

Summary

1. A method of preparation of 3-alkyl- Δ^2 -cyclohexenones is reported.

2. The semicarbazones and 2,4-dinitrophenylhydrazones of the 3-alkyl- Δ^2 -cyclohexenones have been obtained and characterized.

3. Some 3-alkylcyclohexanones have been prepared by hydrogenation of 3-alkyl- Δ^2 -cyclohexenones and their derivatives, the semicarbazones and 2,4-dinitrophenylhydrazones characterized.

COLLEGE PARK, MD.

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[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA]

Antitubercular Compounds. bis-(Aminoaryl)-cyclopropane Derivatives. II.

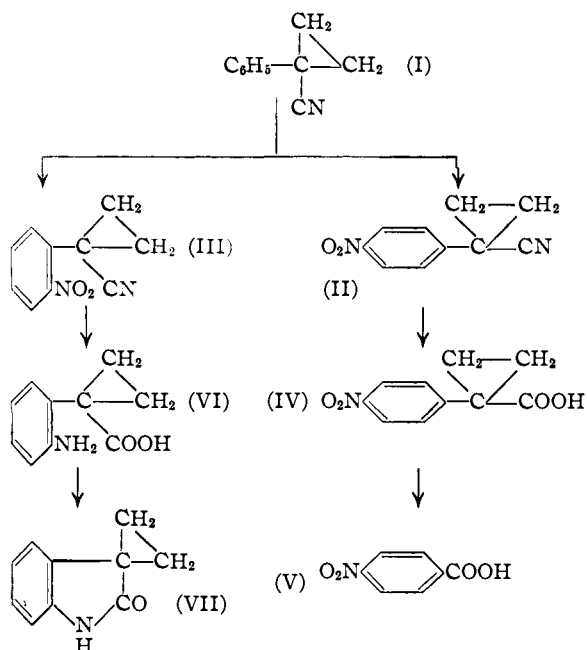
BY DIETER G. MARKEES¹ AND ALFRED BURGER

In the study of the effect of replacing the sulfone group in certain predominantly tuberculostatic sulfones by the aromatic type electron-attracting² cyclopropane group, we recently reported³ that 1-(2-amino-4-thiazolyl)-2-(4-aminophenyl)-cyclopropane exhibits a low *in vitro* tuberculostatic activity. Since bacteriostasis was still produced by 1,1,1-trichloro-2,2-bis-(4-aminophenyl)-ethane⁴ at a dilution of 1×10^{-6} , it appeared desirable to prepare an isomer of the first cyclopropane derivative carrying both basically substituted nuclei on the same carbon atom (X).

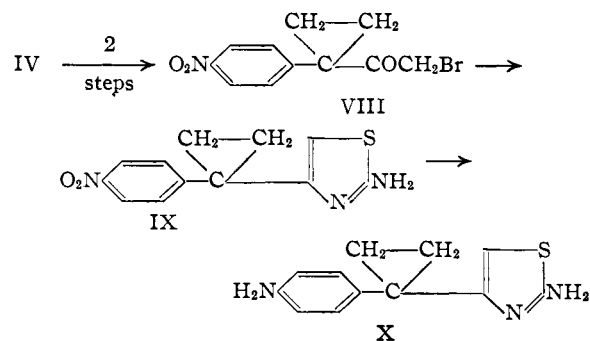
The synthesis of 1-(2-amino-4-thiazolyl)-1-(4-aminophenyl)-cyclopropane was patterned on that of the 1,2-isomer. 1-Phenyl-1-cyanocyclopropane (I)⁵ was nitrated and yielded a mixture which consisted largely of 1-(*p*-nitrophenyl)-1-cyanocyclopropane (II) contaminated by small amounts of the *o*-isomer (III); the latter could be separated readily by crystallization. The position of the nitro group in the main reaction product was elucidated by hydrolyzing the nitrile group to carboxyl (IV), opening the cyclopropane ring with a boiling solution of hydrogen bromide in acetic acid, and oxidizing the side chain with potassium permanganate. This series of reactions furnished *p*-nitrobenzoic acid (V).

