oate (17).—Perchloryl fluoride was bubbled through a solution of 10 g. of methyl 3,11-diketo-4,17(20)-*cis*-pregnadien-21-oate 3-pyrrolidyl enamine (**16**) in 2 l. of dry benzene for 5 min. The reaction mixture was washed with saturated sodium bicarbonate solution. The solution was dried over anhydrous sodium sulfate and evaporated. The crude material, weighing 10 g., was crystallized from ethyl acetate. The crystals, melting at 212–214° and weighing 2.0 g. (21%), were collected by filtration. After two recrystallizations, the material had m.p. 228° dec., λ_{max}^{EtOH} 224 mμ (ε 11,900).

Anal. Calcd. for $C_{22}H_{26}F_2O_4$: C, 67.33; H, 6.68; F, 9.68. Found: C, 67.13; H, 7.10; F, 9.1.

Methyl 4,4-Difluoro-3,11-diketo-5(6)-*cis*-pregnadien-21-oate 3-(2,4-Dinitrophenylhydrazone) (18).—A solution of 110 mg. of 2,4-dinitrophenylhydrazone in 3 ml. of 30% perchloric acid was added to a solution of 200 mg. of (**17**) in 60 ml. of 95% ethyl alcohol. The mixture was stirred for 90 min., crystals forming within 10 min. The orange crystals, weighing 200 mg. (65%) and melting above 360°, were collected by filtration. Ultraviolet absorptions were at 260 mμ (ε 14,750) and 351 (25,500).

Methyl 4-Fluoro-3,11-diketo-4,6,17(20)-*cis*-pregnadien-21-oate 3-(2,4-Dinitrophenylhydrazone) (19).—A solution of 50 mg. of 2,4-dinitrophenylhydrazone (**18**) in 20 ml. of glacial acetic acid was heated under reflux for 15 min. Crystals formed after concentration to 10 ml. The red product, weighing 30 mg. (**19**) and melting at 305° dec., showed the following ultraviolet absorptions: $\lambda_{max}^{CHCl_3}$ 269 mμ (ε 16,150), 296 (12,500), 309 (15,400), and 392 (39,450).

Anal. Calcd. for $C_{28}H_{29}FN_4O_7$: F, 3.2. Found: F, 3.3.

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Geometric Isomers of 2,3-Dimethyl-5-aryl-2,4-pentadienoic Acids. The Steric Factors Favoring 2-*cis* Formation

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The n.m.r. data for the 2-*cis*-4-*trans*- and 2,4-di-*trans*-2,3-dimethyl-5-aryl-2,4-pentadienoic acids and their esters (IV and V) and the nonconjugated isomeric acid (VI) and mixtures thereof have been analyzed and used to determine the relative amounts of the isomers obtained in the formation and dehydration of the Reformatsky product (II). The preponderance of 2-*cis* isomer (45%) over 2-*trans* (30%) and nonconjugated methylene acids (25%) is accounted for in terms of the relative overlap of the groups in the 2- and 3-positions in the transition complexes and in the resulting hydroxy esters. The result indicates less hindrance in the overlapping CH_3–CH_3 and R″–H groups in the transition complex VII leading to the *cis* isomer *via* E2 elimination from IX than in the overlapping CH_3–H and CH_3–R″ in VIII which leads to the *trans* isomer *via* X.

We have described tautomeric and geometric isomers of 3-methyl- and 3,4-dimethyl-5-aryl-2,4-pentadienoic acids and the n.m.r. techniques used in establishing their structures in preceding papers.[1–5] We wish at this time to describe the results of related studies of the 2,3-dimethyl-5-aryl-2,4-pentadienoic acids in which n.m.r. characteristics have been used to assign structures and to analyze the steric factors controlling the proportions in which they are formed.

The Reformatsky reaction of 4-aryl-3-buten-2-ones (I, aryl = phenyl, *p*-tolyl, *p*-chlorophenyl, *p*-methoxyphenyl) and ethyl α-bromopropionate gives β-hydroxy esters (II) in 74–86% yield. Dehydration with *p*-toluenesulfonic acid catalysis gives *cis–trans* mixtures (III) of the ethyl 2,3-dimethyl-5-aryl-2,4-pentadienoates along with the 3-methylene structures (VI) also formed in the 3,4-series. Alkaline saponification gives the *cis–trans* mixture of the acids from which the pure isomers (IV and V) were separated by fractional crystallization. The unfractionated mixture of dehydrated esters (for the phenyl series) contained 45% *cis*, 30% *trans*, and 25% methylene isomers as determined by the integrated areas of characteristic n.m.r. peaks associated with each isomer. The peaks at τ 4.79 and 4.86 (C-3 methylene protons of VI), at 7.87 and 7.95 (C-3 methyl protons *cis* to carbethoxy and C-2 methyl protons of IV), and at 8.09 and 8.04 (C-2 methyl protons and C-3 methyl protons *trans* to carbethoxy of V) were used.

