N-2′-Hydroxyethyl-1,7-dihydroxy-2-aminoheptane (XIX).—Ethyl 2-oximinopimelate (XVII) was prepared according to Dieckmann[12] from 2-carbethoxycyclohexanone (XVI). The oximinoester (25 g.) was reduced to 1,7-dihydroxy-2-aminoheptane (XVIII) by the procedure described for the preparation of XIII. The diolamine XVIII was distilled[10] at 150–155° (0.1 mm.); yield 9 g. (60%). It was then treated with ethylene oxide according to procedure B for the preparation of XV. The triolamine XIX thus formed was distilled[10] at 195–210° (0.1 mm.); yield 4.5 g. (36%).

Anal. Calcd. for $C_9H_{21}NO_3$: C, 56.60; H, 10.98; N, 7.33. Found: C, 57.02; H, 11.04; N, 7.61.

6-Chloro-1-(chloromethyl)-*n*-hexyl-2-chloroethylamine Hydrochloride (VI).—The triolamine XIX, 5 g., suspended in 60 ml. of chloroform and stirred vigorously, was treated with 10 ml. of thionyl chloride followed by three drops of pyridine. The mixture was stirred for 3 hours during which period a clear solution resulted, then allowed to stand at room temperature for 2 days. Solvent and thionyl chloride were distilled under reduced pressure, benzene was added and distilled to remove traces of thionyl chloride. The residue was treated with 10 ml. of ethyl acetate and left overnight in an open flask where it solidified. The product was triturated and washed with cold ethyl acetate, then recrystallized from the same solvent; m.p. 85–87°, yield 3.5 g. (47%).

Anal. Calcd. for $C_9H_{19}NCl_4$: C, 38.20; H, 6.72; N, 4.95; Cl, 50.13. Found: C, 38.14; H, 6.91; N, 4.87; Cl, 49.76.

N-(2-Chloroethyl)-N-(1-chloromethyl-6-chlorohexyl)-phosphoramidic Dichloride (X).—A mixture of the trichloroamine VI (1.0 g.) and freshly distilled phosphorus oxychloride (5 ml., b.p. 105–107°) was heated under reflux for 24 hours. The phosphorus oxychloride was eliminated by distillation and the residue distilled.[10] The fraction, b.p. 180–190° (0.1 mm.), was collected, yield 0.2 g.

Anal. Calcd. for $C_9H_{17}NOCl_5P$: C, 29.71; H, 4.68; N, 3.86; Cl, 48.83. Found: C, 30.07; H, 4.77; N, 4.19; Cl, 48.14.

5-Keto-6-acetoxycaproic Acid Ethyl Ester (XXII).—Monoethylglutarate chloride (XX) was prepared from monoethyl glutarate[13] and thionyl chloride by refluxing for 3–4 hours, the thionyl chloride in excess was then distilled and the acid chloride distilled under reduced pressure, b.p. 125° (35 mm.). From 14 g. of the monoester, 15 g. of the acid chloride was obtained.

A solution of 15 g. of the acid chloride XX in 50 ml. of ether was added, with cooling and stirring, to 450 ml. of a cooled and dried ethereal solution of diazomethane, prepared from 45 g. of nitrosomethylurea.[14] Evolution of nitrogen gas was observed. The solution was stirred in the cold for one-half hour and at room temperature for another two hours. The ether and excess of diazomethane were then eliminated under reduced pressure and the residual diazoketone XXI[15] transferred to a 100-ml. flask, to which was added 35 ml. of glacial acetic acid. The mixture was first stirred at room temperature until the evolution of nitrogen ceased and then heated gradually from 40 to 90°, until evolution of gas was complete. Potassium acetate, 3 g., was added and the whole was heated under reflux in an oil bath at 150–160° for one hour. The mixture was then cooled, poured into water (250 ml.) and extracted with benzene. The benzene layer was washed with water, sodium carbonate solution, and again with water, and finally dried over sodium sulfate. After the benzene was distilled, the ketone was distilled in a high vacuum, b.p. 129–135° (0.1 mm.); 148–151° at 9 mm. The yield was 12.5 g. (69%).

Anal. Calcd. for $C_{10}H_{16}O_5$: C, 55.55; H, 7.41. Found: C, 55.77; H, 7.46.

(12) W. Dieckmann, *Ber.*, **33**, 593 (1900).

(13) Markownikow, *J. Russ. Phys. Chem. Soc.*, **9**, 283; "Beilstein," Vol. II, H 633 (fourth edition, 1920).

(14) Ref. 6, p. 401.

(15) See "Organic Reactions," ed. R. Adams, Vol. I, 1942, p. 43.

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[CONTRIBUTION FROM THE BIOLOGICAL LABORATORIES OF HARVARD UNIVERSITY]

Geometrical Isomerization of Vitamin A, Retinene and Retinene Oxime

BY RUTH HUBBARD[1]

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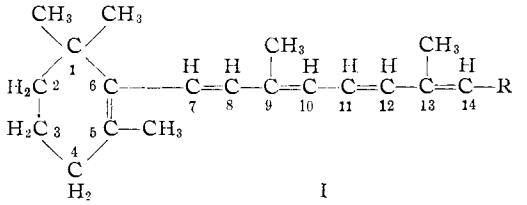
Stereoisomerization experiments have been performed with geometrical isomers of vitamin A, retinene and retinene oxime. These permit comparisons of the isomerization of mono-*cis* and di-*cis* forms, of unhindered and hindered *cis* linkages, and of the effects of terminal $-CH_2OH$, $-\overset{|}{C}=O$ and $-\overset{|}{C}=NOH$ groups.

