# SYNTHESIS OF THE BENZENE ANALOGUE OF VITAMIN A

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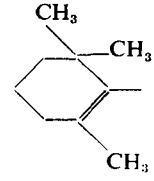
THE successful synthesis of pure crystalline vitamin A by Arens and van Dorp[1] and by Isler *et al.*[2] opened a new field in the chemical study of vitamin A. Thus, it is possible to synthesise various analogues of vitamin A in order to establish the relationship between chemical structure and vitamin A activity. A survey of recent publications on synthetic compounds bearing modified side chains led to the conclusion that although the terminal hydroxyl group might not be of utmost importance, the length and the general skeleton of the side chain could not be altered without a complete loss of activity. (*cf.* Table I.)

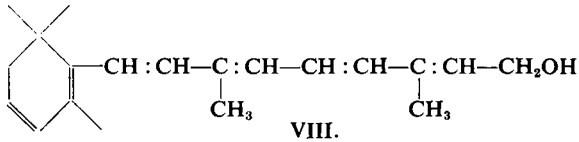
TABLE I.

| Compounds | | Activity (Vitamin A = 1) |
|---|---|---|
| R—CH : CH—C(CH$_3$) : CH—CH : CH—C(CH$_3$) : CH—COOH | I. Ref. 1 | 1 |
| R—CH : CH—C(CH$_3$) : CH—CH : CH—C(CH$_3$) : CH—CH$_3$ | II. Ref. 5 | 1/10 |
| R—CH : CH—C(CH$_3$) : CH—CH : C—C(CH$_3$)$_2$ : CH—CH$_3$ | III. Ref. 5 | 0 |
| R—CH : CH—C(CH$_3$) : CH—CH : CH—C(CH$_3$) : CH—CH$_2$CH$_3$ | IV. Ref. 5 | 0 |
| R—CH : CH—C(CH$_3$) : CH—CH : CH—C(CH$_3$) : CH$_2$ | V. Ref. 5 | 0 |
| R—CH : CH—C(CH$_3$) : CH—CH : CH—CH : CH—CH$_2$OH | VI. Ref. 6 | 1/30 |
| R—CH : CH—C(CH$_3$) : CH—CH : CH—CH : C—CH$_2$OH | VII. Ref. 6 | 0 |

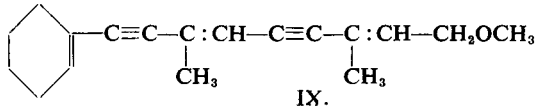
Where R = 

The findings of Morton *et al.*[7] in connection with retinenes gave support to VIII as the correct structure for vitamin $A_2$. Nothing has yet been published on compounds having the full vitamin A side chain attached to a different nucleus. Sobotka and Chanley[8] synthesised a cyclohexenyl analogue with two triple bonds in the side chain (IX); unfortunately, its biological activity was not published. More recently, Heilbron *et al.*[9] reported an acyclohexenyl analogue to vitamin A acid having a single

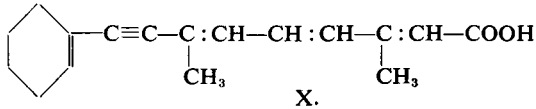
triple bond in the side chain (X) which was stated to have an activity 1/1000 that of Vitamin A. Since the presence of a triple bond next to the ring would have substantially changed the shape of the molecule, then, with the findings of Table I in mind, it may be asked whether this small activity was not due to a reduction *in vivo* into XI?



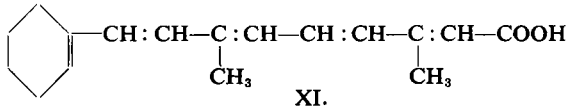
VIII.



IX.

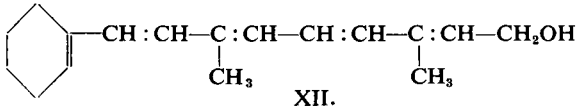


X.

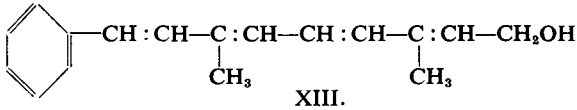


XI.

Attempts have been made in this laboratory to synthesise both the cyclohexenyl and the benzene analogue of vitamin A (XII, XIII). Owing to difficulties in preparing the key intermediate 1-$\Delta^1$-cyclohexenyl-but-1-en-3-one, XII has not yet been obtained. However, the synthesis of the benzene analogue (XIII) has been achieved according to the route used by Isler *et al.*[2]

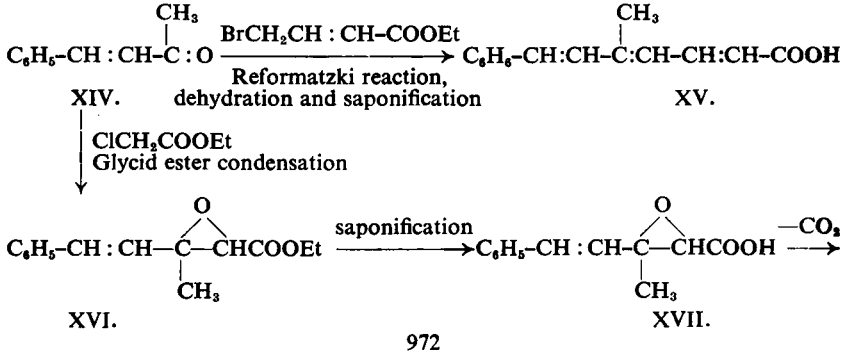


XII.

