265. *The Synthesis of 4-Carboxyvitamin-A Acid.*

By V. Petrow and O. Stephenson.

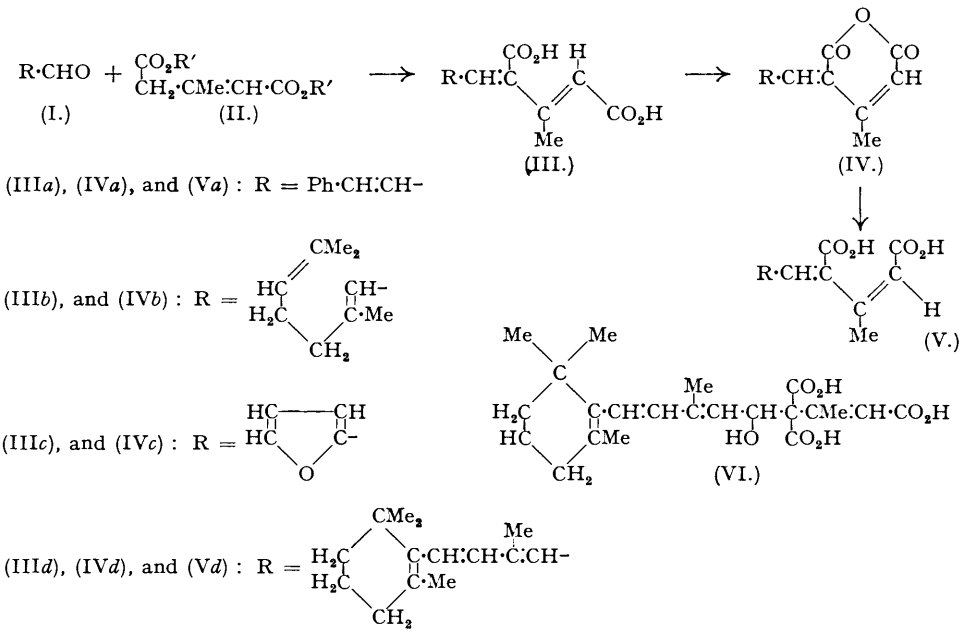
Condensation of cinnamaldehyde with ethyl (*cis* + *trans*)-β-methylglutaconate (II; R′ = Et) yields trans-6-*phenyl*-2-*methylhexa*-1 : 3 : 5-*triene*-1 : 3-*dicarboxylic acid* (III*a*), converted by acetic anhydride into the anhydride (IV*a*), the constitution of which follows from its direct synthesis from β-methylglutaconic anhydride. The corresponding cis-*acid* (V*a*) is obtained by hydrolysis of (IV*a*), into which it reverts when heated. Similar *compounds* are obtained from citral and furfuraldehyde.

When β-ionylideneacetaldehyde (I*d*) is employed in the above condensation, trans-4-*carboxyvitamin-A acid* (III*d*) is obtained, possessing slight vitamin-A activity which is increased after reduction of the compound with lithium aluminium hydride. The derived *anhydride* (IVd) is devoid of biological activity.

Attempts to convert 4-carboxyvitamin-A acid (III*d*) into vitamin-A acid were unsuccessful.

The possibility of using β-methylglutaconic acid (II; R′ = H) for the synthesis of polyenes, foreshadowed by Hurd and Abernethy (*J. Amer. Chem. Soc.*, 1941, **63**, 976), has now been realised by the preparation of trans-4-*carboxyvitamin-A acid* [8-(2 : 6 : 6-*trimethylhex*-1-*en*-1-*yl*)-2 : 6-*dimethylocta*-1 : 3 : 5 : 7-*tetraene*-trans-1 : 3-*dicarboxylic acid*] (III*d*) from β-ionylideneacetaldehyde (I*d*) (Arens and van Dorp, *Nature*, 1947, **160**, 189; Dutch Patent 63015/1949) and (II; R′ = Et). The experimental conditions obtaining for the condensation of the latter compound with aldehydes, however, required prior study for which cinnamaldehyde (I*a*), citral (I*b*), and furfuraldehyde (I*c*) were employed.