Evidence for the presence of the *o*-isomer (III) was obtained by hydrolyzing the crude nitration products from the mother liquors of the *p*-nitro nitrile (II) in acid solution, and reducing the mixture of 1-(nitrophenyl)-cyclopropane-1-carboxylic acids thus obtained to a mixture of 1-(aminophenyl)-cyclopropane-1-carboxylic acids. The *o*-amino isomer (VI) presumably contained in this mixture furnished, on treatment with hydrochloric acid, a neutral product, which showed the properties of the expected 3-(1,1-cyclopropano)-oxindole (VII).

1-(*p*-Nitrophenyl)-cyclopropane-1-carboxylic acid (IV) was converted to the bromo ketone VIII by way of its chloride and diazo ketone, and the



bromo ketone VIII was condensed with thiourea to the thiazole derivative IX in a yield of 80%. Catalytic reduction of this nitro compound led to the desired diamine X.



In the course of this work an analogous synthesis of the unsubstituted 1-phenyl-1-(4-thiazolyl)-cyclopropane (XI) was carried out, starting from 1-phenylcyclopropane-1-carboxylic acid, and using thioformamide in the thiazole ring closure.

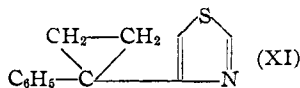
(1) Merck Post-Doctorate Fellow, 1948.

(2) Cloke, Knowles and Anderson, *THIS JOURNAL*, **58**, 2547 (1936).

(3) Markees and Burger, *ibid.*, **70**, 3329 (1948).

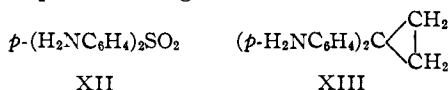
(4) Kirkwood, Phillips and McCoy, *ibid.*, **68**, 2405 (1946).

(5) Knowles and Cloke, *ibid.*, **54**, 2028 (1932); Case, *ibid.*, **56**, 715 (1934); Weston, *ibid.*, **68**, 2345 (1946).

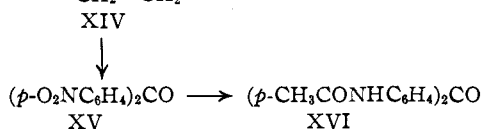
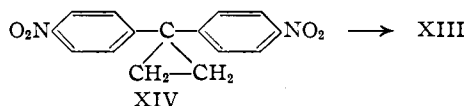


The diamine X inhibited multiplication of an H37Rv strain of *M. tuberculosis* in Dubos medium⁶ at a dilution of 50×10^{-6} , as compared with a value of 500×10^{-6} for the 1,2-isomer.³

It appeared possible that the relatively low tuberculostatic activity of these compounds was partly due to the fact that the amino group of their thiazole portion was not *para* to the cyclopropane linkage. In order to get a closer comparison between cyclopropane derivatives and the highly active bis-(4-aminophenyl) sulfone (XII) we prepared 1,1-bis-(4-aminophenyl)-cyclopropane (XIII), but the bacteriostatic concentration of this compound was again 50×10^{-6} .



The starting material for this synthesis, 1,1-diphenylcyclopropane,⁷ was nitrated with fuming



nitric acid in an acetic acid-acetic anhydride solution. The least soluble (XIV) of the resulting isomeric dinitro products isolated from the reaction was reduced with zinc dust and hydrochloric acid and gave the diamine XIII which was characterized as the benzoyl and acetyl derivatives. In order to prove the positions of the two amino groups, the dinitro derivative XIV was oxidized to a dinitrobenzophenone (XV) of m. p. 187–188° which might have been the 4,4'-dinitro (m. p. 189°) or 2,2'-dinitro derivative (m. p. 188–189°). Reduction of our dinitrobenzophenone, followed by acetylation, led to a diacetamidobenzophenone (XVI), m. p. 233–236°, which was identical with an authentic sample⁸ of 4,4'-diacetamidobenzophenone.

The yield of 1,1-diphenylcyclopropane in the preparation by the method of Wieland and Probst⁷ is not satisfactory, since a large amount of unsaturated products is formed in the decomposition of the intermediate diphenyl pyrazoline. In a search for an improved synthesis, we hoped that a method patterned on the preparation of 1,1-dimethylcyclopropane⁹ would be more fruitful.