The configurations of the acids in this series were assigned on the basis of the n.m.r. characteristics of their solutions in deuteriochloroform, pyridine, and piperidine.[3] The pyridine solutions are useful in that peaks associated with 3-methyl groups *cis* to carboxy groups are subjected to an enhanced deshielding effect which distinguishes the peak associated therewith from the 2-methyl peak. Pyridine obscures the C-4 and C-5 olefinic proton absorption which can, however, be observed in deuteriochloroform or piperidine solutions. With the data available for the pure acids, it is possible to make appropriate assignments to the peaks observed in mixtures of the esters and to determine the relative quantities of each present.

The n.m.r. data for the three acids in the phenyl series (IVa, Va, and VIa, R′ = H) are typical and will be summarized briefly. Complete data on the n.m.r. characteristics of the substituted products are given in Table I. The 2-*cis*-4-*trans* configuration (Va) is assigned to the acid, m.p. 130–131°, on the basis of peaks at τ 7.83 (C-2 methyl), 8.02 (C-3 methyl), 2.22 (*J* = 16 c.p.s., C-4 proton), and 3.68 (J = 16 c.p.s., C-5 proton). The low-field doublet is assigned to the C-4 proton deshielded by the *cis* carboxy. The τ 8.02 peak is assigned to the C-3 methyl protons on the basis of its position, which is typical of that for methyl protons trans to a carboxyl group, and on the basis of splitting (in pyridine and in piperidine) into a doublet (*J* = 1–2 c.p.s.) due to long-range coupling with the C-4 proton. Under these conditions the τ 7.83 peak shows

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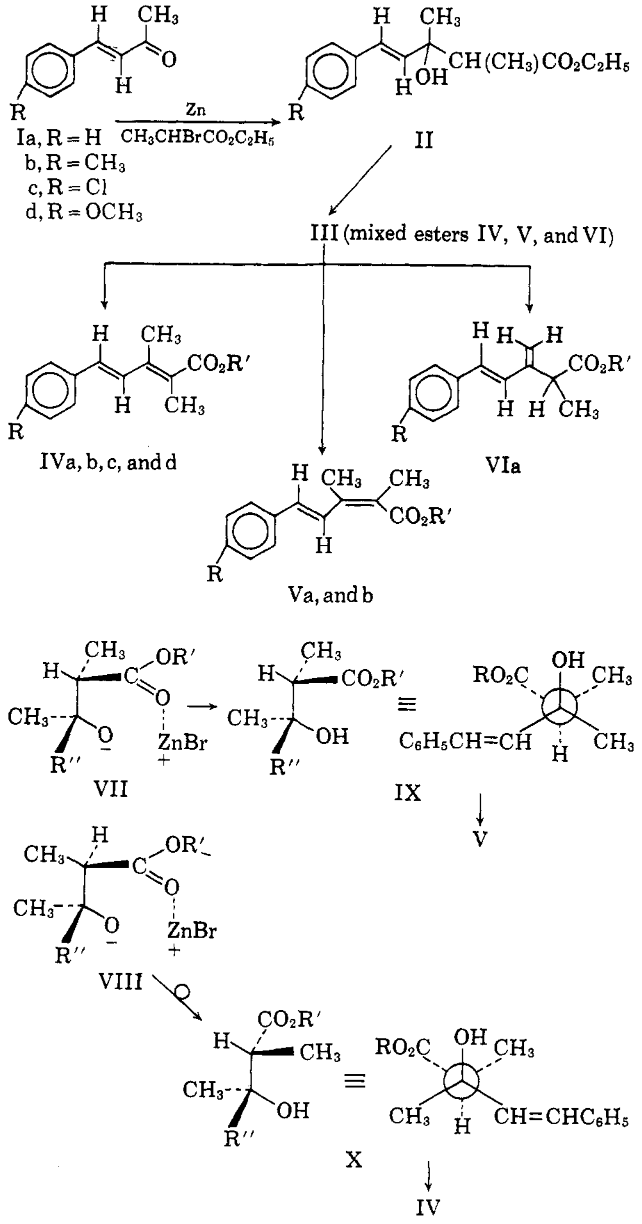

Table I

N.M.R. Data for 2,3-Dimethyl-5-aryl-2,4-pentadienoic Acids and Related Compounds[a]

$ArCH{=}CHC(CH_3){=}C(CH_3)CO_2R$

Compd.[b]	Solvent[c]	2-CH_3	3-CH_3	4-H	5-H
		Ar = phenyl			
2-*cis*-4-*trans*					
* Acid	Pyr.	7.83	8.02	. . .	. . .
* Acid	Pip.			2.22 (16)	3.68 (16)
Acid	DC	7.95	7.95	2.09 (16)	3.30 (16)
* Ester	CCl_4	8.09	8.04	2.13 (16)	3.38 (16)
2-*trans*-4-*trans*					
Acid	Pyr.	7.70	7.62		
Ester	CCl_4	7.95	7.87	2.98 (16)[d]	3.31 (16)
		Ar = 5-*p*-tolyl			
2-*cis*-2-*trans*					
Acid	Pyr.	7.85	8.05		
* Ester	CCl_4	8.06	8.06	2.31 (16)	3.52 (16)
2-*trans*-4-*trans*					
Acid	Pyr.	7.71	7.58		
* Ester	CCl_4	7.98	7.91	3.02 (16)[d]	3.43 (16)
		Ar = 5-*p*-chlorophenyl			
2-*cis*-4-*trans*					
* Ester	CCl_4	8.09	8.09	2.32 (16)	3.56 (16)
2-*trans*-4-*trans*					
Acid	Pyr.	7.77	7.70		
* Ester	CCl_4	8.00	7.96	2.97 (16)[d]	3.48 (16)
		Ar = 5-*p*-methoxyphenyl			
2-*cis*-4-*trans*					
* Acid	Pyr.	7.83	8.02		
* Ester	CCl_4	8.08	8.08	2.36 (16)	3.54 (16)
2-*trans*-4-*trans*					
* Acid	Pyr.	7.72	7.60		
Acid	DC	7.88	7.76		
* Ester	CCl_4	7.99	7.91	3.05 (16)[d]	3.46 (16)[d]
		Ar = phenyl (3-unsubstituted)[e]			
2-*cis*-4-*trans*					
Acid	DC	7.97	[3.25]	2.15 (15)	[3.48]
2-*trans*-4-*trans*					
Acid	DC	7.99	[3.15]	[3.05]	[3.20]
Ester	CCl_4	8.05	[3.32]	[3.18]	[3.38]