Ethyl β-methylglutaconate (II; R′ = Et) (*cis*- + *trans*-forms) failed to condense with cinnamaldehyde (I*a*) in the presence of organic bases such as pyridine, or in acetic anhydride containing a trace of sulphuric acid. When the components were mixed in the presence of 6—8 equivalents of methanolic potassium hydroxide at 5°, however, reaction occurred to give, on acidification after 7 days, a 70% yield of 6-*phenyl*-2-*methylhexa*-1 : 3 : 5-*triene*-1 : 3-*di*-



carboxylic acid, m. p. 200°. The presence of two carboxy-groups in the compound was shown by the preparation of a *bis*-n-*butylamine* salt, whilst its triply unsaturated character was revealed by catalytic hydrogenation to the fully saturated 6-*phenyl*-2-*methyl*-n-*hexane*-1 : 3-*dicarboxylic acid*. When *cis*- or *trans*-β-methylglutaconic acid (II; R′ = H) was employed in place of the mixture of ethyl esters, condensation only occurred in the presence of acetic anhydride at 100°, to give 6-*phenyl*-2-*methylhexa*-1 : 3 : 5-*triene*-1 : 3-*dicarboxylic anhydride* (IV*a*) in good yield. The constitution assigned to this compound followed from its preparation by condensation of

cinnamaldehyde with β-methylglutaconic anhydride in boiling benzene solution in the presence of pyridine. The same anhydride was also obtained by direct treatment of the diacid, m. p. 200°, with acetic anhydride (cf. Rogerson and Thorpe, *J.*, 1905, 1691). Alkaline hydrolysis of (IV*a*) furnished an isomeric *dicarboxylic acid*, which differed sharply from the product of m. p. 200° in its behaviour on heating, for smooth and spontaneous reversion to the anhydride (IV*a*) occurred. This observation leads to its formulation as 6-*phenyl*-2-*methylhexa*-1 : 3 : 5-*triene*-cis-1 : 3-*dicarboxylic acid* (V*a*). The product, m. p. 200°, must therefore be assigned the alternative *trans*-1 : 3-constitution (III*a*). In accordance with these formulations, the absorption spectra of both (III*a*) and (V*a*) showed maxima at 313 mμ. with a slightly higher extinction coefficient in the case of the *trans*-acid (III*a*). The anhydride (IV*a*), in contrast, showed more intense absorption at a longer wave-length (see below).

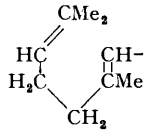
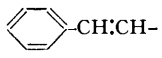
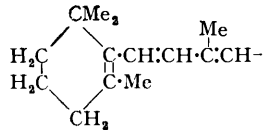
Condensation of ethyl (*cis* + *trans*)-β-methylglutaconate (II; R′ = Et) with citral (I*b*) in the presence of methanolic potassium hydroxide leads to a good yield of a 2 : 6 : 10-*trimethylundeca*-1 : 3 : 5 : 9-*tetraene*-1 : 3-*dicarboxylic acid*, characterised by conversion into a *bis*-n-*butylamine* salt. A *trans*-configuration (III*b*) is tentatively assigned to this compound and is supported by the observation that the compound could not be converted into the corresponding *anhydride* (IV*b*), which was ultimately prepared in low yield from *cis*- or *trans*-β-methylglutaconic acid and citral in acetic anhydride. Furfuraldehyde (I*c*) likewise gave 2-*methyl*-4-(2-*furyl*)*buta*-1 : 3-*diene*-trans-1 : 3-*dicarboxylic acid* (III*c*), readily converted into the *anhydride* (IV*c*) by treatment with acetic anhydride in ethyl acetate.

The reaction between ethyl (*cis* + *trans*)-β-methylgutaconate (II; R′ = Et) and β-ionylideneacetaldehyde (I*d*) in the presence of >3 equivalents of methanolic potassium hydroxide followed essentially the same pattern, the *dipotassium* salt of *trans*-4-carboxyvitamin-A acid being readily obtained in *ca.* 80% yield. The corresponding acid (III*d*), characterised by conversion into the *bis*-n-*butylamine* and *bis*iso*propylamine* salts, rather surprisingly failed to give the Carr–Price reaction. Catalytic hydrogenation gave an oily *octahydro*-derivative. The deep-red 4-*carboxyvitamin-A acid anhydride* (IV*d*) was prepared from β-ionylideneacetaldehyde and β-methylglutaconic anhydride in benzene, with pyridine as a catalyst, or by the carefully controlled action of acetic anhydride on (III*d*). It differed from (III*d*) in giving a ruby-red colour in the Carr–Price reaction. On hydrolysis it furnished the *cis*-acid (V*a*), and on reaction with aniline a cis-4-*carboxyvitamin-A acid monoanilide* (cf. Rogerson and Thorpe, *loc. cit.*).