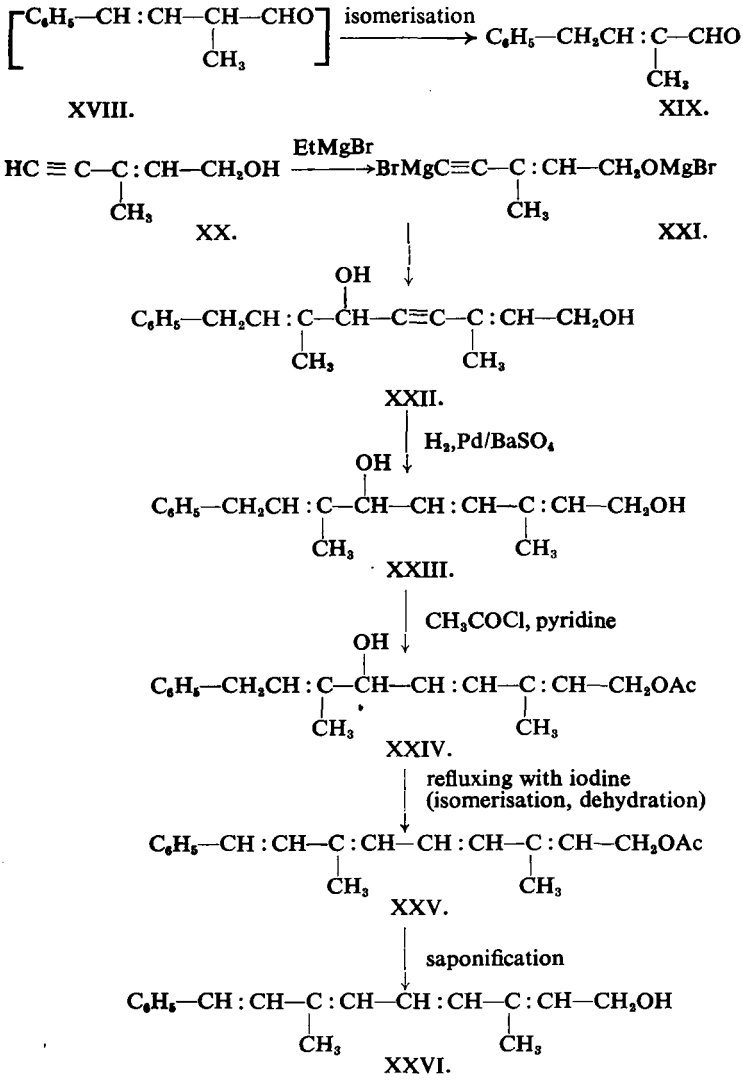


XIII.

This synthesis is summarised as follows, benzalacetone being used as the starting material.




XIV. XV. XVI. XVII.




The Reformatzki reaction between benzalacetone and γ-bromocrotonic ester gave a hydroxy ester which was partially dehydrated upon distillation in high vacuum ($10^{-4}$ mm. Hg pressure). After complete dehydration with anhydrous oxalic acid according to Arens and van Dorp[1], the product showed only a relatively low intensity of absorption in the ultraviolet region (max. 340mμ $E^{1\,per\,cent.}_{1\,cm.}$ 225) (Fig. 1, curve I). Saponification of the ester and recrystallisation of the crude gummy acid obtained from ether or acetone gave a small yield of a lemon yellow coloured crystalline acid. This acid, melting at 190° to 194°C., gave the correct analysis for carbon, hydrogen and active hydrogen required for 5-methyl-7-phenyl-hepta-2:4:6-trienoic acid. Light absorption (Fig.1, curve II),

in ethyl alcohol, showed a maximum at 342μ, log.ε 4·548, with a subsidiary peak at 249mμ. These figures are in close agreement with those expected. However, as the yield of this crystalline acid was small and subsequent work carried out with the crude acid was fruitless, a different approach to the problem was then undertaken.

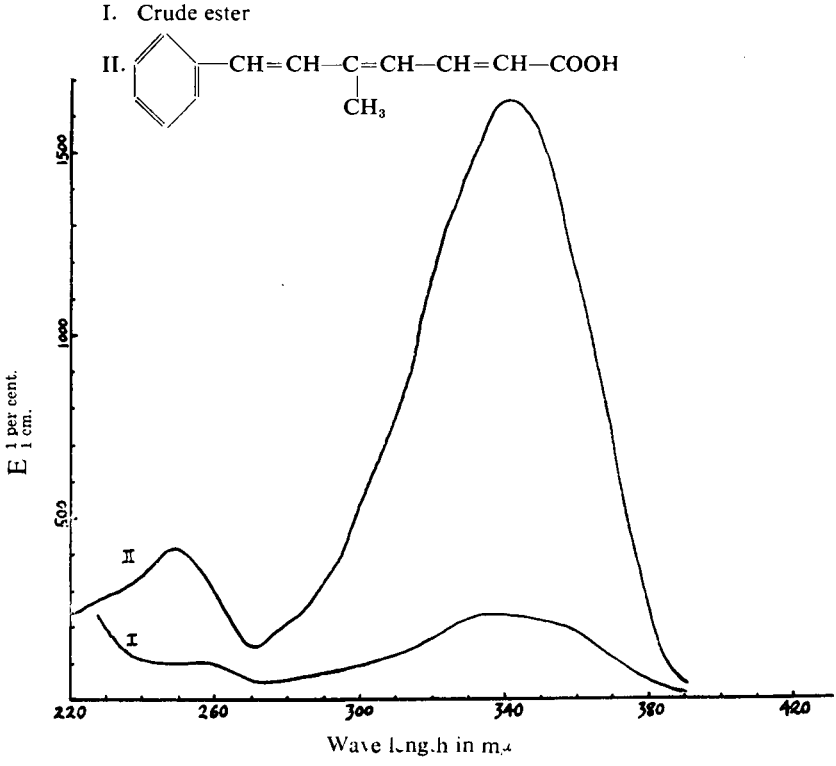


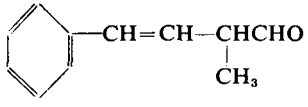

FIG. 1.

The glycid ester condensation was first carried out at −7°C. by Darzen's method[10]. Fractionation of the condensation product gave a 23 per cent. yield of the glycid ester (XVI) as a viscous colourless liquid boiling at 130° to 134°C. at 0·5mm. Hg pressure. Analysis gave figures in close agreement with those required. The glycid ester was found to polymerise easily on heating, redistillation at the same temperature range and under the same pressure giving only 30 per cent. recovery, the rest forming a thick oily residue in the flask, non-distillable without decomposition and solidifying into a glassy mass on cooling.

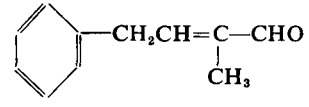
The glycid ester thus obtained was saponified by cold alcoholic potassium hydroxide, formation of some potassium carbonate precipitate indicating a partial decarboxylation during this treatment. On acidification the free glycid acid (XVII) separated as reddish precipitate and was subjected to decarboxylation without further purification. Both Heilbron *et al.*[11] and Milas *et al.*[12] in their preparation of the $C_{14}$ aldehyde, isolated

the crystalline acid and decarboxylated by heating with copper or glass powder. However, with this benzene analogue, decarboxylation was found to be complete in about 15 minutes by simply heating the crude glycid acid over boiling water bath. Purification by fractionation gave about a 15 per cent. yield of the aldehyde based on the ester.

