XI was hydrogenated with platinum oxide catalyst at 30 pounds pressure to 1-cyclohexyl-1-butanol, b.p. 80–81° (3 mm.), $n^{20}D$ 1.4655; reported[50] 115° (40 mm.), $n^{20}D$ 1.4652. Infrared absorption of this was identical with that of 1-cyclohexyl-1-butanol made by hydrogenation of 1-cyclohexyl-2-buten-1-ol.

From 33.5 g. (0.217 mole) of XI and 52 ml. (0.575 mole) of acetic anhydride there was obtained 33 g. (77.5%) of 1-(1-cyclohexenyl)-1-acetoxybutane (VIII), b.p. 78–79° (1 mm.), $n^{20}D$ 1.4602.

Anal. Calcd. for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.54; H, 10.21.

Catalytic hydrogenation of VIII (as for XI) gave 1-cyclohexyl-1-acetoxybutane (XII), b.p. 85–86.5° (2 mm.), $n^{20}D$ 1.4494. Infrared absorption of XII (Table IV) was identical with XII made from 1-cyclohexyl-1-butanol and acetic anhydride.

Anal. Calcd. for VIII, $C_{12}H_{22}O_2$: C, 72.68; H, 11.18. Found: C, 72.97; H, 11.12.

When 40 g. of VIII was pyrolyzed at 475° as described above, 35 g. of pyrolysate was collected. Washing with water, drying with sodium carbonate and fractionally distilling under nitrogen at a reflux ratio of 120/1 gave 16.4 g. (59%) in three fractions. Fraction 1 consisted of 3.7 g. (13.3%) of 1-butylidene-2-cyclohexene (V) distilling at 63–66° (7 mm.), $n^{20}D$ 1.4961. Fraction 3 (5.3 g., 19%) was 1-(1-cyclohexenyl)-1-butene (IV) 73° (7 mm.), $n^{20}D$ 1.5028. Fraction 2, 7.4 g., was a mixture of IV and V.

(50) D. Nightingale and H. D. Radford, *J. Org. Chem.*, **14**, 1089 (1944).

Fraction 3 in 70 ml. of Skellysolve A was passed through an 18 × 1.8 cm. column of activated silica gel, followed by 100 ml. of solvent. Distillation of the solution gave IV, 3.7 g. (70% recovery), b.p. 76° (8 mm.), $n^{20}D$ 1.5030, d^{20}_4 0.8538 (Table II). The maleic anhydride adduct melted at 61.0–61.5°, and there was no depression in a mixed m.p. with the adduct of IV from the thermal isomerization of II.

Anal. Calcd. for IV, $C_{10}H_{16}$: C, 88.16; H, 11.84. Found: C, 88.48; H, 11.60.

Chromatography of fraction 1 gave 2 g. (54% recovery) of 1-butylidene-2-cyclohexene (V), b.p. 68° (8 mm.), $n^{20}D$ 1.4973, d^{20}_4 0.8471 (Table II). The maleic anhydride determination showed 8.5–9.4% reaction.

Anal. Calcd. for V, $C_{10}H_{16}$: C, 88.16; H, 11.84. Found: C, 87.96; H, 12.04.

Catalytic Hydrogenation of II-V.—A sample of each diene (2–4 g.) in 25 ml. of absolute methanol with 0.1 g. of 10% palladium-on-charcoal catalyst was hydrogenated at about 30 pounds pressure. The catalyst was filtered, the product extracted with Skellysolve A, the extract then washed with concentrated sulfuric acid, dried and distilled. Each product distilled at 178–180°, $n^{20}D$ 1.4415–1.4430; reported[51] for 1-cyclohexylbutane, b.p. 180.5°, $n^{20}D$ 1.4410. The infrared spectra of the four products were identical and similar to the A.P.I. spectrogram of 1-cyclohexylbutane.

(51) E. B. Evans, *J. Inst. Petroleum Tech.*, **24**, 332 (1938).

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[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

Phenylcyclohexylcarbinols with Antispasmodic Activity[1]

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New methods of preparation of the antispasmodics (I) proceed *via* the product of a Reformatski reaction of phenyl cyclohexyl ketone. One route involves conversion of the Reformatski ester IV *via* its methylamide to the methylamine Va, and simultaneous alkylation-cyclization of that with 1,4-dibromobutane to II. Other routes go through reduction of IV to the glycol VI and reaction of VI 1-tosylate with secondary and tertiary amines. Some limitations and advantages of these routes are discussed, as well as exploratory attempts to make compounds related to I from phenylcyclohexylethinylcarbinol.

