at the same locations as for VIII but with somewhat altered intensities. A 5.0 g. sample of the crude acid was heated under reflux for 1.5 hr. with 30 ml. of ethyl alcohol and 25.0 ml. of 1.72*N* aqueous KOH. The reaction mixture after dilution with water gave 1.25 g. of crude 2-phenylquinoxaline in the ether extract.

Oxidation of VIII. Compound VIII (10.0 g., 0.0273 mol.) was dissolved in 150 ml. of acetone and a saturated aqueous solution of $KMnO_4$ (170 ml. in all) was added in small portions, with shaking, until the color of the permanganate persisted for a few minutes. During this addition the reaction mixture warmed spontaneously to 35–40°. The precipitate which separated was filtered, was made into a slurry with water, and was acidified with hydrochloric acid. Sodium bisulfite was then added until the manganese dioxide dissolved. The resulting solution was filtered and the precipitate was washed well with water. The precipitate weighed 1.4 g. (23% yield calculated as 2-hydroxy-3-phenylquinoxaline) and after one recrystallization from methyl ethyl ketone had m.p. 244–245°. Recrystallization from methyl ethyl ketone and then from ethyl alcohol gave a very pale yellow product of m.p. 248.5–249.0°.

Anal. Calcd. for $C_{14}H_{10}N_2O$: C, 75.65; H, 4.54; N, 12.61. Found: C, 75.62; H, 4.60; N, 12.52. This compound is identified as 2-hydroxy-3-phenylquinoxaline and gave no depression of melting point with an authentic sample prepared[24] by condensation of *o*-phenylenediamine with benzoylformic acid.[25]

The acetone solution, from which the 2-hydroxy-3-phenylquinoxaline had been removed by filtration, upon evaporation deposited 2.44 g. (24% yield) of crude 2-phenylquinoxaline (m.p. *ca.* 76–78°) contaminated somewhat with 2-hydroxy-3-phenylquinoxaline.

To a solution of 2-phenylquinoxaline (0.56 g.) in 15 ml. of acetone was added a few drops of a saturated aqueous solution of $KMnO_4$. No color change was evident upon mixing at room temperature or even when the solution was boiled for a few minutes.

Acknowledgment. We are indebted to the National Aniline Division, Allied Chemical and Dye Corporation for gifts of the acetylenedicarboxylic acid monopotassium salt used in most of the present work.

ATLANTA 13, GA.

---

[24] J. Buraczewski and L. Marchlewski, *Ber.*, **34**, 4009 (1901).

[25] B. B. Corson *et al.*, *Org. Syntheses*, **Coll. Vol. I**, 244 (1941).

[CONTRIBUTION FROM WALKER LABORATORY, RENSSELAER POLYTECHNIC INSTITUTE]

Cyclopropyl Analogs of Hexestrol and Diethylstilbestrol[1,2]

JAMES G. BENNETT, JR.,[3] AND STANLEY C. BUNCE

Received July 23, 1959

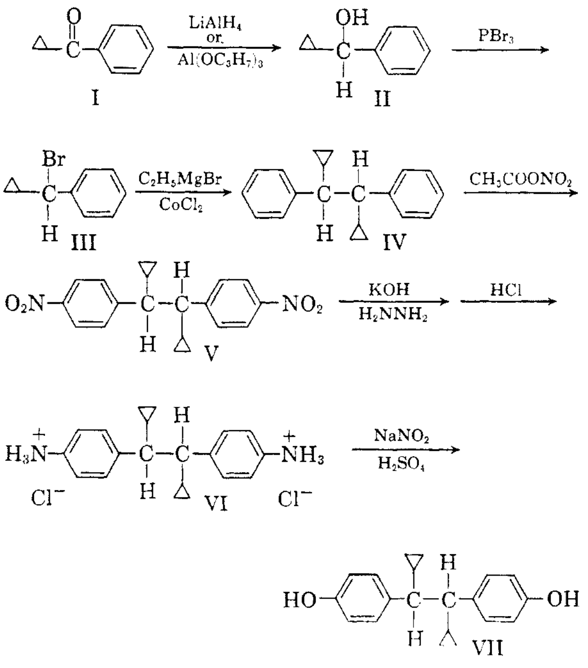
1,2-Dicyclopropyl-1,2-di-*p*-hydroxyphenylethane and 1,2-dicyclopropyl-1,2-di-*p*-anisylethylene, which are cyclopropyl analogs of hexestrol and of the dimethyl ether of diethylstilbestrol, have been prepared.

The purpose of this research was to investigate synthetic routes for the preparation of several cyclopropyl compounds which are structurally related to hexestrol, diethylstilbestrol, and estradiol, namely, 1,2-dicyclopropyl-1,2-di-*p*-hydroxyphenylethane (VII), 1,2-dicyclopropyl-1,2-di-*p*-hydroxyphenylethylene (XI), and 1,1′-di-*p*-hydroxyphenylbicyclopropyl.

The interest in these compounds lies in their possible estrogenic activity and possible action in relation to tumor initiation or cancer chemotherapy.

1,2-Dicyclopropyl-1,2-di-p-hydroxyphenylethane (VII) was successfully synthesized by the sequence of reactions illustrated in 1.1% over-all yield from γ-butyrolactone.

Cyclopropyl phenyl ketone (I), prepared from γ-butyrolactone by the method of Close,[4] was reduced to cyclopropylphenylcarbinol (II) by means of aluminum isopropoxide in 94% yield and also by means of lithium aluminum hydride[4] in 75% aver-



---

[1] Abstracted from the Ph.D. thesis of James G. Bennett, Jr., Rensselaer Polytechnic Institute, 1959.

[2] Presented before the Division of Organic Chemistry at the 135th National Meeting of the American Chemical Society, Boston, Mass., April 1959.

[3] Present address: Research Division, Parke, Davis & Co., Detroit, Mich.

[4] W. J. Close, *J. Am. Chem. Soc.*, **79**, 1455 (1957).

age yield. In several cases the hydride reduction led to the formation of cyclopropylphenylcarbinyl ether in yields up to 76%. Conversion of the carbinol to cyclopropylphenylcarbinyl bromide (III) in 84% average yield was accomplished using phosphorus tribromide at −15° without significant rearrangement. Cyclopropylphenylcarbinyl bromide was also prepared by reduction of cyclopropyl phenyl ketone to cyclopropylphenylmethane in 84% yield followed by bromination with *N*-bromosuccinimide in 31% yield (42% corrected for recovered hydrocarbon).

The preparation of cyclopropylphenylmethyllithium would permit several possible synthetic routes to dicyclopropyldiphenylethane derivatives. That two attempts to form the organolithium derivative from cyclopropylphenylmethane and *n*-butyllithium were unsuccessful was indicated by the recovery, in one case after carbonation and in another after attempted coupling using iodine, of 80 and 89% of the cyclopropylphenylmethane.