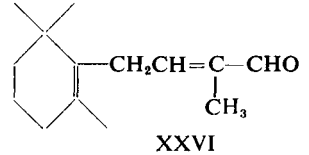
It has been observed previously that the glycid ester (XVI) was very sensitive to heat. Polymerisation during saponification and decarboxylation may be responsible for the low yield of the aldehyde. By adopting Isler's modified method[4], the glycid ester was saponified *in situ* with alcoholic potassium hydroxide at low temperature. After working up in usual manner, a crop of pure aldehyde was obtained in an overall yield of 40 per cent. of the theoretical yield based on benzalacetone. This aldehyde, distilling at 70°C. under 0·05mm. Hg pressure showed the following characteristics: $n_D^{20°C.}$ 1·5537, $d_4^{20°C.}$ 1·0105, exaltation of molecular refraction 1·83 units. It gave analytical figures in close agreement with theory. The 2:4-dinitrophenylhydrazone occurred in red needles from chloroform, melting at 188° to 190°C. gave the correct analysis for nitrogen. The semicarbazone in leaflets from alcohol, had a melting-point 178° to 179°C. The thiosemicarbazone, needles from alcohol, had a melting-point, 132° to 132·5°C. According to classical concepts therefore, this aldehyde would be assigned formua XVIII.




XVIII.




XIX.




XXVI

But on spectroscopic examination (in ethyl alcohol), this aldehyde showed an absorption maximum at 229mμ, log.ε 4·214, indicating a substituted α:β-unsaturated aldehyde structure (XIX as 2-methyl-4-phenyl-crotonaldehyde. A small but definite elevation at 283 to 284 mμ, log.ε 3·375, may correspond to the so-called R band. Its semicarbazone showed an absorption maximum at 266 mμ, log.ε 4·536, thiosemicarbazone at 299 mμ, log.ε 4·409, both typical of the corresponding derivatives of α:β-unsaturated aldehydes in general[13]. This is in agreement with Heilbron's formula for the $C_{14}$ aldehyde (XXVI)[6,11] which was opposed by Milas *et al.*[12]. The light absorption data for these two aldehydes and their derivatives together with those of citral are compared in Table II.

Further, if the aldehyde had the structure XVIII, it should show a maximum for the skeleton $C_6H_5-C=C-$ at around 290 mμ[14]. Sayrene itself shows a maximum at 245 mμ, with two submaxima at 282 mμ and 290·4mμ[15]. The wide differences between these figures and those obtained suggest that the aldehyde in question does not contain the

TABLE II

| | λmax. mμ | log |
|---|---|---|
| 1. 2-Methyl-4-phenyl-crotonaldehyde (XIX) (Fig. 2) ... | 229 | 4·214 |
| 2. $C_{14}$ aldehyde (XXVI)[9] ... ... ... ... ... | 230 | 4·25 |
| 3. Citral (commercial)[9] ... ... ... ... ... | 232 | 4·05 |
| 4. Semicarbazone of 1 (Fig. 2) ... ... ... ... | 266 | 4·536 |
| 5. Semicarbazone of 2[4] ... ... ... ... ... | 265 | 4·47 |
| | 269 | 4·462 |
| 6. Semicarbazone of 3[9] ... ... ... ... ... | 272 | 4·498 |
| 7. Thiosemicarbazone of 1 (Fig. 2)... ... ... ... | 299 | 4·409 |
| 8. Thiosemicarbazone of 2[9] ... ... ... ... | 299 | 4·591 |
| 9. Thiosemicarbazone of 3[9] ... ... ... ... | 303 | 4·66 |

$C_6H_5-C=C-$ system in its structure. This affords a more definite answer pertaining to its structure and lends indirect support to Heilbron's formula for the $C_{14}$ aldehyde.

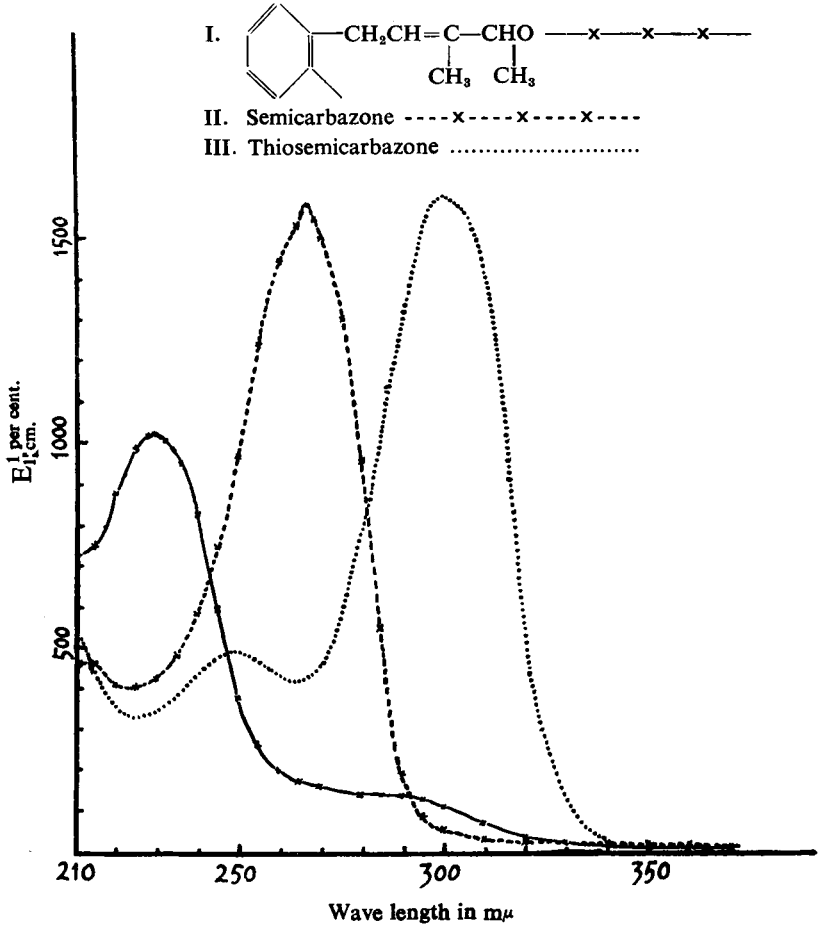



FIG. 2.