Among the compounds with the formula I are a number which have shown high atropine-like antispasmodic activity in laboratory tests by the acetylcholine-stimulated guinea pig ileum method. The compound II, in particular, is used clinically under the generic name tricyclamol,[2] by which it will be referred to below. The methods previously reported for the preparation of the compounds I have involved quaternization of the corresponding phenylcyclohexyldialkylaminoethylcarbinols, III. These amines have been prepared either by the action of a cyclohexyl Grignard reagent on the Mannich base prepared from acetophenone, formaldehyde and a secondary amine,[3] or by partial reduction of the diphenyldialkylaminoethylcarbinols[4] (III, for C_6H_{11} put C_6H_5). Since the Mannich reaction is limited notably with respect to the amine and aldehyde components, and the partial reduction would be expected to be limited especially by steric factors, synthetic procedures were sought which might be broader in scope or more readily applicable.

The methods reported here go by way of the product IVa and b[5] of a Reformatski reaction on phenyl cyclohexyl ketone, the ketone being best prepared by the Friedel–Crafts reaction of cyclohexanoyl chloride and benzene. The Reformatski reaction went readily in excellent yield with ethyl bromoacetate or ethyl α-bromopropionate, provided that moisture was excluded rigorously. The two synthetic schemes using the esters IV are illustrated in the chart.

When the ester IVa[5] was treated with two equivalents of methylamine in methanol, a quantitative uptake of amine was found by titration, and an excellent yield of recrystallized amide could be obtained readily. This gave only a fair yield of secondary amine V when it was heated with ethereal lithium aluminum hydride solution for 5.5 hours under reflux, but substantially all of the unreduced amide could be recovered. When the reflux time was increased to 41 hours an 85% yield of analytically pure amine was isolated as hydrochloride.

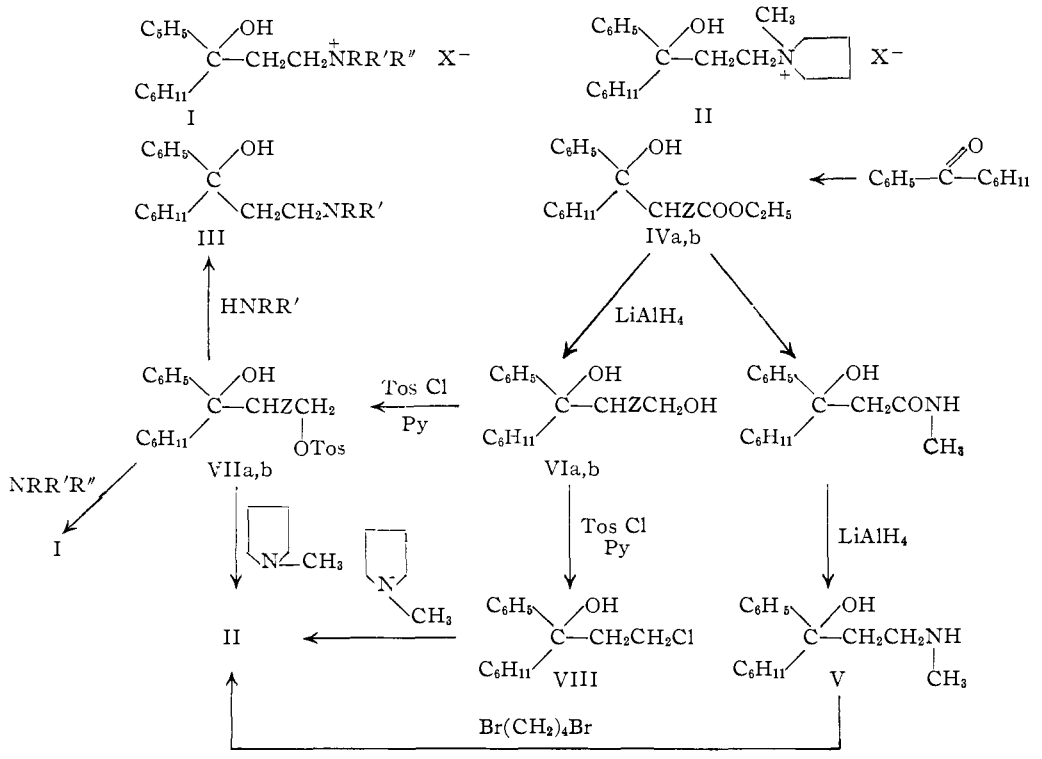
(1) Presented in part before the Division of Organic Chemistry, American Chemical Society, at New York, N. Y., Sept., 1954.

(2) Tricylamol is sold by Burroughs Wellcome & Co. (U.S.A.) Inc. under the trademark Tricoloid.