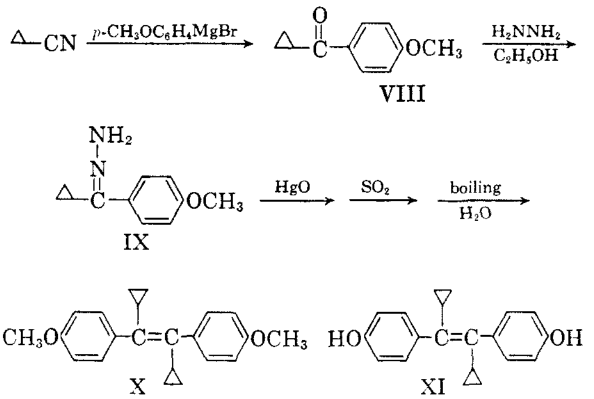
An attempt to prepare the sodium derivative of cyclopropylphenylmethane using *n*-amylsodium and to condense it with cyclopropyl phenyl ketone also gave cyclopropylphenylmethane (73% recovered) as the only identifiable product.

Nitration of cyclopropyl phenyl ketone using a mixture of sulfuric and nitric acids led to cyclopropyl *m*-nitrophenyl ketone in 35% yield.

The nitration of cyclopropylphenylmethane with sulfuric and nitric acids at 4° was unsuccessful; cyclopropylphenylmethane was found to polymerize in the presence of cold sulfuric acid. The reaction of the hydrocarbon with acetyl nitrate at 0° produced a crude material whose infrared spectrum indicated the presence of a nitro group, but attempted distillation led to sudden decomposition.

Cyclopropylphenylcarbinyl bromide was coupled using ethylmagnesium bromide and anhydrous cobaltous chloride to 1,2-dicyclopropyl-1,2-diphenylethane (IV) in 33% yield, following a modified coupling procedure of Wilds and McCormack.[5] Treatment of 1,2-dicyclopropyl-1,2-diphenylethane with acetyl nitrate gave a 22% yield of 1,2-dicyclopropyl-1,2-di-*p*-nitrophenylethane (V), which was reduced using hydrazine hydrate in diethylene glycol to 1,2-dicyclopropyl-1,2-di-*p*-aminophenylethane and isolated as the dihydrochloride (VI) in 95% average yield. Diazotization using 5% sulfuric acid and sodium nitrite followed by treatment with boiling water gave 1,2-dicyclopropyl-1,2-di-*p*-hydroxyphenylethane (VII) in 19% yield.

1,2-Dicyclopropyl-1,2-di-p-anisylethylene (X) was prepared by the sequence of reactions shown below in 0.5% over-all yield from 1-bromo-3-chloropropane. No successful method of demethylation was devised.



Cyclopropyl phenyl ketone was selected as a model compound to investigate the hydrazone oxidation and coupling[6,7] since it was more readily prepared. Cyclopropyl phenyl ketone was converted to its hydrazone by treatment with excess hydrazine in absolute ethanol in 94% average yield. The hydrazone was oxidized using freshly prepared mercuric oxide to obtain cyclopropylphenyldiazomethane which was not isolated but treated in solution with anhydrous sulfur dioxide to yield a sulfone according to the procedure of Staudinger and Pfennenger.[6] The sulfone was not isolated but immediately decomposed with boiling water to obtain 1,2-dicyclopropyl-1,2-diphenylethylene in an average yield of 39%.

p-Methoxyacetophenone was selected as a model compound containing *p*-methoxy substituents to undergo this series of reactions with the intent to find reaction conditions suitable to give the highest yield of 1,2-dicyclopropyl-1,2-di-*p*-anisylethylene. The hydrazone of *p*-methoxyacetophenone was prepared in 87% yield; attempts to prepare 1,2-dimethyl-1,2-di-*p*-anisylethylene from this hydrazone[8] led to the isolation of the azine of *p*-methoxyacetophenone in 0.5–16% yield and to the olefin, only in one case, in 2.0% yield.

These reactions were then applied to cyclopropyl *p*-anisyl ketone (VIII), obtained from the reaction of cyclopropanecarbonitrile and *p*-anisylmagnesium bromide in 71% average yield. Upon attempting to prepare the hydrazone of cyclopropyl *p*-anisyl ketone a liquid was obtained from which no solid material could be isolated. Partial crystallization of a subsequent preparation of the hydrazone permitted the isolation of small amounts of the pure hydrazone (IX) and also of the azine of cyclopropyl *p*-anisyl ketone. Distillation of the crude liquid hydrazone led only to the isolation of the azine. Oki and Urushibara[8] have reported difficulty in obtaining the pure hydrazone of *p*-methoxybutyrophenone. When the crude

---

[5] A. L. Wilds and W. B. McCormack, *J. Org. Chem.*, **14**, 45 (1949).

[6] H. Staudinger and F. P. Pfenninger, *Ber.*, **49**, 1941 (1916).

[7] L. I. Smith and K. L. Howard, *Org. Syntheses*, **Coll. Vol. III**, 351 (1955).

[8] M. Oki and Y. Urushibara, *Bull. Chem. Soc. Japan*, **25**, 109 (1952).

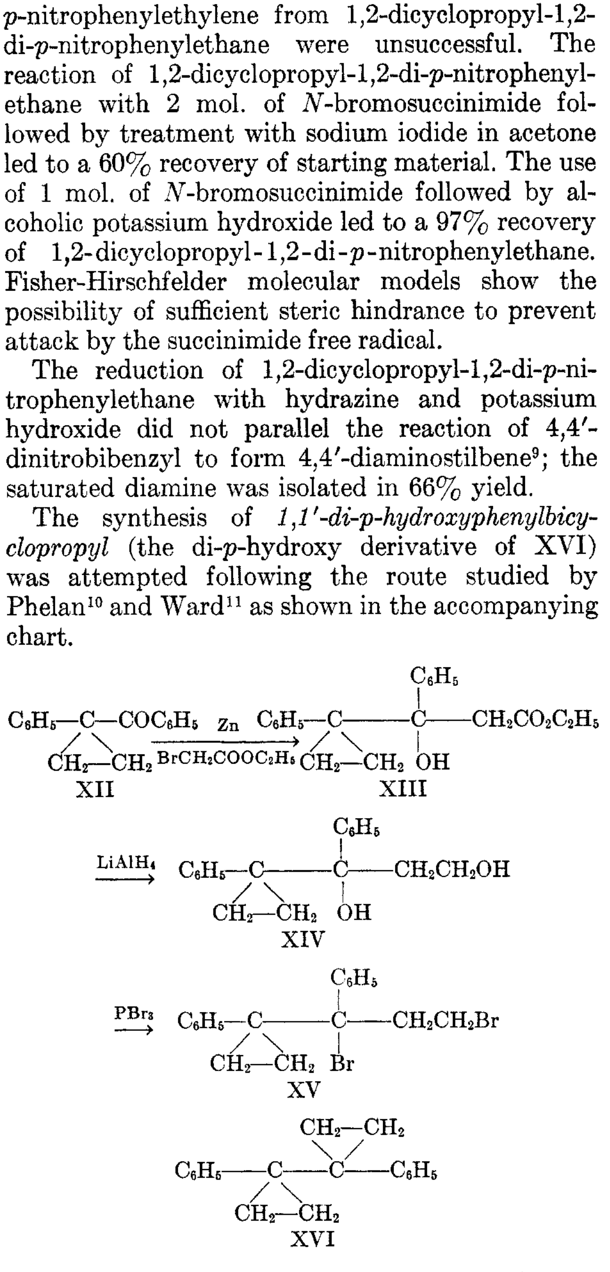
liquid hydrazone was treated with mercuric oxide followed by sulfur dioxide and boiling water, 1,2-dicyclopropyl-1,2-di-*p*-anisylethylene (X) was obtained in yields from 2 to 4%.