3-Methyl-pent-2-en-4-yn-1-ol (XX) was prepared per 3-methylpent-4-en-1-yn-3-ol by condensing methylvinyl ketone with sodium acetylide in liquid ammonia according to the method of Heilbron and Jones[16]. 3-Methylpent-4-en-1-yn-3-ol was found to have a refractive index $n_D^{17.5°C.}$ 1·4438 which is nearer to the figure given by Hennion and Leib[17] ($n^{20°C.}$ 1·4444) than that by Heilbron and Jones ($n_D^{15°C.}$ 1·4490) although the rearranged carbinol 3-methylpent-2-en-4-yn-1-ol had $n_D^{17°C.}$ 1·4850, the same as that given by Heilbron and Jones.

2-Methyl-4-phenylcrotonaldehyde was coupled with the Grignard compound of 3-methylpent-2-en-4-yn-1-ol (XXI) according to Isler *et al.*[4] In view of the fact that the reaction mixture was heterogeneous the mixture was refluxed with constant stirring for 7 hours to ensure complete reaction. After working up in usual way, the unchanged carbinol and aldehyde were removed in high vacuum. The residue so obtained was purified by partition between 75 per cent. aqueous methyl alcohol and light petroleum (40° to 60°C.) during which process the possible hydrocarbon formed was removed in the petroleum layer. The aqueous methyl alcoholic liquor was diluted with water and the oil separated was extracted with ether. Removal of the solvent gave the diol (XXII) as a viscous brownish oil in 78 per cent. yield. It showed the following characteristics: $n_D^{20°C.}$ 1·5756, $d_4^{19°C.}$ 1·0673, exaltation of molecular refraction 2·21 units. It gave analytical figures for carbon, hydrogen and active hydrogen in close agreement with theory. With antimony trichloride in chloroform it gave only a brownish black colouration. Its absorption spectrum showed inflections at 215 mμ and 230mμ which were probably due to the two isolated chromophores, the yn-en system and the benzene ring respectively. (Fig. 3, curve I.)

Semihydrogenation of the triple bond was carried out in the following way. A supported catalyst of palladium on barium sulphate (5 per cent. Pd) was prepared according to Organic Syntheses[18] and was partially inactivated by the use of Rosenmund-Zetzsche sulphur-quinoline poison[19,20]. The diol (XXII) was dissolved in 10 times its volume of methyl alcohol and the hydrogenation was carried out at atmospheric pressure. This hydrogenation process was found to be extremely slow in comparison with a control experiment on 3-methylpent-2-en-4-yn-1-ol, the catalyst used being very soon completely inactivated by impurities present in the diol. Three subsequent additions of fresh partially poisoned catalyst were made and the hydrogenation stopped after nearly 13 hours when the hydrogen uptake was 0·99 mol. per mol. of the diol. The product thus obtained after the removal of catalyst and solvent gave a slightly higher carbon and lower active hydrogen figures than those required for the diol (XXIII), indicating a partial dehydration during the prolonged shaking with the catalyst. This was further confirmed by the fact that with antimony trichloride in chloroform it gave a blue colour changing rapidly into violet then red. The spectroscopic results also showed a significant change. (Fig. 3, curve II.) The maxima at 215 mμ and 240 mμ apparently due to the diol (XXIII) itself, and corresponding to the diene conjugation and the benzene ring respectively,

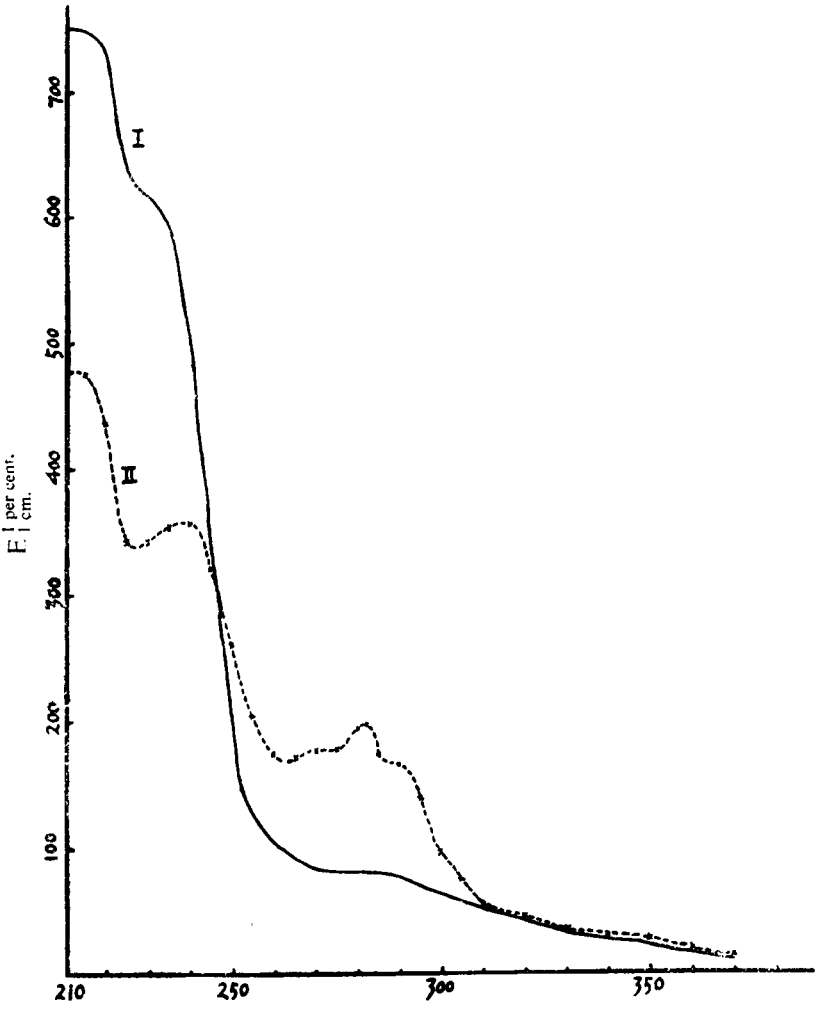
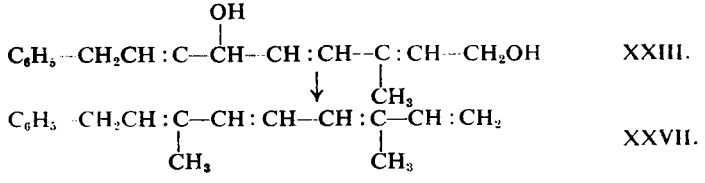



FIG. 3.

were lower than the corresponding inflections in curve I, whilst the newly formed peak at 282 mμ indicated the formation of a compound with 4 conjugated double bonds. This may possibly be explained by the formation of a hydrocarbon (XXVII) from the diol according to the following reaction:




XXIII.