Neither (III*d*) nor (IV*d*) proved suitable intermediates for conversion into vitamin A. Attempts to effect preferential decarboxylation of (III*d*) by heating it with potassium or barium hydroxide, with alcoholic hydrochloric acid, or with pyridine or quinoline, under a variety of conditions, proved uniformly unsuccessful. Hydrogenation of the anhydride (IV*d*) to a phthalide type of structure likewise failed to give useful results. Reduction of *trans*-4-carboxyvitamin A (III*d*) with 2·2 moles of lithium aluminium hydride, however, yielded a pale yellow gum which gave a strong mauve-blue colour with the Carr–Price reagent and had a vitamin A activity of *ca.* 2000 I.U./g.

Condensation of cinnamaldehyde with α-carboxy-β-methylglutaconic acid (cf. Fichter and Schwab, *Annalen*, 1906, **347**, 251; Feist, *ibid.*, **345**, 60) in the presence of hot methanolic potassium hydroxide gave 6-phenyl-2-methylhexa-1 : 3 : 5-triene-*trans*-1 : 3-dicarboxylic acid (III*a*) in low yield. β-Ionylideneacetaldehyde, under similar conditions, but after being kept for 6 days at room temperature, yielded an unstable compound which decomposed on attempted crystallisation and gave analytical figures in agreement with $C_{22}H_{30}O_7$. Although these figures correspond to a 4-hydroxy-8-(2 : 6 : 6-trimethyl*cyclo*hex-1-enyl)-2 : 6-dimethylocta-2 : 5 : 8-triene-1 : 3 : 3-tricarboxylic acid (VI), light-absorption data fail to support this formulation, the absorption maximum lying at 323 mμ., $\varepsilon_{max.}$ = 13,600 (in *cyclo*hexane), *i.e.*, at a much longer wave-length than may be expected for (VI) (cf. Braude, *Ann. Reports*, 1945, **42**, 115). A compound of structure (VI) is claimed by Milas in U.S.P. 2,369,158, who describes its decarboxylation and concomitant dehydration to vitamin-A acid. When our product was treated with pyridine under the conditions specified by the American authors decomposition invariably occurred, to give gummy mixtures which did not give positive Carr–Price reactions and are being assayed for vitamin A activity by Dr. S. W. F. Underhill and Miss B. M. Manley, B.Sc. (Physiological Department, The British Drug Houses, Ltd.), who will report it elsewhere.

Absorption Data.—The light absorptions of the various compounds described in this paper (for which the authors are indebted to Dr. R. E. Stuckey and Mr. P. Stross, B.Sc., Analytical Department, The British Drug Houses Ltd.), together with published values for the related polyenemonocarboxylic acids, are set out in the accompanying Table.

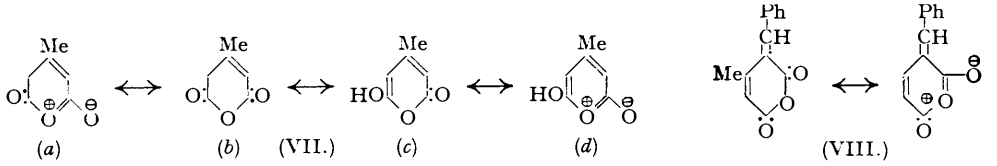
	R.	R′.	Monocarboxylic acid. R·CH:CH·C(R′):CH·CO₂H $\lambda_{max.}$, mμ.	$\varepsilon_{max.}$	*trans*-Dicarboxylic acid. R·CH:C(CO₂H)·C(Me):CH·CO₂H $\lambda'_{max.}$, mμ.	$\varepsilon_{max.}$	Anhydride. $\lambda''_{max.}$, mμ.	$\varepsilon_{max.}$	*cis*-Dicarboxylic acid. $\lambda'''_{max.}$, mμ.	$\varepsilon_{max.}$	$\lambda - \lambda'$.	$\lambda'' - \lambda'$.
(*A*)	Me·CH:CH–	H	303 *n*-H	37,000 [1]	—	—	—	—	—	—	—	—
(*B*)		H	—	—	271 *c*H	14,150	337·5 *i*P	19,300	—	—	—	—
(*C*)		H	—	—	279 *c*H	20,800	357 *i*P	27,950	—	—	24	78
(*D*)	Me·CH:CH·CH:CH–	H	332 *n*-H	49,000 [1]	—	—	—	—	—	—	—	—
(*E*)		H	—	—	313 *c*H	31,500	388 *c*H	38,900	313 *c*H	28,600	19	75
(*F*)		H	337 E	31,400 [2]	300 *i*P	29,300	386 *i*P	63,600	—	—	37	86
(*G*)		Me	343 E	44,700 [3]	320 *i*P	30,400	435 *c*H	34,000	327 W	19,640	23	115
Bis*iso*propylamine salt			—	—	333 (W)	29,600	—	—	—	—	—	—
Bisbutylamine salt			—	—	334 (W)	27,900	—	—	—	—	—	—

Solvents employed in absorption measurements: *c*H = *cyclo*hexane; E = ethanol; *n*-H = *n*-hexane; *i*P = *iso*propyl alcohol; W = water.