Difficulties were encountered in attempting to demethylate 1,2-dicyclopropyl-1,2-di-*p*-anisylethylene by heating with potassium hydroxide in ethanol. Due to the lack of sufficient material further demethylations were not attempted.

Attempts to prepare 1,2-dicyclopropyl-1,2-di-*p*-nitrophenylethylene from 1,2-dicyclopropyl-1,2-di-*p*-nitrophenylethane were unsuccessful. The reaction of 1,2-dicyclopropyl-1,2-di-*p*-nitrophenylethane with 2 mol. of *N*-bromosuccinimide followed by treatment with sodium iodide in acetone led to a 60% recovery of starting material. The use of 1 mol. of *N*-bromosuccinimide followed by alcoholic potassium hydroxide led to a 97% recovery of 1,2-dicyclopropyl-1,2-di-*p*-nitrophenylethane. Fisher-Hirschfelder molecular models show the possibility of sufficient steric hindrance to prevent attack by the succinimide free radical.

The reduction of 1,2-dicyclopropyl-1,2-di-*p*-nitrophenylethane with hydrazine and potassium hydroxide did not parallel the reaction of 4,4′-dinitrobibenzyl to form 4,4′-diaminostilbene[9]; the saturated diamine was isolated in 66% yield.

The synthesis of *1,1′-di-p-hydroxyphenylbicyclopropyl* (the di-*p*-hydroxy derivative of XVI) was attempted following the route studied by Phelan[10] and Ward[11] as shown in the accompanying chart.



XII XIII XIV XV XVI

1-Phenylcyclopropyl phenyl ketone (XII), underwent a Reformatsky reaction with zinc and ethyl bromoacetate to yield ethyl 3-hydroxy-3-phenyl-3-(1-phenylcyclopropyl)propionate (XIII) in 25% yield or a 58% yield based upon unrecovered ketone. Reduction of the ester to 1-phenyl-1-(1-phenylcyclopropyl)propane-1,3-diol (XIV) in 90% average yield was accomplished using lithium aluminum hydride. Reaction of the diol with phosphorus tribromide in ether gave a material from which a compound, m.p. 75.3–75.7°, was isolated in low yield. This compound, tentatively assigned the structure of 1,3-dibromo-1-phenyl-1-(1-phenylcyclopropyl)propane (XV), gave a positive test with alcoholic silver nitrate. From the reaction of the diol with phosphorus tribromide in methylene chloride a compound was obtained, m.p. 145.3–145.9°, which gave a negative test with alcoholic silver nitrate and also analyzed correctly for the dibromide. Both compounds contain a cyclopropane ring and give similar infrared and ultraviolet spectra. The structure of the second compound, which appears not to be isomorphous with the first, is not known. Attempts to close the second cyclopropane ring using crude dibromide with zinc dust and *n*-propyl alcohol led to the isolation of a small amount of liquid material believed to be impure 1,1′-diphenylbicyclopropyl (XVI). Attempted nitration gave no identifiable product.

The structures for all of the compounds presented are verified by infrared data obtained using a Perkin-Elmer Model 21 double-beam recording infrared spectrometer equipped with a sodium chloride prism. The carbon-hydrogen region was further investigated using a Perkin-Elmer Model 12B single-beam recording infrared spectrometer equipped with a lithium fluoride prism. Every cyclopropyl compound synthesized during this research shows a band in the region of 3072–3096 cm.$^{-1}$ and one in the region of 2996–3033 cm.$^{-1}$ confirming the work of Wiberley and Bunce.[12] An additional report on the infrared spectra of these cyclopropane derivatives is planned.

Samples of 1,2-dicyclopropyl-1,2-di-*p*-hydroxyphenylethane, 1,2-dicyclopropyl-1,2-di-*p*-anisylethylene, and the azine of cyclopropyl *p*-anisyl ketone have been sent to the Cancer Chemotherapy National Service Center to be tested for endocrine activity and antitumor properties.

EXPERIMENTAL[13]

Cyclopropylphenylcarbinol (II) *by Meerwein-Ponndorf-Verley reduction.* Cyclopropanecarbonitrile was obtained in

---

(9) Huang-Minlon, *J. Am. Chem. Soc.*, **70**, 2802 (1948).

(10) R. R. Phelan, B.S. thesis, Rensselaer Polytechnic Institute, 1953.

(11) V. E. Ward, B.S. thesis, Rensselaer Polytechnic Institute, 1955.

(12) S. E. Wiberley and S. C. Bunce, *Anal. Chem.*, **24**, 623 (1952).

(13) Boiling points are uncorrected; all reduced pressure distillations were conducted using a Vigreux column unless otherwise specified. Melting points, unless otherwise noted, were obtained by the capillary method with a thermometer calibrated with reference compounds [S. C. Bunce, *Anal. Chem.*, **25**, 825 (1953)]. Elemental analyses, unless otherwise noted, were performed by Drs. G. Weiler and F. B. Strauss, 164 Banbury Road, Oxford, England.

37% over-all yield from 1-bromo-3-chloropropane by the *Organic Syntheses* procedures,[14,15] and converted in 98% yield to cyclopropyl phenyl ketone,[16,17] b.p. 128–133° at 25 mm., n_D^{20} 1.5562 by the procedure of Henze and Gayler.[18] The method of Close[4] afforded a 74% yield from γ-chlorobutyryl chloride which was prepared in 86% yield from γ-butyrolactone; this preparation of cyclopropyl phenyl ketone was shorter and the product was apparently more pure, b.p. 121–124° at 16 mm., n_D^{21} 1.5530 (lit. n_D^{20} 1.5525,[18] n_D^{25} 1.5514[17]). The 2,4-dinitrophenylhydrazone melted at 211.5–212.0° (lit. m.p. 211–213°[17]).

