377. *Studies in the Polyene Series. Part LIII.* The Synthesis of* pseudo*Cumyl Analogues of* β*-Ionone and Vitamin A Acid.*

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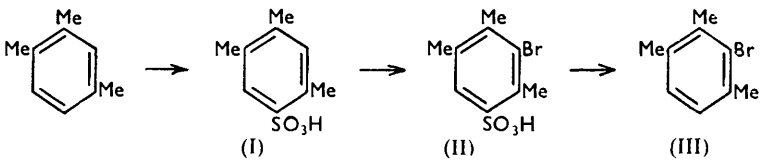
4-(2 : 3 : 6-Trimethylphenyl)but-3-en-2-one, a metabolic product of pregnant mares, has been synthesised by a convenient route and used in a preparation of a biologically active *pseudo*cumyl analogue of vitamin A acid.

The synthesis of three aryl analogues, phenyl, *o*-tolyl, and mesityl, of vitamin A acid has already been reported.[1,2] Of these, only the mesityl compound exhibited growth-promoting activity. It is perhaps significant that this is also the only one for which spectral data indicated a non-planar structure similar to that of vitamin A itself. In continuation of these studies on structure, light-absorption properties, and biological activity, we have prepared the 3-*pseudo*cumyl analogue because the alkyl substitution in both *ortho*-positions was expected to result again in a non-planar structure; furthermore this ring system is encountered in metabolic products which are believed to be of carotenoid origin.[3]

An obvious key intermediate was the β-ionone analogue (V) which occurs naturally in the urine of pregnant mares [3] and has been synthesised on a small scale both from *pseudo*cumene [4] and from β-ionone.[5] To avoid the risk of contamination with β-ionone, which might lead to traces of vitamin A acid in the final product and thus invalidate the biological assay, attention was directed to the former route. In this the first stage is conversion of *pseudo*cumene into 3-bromo*pseudo*cumene after blocking of the more reactive 5-position.



Sulphonation of *pseudo*cumene by the method of Smith and Cass [6] gave the 5-sulphonic acid (I) almost quantitatively. Smith and Moyle [7] described a bromination of the sodium salt of this acid in ethanol–chloroform which gave 3-bromo*pseudo*cumene-5-sulphonic acid (II) exclusively, but Smith and Kiess [8] reported that the reaction was not repeatable. However, they claimed that bromination of the sulphonic acid in 1 : 1 hydrochloric acid gave a readily separable mixture of 5-bromo*pseudo*cumene (60%) and the 3-bromo*pseudo*-cumene-5-sulphonic acid; the latter on hydrolysis with sulphuric acid furnished 3-bromo-*pseudo*cumene (III) in 6% overall yield. Our attempts to reproduce the experimental conditions described by Smith and Kiess were unsuccessful, the starting acid being insoluble in the medium recommended. Various brominations in hydrochloric acid media were therefore examined (see p. 1858), but the yield of 3-bromo*pseudo*cumene, after hydrolysis of the initial bromo-sulphonic acid, did not exceed 9%, the main product being either 5-bromo*pseudo*cumene formed by replacement of the sulphonic acid grouping during

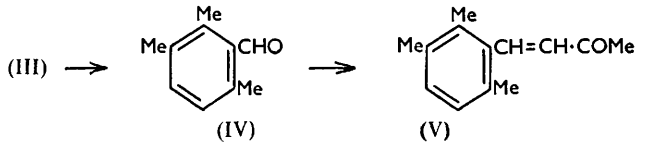
* Part LII, *J.*, 1957, 4909.

[1] Weedon and Woods, *J.*, 1951, 2687.
[2] Bharucha and Weedon, *J.*, 1953, 1571.
[3] Prelog, Führer, Hagenbach, and Schneider, *Helv. Chim. Acta*, 1948, **31**, 1799.
[4] Prelog, Führer, Hagenbach, and Frick, *ibid.*, 1947, **30**, 113.
[5] Braude, Jackman, Linstead, and Lowe, unpublished results; cf. Karrer and Ochsner, *Helv. Chim. Acta*, 1948, **31**, 2093; Büchi, Seitz, and Jeger, *ibid.*, 1949, **32**, 39.
[6] Smith and Cass, *J. Amer. Chem. Soc.*, 1932, **54**, 1603.
[7] Smith and Moyle, *ibid.*, 1936, **58**, 1.
[8] Smith and Kiess, *ibid.*, 1939, **61**, 284.

the bromination, or tribromo*pseudo*cumene by further substitution. Our attempts to effect a Jacobsen rearrangement of the 5-bromo- to the 3-bromo-*pseudo*cumene by both the procedures reported [7,9] were unsuccessful.