XXVII.

Partial acetylation of the diol (XXIII) was carried out by treating the diol with acetyl chloride in presence of dry pyridine. The crude acetylated product gave unsatisfactory analytical figures. With antimony trichloride in chloroform it gave a transient blue colour changing rapidly into violet and red as before. Spectroscopically, it was very similar to the diol before acetylation (Fig. 4, curve I), the slight proportional increase of intensity at 282 mμ probably indicating further dehydration along the suggested direction. This acetylated product was purified by solution in light petroleum (60° to 80°C.), the insoluble portion being a solid was probably a polymerised product. A light golden yellow coloured liquid was obtained from the petroleum fraction corresponding to 66 per cent. of the crude material, the analytical figures being in fair agreement with those required for the monoacetate of the diol (XXIV). This purified monoacetate was used for the following dehydration.

The dehydration was carried by the method used by Isler *et al.*[4] in the synthesis of vitamin A. A solution of the acetate in light petroleum (100° to 120°C.) after being stabilised with α-tocopherol, was refluxed with iodine for 1 hour under nitrogen. The product obtained was examined spectroscopically. (Fig. 4, curve II.) A new absorption peak produced at 325 mμ, with $E^{1\ per\ cent.}_{1\ cm.}$ 245, indicated the formation of 3:7-dimethyl-9-phenylnona-2:4:6:8-tetrane-1-ol acetate (XXV). However, active hydrogen determination gave a figure corresponding to the presence of about 36 per cent. of XXIV, which is thought to be responsible for part of the spectrum.

A number of ways are known to achieve this dehydration. In the synthesis of vitamin A ether, Milas *et al.*[17] described the use of *p*-toluenesulphonic acid, pyridine hydrobromide in presence of pyridine, alcoholic potassium hydroxide, phosphorus tribromide or thionyl chloride in conjunction with pyridine, or sodamide in liquid ammonia. The iodine method has the advantage that it catalyses *cis-trans* isomerisation[22,23], although it has been reported in the literature[24,25,26,27] that dehydration usually resulted in a *trans* bonding, semihydrogenation of the triple bond gave in most instances a *cis* double bond[28]. However, the broadness of the absorption band produced by the product suggests that stereoisomers were probably present.

Saponification of the acetate gave a product containing the free carbinol, 3:7-dimethyl-9-phenylnona-2:4:6:8-tetraene-1-ol (XIII). It showed an absorption maximum at 329 mμ with $E^{1\ per\ cent.}_{1\ cm.}$ 254 (Fig. 4, curve III). Spectroscopically, a benzene ring effects approximately the same bathochromic shift to the absorption peak of a polyene compound as does an extra conjugated double bond. This was found to be the case in α : β-unsaturated ketones by Wilds *et al.*[29] Thus, with a ring double bond, methyl substituted, β-ionone has a maximum (at 293 mμ) 4 units towards the longer wave length than benzalacetone (at 289 mμ). 1-Vinylcyclohexene-1 on the other hand, has a maximum (at 230 mμ)[30] 10 units towards the shorter wave length than styrene (at 240 mμ)[31]. Hence, it was expected that the maximal absorption of the carbinol (XIII) should be in the neighbourhood of that of vitamin A.

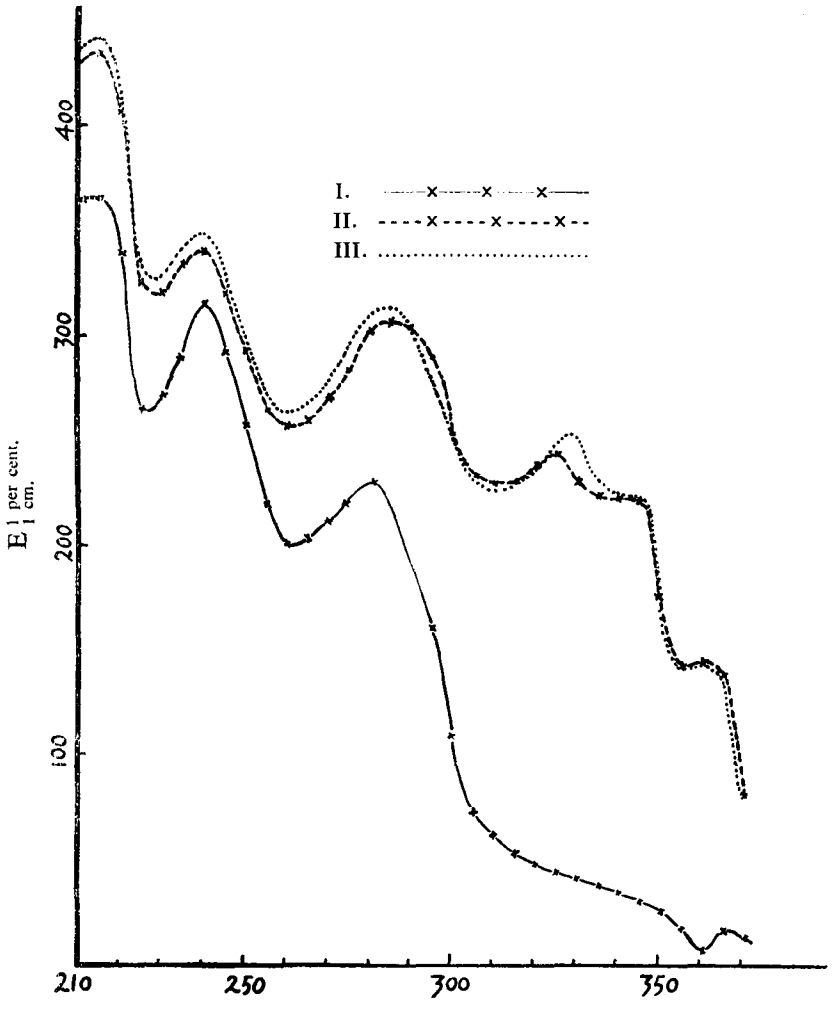



FIG. 4.

It is to be regretted that owing to the great instability of the product obtained, further purification of the sample by chromatographic means was not attainable. The bulk of the sample, stored under nitrogen in the dark, deteriorated during the course of its spectral and biological studies as shown by a loss of the specific absorption properties. The acetate, which was tested biologically, was found to be completely inactive.