Aluminum isopropoxide,[19] 675 g. (3.38 mol.) and 494 g. (3.38 mol.) of cyclopropyl phenyl ketone in 3 l. of dry isopropyl alcohol, b.p. 82–83°, were placed in a flask equipped with a stirrer and a 270-mm. vacuum-jacketed, silvered column packed with glass helices. Acetone, b.p. 62–80°, was removed slowly until the distillate gave a negative test with 2,4-dinitrophenylhydrazine solution. The isopropyl alcohol was removed under vacuum and the residue was stirred with 3 l. of dilute hydrochloric acid and then extracted with ether. The extract was neutralized with saturated sodium bicarbonate, dried over potassium carbonate, concentrated, and distilled twice yielding 471 g. (94%) of cyclopropylphenylcarbinol, b.p. 80–84° at 0.4 mm., n_D^{20} 1.5330 (lit. b.p. 121° at 12 mm., n_D^{25} 1.5390[4]).

Cyclopropylphenylcarbinol (II) *and cyclopropylphenylcarbinyl ether by lithium aluminum hydride reduction.* Cyclopropylphenylcarbinol, b.p. 96–97° at 2.0 mm., n_D^{20} 1.5411, d_4^{20} 1.0443, MR$_D$ 44.49 (calcd., using 0.45 exaltation for cyclopropyl,[20] 44.56), was prepared from cyclopropyl phenyl ketone in 90% yield by the procedure of Close.[4] In several cases the use of lithium aluminum hydride led to the formation of cyclopropylphenylcarbinyl ether. For example, 5.0 g. (0.13 mol.) of lithium aluminum hydride and 50.0 g. (0.34 mol.) of cyclopropyl phenyl ketone were refluxed for 2 hr. and the mixture was hydrolyzed, the ether layer separated, neutralized with saturated sodium bicarbonate, and dried over potassium carbonate. The ether was removed and the residue distilled to yield 35.9 g. (76%) of cyclopropylphenylcarbinyl ether, b.p. 175–181° at 4.0 mm. A portion was redistilled, b.p. 135.9–136.5° at 0.45 mm., to constant refractive index, n_D^{23} 1.5535.

Anal. Calcd. for $C_{20}H_{22}O$: C, 86.28; H, 7.96. Found: C, 86.43, 86.61; H, 8.20, 8.07.

Cyclopropylphenylcarbinyl bromide (III) *from cyclopropylphenylcarbinol.* Phosphorus tribromide, 352.0 g. (1.3 mol.) (Eastman), was cooled to −15° and 148.1 g. (1.0 mol.) of cyclopropylphenylcarbinol was added during 30 min. at −15°. After stirring for 15 min. at −15°, the mixture was poured over ice and extracted with ether. The ether layer was separated, washed with saturated sodium bicarbonate and saturated sodium chloride, and dried over potassium carbonate. The ether was removed and the residue distilled to yield 186.5 g. (88%) of cyclopropylphenylcarbinyl bromide, b.p. 85–87° at 0.3 mm., n_D^{20} 1.5872. An analytical sample, b.p. 73.5–74.0° at 0.1 mm., n_D^{20} 1.5882, did not react with dilute potassium permanganate.

Anal. Calcd. for $C_{10}H_{11}Br$: C, 56.89; H, 5.25; Br, 37.86. Found: C, 57.18, 56.90; H, 5.24, 5.43; Br, 37.5, 37.2.

Cyclopropylphenylcarbinyl bromide from cyclopropylphenylmethane. Cyclopropylphenylmethane, 26.4 g. (0.20 mol.), obtained from cyclopropyl phenyl ketone in 84% yield,[4] was refluxed with 35.6 g. (0.20 mol.) of dried *N*-bromosuccinimide (Halogen Chemicals Inc.) in 400 ml. of carbon tetrachloride, b.p. 76–78°, with a trace of benzoyl peroxide. After 4 hr. the mixture was filtered, washed with warm water and saturated sodium bicarbonate, and dried over potassium carbonate. The carbon tetrachloride was removed under vacuum and the residue distilled, yielding 6.6 g. (25%) of recovered cyclopropylphenylmethane, b.p. 45–46° at 0.4 mm., n_D^{20} 1.5224, and 13.1 g. (31% or a 41% corrected yield) of cyclopropylphenylcarbinyl bromide, b.p. 90–92° at 0.5 mm., n_D^{20} 1.5850.

Cyclopropyl m-nitrophenyl ketone. Cyclopropyl phenyl ketone, 48.3 g. (0.33 mol.), was added during 30 min. to 90 ml. of sulfuric acid and 90 ml. of nitric acid at 0 to −10°. Following 2 hr. of stirring at 0°, the mixture was poured over ice, extracted with ether, and the ether extract dried over potassium carbonate and concentrated to a residue which partly crystallized. The crystals were collected and recrystallized from alcohol, giving 22.1 g. (35%) of cyclopropyl *m*-nitrophenyl ketone, which after four recrystallizations melted at 70.8–71.1°.

Anal. Calcd. for $C_{10}H_9NO_3$: C, 62.82; H, 4.74. Found: C, 62.72; H, 4.82.

Cyclopropyl *m*-nitrophenyl ketone, oxidized according to the procedure of Markees and Burger[21] using hydrobromic acid followed by potassium permanganate, gave *m*-nitrobenzoic acid, m.p. 143–146° uncorr., which did not depress the m.p. of an authentic sample, m.p. 144–145° uncorr.

Attempted preparation of cyclopropylphenylacetic acid. n-Butyllithium was prepared from 3.2 g. (0.46 mol.) of lithium metal and 27.4 g. (0.20 mol.) of *n*-butyl bromide, b.p. 100–101°. Cyclopropylphenylmethane, 25.1 g. (0.19 mol.), in 100 ml. of ether was added over a 30-min. period and the solution refluxed for 90 min. The mixture was poured over crushed Dry Ice, water was added, and the ether layer was separated, washed with water until neutral, and dried. Removal of the ether and distillation of the residue gave 20.0 g. (80% recovery) of cyclopropylphenylmethane, b.p. 52–55° at 2.0 mm., $n_D^{22.5}$ 1.5072.

Attempted preparation of 1,2-dicyclopropyl-1,2-diphenylethane. n-Butyllithium was prepared from 6.4 g. (0.91 mol.) of lithium metal and 57.6 g. (0.42 mol.) of *n*-butyl bromide, b.p. 100–101°. Cyclopropylphenylmethane, 46.3 g. (0.35 mol.) was added and the solution was refluxed for 2 hr. Iodine, 44.4 g. (0.175 mol.), in 750 ml. of anhydrous ether was added over 45 min. and the solution was refluxed for 2$^1/_4$ hr. Water was added and the ether layer was washed with 10% sodium thiosulfate solution and twice with water, and dried. After the ether was removed, the residue gave 41.4 g. (89% recovery) of cyclopropylphenylmethane, b.p. 42–43° at 0.7 mm.