[a] Given as τ-values; coupling constants (c.p.s.) in parenthesis.
[b] Asterisk indicates data from mixtures of *cis* and *trans* forms.
[c] Pyr., pyridine; pip., piperidine; DC, deuteriochloroform.
[d] Assignment based on a doublet one maximum of which appears as a shoulder on the aromatic absorption maximum.
[e] Values in brackets are assigned arbitrarily.

only a broadening. The 2-*trans*-4-*trans* configuration (IVa) is assigned to the acid, m.p. 136–138°, on the basis of n.m.r. maxima at τ 7.62 (C-3 methyl, deshielded by *cis* carboxy), 7.70 (C-2 methyl), and 2.98 (J = 16 c.p.s.) (C-4 proton), and 3.31 (J = 16 c.p.s.) (C-5 proton). The splitting pattern of the τ 7.62 and 7.70 peaks is more complex than that in the 2-*cis* isomer. This suggests a more effective long-range coupling between the C-2 and C-3 methyl protons than was observed in the 2-*cis* isomer. The peak at τ 7.62 shows a more complex pattern than does that at 7.70 and on this basis is assigned to the 3-methyl group split by coupling with both the C-2 methyl and C-4 proton. The peak at τ 2.98 is based on a shoulder on an aromatic absorption maxima and is not as clear as the doublet at τ 3.31.

Data from mixtures of the esters permit the following assignments for the esters (IVa and Va, R′ = C_2H_5). Peaks in the olefinic methyl region were observed at τ 8.04 (C-3 methyl of 2-*cis*), 8.09 (C-2 methyl of 2-*cis*), 7.87 (C-3 methyl of 2-*trans*), and 7.95 (C-2 methyl of 2-*trans*). The peak at τ 8.04 (C-3 methyl of 2-*cis*) in the ester corresponds to that at 8.02 for the acid in pyridine with little change. The peak at τ 7.87 (C-3 methyl in 2-*trans* ester) corresponds to that at 7.62 in the acid in pyridine with a shift of τ 0.25 comparable with that observed in the similar pair of isomeric esters and acids in the 3-methyl-5-phenyl series.[3]

The 3-methylene isomer (VIa) has not been separated from its isomers IVa and Va. It boils lower and thus could presumably be from mixtures with the other two. In unfractionated mixtures its presence is readily detected by the additional peaks all of which can be accounted for and assigned as follows: τ 8.65 (C-2 methyl protons), 6.51 (C-2 proton), 4.79 (methylene proton cisoid to carbethoxy), 4.86 (methylene proton transoid to carbethoxy), and 3.32 (C-4 and C-5 protons, *trans*). As noted, the relative peak heights (or integrated areas) assigned to the C-3 methylenic protons determine the relative amount of this isomer present in the mixture.

Data available for the relative amounts of *cis*, *trans*, and methylene isomers formed in this 2,3-dimethyl series establish differences in comparison with the enynoic[4] and 3,4-dimethyl[5] series. Only in the 2,3-dimethyl and 2-methyl-3-phenyl[5] series has the ratio of 2-*cis* to 2-*trans* isomers exceeded 1. In the other series previously described more 2-*trans* than 2-*cis* was found in the unfractionated mixture of crude dehydration products.

In the 2-methyl-3-phenyl enynoic compounds, formation of 90% of the *cis* isomer was accounted for in terms of a possible E1 reaction *via* a benzylcarbonium ion at the 3-carbon. Since this possibility is lacking in the 2,3-dimethyl series, the slight preponderance of 2-*cis* isomer indicates that the E2 process can involve steric influences favoring 2-*cis* formation. Assuming that the reaction proceeds *via* an E2 mechanism in which the nature of the product is influenced by the formation of the least hindered bromozincate complex, formation of that configuration of the complex with the 2- and 3-methyl groups *cis* must be favored (VII favored over VIII). It is this configuration of the cyclic complex VII which gives on hydrolysis that stereoisomeric pair of hydroxy esters IX which leads to the 2-*cis* structure on dehydration. The conformation of this pair of hydroxy esters with *trans* hydroxyl hydrogen has the two methyl groups skew. This suggests, therefore, that the 2-methyl group involves more steric overlap when skew with the residue of the chain (R″, styryl) than does the carbalkoxy group similarly situated; or, alternatively, that the 3-methyl group involves more overlap when skew with the carbalkoxy group than it does with the 2-methyl group.