Examination of the structure of XIII reveals its differences from vitamin A in two respects: (a) the presence of the benzene ring which brings the whole molecule into coplanarity and hence different from vitamin A slightly in its spatial arrangements. On the other hand, the

presence of a stable benzene nucleus in the molecule may modify its chemical activity. (b) the absence of the three methyl substituent groups from the ring. They may have a certain specific effect. Therefore it can be concluded that the polyene carbinol side chain alone in the vitamin A molecule is not sufficient, though necessary, for producing vitamin A activity. These results stimulate interest in the synethesis of the corresponding cyclohexenyl analogue of the vitamin (XII) in order to determine whether it possesses any biological activity.

## EXPERIMENTAL

All absorption spectroscopic measurements were carried out on solutions in ethyl alcohol. Melting-points are uncorrected.

*Benzalacetone.* Prepared according to Organic Syntheses[32], having m.pt. 42°C.

*Ethyl γ-bromocrotonate.* Prepared according to the method of Ziegler *et al.*[33]. The fraction having b.pt. 91° to 93°C./10mm. Hg. pressure was used.

*Reformatzki condensation of benzalacetone and ethyl γ-bromocrotonate* Benzalacetone (146 g.), ethyl γ-bromocrotonate (193 g.) and benzene (sodium dried, 1000 ml.) were mixed together with zinc wool (washed with acetone and dried, 65·4 g.) and a small crystal of iodine. The whole was heated under a reflux condenser with stirring over a steam bath to start the reaction which occurred a few minutes after the refluxing had started. The heating was then interrupted till the reaction had subsided, the refluxing being then continued for another 4 hours. After cooling the unreacted zinc was collected (12·8 g.). The benzene solution of the complex was decomposed with crushed ice and diluted acetic acid (5 per cent.). Benzene extraction gave 180 g. of a reddish oily liquid after removal of solvent. By subjecting this liquid to distillation at 0·01mm. Hg pressure, partial dehydration occurred at a bath temperature of 40°C. A fraction of benzalacetone, identified by its 2:4-dinitrophenylhydrazone, was recovered at bath temperature 106° to 110°C. (53·7 g.). The distillation was continued at 130°C. for a further half-hour when only a small amount of unidentified material distilled over. The non-distillable material was subjected to high vacuum distillation in a modified short path still of the cold finger type. The material distilled over at 115° to 130°C. (bath temperature) at $10^{-4}$mm. Hg pressure and consisted of a mixture of the hydroxy ester and the dehydrated ester. Active hydrogen (Zer.) corresponding to 0·445 H.

*Ethyl 5-methyl-7-phenylhepta-2:4:6-trienoate* (crude). The partially dehydrated ester (50 g.) was mixed with half its weight of anhydrous oxalic acid and heated at 110°C. under reduced pressure (10mm. Hg) for 1½hours. The product was extracted with benzene, the benzene extract being washed with solution of sodium bicarbonate and water. After the removal of benzene, the product was distilled in high vacuum, when the dehydrated ester distilled over at 93° to 98°C. $10^{-4}$ to $10^{-5}$mm. Hg pressure. Weight: 38 g. Active hydrogen (Zer.): negligible. Light absorption:

(Fig. 1, curve I) maximum 340mμ, $E^{1\ per\ cent.}_{1\ cm.}$ 225; inflection 250 mμ, $E^{1\ per\ cent.}_{1\ cm.}$ 105. Refractive index: $n_D^{20°C.}$ *ca.* 1·55.

*5-Methyl-7-phenylhepta-2:4:6-trienoic acid.* The dehydrated ester (21 g.) was saponified by shaking with alcoholic potassium hydroxide (7 g. of potassium hydroxide in 77 ml. of alcohol (90 per cent.)) overnight. The soap solution was diluted with water (500 ml.) and extracted with ether which yielded on evaporation only about 0·5 g. of a neutral fraction. The soap solution was then acidified with dilute acetic acid (5 per cent.). The crude acid separated as a gummy precipitate which solidified on standing. By dissolving the crude acid in ether and cooling in a refrigerator overnight, a lemon yellow coloured crystalline acid melting at 190° to 194°C. was obtained. Its colour darkened on standing in air, and it was therefore kept in an atmosphere of nitrogen. Yield: 0·8 g. from about 15 g. of crude acid. Found: C, 77·1; H, 6·56; $C_{14}H_{14}O_2$ requires C, 78·5; H. 6·54 per cent. Active hydrogen (Zer.): 1·05 H. Light absorption (Fig. 1, curve II) Maxima: 342 mμ, $E^{1\ per\ cent.}_{1\ cm.}$ 1650, log.ε 4·548; 249 mμ, $E^{1\ per\ cent.}_{1\ cm.}$ 418, log.ε 3·952. The bulk of the acid was non-crystallisable.

*Glycid ester condensation of benzalacetone and ethyl chloroacetate.* The general method given by Darzens was followed[10]. Benzalacetone (28 g.) and ethyl chloroacetate (freshly distilled, 23·8 g.) were mixed together in a flask and the mixture cooled to -7°C. Alcohol free sodium ethoxide (13 g.) was added in small portions with constant stirring over a period of about 1½ hours. The mixture was stirred at room temperature overnight, then heated over a water bath for 1 hour. After cooling, 100 g. of crushed ice was added followed by the gradual addition of dilute acetic acid (60 ml. of 11 per cent. acid). Extraction with ether and subsequent removal of the solvent gave 43 g. of material which was fractionated. The glycid ester distilled over at 133° to 137°C./0·5 mm. Hg. pressure as a colourless viscous oil. Yield: 10 g. (23 per cent. of theory). It had refractive index: $n_D^{33°C.}$ 1·5401. Found: C, 72·41; H, 6·74; $C_{14}H_{16}O_3$ requires C, 72·41; H, 6·95 per cent. Saponification value gave its molecular weight as 227: $C_{14}H_{16}O_3$ requires 232.

*2-Methyl-4-phenylcrotonaldehyde* (XIX). The glycid ester (26·3 g.) in alcohol (40 ml.) was saponified with alcoholic potassium hydroxide (142 ml. of 1·8 N.) by shaking in an atmosphere of nitrogen for 2 hours and then leaving to stand overnight. A small amount of potassium carbonate precipitate formed during this treatment. After dilution with water and acidification, the free glycid acid precipitated as a red coloured gummy solid. This crude acid was not separated and further purified, but the whole mixture was heated over a boiling water-bath. Decarboxylation occurred smoothly and was completed in about 15 minutes when the solid acid changed into an oily liquid. After extraction with ether, the ethereal extract was washed with water and fractionated yielding mainly the crude 2-methyl-4-phenylcrotonaldehyde at 102° to 110°C./0·3 mm. Hg pressure as a pale yellow liquid. Yield, 3 g. (16 per cent. of theory based upon the glycid ester).

