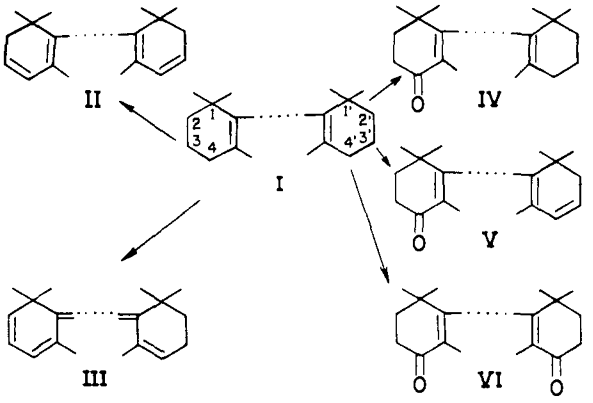

Chart 1.—Conversion of β-carotene (I) by N-bromosuccinimide in chloroform in the presence of 1% ethanol.

So far as we know this reaction represents the first instance of a (partial) conversion of a polyene hydrocarbon into ketones by means of the NBS reagent and should be applicable also in some other fields.

Elementary analyses proved the presence of two oxygen atoms in VI and of one in IV and V. The ketonic character of these compounds was confirmed by the preparation of some derivatives. All carbonyls were reduced with $LiAlH_4$ to hydroxyl groups[6] which caused a considerable shift of the main maxima toward shorter wave lengths. Consequently, the carbonyls had been parts of the respective conjugated systems.[7] The extent of this spectral shift amounted to 16 mμ (in hexane) for the diketone VI and to 8 mμ for the monoketone IV, whereby both extinction curves became identical with that of β-carotene (I). The main maximum of the other monoketone V was displaced on reduction likewise by 8 mμ, but the spectrum then coincided with that of 3,4-dehydro-β-carotene.[2] The conjugated nature of the carbonyls was further confirmed by a shift toward shorter wave lengths in the visible region, when oximes or 2,4-dinitrophenylhydrazones were prepared, and by the presence of a strong band at 6.04 μ in the infrared spectra of the three ketones.

The monoketone IV (λ_{max} at 458 mμ; Fig. 1, A) was identified with echinenone, a pigment first

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(1) L. Zechmeister and L. Wallcave, THIS JOURNAL, **75**, 4493 (1953).

(2) G. Karmakar and L. Zechmeister, *ibid.*, **77**, 55 (1955).

(3) L. Zechmeister and F. J. Petracek, *ibid.*, **77**, 2567 (1955).

(4) H. H. Inhoffen and G. Raspé, *Ann.*, **594**, 165 (1955).

(5) Anhydro-eschscholtzxanthin had been obtained by P. Karrer and E. Leumann, *Helv. Chim Acta*, **34**, 445 (1951), by the elimination of water from naturally occurring eschscholtzxanthin, detected by H. H. Strain, *J. Biol. Chem.*, **123**, 425 (1938).

(6) The reduction of echinenone (IV) with $LiAlH_4$ was carried out earlier by Drs. Ganguly, Pinckard and Krinsky (*cf.* ref. 10).

(7) *Cf.*, *e.g.*, R. Kuhn and H. Brockmann, *Ber.*, **65**, 894 (1932); **66**, 1319 (1933).

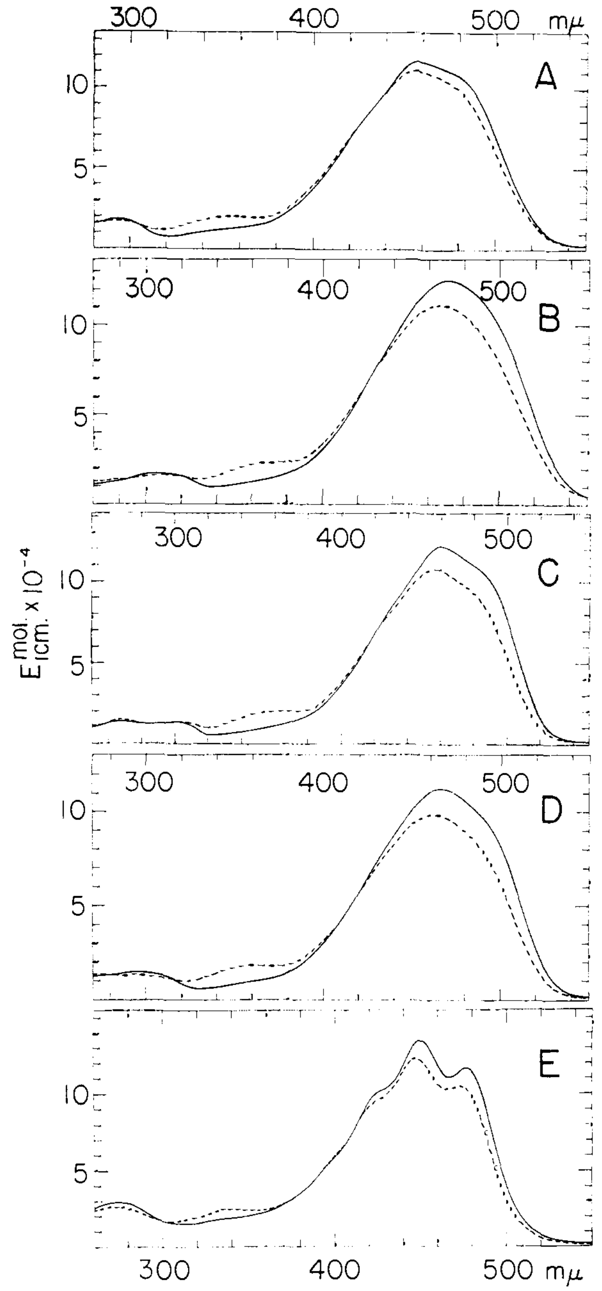

Fig. 1.—Molecular extinction coefficients, in hexane: solid lines, fresh solutions of the all-*trans* compound; dashed lines, spectral curves after iodine catalysis, in light: A, 4-keto-β-carotene; B, 4-keto-3′,4′-dehydro-β-carotene; C, 4-hydroxy-3′,4′-dehydro-β-carotene; D, 4,4′-diketo-β-carotene; and E, 4,4′-dihydroxy-β-carotene.

isolated by Lederer[8] from sea urchins. Goodwin and Taha[9] have advanced some arguments that echinenone is 4-keto-β-carotene and not 3-keto-β-carotene as had been suggested previously. We have been kindly informed by Drs. J. Ganguly, N. I. Krinsky and J. H. Pinckard that the 4-keto structure of this natural product has now been verified and is also in accordance with its provitamin A potency as determined quantitatively by these authors.[10] Thus, our work provides for a second synthesis of echinenone (for the first one, *cf.* ref. 10).