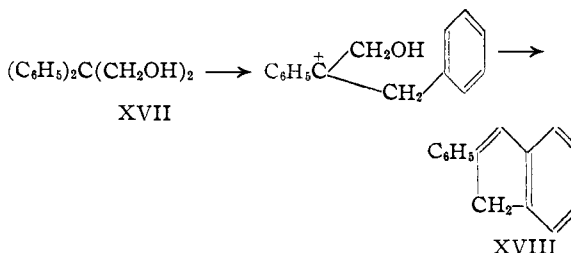
(6) We are grateful to Dr. M. Solotorovsky for carrying out these tests.

(7) Wieland and Probst, *Ann.*, **530**, 274 (1937); cf. Goldsmith and Wheland, *This Journal*, **70**, 2632 (1948).

(8) Fierz and Köchlin, *Helv. Chim. Acta*, **1**, 218 (1918).

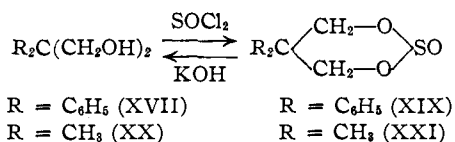
(9) Shortridge, Craig, Greenlee, Derfer and Boord, *This Journal*, **70**, 946 (1948).

Therefore, 2,2-diphenylpropanediol-1,3 (XVII) was prepared from diphenylacetaldehyde and formaldehyde, and characterized as the diacetate and dibenzoate. However, all attempts to convert this glycol to its dihalide which was to be dehalogenated to 1,1-diphenylcyclopropane, failed. When it was heated with phosphorus tribromide, the only reaction product which could be isolated was 2-phenylindene (XVIII) whose formation can best be explained on the basis of a neopentyl type rearrangement with subsequent ring closure.



The 2-phenylindene was identified by comparison with an authentic sample.¹⁰ The 1,2-diphenylpropane-1,2-diol^{10a} from which this sample was prepared by cyclodehydration had the same melting point as the isomeric 2,2-diphenylpropanediol-1,3 (XVII) but proved to differ from it.

In an attempt to replace the two hydroxyl groups in 2,2-diphenylpropane-diol-1,3 by chlorine by means of thionyl chloride, a neutral compound of the formula $\text{C}_{15}\text{H}_{14}\text{O}_3\text{S}$ was formed in good yields. It probably represents the cyclic ester XIX since it can be hydrolyzed easily to the parent glycol XVII and potassium sulfite in alkaline solution.



The formation of cyclic sulfites from 2,2-disubstituted 1,3-propanediols appears to be a general reaction since 2,2-dimethylpropanediol-1,3 (XX)⁹ gives an analogous compound, 1-oxo-4,4-dimethylthiadioxane-2,6 (XXI).¹¹

Acknowledgment.—We are grateful to Merck & Co. for a Fellowship Grant in support of this investigation.

Experimental¹²

1-(4-Nitrophenyl)-1-cyanocyclopropane (II).—To a stirred and cooled mixture of 45 cc. of concentrated sulfuric acid and 45 cc. of nitric acid (d. 1.42) was added dropwise 25 g. of 1-phenyl-1-cyanocyclopropane⁵ at such a rate that the temperature did not exceed 25°. After completion of the addition the mixture was stirred at 5° for another hour, the precipitated crystalline reaction product

(10) (a) Tiffeneau and Dorlencourt, *Ann. chim.*, [8] **16**, 237 (1909); (b) Blum-Bergmann, *Ber.*, **65**, 109 (1932).

(11) Cf. Wiest, German Patent 710,350 (1941).

(12) All melting points are corrected. Several of the C and H determinations were performed by Clark Microanalytical Laboratory, Urbana, Ill.

was filtered, washed with cold concentrated nitric acid and with water, and dried in the air. The yield was 21 g. (64%). After recrystallization from ethanol the pale yellow prisms melted at 156–158°.

Anal. Calcd. for $C_{10}H_8N_2O_2$: N, 14.89. Found: N, 15.15.

Proof of Structure.—A solution of 0.6 g. of 1-(4-nitrophenyl)-1-cyanocyclopropane in 10 cc. of a 32% solution of hydrogen bromide in acetic acid was refluxed for seven and one-half hours, the solvent was stripped under reduced pressure, and the tarry residue was treated slowly with a 5% alkaline solution of potassium permanganate until the violet color persisted for three minutes. A few drops of ethanol were added, the manganese dioxide was filtered, and the filtrate acidified. The precipitated acid was filtered and purified by repeated crystallization and sublimation (150°, 2 mm.). The pale yellow crystals (V) melted at 238.5–240° and did not depress the melting point of an authentic sample of *p*-nitrobenzoic acid.