Introduction

Vitamin A, retinene and retinene oxime possess the same carbon skeleton (I) containing five conjugated double bonds, to which vitamin A (R = $-CH_2OH$) adds an alcohol group, retinene (R = $-C=O$) a conjugated carbonyl group, and retinene oxime (R = $-C=NOH$) a conjugated C=N double bond. The terminal C=O and C=N linkages exert different effects on the conjugated system. The carbonyl group receives a large resonance contribution from the dipole, $\overset{+}{C}-\overset{-}{O}$, thereby enhancing the resonance of the entire conjugated system. The C=N linkage, on the other hand, is hardly more polar than a C=C double bond, so that the conjugated system of retinene oxime is comparable to that of a vitamin A analog containing one additional double bond. This family of compounds therefore presents the opportunity to study the effects of the intramolecular environment on the ease of isomerization of the various double bonds.



I

Six geometrical isomers of vitamin A and retinene have been identified.[2–5a,b] These are the all-

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(2) R. Hubbard, R. I. Gregerman and G. Wald, *J. Gen. Physiol.*, **36**, 415 (1952–53).

(3) C. D. Robeson, J. D. Cawley, L. Weisler, M. H. Stern, C. C. Eddinger and A. J. Chechak, THIS JOURNAL, **77**, 4111 (1955).

trans isomer; two unhindered mono-*cis* isomers: neo-a (13-*cis*) and iso-a (9-*cis*); two hindered *cis* isomers: neo-b (11-*cis*) and neo-c (11,13-di-*cis*); and the unhindered di-*cis* isomer, iso-b (9,13-di-*cis*). In a previous communication[5a] we had assigned the 7-*cis* configuration to the neo-b isomer. The argument was based in part on the synthesis of an 11-*cis*-vitamin A (neo-c), believed to be mono-*cis*. Reëxamination showed that one component of the synthesis, commonly believed to be *trans*, was in fact *cis* and introduced a second *cis* linkage in the 13-position, so that neo-c is the 11,13-di-*cis* isomer. The 11-mono-*cis* isomer has since been synthesized and is indistinguishable in its properties from neo-b.[5b]

The oximes of neo-a (13-*cis*), iso-a (9-*cis*) and neo-b (11-*cis*) retinene have now been prepared. All-*trans* retinene oxime has been previously described.[6]

Carotenoids and other polyenes dissolved in hexane are isomerized by irradiation with light in the presence of catalytic amounts of iodine.[7] Zechmeister and his group[8] have studied this process with a number of polyenes containing hindered and unhindered *cis* linkages. In the isomeric sets which they investigated, the rate of isomerization from *cis* to *trans* of each double bond appears to be essentially independent of the stereochemical configuration of the rest of the molecule.

We have examined the iodine-catalyzed isomerization of a number of isomers of vitamin A, retinene and retinene oxime, in light and darkness. Our observations are concerned mainly with three aspects of this process: (1) the effect of the R-group (CH_2OH, C=O, or C=NOH) on the isomerization of the various double bonds; (2) a comparison of unhindered and hindered *cis* linkages; and (3) the isomerization behavior of mono *cis* and di-*cis* isomers.

Materials and Methods

Stereoisomers of Retinene.—All the isomers were crystalline. The all-*trans* isomer was prepared by oxidation of crystalline all-*trans*-vitamin A on manganese dioxide.[9] Its properties have been described.[4,6] Neo-a (13-*cis*) and neo-b (11-*cis*) retinene were prepared by Mr. P. K. Brown in this Laboratory by fractional crystallization from the mixture of isomers produced by irradiating a solution of the all-*trans* isomer in ethanol.[10] Iso-a (9-*cis*) and iso-b (9,13-di-*cis*) retinene were prepared by Robeson, *et al.*,[4] and were gifts from Dr. J. G. Baxter of Distillation Products Industries; the iso-a isomer was recrystallized from petroleum ether by Mr. Brown. The isomers were dissolved in hexane and shielded from white light throughout, as retinene is isomerized by simple exposure to light.[11]

Stereoisomers of Vitamin A.—Crystalline all-*trans*-vitamin A was a gift from Dr. N. Embree of Distillation Products Industries. The other isomers were prepared by reduction of the corresponding crystalline isomers of retinene with potassium borohydride. Retinene was dissolved in ethanol and treated with powdered KBH_4 for about 15 minutes. The reduction was followed spectrophotometrically. The method is described in detail elsewhere.[10] The solutions were shielded from white light until all retinene had disappeared. The solvent was evaporated under reduced pressure, and the vitamin A taken up in petroleum ether. The solution was washed twice with distilled water, and the solvent again removed under reduced pressure. The vitamin A was then taken up in hexane; it was prepared fresh for each experiment. The isomers so prepared agree in their spectrophotometric properties with the crystalline isomers described by Robeson, *et al.*[3]