The assignment to V of the 4-keto-3′,4′-dehydro-β-carotene structure on the basis of spectral considerations ($\lambda_{\max}$ 469 mμ; Fig. 1B) was confirmed by the three conversions a, b and c of which a and b represent partial syntheses of V from structurally clarified starting materials (Chart 2): (a) Preparation of V by the simultaneous dehydrogenation and oxidation of isocryptoxanthin[11] (4-hydroxy-β-carotene, $\lambda_{\max}$ at 451 mμ); (b) dehydrogenation of 4-keto-β-carotene (IV) to V by 1 mole of NBS; and (c) the hydroxy compound VII (Fig. 1,C) obtained by $LiAlH_4$ reduction of V suffered facile dehydration under acid conditions to yield two structurally clarified hydrocarbons, *viz.* 3,4,3′,4′-bisdehydro-β-carotene (II) ($\lambda_{\max}$ at 472 mμ)[4] and *retro*-bisdehydrocarotene (III) ($\lambda_{\max}$ 487 mμ). In this instance, as had been shown earlier for the analogous dehydration of isocryptoxanthin,[11] a *retro* structure,[12] resulting from an allylic rearrangement, was preponderantly formed. The allylic position of the hydroxyl group with reference to the 5,6-double bond in VII was also demonstrated by the smooth formation of its methyl ether, *viz.*, 4-methoxy-3′,4′-dehydro-β-carotene (VIII) under the influence of acid in methanol.[13]

Experiments have shown that 4-keto-3′,4′-dehydro-β-carotene remains unaltered when treated with NBS under the conditions described, demonstrating the inertness of the 3-position which is oxygenated in the molecules of many natural xanthophylls.

The conversions mentioned also prove the structure of the parent hydrocarbon of VII, *viz.*, that of "dehydrocarotene II" which was tentatively interpreted as 3,4-dehydro-β-carotene by Karmakar and one of the writers.[2] The two compounds have identical spectra and hence the same chromophore. The conversion VII → III gave much higher yields than the direct method described in ref. 2.

The clarification of the 4,4′-diketo structure of our compound VI as well as some other interrelationships of pigments encountered in the present study are summarized in Chart 3.[13a]

The monoketone V yielded in chloroform solution a dark purple boron trifluoride complex[14] which was hydrolyzed (in part) to the hydroxy-ketone XII ($\lambda_{\max}$ 458 mμ). The position of the hydroxyl group thus formed is allylic because of the smooth reversion (by dehydration) of XII to V under the influence of acid chloroform. Further-

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[8] E. Lederer, *Compt. rend. acad. sci. Paris*, **201**, 300 (1935).

[9] T. W. Goodwin and M. M. Taha, *Biochem. J.*, **47**, 244 (1950).

[10] J. Ganguly, N. I. Krinsky and J. H. Pinckard, *Arch. Biochem. Biophys.*, **60**, 345 (1956); *cf.* the same authors and H. J. Deuel, Jr., 123rd Annual Meeting of the American Chemical Society in Los Angeles, Calif., March, 1953.

[11] L. Wallcave and L. Zechmeister, This Journal, **75**, 4495 (1953).

[12] W. Oroshnik, G. Karmas and A. D. Mebane, *ibid.*, **74**, 295 (1952).

[13] *Cf.* I. M. Heilbron, E. R. H. Jones, J. T. McCombie and B. C. L. Weedon, *J. Chem. Soc.*, 88 (1945).

[13a] Added in proof.—Recently, 4,4′-diketo-β-carotene has been identified with naturally occuring canthaxanthin; *cf. Arch. Biochem. Biophys.*, in press.

[14] For previous reports on polyene–boron trifluoride complexes *cf.*, *e.g.*, H. H. Strain, This Journal, **63**, 3448 (1941); L. Wallcave, J. Leemann and L. Zechmeister, *Proc. Nat. Acad. Sc.* (USA), **39**, 604 (1953); K. Lunde and L. Zechmeister, This Journal, **76**, 2308 (1954); *cf.* also Ref. 2 and 11.

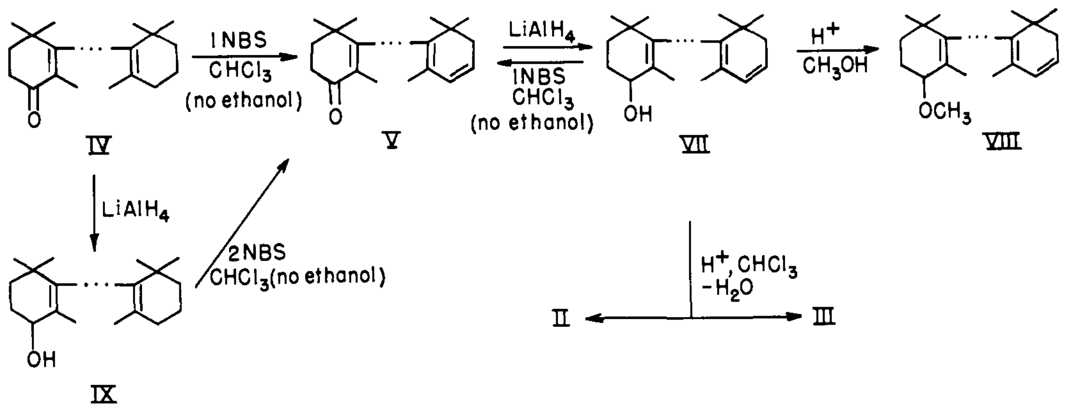


Chart 2.—Formation and some conversions of 4-keto-3′,4′-dehydro-β-carotene (V).

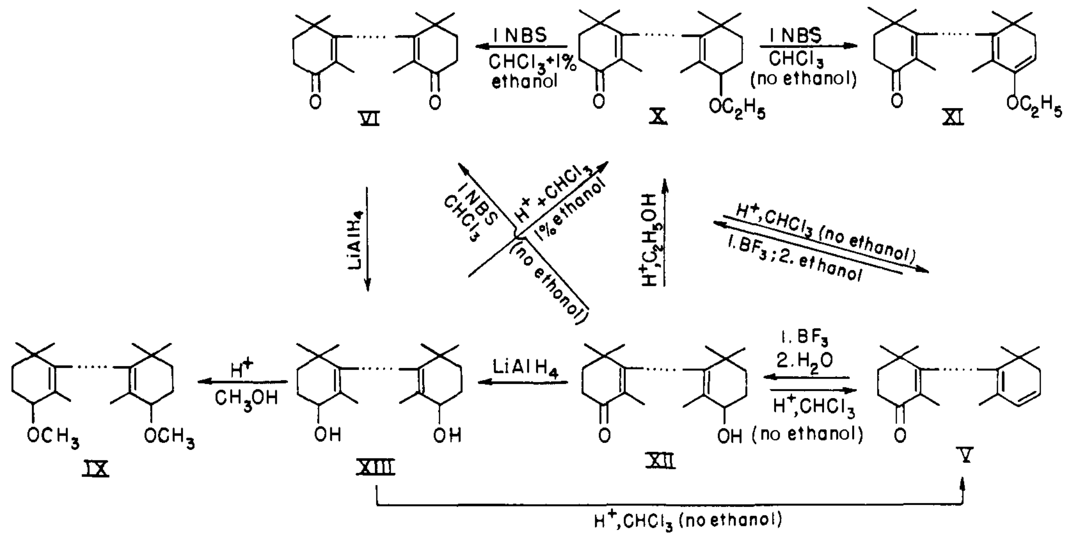
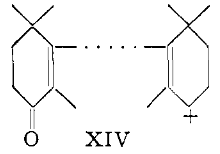


Chart 3.—Formation and some conversions of 4-keto-4′-hydroxy-β-carotene (XII) and of 4,4′-diketo-β-carotene (VI).

more, the spectrum of XII is identical with that of 4-keto-β-carotene (IV). On the basis of these observations XII must represent 4-keto-4′-hydroxy-β-carotene. Its easy conversion to the ethyl ether X under acid conditions in ethanol further confirms this interpretation.