(3) J. J. Denton and V. A. Lawson, THIS JOURNAL, **72**, 3279 (1950); A. W. Ruddy and J. S. Buckley, Jr., *ibid.*, **72**, 718 (1950), and references given in these.

(4) D. W. Adamson, P. A. Barrett and S. Wilkinson, *J. Chem. Soc.*, 52 (1951).

(5) The final "a" in compounds numbered in this paper indicates that the compounds so numbered bear two hydrogens on the center carbon of the straight chain, *e.g.*, in IVa, Z = H. The "b" series have one methyl group on the same carbon, *e.g.*, IVb, where Z = CH_3.



C_6H_{11} = cyclohexyl; Z = H for compounds of "a" series; Z = CH_3 for "b" series.

Thus, at least in this case, lithium aluminum hydride reduction of an amide to the amine is much slower than the reduction of the related ethyl ester (see below).

When the amine V was treated with 1,4-dibromobutane and potassium carbonate in refluxing ethanol–benzene,[6] a 73% yield of analytically pure tricyclamol bromide was obtained, as well as an additional amount of less pure product. No attempt to use high dilution methods was made. Another example of this preferential cyclization to a pyrrolidinium compound had been reported before our first report[1] and others have appeared since this work was completed.[7]

An alternative, more general synthetic route from the esters IV to the quaternaries I involved lithium aluminum hydride reduction of the esters IVa and b to the glycols VIa and b. Tosylation of VIa with *p*-toluenesulfonyl chloride in benzene in the presence of pyridine under mild conditions gave an excellent yield of the primary tosyl ester VIIa. This, on treatment with N-methylpyrrolidine, gave an excellent yield of tricyclamol tosylate, identical with a known sample. Similarly, treatment of VIIa with N-methylhexamethyleneimine yielded the expected new tricyclamol analog (Ia, R'–R" = $-(CH_2)_6-$, R = CH_3).

When a tosylation reaction containing the glycol VIa, tosyl chloride, pyridine and benzene was heated, however, the crystalline product obtained after cooling was found to be pyridinium tosylate. More pyridine hydrochloride was added, and heating continued until nearly the theoretical amount of pyridinium tosylate was formed. An oil was thus obtained as the neutral, water-insoluble fraction. This could not be induced to crystallize, but was at least largely the primary chloro-compound VIII, since treatment with N-methylpyrrolidine converted it in good yield to tricyclamol chloride, identical to a known sample. This conversion offered no advantage over the direct use of the tosyl ester in the present case, since alkylations normally proceed more rapidly with the latter.[8] Formation of the methylated tosyl ester VIIb by way of VIb went well, although the extreme slowness of the tosylation of VIb as compared to VIa is noteworthy. VIIb was converted by treatment with N-methylpyrrolidine to the expected quaternary analog of II, although a large amount of methylpyrrolidinium tosylate was produced simultaneously.

One attempt to quaternize 1,2-dimethylhexamethyleneimine with VIIa to prepare I, R = CH_3, R'–R" = $-CH(CH_3)(CH_2)_5-$ gave a mixture, but the route *via* the alkylation by VIIa of 2-methylhexamethyleneimine to give the cyclic tertiary amine III, R–R' = $-CH(CH_3)(CH_2)_5-$, and subsequent quaternization of that with methyl iodide, gave the desired quaternary. This is of special interest since the Mannich reaction with acetophenone, formaldehyde and 2-methylhexamethyleneimine is

(6) The authors acknowledge the suggestion of Dr. J. W. Billinghurst, based on other studies, that this reaction be tried.

(7) E. R. Littman and C. S. Marvel, THIS JOURNAL, **52**, 288 (1930); G. E. McCasland and S. Proskow, *ibid.*, **76**, 3486 (1954); G. B. Butler and R. J. Angelo, *ibid.*, **77**, 1767 (1955); J. G. Erickson and J. S. Keps, *ibid.*, **77**, 485 (1955).

(8) Pyridinium chloride has been used preparatively in a few cases for replacement of tosylate by chloride, especially in the sugar field; *cf.* K. Hess and H. Stenzel, *Ber.*, **68**, 981 (1935); H. Rapoport, THIS JOURNAL, **68**, 341 (1946). The reaction is applicable even to a β,γ-acetylenic alcohol: G. Eglinton and M. C. Whiting, *J. Chem. Soc.*, 3650 (1950). Use of this or a related salt would seem to offer advantages over lithium chloride as a source of Cl^- in non-hydroxylic solvents such as benzene, in which LiCl is essentially insoluble.

reported[9] to fail, so that at least one of the alternative routes to this product is unavailable. Similarly, the reaction of VIIa with triethylamine gave an oil which appeared to contain some of the desired triethylammonium analog of Tricoloid (I, R = R′ = R″ = C_2H_5), but which could not be induced to crystallize. Again, the quaternary iodide was finally prepared by alkylating diethylamine with VIIa, and quaternizing the tertiary amine so produced (III, R = R′ = C_2H_5) with ethyl iodide. The iodide proved difficult to crystallize for the first time.