The data for 2-methyl-5-phenyl-2-*trans*-4-*trans* acid and its ester were obtained for comparison purposes and are recorded in Experimental.

The ability of the 2,3-dimethyl-5-phenyl-2-*trans*-4-*trans*-pentadienoic acid to inhibit the enzymatic incorporation of C^{14}-labeled acetate into cholesterol and to depress blood cholesterol levels in the rat have been reported elsewhere.[6] The samples used in the biochemical studies were prepared as described herein.

Experimental

Ultraviolet absorption measurements were made with a Beckman DK-2 recording spectrophotometer in Spectrograde solvents. The measurements for the isomeric α,β-unsaturated acids were made in methanol and in acidic (0.003 *N*) methanol. In methanol the spectra of the various 5-aryl acids showed hypsochromic shifts of 1–18 mμ with respect to those of the corresponding esters. The 18-mμ shift was observed for 2,3-dimethyl-5-(*p*-methoxyphenyl)-2-*trans*-4-*trans*-pentadienoic acid. In acidic methanol the absorption maxima occurred at nearly the same wave length (299.5–306.5 mμ except for the *p*-methoxy derivative) as did the maxima of the esters in methanol. Hypsochromic shifts for other α,β-unsaturated carboxylic acids have been reported to occur under similar conditions[7,8] and have been attributed to absorption by the anion of the acid. The 2-*cis* isomers showed maxima at 299.5 and 304.5 mμ, 2 mμ below those of the corresponding 2-*trans* isomers.

N.m.r. measurements were made with a Varian Associates HR-4302 high resolution spectrometer with a 60-Mc. oscillator with super stabilizer, field homogeneity control, and magnet coolant control. The calibrations were made by the side-band technique at several frequencies. Tetramethylsilane was used as an internal reference standard and the chemical shifts are given as τ-values.[9] Samples were examined in 10–15% concentration with pyridine or carbon tetrachloride as solvent. The infrared absorption measurements were made with a Baird double-beam recording spectrometer with sodium chloride optics in chloroform (5% solutions) or as potassium bromide pellets. Melting points are uncorrected.

Ethyl 2,3-Dimethyl-3-hydroxy-5-phenyl-4-pentenoate (IIa).—A solution of 7.30 g. (0.050 mole) of 4-phenyl-3-buten-2-one and 10.9 g. (0.060 mole) of ethyl α-bromopropionate in 65 ml. of dry benzene was added to 4.00 g. (0.062 mole) of dry, acid-etched zinc at a rate sufficient to keep the benzene gently refluxing. When the addition was completed, the reaction mixture was refluxed for 15 min., cooled, diluted with 50 ml. of ether, and decomposed by shaking with 6 ml. of glacial acetic acid in 100 ml. of water. After washing successively with water, saturated bicarbonate solution, and water, the organic phase was dried over anhydrous magnesium sulfate. A vacuum distillation of residual oil gave 10.6 g. (86%) of hydroxy ester, b.p. 112–119° (0.15–0.30 mm.). Redistillation of a portion of this material gave an almost colorless analytical sample, b.p. 109° (0.13 mm.), $n^{25}\mathrm{D}$ 1.5270. An infrared spectrum showed bands at 3520 (OH), 1706 (saturated C=O), 1179 (C–O–), and 971 cm.$^{-1}$ (*trans* –CH=CH–).

Anal. Calcd. for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.56; H, 8.18.

Ethyl 2,3-Dimethyl-5-phenyl-2,4-pentadienoate (IIIa).—The hydroxy ester above (13.2 g., 0.053 mole) was refluxed for 1 hr. with a solution of 0.50 g. of *p*-toluenesulfonic acid in 250 ml. of benzene. The theoretical volume of water (0.90 ml.) was collected in a Dean–Stark water trap. The reaction mixture was cooled, washed successively with water, saturated bicarbonate solution, and water, and dried over anhydrous magnesium sulfate. After removal of solvent, the reaction product was distilled *in vacuo* to yield 8.53 g. (70%) of the unsaturated ester, b.p. 100–112° (0.12–0.17 mm.), $n^{25}\mathrm{D}$ 1.5894–1.5918. Redistillation of a portion of this material gave an almost colorless analytical sample, b.p. 115° (0.20 mm.), $n^{25}\mathrm{D}$ 1.5938. An infrared spectrum (in $CHCl_3$) showed broad carbonyl absorption at 1700–1694, benzene ring absorption at 1600 and 1495, and *trans* –CH=CH– absorption at 959 cm.$^{-1}$; ultraviolet absorption: $\lambda_{\max}^{\mathrm{CH_3OH}}$ 298.5–300.5 mμ (ϵ 26,400), 234–235 (9500 sh), and 227 (10,900). The intensity of olefinic methyl proton absorption at τ 8.04 (C-3 methyl protons *trans* to carbethoxy) and 8.09 (C-2 methyl protons) showed that approximately 60% of the 2-*cis* isomer was present in the analytical sample. The 2-*trans* isomer was also shown to be present (40%) by absorption at τ 7.87 (C-3 methyl protons *cis* to carbethoxy) and 7.95 (C-2 methyl protons).