From the above consideration the 4,4′-diketo structure of compound VI (λ_{max}, 467 mμ; Fig. 1,D) also follows, since VI was obtained as the main product of the oxidation of 4-keto-4′-hydroxy-β-carotene (XII) by means of 1 mole of NBS. Furthermore, the ketones VI and XII, when treated with $LiAlH_4$, yielded the same diol XIII showing the β-carotene spectrum (Fig. 1,E). That both hydroxyls in XIII, and hence the two corresponding keto groups in VI, occupy the positions 4 and 4′, is further supported by the following reaction: the diol XIII was easily converted by acid in methanol solution into the corresponding dimethoxy derivative IX (identified with the compound obtained earlier by methanolysis of the dehydro-β-carotene–boron trifluoride complex).[10] Furthermore, XIII yielded 4-keto-3′,4′-dehydro-β-carotene (V) when treated with acid in ethanol-free chloroform; however, in the presence of 1% ethanol the ethoxy derivative X was obtained.

The formation of 4-keto-4′-ethoxy-β-carotene (X) from 4,4′-dihydroxy-β-carotene (XIII) under the influence of acid in ethanol-containing chloroform, but of 4-keto-3′,4′-dehydro-β-carotene (V) under similar conditions in the absence of ethanol (Chart 3), is not yet understood. The introduction of the carbonyl into the 4-position in both instances could be *a priori* explained by the intermediate formation of a 4-hydroxy-4′-carbonium ion and subsequent rearrangement, *via* a *retro*-carbonium ion, to the *retro* product containing an enolic 4-hydroxyl group; this would then tautomerize to the 4-ketone. Hence, one would expect 4-keto-β-carotene to be a main reaction product. The experiment showed, however, that this ketone was absent from ethanol-containing as well as from ethanol-free media. Neither could it have functioned as an intermediate, since it was found to be stable in acid chloroform, both in the presence and in the absence of ethanol. Possibly, the carbonium ion XIV is an intermediate that would give rise to either 4-keto-4′-ethoxy-β-carotene (X) or 4-keto-3′,4′-dehydro-β-carotene (V), although no direct evidence is available at the present time.



XIV

Some understanding of the discussed formation of ketones from a polyene-hydrocarbon can be gained by studying the conversion, X → VI and X → XI. As seen from Chart 3, the ethoxy group in 4-keto-4′-ethoxy-β-carotene (X) when treated with NBS, is preserved only in the absence of alcohol; only in this instance is the 3′,4′-dehydro derivative XI formed. However, $-OC_2H_5$ is replaced by $>C=O$ (*cf.* X → VI) in the presence of alcohol. We propose that in the course of the conversion, X → XI, in the absence of ethanol, the main effects of NBS, followed by a treatment with N-phenylmorpholine, are, bromination (in 4) and subsequent dehydrobromination, resulting in the appearance of the dehydrogenated ethoxy derivative XI. In contrast, the presence of alcohol would cause first the conversion of the 4′-brominated ethoxy compound X to the corresponding 4′,4′-diethoxy grouping, and then the formation of a carbonyl from this ketal would take place. Accordingly, in the presence of alcohol, the formation of the main product of the interconversion or β-carotene and 3 NBS, may take place as follows: β-carotene (I) → 4,4,4′-tribromo-β-carotene → 4,4-diethoxy-4′-bromo-β-carotene → 4-keto-3′,4′-dehydro-β-carotene (V).

With reference to spectral phenomena the present study has shown that when the chromophore of β-carotene is lengthened either by a conjugated carbonyl group or by a conjugated ring double bond or both, the main maximum in the visible region is shifted toward longer wave lengths by definite and additive amounts. Hence, on the basis of the data listed in Table I, the structure of chromophores in some new carotenoid derivatives may be predicted and identified.

TABLE I

BATHOCHROMIC EFFECT OF CONJUGATED CARBONYLS AND RING DOUBLE BONDS ATTACHED TO THE END(S) OF THE β-CAROTENE CHROMOPHORE

Group	Shift at λ_{max}, in hexane, mμ
1 Carbonyl	7
2 Carbonyls	15
1 Double bond	10
2 Double bonds	21
1 Carbonyl and 1 double bond	19

Such lengthening of the conjugated system at one end substantially diminishes the extent of the fine structure in the spectral curve (visible region) (*cf.* Figs. 1, A and C); and if both ends are affected simultaneously, the fine structure disappears altogether (Figs. 1, B and D).[15] The validity of these considerations seems to extend the framework of the present study. For example, we conclude that in the curve of astacene (3,4,3′,4′-tetraketo-β-carotene)[16a] not all four carbonyls are responsible for the lack of fine structure, since the corresponding 4,4′-diketo derivative VI shows the same effect.

The statement made by Bohlmann[16b] that "in the field of dicarbonyl compounds themselves the position of the maximum is influenced practically only by one CO group" is certainly not valid for the spectrum of 4,4′-diketo-β-carotene and some other polyene-ketones.

Finally, we wish to mention that the observed provitamin A potencies are in accordance with the respective structures, considering the well-established fact[17] that vitamin A_2, a 3,4-dehydro compound, is much less active than vitamin A_1 whose ring contains one double bond only. The following potencies were found in the rat (β-carotene, 100%): 4,4′-keto-β-carotene, 0%; 3,4,3′,4′-bisdehydro-β-carotene, 43%; 4-hydroxy-3′,4′-dehydro-β-carotene, 16%; and 4-keto-3′,4′-dehydro-β-carotene, 17%.

Acknowledgments.—We are obliged to Drs. J. Ganguly, J. H. Pinckard and N. I. Krinsky for the private communication of their findings and for an echinenone sample; furthermore, we wish to thank Dr. Harry J. Deuel, Jr., and Mr. A. Wells of the University of Southern California for bioassays. The microanalyses have been carried out by Mr. G. Swinehart, in Dr. A. J. Haagen-Smit's Laboratory, and by Dr. A. Elek (Los Angeles, Calif.).

Experimental

Materials and Methods.—Adsorbents: lime–Celite 2:1 (lime, Sierra Superfine, U. S. Lime Prod., and Celite No. 545, Johns–Manville); magnesia–lime–Celite 3:1:1 (magnesia, Seasorb 43, Food, Mach. and Chem. Corp.); calcium carbonate–Celite 2:1 ($CaCO_3$, precipitated, U.S.P. XIII, Heavy; Mallinckrodt). When no adsorbent is mentioned, the experiment refers to the lime–Celite mixture; and in the absence of other data the size of the column was 27 × 8 cm. Elutions of zones were effected with acetone (exceptionally, with acetone–methanol). Washing of solutions was carried out in the LeRosen automatic device[18] and drying was effected with sodium sulfate.

The spectral data refer, if not otherwise stated, to solutions in optical grade hexane. The following instruments were used: Beckman spectrophotometer model DU, Cary recording spectrophotometer model 11M and Perkin–Elmer infrared spectrophotometer model 21.