In connection with an exploratory study of alternative routes to compounds of type I, phenyl cyclohexyl ketone was converted to the ethinylcarbinol in quantitative yield by means of sodium acetylide in liquid ammonia. The carbinol was recovered unchanged from an attempt to form the quaternary by addition of methylpyrrolidine across the triple bond, in *t*-butyl alcohol–water solution.[10] Ethinylcarbinols are known not to undergo some other addition reactions of isolated acetylenic linkages. Phenylcyclohexylethinylcarbinol also was reduced by the Lindlar[11] catalyst to the phenylcyclohexylvinylcarbinol.

Antispasmodic Activity.—The quaternary compounds reported above have undergone preliminary screening for atropine-like activity by the guinea pig ileum method. Tricoloid, its triethylammonium analog, and its N-methylhexamethyleneimonium analog had substantial activity, although they were somewhat lower than atropine in maximum specific activity. (The duration of activity of Tricoloid appeared to be greater than that of atropine.) However, the two quaternaries containing methyl group branchings on carbon, 1-methyl-1-(3-phenyl-3-cyclohexyl-3-hydroxypropyl)-2-methylhexamethyleneimonium chloride and 1-methyl-1-(2-methyl-3-phenyl-3-cyclohexyl-3-hydroxypropyl)-pyrrolidinium *p*-tosylate had about 1% of the activity of their non-methylated congeners.

The authors wish to acknowledge many helpful discussions with Dr. Richard Baltzly, and the kind permission of Mr. Amos Light to mention the results of his antispasmodic tests in advance of their publication. Most of the elemental analyses were done by Mr. S. Blackman.

Experimental

Phenyl Cyclohexyl Ketone.—A suspension of 401 g. of powdered anhydrous aluminum chloride in 1150 ml. of benzene which had previously been dried by distillation, was treated with 286 g. of distilled cyclohexanoyl chloride, added in 20 minutes. The resulting dark solution was stirred an additional 10 minutes, then heated under reflux with continued stirring for 3.5 hours, and poured into ice containing 200 ml. of concd. HCl. Separation of the benzene layer, washing the aqueous layer with benzene, washing the benzene extracts successively with dilute aqueous HCl and with aqueous sodium bicarbonate solution, and distillation of the benzene solutions gave 259 g. of crude ketone distilling at 166–173° (22 mm.). From this by recrystallization from Skellysolve B, 217 g. (75%), m.p. 55.5–57.3°, was obtained in two crops.

Ethyl 3-Phenyl-3-cyclohexyl-3-hydroxypropionate.—A solution of 93.5 g. (0.5 mole) of phenyl cyclohexyl ketone and 100 g. (0.6 mole) of freshly distilled ethyl bromoacetate in 250 ml. of dried benzene was added, at a rate which would maintain refluxing, to 39.2 g. (0.6 mole) of HBr-etched 20 mesh zinc granules. A large flask was necessary to prevent losses due to foaming, while still operating at a convenient rate. The reaction started readily when the etched zinc was used and the apparatus had been dried by distilling some benzene through it. After the addition had been completed, the reaction was heated under reflux for an additional 2 hours, cooled, and decomposed by the addition of a saturated aqueous ammonium chloride solution containing 131 g. of NH_4Cl. The benzene layer and two benzene washes were washed, dried, filtered using Supercel, and the benzene was removed at the water-pump. The resulting tan solid was dissolved in ethanol and treated with water to incipient turbidity at 40°. Cooling to about 10° gave 127 g. in two crops, m.p. 55–57°, mixed m.p. depression with starting ketone.

Anal. Calcd. for $C_{17}H_{23}O_3$: C, 74.15; H, 8.37. Found: C, 74.21; H, 8.40.

Ethyl 2-Methyl-3-phenyl-3-cyclohexyl-3-hydroxypropionate.—This compound was prepared in the same way, although the reaction had to be started by addition of a crystal of iodine.

The product was recrystallized from pentane, using Dry Ice cooling, to give an 85.5% yield in two crops of analytically pure ester, m.p. 40–45°.

Anal. Calcd. for $C_{18}H_{26}O_3$: C, 74.44; H, 9.03. Found: C, 74.61; H, 9.39.

