

2-Benzyl-2,3-diphenylpropanol, X.—A butyl ether solution of 1 g. of VIII was reduced by the method previously described for VII. Evaporation of the ether left 0.68 g. of massive crystals, m. p. 99–101°. Crystallization from dilute ethanol gave 0.45 g., m. p. 101–103°. A mixture of this and the alcohol isolated from the ether preparation was fused, allowed to solidify and remelted at 103–105°.

The mother liquor from the ethanol crystallization gave a second crop, 0.10 g., m. p. 101–102°. This was converted into the acetate by the anhydride method, yield 0.06 g., m. p. 85–87° and 101–102°.

Summary

2-Benzyl-2,3-diphenylpropanol has been shown

to be a by-product in the production of benzyl phenethyl ether *via* sodium phenethyl oxide and benzyl chloride.

Two series of compounds have been carried from 2-benzyl-2,4-diphenylbutanonitrile and 2-benzyl-2,3-diphenylpropanonitrile through their amides and acids to the corresponding alcohols.

The reduction of highly hindered acids to alcohols by lithium aluminum hydride in boiling butyl ether has been described.

EVANSTON, ILLINOIS

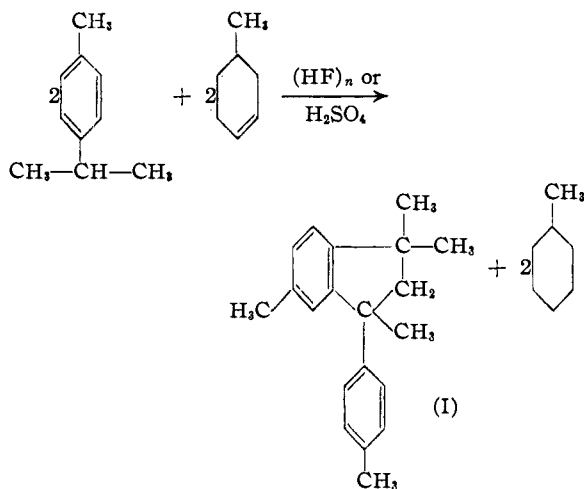
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[CONTRIBUTION FROM THE IPATIEFF HIGH PRESSURE AND CATALYTIC LABORATORY, DEPARTMENT OF CHEMISTRY, NORTHWESTERN UNIVERSITY]

Hydrogen Transfer. II. Reaction of Diisopropyltoluene and Isopropylcyclohexyltoluene with Methylcyclohexene¹

BY HERMAN PINES, ANNA WEIZMANN^{1a} AND V. N. IPATIEFF

In the previous paper of this series² it was shown that an abnormal reaction occurs when *p*-cymene (*p*-isopropyltoluene) is contacted, in the presence of sulfuric acid or hydrogen fluoride, with branched chain olefins, such as trimethyl-ethylene or with a substituted cyclohexene such as methylcyclohexene. Instead of only the expected alkylation and cycloalkylation, a hydrogen transfer was the main reaction causing the formation of the corresponding saturated hydrocarbons and 1,3,3,6-tetramethyl-1-*p*-tolylindan (I). The olefinic hydrocarbons acted as hydrogen acceptors while the *p*-cymene acted as a hydrogen donor. The reaction proceeded as follows



It was of interest to determine whether such a reaction would proceed also with a substituted *p*-

(1) This work was made possible in part by the financial assistance of Universal Oil Products Company.

(1a) Present address: Daniel Sieff Research Institute, Rehovoth, Israel.

(2) V. N. Ipatieff, H. Pines and R. C. Olberg, *THIS JOURNAL*, **70**, 2123 (1948).

