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: $\lambda_{max}^{0.003\ N\ H^+CH_3OH}$ 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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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).

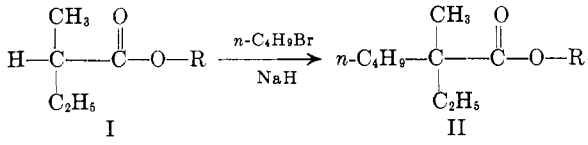
(4) B. E. Hudson, Jr., and C. R. Hauser, *J. Am. Chem. Soc.*, **62**, 2456 (1940).

(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).



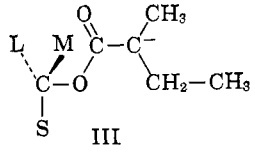
a, R = C_2H_5
b, R = (−)-isobornyl
c, R = (−)-menthyl

than methods involving other alkylation conditions and reagents.

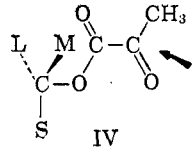
Attempts to obtain better yields by use of benzene or ether mixed with the carbanion activating agent, dimethyl sulfoxide,[9,10] as solvents gave lower yields of product accompanied by side products more difficult to remove. Since enhanced reactivity of enolates in alkylation reactions using glyme or diglyme has been noted,[11] diglyme was used in further alkylation runs.

The isobornyl and menthol esters of 2-methylbutyric acid were alkylated with *n*-butyl bromide–sodium hydride in diglyme. The progress of the alkylation was followed by v.p.c. analysis of reaction samples and intermittent addition of *n*-butyl bromide and sodium hydride was shown to be necessary to complete the reaction. The alkylation of these esters required longer times and higher temperatures (100°) than did the ethyl ester. The main side products are the corresponding *n*-butyl ethers of menthol or isoborneol.

This reaction of *n*-butyl bromide with the enolate anion of optically active methylethylacetate esters bears some resemblance to the asymmetric addition of Grignard reagents to α-keto esters.[12] Both reactions involve the bonding of an alkyl group to a trigonal carbon atom situated the same number of atoms away from an asymmetric group. The reactants for the two reactions are represented as III and IV, respectively.



III



IV

With the assumptions that the two carbonyl groups of the α-keto ester prefer a *trans* orientation and that the orientation of the large (L), medium (M), and small (S) groups control the approach of reagent as shown in IV, Prelog was able to predict the configuration of the α-hydroxy ester obtained in the Grignard reaction. In either the alkylation of an enolate anion (III) or the Grignard reaction of an α-keto ester (IV) the –O–CO– grouping has separated the reaction center from the asymmetric center by a distance greater than present between these centers in some similar reactions[13] which occur with asymmetric induction. However, the results of McKenzie and of Prelog show that this greater distance, while probably decreasing the influence of the centers on each other, still does not completely eliminate steric effects leading to asymmetric induction.[14] Since even a small difference in free energy of activation leads to a relatively large per cent of asymmetric synthesis,[12] it was possible that some model similar to that of Prelog and Cram would be applicable to alkylation reactions.

The possibility of asymmetric induction in this alkylation reaction was checked as follows. The trialkyl esters (IIb and IIc) were each obtained from the alkylation reaction in 40% yield and were characterized by v.p.c. retention times and infrared spectral comparisons with authentic isobornyl or menthyl 2-methyl-2-ethylhexanoates prepared separately from 2-methyl-2-ethylhexanoyl chloride and the two optically active alcohols. The menthol ester IIc is inert to hearty acidic or basic hydrolysis conditions but was cleaved with sodium amide in diglyme at 150°. The amide formed yielded 2-methyl-2-ethylhexanoic acid in low yield on reaction with *n*-butyl nitrite and hydrogen chloride. This difficulty in obtaining sufficient pure acid in order to check for optical activity required a more direct way to obtain a readily purified derivative of the acid moiety of the menthol and isobornyl esters. The esters were reduced with lithium aluminum hydride to yield samples of 2-methyl-2-ethylhexanol. These were subjected to thorough purification by v.p.c. to remove traces of optically active impurities. The resulting samples of alcohol from both esters were optically inactive over the range 320 to 700 mμ.