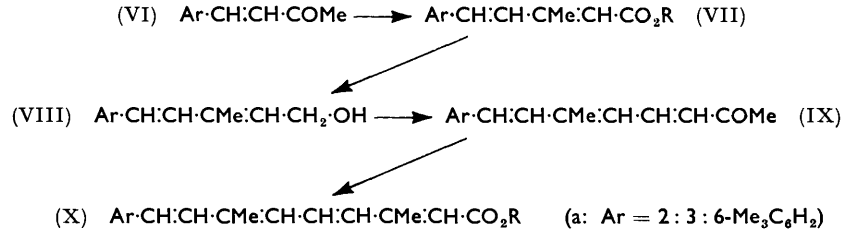
In the belief that the formation of 5-bromo- and tribromo-*pseudo*cumene in the above reactions was associated with the ease of hydrolysis of *pseudo*cumene-5-sulphonic acid in aqueous media, the bromination was repeated in concentrated sulphuric acid. This gave a readily separable mixture of tribromo*pseudo*cumene (9%) and 3-bromo*pseudo*-cumene-5-sulphonic acid. The latter was hydrolysed directly and furnished 3-bromo-*pseudo*cumene in *ca.* 80% overall yield from *pseudo*cumene.

Reaction of the Grignard reagent from 3-bromo*pseudo*cumene with ethyl orthoformate, and hydrolysis of the product, provided 2 : 3 : 6-trimethylbenzaldehyde (IV) in 77% yield. Condensation with acetone in the presence of sodium hydroxide then gave (60%) the required ionone analogue (V) which was characterised by a number of crystalline derivatives.



(IV) (V)

Its properties, and those of its phenylsemicarbazone, agree well with those reported for the specimens of natural origin.[3,4] In connection with the spectral studies, the isomeric 4-(2 : 4 : 5-trimethylphenyl)but-2-en-2-one (VI) was prepared from 2 : 4 : 5-trimethylbenzaldehyde.



A Reformatsky reaction of the ketone (V = VIa) with ethyl bromoacetate, and dehydration of the initial product, yielded the ester (VIIa), which was reduced with lithium aluminium hydride to the alcohol (VIIIa). Oxidation with acetone and aluminium *tert.*-butoxide then gave the ketone (IXa) directly by condensation of the aldehyde first formed with excess of acetone. A Reformatsky reaction of this ketone with methyl bromoacetate led to the acid (Xa; R = H) which was converted by diazomethane into the crystalline methyl ester (Xa; R = Me).

The crystalline ester was fed in arachis oil to young rats reared on a diet free from vitamin A, in doses intended to reveal potency of the same order as that of the mesityl analogue. Under these conditions the rats grew normally. The *pseudo*cumyl ester must therefore possess at least 0·2% of the growth-promoting activity of vitamin A. Further biological assays, designed to determine the upper limit of activity, will be carried out when material is available.

Spectral properties of many of the compounds mentioned above are summarised in the accompanying Tables. The data for the trimethylbenzaldehydes (Table 1) and the derived ionone analogues (Table 2) supplement previous results on the influence of alkyl substitution in the benzaldehyde and benzylideneacetone series.[2,10,11] 2 : 3 : 6-Trimethylbenzaldehyde, like 2 : 6-dimethylbenzaldehyde, exhibits absorption at a longer

[9] Smith, *Organic Reactions*, 1942, **1**, 370.
[10] Braude and Sondheimer, *J.*, 1955, 3754.
[11] *Idem, ibid.*, p. 3773.

wavelength than benzaldehyde, but of appreciably lower intensity. These bathochromic shifts are doubtless due to the increased alkyl substitution, whilst the hypochromic shifts may be explained in terms of steric interference between the *o*-methyl groups and the formyl group. The greater drop in intensity for the 2 : 3 : 6-trimethyl than for the 2 : 6-dimethyl compound is interesting, and indicates that the steric effect of an *o*-methyl group is enhanced by a further methyl group on the adjacent (*i.e.*, *meta*-)position. This " buttressing " effect is even more evident in the spectra of the corresponding semicarbazone and 2 : 4-dinitrophenylhydrazone, and in those of the benzylideneacetone and its derivatives.

