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Some Reactions and Derivatives of 2,2-Diphenylcyclopentanone[1a]

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The preparation of several potential analgetics derived from 2,2-diphenylcyclopentanone and the reaction of some intermediate compounds is reported. An improved synthesis of the ketone is demonstrated.

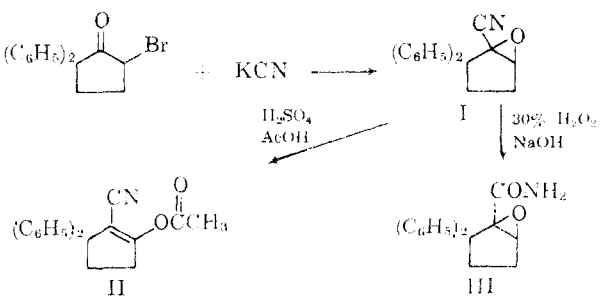
Previous publications[2-4] have disclosed the preparation of several substituted 2,2-diphenylcyclopentanones and have pointed out the structural relationships to the methadone class of analgetics. It was of interest to us to enlarge the scope of this synthesis and study various derivatives of these ketones.

The preparation of 2,2-diphenylcyclopentanone[3] consisted of the alkylation of diphenylacetonitrile with γ-chlorobutyronitrile followed by cyclization of the dinitrile and vigorous hydrolysis of the 2,2-diphenyl-5-cyanocyclopentanoneimine. Since the alkylation gave a mixture of products which was difficult to separate, this method gave a poor yield of the 2,2-diphenyladiponitrile. It was felt that if a trimethylene halide were used in the alkylation, the resulting halonitrile could be transformed to the dinitrile readily. Trimethylene iodide and trimethylene bromide gave largely 2,2,6,6-tetraphenylpimelonitrile, but the use of trimethylene chlorobromide, with dioxane as the solvent, gave virtually a quantitative yield of 5-chloro-2,2-diphenylpentanenitrile. The replacement of the halide with a nitrile group, using dimethylformamide as the solvent, was accomplished in an 87% yield. The 2,2-diphenyladiponitrile[5,6] melted at 66–67°, which confirms previous[3] results from these Laboratories.

Cyclization of the dinitrile gave 2,2-diphenyl-5-cyanocyclopentanoneimine[3] and a small quantity of a high melting compound which analyzed for the cyclic dimer,[7] 2,2,7,7-tetraphenyl-5,10-dicyano-1,6-diiminocyclodecane. Although the 5-membered imino nitrile has been hydrolyzed to give several products,[3,8] at no time has 2,2-diphenyl-5-cyanocyclopentanone been isolated. This keto nitrile and the corresponding keto acid were of interest to us. The inability to obtain this keto nitrile by preferential hydrolysis of the imino group is in contrast to the reactivity of other 2,2-disubstituted-5-cyanocyclopentanoneimines.[8] The bulky phenyl groups undoubtedly decrease the reactivity of the imino function as has been observed for other hindered imines.[9] The imino nitrile did not form a hydrochloride when an ether solution of the free base was saturated with hydrogen chloride. Diazotization of the imine-enamine nitrile with butyl nitrite–hydrogen chloride[10] gave a minute quantity of a solid which was not the desired material.

It appeared feasible to prepare 2,2-diphenyl-5-cyanocyclopentanone in the way 2-cyanocyclohexanone has been prepared from 2-bromocyclohexanone.[11] Treatment of 5-bromo-2,2-diphenylcyclopentanone[3] with potassium cyanide in water, ethanol, or dimethylformamide gave a product (I) isomeric with the desired keto nitrile. The infrared spectrum of I did not have any carbonyl absorption but did show the presence of nitrile and a strong absorption at 11.3 μ due to the 1,2-epoxide linkage.[12] The formation of I under these conditions had been predicted by Tchoubar.[13] Since it has been shown[14] in a hindered α-bromo ketone that the displacement of the bromine by methoxide was facilitated in liquid ammonia, the use of sodium cyanide in liquid ammonia was attempted, but this was also unsuccessful. Treatment of I with sulfuric acid followed by acetic acid gave an enol ester (II). Treatment of I with 30% hydrogen peroxide in the presence of sodium hydroxide gave the epoxy amide III.

CHART I



(1) (a) From the Ph.D. thesis of S. S. K., Lehigh University, 1957; (b) author to whom inquires should be addressed at Moravian College, Bethlehem, Pa.

(2) P. N. Craig and I. H. Witt, *J. Am. Chem. Soc.*, **72**, 4025 (1950).