Stereoisomers of Retinene Oxime.—The isomers of retinene oxime were prepared by treating the crystalline isomers of retinene in ethanol with excess hydroxylamine. Hydroxylamine hydrochloride was dissolved in distilled water and neutralized to *p*H 6.3 with concentrated sodium hydroxide. For crystallization, 50 mg. of retinene in 10 ml. of ethanol was treated with 2 ml. of *M* hydroxylamine. For the non-crystalline preparations, 10–100 μg. of retinene in about 3 ml. of ethanol was treated with 0.1–0.8 ml. of *M* hydroxylamine. Oxime formation was followed spectrophotometrically. The solutions were shielded from white light until all retinene had disappeared. They were then diluted with distilled water to about 50% ethanol, and extracted twice with petroleum ether. The petroleum ether layers were pooled, washed with distilled water, and the solvent evaporated off under reduced pressure. The oximes were then taken up in the appropriate solvent.

The all-*trans* isomer was crystallized from petroleum ether, and recrystallized three times from methanol. Its spectrophotometric properties agree with those previously described[6]; it melted at 141–143°, about 12° lower than the m.p. reported by Wald and Brown,[6] and close to the m.p. observed by Pitt, *et al.* (139–142°).[12] This may be due to differences in crystal structure; dimorphic crystals with two different melting points have been described also for all-*trans*-retinene.[4]

The neo-a isomer was prepared from neo-a-retinene and recrystallized five times from petroleum ether. It crystallized in microscopic yellow spheres which grew into large colonies on the walls of the vessel (m.p. 100–103°). Its spectrophotometric properties in hexane are shown in Fig. 7. In ethanol, the absorption maximum lies at 356 mμ, with an extinction coefficient ($E^{1\%}_{1cm.}$) of 1835.

The neo-b and iso-a isomers were prepared from the corresponding isomers of retinene, but not in sufficient quantities to permit crystallization. Their absorption properties in hexane are shown in Fig. 7. In ethanol, their absorption maxima lie at 356 and 354 mμ, respectively; their extinction coefficients ($E^{1\%}_{1cm.}$) are 1240 and 1880. These were determined by measuring the extinctions at λ_{max} of solutions of the neo-b and iso-a isomers of retinene in ethanol before and after oximation. The ratio of extinctions (oxime/retinene) was 1.50 for neo-b and 1.48 for iso-a. When this procedure was applied to the all-*trans* and neo-a isomers, it gave ratios of 1.41 and 1.47, yielding extinction coefficients ($E^{1\%}_{1cm.}$) at λ_{max} of 2130 and 1840 for all-*trans* and neo-a-oxime, respectively (*viz.*, $E^{1\%}_{1cm.}$ of 2020 and 1835 for crystalline all-*trans* and neo-a oxime in ethanol). This method is therefore accurate to within about 5%, and does not appear to involve appreciable isomerization.

Iodine-catalyzed Isomerizations.—All data were recorded with the Cary spectrophotometer. Solutions of the isomers in hexane (containing 5–10 μg. of polyene per ml.) were pipetted into stoppered quartz cells 1 cm. in depth. Since some of the compounds are isomerized by iodine in the dark, the spectrum was always measured before addition of iodine. One drop of iodine (1–2 μg.) in hexane was then added, and the mixture irradiated with a 160-watt microscope lamp shielded by a water cell (1.5 inch deep), an opal glass diffusing screen, a heat filter (Corning No. 3965), and a neutral filter of optical density 2.5 or 3.0. The light incident on the samples had a brightness of about 7 or 1.5 foot-candles, depending on the neutral filter used. The

(4) C. D. Robeson, W. P. Blum, J. M. Dieterle, J. D. Cawley and J. G. Baxter, THIS JOURNAL, **77**, 4120 (1955).

(5) (a) G. Wald, P. K. Brown, R. Hubbard and W. Oroshnik, *Proc. Nat. Acad. Sci.*, **41**, 438 (1955); (b) W. Oroshnik, THIS JOURNAL, **78**, 2651 (1956); G. Wald, P. K. Brown, R. Hubbard and W. Oroshnik, *Proc. Nat. Acad. Sci.*, in press.

(6) G. Wald and P. K. Brown, *J. Gen. Physiol.*, **37**, 189 (1953–54).

(7) L. Zechmeister, *Chem. Revs.*, **34**, 267 (1944); *Experientia*, **10**, 1 (1954).

(8) J. H. Pinckard, B. Wille and L. Zechmeister, THIS JOURNAL, **70**, 1938 (1948); L. Zechmeister and J. H. Pinckard, *ibid.*, **76**, 4144 (1954); K. Lunde and L. Zechmeister, *ibid.*, **76**, 2308 (1954); E. F. Magoon and L. Zechmeister, *ibid.*, **77**, 5642 (1955).

(9) G. Wald, *J. Gen. Physiol.*, **31**, 489 (1947–48).

(10) P. K. Brown and G. Wald, *J. Biol. Chem.*, in press.

(11) R. Hubbard and G. Wald, *J. Gen. Physiol*, **36**, 269 (1952–53); R. Hubbard, *ibid.*, **39**, 935 (1955–56).