TABLE 1. *Ultraviolet-light absorption* ($\lambda_{max.}$, *followed by* ε) *of alkylated benzaldehydes and their derivatives.*

Ph·CHO derivative	Aldehyde		Semicarbazone [a]		2 : 4-Dinitrophenylhydrazone [b]	
Unsubstd.[c]	242 [d]	14,000	281	22,000	—	—
	248	12,500				
2-Me [c]	243	12,500	281	17,700	386	30,600
	251	13,000	291	17,300		
2 : 6-Me_2 [c]	251 [d]	12,500	281	17,600	380	30,800
	256	11,500	291	16,200		
2 : 3 : 6-Me_3	256 [a]	8,000	268 *	13,000	376	30,000
			280	14,500		
2 : 4 : 6-Me_3 [c]	264 [d]	14,500	281	18,500	386	29,500
			290	17,800		
2 : 4 : 5-Me_3	262 [a]	13,000	286	22,000	386	27,000

TABLE 2. *Ultraviolet-light absorption* ($\lambda_{max.}$, *followed by* ε) *of alkylated benzylideneacetones (arylbut-3-en-2-ones) and their derivatives.*

Ph·CH:CH·CO·Me derivative	Ketone [a]		Semicarbazone [a]		2 : 4-Dinitrophenylhydrazone [b]	
Unsubstd.[e]	286	22,200	305	38,600	—	—
2-Me [e,f]	290	17,000	304	32,500	—	—
2 : 6-Me_2 [e]	291	10,500	282	23,300	—	—
2 : 3 : 6-Me_3	284	9,400	280	21,000	384	29,000
2 : 4 : 6-Me_3 [f]	293	14,000	—	—	394	23,000
2 : 4 : 5-Me_3	304	16,000	310	28,500	395	33,000

TABLE 3. *Ultraviolet-light absorption* ($\lambda_{max.}$, *followed by* ε) *of phenylpolyene derivatives.*

Ar	Diene acid (VII; R = H)		Triene ketone (IX)		Tetraene ester (X; R = Me)	
C_6H_5 [g]	229	13,500	360	42,000	354 *	44,500
	309	28,000			367	48,500
2-Me·C_6H_4 [f]	227 [h]	10,500	360	42,500	369	52,000
	307	27,500				
	312 *	24,000				
2 : 3 : 6-$Me_3C_6H_2$	292	13,800	343	24,000	352	37,800
2 : 4 : 6-$Me_3C_6H_2$ [f]	227	10,500	348	28,000	358	37,500
	290 *	14,000				
	304	16,000				
	312 *	14,000				

Footnotes to all Tables:
* Inflexion. [a] In alcohol. [b] In chloroform. [c] Braude and Sondheimer, *J.*, 1955, 3754. [d] In *n*-hexane or *cyclo*hexane. [e] Braude and Sondheimer, *J.*, 1955, 3773. Bharucha and Weedon, *J.*, 1953, 1571. [g] Weedon and Woods, *J.*, 1951, 2687. [h] Ethyl ester.

These 2 : 3 : 6-trimethyl compounds exhibit maximal absorption at slightly lower wavelengths, as well as of lower intensity, than either the 2 : 6-dimethyl or the unmethylated compounds. The spectra of the 2 : 4 : 5-trimethyl compounds show the normal bathochromic shifts due to the methyl substitution, the presence of only one *o*-methyl group giving rise to comparatively little steric hindrance, as was noted previously in the *o*-tolyl series.[2]

With the 3-*pseudo*cumyl polyenes (Table 3) strong hypsochromic and hypochromic effects are observed. These, like those in the mesityl series,[2] are attributed to steric inhibition of resonance, the unsaturated side-chain being displaced out of the plane of the benzene ring by the *o*-methyl groups.