Partition values were obtained by shaking the hexane solution (saturated with 95% methanol) with 95% methanol (saturated with hexane) and determining the ratio of the concentrations in hexane:95% methanol by estimating, photometrically, at λ_{max}, the concentration in the hexane solution before and after shaking with an equal volume of the methanol.

The commercial NBS (Arapahoe Chemicals, Inc.) was used without further purification. The preparation of boron trifluororide etherate has been described earlier.[11] The "acid chloroform reagent"[19] was obtained by saturating Merck R. G. chloroform with dry HCl gas at room temperature for 10 min. If a pigment dissolved in pure chloroform (concn. about 3 mg./l.), showed upon the addition of a few drops of the reagent marked deepening of its color within a few min., the presence of an allylic OH group (or O-alkyl or O-acetyl) was indicated.

Analytical samples were dried over P_2O_5 at 50° and 1 mm. The m.p. (cor.) refer to an electrically heated Berl block.

The samples of one and the same compound obtained by different routes were identified by melting points, spectra, partition behavior, mixed chromatogram test, etc., even if this is not stated below.

Large Scale Preparation of β-Carotene.—The commercial carotene sample (8 g.; Barnett Lab., Long Beach, Calif.) was dissolved in 200 ml. of warm benzene, diluted with hexane to 1.5 l., adsorbed on magnesia–lime–Celite in a conic percolator (45 × 22 × 8 cm.) and developed with

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[15] This is in accordance with the well-known effect of the carbonyl group on the spectra of shorter polyenes as well as with the partial loss of fine structure in the process, vitamin $A_1 \rightarrow A_2$; *cf.* ref. 17.

[16] (a) R. Kuhn and E. Lederer, *Ber.*, **66**, 488 (1933); P. Karrer, *et al.*, *Helv. Chim. Acta*, **17**, 412, 745 (1934); **19**, 479 (1936); (b) F. Bohlmann, *Ber.*, **84**, 860 (1951).

[17] K. Farrar, J. C. Hamlet, H. B. Henbest and E. R. H. Jones, *J. Chem. Soc.*, 2657 (1952); E. M. Shantz and J. H. Brinkman, *J. Biol. Chem.*, **183**, 457 (1950).

[18] A. L. LeRosen, *Ind. Eng. Chem.*, *Anal. Ed.*, **14**, 165 (1942).

[19] *Cf. e.g.*, P. Karrer and E. Leumann, Ref. 5.

about 6 l. of benzene–hexane 1:2. Then the well-separated β- and α-carotene zones were eluted, transferred to benzene–hexane, dried, evaporated and crystallized from benzene–methanol or chloroform-methanol; yield 4 g. of β-carotene, m.p. 182–183°, and 1.2 g. of α-carotene, m.p. 187–188°. In all, 25 g. of β-carotene was prepared from 48 g. of crude carotene.

Conversion of β-Carotene with NBS in Commercial Chloroform to a Pigment Mixture.—To 100 mg. of substance in 10 ml. of the solvent (−18°) was rapidly added 100 mg. of NBS (3 moles per mole pigment) in 10 ml. of the same solvent (−18°), while a nitrogen stream bubbled through. Half a minute later 200 mg. of powdered N-phenylmorpholine was introduced, the dark brown liquid was stirred for 2 more min. and then refluxed for 15 min., whereby the initial red color returned. The cooled solution was diluted with 40 ml. of hexane and shaken several times with 0.1 *N* HCl; the epiphase was washed acid-free, dried and evaporated. A solution of the oily residue in 25 ml. of hexane was adsorbed on a column and developed with hexane + 5% acetone (the figures on the left denote the width of the zones, in mm.)

5	brown
10	red: 4,4′-diketo-β-carotene (zone A)
50	3 diffuse pink zones: *retro*-bisdehydro-carotenes (zone B)
30	deep red: all-*trans*-4-keto-3′,4′-dehydro-β-carotene (zone C)
80	six pink-orange zones: *cis* forms of the former and 4-keto-β-carotene (zone D)
10	light orange: 3,4,3′,4′-bisdehydrocarotene (zone E)
15	yellow: *cis* forms of the former (free of unreacted β-carotene)

***retro*-Bisdehydrocarotene (III).**—Zone B (see above), *ex* 1 g. β-carotene, was rechromatographed on two columns (developer, hexane + 7% acetone). The chromatogram showed an intense pink main zone of all-*trans-retro*-bisdehydrocarotene followed by some *cis* isomers and by a bottom zone containing some 4-keto-3′,4′-dehydro-β-carotene (V). The main pigment (5.5% of the β-carotene employed, as estimated photometrically, including *cis* forms) was rechromatographed on two columns as described and yielded 10 mg. of long, quadrangular plates with jagged ends, m.p. 205–206°.

Anal. Calcd. for $C_{40}H_{52}$: C, 90.16; H, 9.84. Found: C, 90.10; H, 10.03.

Partition behavior, entirely epiphasic (100:0). The spectral curve coincided with that reported earlier for III (λ_{max} 487 mμ),[1] and a mixed chromatogram test also showed identity.

3,4,3′,4′-Bisdehydro-β-carotene (II).—Zone E (see above), *ex* 1 g., β-carotene, after rechromatography, yielded 10 mg. of this compound as estimated photometrically and then 4 mg. of crystals, m.p. 196–198°, $E^{mol}_{1\,cm}$ 12.7 × 10^4 at λ_{max} 471 mμ. This sample was found to be identical with both Inhoffen's synthetic product[4] and "dehydrocarotene III."[2]

Anal. Calcd. for $C_{40}H_{52}$: C, 90.16; H, 9.84. Found: C, 89.96; H, 9.94.

4-Keto-β-carotene (IV).—Zone D (see above), *ex* 2 g. β-carotene, was transferred to hexane and rechromatographed on three columns (hexane + 4% acetone). The main zone contained 4-keto-β-carotene and was followed by several stereoisomeric 4-keto-3′,4′-dehydro-β-carotenes (V). The combined three 4-keto-β-carotene zones were rechromatographed on a single magnesia–lime–Celite column (benzene–hexane 1:4 + 15% acetone). The main, brick-red zone yielded 24 mg. of dull-red, rectangular plates (from benzene–methanol); m.p. 175–178°. In a parallel experiment in which only 2 moles of NBS per mole carotene had been used, the yield amounted to 100 mg.

Anal. Calcd. for $C_{40}H_{54}O$: C, 87.22; H, 9.88. Found: C, 87.41; H, 10.05.

Partition behavior: 93:7. λ_{max} at 458 mμ (for $E^{mol}_{1\,cm}$ *cf.* ref. 10 and Fig. 1A); strong band at 6.04 μ. Chromatographic sequence (lime–Celite, hexane + 5% acetone): 4-keto-3′,4′-dehydro-β-carotene (top), 4-keto-β-carotene, and β-carotene. A mixed chromatogram test with an echinenone sample originating from sea urchins[9] did not result in separation. The **oxime**[9] was prepared as described below for that of 4-keto-3′,4′-dehydro-β-carotene; small plates, m.p. 203–206°.

Anal. Calcd. for $C_{40}H_{55}ON$: N, 2.48. Found: N, 3.02. λ_{max} at 456 mμ.