[1] Hausser, Smakula, Kuhn, and Hoffer, *Z. physiol. Chem.*, 1935, *B*, **29**, 371. [2] Hausser, Kuhn, Smakula, and Deutsch, *ibid.*, p. 378. [3] Arens and van Dorp, *Nature*, 1946, **157**, 190.

In passing from octatrienoic acid (*A*) to the model compound benzylidene-β-methylglutaconic acid (*B*), the absorption maximum was found to shift to a shorter wave-length while, at the same time, there was a pronounced lowering in the intensity. These changes could hardly be due to the additional carboxyl group present in the latter acid. A more fundamental structural difference was clearly involved and, in seeking to establish this factor, recourse was had to scale models, examination of which revealed the presence of steric inhibition in benzylidene-β-methylglutaconic acid (cf. Pauling, *Helv. Chim. Acta*, 1949, **32**, 2241). Now steric interference, when sufficiently large, is known to decrease the planarity of a conjugated system, the energy content of the contributing resonance forms being thereby increased and the energy level of the excited state raised relatively to that of the ground state, *i.e.*, " the characteristic band itself will be displaced towards shorter wave-lengths " (Braude *et al.*, *J.*, 1949, 1890) and will be less intense (Braude *et al.*, *ibid.*, p. 607). The same factors obtain in all the dicarboxylic acids prepared in this investigation. The absorption maxima (λ′) of (*C*), (*E*), (*F*), and (*G*) should therefore lie at shorter wave-lengths than those (λ) of their monocarboxylic acid analogues (*A*), (*D*), (*F*), and (*G*), and this is indeed found to be the case. Smaller values for $\varepsilon_{max.}$ were also observed as expected.

β-Methylglutaconic acid itself (II; R′ = H) may be regarded as a γ-carboxy-β-methylcrotonic acid. As crotonic acid in aqueous solution shows an absorption band at 200 mμ. ($\varepsilon_{max.}$ = 10,000) (Mohler and Lohr, *Helv. Chim. Acta*, 1938, **21**, 485), its γ-carboxy-derivative (II) should likewise show an absorption band at *ca.* 200 mμ. (cf. Morton, *Ann. Reports*, 1941, **38**, 18; Braude, *ibid.*, 1945, **42**, 112). Actually selective absorption was not observed with either *cis*- or *trans*-β-methylglutaconic acid at wave-lengths greater than 220 mμ. β-Methylglutaconic anhydride, however, showed a maximum at 327 mμ., $\varepsilon_{max.}$ = 6050 (in *cyclo*hexane), *i.e.*, conversion of (II; R′ = H) into the anhydride had led to the appearance of a band at a much longer wave-length. This is hardly surprising as the anhydride of (II) is in reality a pyrone derivative (Bland and Thorp, *J.*, 1912, 856) which exists as a resonance hybrid derived from the canonical forms (VII*a*—*d*) (cf. Cavalier, *Chem. Reviews*, 1947, **41**, 525).



(*a*) (*b*) (VII.) (*c*) (*d*) (VIII.)

The position is somewhat more complicated with *benzylidene-β-methylglutaconic anhydride*. This compound (VIII) bears a structural resemblance to a *p*-quinone and is pale yellow. Replacement of the phenyl group in (VIII) by a more extended conjugated system produces the expected increase in $\lambda_{max.}$ and $\varepsilon_{max.}$, accompanied by a corresponding bathochromic effect, the anhydrides (*E*) and (*F*) being orange-yellow. Further lengthening of the conjugated chain produces a further increase in $\lambda_{max.}$ and a deepening in colour, the anhydride (*G*) being bright red, but it does not leads in this instance to a further increase in $\varepsilon_{max.}$. This result falls into line with the earlier observations of Buroway (*J.*, 1941, 20) and Braude *et al.* (*J.*, 1949, 1890) on the abnormal light-absorption properties of the β-ionone residue with its relatively low values for $\varepsilon_{max.}$ which are apparently due to the " steric hindrance effect " (Braude, *loc. cit.*).