Attempted preparation of 1,2-dicyclopropyl-1,2-diphenylethanol. A sodium dispersion was prepared from 11.5 g. (0.50 mol.) of metallic sodium and 500 ml. of *n*-butyl ether, b.p. 142–143°, with high speed stirring under nitrogen. *n*-Amyl chloride, 26.6 g. (0.25 mol.), b.p. 106–107°, in 125 ml. of *n*-butyl ether was added over a 50-min. period at 0°, followed by stirring at 0° for 1 hr. A solution of 23.4 g. (0.18 mol.) of cyclopropylphenylmethane in 150 ml. of *n*-butyl ether was added at 0° during 40 min., followed by heating at 60° for 30 min. After cooling to 0°, 14.6 g. (0.10 mol.) of cyclopropyl phenyl ketone in 100 ml. of *n*-butyl ether was added slowly and the mixture was allowed to stir for 2 hr. while warming to room temperature. The mixture was poured over crushed ice and steam-distilled. The distillate, after 2 hr. of steam-distilling, was salted out with potassium carbonate, extracted with ether, dried, and distilled to remove both ethers. The residue was distilled giving 17.1 g. (73% recovery) of cyclopropylphenylmethane, b.p. 70° at

---

(14) C. F. H. Allen, *Org. Syntheses,* **Coll. Voll. I,** 156 (1941).

(15) M. J. Schlatter, *Org. Syntheses,* **Coll. Voll. III,** 223 (1955).

(16) A. Haller and E. Benoist, *Ann. chim.* (Paris), IX, **17,** 25 (1922).

(17) R. P. Mariella and R. R. Raube, *J. Am. Chem. Soc.,* **74,** 521 (1952).

(18) H. R. Henze and C. W. Gayler, *J. Am. Chem. Soc.,* **74,** 3615 (1952).

(19) We are indebted to the Harshaw Chemical Co. for gifts of this material.

(20) V. A. Slabey, *J. Am. Chem. Soc.,* **76,** 3603 (1954).

(21) D. G. Markees and A. Burger, *J. Am. Chem. Soc.,* **71,** 2031 (1949).

10 mm. and 26.1 g. of unidentified material, b.p. 113° at 10 mm. The distillate obtained by steam-distilling for 4 additional hr. was salted out, extracted, dried, and concentrated to 4.6 g. of a red liquid whose infrared spectrum showed a strong hydroxyl band at 3546 cm.$^{-1}$ and a strong carbonyl band at 1681 cm.$^{-1}$ After standing for 1 yr. a small quantity of cubic crystals had appeared. The residue from the steam distillation was extracted, dried, and concentrated to 4.8 g. of a red liquid whose infrared spectrum showed a weak hydroxyl band at 3623 cm.$^{-1}$ and a moderate carbonyl band at 1698 cm.$^{-1}$

1,2-Dicyclopropyl-1,2-diphenylethane (IV). The coupling procedure of Wilds and McCormack[5] was modified with respect to order of addition. Ethylmagnesium bromide was prepared in a flask with a bottom stopcock from 43.5 g. (1.79 mol.) of magnesium and 193.5 g. (1.76 mol.) of bromoethane, b.p. 38–39°, and filtered through glass wool into an ether solution containing 217.8 g. (1.03 mol.) of cyclopropylphenylcarbinyl bromide and 10.2 g. (0.08 mol.) of anhydrous cobaltous chloride, over a 90-min. period. A vigorous evolution of gas was noted which stopped immediately when the addition was completed; thereafter the mixture was stirred for 15 min., cooled, and poured over ice and hydrochloric acid. The ether layer was separated, washed with water and saturated sodium bicarbonate, and dried over potassium carbonate. The ether was removed and the remaining oil distilled at 1.2 mm. yielding 54.7 g. (42%) of solid 1,2-dicyclopropyl-1,2-diphenylethane boiling at 132–135°. Recrystallization from alcohol gave 47.8 g. (37%) melting at 72.2–72.8°.

Anal. Calcd. for $C_{20}H_{22}$: C, 91.55; H, 8.45. Found: C, 91.22, 91.36; H, 8.23, 8.47.

1,2-Dicyclopropyl-1,2-di-p-nitrophenylethane (V). The method of nitration is that of Markees and Burger.[21] Acetic anhydride, 15 ml., b.p. 138°, 8 ml. of glacial acetic acid, and 9 ml. of nitric acid (*d.* 1.5) were cooled to −20° and 8.9 g. (0.03 mol.) of 1,2-cyclopropyl-1,2-diphenylethane was added over a 15-min. period at −10°. After stirring at 0° for 1 hr. the mixture was poured over ice, the solid collected and recrystallized twice from an alcohol–ethyl acetate mixture yielding 3.1 g. (26%) of 1,2-dicyclopropyl-1,2-di-*p*-nitrophenylethane melting at 199.8–200.6°.

Anal. Calcd. for $C_{20}H_{20}N_2O_4$: C, 68.16; H, 5.72; N, 7.95. Found: C, 68.14, 67.97; H, 5.88, 5.78; N, 8.14, 8.08.

1,2-Dicyclopropyl-1,2-di-*p*-nitrophenylethane was oxidized[21] to *p*-nitrobenzoic acid, isolated by sublimation, m.p. 242–245° uncorr., which did not depress the m.p. of an authentic sample.

1,2-Dicyclopropyl-1,2-di-p-aminophenylethane dihydrochloride (VI). The procedure for the reduction is that of Huang-Minlon.[22] 1,2-Dicyclopropyl-1,2-di-*p*-nitrophenylethane, 2.0 g. (0.006 mol.), 100 ml. of diethylene glycol, and 20 ml. of hydrazine hydrate were heated at 140° for 30 min. and at 204° for 3 hr. The cooled solution was poured into water, extracted with ether, the extract dried over potassium carbonate, and saturated with gaseous hydrogen chloride precipitating a quantitative yield of diamine dihydrochloride, neut. equiv. 181.8, 182.1 (calcd. 182.7).

1,2-Dicyclopropyl-1,2-di-p-hydroxyphenylethane (VII). 1,2-Dicyclopropyl-1,2-di-*p*-aminophenylethane dihydrochloride, 13.4 g. (0.037 mol.), was dissolved in 250 ml. of 5% sulfuric acid and 5.2 g. of sodium nitrite in 30 ml. of water was added dropwise to the solution until a positive test for nitrous acid was obtained. After stirring at 3° for 20 min., the mixture was filtered and added dropwise to boiling water precipitating 1,2-dicyclopropyl-1,2-di-*p*-hydroxyphenylethane. Recrystallization was best accomplished by using an alcohol-water mixture yielding 2.1 g. (19%), m.p. 190.3–191.0°.