When the ketone IV was kept for an hour in acidified chloroform (4 ml. of pure chloroform + 4 drops of the "acid chloroform reagent"), either in the presence or in the absence of ethanol, and then chromatographed, a single main zone appeared that contained unaltered 4-keto-β-carotene.

4-Keto-3′,4′-dehydro-β-carotene (V). (a) **From β-Carotene (I) direct.**—From the acetone eluate of Zone B (*ex* 0.1 g. β-carotene) the pigment was transferred to hexane by water addition and rechromatographed (hexane + 5% acetone). The main zone was eluted, evaporated and crystallized from benzene–methanol or chloroform–methanol; yield 16 mg. of red-purple, oval plates with pointed ends (from benzene–methanol), m.p. 192–194°.

Anal. Calcd. for $C_{40}H_{52}O$: C, 87.53; H, 9.55. Found: C, 87.44; H, 9.73.

The compound is sparingly soluble in hexane, soluble in warm benzene, easily in chloroform, insoluble in methanol or ethanol. Partition behavior, 92:8; $E^{mol}_{1\,cm}$ 12.6 × 10^4 at λ_{max} 470 mμ (Fig. 1B). In the infrared region a strong band appeared at 6.04 μ. On lime–Celite this pigment is adsorbed above 4-keto-β-carotene from which it is well separated.

Oxime.—Thirty mg. of the ketone and 120 mg. of hydroxylamine hydrochloride in 5 ml. of dry pyridine were heated on the steam-bath for 45 min., then diluted with 20 ml. of benzene–hexane 1:1, washed pyridine-free, diluted with 50 ml. of hexane, dried and developed with hexane + 35% benzene on calcium carbonat-Celite. The main, dark-orange zone yielded 8 mg. of the oxime, when crystallized from benzene–methanol; m.p. 200–201°.

Anal. Calcd. for $C_{40}H_{53}ON$: N, 2.48. Found: N, 2.64.

(b) **From 4-Hydroxy-3′,4′-dehydro-β-carotene (VII).**—To 31 mg. of substance in 10 ml. of ethanol-free chloroform was added at 0°, in a vigorous N_2 stream, 11 mg. of NBS in 10 ml. of the same grade of chloroform. On 1 min. standing the solution was refluxed with 20 mg. of N-phenylmorpholine for 15 min. After shaking with HCl, washing, drying and evaporating, the pigment was developed with hexane + 5% acetone on a column. The chromatogram contained only the desired ketone and some *cis* isomers; total yield 19.5 mg. (63%) as estimated photometrically. Six milligrams of all-*trans* crystals was isolated, m.p. 188–190°.

(c) **From 4-Keto-β-carotene (IV).**—To a solution of 14 mg. of IV in 10 ml. of ethanol-free chloroform, kept at 0°, a cooled solution of 6.5 mg. of NBS in 10 ml. of the same grade chloroform was added in an N_2-stream. Two minutes later 15 mg. of N-phenylmorpholine was introduced and the solution refluxed for 15 min. The cooled solution was then diluted with hexane and shaken with 0.1 *N* HCl. The epiphase was washed acid-free, dried and evaporated. The product when developed on lime–Celite (23 × 4.8 cm.) with benzene–hexane 1:2 gave a single main deep red zone of all-*trans*-4-keto-3′,4′-dehydro-β-carotene, followed by several minor *cis* zones. As estimated photometrically, these stereoisomers represented a total yield of 50%. The all-*trans* fraction was crystallized from benzene–methanol; yield 3 mg., m.p. 189–190°.

Anal. Calcd. for $C_{40}H_{52}O$: C, 87.53; H, 9.55. Found: C, 87.63; H, 9.75.

The sample was spectroscopically and chromatographically identical with that obtained according to procedure (a).

(d) **From 4-Hydroxy-β-carotene** (isocryptoxanthin) **(IX).**—To 33 mg. of IX in 15 ml. of ethanol-free chloroform was added, with stirring, at 0°, 24 mg. of NBS (2 moles per mole pigment) in 15 ml. of the same grade chloroform. The stirring was continued for 1 more min. Then 30 mg. of N-phenylmorpholine was introduced and the liquid refluxed for 15 min. There followed a treatment as described under (c) whereupon the mixture was resolved on a column using hexane + 5% acetone. The single main zone of all-*trans*-4-keto-3′,4′-dehydro-β-carotene was followed by some minor *cis* zones. The combined yield was 11 mg. as estimated photometrically. The all-*trans* fraction yielded 4 mg. of reddish-purple, oval plates, m.p. 188–189°, identical with the preparations described above.

(e) **From 4,4′-Dihydroxy-β-carotene (XIII).**—To a solution of 22 mg. of the diol in 10 ml. of ethanol-free chloroform 15 drops of the acid–chloroform reagent were added dropwise. During 30 min. standing the partition behavior became epiphasic. The solution was then further treated and chromatographed as described under (c) (column size, 30 × 6 cm.). The main, scarlet-red zone was rechromatographed on magnesia–lime–Celite (25 × 6 cm.; developer, a 2:3 benzene–hexane mixture containing 10% acetone). The pigment of the main zone yielded 3 mg. of V as reddish-purple plates, m.p. 188°.

(f) **From 4-Keto-4′-hydroxy-β-carotene (XII).**—The solution of 10 mg. of the keto-alcohol in 5 ml. of ethanol-free chloroform was mixed with 15 drops of the acid chloroform reagent and kept at 20°. The progress of the dehydration was followed by checking the partition behavior of smal samples. Essentially epiphasic behavior was observed after 40 min. The solution, deeper in color than before the treatment, was diluted with 40 ml. of hexane, shaken with saturated bicarbonate, dried, and evaporated. A hexane solution of the oily residue was developed with hexane + 6% acetone on lime–Celite (25 × 6 cm.). The pigment of the main, all-*trans* zone was crystallized from benzene–methanol; yield 3.5 mg., m.p. 189–190°. *Cf.* also under "4-keto-4′-ethoxy-β-carotene."

(g) **From 4-Keto-4′-ethoxy-β-carotene (X).**—The same result as described under (f) was obtained by an analogous treatment of the ethoxy compound X.

4,4′-Diketo-β-carotene (VI). (a) **From β-Carotene.**—Zone A (see above) *ex* 2 g. β-carotene was rechromatographed on two columns (benzene–hexane 3:1)

15	minor zones
30	deep red: all-*trans*-4,4′-diketo-β-carotene
10	orange: *cis* isomer of the former
45	several yellow and pink minor zones

The 30-mm. zone was eluted, transferred to benzene–hexane, dried and evaporated. The powdery red residue was crystallized from chloroform–ethanol or from benzene–methanol; yield 24 mg. as trapezoidal prisms from benzene–methanol but long needles from chloroform–ethanol; m.p. 213–214°.

Anal. Calcd. for $C_{40}H_{52}O_2$: C, 85.05; H, 9.28. Found: C, 85.18; H, 9.31.

The compound is less soluble than the 4-monoketone or β-carotene. Partition behavior, 50:50; maximum in hexane at 466 mμ; in ethanol, at 478 mμ; and in benzene, at 480 mμ. $E^{\text{mol}}_{1\text{ cm}}$ 11.4 × 10^4 in hexane (Fig. 1C). No fine structure was observed in any of these solvents. In the infrared region, a strong band appeared at 6.04 μ.