Anal. Calcd. for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88. Found: C, 78.49; H, 7.87.

An n.m.r. analysis of the distilled, but unfractionated (b.p. 90–112° at 0.05 mm., $n^{24}\mathrm{D}$ 1.5851) ester obtained by *p*-toluenesulfonic acid dehydration of the Reformatsky reaction product showed that it contained approximately 45% of the 2-*cis*-4-*trans*, 30% of the 2-*trans*-4-*trans*, and 25% of the 3-methylene isomer formed by dehydration into the 3-methyl group of the hydroxy ester. The analysis was based on peak areas at τ 4.79 and 4.86 (C-3 methylene protons), 7.87 and 7.95 (C-3 methyl protons *cis* to carbethoxy, and C-2 methyl protons) of IVa, and 8.09 and 8.04 (C-2 methyl protons and C-3 methyl protons *trans* to carbethoxy) of Va.

2,3-Dimethyl-5-phenyl-2-*trans*-4-*trans*-pentadienoic Acid (IVa).—The unsaturated ester above (10.8 g., 0.048 mole) was saponified by refluxing for 2.5 hr. with a solution of 3.95 g. (0.070 mole) of potassium hydroxide in 40 ml. of methanol. Most of the methanol was removed under reduced pressure. The residue was diluted with 200 ml. of water. Unreacted ester was removed by extracting with ether. Acidification of the aqueous phase precipitated a pale yellow, oily acid which was extracted with ether. Removal of solvent left 7.45 g. (79%) of the crude, unsaturated acids. Recrystallization of the crude material from 25 ml. of nitromethane at 0° gave 3.84 g. (40%) of white crystalline acid,

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m.p. 73–105°. Partial evaporation during 2 days of a solution of 1.0 g. of the acid (m.p. 73–105°) in 20 ml. of cyclohexane provided a residue of numerous clusters of colorless needles which appeared to be growing out of small, round nodules of a white solid. By decanting the remaining solvent and evaporating the solvent from the residue with a stream of nitrogen, 0.20 g. of needles, m.p. 130–136°, was obtained by careful removal with a spatula. Additional recrystallization from hexane (EK-P1135) gave the analytical sample as colorless needles, m.p. 136–138°; infrared absorption (in KBr): 1667 (C═O), 1295 and 1245 (C–O–), 952 (*trans* –CH═CH–), and 748 and 686 cm.$^{-1}$ (monosubstituted phenyl group); ultraviolet absorption: $\lambda_{\max}^{0.003\,N\ \mathrm{H^+CH_3OH}}$ 301.5 mμ (ϵ 31,400) and 230 (10,100). N.m.r. absorption characteristics are given in Table I.

Anal. Calcd. for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 77.30; H, 6.89.

2,3-Dimethyl-5-phenyl-2-*cis*-4-*trans*-pentadienoic Acid (Va).—The small, round nodules of white solid (0.65 g., m.p. 96–123°) remaining after removal of the colorless needles (above) were collected and purified further by the mechanical removal of an additional small amount of colorless needles. Several recrystallizations from 50 ml. of hexane (EK-P1135) gave 0.38 g. of fine, fluffy, colorless needles, m.p. 130–131°; infrared absorption (in KBr): 1642 (C═O), 1299 (w), 1278 (w), and 1241 (s) (C—O), 971 (*trans* –CH═CH–), and 751 and 690 cm.$^{-1}$ (monosubstituted phenyl group); ultraviolet absorption: $\lambda_{\max}^{0.003\,N\ \mathrm{H^+CH_3OH}}$ 299.5 mμ (ϵ 29,000) and 229–230 (13,700). N.m.r. absorption characteristics are given in Table I.

Anal. Calcd. for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 77.10; H, 6.83.

Ethyl 2,3-Dimethyl-3-hydroxy-5-(*p*-tolyl)-4-pentenoate (IIb).—The hydroxy ester (b.p. 128–130° at 0.15 mm., $n^{24}\mathrm{D}$ 1.5314) was prepared in 74% yield from 4-(*p*-tolyl)-3-buten-2-one (11.2 g., 0.070 mole), ethyl α-bromopropionate (15.2 g., 0.084 mole), and zinc (5.65 g., 0.086 g.-atom). The ketone (Ib, b.p. 90–95° at 0.30 mm.) was prepared in 79% yield from *p*-tolualdehyde and acetone according to the procedure described previously[10] for 4-phenyl-3-buten-2-one. An infrared spectrum of the hydroxy ester (in $CHCl_3$) showed bands at 3510 (OH), 1709 (saturated C═O), 1181 (C-O-), and 973 cm.$^{-1}$ (*trans* –CH═CH–). The analysis indicates partial dehydration.

Anal. Calcd. for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 74.11; H, 8.29.