Only one *cis*-acid, (*E*), was obtained pure. Its light absorption supports its structure, the value for $\lambda_{max.}$ being the same for both isomers, and $\varepsilon_{max.}$ slightly higher for the more linear *trans*-dicarboxylic acid (cf. Braude, *loc. cit.*).

Experimental.

(M. p.s are uncorrected. Microanalyses are by Drs. Weiler and Strauss, Oxford.)

6-Phenyl-2-methylhexa-1 : 3 : 5-*triene*-trans-1 : 3-*dicarboxylic Acid* (IIIa).—To a solution of potassium hydroxide (43 g.) in methanol (300 ml.) at −20° was added a mixture of ethyl (*cis* + *trans*)-β-methylglutaconate (22·5 g.) and cinnamaldehyde (13·2 g.) in methanol (25 ml.) cooled to the same temperature. The mixture was then kept for 1 hour at −20° and stored at 0—5° for 7 days. The potassium salt was collected and acidified, and the product (18·5 g.; m. p. 190—194°) recrystallised from aqueous methanol giving *6-phenyl-2-methylhexa*-1 : 3 : 5-*triene*-trans-1 : 3-*dicarboxylic acid*, bright yellow needles (16 g.), m. p. 199—200° (decomp.) (Found : C, 69·4; H, 5·4. $C_{15}H_{14}O_4$ requires C, 69·8; H, 5·5%).

The *bis*-n-*butylamine* salt, white needles, m. p. 141—142°, from ethyl acetate containing a trace of methanol (Found : C, 67·6; H, 8·7; N, 6·6. $C_{23}H_{36}O_4N_2$ requires C, 68·3; H, 9·0; N, 6·9%), was obtained when a methanolic solution of the foregoing acid was treated with a slight excess of *n*-butylamine.

6-*Phenyl*-2-*methyl*-n-*hexane*-1 : 3-*dicarboxylic acid*, white needles, m. p. 109°, from ethyl acetate–light petroleum (b. p. 80—100°) (Found : C, 68·6; H, 7·6. $C_{15}H_{20}O_4$ requires C, 68·2; H, 7·6%), was obtained when a solution of the foregoing acid (2 g.) in ethyl acetate (200 ml.) was completely hydrogenated in the presence of palladium black (0·5 g.), six equivalents of hydrogen being absorbed.

6-*Phenyl*-2-*methylhexa*-1 : 3 : 5-*triene*-1 : 3-*dicarboxylic Anhydride* (IV*a*).—(*a*) A solution of β-methylglutaconic anhydride (7 g.) in benzene (100 ml.) was treated with cinnamaldehyde (7·35 g.), followed by pyridine (3 drops), and the mixture heated under reflux for 3 hours, whereupon the colour changed slowly from pale orange to deep red. Deposition of solid began after *ca.* 1 hour. After the mixture had cooled, the product [10 g.; m. p. 168—176° (decomp.)] was collected, washed with cold methanol, and crystallised from benzene or ethyl acetate. 6-*Phenyl*-2-*methylhexa*-1 : 3 : 5-*triene*-1 : 3-*dicarboxylic anhydride* formed small orange-yellow plates, m. p. 180° (decomp.) (Found : C, 75·4; H, 4·9. $C_{15}H_{12}O_3$ requires C, 75·0; H, 5·0%).

(*b*) β-Methylglutaconic acid (*cis*- or *trans*-) (4·8 g.) was dissolved in warm acetic anhydride (20 ml.), and cinnamaldehyde (8·8 g.) in acetic anhydride (5 ml.) added. The cherry-red solution was heated on the water-bath for 4 hours, solids beginning to separate after *ca.* 1 hour. After the mixture had cooled, the product (7 g.; m. p. 164—174°) was collected and crystallised from benzene, yielding (IV*a*), m. p. 178—179° (decomp.), not depressed on admixture with a sample prepared by method (*a*).

(*c*) The acid (III*a*) (1 g.), dissolved in acetic anhydride (10 ml.), was warmed on the steam-bath for 1 hour. The cooled solution was diluted with methanol and the product recrystallised from benzene giving (IV*a*) (0·65 g.), m. p. 180° (decomp.), alone or on admixture with an authentic specimen.