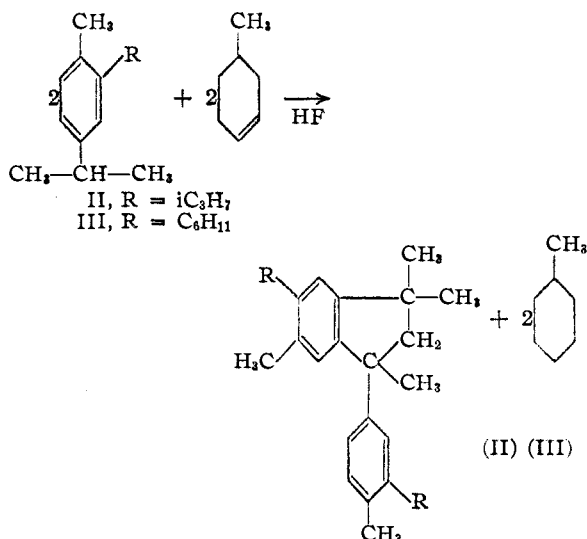
cymene. For that reason 2,4-diisopropyltoluene and 4-isopropyl-2-cyclohexyltoluene have now been prepared by the reaction of *p*-cymene with propene and cyclohexene, respectively, in the presence of sulfuric acid. The structure of the diisopropyltoluene was determined by comparing the infrared absorption spectra of this hydrocarbon with that of the hydrocarbon synthesized from 2-bromo-4-isopropyltoluene and acetone *via* the Grignard reaction. Both spectra were identical. The 2,4-dinitrophenylhydrazones of the acetyl compounds prepared from the two samples of diisopropyltoluene were identical.

The structure of cyclohexyl-*p*-cymene was not determined directly but, by comparison with diisopropyltoluene, it is fair to assume that this hydrocarbon is 2-cyclohexyl-4-isopropyltoluene. This was further substantiated by the fact that the tetranitrocompounds of the indans produced from the 2,4-diisopropyl- and 2-cyclohexyl-4-isopropyltoluene were identical.

The diisopropyltoluene and the cyclohexylisopropyltoluene were treated separately with methylcyclohexene in the presence of hydrogen fluoride at 0°. Hydrogen transfer occurred in each case; the products consisted of methylcyclohexane and 1,3,3,6-tetramethyl-5-isopropyl-1-(4-methyl-3-isopropylphenyl)-indan (II) and 1,3,3,6-tetramethyl-5-cyclohexyl-1-(4-methyl-3-cyclohexylphenyl)-indan (III). The hydrogen transfer was the primary reaction and amounted to about 60–70% of the total reaction. Part of the substituted *p*-cymene seemed also to react with methylcyclohexene to form the addition product.

The hydrogen transfer reaction proceeded according to the equation shown.

Compound II melted at 79.5° and analyzed as $C_{26}H_{36}$. On nitration under controlled conditions it yielded a dinitroderivative melting at 115–116° and corresponding to 1,3,3,6-tetramethyl-5-nitro-



1-(4-methyl-3-nitrophenyl)-indan (IV); the two isopropyl groups were replaced by nitro groups. A tetranitro derivative melting at 251° was also obtained, corresponding to 1,3,3,6-tetramethyl-5,7-dinitro-1-(4-methyl-3,5-dinitrophenyl)-indan (V). These nitro compounds were identical with those obtained previously by known synthetic procedure.²

Compound III on nitration yielded also a tetranitroderivative identical with Compound V. On a mild nitration a dinitroderivative was obtained melting at 162 – 163° and corresponding to $\text{C}_{26}\text{H}_{33}\text{N}_2\text{O}_4$. During the nitration only one of the cyclohexyl groups was replaced by a nitro group,³ yielding most probably a compound corresponding to 1,3,3,6-tetramethyl-5-nitro-1-(4-methyl-3-cyclohexyl-5-nitrophenyl)-indan (VI). The results obtained are summarized by the equations.