Experimental

See notes preceding the Experimental section in Part XLVI.[2] M. p.s marked (K) were determined on a Kofler block and are corrected.

3-*Bromo*pseudo*cumene* (III).—Concentrated sulphuric acid (700 c.c.) was added slowly to vigorously stirred *pseudo*cumene (300 g.). After the temperature of the mixture had fallen to 20°, bromine (450 g.) was added during 2 hr. Hydrogen bromide was evolved and a solid separated. When all the bromine had reacted water (700 c.c.) was added and the mixture was cooled. The solid, a mixture of tribromo*pseudo*cumene and 3-bromo*pseudo*cumene-5-sulphonic acid, was separated and extracted with hot water. The water-insoluble fraction (80 g.), m. p. 228—232°, was filtered off and crystallised from aqueous methanol, giving tribromo*pseudo*cumene as colourless needles, m. p. 232° (Smith and Moyle [7] give m. p. 231·5°). The aqueous solution of the bromo-sulphonic acid was concentrated and then added slowly to hot (*ca.* 175—180°) 80% (w/w) sulphuric acid through which steam was passed. Isolation of the product from the steam-distillate and distillation gave a liquid (416 g., 84%), b. p. 111—118°/5 mm., n_D^{23} 1·5555. Redistillation gave 3-bromo*pseudo*cumene (342 g., 69%), b. p. 111—114°/5 mm., n_D^{23} 1·5550 (Smith and Kiess [8] give b. p. 85·5—86·5°/5 mm., n_D^{20} 1·5575).

Bromination of pseudo*Cumene-5-sulphonic Acid.*—(a) *In cold hydrochloric acid.* A mixture of bromine (500 g.), water (112 c.c.), and concentrated hydrochloric acid (112 c.c.) was added during 24 hr. to a stirred suspension of *pseudo*cumene-5-sulphonic acid (from 360 g. of *pseudo*cumene [6]) in water (225 c.c.) and concentrated hydrochloric acid (225 c.c.). The solid (440 g.), m. p. 60—90°, was filtered off; steam-distillation and crystallisation from aqueous methanol gave 5-bromo*pseudo*cumene as plates, m. p. 72° (Smith and Moyle [7] give m. p. 71·5—72·5°). The aqueous filtrate of bromo-sulphonic acid was processed as described above and gave 3-bromo*pseudo*cumene (12 g., 2%), b. p. 78—79°/1 mm.

Bromination of the sulphonic acid (from 20 g. of *pseudo*cumene) in N-hydrochloric acid gave 3-bromo*pseudo*cumene in 9% yield.

(b) *In hot hydrochloric acid.* A mixture of bromine (165 g.), water (38 c.c.) and concentrated hydrochloric acid (38 c.c.) was added slowly to a warm saturated solution of *pseudo*cumene-5-sulphonic acid (from 120 g. of *pseudo*cumene) in water (75 c.c.) and concentrated hydrochloric acid (75 c.c.). The solid (110 g.), m. p. 180—200°, which separated was collected; from it 5-bromo*pseudo*cumene (9 g.), m. p. 71°, was isolated by steam-distillation, and tribromo*pseudo*cumene, m. p. 232°, by crystallisation from aqueous methanol. The aqueous filtrate of bromosulphonic acid was processed in the usual way and gave 3-bromo*pseudo*cumene (16 g., 7·7%), b. p. 77—78°/0·8 mm.

(c) *In organic solvents.* Addition of bromine (28 g.) in chloroform (11 c.c.) and concentrated hydrochloric acid (1 c.c.) to a solution of the sulphonic acid (from 20 g. of *pseudo*cumene) in alcohol (35 c.c.) and concentrated hydrochloric acid (15 c.c.), and hydrolysis of the resulting bromo-sulphonic acid, gave 3-bromo*pseudo*cumene (2·9 g., 9%).

Bromination of the sulphonic acid (from 20 g. of *pseudo*cumene) in acetic acid (50 c.c.) and water (20 c.c.) with bromine (28 g.) in acetic acid (12 c.c.), and treatment of the product in the usual way, gave a negligible yield of 3-bromo*pseudo*cumene.