1-(4-Nitrophenyl)-cyclopropane-1-carboxylic Acid (IV).—A mixture of 19 g. of 1-(4-nitrophenyl)-1-cyanocyclopropane and 90 cc. of 65% sulfuric acid was refluxed for one hour. The reaction product precipitated out, was filtered and reprecipitated from a sodium carbonate solution by means of hydrochloric acid. The yield was 99%. The pale yellow needles were recrystallized from 25% ethanol and finally from water and melted at 190.5–193° (closed tube).

Anal. Calcd. for $C_{10}H_9NO_4$: N, 6.76. Found: N, 6.56.

Methylation with diazomethane in ether solution furnished the methyl ester which crystallized from ligroin as almost colorless prisms, m. p. 98–101°.

Anal. Calcd. for $C_{11}H_{11}NO_4$: N, 6.33. Found: N, 6.49.

1-(4-Nitrophenyl)-cyclopropane-1-carbonyl chloride was prepared from the nitro acid IV by the reaction with thionyl chloride in hot benzene for three hours; yield, 86%; the pale yellow leaflets melted at 76–78° after crystallization from petroleum ether.

Anal. Calcd. for $C_{10}H_8ClNO_3$: N, 6.21. Found: N, 6.31.

1-(4-Nitrophenyl)-cyclopropane-1-carboxamide, prepared from the above acid chloride by the action of ammonium hydroxide, crystallized from 95% ethanol as colorless prisms which melted at 238–240°.

Anal. Calcd. for $C_{10}H_{10}N_2O_3$: N, 13.59. Found: N, 13.46.

1-(4-Nitrophenyl)-cyclopropane-1-carboxanilide, after crystallization from 65% ethanol and sublimation at 150–170° (3 mm.), was colorless, m. p. 152.5–153.5°.

Anal. Calcd. for $C_{16}H_{14}N_2O_3$: N, 9.92. Found: N, 9.67.

1-(4-Nitrophenyl)-1-diazoacetylcyclopropane.—To a stirred solution of 6 g. of diazomethane in 300 cc. of alcohol-free ether was added a solution of 13 g. of crude 1-(4-nitrophenyl)-cyclopropane-1-carbonyl chloride in 50 cc. of benzene at 5°. The mixture was stirred for four hours at this temperature and allowed to stand for two hours at 25°. Part of the diazo ketone crystallized out while the rest was recovered after evaporation of the solvents under reduced pressure. The yield was 10.5 g. (79%). A sample was recrystallized from a 1:1 mixture of benzene and petroleum ether; the yellow prisms melted at 109.5–110.5°.

Anal. Calcd. for $C_{11}H_9N_3O_3$: N, 18.18. Found: N, 17.94.

1-(4-Nitrophenyl)-1-bromoacetylcyclopropane (VIII).—A mixture of 10 cc. of 42% hydrobromic acid and 20 cc. of dioxane was added to a suspension of 10 g. of the crude diazo ketone in 30 cc. of dioxane with occasional agitation. An exothermic reaction took place and was completed by heating to 90° for ten minutes. The reaction mixture was poured into 900 cc. of ice-water; the bromo ketone separated in a practically quantitative yield and crystal-

lized soon. Recrystallization of a sample from methanol gave colorless leaflets, m. p. 111–112°.

Anal. Calcd. for $C_{11}H_{10}BrNO$: N, 4.93. Found: N, 4.95.

1-(4-Nitrophenyl)-1-(2-amino-4-thiazolyl)-cyclopropane (IX).—The condensation of 8 g. of the bromo ketone VIII and 3.2 g. of thiourea was carried out in 75 cc. of 95% ethanol. After the end of the initial reaction, the clear mixture was refluxed for one hour, filtered while hot, and poured into an excess of an ice-cold solution of 1% ammonium hydroxide. The yellow precipitate was filtered and dried. It weighed 6.8 g. (92%). A small sample was recrystallized from a 1:1 mixture of ethanol and pyridine until the yellow needles melted at 219.5–221°.

Anal. Calcd. for $C_{12}H_{11}N_3O_2S$: N, 16.09. Found: N, 16.06.

The acetyl derivative, prepared with acetic anhydride, crystallized from 50% aqueous pyridine as colorless needles, m. p. 236–238°.