6-*Phenyl*-2-*methylhexa*-1 : 3 : 5-*triene*-cis-1 : 3-*dicarboxylic Acid* (V*a*).—The foregoing anhydride (IV*a*) (2·3 g.) was suspended in water (100 ml.) containing potassium hydroxide (5 g.), and the mixture heated on the steam-bath for 2 hours. Solution was complete in *ca.* 20 minutes. The cooled mixture was carefully acidified with hydrochloric acid, unchanged material [0·15 g.; m. p. 178—180° (decomp.)] being recovered. The filtrate, on further dilution, gave the yellow crystalline cis-1 : 3-*dicarboxylic acid*, which was purified from methanol (Found : C, 69·7; H, 5·7. $C_{15}H_{14}O_4$ requires C, 69·8; H, 5·5%). The substance dehydrated on heating, finally melting with decomposition at the same temperature as the original anhydride (IV*a*). The bis-*n*-butylamine salt, m. p. 119° (frothing) after three recrystallisations from ethyl acetate–methanol, was very hygroscopic and a satisfactory analysis could not be obtained.

2 : 6 : 10-*Trimethylundeca*-1 : 3 : 5 : 9-*tetraene*-trans-1 : 3-*dicarboxylic Acid* (III*b*).—Ethyl β-methylglutaconate (20 g.) was added to a solution of potassium hydroxide (33·6 g.) in methanol (300 ml.) at 0°. After 5 minutes citral (15·2 g.) was added and the mixture warmed on the water-bath. Rapid separation of a crystalline potassium salt occurred in about 15 minutes and appeared to be complete after 30 minutes. After being kept overnight the potassium salt (20 g.) was collected. Water (2 ml.) was then added to the methanolic mother-liquors, and the solution boiled for 15 minutes and allowed to cool. A further quantity (6·5 g.) of potassium salt separated and was removed. A third crop (4·2 g.) of less pure material was obtained by concentration of the aqueous-methanolic mother-liquors. When the potassium salt (20 g.) was dissolved in water (200 ml.) and the cooled solution carefully acidified, 2 : 6 : 10-*trimethylundeca*-1 : 3 : 5 : 9-*tetraene*-trans-1 : 3-*dicarboxylic acid* was obtained; it formed small needles, m. p. 148°, from aqueous methanol (Found : C, 68·8; H, 7·7. $C_{16}H_{22}O_4$ requires C, 69·0; H, 8·0%). The *bis*-n-*butylamine* salt separated from ethyl acetate–methanol in crystals, m. p. 117° (Found : C, 67·2; H, 10·2; N, 6·03. $C_{24}H_{44}O_4N_2$ requires C, 67·9; H, 10·4; N, 6·6%). Attempts to convert the dicarboxylic acid into the anhydride by treatment with acetic anhydride under a variety of conditions proved unsuccessful, intractable tars being obtained.

2 : 6 : 10-*Trimethylundeca*-1 : 3 : 5 : 9-*tetraene*-1 : 3-*dicarboxylic Anhydride* (IV*b*).—Citral (3·8 g.) and either *cis*- or *trans*-β-methylglutaconic acid (3·6 g.) dissolved in warm acetic anhydride (20 ml.) were heated on the water-bath for 3½ hours. The product obtained by decomposition of the mixture with aqueous ethanol yielded the *anhydride*, buff-coloured needles, m. p. 110°, from ethyl acetate–light petroleum (b. p. 80—100°) (Found : C, 73·5; H, 7·6. $C_{16}H_{20}O_3$ requires C, 73·9; H, 7·8%).

2-*Methyl*-4-(2-*furyl*)*buta*-1 : 3-*diene*-trans-1 : 3-*dicarboxylic Acid* (III*c*).—Ethyl β-methylglutaconate (20 g.) was added to a solution of potassium hydroxide (33·6 g.) in methanol (330 ml.), followed, after 10 minutes, by a solution of furfuraldehyde (9·6 g.) in methanol (15 ml.). The product was collected after 3 days at room temperature and, on acidification and ether extraction, yielded (73%) 2-*methyl*-4-(2-*furyl*)*buta*-1 : 3-*diene*-trans-1 : 3-*dicarboxylic acid*, small needles from hot water, m. p. 213° (decomp.) (Found : C, 59·1; H, 4·7. $C_{11}H_{10}O_5$ requires C, 59·4; H, 4·5%).