That butylation of menthyl and isobornyl esters of 2-methylbutyric acid followed by reduction gave 2-methyl-2-ethylhexan-1-ol with no observable rotation indicates that no appreciable asymmetric induction occurred.[15] The higher temperature (compared with that in Grignard addition reactions of α-keto esters) required to bring about the alkylation reaction tends to decrease the effect of a difference in free energy of activation leading to two products. The small difference in size of methyl and ethyl groups in enolate III, and therefore the small difference in free energy of various conformations in the reaction, is not sufficient to cause an asymmetric synthesis. The results only indicate no asymmetric influence of the alkoxyl portion of the esters on the formation of a new asymmetric center at the α-carbon and can not be used to indicate further stereochemical features of the alkylation reaction nor to predict the configuration of the products.

Experimental

Materials.—Sodium hydride was a 51% dispersion in mineral oil obtained from Metal Hydrides Incorporated. Diglyme (bis-2-methoxyethyl ether) was freshly distilled from lithium aluminum hydride or from sodium. (−)-Isoborneol, m.p. 213–214°, $[\alpha]^{26}D$ −29.06 (*c* 2.67, methanol), was prepared by reduction of (+)-camphor.[16] The menthol used had $[\alpha]^{26}D$ −40.8 (*c* 2.34, chloroform).

(9) H. E. Zaugg, B. W. Horrom, and S. Borgwardt, *J. Am. Chem. Soc.*, **82**, 2895 (1960).

(10) D. J. Cram, B. Rickborn, C. A. Kingsbury, and P. Haberfield, *ibid.*, **83**, 3678 (1961).

(11) H. D. Zook and T. J. Russo, *ibid.*, **82**, 1258 (1960).

(12) See V. Prelog, *Helv. Chim. Acta*, **396**, 308 (1953),; V. Prelog and H. L. Meier, *ibid.*, **36**, 320 (1953), and references to earlier work by A. McKenzie contained therein.

(13) D. J. Cram and F. Abd Elhafez, *J. Am. Chem. Soc.*, **74**, 5828 (1952).

(14) Equilibration studies involving enolate anion formation from bornyl and from menthyl esters of disubstituted acetic acids also show a preference for one diastereomer: A. McKenzie and I. A. Smith, *Ber.*, **58**, 894 (1925).

(15) The optical rotations arising from asymmetry around a quaternary carbon atom, as in 2-methyl-2-ethylhexan-1-ol, are expected to be small. However the rotation of a similar alcohol, 2,4-dimethyl-2-ethylpentan-1-ol, when 6.4% optically pure is $[\alpha]^{25}D$ +0.09. The rotation of 2-methyl-2-ethylhexan-1-ol should be great enough so that a sample low optical purity would show a measurable rotation. See J. H. Brewster, *J. Am. Chem. Soc.*, **81**, 5475 (1959), and W. von E. Doering, M. Farber, M. Sprecher, and K. B. Wiberg, *ibid.*, **74**, 3000 (1952).

(16) W. G. Brown, *ibid.*, **71**, 1645 (1949).

Ethyl 2-Methyl-2-ethylhexanoate.—Sodium hydride, 0.16 mole, was added to 75 ml. of magnetically stirred diglyme in a three-necked flask protected from atmospheric moisture and flushed with nitrogen. Twenty grams of ethyl 2-methylbutyrate (0.15 mole) and 32.5 ml. (0.30 mole) of 1-bromobutane were added simultaneously, and the temperature was then raised to 80°. Steady evolution of hydrogen occurred. Two further additions, each of 0.08 mole of sodium hydride and 0.075 mole of 1-bromobutane, were made at 24 and 48 hr., and the reaction was held at 80° for a total of 72 hr. After cooling, addition of 300 ml. of water and acidification with concentrated hydrochloric acid, the oil which separated was extracted into ether. The combined ether extracts were dried with magnesium sulfate and distilled, yielding 11.0 g. (38%) of ethyl 2-methyl-2-ethylhexanoate, b.p. 79–80° (10 mm.), lit.[17] b.p. 76–78° (8 mm.), which showed only one component by vapor phase chromatography (5-ft., 20% Apiezon J column at 190°) and was free from unalkylated ester.

Anal. Calcd. for $C_{11}H_{22}O_2$: C, 70.92; H, 11.90. Found: C, 71.09; H, 11.94.