(12) G. A. J. Pitt, F. D. Collins, R. A. Morton and P. Stock, *Biochem. J.*, **59**, 122 (1955).

temperature did not change appreciably during irradiation. The irradiation was interrupted periodically and the spectrum recorded (*cf.* Fig. 6). The light emitted by the spectrophotometer was too dim to cause isomerization.

Results

The Isomerization of Vitamin A.—We have examined the iodine-catalyzed light isomerization of four stereoisomers of vitamin A. Their absorption spectra in hexane are shown in Fig. 1. The course of the isomerizations is shown in Fig. 2; and the relative rates of isomerization summarized in Table I. Iodine also catalyzes the isomerization of neo-b (11-*cis*) vitamin A in the dark, though more slowly than in the light.

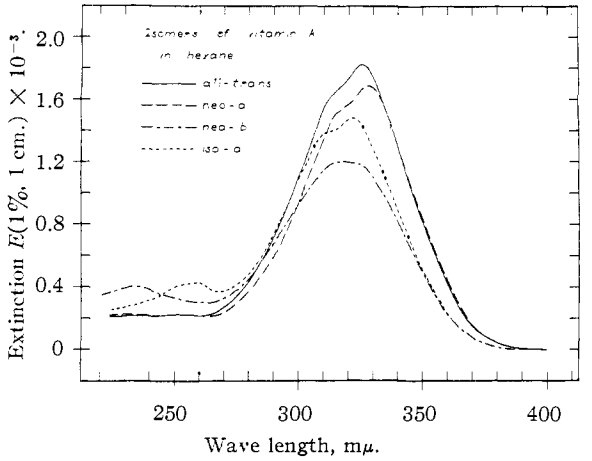


Fig. 1.—Absorption spectra of stereoisomers of vitamin A in hexane. The main absorption bands of the unhindered isomers show fine structure; the main band of neo-b is symmetrical but has a flattened peak. Iso-a has a *cis* peak (259 mμ); the extinction of neo-b is raised in the *cis* peak region, and it has a subsidiary band at 233 mμ.

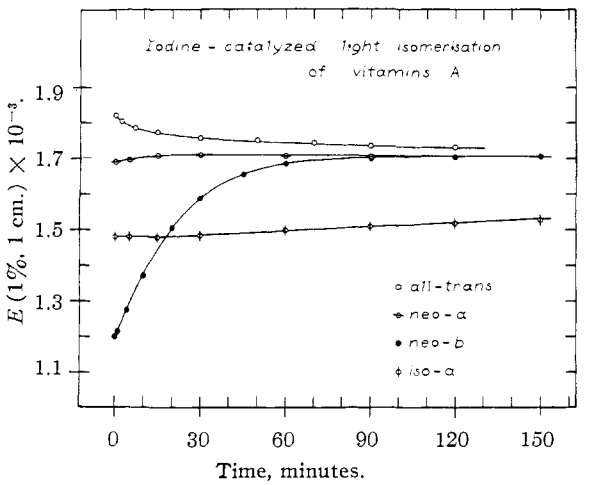


Fig. 2.—Iodine-catalyzed light isomerization of four stereoisomers of vitamin A. Vitamin A, 5 μg. per ml.; iodine, 0.5 μg. per ml. Irradiation with white light of brightness of about 7 foot-candles.

The Isomerization of Retinene.—We have studied the isomerization of five retinene isomers. Their absorption spectra in hexane are shown in Fig. 3. The course of isomerization is illustrated in Figs. 4 and 5. The rates are summarized in

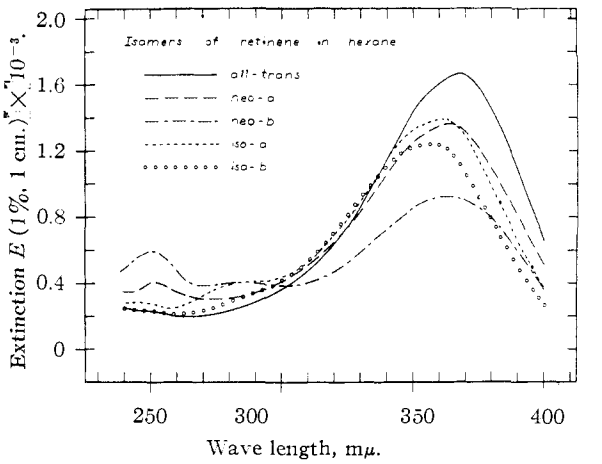


Fig. 3.—Absorption spectra of five stereoisomers of retinene in hexane. Iso-a displays a *cis* peak (282.5 mμ); neo-b, a *cis* peak and a large subsidiary band (251 mμ); neo-a, raised absorption in the *cis* peak region and a small subsidiary band (252 mμ).