Anal. Calcd. for $C_{14}H_{13}N_3O_3S$: N, 13.85. Found: N, 14.08.

1-(4-Aminophenyl)-1-(2-amino-4-thiazolyl)-cyclopropane (X).—Hydrogenation of 6.2 g. of the nitro-amine IX in 230 cc. of acetone in the presence of 4 g. of Raney nickel catalyst under atmospheric pressure furnished, in ten hours, a practically quantitative yield of colorless leaflets which were recrystallized from dilute ethanol and sublimed at 150° (3 mm.). The melting point was 186–187°.

Anal. Calcd. for $C_{12}H_{13}N_3S$: C, 62.31; H, 5.66; N, 18.17. Found: C, 62.20; H, 5.74; N, 18.35.

A diacetyl derivative, obtained in hot acetic anhydride, crystallized from dilute acetic acid as a colorless powder, m. p. 279–281°.

Anal. Calcd. for $C_{16}H_{17}N_3O_4S$: N, 13.33. Found: N, 13.09.

The water-soluble hydrochloride of the diamine could not be crystallized.

1-(4-Aminophenyl)-cyclopropane-1-carboxylic Acid.—Hydrogenation of a small sample of 1-(4-nitrophenyl)-cyclopropane-1-carboxylic acid in acetone solution with Raney nickel catalyst at atmospheric pressure was completed in five hours. The amino acid crystallized best from methanol as colorless prisms, m. p. 235–237° (dec.) after some darkening.

Anal. Calcd. for $C_{10}H_{11}NO_2$: N, 7.91. Found: N, 7.71.

The acetyl derivative, prepared by heating the amino acid with excess acetic anhydride and a drop of concentrated sulfuric acid, crystallized from 10% ethanol as shiny colorless needles, m. p. 217.5–220°.

Anal. Calcd. for $C_{12}H_{13}NO_3$: N, 6.39. Found: N, 6.22.

3-(1,1-Cyclopropano)-oxindole (VII).—After the removal of 1-(4-nitrophenyl)-1-cyanocyclopropane from the mixture obtained by nitration of 1-phenyl-1-cyanocyclopropane, a considerable amount of crystalline mixed fractions was recovered from the mother liquors. This crude mixture was hydrolyzed with 65% sulfuric acid, and the crude crystalline reaction products consisting of a mixture of 1-(4-nitrophenyl)- and 1-(2-nitrophenyl)-cyclopropane-1-carboxylic acids were hydrogenated in acetone solution with Raney nickel catalyst. The crystalline mixture of hydrogenation products obtained in good yield was refluxed with 35% hydrochloric acid for ten minutes, cooled, and diluted to 300 cc. The gummy insoluble material was washed thoroughly with hot 5% sodium carbonate solution and with water. The now crystalline material was sublimed at 150° (3 mm.) and the colorless sublimate was recrystallized from ethyl acetate; m. p. 181–183°.

Anal. Calcd. for $C_{10}H_9NO$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.47; H, 5.63; N, 8.78.

1-Phenyl-1-(4-thiazolyl)-cyclopropane (XI) was prepared from 1-phenylcyclopropane-1-carbonyl chloride⁴ essentially as described above for IX without purification.

of the intermediate diazo or bromo ketones. Conversion of the crude bromo ketone to XI was accomplished by the action of thioformamide in 95% ethanol. The basic fraction from this reaction (b. p. 145–165° [3 mm.]) boiled on redistillation at a bath temperature of 80° (0.5 mm.) as a yellow oil.

Anal. Calcd. for $C_{12}H_{11}NS$: N, 6.96. Found: N, 6.67.

The picrate crystallized from 50% ethanol as yellow needles, m. p. 140–141°.

Anal. Calcd. for $C_{13}H_{14}N_4O_7S$: N, 13.02. Found: N, 12.82.

1,1-bis-(Nitrophenyl)-cyclopropane.—Over a period of one hour, 16.5 g. of 1,1-diphenylcyclopropane⁷ was added to a stirred mixture of 40 cc. of acetic anhydride, 24 cc. of acetic acid and 26 cc. of nitric acid (d. 1.5) at –5°, and the temperature was kept below 10°. The reaction mixture turned green, and yellow crystals separated; they were filtered through sintered glass after another thirty minutes, washed with nitric acid and then with water, and weighed 13 g. Eight crystallizations from 15 to 20 volumes of ethanol gave pale yellow needles, m. p. 159.5–160.5°. This product was shown to be 1,1-bis-(4-nitrophenyl)cyclopropane (XIV) by oxidative degradation as described below.