This ester was hydrolyzed by heating at 110° in a potassium hydroxide 1:1 xylene–ethyleneglycol monoethyl ether mixture[17] and the acid was converted to acid chloride, b.p. 70–73° (10 mm.), by reaction with thionyl chloride.

Menthyl 2-Methyl-2-ethylhexanoate.—Menthol, 4.1 g., and 4.3 g. of 2-methyl-2-ethylhexanoyl chloride in 10 ml. of anhydrous pyridine were heated at 105° for 24 hr. The reaction mixture was dissolved in 50 ml. of petroleum ether (b.p. 30–60°) and extracted with 5% hydrochloric acid and then with 5% sodium bicarbonate. The petroleum ether layer was dried, then evaporated down, and the residue was passed through an alumina column (eluted with petroleum ether) to remove unreacted menthol. Evaporation and distillation gave 3.7 g. (48%) of menthyl 2-methyl-2-ethylhexanoate. The infrared spectrum of this compound showed peaks at 2945, 2855, 1717, 1460, and 1150 cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{36}O_2$: C, 76.97; H, 12.24. Found: C, 77.02; H, 11.75.

Isobornyl 2-Methyl-2-ethylhexanoate.—Reaction of isoborneol with 2-methyl-2-ethylhexanoyl chloride in pyridine according to the procedure outlined for the menthyl ester above, removal of excess isoborneol by fractional sublimation (40°, 1 mm.), and final distillation gave a 35% yield of isobornyl 2-methyl-2-ethylhexanoate, b.p. 129–130° (1 mm.). Vapor phase chromatography of this material on several columns showed only one peak. The infrared spectrum showed bands at 2960, 2885, 1725, 1465, and 1150 cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{34}O_2$: C, 77.50; H, 11.64. Found: C, 77.77; H, 11.28.

Menthyl 2-Methylbutyrate.—Equivalent quantities of menthol and 2-methylbutanoyl chloride in pyridine were maintained at 100 for 25 hr. Work-up was similar to that described above. Unreacted menthol was removed by passing the crude product through a column of alumina. Evaporation of solvent and distillation gave a center fraction (66% yields), b.p. 102–104 (1 mm.) of menthyl 2-methylbutyrate. This showed strong infrared absorption at 2930, 2860, 1725, 1460, 1185, and 1155 cm.$^{-1}$.

Anal. Calcd. for $C_{15}H_{28}O_2$: C, 74.95; H, 11.74. Found: C, 74.53; H, 11.84.

Isobornyl 2-Methylbutyrate.—Equivalent quantities of isoborneol and 2-methylbutanoyl chloride in pyridine were maintained at 85° for 48 hr. Work-up by extractions as outlined for the menthyl ester above followed by fractional sublimation (up to 95°, 2 mm.) several times to remove isobornyl and final distillation gave 50% yields of isobornyl 2-methylbutyrate, b.p. 100–101° (2 mm.). For analysis, a sample of this ester, free of a minor impurity, was obtained by gas chromatography on a 10-ft. 20% Carbowax 20 M on firebrick column at 80°. Infrared absorption peaks of this compound were at 2960, 2880, 1725, 1460, 1185, and 1155 cm.$^{-1}$.

Anal. Calcd. for $C_{15}H_{26}O_2$: C, 75.58; H, 10.99. Found: C, 75.39; H, 11.06.

Alkylation of Isobornyl 2-Methylbutyrate.—Sodium hydride, 2.0 g., washed free of mineral oil with anhydrous ether, was added to 30 ml. of diglyme followed by 7.5 g. of isobornyl 2-methylbutyrate and 8.6 g. of 1-bromobutane. The temperature was raised to 100 ± 5° and stirring was continued. After 24 hr. a sample was taken out for analysis and 8.6 g. of 1-bromobutane was added. Every 24 hr. thereafter a reaction sample was taken, 1.0 g. of sodium hydride and 13.0 g. of 1-bromobutane were added, and stirring and heating were continued at 100°. After a total of 120 hr., 69.2 g. of 1-bromobutane and 6.0 g. of sodium hydride and been added. The reaction was continued still another 24 hr.