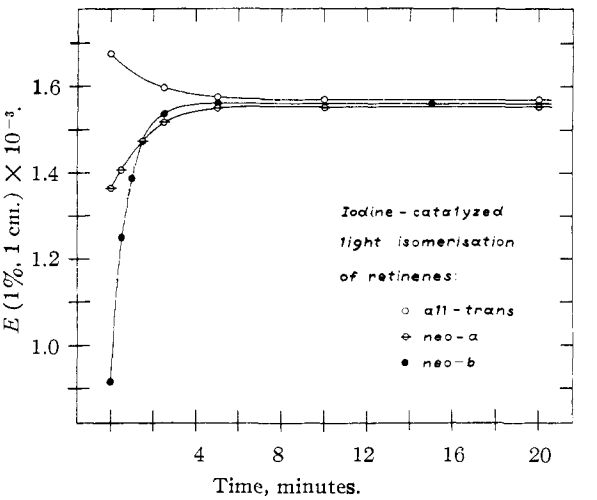


Fig. 4.—Iodine-catalyzed light isomerization of all-*trans*-, neo-a-, and neo-b-retinene. Retinene, 8 μg. per ml.; iodine, 1 μg. per ml. Irradiation with white light of brightness of about 7 foot-candles.

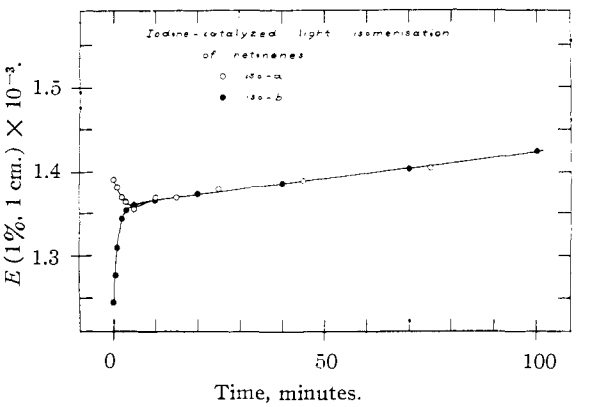


Fig. 5.—Iodine-catalyzed light isomerization of iso-a- and iso-b-retinene. Conditions same as in Fig. 4.

Table I. The isomerizations of both neo-b (11-*cis*) and neo-a (13-*cis*) follow a smooth course (Fig.

4). This is apparent also in Fig. 6 which shows spectrophometric tracings of the isomerization of neo-b-retinene. The reaction is characterized by a single isosbestic point (302 mμ), implying that neo-b is converted to the isomerate without the accumulation of intermediates.

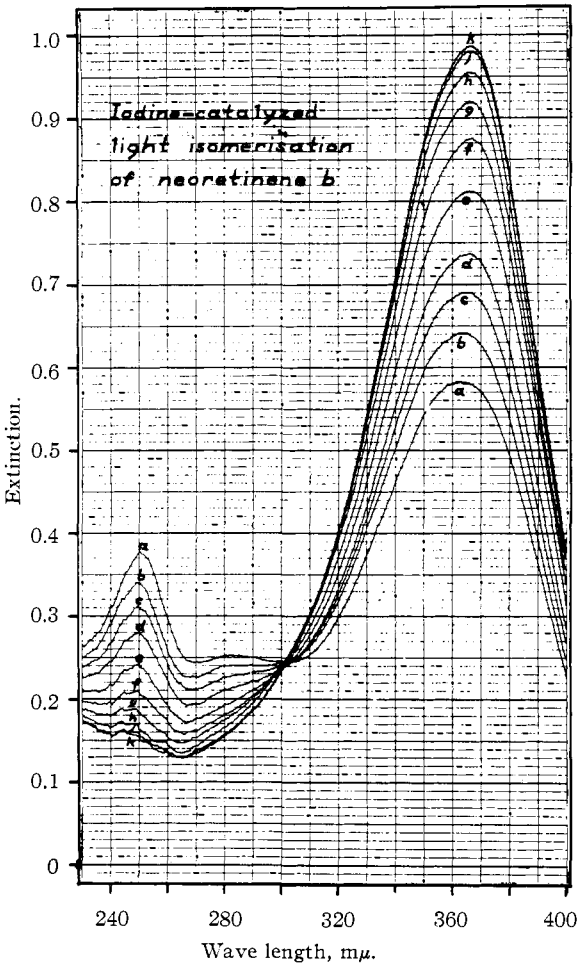


Fig. 6.—Iodine-catalyzed light isomerization of neo-b-retinene. Retinene, 6 μg. per ml.; iodine, 0.4 μg. per ml. Irradiation with white light of brightness of about 1.5 foot-candles. The irradiation was interrupted periodically, and the spectra recorded: a, at once; b, after 0.5 min.; c, 1 min.; d, 1.5 min.; e, 2.5 min.; f, 3.5 min.; g, 4.5 min.; h, 6 min.; j, 10 min.; k, 15 min. The extinction of the main band rises, and the extinctions of the *cis* peak (282.5 mμ) and the subsidiary band (251 mμ) fall. There is an isosbestic point at 302 mμ.

The course of isomerization of iso-a (9-*cis*) and iso-b (9,13-di-*cis*) retinene is complex (Fig. 5). Both curves show discontinuities. The extinction of iso-a falls and that of iso-b rises rapidly for about 5 minutes, when both have the same extinction. From then on they isomerize together. The first segment of the isomerization curves represents the equilibration of the 13-double bond (as in all-*trans* and neo-a (13-*cis*) retinene). The half-completion times are approximately the same as for the equilibration of the all-*trans* and neo-a isomers. The second slow phase represents the isomerization of the 9-*cis* configuration. We have followed it for 300 minutes; it was half-complete after 175 minutes.