Anal. Calcd. for $C_{20}H_{22}O_2$: C, 81.60; H, 7.53. Found: C, 81.76, 81.26; H, 7.33, 7.59.

Hydrazone of cyclopropyl phenyl ketone. Cyclopropyl phenyl ketone, 32.1 g. (0.22 mol.), 41.2 g. (1.28 mol.) of 95% hydrazine, and 150 ml. of absolute alcohol were refluxed for 19 hr. After cooling in a Dry Ice–acetone bath, the crude hydrazone was collected and recrystallized from absolute alcohol to give 34.6 g. (98%) of the hydrazone of cyclopropyl phenyl ketone melting at 64.8–65.6°.

Anal. Calcd. for $C_{10}H_{12}N_2$: C, 74.97; H, 7.55; N, 17.49. Found: C, 74.58; H, 7.48; N, 17.6.

1,2-Dicyclopropyl-1,2-diphenylethylene. The procedure is that of *Organic Syntheses*[7] and Staudinger and Pfennenger.[6] The hydrazone of cyclopropyl phenyl ketone, 16.0 g. (0.10 mol.), and 43.2 g. (0.20 mol.) of freshly prepared yellow mercuric oxide[23] in 500 ml. of *n*-hexane, b.p. 67–69°, were shaken for 20 hr. The cherry-red hexane solution was filtered and anhydrous sulfur dioxide passed in with dissipation of the color. Upon removal of the hexane a solid was obtained which was boiled with water for 2 hr., then extracted with ether. The extract was dried over potassium carbonate and the ether removed leaving fine needles which were recrystallized from alcohol using charcoal to yield 5.6 g. (43%) of 1,2-dicyclopropyl-1,2-diphenylethylene, m.p. 139.8–140.2°. An additional 1.1 g. (9%) was recovered from the mother liquors.

Anal. Calcd. for $C_{20}H_{20}$: C, 92.26; H, 7.74. Found: C, 92.23, 92.19; H, 7.94, 7.92.

Hydrazone of p-methoxyacetophenone. Using a procedure similar to that used for the preparation of the hydrazone of cyclopropyl phenyl ketone, there was obtained 94.3 g. (87%) of the hydrazone of *p*-methoxyacetophenone, m.p. 116.9–117.6° (lit. m.p. 118.5–120.0[8]), from 100.0 g. (0.663 mol.) of *p*-methoxyacetophenone and 160.0 g. (5.0 mol.) of 95% hydrazine.

Anal. Calcd. for $C_9H_{12}N_2O$: N, 17.06. Found: N, 17.17, 16.93.[24]

1,2-Dimethyl-1,2-di-p-anisylethylene; azine of p-methoxyacetophenone. The hydrazone of *p*-methoxyacetophenone, 12.0 g. (0.073 mol.), 32.4 g. (1.5 mol.) of mercuric oxide, and 23.0 g. (1.5 mol.) of anhydrous barium oxide in 200 ml. of low-boiling petroleum ether were treated as in the preparation of 1,2-dicyclopropyl-1,2-diphenylethylene. There was isolated 1.7 g. (16%) of yellow material, m.p. 199.3–199.7°, which was found by infrared and elemental analysis to be the azine of *p*-methoxyacetophenone.

Anal. Calcd. for $C_{18}H_{20}N_2O_2$: C, 72.95; H, 6.80; N, 9.45. Found: C, 72.97; H, 6.79; N, 9.54.

There was also isolated 0.1 g. (2.0% corrected for isolated azine) of 1,2-dimethyl-1,2-di-*p*-anisylethylene, m.p. 127.3–128.1° (lit. m.p. 127–128°,[25] 131°,[26] and 140.5–142°[8]). Four other attempted preparations of the olefin led only to isolation of the azine; it was not ascertained whether the use of barium oxide in this instance led to the formation of the olefin.

Cyclopropyl p-anisyl ketone (VIII). The reaction of 87.2 g. (1.30 mol.) of cyclopropanecarbonitrile with the Grignard reagent prepared from 251.6 g. (1.34 mol.) of *p*-bromoanisole, b.p. 104–105° at 17 mm., gave 168.5 g. (73%) of solid cyclopropyl *p*-anisyl ketone, b.p. 101–104° at 0.05 mm., which, when recrystallized from petroleum ether (100–140°) melted at 40.3–40.8°.

Anal. Calcd. for $C_{11}H_{12}O_2$: C, 74.98; H, 6.87. Found: C, 74.98; H, 6.71.

---

[22] Huang-Minlon, *J. Am. Chem. Soc.*, **70**, 2802 (1948).

[23] Obtained from the addition of 135.8 g. (0.5 mole) of mercuric chloride (Fisher) dissolved in 2 l. of water to 280.5 g. (5.0 moles) of potassium hydroxide dissolved in 1 l. of water. The product after washing twice with ethanol and drying was obtained in 93% yield.

[24] Analysis by Robert P. Yunick of this laboratory.

[25] E. C. Dodds, L. Goldberg, W. Lawson, and R. Robinson, *Proc. Roy. Soc.* (*London*), **B127**, 140 (1939).

[26] F. Wessely, A. Bauer, Ch. Chwala, I. Plaichinger, and R. Schonbeck, *Monatsh.*, **79**, 596 (1948); *Chem. Abstr.*, **43**, 6605 (1949).

It gave[27] a *2,4-dinitrophenylhydrazone*, m.p. 209.8–210.7°.

Azine and hydrazone (IX) *of cyclopropyl p-anisyl ketone.* Cyclopropyl *p*-anisyl ketone, 88.1 g. (0.50 mol.), and 64.1 g. (2.0 mol.) of 95% hydrazine in 150 ml. of absolute alcohol were refluxed for 24 hr., poured over ice, and extracted with ether. The extract was washed until neutral and dried over potassium carbonate. Upon removal of the ether there was obtained 88.8 g. of crude liquid hydrazone, which resisted attempts at crystallization from various solvents in a Dry Ice–acetone bath. Upon attempting to purify the hydrazone by distillation only a small fraction of liquid was distilled and the residue solidified; it was recrystallized three times from alcohol, and was found by infrared and elemental analysis to be the azine of cyclopropyl *p*-anisyl ketone, 11.1 g. (13%), m.p. 75.9–76.3°.

Anal. Calcd. for $C_{22}H_{24}N_2O_2$: C, 75.83; H, 6.94; N, 8.04. Found: C, 76.22; H, 7.28; N, 7.74.

One preparation of the hydrazone using 1.16 mol. of ketone and 7.0 mol. of hydrazine partly crystallized upon standing and from it 39.0 g. of solid material was isolated by recrystallization from petroleum ether (100–140°). The first crop of crystals, after four recrystallizations, yielded the hydrazone of cyclopropyl *p*-anisyl ketone, m.p. 66.0–66.8°.