Anal. Calcd. for $C_{18}H_{12}N_2O_4$: C, 63.37; H, 4.26; N, 9.86. Found: C, 63.56; H, 4.23; N, 9.84.

The nitration mixture from which the dinitro compound XIV had been filtered, deposited a small batch of colorless transparent crystals on prolonged standing and cooling. They were sublimed at 100–150° (3 mm.) and recrystallized from dilute acetic acid; m. p. 185–186°. According to its analysis the compound was isomeric with compound XIV but its structure was not determined.

Anal. Calcd. for $C_{18}H_{12}N_2O_4$: N, 9.86. Found: N, 10.09.

A third isomer was isolated from the ethanolic mother liquors of the dinitro derivative XIV and recrystallized from benzene. The pale yellow stout prisms melted at 148–150°.

Anal. Calcd. for $C_{18}H_{12}N_2O_4$: N, 9.86. Found: N, 9.61.

Structural Proof of 1,1-bis-(4-Nitrophenyl)-cyclopropane.—A solution of 0.7 g. of sodium bichromate in 4 cc. of water was added slowly to a stirred solution of 0.3 g. of compound XIV in 3 cc. of concentrated sulfuric acid. The temperature was kept below 80° by occasional cooling, the mixture was stirred for another fifteen minutes, diluted with 15 cc. of water, and the precipitated oxidation product was filtered. It was sublimed at 150° (3 mm.), recrystallized from ethanol and then from ethyl acetate. The yellow prisms melted at 187–188°.

Reduction¹³ of 0.05 g. of this dinitrobenzophenone with a solution of 0.4 g. of stannous chloride in 1.25 cc. of 35% hydrochloric acid and 0.5 cc. of water, extraction of non-basic materials from the acid solution and alkalization furnished grayish crystals which were acetylated with acetic anhydride. The compound was recrystallized from dilute dioxane and appeared as colorless crystals, m. p. 233–236°. They did not depress the melting point of an authentic sample of bis-(4-acetamido)-benzophenone.⁸

1,1-bis-(4-Aminophenyl)-cyclopropane (XIII).—To a stirred solution of 0.9 g. of 1,1-bis-(4-nitrophenyl)-cyclopropane in 10 cc. of glacial acetic acid was added 3 g. of zinc dust, and 5 cc. of hydrochloric acid was dropped in over a period of fifteen minutes. The dark red mixture, kept at 70°, turned yellow as the reduction proceeded. It was diluted with 60 cc. of ice water and made strongly alkaline. The diamine was extracted into ether, dried over sodium sulfate, and the solvent was distilled. The solid residue was recrystallized from water. The silky needles melted at 58–62° with loss of water of crystallization. The dehydration was also effected by drying over sulfuric acid *in vacuo*, and resulted in a grayish material, m. p. 76–78°.

(13) *Staedel, Ann.*, **218**, 339 (1883).

Anal. Calcd. for $C_{18}H_{16}N_2$: N, 12.49. Found: N, 12.32, 12.32.

The diacetyl derivative, obtained with acetic anhydride, melted at 249–251°.

Anal. Calcd. for $C_{19}H_{20}N_2O_2$: N, 9.09. Found: N, 9.20.

The dibenzoyl derivative was prepared by the Schotten-Baumann reaction in pyridine. The colorless needles melted at 260–261°.

Anal. Calcd. for $C_{29}H_{24}N_2O_2$: N, 6.48. Found: N, 6.43.

Diphenylacetaldehyde was prepared in 87% yield essentially according to the method of Danilov and Venus-Danilova¹⁴ but using formic in place of oxalic acid. Its semicarbazone melted at 159–160° in agreement with reported values.¹⁵

2,2-Diphenylpropane-1,3-diol (XVII).—A mixture of 56 g. of diphenylacetaldehyde, 21.3 g. of anhydrous potassium carbonate, 70 cc. of 35% aqueous formaldehyde solution, 56 cc. of water and 280 cc. of ethanol was refluxed for twenty-one hours, and the volatile portions were distilled. The oily residue solidified soon. It was triturated with water, dried, and recrystallized from benzene, methanol or water.