2-*Methyl*-4-(2-*furyl*)*buta*-1 : 3-*diene*-1 : 3-*dicarboxylic anhydride* (IV*c*) separated in orange-yellow plates (1·3 g.), m. p. 138° (Found : C, 65·0; H, 4·1. $C_{11}H_8O_4$ requires C, 64·7; H, 4·0%), when light petroleum (b. p. 60—80°) was added to the mixture obtained by refluxing the foregoing acid (2 g.), ethyl acetate (30 ml.), and acetic anhydride (5 ml.) for 1 hour.

trans-4-*Carboxyvitamin-A Acid* (III*d*).—β-Ionylideneacetaldehyde (Arens and van Dorp, *loc. cit.*) (13·08 g.) and ethyl β-methylglutaconate (12·0 g.) in methanol (5 ml.) were added to a solution of potassium hydroxide (20·16 g.) in methanol (125 ml.), and the mixture was heated to 60°. Rapid separation of solids began after 5 minutes and appeared to be complete after 35 minutes. After being kept overnight the *dipotassium* salt (21 g., 80%) of *trans*-4-carboxyvitamin-A acid was collected and dried at 90° (Found : C, 58·5; H, 6·3; K, 17·5. $C_{21}H_{26}O_4K_2,\frac{1}{2}H_2O$ requires C, 58·7; H, 6·3; K, 18·2%). The free *acid* separated from aqueous methanol in small yellow needles, m. p. 203—205° (decomp.) (Found : C, 72·8; H, 8·1. $C_{21}H_{28}O_4$ requires C, 73·2; H, 8·2%). The *bis*-n-*butylamine* salt separated from methanol–ethyl acetate in white crystals, m. p. 170° (decomp.) (Found : C, 70·9; H, 10·3; N, 5·7. $C_{29}H_{50}O_4N_2$ requires C, 71·0; H, 10·3; N, 5·7%). The *bis*-iso*propylamine* salt had m. p. 176° (decomp.) (Found : C, 69·6; H, 10·0; N, 5·8. $C_{27}H_{46}O_4N_2$ requires C, 70·1; H, 10·0; N, 6·1%). On catalytic hydrogenation in absolute ethanol in presence of platinum oxide, 1·72 g. of the acid absorbed 467 ml. of hydrogen (4$\overline{|}$ = 448 ml.), to give a gummy *product* which failed to crystallise (Found : C, 70·9; H, 10·1. $C_{21}H_{36}O_4$ requires C, 71·5; H, 10·3%).

When β-ionylideneacetaldehyde (4·77 g.) was treated with ethyl β-methylglutaconate (4·4 g.) in the

presence of piperidine acetate (8 drops), and the mixture left at room temperature for 10 days, a dark reddish-brown oil was obtained which, after stripping at 0·05 mm. from unchanged ester (4·2 g.) and aldehyde (1·53 g.), appeared to be the *aldol* (Found: C, 82·0; H, 9·7. $C_{30}H_{44}O_2$ requires C, 82·6; H, 10·2%) (yield, 2·3 g.). The compound gives a deep-blue colour with the Carr–Price reagent.

4-Carboxyvitamin-A Acid Anhydride (IV*d*).—(*a*) Addition of pyridine (1 ml.) to a hot solution of β-ionylideneacetaldehyde (15·9 g. of 65% aldehyde content) and β-methylglutaconic anhydride (6·3 g.) in benzene (20 ml.) led to an exothermic condensation, completed by heating the mixture for 1 hour under reflux. *4-Carboxyvitamin-A acid anhydride* (9 g.) was obtained from the viscous residue, and formed dark red needles, m. p. 126°, from light petroleum (b. p. 60—80°) (Found: C, 77·0; H, 7·7. $C_{21}H_{26}O_3$ requires C, 77·3; H, 8·1%). Hydrolysis with aqueous potassium hydroxide furnished the yellow *cis*-acid which reverted spontaneously to the anhydride on warming.

(*b*) When *trans*-4-carboxyvitamin-A acid was warmed for 10—15 minutes with a 10% solution of acetic anhydride in benzene, ethyl acetate, or alcohol, quantitative conversion into the dark red anhydride occurred, it being identified by m. p. and mixed m. p. with a sample prepared by method (*a*). When acetic anhydride alone was employed some decomposition occurred on heating, but slow conversion into the anhydride took place even at room temperature.

(*c*) When the anhydride (0·5 g.) was heated with aniline (1 ml.) and benzene (10 ml.) under reflux for 10 minutes, cis-*4-carboxyvitamin-A acid monoanilide* was obtained; it formed small orange needles, m. p. 158°, from aqueous methanol (decomp.) (Found: C, 76·8; H, 7·6; N, 3·5. $C_{27}H_{33}O_3N$ requires C, 77·3; H, 7·9; N, 3·3%).