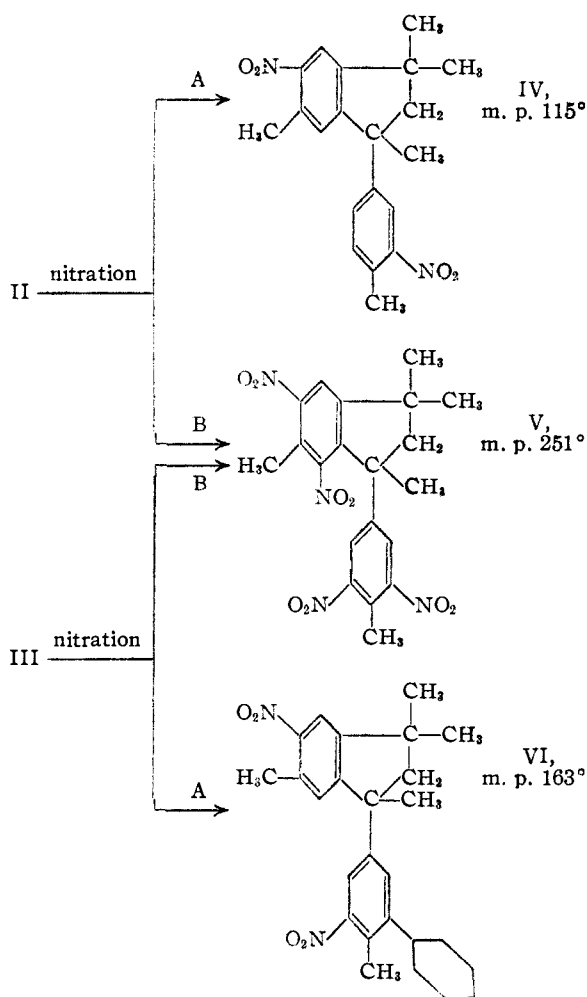
Experimental Part

Preparation of Diisopropyltoluene.—The procedure was the same as described previously.⁴ Reagents used: *p*-cymene, 536 g. (4 moles); propene, 135 g. (3.2 moles); sulfuric acid (96%), 135 g. The reaction temperature was maintained at 8 – 10° ; the time of addition of propene was four and one-half hours. The product obtained from the reaction consisted of two layers, the upper weighing 654 g. and the lower weighing 145 g. The upper layer was treated twice with 60-ml. portions of 96% sulfuric acid in order to remove any diisopropyl sulfate present, washed, dried and distilled. About 55% or 2.2 moles of *p*-cymene was recovered unchanged. Two hundred and seventy grams (1.5 moles) of crude diisopropyltoluene was produced boiling at 152 – 168° (95 mm.) and amounting to 85 mole per cent. of *p*-cymene reacted. The crude diisopropyltoluene was redistilled, 80% distilled at 80 – 82° (7 mm.), n_D^{20} 1.4959, d_4^{20} 0.8656. This material was identical, according to infrared and solid derivatives, with 2,4-diisopropyltoluene synthesized from 2-bromo-4-isopropyltoluene and acetone *via* a Grignard reaction.

1-Methyl-2,4-diisopropyl-*x*-acetylbenzene.—2,4-Diisopropyltoluene (5.2 g., b. p. 80 – 82° (7 mm.)) was added at

(3) The replacement of substituents in an aromatic ring by a nitro group was recently reviewed by D. Nightingale, *Chem. Revs.*, **40**, 117 (1947).

(4) V. N. Ipatieff, B. B. Corson and H. Pines, *THIS JOURNAL*, **58**, 919 (1936).



0° to a mixture consisting of 2.6 g. of acetyl chloride, 4.4 g. of aluminum chloride and 15 ml. of carbon disulfide. The solution, after being allowed to stand for fifteen minutes, was poured onto ice, washed with hydrochloric acid, water, aqueous solution of sodium carbonate, water, and dried over sodium sulfate. 4.8 g. of the ketone was obtained which distilled at 106° (3 mm.), n_D^{20} 1.5178.

The ketone formed a solid 2,4-dinitrophenylhydrazone, which after two crystallizations from 75% ethanol containing a few drops of pyridine, yielded yellow needles which softened at 160° and melted at 162 – 163° .

Anal. Calcd. for $\text{C}_{21}\text{H}_{25}\text{N}_2\text{O}_4$: N, 14.1. Found: N, 14.6.

It did not depress the melting point of the dinitrophenylhydrazone of the ketone from an authentic sample of 2,4-diisopropyltoluene.