*2-Methyl-4-phenylcrotonaldehyde (pure) by improved method.* The method used by Isler *et al.*[4] was followed. Benzalacetone (56 g.) and ethyl chloroacetate (46·5 g.) were mixed in a flask cooled in a solid carbon-dioxide-acetone bath. Sodium ethoxide (26 g.) was added in small portions with stirring as before, the whole being left overnight at room temperature. Alcoholic potassium hydroxide (220 ml. of 1·8 N.) was added to the mixture gradually with constant stirring, cooling as before. After being stirred for 3 hours, the whole was left over the week-end. Water (600 ml.) was then added with cooling followed by extraction with ether. The aqueous saponaceous liquor on acidification gave only a negligible amount of oily liquid, which indicated almost complete decarboxylation of the glycidate under these conditions. The ethereal extract, after being washed with water and dried, was distilled to remove the solvent, giving 53·3 g. of product which was fractionated:

Fraction 1: 80° to 82°C./0·05 mm. Hg pressure, 25 g. $n^{22°C.}$ 1·5539.
Fraction 2: 84° to 92°C./0·05 mm. Hg pressure, 3 g. $n^{22°C.}$ 1·5549.
Fraction 3: 110° to 40°C./0·05 mm. Hg pressure, 3 g. $n^{22°C.}$ 1·5660.

Fraction 1 was apparently the main crop of the required aldehyde which on redistillation at 70°C./0·05 mm. Hg gave a yield of 22 g. of the pure aldehyde (about 40 per cent. of theory overall) The aldehyde gave the following constants: $n_D^{20°C.}$, 1·5537; $d_4^{20°C.}$, 1·0105; molecular refraction: found 50·77, calculated for $C_{11}$, $H_{12}$, O″, $F_4$ 48·94, exaltation 1·83 units. Found: C, 82·11; H, 7·69; $C_{11}H_{12}O$ requires C, 82·50; H, 7·50 per cent. Semicarbazone, leaflets from alcohol, m.p. 178° to 179°C.; thiosemicarbazone, needles from alcohol, m.p. 132° to 132·5°C.; 2:4-dinitrophenylhydrazone, red needles from chloroform, m.p. 188° to 190°C. Found: N, 16·1; $C_{17}H_{16}N_4O_4$ requires N, 16·47 per cent.

Light absorption data: (in ethyl alcohol) (Fig. 2).

*The aldehyde:* Maxima: 229 mμ, $E^{1\ per\ cent.}_{1\ cm.}$ 1021, log ε 4·214; 283 to 284 mμ, $E^{1\ per\ cent.}_{1\ cm.}$ 142, log ε 3·357.

*The semicarbazone:* Maximum 266 mμ, $E^{1\ per\ cent.}_{1\ cm.}$ 1581, log ε 4·536.

*The thiosemicarbazone:* Maxima 299 mμ, $E^{1\ per\ cent.}_{1\ cm.}$ 1601, log ε 4·409; 249 mμ, $E^{1\ per\ cent}_{1\ cm.}$ 490, log ε 3·895.

Fraction 2 on redistillation yielded mainly the same aldehyde distilling at 70° to 72°C./0·05 mm. Hg pressure.

Fraction 3 yielded a 2:4-dinitrophenylhydrazone, but was apparently a complex mixture and was not investigated further.

*3-Methylpent-4-en-1-yn-3-ol* was prepared by the method given by Heilbron and Jones[14]. The product on careful fractionation through a Widmer column gave the pure carbinol distilling at 66° to 66·5°C./50 mm. Hg pressure. It had refractive index: $n_D^{17·5°C.}$ 1·4438 (Lit., $n_D^{15°C.}$, 1·4490[14]; $n^{20°C.}$, 1·4444[15]). Active hydrogen: (Zer.) 1·09 H at room temperature, 2·03 H after heating at 100°C.

3-*Methylpent*-2-*en*-4-*yn*-1-*ol* (XX) was obtained by anionotropic rearrangement of 3-methylpent-4-en-1-yn-3-ol according to Heilbron and

Jones[14]. The carbinol distilled at 77° to 78°C./18 mm. Hg pressure. Refractive index $n_D^{17°C.}$ 1·4850 (Lit., $n_D^{16°C.}$ 1·4850[14]). Active hydrogen (Zer.); 1·93 H. after warming. α-Naphthylurethane: m.pt. 118° to 119°C. (Lit., 119°C.[16]).

*3:7-Dimethyl-9-phenylnona-2:7-dien-4-yn-1:6-diol* (XXII). The condensation was carried out in a similar way to that used by Isler *et al.*[4] To the Grignard compound of 3-methylpent-2-en-4-yn-1-ol (XXI) (from 5·1 g. of the carbinol) in ether was added a solution of 2-methyl-4-phenylcrotonaldehyde (8·0 g.) in ether (12·5 ml.) over a period of 15 minutes, the whole being cooled in an ice water bath. Vigorous stirring was maintained and a slow stream of nitrogen was passed into the apparatus all the time. After the completion of the addition of the aldehyde, the whole mixture turned into a stiff mass insoluble in ether and was then refluxed over a warm water-bath with efficient stirring when the mass gradually softened. The refluxing was continued for 7 hours. It was then decomposed by shaking with crushed ice and ammonium chloride solution in nitrogen overnight. The product was then extracted with ether, the ethereal extract being dried and fractionated. About 1 ml. of the 3-methylpent-2-en-4-yn-1-ol and a small amount of the 2-methyl-4-phenylcrotonaldehyde were recovered. The product, after being deprived of low-boiling material under 0·04 mm. Hg pressure over a water-bath for 1 hour, was purified by a partition between light petroleum and aqueous methyl alcohol: The product was dissolved in methyl alcohol (100 ml. of 75 per cent.) and extracted with light petroleum (3 quantities, each of 30 ml.). The petroleum fraction which contained some hydrocarbon was not investigated further. The aqueous methyl alcohol fraction was diluted with water (400 ml.) and extracted with ether (4 quantities, each of 70 ml.). After the removal of the last trace of solvent from the ethereal extract at 70° to 80°C./0·05 mm. Hg pressure, 3:7-dimethyl-9-phenylnona-2:7-dien-4-yn-1:6-diol was obtained as a viscous brownish liquid. Yield: 10 g. (78 per cent. of theory). It had the following characteristics: $n_D^{20°C.}$ 1·5756; $d_4^{19°C.}$ 1·0673; Molecular refraction: found 79·43, calculated for $C_{17}H_{20}O_2$, $F_5$ 77·22; exaltation: 2·21 units. Found C, 79·86; H. 7·95; $C_{17}H_{20}O_2$ requires C, 79·68; H, 7·88 per cent. Active hydrogen (Zer.): 2·04 H. Light absorption: (Fig. 3, curve I) inflections at 215 mμ, $E_{1\text{ cm.}}^{1\text{ per cent.}}$ about 750: 230 mμ $E_{1\text{ cm.}}^{1\text{ per cent.}}$ about 615.