When developed with benzene on lime–Celite, the diketone is adsorbed considerably above the 4-keto-β-carotene or *retro*-bisdehydrocarotene zone but below zeaxanthin (3,3′-dihydroxy-β-carotene).

Di-2,4-dinitrophenylhydrazone.—To 9 mg. of the diketone in 5 ml. of nitrobenzene and 6 ml. of abs. alcohol, 3 ml. of the reagent[20] was added and the dark, micro-crystalline precipitate centrifuged an hour later. After washing with ethanol and drying, yield 10 mg., m.p. > 300°.

Anal. Calcd. for $C_{52}H_{58}O_8N_8$: N, 12.11. Found: N, 12.92.

The corresponding monohydrazone can also be obtained, *viz.*, by starting from 9 mg. of diketone, 3 ml. of benzene, 6 ml. of ethanol and 3 ml. of the reagent; feathery needles, m.p. 250°; a nitrobenzene solution was converted into the di-derivative.

(b) **From 4-Keto-4′-hydroxy-β-carotene (XII).**—To 30 mg. of XII in 10 ml. of ethanol-free chloroform was added, at 0°, 10 mg. of NBS (molar ratio, 1:1) in 10 ml. of the same grade solvent. One minute later 10 mg. of N-phenylmorpholine was introduced and the solution refluxed for 15 min. After a treatment as described above for the preparation of 4-keto-3′,4′-dehydro-β-carotene, the product was developed with benzene on a column and the pigment of the 60 mm. broad main zone was crystallized from chloroform–ethanol; yield 16 mg., m.p. 211–212°.

Anal. Calcd. for $C_{40}H_{52}O_2$: C, 85.05; H, 9.28. Found: C, 85.28; H, 9.51.

(c) **From 4-Keto-4′-ethoxy-β-carotene (X).**—To 3.6 mg. of X in 1 ml. of ethanol-containing chloroform (Merck R.G.) was added, at 0°, 1.6 mg. of NBS in 1 ml. of the same grade chloroform. The stirring with a nitrogen stream was continued for 1 more minute; then 20 mg. of N-phenylmorpholine was introduced and the liquid was kept at 50° for 15 min. After a treatment as described above the mixture was developed with benzene–hexane 1:4 + 10% acetone on a 20 × 4 cm. lime–Celite column. The main zone contained the all-*trans* diketone and was followed by a *cis* isomer; yield 0.6 mg. (estimated photometrically).

4-Keto-4′-ethoxy-3′,4′-dehydro-β-carotene (XI).—In a similar experiment carried out in the *absence of ethanol* (15 mg. of X, 7 mg. of NBS, at 0°) besides the diketone VI also the ethoxy compound XI was formed. Fifteen seconds after the addition of the reagent, the red solution suddenly turned brown. N-Phenylmorpholine (25 mg.) was added 40 sec. later and the solution was refluxed for 15 min. Chromatographic resolution (benzene–hexane 1:4 + 10% acetone) showed the presence of 3 mg. of 4-keto-4′-ethoxy-3′,4′-dehydro-β-carotene (XI); yield after crystallization from chloroform–ethanol, 1–2 mg., m.p. 209–210°.

Anal. Calcd. for $C_{40}H_{51}O(OC_2H_5)$: OC_2H_5, 7.58. Found: OC_2H_5, 6.51.

The spectral curve ($\lambda_{\max}$ at 470 mμ) was practically identical with that of V (Fig. 1B). Partition behavior, 44:56. On lime–Celite this compound is adsorbed slightly above the 4,4′-diketo-β-carotene zone.

4-Keto-4′-hydroxy-β-carotene (XII). From 4-Keto-3′,4′-dehydro-β-carotene (V), *via* the BF_3 Complex.—To 33 mg. of substance in 33 ml. of ethanol-free chloroform was rapidly added, with stirring, 3.3 ml. of BF_3 etherate. The solution turned blue, green and then dark purple within 2 min. At this point it was rapidly poured, while stirring, into 400 ml. of a 1:4 water–acetone mixture. After the addition of 60 ml. of hexane, the epiphase was washed for 30 min., dried and evaporated. A solution of the oily residue in 25 ml. of benzene–hexane 1:3 was adsorbed and developed with pure benzene on a column. The 30 mm. broad main pink zone was transferred to benzene, washed, dried, evaporated, and the powdery residue was crystallized from chloroform–hexane; yield 6 mg. of diamond-shaped plates, m.p. 164–167°.

Anal. Calcd. for $C_{40}H_{54}O_2$: C, 84.75; H, 9.60. Found: C, 84.41; H, 9.72.

Partition behavior, 34:66. The spectrum was identical with that of 4-keto-β-carotene (V): $E^{\text{mol}}_{1\text{ cm}}$ 12.2 × 10^4 at $\lambda_{\max}$ 458 mμ. The infrared curve showed the presence of conjugated carbonyl (6.04 μ) and of hydroxyl (2.90 μ).

The ethyl ether, 4-keto-4′-ethoxy-β-carotene (X), is described below.

4,4′-Dihydroxy-β-carotene (XIII). (a) **From 4,4′-Diketo-β-carotene (VI).**—To a solution of 50 mg. of the diketone in 100 ml. of benzene–ether 1:9, 100 mg. of $LiAlH_4$ in 100 ml. of abs. ether was added, with swirling. Fifteen minutes later the excess hydride was decomposed at 0° by dropwise addition of methanol. The solution was washed free of the gel, dried and evaporated. The solution of the powdery residue in 50 ml. of benzene–hexane 1:1 was developed on two columns with benzene + 5% acetone or hexane + 30% chloroform. The main, yellow zone contained the diol in 90% yield (estimated photometrically) and gave 30 mg. of red-orange needles, m.p., from chloroform–hexane, 142–145°; and from methylene chloride–hexane, 146–148°.

Anal. Calcd. for $C_{40}H_{56}O_2$: C, 84.44; H, 9.30. Found: C, 84.60; H, 9.43.

In benzene the diol is less easily soluble than the diketone. The spectrum was identical with that of β-carotene, $E^{\text{mol}}_{1\text{ cm}}$ 13.4 × 10^4 at $\lambda_{\max}$ 450 mμ (Fig 1,D). No band appeared at 6.04 μ. Partition behavior, 22:78. When developed with benzene on lime–Celite or calcium carbonate–Celite the diol is adsorbed above the parent diketone. The response to acid chloroform was strongly positive.

The **diacetate** was prepared from 50 mg. of the diol as described for the acetylation of 4-hydroxy-3′,4′-dehydro-β-carotene (VII). It was chromatographed using hexane + 3% acetone and crystallized from benzene–methanol as stubby prisms with blunt ends, m.p. 142–143°.

Anal. Calcd. for $C_{44}H_{66}O_4$: C, 80.93; H, 9.26. Found: C, 80.49; H, 9.60.

Partition behavior, 86:14. The spectrum of the diacetate was identical with that of the diol.

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(20) *Cf.* R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," 3rd ed., John Wiley and Sons, Inc., New York, N. Y., 1948, p. 171.

(b) **From 4-Keto-4′-hydroxy-β-carotene (XII).**—Ten mg. of the keto-alcohol was reduced as described under (a). The chromatogram showed a single main zone; yield 5 mg., m.p. 142–143°. The product did not separate in the mixed-chromatogram test from a sample prepared according to (a).