(3) N. R. Easton and S. J. Nelson, *ibid.*, **75**, 640 (1953).

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(5) (a) F. Salmon-Legagneur and C. Neven, *Compt. rend.*, **237**, 64 (1953); (b) F. Salmon-Legagneur and C. Neven, *ibid.*, **239**, 1809 (1954); (c) F. Salmon-Legagneur, *Bull. soc. chim. France*, (5) **23**, 411 (1956); (d) F. Salmon-Legagneur, *ibid.*, (5) **23**, 920 (1956).

(6) E. Tagmann, E. Sory, and K. Hoffmann, *Helv. Chim. Acta.*, **35**, 1541 (1952).

(7) K. Ziegler and R. Aumüllamper, *Ann.*, **513**, 43 (1934).

(8) To be published.

(9) (a) P. L. Pickard and E. F. Engles, *J. Am. Chem. Soc.*, **74**, 4607 (1952); (b) P. L. Pickard and E. F. Engles, *ibid.*, **72**, 876 (1950); (c) D. J. Cram, F. A. A. Elhafez, and H. L. Nyquist, *ibid.*, **76**, 22 (1954); (d) R. C. Fuson, W. D. Emmons, and J. P. Freeman, *ibid.*, **75**, 5321 (1953); (e) F. A. Vingiello and A. Borkovec, *ibid.*, **77**, 3413 (1955); (f) J. B. Culbertson, *ibid.*, **73**, 4818 (1951).

(10) N. Sperber, D. Papa, and E. Schwenk, *ibid.*, **70**, 3091 (1948).

(11) K. V. Auwers, *Ber.*, **61**, 415 (1928).

(12) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, New York, N. Y., 1954, p. 103.

(13) B. Tchoubar, *Bull. Soc. Chim. France*, (5) **22**, 1363 (1955).

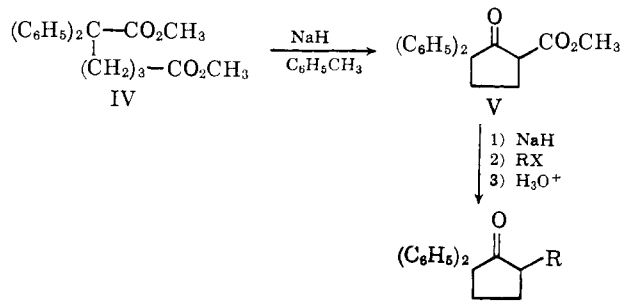
(14) C. L. Stevens and A. J. Weinheimer, *J. Am. Chem. Soc.*, **80**, 1072 (1958).

Two other routes to the desired keto nitrile were unsuccessful, since only starting materials were recovered when ethyl diphenylacetate was reacted with trimethylene chlorobromide and the partial saponification of methyl 2,2-diphenyladipate to 5,5-diphenyl-5-carbomethoxypentanoic acid[5] gave an inseparable mixture of products in our hands.

Attempts to prepare the 5-carbethoxy compound by acylation of the cyclopentanone were unsuccessful. No product was obtained when 2,2-diphenylcyclopentanone was treated with ethyl oxalate and either sodium methoxide or potassium *t*-butoxide, or ethyl carbonate and sodamide.

Although it is reported[5] that 2,2-diphenyladipic acid could not be obtained from the hydrolysis of the 2,2-diphenyladiponitrile, we were able to effect this conversion. An over-all yield of 80% was obtained *via* the diamide and amide acid. Analyses and infrared spectra of our intermediates were compatible with the assigned structures (see Experimental). The diacid could then be converted to the diester (IV) and on cyclization gave 5-carbomethoxy-2,2-diphenylcyclopentanone (V). Although this keto ester was difficult to purify, its copper chelate was obtained in a reasonably pure state. The crude material could be alkylated with methyl iodide, diethylaminoethyl chloride, and dimethylaminoethyl chloride. Alkylation with 3-dimethylaminopropyl chloride was unsuccessful. The alkylated products could be hydrolyzed and decarboxylated to give the corresponding diphenylcyclopentanone derivatives.

CHART II



VI, R = CH_3
VII, R = $CH_2CH_2NEt_2 \cdot HCl$
VIII, R = $CH_2CH_2NMe_2 \cdot HCl$
IX, R = $CH_2NMe_2 \cdot HCl$

Compounds VII–IX (Chart II), when tested by a modification[15] of the method of Davies[16] and co-workers, at doses approximately $LD_{50}/_{10}$, showed no appreciable analgetic activity.