Synthesis of 2,4-Diisopropyltoluene.—2-Bromo-4-isopropyltoluene was prepared according to the method of Bogert and Tuttle⁵ from 537 g. (4 moles) of *p*-cymene, 704 g. (4.4 moles) of bromine and 7 g. of iron powder. 2-Bromo-4-isopropyltoluene (554 g., 2.6 moles) was obtained, b. p. 99° (9 mm.), n_D^{20} 1.5360, yield 65%.

Anal. Calcd. for $\text{C}_{10}\text{H}_{13}\text{Br}$: C, 56.34; H, 6.13. Found: C, 56.28; H, 6.37.

Dimethyl-(2-methyl-4-isopropylphenyl)-carbinol.—The carbinol was synthesized by the usual procedure *via* a Grignard reagent from 64 g. (0.3 mole) of 2-bromo-4-isopropyltoluene, 7.2 g. (0.3 mole) of magnesium and 17 g.

(5) M. T. Bogert and J. R. Tuttle, *ibid.*, **35**, 1352 (1916).

(0.35 mole) of acetone. The yield of carbinol was 24 g. (40%), b. p. 106° (6 mm.), n_D^{20} 1.5159, d_4^{20} 0.9578.

Anal. Calcd. for $C_{12}H_{20}O$: C, 81.25; H, 10.41. Found: C, 80.91; H, 10.68.

2-Isopropenyl-4-isopropyltoluene.—The carbinol (9 g.) was dissolved in 20 ml. of benzene and refluxed one and one-half hours in the presence of 0.5 g. of oxalic acid. The product was washed with a 5% aqueous solution of sodium hydroxide, dried and distilled. The 2-isopropenyl-4-isopropyltoluene distilled at 64° (3 mm.), n_D^{20} 1.5100, d_4^{20} 0.8856.

Anal. Calcd. for $C_{12}H_{18}$: C, 89.59; H, 10.41. Found: C, 89.57; H, 10.28.

2,4-Diisopropyltoluene.—2-Isopropenyl-4-isopropyltoluene (5 g.) was dissolved in 5 ml. of pentane and hydrogenated at 40° in the presence of 0.4 g. of a nickel catalyst⁶ and under 50 atmospheres of hydrogen pressure. One mole of hydrogen was absorbed per mole of hydrocarbon charged. The 2,4-diisopropyltoluene formed distilled at 82° (7 mm.), n_D^{20} 1.4912, d_4^{20} 0.8636.

Anal. Calcd. for $C_{12}H_{20}$: C, 88.56; H, 11.44. Found: C, 88.76; H, 11.54.

1-Methyl-2,4-diisopropyl-x-acetylbenzene.—2,4-Diisopropyltoluene (1 g.) was added to a cold mixture of 0.5 g. of acetyl chloride, 0.8 g. of aluminum chloride and 5 ml. of carbon disulfide; the product was hydrolyzed, washed and dried.

The 2,4-dinitrophenylhydrazone of the ketone melted at 160–162°.

Preparation of 4-Isopropyl-2-cyclohexyltoluene.—Cyclohexene (125 g., 1.5 moles) was added over a period of three hours to an agitated mixture consisting of 268 g. (2 moles) of *p*-cymene and 75 g. of 96% sulfuric acid. The reaction was maintained at 0–5°. The upper layer amounting to 385 g. was washed with 20 ml. of 96% sulfuric acid, followed by a washing with water, dilute sodium hydroxide solution, and again with water. The product from the reaction (375 g.) was distilled through a column of 10–12 plate efficiency. From the distillation 175 g. of *p*-cymene and 102 g. (0.47 mole) of 2-cyclohexyl-*p*-cymene, b. p. 97–98° (2 mm.), n_D^{20} 1.5195, was obtained.

Anal. Calcd. for $C_{16}H_{24}$: C, 88.82; H, 11.18. Found: C, 89.03; H, 11.28.

1-Methyl-2-cyclohexyl-4-isopropyl-x-acetylbenzene.—The ketone was prepared from 0.5 g. of the hydrocarbon. The 2,4-dinitrophenylhydrazone of the ketone melted at 169–170°; it consisted of a powder.

Anal. Calcd. for $C_{24}H_{34}O_4N_4$: N, 12.83. Found: N, 12.70.