Reduction of 4-Carboxyvitamin-A Acid with Lithium Aluminium Hydride.—A cooled solution of 4-carboxyvitamin A acid (1·72 g.) in absolute ether (250 ml.) was slowly treated with a solution of lithium aluminium hydride (0·42 g., 2·2 mols.) in ether (30 ml.), a vigorous reaction occurring. The mixture was heated under reflux for 30 minutes, whereupon the solid which had separated in the early stages of the reaction disappeared. The cooled mixture was carefully decomposed with ice, dilute sulphuric acid added, and the *product* present in the ethereal layer isolated as a pale yellow gum (Found: C, 76·2; H, 9·7. $C_{21}H_{30}O_3$ requires C, 76·3; H, 9·2%). The absorption (in *cyclo*hexane) gave a maximum at 303 mμ., $E^{1\%}_{1\,cm.} = 690$.

Ethyl α-Carbethoxy-β-methylglutaconate Condensations.—(*a*) The tri-ester (27·2 g.) was added in one portion to an ice-cold solution of potassium hydroxide (33·6 g.) in methanol (300 ml.), followed by a solution of cinnamaldehyde (13·2 g.) in methanol (25 ml.). After being heated under reflux for 30 minutes the mixture was cooled and the potassium salt which had separated was collected. On acidification of its solution, carbon dioxide was evolved and 6-phenyl-2-methylhexa-1 : 3 : 5-triene-*trans*-1 : 3-dicarboxylic acid (4·4 g.) was precipitated, identified by m. p. and mixed m. p. with an authentic specimen.

(*b*) When the above reaction was carried out at room temperature for 3 days, acidification of the resultant potassium salt yielded a non-crystallisable gum which was converted into 6-phenyl-2-methylhexa-1 : 3 : 5-triene-*trans*-1 : 3-dicarboxylic acid by decarboxylation with boiling aqueous-alcoholic potassium hydroxide.

(*c*) β-Ionylideneacetaldehyde (6·54 g.) and the tri-ester (8·16 g.) in ethanol (20 ml.) at −10° were added to a cooled solution of potassium hydroxide (6·72 g.) in ethanol (60 ml.). After 6 days at room temperature the deposited potassium salt was collected, washed with cold ethanol until colourless, dissolved in water (100 ml.), and carefully acidified with hydrochloric acid at 0°. The precipitated solids were removed in ether at <30°, giving a *solid*, m. p. *ca.* 80° (decomp.) (Found: C, 65·0; H, 7·8. $C_{22}H_{30}O_7$ requires C, 65·0; H, 7·5%), which gave a trace of mauve colour with the Carr–Price reagent, probably due to an impurity. Decarboxylation experiments using pyridine gave products consisting largely of unchanged material (*e.g.*: Found: C, 67·8; H, 7·8%). Similar results were obtained on using quinoline, the product (Found: C, 71·9; H, 8·9%) obtained after 3 hours' heating in quinoline–ether having an absorption maximum (in *iso*propyl alcohol) at 330 mμ., $E^{1\%}_{1\,cm.} = 505$.

Benzylidene-β-methylglutaconic Acid (cf. Feist and Beyer, *Annalen*, 1906, **345**, 125).—A mixture of benzaldehyde (10·6 g.) and β-methylglutaconic ester (20·0 g.) was added to a cooled solution of potassium hydroxide (16·8 g.) in methanol, and the mixture left at room temperature for 2 days. The potassium salt was collected and dissolved in water (50 ml.), and the solution acidified with hydrochloric acid. The product was washed with cold water and recrystallised from water containing a little ethanol, yielding needles of *benzylidene-β-methylglutaconic acid* (6 g.), m. p. 180° (decomp.) (Found: C, 67·3; H, 5·4. Calc. for $C_{13}H_{12}O_4$: C, 67·2; H, 5·2%) (Feist and Beyer, *loc. cit.*, give m. p. 169°).

Benzylidene-β-methylglutaconic Anhydride.—A suspension of the foregoing acid (0·8 g.) was heated under reflux with acetyl chloride (5 ml.), solution occurring in about 15 minutes. After a further 3 hours excess of acetyl chloride was distilled off, and the residue dissolved in ethyl acetate (10 ml.) and again evaporated to dryness. The residue on crystallisation from ethyl acetate–light petroleum (b. p. 80—100°) yielded *benzylidene-β-methylglutaconic anhydride* (700 mg.), shining yellow plates, m. p. 114—116° (Found: C, 72·8; H, 4·6. $C_{13}H_{10}O_3$ requires C, 72·9; H, 4·7%).

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