2 : 3 : 6-*Trimethylbenzaldehyde* (IV).—3-Bromo*pseudo*cumene (50 g.) in ether (80 c.c.) was added to a stirred suspension of magnesium turnings (13·3 g.) in ether (35 c.c.) containing a trace of iodine. Ethyl bromide (27 g.) in ether (150 c.c.) was added slowly and the mixture then boiled under reflux for 3 hr. during which most of the magnesium reacted. Ethyl orthoformate (77 g.) in ether (50 c.c.) was added and the mixture was boiled for 5 hr. The ether was then distilled off and the residue was kept at 20° overnight. Ice (80 g.) and 5N-hydrochloric acid (200 c.c.) were added. The mixture was boiled under reflux for 30 min. in an atmosphere of carbon dioxide and then steam-distilled. Extraction of the product from the distillate with ether and distillation gave 2 : 3 : 6-trimethylbenzaldehyde (28·5 g.), b. p. 74°/1 mm., n_D^{26} 1·5430 (Smith and Nichols [12] give b. p. 115—116°/12 mm.). Light absorption: see Table 1. The

semicarbazone crystallised from aqueous alcohol and had m. p. 166—167° (lit.,[12] m. p. 167—169°). Light absorption: see Table 1. The oxime, after vacuum-sublimation and crystallisation from aqueous alcohol, had m. p. 138° (lit.,[12] m. p. 124—126°) (Found: C, 73·85; H, 8·55. Calc. for $C_{10}H_{13}ON$: C, 73·6; H, 8·05%). The 2 : 4-*dinitrophenylhydrazone* crystallised from aqueous acetic acid or ethyl acetate in red prisms, m. p. 222—223° (corr.) (Found: C, 59·05; H, 4·95; N, 17·05. $C_{16}H_{16}O_4N_4$ requires C, 58·55; H, 4·9; N, 17·05%). Light absorption: see Table 1.

The use of activated magnesium powder in the Grignard reaction, as advocated by Smith and Nichols,[12] was found unnecessary.

2 : 4 : 5-*Trimethylbenzaldehyde*.—Hydrogen cyanide (48 c.c.) was added during 15 min. to a stirred suspension of aluminium chloride (107 g.) in tetrachloroethane (200 c.c.) at 0°. After the mixture had been stirred at 20° for 15 min., *pseudo*cumene (25 g.) was added and a slow stream of dry hydrogen chloride was bubbled through the mixture for 15 min. at 20° and then for 4 hr. at 80°. The product was cooled and poured on ice and concentrated hydrochloric acid. This mixture was boiled for 15 min. under reflux and then steam-distilled. Extraction of the distillate with ether, and distillation, gave a liquid which partly solidified at 8°. The solid was collected and crystallised from aqueous alcohol, to give 2 : 4 : 5-trimethylbenzaldehyde (2·0 g.) as prisms, m. p. 45°, undepressed on admixture with a specimen prepared according to Smith and Nichols's method [12] (Gattermann [13] gives m. p. 42°). Light absorption: see Table 1. The 2 : 4-*dinitrophenylhydrazone* crystallised from aqueous acetic acid or ethyl acetate in orange prisms, m. p. 223° (corr.) (Found: C, 58·75; H, 5·25; N, 17·15%). Light absorption: see Table 1. A mixed m. p. with the derivative of 2 : 3 : 6-trimethylbenzaldehyde showed a marked depression. The *semicarbazone* crystallised from methanol–chloroform and had m. p. 244° (Found: C, 64·11; H, 7·35. $C_{11}H_{15}ON_3$ requires C, 64·35; H, 7·35%). Light absorption: see Table 1. The oxime crystallised from aqueous alcohol and had m. p. 112° (Gattermann [13] gives m. p. 102°) (Found: C, 73·9; H, 8·2%), $\lambda_{max.}$ 262 mμ (ε 15,500).