Dicyclohexyl-*p*-cymene.—The higher boiling hydrocarbons remaining from the distillation of 4-isopropyl-2-cyclohexyltoluene were distilled through a column of about four theoretical plates. The dicyclohexyl-*p*-cymene (66 g., 0.22 mole) which was obtained distilled at 183° (5 mm.) and melted at 98°; after recrystallization from ethanol the melting point was raised to 106°.

Anal. Calcd. for $C_{22}H_{34}$: C, 88.52; H, 11.48. Found: C, 88.21; H, 11.52.

Reaction of 2,4-Diisopropyltoluene with Methylcyclohexene.—The apparatus consisted of a 250-ml. copper flask provided with a stirrer, dropping funnel and a thermocouple well. Twenty-five grams of hydrogen fluoride and 36 g. (0.2 mole) of diisopropyltoluene, b. p. 80–82° (7 mm.) were placed in the flask. The mixture was stirred and to it was added, over a period of half an hour, 10 g. (0.1 mole) of methylcyclohexene. The latter was prepared by the dehydration of 4-methylcyclohexanol over activated alumina at 350°. The temperature of the reaction was maintained at 3–10°; the contents of the flask was poured over ice pre-cooled to –60°. The hydrocarbon layer was separated, washed with a dilute solution of potassium hydroxide, followed by a water wash, and dried

over calcium chloride. The product did not contain any organic fluorides or olefinic hydrocarbons as indicated by its respective stability toward distillation and toward a 2% aqueous potassium permanganate solution. Thirty-eight grams of the product yielded on distillation the following fractions: (1) b. p. 99–101°, 6.2 g., n_D^{20} 1.4241; (2) 97–104° (42 mm.), 15.0 g., n_D^{20} 1.4953; (3) 104–117° (43 mm.), 2.8 g., n_D^{20} 1.4980; (4) 117–125° (40 mm.), 1.1 g., n_D^{20} 1.5028; (5) 125–147° (13 mm.), 1.5 g., n_D^{20} 1.5171; (6) residue 14.0 g., n_D^{20} 1.5397.

Cut 1 corresponds to methylcyclohexane. On dehydrogenation it yielded toluene.²

Cut 2 was recovered diisopropyltoluene.

Cut 5 was not investigated; according to physical constants it corresponds to a product resulting from the interaction of diisopropyltoluene with methylcyclohexene.

Cut 6: The residue was macerated with small amount of methanol. The methanol was decanted, and the sticky product which remained was crystallized from absolute alcohol to which was added a small quantity of acetone. Ten grams of crystals were obtained, which softened at 75° and melted at 76°. On recrystallization from absolute alcohol, the product melted at 79.5°. The yield of II amounted to 60% based on methylcyclohexene used in the reaction.

Anal. Calcd. for $C_{26}H_{40}$: C, 89.65; H, 10.35. Found: C, 89.55; H, 10.23.

Nitration A.—One gram of II was dissolved in 5 ml. of chloroform. The solution was cooled to 0° and to it was added 1.5 ml. of 96% sulfuric acid and 0.5 ml. of 72% nitric acid; the latter was added in three portions. The temperature was then raised to 20°. A crystalline nitroderivative was obtained, melting at 238–240°. After recrystallization from a solution of ethanol and chloroform, it melted at 250°; the melting point was not depressed when mixed with a known sample of compound V.²

The mother liquor from the nitration yielded a solid melting at 112–113°. After recrystallization from ethanol it melted at 115–116°. According to mixed melting point and analysis, it corresponds to compound IV.⁷

Anal. Calcd. for $C_{26}H_{33}N_2O_4$: C, 67.80; H, 6.21; N, 7.90. Found: C, 67.95; H, 6.38; N, 8.28.

Nitration B.—About 0.3 g. of II was nitrated with 5 ml. of a solution consisting of 1 vol. of 72% nitric acid and 2 vol. of 96% sulfuric acid. The mixture was heated for one minute at 60–70°. A solid nitro product was obtained, melting at 250° after crystallization from a solution of ethanol and chloroform. According to a mixed melting point the product corresponds to compound V.