To compare the rates of isomerization of neo-b (11-*cis*) retinene and vitamin A, the two were isomerized under identical conditions (5 μg. of neo-*b* and 0.5 μg. of iodine per ml.; light intensity of about 7 foot-candles). The isomerization of neo-b-retinene was half-complete in 4 minutes, that of neo-b vitamin A in 16 minutes. Iodine in the dark isomerizes neo-b (11-*cis*) and neo-a (13-*cis*) retinene, but not iso-a (9-*cis*). With retinene and iodine in the proportion of 10:1, the half-completion times for isomerization in the dark are 18 minutes for neo-b and about 100 minutes for neo-a.

TABLE I

RATES OF THE IODINE-CATALYZED LIGHT ISOMERIZATION OF VITAMIN A, RETINENE AND RETINENE OXIME

Proportions of polyene and iodine: vitamin A, 5 μg. per ml.; iodine, 0.5 μg. per ml.; retinene or retinene oxime, 8–9 μg. per ml., iodine, 1 μg. per ml. All samples irradiated with white light (about 7 foot-candles).

	Half-completion time[a] (min.)		
Isomer	Vitamin A	Retinene	Retinene oxime
all-*trans*	8[b]	1.7	6.5
neo-*a*	8[b]	1.3	6.5
neo-*b*	16	0.5	1.0
iso-*a*	400	1.5; 175[c]	Very slow
iso-*b*		1.0; 175[c]	

[a] The half-completion time constitutes a rough measure of rate, since the rates of isomerization are approximately constant until well past this point. [b] Since the extinction changes very little during this isomerization, the half-completion time is less accurate than those for the other compounds. [c] Half-times for the fast and slow phases of isomerization.

The Isomerization of Retinene Oxime.—The absorption spectra of four stereoisomers of retinene oxime in hexane are shown in Fig. 7; the course of

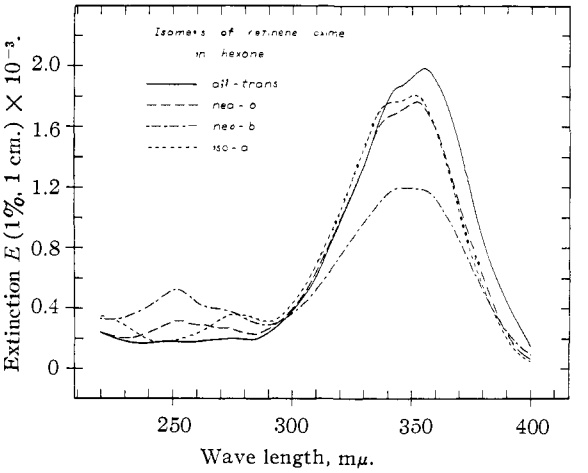


Fig. 7.—Absorption spectra of four stereoisomers of retinene oxime in hexane. The main bands of the unhindered isomers show fine structure; that of neo-b is roughly symmetrical with a flattened peak. Iso-a has a *cis* peak (277 mμ); neo-b a *cis* peak and a subsidiary band (252 mμ). Neo-a has a small *cis* peak and subsidiary band (252.5 mμ).

isomerization in Fig. 8. The half-times for isomerization are summarized in Table I. Iso-a

(9-*cis*) is not included in Fig. 7, as it isomerizes so slowly that destruction prevents an accurate rate measurement.

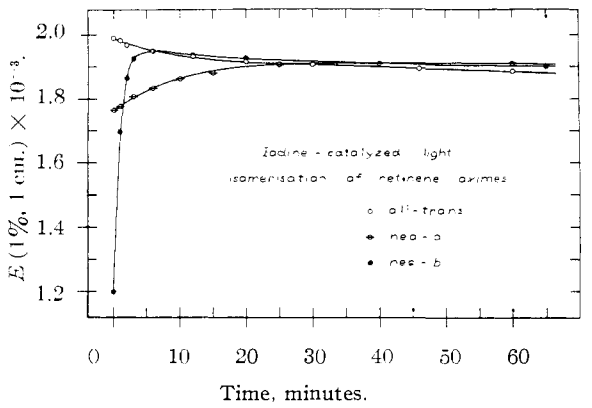


Fig. 8.—Iodine-catalyzed light isomerization of three stereoisomers of retinene oxime. Retinene oxime, 9 μg. per ml.; iodine, 1 μg. per ml. Irradiation with white light of about 7 foot-candles.

The course of isomerization of neo-b (11-*cis*) oxime is complex. The extinction at λ_{max} overshoots the value for the isomerate ($E^{1\%}_{1\,cm}$ 1900), and after 6 minutes joins the all-*trans* curve. Thereafter it isomerizes together with the all-*trans* isomer. In other words, the all-*trans* isomer accumulates as an intermediate since its rate of formation from neo-b oxime considerably exceeds its own rate of isomerization. With neo-b retinene or vitamin A, the rate of isomerization of the all-*trans* isomer keeps pace with its formation, so that the over-all course of the isomerization is smooth.