Anal. Calcd. for $C_{11}H_{14}N_2O$: C, 69.44; H, 7.42; N, 14.73. Found: C, 69.12; H, 7.28; N, 14.55.

It was later indicated that the remainder of the 39.0 g. isolated from petroleum ether was a mixture of hydrazone and unreacted ketone, while the mother liquors, which partly crystallized again after removal of the solvent, afforded no more pure hydrazone, but only small amounts of azine. It was attempted to convert the azine present in these residues to hydrazone by heating at 125° for 38 hr. with a seven-fold excess of hydrazine,[28] but when this solution was poured into ice water, extracted with ether, and dried over potassium carbonate an oil was again obtained.

1,2-Dicyclopropyl-1,2-di-p-anisylethylene (X). Following the same procedure as for the preparation of 1,2-dicyclopropyl-1,2-diphenylethylene, 65.4 g. (0.342 mol.) of crude liquid hydrazone of cyclopropyl *p*-anisyl ketone, in 600 ml. of *n*-hexane, b.p. 67.4–69.5°, and 216.6 g. (1.0 mol.) of mercuric oxide were shaken for 21 hr. The hexane was a very deep cherry-violet color which slowly faded as sulfur dioxide was passed into the solution. More heat and foaming were observed than with the hydrazone of cyclopropyl phenyl ketone. The hexane was removed leaving a black oil, water was added, and the solution was boiled for 3 hr., cooled, and extracted with ether. The ether solution was dried over potassium carbonate and the ether was removed leaving a deep red oil from which, after standing, a small amount of fine needles was separated. Recrystallization from alcohol yielded 1.1 g. (2.0%) of 1,2-dicyclopropyl-1,2-di-*p*-anisylethylene which after two more recrystallizations melted at 175.5–175.9°.

Anal. Calcd. for $C_{22}H_{24}O_2$: C, 82.46; H, 7.55. Found: C, 82.22, 82.20; H, 7.39, 7.54.

In one experiment, in which barium oxide was added, a 3% yield of the azine of cyclopropyl *p*-anisyl ketone and no olefin were isolated.

Attempts to decompose the addition compound by heating at 130°[6] led to a dark polymeric material from which no solid material could be isolated.

1,2-Dicyclopropyl-1,2-di-*p*-anisylethylene, 0.1 g. (0.0003 mol.), was placed in a Carius tube with 0.5 g. of potassium hydroxide and 3 ml. of absolute ethanol and sealed. The tube shattered after heating for 20 min. in a Carius furnace at 220°. A second tube also shattered.

Attempted preparation of 1,2-dicyclopropyl-1,2-di-p-nitrophenylethylene. 1,2-Dicyclopropyl-1,2-di-*p*-nitrophenylethane, 3.0 g. (0.008 mol.), 200 ml. of distilled carbon tetrachloride, 100 ml. of glacial acetic acid, and a trace of benzoyl peroxide were mixed and 3.12 g. (0.017 mol.) of *N*-bromosuccinimide (Allied Chemical & Dye Corporation) was added and the solution was refluxed for 18 hr. The solvents were removed and a solution of sodium iodide in anhydrous acetone was added. The acetone turned a deep red with the precipitation of a yellow solid. After removal of the acetone, water was added, the solution extracted with ether, and the ether layer dried. Upon removal of the ether 1.8 g. (60%) of 1,2-dicyclopropyl-1,2-di-*p*-nitrophenylethane, m.p. 210–213° uncorr., was recovered.

1,2-Dicyclopropyl-1,2-di-*p*-nitrophenylethane, 3.0 g. (0.008 mol.), was treated as before except that 1.52 g. (0.008 mol.) of *N*-bromosuccinimide was used. Upon removal of the solvents potassium hydroxide in absolute methanol was added. Dilution with water, filtration, and recrystallization afforded only 2.9 g. (97%) of recovered starting material.

Ethyl 3-hydroxy-3-phenyl-3-(1-phenylcyclopropyl)propionate (XIII). 1-Phenylcyclopropyl phenyl ketone (XII), 145.9 g. (88%), b.p. 150–156° at 2.5 mm., was prepared by the procedure of Bunce and Cloke[29] from 120.0 g. (0.76 mol.) of bromobenzene, b.p. 154–159°, 18.7 g. (0.77 mol.) of magnesium turnings, and 108.0 g. (0.75 mol.) of 1-phenylcyclopropanecarbonitrile.[30] A portion recrystallized twice from *n*-heptane and twice from alcohol melted at 72.6–72.9° (lit. m.p. 73.6–73.9°[29]). Its 2,4-dinitrophenylhydrazone[27] melted at 182.6–183.0° (lit. m.p. 184.8–185.3°[29]).

A solution of 750 ml. of anhydrous thiophene-free benzene containing 100.0 g. (0.60 mol.) of ethyl bromoacetate, b.p. 167–170°, and 72.8 g. (0.33 mol.) of 1-phenylcyclopropyl phenyl ketone was added to 42.5 g. (0.60 mol.) of 20-mesh zinc and a few crystals of iodine over a period of 4 hr. Following 17 hr. of refluxing, the reaction mixture was hydrolyzed using dilute sulfuric acid and the benzene layer was separated, neutralized with saturated sodium bicarbonate, and dried over sodium sulfate. The benzene was removed and the residue distilled to yield 40.4 g. of unreacted ketone boiling at 145–170° at 1.4 mm. and 39.5 g. (47% or 94% corrected yield) of ethyl 3-hydroxy-3-phenyl-3-(1-phenylcyclopropyl)propionate, b.p. 167–168° at 0.09 mm. A portion, recrystallized from petroleum ether (100–140°), melted at 48.2–48.8°. Ward[11] reported a m.p. of 40–41°.

Anal. Calcd. for $C_{20}H_{22}O_3$: C, 77.39; H, 7.14. Found: C, 77.25; H, 7.02.[31]

The above procedure was found to give the highest yield of several variants of the Reformatsky reaction which were investigated.

1-Phenyl-1-(1-phenylcyclopropyl)propane-1,3-diol (XIV). Lithium aluminum hydride, 9.8 g. (0.258 mol.), was ground under an atmosphere of nitrogen and added to 500 ml. of anhydrous ether. Following 2 hr. of refluxing, 39.5 g. (0.127 mol.) of ethyl 3-hydroxy-3-phenyl-3-(1-phenylcyclopropyl)-propionate dissolved in 500 ml. of absolute ether was added over a period of 3 hr. After refluxing for 21 hr. the reaction mixture was hydrolyzed with water followed by dilute sulfuric acid. The ether layer was separated, neutralized with saturated sodium bicarbonate, and dried over magnesium sulfate. After removal of the ether, the diol crystallized upon standing. It was found to be insoluble in petroleum ether at 50° and was washed free of contaminants. The white granular solid, 32.5 g. (96%), melted at 71.2–71.8°.