A higher yield of 2 : 4 : 5-trimethylbenzaldehyde is obtained by the original method of Gattermann.[13]

4-(2 : 3 : 6-*Trimethylphenyl*)*but*-3-*en*-2-*one*.—Sodium hydroxide (2·5 g.) was added to a solution of 2 : 3 : 6-trimethylbenzaldehyde (27·4 g.) in acetone (142 c.c.) and water (14·5 c.c.). The mixture was stirred at 20° for 20 hr., then poured into 2N-sulphuric acid (290 c.c.). A solid (1·2 g.) was filtered off and crystallised from ethyl acetate, to give 1 : 5-*di*-(2 : 3 : 6-*trimethylphenyl*)*penta*-1 : 4-*dien*-3-*one* as yellow needles, m. p. 152° (Found: C, 86·4; H, 8·4. $C_{23}H_{26}O$ requires C, 86·75; H, 8·25%), $\lambda_{max.}$ 314 mμ (ε 17,000).

The aqueous-acetone filtrate was extracted with ether, and the extract was washed with water, dried, and evaporated. Distillation of the residue gave 4-(2 : 3 : 6-trimethylphenyl)-but-3-en-2-one (21 g.), b. p. 97°/0·1 mm., n_D^{19} 1·5632 (Found: C, 82·6; H, 8·65. Calc. for $C_{13}H_{16}O$: C, 82·9; H, 8·55%). Light absorption: see Table 2. (Prelog, Führer, Hagenbach, and Frick [4] give b. p. 115—130°/0·2 mm.). The semicarbazone crystallised from alcohol and had m. p. 215° (lit.,[4] m. p. 216—217°). Light absorption: see Table 2. The phenylsemicarbazone crystallised from alcohol in needles, m. p. 203—205° (lit.,[4] m. p. 202—204°) (Found: C, 74·8; H, 7·25; N, 13·35. Calc. for $C_{20}H_{23}ON_3$: C, 74·75; H, 7·2; N, 13·05%), $\lambda_{max.}$ 228 and 292 mμ (ε 23,000 and 32,000 respectively). The 2 : 4-*dinitrophenylhydrazone* crystallised from alcohol in needles, m. p. 154° (Found: C, 61·85; H, 5·65. $C_{19}H_{20}O_4N_4$ requires C, 61·95; H, 5·45%). Light absorption: see Table 2. The *oxime*, which was formed slowly, crystallised from aqueous alcohol and had m. p. 106° (Found: C, 76·35; H, 8·5. $C_{13}H_{17}ON$ requires C, 76·8; H, 8·45%), $\lambda_{max.}$ 266 mμ (ε 15,000).

4-(2 : 4 : 5-*Trimethylphenyl*)*but*-3-*en*-2-*one*.—Sodium hydroxide (0·154 g.) was added to a solution of 2 : 4 : 5-trimethylbenzaldehyde (1·67 g.) in acetone (7·8 c.c.) and water (0·88 c.c.). The mixture was stirred at 20° overnight and then poured into 2N-sulphuric acid (18 c.c.). The product was isolated by extraction with ether. Crystallisation from aqueous methanol and from *n*-pentane gave the ketone (1·0 g., 47%) as needles, m. p. 45° (John and Gunther [14] give m. p. 51°) (Found: C, 82·9; H, 8·85%). Light absorption: see Table 2. The semicarbazone crystallised from chloroform and had m. p. 222° (decomp.) [lit.,[14] m. p. 220° (decomp.)]. Light absorption: see Table 2. The 2 : 4-*dinitrophenylhydrazone* crystallised from alcohol in

[12] Smith and Nichols, *J. Org. Chem.*, 1941, **6**, 489.
[13] Gattermann, *Annalen*, 1906, **347**, 347.
[14] John and Gunther, *Ber.*, 1941, **74**, 879.

needles, m. p. 240° (Found: C, 61·5; H, 5·5%). Light absorption: see Table 2. The *oxime* crystallised from aqueous methanol and had m. p. 140° (decomp.) (Found: C, 76·3; H, 8·7%), $\lambda_{max.}$ 288 mμ (ε 21,000).