Iodine in the dark isomerizes only the neo-b (11-*cis*) oxime (Fig. 9). In contrast with neo-a

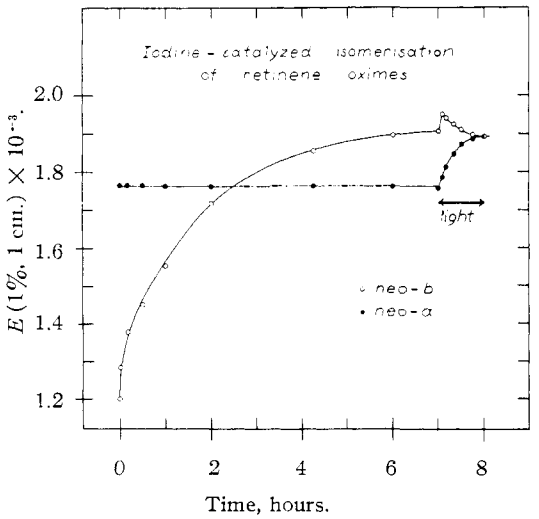


Fig. 9.—Iodine-catalyzed dark isomerization of neo-a- and neo-b-retinene oximes. Retinene oxime, 5 μg. per ml.; iodine, 0.5 μg. per ml. In the dark (20°), neo-b isomerizes, but neo-a does not. After 7 hours, both samples were irradiated with white light (7 foot-candles). Neo-a now is isomerized, and the isomerization of neo-b completed.

(13-*cis*) retinene, neo-a oxime is not isomerized. The latter is stable as long as it is protected from light. In the present experiment, after 7 hours in the dark, both oximes were irradiated with light. The neo-a (13-*cis*) oxime immediately began to isomerize, following the same course shown in Fig. 8. The extinction of neo-b (11-*cis*) oxime, which had almost completely isomerized *in the dark*, rose slightly and then fell to the extinction of the pseudo-equilibrium mixture. Under identical conditions in the dark, the half-times for isomerization were 75 minutes for neo-b oxime, and 18 minutes for neo-b-retinene.

Discussion

Absorption Spectra.—(1) The neo-a (13-*cis*) isomer is in a special position. In neo-a vitamin A, the *cis* linkage is at the end of the conjugated system. In general, the spectroscopic properties of isomers containing an unhindered terminal *cis* configuration are similar to those of the all-*trans* compound, since the over-all length of the chromophore is the same in both.[13] Usually, the specific extinction of the *cis* compound is slightly lower and its absorption maximum (λ_{max}) lies at somewhat longer wave lengths than those of the all-*trans* isomer. Neo-a-vitamin A follows this rule: its main band is at the longest wave length of all the vitamin A isomers, and it possesses no *cis* peak. Neo-a-retinene and retinene oxime, in which the *cis* linkage is internal to the C=O or C=N double bonds, show the normal relationships for an unhindered mono-*cis* isomer: the main absorption band is displaced about 5 mμ toward shorter wave lengths from that of the all-*trans* isomer, and the extinction is raised in the region of the *cis* peak.[14]

(2) The main bands of the unhindered isomers of vitamin A and retinene oxime show some fine structure. This is most pronounced in iso-a (9-*cis*). It is lacking in neo-b (11-*cis*), one aspect of the degradation of the absorption spectrum associated with a hindered *cis* linkage.

(3) The neo-b (11-*cis*) and iso-a (9-*cis*) isomers of retinene and retinene oxime have the same extinction at the *cis* peak, indicating a comparable degree of bending.

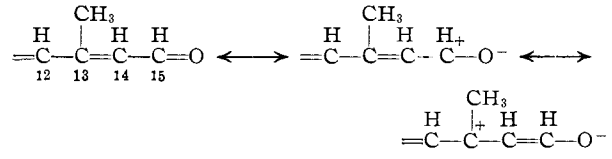
(4) The subsidiary bands in the ultraviolet, exhibited by the neo-b (11-*cis*) isomer of vitamin A, retinene and retinene oxime, and by the neo-a (13-*cis*) isomer of retinene and the oxime, all lie about 30 mμ below the *cis* peak.

Isomerization.—The *cis* configuration of neo-b (11-*cis*) is the most labile, and the *cis* configuration of iso-a (9-*cis*) the stablest in all three compounds.

All the isomers of retinene isomerize faster than the corresponding isomers of vitamin A or retinene oxime. This is particularly true for the neo-a (13-*cis*) isomer, and is probably due to labilization of the double bonds by the carbonyl group through resonance of the type

(13) W. Oroshnik and A. D. Mebane, THIS JOURNAL, **76**, 5719 (1954).

(14) All-*trans* and neo-a (13-*cis*) vitamin A acid do not follow this rule. In vitamin A acid the 13-double bond is internal to the acid C=O group; yet the absorption maximum of the neo-a isomer lies 4 mμ toward longer wave lengths than that of the all-*trans* compounds.[3]



Stability of *cis* Isomers.—Hindered *cis* isomers have a much lower thermodynamic stability (*i.e.*, a higher free energy) than unhindered *cis* forms.[15] Until recently, it has therefore been thought that they are in fact highly unstable. A number of stable hindered *cis* forms have now been isolated.[4,5,8,13,16] The isomerization data presented above bear out the fact that the actual (kinetic) stability of a compound does not necessarily reflect its thermodynamic stability. In terms of free energy content, the neo-a (13-*cis*) isomer of retinene and retinene oxime is probably much closer to iso-a (9-*cis*) than to neo-b (11-*cis*). Yet, kinetically it behaves more like the neo-b isomer.