The compound crystallized as glistening leaflets or needles, m. p. 102–104°. The yield was 60 g. (92%).

Anal. Calcd. for $C_{15}H_{16}O_2$: C, 78.91; H, 7.07. Found: C, 78.91; H, 7.29.

Concentrated sulfuric acid gives a green color with this glycol which changes rapidly through brown to purple.

The diacetate, prepared from the diol with acetic anhydride and one drop of sulfuric acid, crystallized from methanol as prisms, m. p. 90–92°.

Anal. Calcd. for $C_{19}H_{20}O_4$: C, 73.08; H, 6.46. Found: C, 72.83; H, 6.41.

The dibenzoate was prepared with benzoyl chloride in pyridine solution and recrystallized from methanol. It melted at 115–117°.

Anal. Calcd. for $C_{29}H_{24}O_4$: C, 79.79; H, 5.54. Found: C, 79.60; H, 5.76.

The cyclic carbonate, $(C_6H_5)_2C(CH_2O)_2CO$, prepared from the glycol with phosgene in benzene solution, crystallized from dilute acetone as colorless needles, m. p. 153.5–155.5°.

Anal. Calcd. for $C_{16}H_{14}O_3$: C, 75.57; H, 5.55. Found: C, 75.49; H, 5.62.

2-Phenylindene (XVIII).—A solution of 55 g. of phosphorus tribromide in 25 cc. of carbon tetrachloride was added to a boiling solution of 22 g. of 2,2-diphenylpropane-1,3-diol in 100 cc. of the same solvent at such a rate that gentle boiling was maintained. The mixture was refluxed for three hours and allowed to stand overnight. The solution was decanted from some inorganic material and decomposed with 1500 cc. of ice-water. A tan precipitate weighing 17 g. was filtered and kept in a desiccator where its solid appearance deteriorated. It was probably an intermediate in the molecular rearrangement, and was combined with the oily residue obtained from the carbon tetrachloride layer. Distillation at 10–15 mm. pressure and about 160° furnished 8 g. of a semi-solid from which a crystalline portion was separated by filtration. Recrystallization from ethanol yielded glittering leaflets, m. p. 165–166°.

Anal. Calcd. for $C_{15}H_{12}$: C, 93.71; H, 6.29; mol. weight, 192.25. Found: C, 93.42; H, 6.45; mol. weight, 193.

A mixture melting point with an authentic sample of 2-phenylindene^{10a, 10b} showed no depression.

1-Oxo-4,4-diphenylthiadioxane-2,6 (XIX).—A mixture of 5 g. of 2,2-diphenylpropanediol-1,3 and 10 cc. of thionyl chloride was refluxed for one hour after the first reaction had ceased. Excess thionyl chloride was distilled off, and the crystalline residue (5.5 g.) (60%) was purified by distillation; it boiled at approximately 190° (3 mm.) and solidified in the receiver. The distillate was recrystallized

(14) Danilov and Venus-Danilova, *Ber.*, **59**, 1032 (1926).

(15) Klages and Kessler, *Ber.*, **39**, 1753 (1906).

from ethanol, and the colorless prisms melted at 103–104°.

Anal. Calcd. for $C_{15}H_{14}O_3S$: C, 65.67; H, 5.14; S, 11.69. Found: C, 65.77; H, 5.34; S, 11.83.

Hydrolysis with 2.5% ethanolic potassium hydroxide solution furnished a 95% yield of the diol XVII.

1-Oxo-4,4-dimethylthiadioxane-2,6 (XXI).—This sulfide was prepared from 2,2-dimethylpropanediol-1,3⁹ in an analogous manner as the diphenyl derivative. The mobile colorless liquid boiled at 89° (33 mm.), n_D^{20} 1.4465. The yield was 70%.

Anal. Calcd. for $C_8H_{10}O_3S$: C, 39.98; H, 6.71; S, 21.35. Found: C, 40.10; H, 6.63; S, 21.53.

Summary

1. The nitration of 1-phenyl-1-cyanocyclopropane has been studied.

2. The synthesis of 1-(4-aminophenyl)-1-(2-amino-4-thiazolyl)-cyclopropane from 1-(4-nitrophenyl)-cyanocyclopropane in six steps has been described.

3. 1,1-bis-(4-Aminophenyl)-cyclopropane has been prepared from 1,1-diphenylcyclopropane and its structure has been established.