N-Methyl-3-phenyl-3-cyclohexyl-3-hydroxypropionamide.—A solution of 27.5 g. (0.1 mole) of the ester IVa and 0.209 mole of methylamine (titration) in 100 ml. of methanol was kept in a pressure bottle at 30–40° until the titer of aliquots with standardized hydrochloric acid and methyl red–methylene blue mixed indicator became constant at the consumption of 0.099 *M* of amine (after 7 days). The solvent and excess amine were removed *in vacuo* at room temperature, and the residue (25.7 g., m.p. 102–108°) was crystallized from methanol–water and recrystallized from nitromethane to yield 19.8 g. of pure product, m.p. 114–116°.

Anal. Calcd. for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.83. Found: C, 73.50; H, 9.09.

1-Phenyl-1-cyclohexyl-1-hydroxy-3-methylaminopropane was prepared by heating a mixture of 4.32 g. (0.11 mole) of lithium aluminum hydride, 9.7 g. (0.037 mole) of N-methyl-3-phenyl-3-cyclohexyl-3-hydroxypropionamide and 200 ml. of absolute ether under reflux for 41 hours. Cautious addition of 11 ml. of water followed by addition of a saturated aqueous solution containing 9 g. of ammonium chloride, separation of the ethereal solution of the amine and conversion of the amine to its hydrochloride gave 9.1 g. of analytically pure product, m.p. 202–204°, not raised on recrystallization from methanol–absolute ether.

Anal. Calcd. for $C_{16}H_{26}NOCl$: Cl^-, 12.50. Found: Cl^-, 12.53.

Essentially the same procedure except for a reflux time of 5.5 hours gave 39% of amine (titration), the remainder of the crude product being unchanged amide.

Tricyclamol Bromide by Alkylation-cyclization.—The amine V obtained from 6.5 g. of hydrochloride (0.0229 mole) by benzene extraction from its alkalized solution was heated under reflux for 21 hours with 5.2 g. (0.024 mole) of 1,4-dibromobutane, 1.6 g. (0.012 mole) of finely powdered anhydrous potassium carbonate, 40 ml. of benzene and 200 ml. of absolute ethanol. The reaction mixture was then cooled and filtered, and the solid washed with ethanol–benzene. The oil remaining on removal of the solvent from the combined solutions was dissolved in a warm mixture of absolute ethanol–benzene (1:6 by volume), filtered to remove a little inorganic solid, and treated with absolute ether to faint turbidity. A first crop of 6.4 g. (73%), m.p. 191–195°, was obtained.

Anal. Calcd. for $C_{20}H_{32}NOBr$: Br, 20.90. Found: Br, 20.71.

(9) F. F. Blicke and W. J. Doorenbos, THIS JOURNAL, **76**, 2317 (1954).

(10) C. Gardner, *et al.*, *J. Chem. Soc.*, 789 (1949), describes in detail the addition of acetylene to aqueous trimethylamine to give trimethylvinylammonium hydroxide. W. Reppe, "Neue Entwicklungen auf dem Gebiete der Chemie des Acetylens und Kohlenoxyds," Springer, Berlin, 1949, p. 22, mentions use of other hydrocarbon-substituted acetylenes in this reaction. No attempt to cause ethinylcarbinols to react with tertiary amines in this way has been noted by the authors.

(11) H. Lindlar, *Helv. Chim. Acta*, **35**, 446 (1952).

A less pure second crop, 1.06 g., m.p. 158–180°, was obtained by further dilution with ether.

A portion of the purer first crop of bromide was converted to the chloride in quantitative yield by means of silver chloride suspended in methanol. The chloride gave no m.p. depression when admixed with a known sample.

1-Phenyl-1-cyclohexyl-1,3-propanediol.—The reduction of 27.5 g. of compound IVa by 5.7 g. of lithium aluminum hydride in a total of 350 ml. of absolute ether gave, after 1.5 hours under reflux and the usual decomposition with water, solution of inorganics in dilute sulfuric acid, bicarbonate wash, drying and removal of solvent by distillation, 23.1 g. (99.5%) of white crystalline solid, m.p. 92–96°. A portion was recrystallized from hexane to constant m.p. 93–94°.

Anal. Calcd. for $C_{15}H_{22}O_2$: C, 76.88; H, 9.45. Found: C, 77.36; H, 8.94.

1-Phenyl-1-cyclohexyl-2-methyl-1,3-propanediol was prepared and recrystallized analogously; m.p. 141–142°.

Anal. Calcd. for $C_{16}H_{24}O_2$: C, 77.39; H, 9.75. Found: C, 77.31; H, 9.68.