Course of Isomerization.—The course of isomerization is governed by the fact that the individual double bonds appear to retain their rates of isomerization irrespective of the stereochemical configuration of the rest of the molecule.[8] Mono-*cis* compounds often have smooth isomerization curves.[8] But when in a mono-*cis* compound, the *cis* linkage isomerizes slowly to *trans*, while the *trans* linkages isomerize much faster to *cis*, the extinction first falls and then rises (*cf.* iso-a (9-*cis*) retinene). Conversely, if the isomerization from *cis* to *trans* is much more rapid than the isomerization of the all-*trans* isomer, the extinction first rises and then falls (*cf.* neo-b (11-*cis*) retinene oxime). If a mono-*cis* isomer therefore has a discontinuous isomerization curve, it will display a *reversal* in the change of extinction. A discontinuous isomerization curve in which the change in extinction continues upward, implies that one is dealing with a di-*cis* compound (*cf.* iso-b (9,13-di-*cis*) retinene). A di-*cis* compound could isomerize smoothly, if the rates of isomerization of both double bonds were sufficiently similar. Its isomerization would, however, differ from that of a mono-*cis* compound since the change in extinction in the *cis* peak region would almost surely be discontinuous,[8] as the mono-*cis* intermediate of isomerization would be expected to show increased absorption at the *cis* peak.

Structure of the Neo-b Isomer.—Robeson, *et al.*,[4] have postulated that neo-b is the 11,13-di-*cis* isomer. We have shown that it is a hindered mono-*cis* isomer (11-*cis*).[5] The data presented above conform with this assignment of configuration.

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(15) L. Pauling, *Fortschr. Chem. org. Naturst.*, **3**, 203 (1939); *Helv. Chim. Acta*, **32**, 2241 (1949).

(16) W. Oroshnik, G. Karmas and A. D. Mebane, THIS JOURNAL, **74**, 295, 3807 (1952); **75**, 1050 (1953).

[CONTRIBUTION FROM THE RESEARCH DIVISION OF ARMOUR AND COMPANY]

Polymorphic Behavior of 1,3,5-Tridodecyl- and 1,3,5-Trioctadecylhexahydro-*sym*-triazines

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Two high molecular weight 1,3,5-trialkylhexahydro-*sym*-triazines have been prepared by the reaction of primary amines with formaldehyde in aqueous methanol. The products were characterized by their infrared absorption spectra and by the preparation of their oxalate salts. The solubilities of these representative alkyl-triazines were determined in hexane, benzene, chloroform, ethyl acetate, acetone and 95% ethanol over wide ranges of concentration and temperature. The C_{12} derivative exhibited three polymorphic modifications in its purified state, whereas the C_{18} derivative exhibited corresponding polymorphic behavior only in the presence of certain solvents. The highly polar solvents tend to promote precipitation of the higher melting polymorphs; non-polar and slightly polar solvents appear to stabilize the lower melting forms by inhibiting transformation.

The reaction between formaldehyde and various primary amines has been the subject of considerable study.[1] Henry[2] was among the earliest workers to investigate this reaction and much confusion has resulted from misinterpretation of his work. Although he was able to isolate benzylaminomethanol from the reaction of formaldehyde with benzylamine[3] inferences that methylol derivatives of this type or their dehydration products, the Schiff bases, are the usual end-products of the reaction of formaldehyde with primary amines must be discounted in view of later work.

In a series of papers Graymore[4] reported on the reaction of formaldehyde with methyl, ethyl, butyl and other lower primary amines and demonstrated conclusively that the reaction products were trimers of the hypothetical alkylmethyleneimine postulated by Henry.[2] The 1,3,5-trialkylhexahydro-*sym*-triazine structure was assigned to these products upon the basis of early speculations regarding the nature and mode of formation of hexamethylenetetramine from formaldehyde and ammonia.[5] Raman spectra of many of these compounds confirm this widely accepted structure.[6]

The present paper reports the preparation of 1,3,5-tridodecylhexahydro-*sym*-triazine and its trioctadecyl homolog in high yield by treating the appropriate highly purified alkylamines with aqueous formaldehyde in methanol. The solubilities of the

(1) I. Walker, "Formaldehyde," 2nd Ed., Reinhold Publ. Corp., New York, N. Y., 1953, p. 281.

(2) L. Henry, *Bull. acad. roy. Belg.*, **29**, 355 (1895).

(3) L. Henry, *ibid.*, **28**, 359 (1894).

(4) J. Graymore, *J. Chem. Soc.*, **125**, 2283 (1924); 1490 (1931); 1490 (1932); 865 (1935); 1311 (1938); 39 (1941).

(5) P. Duden and M. Scharff, *Ann.*, **288**, 218 (1895).

(6) L. Kahovec, *Z. physik. Chem.*, **B43**, 364 (1939).