The final reaction mixture (the samples for analysis were treated similarly except they were not distilled before analysis by v.p.c.) was hydrolyzed by slowly adding water (500 ml. for the reaction mixture) and acidifying with dilute sulfuric acid. Ether extraction, drying, evaporation of the ether, and removal of more volatile components by distillation at up to 165° (25 mm.) gave an initial separation. Final distillation at 120–130° (1 mm.) gave 3.8 g. (42%) of isobornyl 2-methyl-2-ethylhexanoate, with an infrared spectrum and v.p.c. retention time identical with an authentic sample.

Anal. Calcd. C, 77.51; H, 11.53.

The major component present in the distillate of the initial distillation was isolated by v.p.c. and shown to be isobornyl *n*-butyl ether by comparing retention times and infrared spectra with those of an authentic sample.

Alkylation of Menthyl 2-Methylbutyrate.—A procedure similar to that given above, but with 16.0 g. of menthyl 2-methylbutyrate, 3.4 g. of sodium hydride, free from mineral oil, and 17.6 g. of 1-bromobutane at 100°, was followed. At intervals of 16–20 hr., further additions of sodium hydride and 1-bromobutane were made until at 72 hr. 10.2 g. of sodium hydride and 88.0 g. of 1-bromobutane had been added. After 92 hr. the reaction was worked up as described for the isobornyl ester. The initial fraction of the distillation, b.p. 145–150° (20 mm.), was purified further by gas chromatography on a 10-ft. Carbowax 20 M column at 100°. The major component was identified as menthyl *n*-butyl ether by comparison with authentic material.

The second fraction, 8.3 g. (42%), distilled at 178–182° (20 mm.) and had an infrared spectrum identical with that of menthyl 2-methyl-2-ethylhexanoate. This ester is inert to basic hydrolysis (110° after 24 hr. with KOH in xylene–Cellosolve)[17] and acidic hydrolysis (50–50% v./v. concentrated hydrochloric acid–diglyme at 180° for 24 hr.) conditions, but reaction with sodium amide in diglyme at 150° for 4 hr. gave crude amide which yielded 2-methyl-2-ethylhexanoic acid (28% yield from ester) on reaction with *n*-butyl nitrite and dry HCl in benzene.[18]

2-Methyl-2-ethylhexan-1-ol.—A 3.8-g. sample of isobornyl 2-methyl-2-ethylhexanoate from the alkylation reaction was reduced with excess lithium aluminum hydride in refluxing ether over 24 hr. After normal acid hydrolysis and work-up, a mixture of isoborneol and product alcohol was obtained. These were separated by v.p.c. on a 5-ft. Apiezon J preparative column at 130°. After rechromatography on the same column, the optical rotation of this sample of 2-methyl-2-ethylhexan-1-ol was determined with an automatic polarimeter using a 0.5-cm. cell.[19] The observed rotation was 0.000 ± 0.001.[20] A sample, 0.5 ml. with 0.2 ml. of methanol in a 1-cm. cell, showed no optical rotation between 320 and 700 mμ.[21]

Anal. Calcd. for $C_9H_{20}O$: C, 74.93; H, 13.97. Found: C, 74.91; H, 14.32.

Similarly a 8.0-g. sample of menthyl 2-methyl-2-ethylhexanoate, from alkylation of menthyl ester, was reduced with lithium aluminum hydride. The observed rotation of the product alcohol, after separation by v.p.c. on a 10-ft. Apiezon J column at 160°, was 0.000 ± 0.001.[20] An O.R.D. measurement (320 to 700 mμ) showed no optical activity.[21]

Anal. Calcd. for $C_9H_{20}O$: C, 74.93; H, 13.97. Found: C, 74.99; H, 13.98.

Acknowledgment.—We thank the National Research Council of Canada and the Committee on Research, University of British Columbia, for support of this work.

(17) A. Brändström and I. Forsblad, *Arkiv Kemi*, **6**, 351 (1953).

(18) N. Sperber, D. Papa, and E. Schwenk *J. Am. Chem. Soc.*, **70**, 3091 (1948).

(19) A Bendix Ericsson ETL-NPL automatic polarimeter, type 143 A, with a mercury light source (5461 Å) was used.

(20) Maximum deviation in several measurements of the observed rotation at low rotational values for a solution of some optically active material.

(21) We thank Dr. W. A. Ayer, University of Alberta, for checking our samples for rotation by O.R.D. analysis.