Ethyl 2,3-Dimethyl-5-(*p*-tolyl)-2,4-pentadienoate (IIIb).—A *p*-toluenesulfonic acid dehydration of the hydroxy ester above (13.1 g., 0.050 mole) according to the procedure described previously gave 6.62 g. (54%) of the crude unsaturated ester, b.p. 97–127° (0.05–0.12 mm.), $n^{24}\mathrm{D}$ 1.5800–1.5893. Redistillation of a portion of this material gave a nearly colorless analytical sample, b.p. 123–126° (0.12 mm.), $n^{24}\mathrm{D}$ 1.5893. An infrared spectrum (in $CHCl_3$) showed bands at 1698–1689 (C═O), 1297 and 1236 (C-O–), and 961 cm.$^{-1}$ (*trans*-CH═CH–); ultraviolet absorption: $\lambda_{\max}^{\mathrm{CH_3OH}}$ 306–308 mμ (ϵ 25,600), 238 (11,100 sh), and 228–229 (13,100). N.m.r. absorption characteristics are given in Table I.

Anal. Calcd. for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.51; H, 8.24.

2,3-Dimethyl-5-(*p*-tolyl)-2-*trans*-4-*trans*-pentadienoic Acid (IVb).—Saponification of 9.68 g. (0.040 mole) of the unsaturated ester above with methanolic potassium hydroxide (3.35 g. in 50 ml.) gave the crude unsaturated acid (7.73 g., 90%). One recrystallization from nitromethane gave 3.06 g. (35%) of crystalline acid, m.p. 144–170°. Five additional recrystallizations from nitromethane gave the analytical sample as tiny, colorless flakes, m.p. 192–193°. An infrared spectrum (in KBr) showed bands at 1656 (α,β-unsaturated C═O), 1287 (s) and 1245 (s) (C—O), 956 (*trans* –CH═CH–), and 805 cm.$^{-1}$ (1,4-disubstituted phenyl group); ultraviolet absorption: $\lambda_{\max}^{0.003\,N\ \mathrm{H^+CH_3OH}}$ 306.5 mμ (ϵ 31,100) and 230 (9000). N.m.r. absorption characteristics are given in Table I.

Anal. Calcd. for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.63; H, 7.54.

2,3-Dimethyl-5-(*p*-tolyl)-2-*cis*-4-*trans*-pentadienoic Acid (Vb).—When the liquors from recrystallization of the crude acid above were cooled at −20° for 24 hr., 1.12 g. (13%) of crystalline acid, m.p. 143–156°, was collected. Fractional crystallization of this material from nitromethane gave 0.20 g. (2%) of colorless blades, m.p. 167.5–169°. An infrared spectrum (in KBr) showed bands in 1645 (α,β-unsaturated C═O), 1289 (w), 1271 (sh), and 1244 (s) (C-O–), 971 (*trans* –CH═CH–), and 810 cm.$^{-1}$ (1,4-disubstituted phenyl group); ultraviolet absorption: $\lambda_{\max}^{0.003\,N\ \mathrm{H^+CH_3OH}}$ 304.5 mμ (ϵ 31,400). N.m.r. absorption characteristics are given in Table I.

Anal. Calcd. for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.67; H, 7.50.

Ethyl 2,3-Dimethyl-5-(*p*-chlorophenyl)-2,4-pentadienoate (IIIc).—A Reformatsky reaction of 4-(*p*-chlorophenyl)-3-buten-2-one[11] (9.95 g., 0.055 mole), ethyl α-bromopropionate (12.0 g., 0.066 mole), and zinc (4.45 g., 0.068 g.-atom) gave the crude hydroxy ester, which was dehydrated directly with *p*-toluenesulfonic acid. After the usual work-up, the dehydration product was distilled *in vacuo* to yield 8.53 g. (59%), b.p. 113–134° (0.08–0.12 mm.), $n^{25}\mathrm{D}$ 1.5825–1.5929. Redistillation of a portion of this material gave an almost colorless analytical sample, b.p. 127° (0.08 mm.), $n^{25}\mathrm{D}$ 1.5880. An infrared spectrum showed bands at 1708 (α,β-unsaturated C═O), 1304 and 1238 (C-O–), and 963 cm.$^{-1}$ (*trans*-CH═CH–). N.m.r. absorption (in CCl_4) at τ 8.09 (C-2 methyl protons and C-3 methyl protons *trans* to carbethoxy) showed that the analytical sample contained approximately 60% of the 2-*cis* isomer. Absorption at τ 7.96 (C-3 methyl protons *cis* to carbethoxy) and at 8.00 (C-2 methyl protons) corresponded to approximately 40% of the 2-*trans* isomer. Additional n.m.r. data are given in Table I.

Anal. Calcd. for $C_{15}H_{17}ClO_2$: C, 68.05; H, 6.47. Found: C, 67.73; H, 6.66.

2,3-Dimethyl-5-(*p*-chlorophenyl)-2-*trans*-4-*trans*-pentadienoic Acid (IVc).—The unsaturated ester above (7.50 g., 0.028 mole) was saponified with 10% methanolic potassium hydroxide according to the procedure described previously. Recrystallization of the crude acid (5.0 g., 75%, m.p. 102–161°) from cyclohexane gave 0.63 g. (9%) of fluffy, colorless crystals, m.p. 190–199°. Additional recrystallization from cyclohexane raised the melting point to 199–200°. An infrared spectrum (in KBr) showed bands at 1667 (α,β-unsaturated C═O), 952 (*trans* –CH═CH–), and 816 cm.$^{-1}$ (1,4-disubstituted phenyl group); ultraviolet absorption: $\lambda_{\max}^{0.003\,N\ \mathrm{H^+CH_3OH}}$ 306 mμ (ϵ 32,100) and 228 (10,900).