*Partially poisoned catalyst.* A supported catalyst of 5 per cent. palladium over barium sulphate (6 g., prepared according to Organic Syntheses[15]) suspended in purified alcohol (30 ml.) was treated with quinoline sulphur poison[16] (0·6 ml.). After being stirred for ½ hour, the catalyst was collected on a filter, washed with a little alcohol and dried *in vacuo*.

*3:7-Dimethyl-9-phenylnona-2:4:7-trien-1:6-diol* (XXIII). 3:7-Dimethyl-9-phenylnona-2:7-dien-4-yn-1:6-diol (9 g.) was dissolved in methyl alcohol (90 ml.) to which the partially poisoned catalyst (1 g.) was

added. Hydrogenation was carried out under approximately atmospheric pressure. However, after the hydrogenation had proceeded slowly for about 4 hours, the rate of absorption of hydrogen became very slow. Fresh additions of catalyst were made and the hydrogenation stopped when 0.99 mol. proportion of hydrogen was absorbed. Total amount of catalyst used was 2·3 g. The catalyst was removed from the solution and the solvent distilled off in nitrogen, the final trace of volatile matter being removed at 80° to 90°C./0·05 mm. Hg pressure. Yield: 9·0 g. of brownish liquid. Found: C. 80·75; H, 8·84; $C_{17}H_{22}O_2$ requires C, 79·02; H, 8·58 per cent. It had the following characteristics: $n_D^{17°C.}$ 1·5673, $d_4^{17°C.}$ 1·039. Molecular refraction: found: 81·15, calculated for $C_{17}H_{22}O'_2F_6$: 78·75; exaltation 1, 2·40 units. Active hydrogen (Zer.): found 0·63 per cent., $C_{17}H_{22}O_2$ requires 0·78 per cent. for 2H. With chloroformic solution of antimony trichloride it gave an instantaneous blue coloration changing rapidly through violet to red. Light absorption: (Fig. 3, curve II) Maxima 215 mμ, $E_{1\text{ cm.}}^{1\text{ per cent.}}$ 357; 282 mμ, $E_{1\text{ cm.}}^{1\text{ per cent.}}$ 197.

3:7-*Dimethyl*-9-*phenylnona*-2:4:7-*trien*-1:6-*diol monoacetate* (XXIV). The diol obtained above (6·5 g.) was dissolved in a mixture of benzene (40 ml.) and dry pyridine (40 ml.). The solution was cooled in a solid carbon dioxide-acetone bath, and freshly distilled acetyl chloride (2·3 g.) was added drop by drop with stirring in nitrogen. After the completion of the addition, the cooling bath was removed and the whole was stirred at room temperature for ¾ hour, then refluxed for 1 hour. The mixture was then cooled to below 0°C., decomposed with water and extracted with benzene. Removal of solvent gave the crude monoacetate as a brownish viscous liquid. Yield: 7·4 g. Light absorption: (Fig. 4, curve I) Maxima 215 mμ $E_{1\text{ cm.}}^{1\text{ per cent.}}$ 367; 240 mμ, $E_{1\text{ cm.}}^{1\text{ per cent.}}$ 316; 282mμ, $E_{1\text{ cm.}}^{1\text{ per cent.}}$ 232.

*Purification of the monoacetate.* The crude acetate (6·6 g.) was extracted repeatedly with hot petroleum (100°C.), the residue insoluble in petroleum being a dark browish gummy solid, probably a polymerised product. The petroleum extract was evaporated to remove the solvent and a light golden yellow liquid was obtained. Found: C. 75·06; H, 7·63; $C_{19}H_{24}O_3$ requires C, 75·97; H, 8·05 per cent. Refractive index: $n_D^{20°C.}$ 1·557. Active hydrogen (Zer.): 1·1 H.

3:7-*Dimethyl*-9-*phenylnona*-2:4:6:8-*tetrane*-1-*ol acetate* (XXV). The dehydration was carried out according to Isler *et al.*[4] The monoacetate obtained from above (4·2 g.), α-tocopherol (40 mg.), were dissolved in light petroleum (80° to 100°C., 70 ml.). Iodine (40 mg.) in light petroleum (10 ml.) was added and the whole was refluxed for 1 hour. After cooling, the solution was washed with solution of sodium thiosulphate and then with water. Removal of solvent gave a dark brown oil. Yield: 3·8 g. With antimony trichloride in chloroform a transient blue colour which changed rapidly through violet to red was produced. Light absorption (Fig. 4, curve II) Maxima 215 mμ, $E_{1\text{ cm.}}^{1\text{ per cent.}}$ 435; 240 mμ, $E_{1\text{ cm.}}^{1\text{ per cent.}}$ 340; 282 mμ, $E_{1\text{ cm.}}^{1\text{ per cent.}}$ 306; 325 mμ, $E_{1\text{ cm.}}^{1\text{ per cent.}}$ 245. Active hydrogen: 0·36 H.

3 : 7-*Dimethyl*-9-*phenylnona*-2 : 4 : 6 : 8-*tetraene*-1-*ol* (XIII). The acetate (0·5 g.) was dissolved in absolute alcohol (3 ml.), to which, with stirring and cooling, was added alcoholic potassium hydroxide (3 ml. of N) in an atmosphere of nitrogen. After standing overnight, the solution was diluted with water (50 ml.) and extracted with ether. The ethereal extract was washed and dried, and the solvent removed. A brownish viscous oil was obtained, weighing 0·35 g. With antimony trichloride in chloroform: An instantaneous blue coloration which changed rapidly through violet to red. Light absorption: Fig. 4, curve III) Maxima 215 mμ, $E_{1\,cm.}^{1\ per\ cent.}$ 446; 240 mμ, $E_{1\,cm.}^{1\ per\ cent.}$ 350; 282 mμ, $E_{1\,cm.}^{1\ per\ cent.}$ 307; 329 mμ $E_{1\,cm.}^{1\ per\ cent.}$ 254.

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