1-Phenyl-1-cyclohexyl-3-*p*-toluenesulfonoxypropanol.—A solution of 30 g. of 1-phenyl-1-cyclohexyl-1,3-propanediol in 40.5 g. of dry pyridine and 40 ml. of dry benzene was cooled in an ice–salt-bath and a solution of 27 g. of freshly recrystallized *p*-toluenesulfonyl chloride in 40 ml. of dry benzene was added with stirring during ten minutes. The temperature of the reaction was maintained between its freezing point and 20° during the addition. The reaction mixture was then stirred at 20° for 6.5 hours with exclusion of moisture, washed with dilute aqueous hydrochloric acid, then with aqueous sodium bicarbonate, then with water, and concentrated on the steam-bath at water-pump pressure. Addition of hexane to the resulting oil caused it to solidify, yielding 42.5 g., m.p. 80–85°. Recrystallization of this and of other batches of this compound from benzene–hexane gave m.p. varying from 74 to 102°, depending on the rate of heating and on the observer. A sample was recrystallized twice for analysis, m.p. 93–97° (3°/min.).

Anal. Calcd. for $C_{22}H_{28}SO_4$: C, 68.02; H, 7.26. Found: C, 67.85; H, 7.47.

1-Phenyl-1-cyclohexyl-2-methyl-3-*p*-toluenesulfonoxypropanol.—A mixture of 9.6 g. of the glycol, 12.2 g. of pyridine and 45 ml. of dry benzene was treated with 8.1 g. of *p*-toluenesulfonyl chloride in 25 ml. of dry benzene. After having remained for 3 days, the solution was diluted to 225 ml. with benzene, and kept at room temperature until no more pyridine hydrochloride crystallized. This required 11 additional days, after which the crystals represented 34 of the theoretical 38.7 millimoles of Cl^-. A yield of 11.7 g., m.p. 100–103°, was obtained from the benzene solution, and was recrystallized from benzene–hexane.

Anal. Calcd. for $C_{23}H_{30}SO_4$: C, 68.62; H, 7.53. Found: C, 68.36; H, 7.43.

Tricyclamol (II) *p*-Toluenesulfonate.—A mixture of 3.89 g. of 1-phenyl-1-cyclohexyl-3-*p*-toluenesulfonoxypropanol, 1.70 g. of N-methylpyrrolidine, 18 ml. of absolute ethanol and a trace of phenol was heated at 65–80° for 4 days. Addition of benzene and absolute ether caused crystallization of 3.9 g., identical in m.p. (168.3–169°) and mixed m.p. with a known sample prepared from methyl *p*-toluenesulfonate and the appropriate tertiary amine.

1-Methyl-1-(3-phenyl-3-cyclohexyl-3-hydroxypropyl)-hexamethyleneimonium *p*-Toluenesulfonate.—The same quaternization procedure outlined above for the preparation of tricyclamol *p*-toluenesulfonate gave 70% of crude product, m.p. 171–173.5°. Two recrystallizations from anhydrous ethanol–ether gave white platelets, m.p. 174–175°.

Anal. Calcd. for $C_{29}H_{43}NSO_4$: C, 69.47; H, 8.62. Found: C, 69.40; H, 8.74.

1-Phenyl-1-cyclohexyl-3-(2-methylhexamethyleneimine-1-yl)-propanol.—A solution of 11.7 g. of the tosyl ester IVa and 6.8 g. of 2-methylhexamethyleneimine in 100 ml. of methanol was heated in a sealed bottle at 80° for 5 days. Most of the methanol was removed *in vacuo*, and the residue was partitioned between ether and aqueous sodium bicarbonate. The ether layer was extracted with dilute aqueous hydrochloric acid, and the aqueous acid layer as well as an oily layer which formed at this point, were alkalized and extracted first with ether, then with benzene. The dried solvent layers were combined and all possible solvent was removed *in vacuo* on the steam-bath. The residue was 7.3 g. of a tan oil, which had an equivalent weight of 343 by electrometric titration (theory 329.5). This amine was quaternized without further purification.

1-Methyl-(3-phenyl-3-cyclohexyl-3-hydroxypropyl)-2-methylhexamethyleneimonium Chloride.—A solution of 7.3 g. of crude 1-phenyl-1-cyclohexyl-3-(2-methylhexamethyleneimine-yl)-propanol and 6.4 g. of methyl iodide in 30 ml. of methanol was heated in a sealed bottle for two days at 80°, and then kept at room temperature an additional 3 days. The crude brown quaternary iodide (12.5 g.) was caused to crystallize by evaporation of the solvent at the water-pump, and addition of ether to the resulting gum. It was substantially insoluble in water, and so was converted to the chloride by shaking it for two hours in methanolic solution with the silver chloride freshly precipitated from 8.9 g. of silver nitrate by aqueous hydrochloric acid. Evaporation of solvent gave the crude chloride, which was recrystallized in rather poor recovery from methanol (little)–acetone, m.p. 225–228° dec.