4. 2,2-Diphenylpropanediol-1,3, prepared from diphenylacetaldehyde, could not be converted to the corresponding 1,3-dihalide. Under the influence of phosphorus tribromide it yields 2-phenylindene, while thionyl chloride converts it to a cyclic sulfite.

CHARLOTTESVILLE, VA. RECEIVED DECEMBER 7, 1948

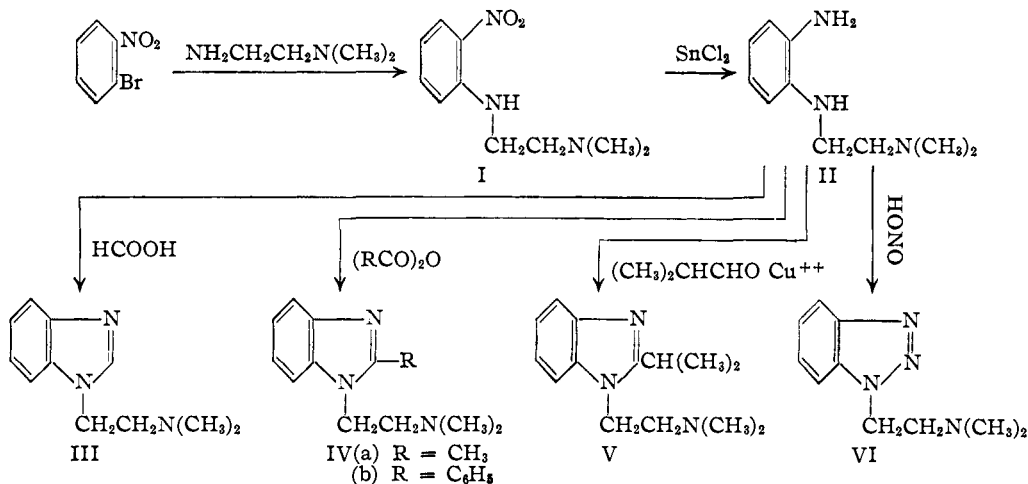
[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

Histamine Antagonists. V. Some 1-(β -Dimethylaminoethyl)-benzimidazole Derivatives

By JOHN B. WRIGHT

In continuation of a study of histamine antagonists in progress in this Laboratory¹⁻⁴ several 1-(β -dimethylaminoethyl)-benzimidazole derivatives and 1-(β -dimethylaminoethyl)-benzotriazole

the benzimidazole derivatives mentioned above this compound was synthesized and investigated also. These compounds were prepared according to the scheme



have been synthesized and screened for antihistaminic activity.

Benzimidazole derivatives appeared to be of interest because they have the $-\text{N}-\text{C}=\text{N}-$ grouping present in *N,N*-dimethyl-*N'*-benzyl-*N'*-(α -pyridyl)-ethylenediamine and certain other well-known antihistaminic agents as well as structures analogous to the imidazole ring of histamine. Since 1-(β -dimethylaminoethyl)-benzotriazole could be prepared readily from the same intermediary compounds necessary for the synthesis of

o-(β -Dimethylaminoethylamino)-nitrobenzene (I) was prepared by the reaction between *o*-bromonitrobenzene and β -dimethylaminoethylamine in the presence of anhydrous sodium acetate. Reduction of the nitro compound with stannous chloride gave the diamine (II) which, upon treatment with anhydrous formic acid,⁵ acetic anhydride,⁵ benzoic anhydride, isobutyraldehyde and cupric acetate⁶ and nitrous acid,⁷ gave the benzimidazole and benzotriazole derivatives shown above (III–VI).

(1) Wright, Kolloff and Hunter, *This Journal*, **70**, 3098 (1948).
 (2) Reid, Wright, Kolloff and Hunter, *ibid.*, **70**, 3100 (1948).
 (3) Reitsema and Hunter, *ibid.*, **70**, 4009 (1948).
 (4) Wright, *ibid.*, **71**, 1028 (1949).

(5) Clemo and Swan, *J. Chem. Soc.*, 274 (1944).
 (6) Weidenhagen, *Ber.*, **69**, 2263 (1936); Weidenhagen and Train, *ibid.*, **75**, 1936 (1942).
 (7) Ladenburg, *Ber.*, **9**, 219 (1876).