4,4′-Dimethoxy-β-carotene (IX).—To a solution of 5 mg. of the corresponding diol XIII in 8 ml. of 95% methanol a drop of the acid chloroform reagent was added. After 7 min. standing the pigment showed epiphasic behavior, in contrast to the starting material. After transfer into hexane the mixture was developed with hexane + 3% acetone on a 20 × 4 cm. lime–Celite column. The chromatogram showed a main zone containing all-*trans*-4,4′-dimethoxy-β-carotene followed by a *cis* isomer; yield 1 mg. of the *trans* form as rectangular plates with split ends, m.p. 153–154°. The spectrum was identical with that of the diol and of β-carotene. The compound did not separate in the mixed chromatogram test from a sample prepared earlier by methanolysis of the BF_3 complex of dehydro-β-carotene.[11]

4-Methoxy-3′,4′-dehydro-β-carotene (VIII).—To a solution of 25 mg. of VII in 5 ml. of chloroform and 25 ml. of methanol (99.5%), 10 drops of the acid chloroform reagent was added, and the liquid was kept standing for exactly 7 min. (longer standing may cause partial destruction). After dilution with 25 ml. of hexane the epiphase was washed, dried and evaporated. A solution of the oily residue in hexane was developed with hexane + 2% acetone. The main zone represented the all-*trans* methoxy compound, followed by a *cis* isomer. The *trans* pigment was crystallized from benzene–methanol; yield 6 mg. of irregular plates, m.p. 142–144°.

Anal. Calcd. for $C_{40}H_{53}(OCH_3)$: C, 87.17; H, 9.99; OCH_3, 5.48. Found: C, 87.53; H, 10.02; OCH_3, 5.57.

The spectrum was not affected by the introduction of methoxyl. Partition behavior, 99:1. The methoxy derivative was absorbed below the hydroxy compound. It gave a positive test for an allylic functional group.

4-Keto-4′-ethoxy-β-carotene (X). (a) **From 4-Keto-4′-hydroxy-β-carotene (XII) in Alcohol.**—To a solution of 25 mg. of XII in 25 ml. of abs. ethanol 5 drops of the acid chloroform reagent was added. The partition behavior became epiphasic after 5 min. At this point the solution was made slightly basic with a few ml. of saturated bicarbonate solution. After dilution with 20 ml. of hexane the epiphase was washed, dried and developed with hexane + 6% acetone. The pigment of the main, brick-red zone (20 mm. broad) was crystallized from chloroform–ethanol; yield 10 mg., m.p. 154–156°.

Anal. Calcd. for $C_{40}H_{53}(OC_2H_5)$: OC_2H_5, 7.58. Found: OC_2H_5, 9.06.

The spectrum coincided with that of 4-keto-4′-hydroxy-β-carotene (XII).

(b) **From 4-Keto-3′,4′-dehydro-β-carotene (V) *via* the BF_3 Complex.**—To 50 mg. of substance in 50 ml. of chloroform (Merck, R.G.) 5 ml. of boron trifluoride etherate was added rapidly, with swirling, and 3 min. later the dark liquid was poured into 250 ml. of abs. ethanol. Water and 125 ml. of hexane were then added and the epiphase was deacidified with bicarbonate. The hexane–chloroform solution was diluted with 500 ml. of acetone, the acetone was washed out, and this treatment was repeated.[21] Finally, the solution was washed acetone-free, dried, evaporated and the residue developed on a 50 × 8 cm. magnesia–lime–Celite column with benzene–hexane 2:3 + 10% acetone. The main zone contained 19 mg. of the product (including some *cis* forms). The all-*trans* compound was isolated in crystals upon rechromatography (lime-Celite, hexane + 5% acetone); yield 8 mg. (from benzene–methanol), m.p. 156–158°.

Anal. Calcd. for $C_{42}H_{58}O_2$: C, 84.79; H, 9.83. Found: C, 85.02; H, 10.05.

(c) **From 4,4′-Dihydroxy-β-carotene (XIII).**—Twenty mg. of the diol in 10 ml. of commercial chloroform (Merck, R.G.) was treated with 10 drops of the acid chloroform reagent. When epiphasic behavior was observed, *i.e.* in about 10 min., the solution was shaken with bicarbonate, dried and evaporated. The oily residue was dissolved in hexane and developed with hexane + 5% acetone. The 14 mm. broad, main pink zone, containing 4 mg. of the ethoxy-ketone was eluted, transferred to hexane, dried and evaporated. The residue was crystallized from chloroform–ethanol as plates, m.p. 154–156°. The spectrum was identical with that of 4-keto-β-carotene. A mixed chromatogram test showed no separation from a sample obtained as described above (b).

(d) **From 4-Keto-4′-hydroxy-β-carotene (XII) (in Ethanol-containing Chloroform).**—To 40 mg. of XII in 25 ml. of chloroform (Merck, R.G.) 25 drops of the acid chloroform reagent was added dropwise, with stirring. The partition behavior became epiphasic within 5 min. Excess acid was removed with bicarbonate, the dried solution was evaporated, and a hexane solution of the residue was developed with a 1:1 benzene–hexane mixture on a 60 × 8 cm. column. Besides numerous minor pigments, two main products were observed, *viz.*, a 70-mm. red-orange zone of 4-keto-4′-ethoxy-β-carotene and, located just below it, a 35-mm. scarlet zone of 4-keto-3′,4′-dehydro-β-carotene (V).[22]

The ethoxy compound (10 mg. as estimated photometrically) was transferred to hexane–benzene (1:1), washed, dried and evaporated. The powdery residue was crystallized from chloroform-ethanol; yield, 6 mg. of plates, m.p. 154–156°.

Anal. Calcd. for $C_{42}H_{58}O_2$: C, 84.79; H, 9.83. Found: C, 84.66; H, 9.35 (values corrected for 0.8% ash).

The spectrum was identical with that of the parent hydroxy compound.

The 35-mm. scarlet zone contained 4 mg. of 4-keto-3′,4′-dehydro-β-carotene (estimated photometrically); yield, 3 mg. of oval plates, m.p. 187–189°.

Anal. Calcd. for $C_{40}H_{52}O$: C, 87.53; H, 9.55. Found: C, 87.38; H, 9.86.

4-Hydroxy-3′,4′-dehydro-β-carotene (3′,4′-Dehydroisocryptoxanthin) (VII).—Fifty milligrams of 4-keto-3′,4′-dehydro-β-carotene (V), in 100 ml. of a 1:9 mixture of anhydrous benzene and ether was slowly added, with stirring, to 500 mg. of $LiAlH_4$ in 200 ml. of anhydrous ether. The liquid was allowed to stand for 15 min. It was then cooled to 0°, methanol was added dropwise and the gel removed by washing. The dried benzene–ether solution was evaporated. The solution of the bright-orange, powdery residue in 50 ml. of benzene–hexane 1:4 was developed with hexane + 7% acetone and the pigment contained in the main, 90-mm. broad zone was crystallized from benzene–methanol or chloroform–ethanol: yield 30 mg. of bright-orange, irregular platelets with metallic luster, m.p. 174–175°.