Anal. Calcd. for $C_{13}H_{13}ClO_2$: C, 65.96; H, 5.54. Found: C, 65.83; H, 5.55.

Fractional crystallization of residues from the recrystallization liquors of the crude acid above gave an acid of m.p. 125–148°. N.m.r. absorption (in pyridine) at τ 7.84 (C-2 methyl protons) and 8.07 (C-3 methyl protons *trans* to carboxyl) showed that this acid contained approximately 85% of the 2-*cis* isomer (Vc). An infrared spectrum (in KBr) showed bands at 1652 (α,β-unsaturated C═O), 1295 and 1249 (C-O–), 971 (*trans* –CH═CH–), and 817 cm.$^{-1}$ (1,4-disubstituted phenyl group).

Ethyl 2,3-dimethyl-5-(*p*-methoxyphenyl)-2,4-pentadienoate (IIId).—A Reformatsky reaction of 4-(*p*-methoxyphenyl)-3-buten-2-one (13.2 g., 0.075 mole), ethyl α-bromopropionate (16.3 g., 0.090 mole), and zinc (6.05 g., 0.092 g.-atom) gave the crude hydroxy ester which was dehydrated directly with *p*-toluenesulfonic acid (0.50 g.) in benzene (250 ml.) to yield 6.97 g. (36%) of the unsaturated ester, b.p. 137–152° (0.04 mm.). The following fractions were collected: (1) 0.74 g., b.p. to 137° (0.04 mm.); (2) 4.50 g., b.p. 137–143° (0.04 mm.); (3) 1.70 g., b.p. 143° (0.04 mm.), $n^{25}\mathrm{D}$ 1.6073; and (4) 0.77 g., b.p. 143–152° (0.04 mm.). A sample of fraction 3 was analyzed. An infrared spectrum of fraction 3 (in $CHCl_3$) showed bands at 1705–1688 (C═O, broad), 1279 and 1253–1247 (C-O–), and 959 cm.$^{-1}$ (*trans* –CH═CH–); ultraviolet absorption (fraction 3): $\lambda_{\max}^{\mathrm{CH_3OH}}$ 320–322 mμ (ϵ 26,400) and 228–230 (10,200). N.m.r. absorption (in CCl_4) at τ 8.08 (C-2 methyl protons and C-3 methyl protons *cis* to carbethoxy) showed that the analytical sample contained approximately 60% of the 2-*cis* isomer. Absorption at τ 7.99 and 7.91 (C-2 and C-3 methyl protons *cis* to carbethoxy) can be attributed to approximately 40% of the 2-*trans* isomer.

Anal. Calcd. for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 73.56; H, 7.76.

2,3-Dimethyl-5-(*p*-methoxyphenyl)-2,4-pentadienoic Acid (Mixture of IVd and Vd).—A portion of the unsaturated ester (4.50 g., 0.017 mole, fraction 2 above) was saponified by refluxing for 2.5 hr. with a solution of 1.45 g. of potassium hydroxide in 20 ml. of methanol. The usual isolation procedure gave 2.82 g. (70%) of crude, yellow acid, m.p. 116–136°. Three recrystal-

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[10] C. S. Marvel and P. Allen, Jr., "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 77.

[11] R. E. Lutz, *et al.*, *J. Org. Chem.*, **14**, 982 (1949).

lizations of the crude acid from nitromethane gave pale yellow needles, m.p. 140–155°. N.m.r. absorption (in pyridine) at τ 8.02 (C-3 methyl protons *trans* to carboxyl) and 7.60 (C-3 methyl protons *cis* to carboxyl) showed that the analytical sample was a mixture containing approximately 65% of the 2-*cis* and 35% of the 2-*trans* isomers. Additional n.m.r. data are given in Table I.

Anal. Calcd. for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94; neut. equiv., 232. Found: C, 72.37; H, 6.96; neut. equiv., 234.

Repeated crystallization of the mixture of isomers above from nitromethane gave a few milligrams of pale yellow needles, m.p. 175–177° and 181–182°. Although no analytical data were obtained for this compound, n.m.r. absorption (in $CDCl_3$) at τ 7.88 (C-2 methyl protons) and 7.76 (C-3 methyl protons *cis* to carboxyl) showed that this acid was the pure 2-*trans* isomer; infrared absorption (in KBr): 1656 (α,β-unsaturated C=O), 1252 (C–O–), 1174 (CH_3O–), 957 (*trans* –CH=CH–), and 816 cm.$^{-1}$ (1,4-disubstituted phenyl group); ultraviolet absorption: $\lambda_{\max}^{0.003\ N\ \mathrm{H^+CH_3OH}}$ 321 mμ (ϵ 29,000) and 230–232 (10,100).