Experimental[17]

5-Chloro-2,2-diphenylpentanenitrile.—Sodio-diphenylacetonitrile was prepared under nitrogen from 21.6 g. (0.555 mole) of sodamide and 107 g. (0.555 mole) of diphenylacetonitrile in 500 ml. of dry dioxane by heating the mixture under reflux for 8 hr. Upon cooling in an ice bath, solidification occurred and stirring was stopped. A solution of 174 g. (1.111 moles) of trimethylene chlorobromide in an equal volume of dry dioxane was added in one portion. The ice bath was removed temporarily and the entire apparatus shaken manually until an exothermic reaction started. Mechanical stirring was resumed (cooling when necessary). After the reaction ceased to be exothermic (*ca.* 2 hr.), the mixture was refluxed for 10 hr., cooled, and filtered with suction. The filter cake was dissolved in water, extracted with benzene, and the extract was added to the filtrate. The combined organic solutions were evaporated initially at about 20 mm. and finally at 1 mm. pressure and 55°. The residue solidified upon cooling and standing overnight to yield 145 g. (97%) of product melting at 89–92.5°. The analytical sample was recrystallized several times from methanol to constant m.p. 92–93°.

Anal. Calcd. for $C_{17}H_{16}ClN$: C, 75.67; H, 5.99; N, 5.19. Found: C, 75.35; H, 5.97; N, 5.09.

When the dihalide was added too slowly or the exothermic reaction was not controlled, the substituted pimelonitrile described below was obtained as the major product or as an appreciable contaminant.

5-Chloro-2,2-diphenylpentanoamide.—A mixture of 37 g. of the nitrile in 150 ml. of concentrated sulfuric acid, 30 ml. of acetic acid, and 30 ml. of water was heated overnight on the steam bath with stirring. Work-up gave 32 g. (80%) of white solid, m.p. 109.5–111.5°. After recrystallization from methanol and then from isopropyl ether, the analytical sample melted at 113–114°.

Anal. Calcd. for $C_{17}H_{18}ClNO$: C, 70.95; H, 6.30; N, 4.87. Found: C, 71.05; H, 6.50; N, 4.88.

5-Bromo-2,2-diphenylpentanenitrile.—This compound was prepared like the chloro analog but using trimethylene bromide. The crude reaction product was fractionally distilled to give the main product, b.p. 170–200° (0.2–0.5 mm.), and a residue. The distillate crystallized from methanol and after recrystallization from methanol appeared as white crystals, m.p. 93–94.5° (lit.[18] m.p. 77–78°).

Anal. Calcd. for $C_{17}H_{16}BrN$: C, 64.97; H, 5.13; N, 4.46. Found: C, 65.15; H, 5.15; N, 4.51.

The residue crystallized from ethanol and was the dicondensation product described below.

2,2,6,6-Tetraphenylpimelonitrile.—This compound was prepared by reacting sodio-diphenylacetonitrile with trimethylene bromide in 2:1 *M* ratio. The crude oil obtained was dissolved in the minimum amount of methanol and gave crystals (m.p. 113–116°) when an equal volume of petroleum ether (28–38°) was added. A sample after recrystallization from methanol melted at 117–118.5°.

Anal. Calcd. for $C_{41}H_{26}N_2$: C, 87.30; H, 6.14. Found: C, 87.70; H, 6.42.

2,2,6,6-Tetraphenylpimelamide.—This diamide was obtained by heating the above dinitrile with 90% sulfuric acid for 2 hr. on a steam bath with stirring. After quenching with ice–water, the mixture was extracted with ether. Evaporation of the solvent left a white solid, m.p. 192.5–195°. Recrystallization from ethyl acetate gave crystals, m.p. 195–196.5°.

Anal. Calcd. for $C_{31}H_{30}N_2O_2$: C, 80.49; H, 6.54. Found: C, 80.65; H, 6.48.

2,2-Diphenyladiponitrile.—A solution of 270 g. (1.0 mole) of 5-chloro-2,2-diphenylpentanenitrile in 700 ml. of dimethylformamide was added dropwise over about 3 hr. to a stirred, refluxing mixture of 60 g. (1.2 moles) of powdered sodium cyanide, 350 ml. of dimethylformamide, and 20 ml. of water. Refluxing and stirring were maintained for about 75 hr. After cooling, the mixture was poured on 2 l. of ice and allowed to stand in ice overnight. The liquid portion was extracted 3 times with benzene and the combined benzene extracts were used to dissolve the semisolid. After removing the benzene at reduced pressure, the organic material was distilled *in vacuo*. A total of 207 g. (86%) of product was obtained within the b.p. range 160–180° (0.1 mm.). Crystallization from methanol gave a white solid, m.p. 64–65° (lit.[3] 66–67°).