Anal. Calcd. for $C_{23}H_{38}NOCl$: Cl^-, 23.35. Found: Cl^-, 22.90.

1-Phenyl-1-cyclohexyl-3-diethylaminopropanol.[12]—A solution of 7.77 g. of the tosyl ester VIIa and 2.92 g. of diethylamine in a total volume of 100 ml. of anhydrous methanol was heated for 3 days at 80° in a pressure bottle, and allowed to stand for 5 days more at room temperature. The methanolic solution was concentrated to half its volume and partitioned between benzene and dilute aqueous hydrochloric acid. The hydrochloride was then reconverted to base, extracted with ether, and the ethereal solution dried and concentrated on the steam-bath to yield 3.2 g. of residual base. A portion was converted to its hydrochloride, which was recrystallized from methanol–ether for analysis, m.p. 182–185°.

Anal. Calcd. for $C_{19}H_{32}NOCl$: C, 70.08; H, 9.60. Found: C, 69.88; H, 9.42.

1,1,1-Triethyl-1-(3-phenyl-3-cyclohexyl-3-hydroxypropyl)-ammonium Iodide.—A solution of 3 g. of the above diethylaminopropanol and 4 g. of ethyl iodide in 30 ml. of absolute ethanol was kept at room temperature shielded from light for 9 days. The gum resulting from distillation of the solvent on the steam-bath *in vacuo* was eventually crystallized from methanol–ether, and could then be recrystallized readily, m.p. 175–178°.

Anal. Calcd. for $C_{21}H_{36}NOI$: I^-, 28.45. Found: I^-, 28.40.

1-Methyl-1-(3-phenyl-3-cyclohexyl-3-hydroxy-2-methylpropyl)-pyrrolidinium *p*-Toluenesulfonate.—A solution of 6 g. of 1-phenyl-1-cyclohexyl-2-methyl-3-*p*-toluenesulfonoxypropanol and 2.6 g. of methylpyrrolidine in 80 ml. of absolute methanol was maintained in a sealed bottle for 13 days at 40°. The methanol and excess methylpyrrolidine were then evaporated off on the steam-bath. The residue was dissolved in a minimal amount of methanol and absolute ether was added to precipitate a light brown oil which gradually crystallized to yield 3.1 g., m.p. 75–79°. Repeated extraction of this material with boiling ethyl acetate, and cooling of the extracts gave 1.76 g. of crude N-methylpyrrolidinium *p*-tosylate as a crystalline filtration residue. The combined filtrates, on evaporation and recrystallization of the resulting residue from methanol–ether gave 1.4 g. of an oil, which crystallized slowly, m.p. 80–103°. This was again dissolved in hot ethyl acetate, treated with charcoal, filtered, concentrated and cooled to give 560 mg. of colorless crystals, m.p. 156–158°, not raised on recrystallization.

Anal. Calcd. for $C_{29}H_{41}NO_4S$: C, 69.00; H, 8.48. Found: C, 69.11; H, 8.50.

Phenylcyclohexylethinylcarbinol.—To two liters of liquid ammonia was added, with slow stirring, 23 g. of sodium, as rapidly as possible, followed immediately by addition of acetylene (acetone was removed by precooling the gas in a Dry Ice trap without solvent) at about 3 l./min. until a slightly hazy gray solution was obtained, and for an additional 5 minutes to ensure complete conversion to monosodium compound. A stiff steel wire must be used occasionally to keep sodium salts from clogging the acetylene inlet tube. The acetylene inlet was then replaced by a

(12) J. J. Denton, W. B. Neier and V. A. Lawson, THIS JOURNAL, **71**, 2053 (1949).

dropping funnel, and a solution of 150 g. of phenyl cyclohexyl ketone in 200 ml. of ether was added dropwise with stirring, followed by addition of another 500 ml. of absolute ether to bring the resulting precipitate largely into solution. After 5 hours, the Dry Ice condenser was replaced by a water-cooled condenser. An additional 500 ml. of absolute ether was added to replace the ammonia lost, and the mixture allowed to stir slowly overnight. The remaining ammonia was then removed by warming the solution until ether could be seen to reflux vigorously, and the reaction mixture was brought to *p*H 4–5 by addition of aqueous (25%) acetic acid. The ether layer was separated, washed once with acetic acid and once with aqueous sodium bicarbonate. The aqueous layers were re-extracted with ether and the combined ether layers were distilled. The 167 g. of moderately viscous clear liquid product boiled at 109° (0.5 mm.) on slow distillation, at 115° (0.05 mm.) on rapid distillation. It had $n^{25}D$ 1.5469, and 1.03 acetylenic H/mole.[13]