Reaction of Cyclohexyl-*p*-cymene with Methylcyclohexene.—The procedure was similar to the one described above. The following reagents were used: 2-cyclohexyl-*p*-cymene (b. p. 97–98° (2 mm.)), 43 g. (0.2 mole); methylcyclohexene, 10 g. (0.1 mole); hydrogen fluoride, 25 g. The reaction product was distilled through a column of about 5–10 plate efficiency. The following fractions were collected: (1) 98–100°, 4.8 g., (2) 110–117° (2 mm.), 29.4 g., n_D^{20} 1.5179; (3) 117–174° (2 mm.), 1.0 g., n_D^{20} 1.5220; (4) 174–184° (2 mm.), 5.0 g., n_D^{20} 1.5330; (5) residue 11.2 g.

Cut 1 is completely saturated, corresponds to methylcyclohexane.

Cut 2 corresponds to unreacted cyclohexyl-*p*-cymene.

Cut 4 corresponds to a product of condensation of 1-methyl-4-isopropyl-2-cyclohexylbenzene with methylcyclohexene.

Anal. Calcd. for $C_{23}H_{36}$: C, 88.39; H, 11.61. Found: C, 88.48; H, 11.32.

Cut 5: The residue was distilled from a Claisen flask, 7.4 g. of a glass-like product boiling at 270° (4 mm.), was obtained which hardened on cooling. The powdered product melted at 52–53°. Unsuccessful attempts were made to recrystallize it from various solvents.

(6) V. N. Ipatieff and B. B. Corson, *Ind. Eng. Chem.*, **26**, 1838 (1934).

(7) 1,3,3,6-Tetramethyl-5-nitro-1-(4-methyl-3-nitrophenyl)-indan (compound IV) was prepared by controlled nitration of 1,3,3,6-tetramethyl-*p*-tolylindan; ref. 2.

Anal. Calcd. for $C_{32}H_{44}$: C, 89.71; H, 10.29. Found: C, 89.10; H, 10.63.

Nitration A.—The nitration of III was carried out in a chloroform solution as described above. A solid was obtained melting at 150–153°. After two crystallizations from ethanol-chloroform solution the melting point of the nitroderivative VI was 162–163°.

Anal. Calcd. for $C_{26}H_{33}N_2O_4$: C, 70.39; H, 7.55; N, 6.40. Found: C, 70.68; H, 7.37; N, 6.50.

Nitration B.—The hydrocarbon III was nitrated with a solution consisting of 2 vol. of 96% sulfuric acid and 1 vol. of 72% nitric acid. A tetranitroderivative was obtained melting at 251–252°, which was identical with compound V.

Anal. Calcd. for $C_{20}H_{20}N_4O_8$: C, 54.05; H, 4.50; N, 12.61. Found: C, 54.69; H, 4.71; N, 12.31.

Acknowledgment.—We are indebted to Patricia Craig and Nelda Mold for the microanalyses.

Summary

Isopropyl-*p*-cymene and cyclohexyl-*p*-cymene reacted with 3-methylcyclohexene in the presence

of hydrogen fluoride as a catalyst. Hydrogen transfer was the main reaction; the aromatic hydrocarbons acted as a hydrogen donor and methylcyclohexene as a hydrogen acceptor. The hydrogen transfer amounted to over 60 and 40%, respectively, based on methylcyclohexene charged.

The products obtained from the respective aromatic hydrocarbons through a hydrogen transfer were: 1,3,3,6-tetramethyl-5-isopropyl-1-(4-methyl-3-isopropylphenyl)-indan and 1,3,3,6-tetramethyl-5-cyclohexyl-1-(4-methyl-3-cyclohexylphenyl)-indan.

The structure of these compounds was proven by nitration and conversion to known nitro derivatives.

Part of the substituted *p*-cymene apparently reacted with methylcyclohexene to form the expected cycloalkylation product.