2-Methyl-5-phenyl-2-*trans*-4-*trans*-pentadienoic Acid.—A solution of 13.2 g. (0.100 mole) of freshly distilled cinnamaldehyde and 21.7 g. (0.120 mole) of ethyl α-bromopropionate in 60 ml. of dry tetrahydrofuran was added during 20 min. to 8.05 g. (0.123 mole) of dry, acid-etched zinc. The reaction mixture was refluxed for 35 min. The hydroxy ester was obtained crude according to the procedure described previously, and ester was dehydrated directly by refluxing for 2.5 hr. with a solution of 0.70 g. of *p*-toluenesulfonic acid in 250 ml. of benzene. The bicarbonate-washed reaction mixture was dried over anhydrous magnesium sulfate, the solvent was removed by distillation, and the dehydration product was distilled *in vacuo*, to give 17.29 g. (80%) of pale yellow oil, b.p. 112–124° (0.10 mm.), largely 123–124° (0.10 mm.). This unsaturated ester (17.1 g., 0.079 mole) was saponified by refluxing for 2.5 hr. with a solution of 6.65 g. (0.119 mole) of potassium hydroxide in 65 ml. of methanol. Mechanical stirring was necessary during this saponification owing to the separation of an insoluble, crystalline potassium salt. The potassium salt (14.25 g.) was collected, washed with ether, dried *in vacuo*, and acidified to precipitate 11.8 g. (80%) of acid, m.p. 156–159°. Three recrystallizations of a small portion of this material from benzene–cyclohexane gave colorless prisms, m.p. 159.5–161° (lit.[12] m.p. 157–158°). N.m.r. absorption characteristics are given in Table I.

2-Methyl-5-phenyl-2-*cis*-4-*trans*-pentadienoic Acid.—The liquors from the potassium salt above were diluted with 300 ml. of water, extracted with ether, and acidified to precipitate 2.23 g. (15%) of crude, pale yellow acid, m.p. 145–167°. One recrystallization of this acid from benzene–cyclohexane gave 1.50 g. (10%) of short, colorless needles, m.p. 173–175.5°. Two additional recrystallizations from benzene raised the melting point to 176–177°. N.m.r. absorption characteristics are given in Table I.

Anal. Calcd. for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.67; H, 6.54.

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[12] K. v. Auwers, *J. prakt. Chem.*, **105**, 361 (1923).

Alkylation of Ethyl, Isobornyl, and Menthyl Esters of 2-Methylbutanoic Acid

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Alkylation of ethyl 2-methylbutyrate with excess *n*-butyl bromide and sodium hydride in diglyme gave relatively good yields (38%) of ethyl 2-methyl-2-ethylhexanoate. To investigate the possibility of asymmetric induction in this alkylation reaction the isobornyl and menthyl esters of 2-methylbutyric acid were treated with *n*-butyl bromide–sodium hydride and the products were reduced with lithium aluminum hydride. The samples of 2-methyl-2-ethylhexan-1-ol produced, after purification by gas phase chromatography, were optically inactive (320 to 700 mμ).

Several general synthetic methods have been used to obtain various trialkylacetic acids.[1–3] Of these, perhaps the most direct method involves alkylation of a dialkylacetate ester using sodium amide[1] or sodium triphenylmethide.[4] We have recently required an optically active trialkyl-substituted acetic acid of known configuration. Since there are few examples[5] of such resolved or partially resolved compounds, and the syntheses involved are lengthy, we have looked at the alkylation reaction as a means of easily obtaining a *dl*-trialkylacetic acid. As a potential means of assigning absolute configuration to such acids, we have investigated the possibility of asymmetric synthesis in alkylation of isobornyl and menthol esters of 2-methylbutyric acid.[6]

Results and Discussion

Excess *n*-butylbromide reacts in diglyme at 80° with ethyl 2-methylbutyrate in the presence of sodium hydride to give a 38% yield of ethyl 2-methyl-2-ethylhexanoate. Although the reaction is slow and several additions of sodium hydride and *n*-butyl bromide are necessary, the method is simpler and more convenient

[1] See C. R. Hauser and W. J. Chambers, *J. Am. Chem. Soc.*, **78**, 3837 (1956), for a comparison of methods and references.

[2] G. L. Goerner and A. A. Holzschuh, *J. Org. Chem.*, **23**, 1346 (1958).

[3] H. Koch and W. Haaf, *Ann.*, **618**, 251 (1958).

[4] B. E. Hudson, Jr., and C. R. Hauser, *J. Am. Chem. Soc.*, **62**, 2456 (1940).

[5] W. von E. Doering and K. B. Wiberg, *ibid.*, **72**, 2608 (1950).

[6] Esters of this acid have deficiencies in any attempt to demonstrate asymmetric alkylation at the α-carbon since the small difference in sizes of methyl and ethyl groups minimizes differences in steric effects. This acid was chosen because the product acid, 2-methyl-2-ethylhexanoic acid, by degradation, could be configurationally related to 3-methyl-3-heptanol[7] and because of possible (but as yet unsuccessful) resolution by vapor phase chromatography of the relatively volatile diastereomers of Ib and c and IIb and c.[8]

[7] K. B. Wiberg and G. Foster, *J. Am. Chem. Soc.*, **83**, 423 (1961).

[8] See E. Gil-Av and D. Nurok, *Proc. Chem. Soc.*, 146 (1962).