Ethyl 2-*Methyl*-4-(2 : 3 : 6-*trimethylphenyl*)*buta*-1 : 3-*diene*-1-*carboxylate* (VII; R = Et).—About half of a mixture of 4-(2 : 3 : 6-trimethylphenyl)but-3-en-2-one (31·2 g.) and ethyl bromoacetate (31·2 g.) was added to zinc wool (12·5 g.) and benzene (110 c.c.). The mixture was heated under reflux until reaction commenced, and the remainder of the ketone-ester mixture was then added at such a rate that gentle refluxing was maintained. Heating was then recommenced and continued for ½ hr. The mixture was cooled and shaken with N-acetic acid (1 l.). The benzene layer was separated, washed with saturated sodium hydrogen carbonate solution, and dried (Na_2SO_4). The solution was diluted (to 500 c.c.) with the same solvent and heated under reflux for 5 hr. with toluene-*p*-sulphonic acid (0·5 g.), water being removed by azeotropic distillation. The resulting benzene solution was washed with aqueous sodium hydrogen carbonate, dried and evaporated. Distillation gave the *ester* (35·5 g.), b. p. 85—95° (bath temp.)/10^{-5} mm., n_D^{21} 1·5750 (Found: C, 79·25; H, 8·75. $C_{17}H_{22}O_2$ requires C, 79·05; H, 8·6%), $\lambda_{max.}$ 294 mμ (ε 19,000).

2-*Methyl*-4-(2 : 3 : 6-*trimethylphenyl*)*buta*-1 : 3-*diene*-1-*carboxylic Acid* (VII; R = H).—Hydrolysis of the preceding ester (740 mg.) with boiling methanolic 10% (w/v) potassium hydroxide (15 c.c.) for 3 hr., and isolation of the acidic product in the usual way, gave a solid (500 mg.), m. p. 134—170°. Fractional crystallisation from benzene–light petroleum (b. p. 60—80°) yielded one stereoisomer of the *acid* (200 mg.), m. p. (K) 172—174° (Found: C, 78·2; H, 8·0. $C_{15}H_{18}O_2$ requires C, 78·25; H, 7·9%). Light absorption: see Table 3.

3-*Methyl*-4-(2 : 3 : 6-*trimethylphenyl*)*penta*-2 : 4-*dien*-1-*ol* (VIII).—The above ester (40·8 g.) in ether (175 c.c.) was added during 3 hr. to a stirred solution of lithium aluminium hydride (8 g.) in ether (200 c.c.) at −60°. The mixture was then stirred for 1½ hr. at −30°. Ethyl acetate (10 c.c.) was added to decompose any excess of hydride, and then a saturated solution of ammonium chloride (50 c.c.). The mixture was filtered and the product was isolated in the usual way, giving the *alcohol* (28·0 g.), b. p. 95—115° (bath-temp.)/10^{-5} mm., n_D^{19} 1·5816 (Found: C, 83·15; H, 9·6. $C_{15}H_{20}O$ requires C, 83·3; H, 9·3%), $\lambda_{max.}$ 223 and 267 mμ (ε 19,500 and 16,000 respectively).

A small portion (0·7 g.) of the alcohol in light petroleum (b. p. 40—60°) (30 c.c.) was shaken with manganese dioxide (3·5 g.) at 20° for 96 hr. Removal of oxide and solvent, and distillation of the residue, gave an impure aldehyde (0·2 g.), b. p. 100—110° (bath-temp.)/10^{-5} mm., n_D^{21} 1·6090 (Found: C, 83·95; H, 8·75. $C_{15}H_{18}O$ requires C, 84·05; H, 8·45%), $\lambda_{max.}$ 258, 268, and 280 mμ ($E_{1\,cm.}^{1\%}$ 620). The *semicarbazone* crystallised from ethanol and had m. p. (K) 176° (Found: N, 15·6. $C_{16}H_{21}ON_3$ requires N, 15·5%), $\lambda_{max.}$ 320 mμ (ε 40,000).

6-*Methyl*-8-(2 : 3 : 6-*trimethylphenyl*)*octa*-3 : 5 : 7-*trien*-2-*one* (IX).—The preceding alcohol (21·8 g.) and aluminium *tert.*-butoxide (37 g.) in acetone (185 c.c.) and benzene (500 c.c.) were heated under reflux for 46 hr. The mixture was cooled and shaken with 2N-sulphuric acid. The benzene layer was separated, washed with aqueous sodium hydrogen carbonate, dried (Na_2SO_4), and evaporated under reduced pressure. A solution of the residual oil (27·5 g., n_D^{21} 1·663) and Girard reagent T [15] (20 g.) in alcohol (225 c.c.) and glacial acetic acid (18 g.) was heated under reflux for 1 hr. and then cooled. Ice and water (1700 c.c.) were added, and the mixture was brought to pH 6 by the addition of 2N-sodium hydroxide. The non-ketonic fraction was extracted with ether. 2N-Sulphuric acid (600 c.c.) was added to the aqueous layer and, after the mixture had been kept for 1 hr., the liberated ketone was isolated with ether in the usual way, giving an oil (12·3 g.), n_D^{23} 1·644. This crude product was treated with excess of methanolic semicarbazide acetate and gave a solid (16·9 g.), m. p. 171—177°. Crystallisation from alcohol yielded the *semicarbazone* as yellow needles, m. p. (K) 181—182° (Found: N, 13·55. $C_{19}H_{25}ON_3$ requires N, 13·5%), $\lambda_{max.}$ 339 mμ (ε 62,000).