Anal. Calcd. for $C_{40}H_{54}O$: C, 87.22; H, 9.88. Found: C, 87.33; H, 9.95.

The spectral curve was identical with that of 3,4-dehydro-β-carotene ("dehydrocarotene II")[2]; $E^{\text{mol}}_{1\text{ cm}}$ 12.4 × 10^4 at $\lambda_{\max}$ 461 mμ (Fig 1, E). No ketone band appeared in the infrared region.

The compound was sparingly soluble in hexane or methanol, easily in cold chloroform or warm benzene. Partition behavior, 80:20. The pigment is adsorbed on lime–Celite slightly above the 4-keto-3′,4′-dehydro-β-carotene or the isocryptoxanthin zone.

Acetate.—A solution of 60 mg. of VII in 3 ml. of dry pyridine and 1 ml. of acetic anhydride was kept at 60° for an hour, then diluted with 60 ml. of hexane, washed, dried and chromatographed (hexane + 2% acetone). The pigment of the main zone was crystallized from benzene–methanol; yield 10 mg. of dull-orange, irregular plates, m.p. 131–133°.

Anal. Calcd. for $C_{41}H_{56}O_2$: C, 85.08; H, 9.52. Found: C, 85.04; H, 9.72.

The spectrum was not affected by the acetylation. Partition behavior, 94:6. On lime–Celite the acetate is adsorbed below the hydroxyl compound. Methyl ether VIII, see above.

Dehydration of 4-Hydroxy-3′,4′-dehydro-β-carotene (VII) to II and III.—Twenty-five drops of the acid chloroform reagent was added, with stirring, to 100 mg. of VII in 25 ml. of chloroform (Merck, R.G.) and 10 min. later the solution was washed with sodium bicarbonate. After drying and evaporation a hexane solution of the oily residue

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[21] This operation prevented an unexplained, rapid discoloration of the pigment from red to brown during the subsequent evaporation, and a decrease in the yields.

[22] It was found recently that the separation of these two pigments can be carried out more advantageously by developing with benzene–hexane 2:3 + 10% acetone on a magnesia–lime–Celite column. Interestingly, the top-to-bottom sequence is then inverted.

was developed with hexane + 5% acetone (45 × 8 cm.). The top-to-bottom sequence was (besides minor zones): all-*trans-retro*-bisdehydrocarotene and *cis* forms (54.5 mg., photometrically estimated); all-*trans*-3,4,3′,4′-bisdehydro-β-carotene and *cis* forms (4.5 mg.); combined yield, 60%; m.p. 204–207° (III) and 195–197° (II).

Anal. (III). Calcd. for $C_{40}H_{52}$: C, 90.16; H, 9.84. Found: C, 90.54; H, 9.81 (after correction for 0.8% ash).

Mixed chromatogram tests showed identity, respectively, with authentic samples of III and II.

PASADENA, CALIF.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, ILLINOIS INSTITUTE OF TECHNOLOGY]

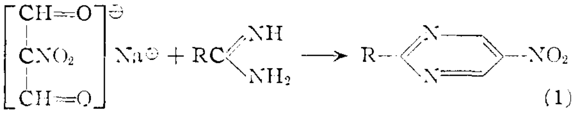
2-Substituted-5-nitropyrimidines by the Condensation of Sodium Nitromalonaldehyde with Amidines[1]

BY PAUL E. FANTA AND EDWARD A. HEDMAN[2]

RECEIVED JUNE 30, 1955

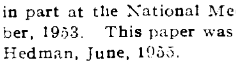
In an aqueous solution of Triton B, sodium nitromalonaldehyde condenses with a wide variety of aryl and aryl-alkyl amidines to form the corresponding 2-substituted-5-nitropyrimidines. With alkyl and hydroxyalkyl amidines, no pyrimidines are formed. The reduction of some 5-nitropyrimidines was studied and the diazotization of 5-amino-2-phenylpyrimidine was attempted.

As part of a program[3] concerned with the investigation of new applications of sodium nitromalonaldehyde (I) to the synthesis of nitro-substituted heterocyclic compounds, we have studied the scope of the reaction of I with amidines. Previously reported reactions of I with compounds containing the guanyl group as illustrated in equation 1 led to the formation of 2-hydroxy-5-nitropyrimidine from urea (R = OH),[4] 2-amino-5-nitropyrimidine in "almost quantitative yield" from guanidine (R = NH_2),[4-6] 5-nitro-2-phenylpyrimidine from benzamidine (R = C_6H_5)[4] and 2-methylthio-5-nitropyrimidine from S-methylthiourea (R = SCH_3).[7]

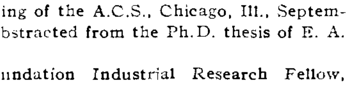


I II III (1)

Compounds containing a guanyl group which were reported not to react with sodium nitromalonaldehyde to form a pyrimidine according to equation 1 are thiourea, which formed 2-imino-5-nitrometathiazine (IV)[4,7] and formamidine,[6] which gave no isolable condensation product.



IV



$$\left[CH_3C_6H_4C{\left\langle{NH_2 \atop NH_2}\right.}\right]^{\oplus}\left[{CH{=}O \atop {CNO_2 \atop CH{=}O}}\right]^{\ominus}$$

V

Although it has previously been inferred[4,8] that the precipitate obtained immediately on mixing aqueous solutions of benzamidine hydrochloride and sodium nitromalonaldehyde is a nitropyrimidine, isolation of the product demonstrated that it is a simple salt, which is unstable at room temperature and decomposes on standing to form a black resin. The crystalline precipitate obtained immediately on mixing aqueous solutions of *p*-toluamidine hydrochloride and sodium nitromalonaldehyde is a more stable salt which gives an elemental analysis corresponding to formula V. Heating aqueous solutions of either of these salts with a small amount of Triton B results in the formation of the expected pyrimidines.

The effect of various reaction media on the condensation of sodium nitromalonaldehyde with benzamidine was studied in order to establish a procedure resulting in an optimum yield of the pyrimidine. In aqueous solution, heating at 70° with Triton B for four hours was significantly superior to the other conditions tried, and was adopted as the standard conditions for a study of the condensation of other amidines. Of the various non-aqueous media studied, acetic anhydride-pyridine at 90° gave an exceptionally high yield of clean product in a short reaction time.

In order to determine the effect of variations in group R on the formation of pyrimidines according to equation 1, a variety of amidine hydrochlorides in aqueous solution were treated with sodium nitromalonaldehyde in the presence of Triton B. Triton B is a 40% aqueous solution of benzyl trimethylammonium hydroxide technical grade. The results of this study are summarized in Table I.

From these data it is evident that reaction conditions successful for the condensation of various aryl and aryl-alkyl amidines with sodium nitromalonaldehyde cannot be extended to alkyl and hydroxyalkyl amidines. A wide variety of media and temperatures were tried for the condensation of acetamidine hydrochloride and sodium nitromalonaldehyde, and a very poor yield of 2-methyl-5-nitropyrimidine was obtained when the reaction was run with sodium hydroxide in ethanol at 25° or with piperidine in the absence of solvent at 90°. Under other conditions either an intractable tar was formed or unreacted sodium nitromalonaldehyde was recovered

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[2] Armour Research Foundation Industrial Research Fellow, 1952–1955.

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