EVANSTON, ILLINOIS

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

Antispasmodics. I. Pyrrolidylalkyl Esters of Disubstituted Acetic Acids

BY H. G. KOLLOFF, JAMES H. HUNTER, E. H. WOODRUFF AND ROBERT BRUCE MOFFETT

In a search for new compounds which might have desirable spasmolytic activity, we have prepared a series of esters of β -(1-pyrrolidyl)-ethanol and γ -(1-pyrrolidyl)-propanol.

These esters were prepared by allowing the acid chloride of the requisite acid to react with the appropriate pyrrolidyl alkanol. β -(1-Pyrrolidyl)-ethanol has been reported¹ previously and γ -(1-pyrrolidyl)-propanol was made from pyrrolidine and trimethylene chlorohydrin. The acids used in making these esters were prepared by the methods indicated in Table I. In a few instances new intermediate malonic acids were isolated.

The free basic esters were isolated, characterized, and converted to their hydrochloride salts; when the hydrochlorides proved very difficult to crystallize the acid citrate salts were prepared instead. Some of these basic esters were further characterized by converting them to quaternary salts with various alkyl halides.

Preliminary pharmacological assays by Dr. Milton J. Vander Brook of our Department of Pharmacology indicate that the salts of β -(1-pyrrolidyl)-ethyl esters of phenyl- Δ^2 -cyclopentenyl-, phenyl- Δ^2 -cyclohexenyl-, phenylcyclopentyl-, phenylcyclohexenyl-, cyclopentyl-*n*-propyl-, cyclopentyl-*n*-butyl- and Δ^2 -cyclopentenyl- Δ^2 -cyclohexenyl-acetic acids, all have antispasmodic activity, of the order of one-eighth or better than that of atropine sulfate, when tested on isolated rabbit intestine stimulated with acetylcholine chloride. The corresponding γ -(1-pyrrolidyl)-propyl esters were less active. Further pharmacological investi-

gation of these compounds is in progress, and the results will be published elsewhere.

Experimental^{2,3}

γ -(1-Pyrrolidyl)-propanol.—To a hot solution of 507 g. of sodium hydroxide in 457 ml. of water was added 605 g. (8.5 moles) of pyrrolidine with stirring. To this was slowly added 1 kg. (10.6 moles) of trimethylene chlorohydrin. When the temperature had risen to 100° the mixture was allowed to cool to approximately 70°. After stirring for one-half hour and standing overnight the mixture was saturated with sodium hydroxide and extracted with benzene. After removing the solvent the product was distilled; b. p. 98° (18 mm.), n_D^{25} 1.4707.

Anal. Calcd. for $C_7H_{13}NO$: N, 10.84. Found: N, 10.43.

Diethyl Phenyl- Δ^2 -cyclohexenylmalonate.—To a solution of 48.4 g. (2.1 moles) of sodium in 800 ml. of absolute alcohol was added 236.3 g. (1 mole) of diethyl phenylmalonate,⁴ and then 254 g. (1.05 moles) of 1,2-dibromocyclohexane was slowly added with stirring at reflux temperature. After heating under reflux for six hours the reaction mixture was acidified with acetic acid and most of the solvent was removed by distillation. Water was added, the organic layer was separated, and distilled first from a Claisen flask and then through a 6-inch column packed with $\frac{1}{8}$ -inch glass helices. A yield of 174 g. (55%) of nearly colorless liquid, b. p. 126° (0.07 mm.), was obtained; n_D^{25} 1.5169; d_4^{25} 1.0933.

Anal. Calcd. for $C_{19}H_{24}O_4$: C, 72.13; H, 7.64. Found: C, 71.67; H, 7.64.

Phenyl- Δ^2 -cyclohexenylacetic Acid.—A solution of 68 g. (0.215 mole) of diethyl phenyl- Δ^2 -cyclohexenylmalonate and 75 g. of potassium hydroxide in 350 ml. of 95% ethanol was heated under reflux for six hours. Water was added

(2) Analyses by Mr. Harold Emerson and Staff of our Micro-analytical Laboratory.

(3) Melting points are uncorrected.

(4) "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 288.

(1) v. Braun, Braunsdorf and R ath, *Ber.*, **55**, 1666 (1922).