A mixture of the finely powdered semicarbazone (8·3 g.; m. p. 176—181°), 2N-sulphuric acid (170 c.c.), and light petroleum (b. p. 100—120°) (120 c.c.) was stirred vigorously and heated under reflux for 1 hr. The mixture was cooled, and unchanged semicarbazone was filtered off and again treated with acid in the above manner. The petroleum solutions were combined, washed with water, dried (Na_2SO_4), and evaporated. Chromatography of the residual red oil (5 g.) on alumina (30 g.; Grade IV) from light petroleum (b. p. 40—60°), and elution of the

[15] Girard and Sandulesco, *Helv. Chim. Acta*, 1936, **19**, 1095.

least strongly adsorbed band, gave the ketone (4·5 g.) as a highly unstable, viscous yellow gum. Light absorption: see Table 3.

Methyl 2 : 6-*Dimethyl*-8-(2 : 3 : 6-*trimethylphenyl*)*octa*-1 : 3 : 5 : 7-*tetraene*-1-*carboxylate* (X; R = Me).—A mixture of the preceding ketone (4·5 g.), zinc wool (2 g.), methyl bromoacetate (4·5 g.), and benzene (50 c.c.) was heated under reflux until the reaction ceased (½ hr.). Decomposition of the complex, and dehydration of the hydroxy-ester with toluene-*p*-sulphonic acid as in the previous Reformatsky reaction, gave a yellow oil (3·2 g., n_D^{19} 1·64). Chromatography on alumina (200 g.; Grade IV) from light petroleum (b. p. 40—60°), and elution of the least strongly adsorbed band, gave an oil (3·0 g.), n_D^{18} 1·66, $\lambda_{max.}$ 351 mμ ($E_{1\,cm.}^{1\%}$ 700).

The crude ester (2·8 g.) was hydrolysed with boiling methanolic 10% (w/v) potassium hydroxide for 2 hr. The resulting solution was cooled, diluted with water, and then acidified with dilute (1 : 1) phosphoric acid. The liberated acid was extracted with ether. The ethereal solution was washed with water, dried (Na_2SO_4), and evaporated to a small volume. The solid (0·4 g.) which had separated was removed and had m. p. (K) 159—163°. Crystallisation of a portion from methanol gave one isomer of 2 : 6-*dimethyl*-8-(2 : 3 : 6-*trimethylphenyl*)*octa*-1 : 3 : 5 : 7-*tetraene*-1-*carboxylic acid* as yellow needles, m. p. (K) 162—163° (Found: C, 80·75; H, 8·4. $C_{20}H_{24}O_2$ requires C, 81·05; H, 8·15%), $\lambda_{max.}$ 349 mμ (ε 44,000). Evaporation of the ethereal mother-liquors gave a yellow solid (0·74 g.), m. p. (K) 140—150°.

A cooled (0°) suspension of the acid (316 mg.; m. p. 159—163°) in ether was treated with excess of ethereal diazomethane. The solvent was evaporated. Chromatography of the residual oil (330 mg.) in light petroleum (b. p. 40—60°) on alumina (30 g.; Grade IV), elution of the yellow band, and evaporation gave a solid (274 mg.). Crystallisation from methanol gave the *ester* (154 mg.) as yellow needles, m. p. (K) 73—75° (Found: C, 81·45; H, 8·7. $C_{21}H_{26}O_2$ requires C, 81·25; H, 8·45%). Light absorption: see Table 3.

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