Phenylcyclohexylvinylcarbinol.—The reduction of 33 g. of phenylcyclohexylethinylcarbinol, run according to Lindlar (ref. 11), became too slow to detect after 1.05 moles of H_2 was taken up per mole of the ethinylcarbinol. The product was worked up by filtration, extraction with dilute acetic acid to *p*H 4, and distillation, and 30.8 g., b.p. 100–101° (0.2 mm.), was obtained. This had no detectable acetylenic H, $n^{25}D$ 1.5453.

Anal. Calcd. for $C_{15}H_{20}O$: C, 83.23; H, 9.31. Found: C, 82.77; H, 9.04.

(13) S. Siggia, "Quantitative Organic Analysis *via* Functional Groups," John Wiley & Sons, Inc., New York, N. Y., 1949, p. 55.

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Molecular Complex Formation of 2,5-Diphenyl-1,4-dithiadiene

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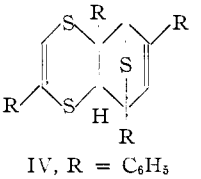
The previously reported substance obtained during the oxidation of 2,5-diphenyl-1,4-dithiadiene is shown to be a complex of the starting material and 2,4-diphenylthiophene which exists only in the solid state. A similar complex is formed with 2,4-diphenylfuran but not with 2,5-diphenylthiophene. The monosulfone of 2,5-diphenyl-1,4-dithiadiene is proven not to be the intermediate in the formation of 2,4-diphenylthiophene contrary to a recent claim to that effect.

The substance I isolated[2] during the oxidation of 2,5-diphenyl-1,4-dithiadiene II with equimolar quantities of hydrogen peroxide was carefully investigated in order to determine its structure. It was soon found that, when subjected to various reactions, this material gave derivatives of either II or of 2,4-diphenylthiophene III. Thus, on further oxidation of I under mild conditions there was isolated the monosulfone of II and unreacted III, and on more vigorous oxidation I gave the previously reported disulfone of II.[2] Bromination of I led to a dibromo derivative of II identical with the product of direct bromination of II. On the other hand, chloromercuration of I was shown to give the chloromercuri derivative of III.

The redetermination of the molecular weight of I gave a value which agreed with the average of the molecular weights of II and III, and the ultraviolet spectrum of I was shown to be identical with the curve calculated for an equimolar mixture of II and III. Finally, it was shown that crystallization of an equimolar mixture of II and III gave essentially quantitative yields of I.

All of these experimental facts still did not seem definitive in distinguishing with complete certainty between the possibilities that I is a molecular complex of II and III, or that I is a Diels–Alder adduct of structure IV which, because of the sulfur bridge and the generally recognized inhibition of thiophene derivatives to form Diels–Alder adducts,[3] could easily dissociate into the original components. Such a dissociation would explain the ultraviolet spectrum of I and the molecular weight data since these determinations are performed with solutions of high dilution. For this reason an attempt to separate the components of I by chromatography seemed to be particularly significant since this technique involves the use of concentrated solutions. This experiment proved successful and it is thus concluded that I is a molecular complex of II and III which exists only in the solid state.[4]



IV, R = C_6H_5

In view of the apparent absence in II and III of electron-donating and electron-accepting properties which ordinarily are associated with complex formation,[5,6] it was of interest to examine possible complex formation of II with other substances. The isomer of III, namely, 2,5-diphenylthiophene was shown not to form a complex, while 2,4-diphenylfuran gave a molecular complex the ultraviolet spectrum of which was again identical with that calculated for an equimolar mixture of the two components. These facts indicate that successful complex formation of II depends on the location of the phenyl groups in the five-membered

(1) From the M.S. thesis of L.M.A., Duquesne University, 1955.

(2) H. H. Szmant and J. Dixon, THIS JOURNAL, **75**, 4354 (1953).

(3) See the discussion by O. Dann, M. Kokorudz and R. Gropper in *Ber.*, **87**, 140 (1954).

(4) While this work was in progress Parham and Traynelis (THIS JOURNAL, **76**, 4960 (1954)) also concluded that I was a complex on the basis of ultraviolet absorption data, chloromercuration and formation from the components.

(5) R. S. Mulliken, *J. Phys. Chem.*, **56**, 801 (1952).

(6) L. N. Ferguson, *J. Chem. Ed.* **31** 626 (1954).