Anal. Calcd. for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51. Found: C, 80.80; H, 7.61.[31]

1,3-Dibromo-1-phenyl-1-(1-phenylcyclopropyl)propane (XV). *A. Using phosphorus tribromide in ether.* Phosphorus

---

[27] R. L. Shriner, R. C. Fuson, and D. Y. Curtin, *The Systematic Identification of Organic Compounds*, Fourth Edition, John Wiley & Sons, New York, N. Y., 1956, p. 219.

[28] L. Vargha and E. Kovacs, *Ber.*, **75**, 794 (1942).

[29] S. C. Bunce and J. B. Cloke, *J. Am. Chem. Soc.*, **76**, 2244 (1954).

[30] E. C. Knowles and J. B. Cloke, *J. Am. Chem. Soc.*, **54**, 2028 (1932).

[31] Analysis by George H. Potter of this laboratory.

tribromide, 34.6 g. (0.13 mol.) (Eastman), was added to 200 ml. of absolute ether and cooled to −12°. 1-Phenyl-1-(1-phenylcyclopropyl)propane-1,3-diol, 23.8 g. (0.09 mol.), in 125 ml. of anhydrous ether was added over a period of 2 hr. at −5 to 0°. Following stirring for 48 hr. the solution was poured into ice water, the ether layer was separated and neutralized with saturated sodium bicarbonate and dried over sodium sulfate. Upon removal of the ether under vacuum there remained 16.1 g. of dark, partly crystalline product. Attempted recrystallization from absolute methanol yielded 0.7 g. of fine needles, m.p. 141.8–143.8°, which gave a negative test with alcoholic silver nitrate; the methanol-soluble portion after many treatments with charcoal, in acetone solution, yielded a brown solid. A sample of this material, after six recrystallizations from absolute alcohol, melted at 75.3–75.7° and gave a positive test with alcoholic silver nitrate.

Anal. Calcd. for $C_{18}H_{18}Br_2$: C, 54.84; H, 4.60; Br, 40.55. Found: C, 54.66; H, 4.43; Br, 40.5.

B. Using phosphorus tribromide in methylene chloride. A solution of 5 g. (0.019 mol.) of diol in 25 ml. of methylene chloride was cooled to −12°, and 5.4 g. (0.02 mol.) of phosphorus tribromide was added during 10 min.. maintaining the temperature below 10°. After standing for 10 days, the mixture was poured over ice and the methylene chloride layer was separated, neutralized, and dried. Removal of the solvent under vacuum gave 7.3 g. of an oil which solidified rapidly. Recrystallization from absolute alcohol using charcoal yielded 1.7 g. (23%) of material, m.p. 69.7–71.0°, with an additional 2.2 g. (30%) isolated from the mother liquors. Subsequent work with this material showed it to be impure, containing some of the higher melting dibromide, m.p. 145.7–146.1°.

One experiment using 5.0 g. (0.019 mol.) of diol and 10.8 g. (0.04 mol.) of phosphorus tribromide was allowed to stand for 1 week. On removal of the methylene chloride, 3.0 g. of an oil was obtained which solidified upon the addition of absolute methanol. Recrystallization from methanol yielded a dibromide, m.p. 144.3–144.9°, which gave a negative test with alcoholic silver nitrate and whose mixed melting point with the higher melting dibromide previously obtained showed no depression.

Anal. Calcd. for $C_{18}H_{18}Br_2$: C, 54.84; H, 4.60. Found: C, 54.88, 55.19; H, 4.90, 5.22.

1,1′-Diphenylbicyclopropyl (XVI). The cyclization procedure is that of Bartleson, Burk, and Lankelma.[32] *n*-Propyl alcohol (100 ml.) and 13.08 g. (0.2 mol.) of zinc dust were cooled to −5° and the crude product from the reaction of 32.5 g. (0.12 mol.) of diol with phosphorus tribromide in ether was added in 90 min. at −3° to −5°. After stirring for 3 days, water was added, the alcohol distilled from the reaction mixture, and the mixture extracted with ether. The ether was washed with saturated sodium bicarbonate and dried over sodium sulfate. Upon removal of the ether, the residue was distilled at 0.1 mm.; 3.5 g. of material distilled between 124–130° and a large amount of tar remained in the distilling flask. The distilled material gave a negative test for halogens using the sodium fusion method. Its infrared spectrum agreed qualitatively with that expected for 1,1′-diphenylbicyclopropyl; it could not be induced to crystallize upon long standing.

Treatment of 2.0 g. of crude 1,1′-diphenylbicyclopropyl with a mixture of 10 ml. of acetic anhydride, 7 ml. of glacial acetic acid, and 7 ml. of nitric acid (*d* 1.5) at −15° gave a small amount of material which could not be recrystallized satisfactorily.

Acknowledgment. The authors wish to express their appreciation for the support of this work by research grant C-3113 from the National Cancer Institute of the National Institutes of Health. Support of the junior author, J.G.B., by the Sterling-Winthrop Research Institute in July and August, 1958 is also gratefully acknowledged.

TROY, N. Y.

---

[32] J. D. Bartleson, R. E. Burk, and H. P. Lankelma, *J. Am. Chem. Soc.*, **68**, 2513 (1946).

[CONTRIBUTION NO. 1566 FROM THE STERLING CHEMISTRY LABORATORY, YALE UNIVERSITY]

20-Methylpregnane and Derivatives[1,2]

JOHN P. DUSZA[3] AND WERNER BERGMANN*

Received July 9, 1959

20-Methylpregnane and several of its significant derivatives have been prepared by the Wittig reaction and by other methods.

In calculating the contributions of side chains to the optical rotations of sterols,[4] the molecular rotations of the respective sterols are generally compared with those of corresponding derivatives of pregnane. Pregnane, however, is not an ideal reference compound for such purposes. It has its C-17 attached to a β-oriented, secondary C-20 atom, while in the natural sterols C-17 is joined to β-oriented, tertiary C-20 atom. 20-Methylpregnane and its derivatives would therefore be more suitable reference compounds. At the beginning of this investigation, however, surprisingly little was known about this series of compounds or of others with relatively short alkyl side chains.

A number of derivatives of 20-methylpregnane have now been prepared by several methods. In one approach, 3β-acetoxydinor-5-cholenic acid (I), which possesses the desired carbon skeleton, was reduced to the known diol (IIa). This was converted

---

[1] The material presented in this paper constitutes part of a dissertation submitted by John P. Dusza in partial fulfillment of the requirements for the Ph.D. degree, Yale University, 1958.

[2] The investigation was in part supported by a research grant, Nonr 253(00), from the Office of Naval Research.

[3] F. W. Heyl Fellow, 1957–58. Present address: Organic Chemical Research Division, American Cyanamid Company, Pearl River, N. Y.

[4] W. M. Stokes and W. Bergmann, *J. Org. Chem.*, **16**, 1817 (1951).

*Deceased.