5-Cyano-2,2-diphenylcyclopentanoneimine.—This compound was prepared according to the literature.[3] In one run starting with 12.5 g. of linear dinitrile the crude product obtained, after the reaction solvent had been removed, was partially dissolved in isopropyl ether. The ether extract was washed with water, dried over magnesium sulfate, and filtered. Saturation of the dry ether solution at 0° with hydrogen chloride caused precipitation of 10 g. of solid which was the free ketimine and not the expected hydrochloride. The 1.5 g. of solid which had not dissolved in the isopropyl ether originally gave white crystals,

(15) "Research Today," Vol. IX, No. 1, Eli Lilly and Company, Indianapolis, Indiana, 1953, p. 22.

(16) O. L. Davies, J. Raventas, and A. L. Walpole, *Brit. J. Pharmacol.*, **1**, 255 (1946).

(17) Melting points are corrected and were determined in a Mel-Temp apparatus.

(18) D. J. Dupre, J. Elks, B. A. Hems, K. N. Speyer, and R. M. Evans, *J. Chem. Soc.*, 500 (1949).

m.p. 221.5–222.5°, from benzene–ethanol and analyzed for the cyclic dicyanodiimino compound.[7]

Anal. Calcd. for $C_{16}H_{32}N_4$: C, 83.04; H, 6.20; N, 10.72. Found: C, 82.70; H, 6.40; N, 10.72.

Attempted Partial Hydrolysis of 5-Cyano-2,2-diphenylcyclopentanoneimine.—All attempts to obtain 2,2-diphenyl-5-cyanocyclopentanone were unsuccessful. The conditions used included 8 *N* sulfuric acid, 100% phosphoric acid, hydrochloric acid, pyruvic acid,[19] and inert solvents in various amounts.

A solution of 2 g. of the cyclic imino nitrile (existing mainly in the enamine tautomer) in dioxane was treated with a slow stream of hydrogen chloride for 1 min. Butyl nitrite was added dropwise with shaking over 15 min. until the reaction flask had gained 1.6 g. During most of the addition gas evolution occurred and heat was evolved. The mixture was allowed to stand at room temperature for 0.5 hr., then was heated on the steam bath 0.75 hr. with intermittent shaking. After cooling, the solvent was removed under reduced pressure. Isopropyl ether was added to the residual oil and upon standing in the refrigerator for several days crystals which melted at 145–148° were obtained. These crystals after being recrystallized from methanol and from isopropyl ether melted at 156–157° and gave a strong Beilstein test. Insufficient pure material was obtained for analysis. A tentative structural assignment for this compound is 2-chloro-3,3-diphenylcyanocyclopentene.

5-Bromo-2,2-diphenylcyclopentanone.—A solution of 30 g. (0.127 mole) of 2,2-diphenylcyclopentanone[3] in dry dioxane was cooled and 31.6 g. (0.127 mole) of solid dioxane–bromide complex[20] was added with shaking and cooling in an ice bath. The solution was allowed to warm to room temperature overnight, refluxed 1 hr., and solvent was slowly distilled until no further evolution of hydrogen bromide occurred. The remaining solvent was removed under reduced pressure. The residue was dissolved in benzene and this solution was washed with water. The benzene was removed under reduced pressure and the residue crystallized *in vacuo* upon cooling. The crude product weighed 40.5 g. (*ca.* 100%) and a sample upon recrystallization from methanol melted at 94.5–96.5° (lit.[3] 99.5–100.5°).

2-Cyano-3,3-diphenyl-1,2-epoxycyclopentane.—An ethanolic solution of 40.5 g. (0.13 mole) of 5-bromo-2,2-diphenylcyclopentanone was added rapidly to a refluxing aqueous solution of 13.0 g. (0.20 mole) of potassium cyanide. Stirring and heating were maintained overnight. Most of the solvent was removed under reduced pressure and water was added to the residue. Extraction with benzene, followed by removal of the benzene, left an oil which was crystallized from methanol. The crude crystalline product weighed 22.2 g. (67%). Several recrystallizations from methanol gave a white solid, m.p. 131–132°.

Anal. Calcd. for $C_{18}H_{15}NO$: C, 82.72; H, 5.80; N, 5.36. Found: C, 82.60, 82.90; H, 5.97, 6.00; N, 5.41.

The infrared spectrum ($CHCl_3$ solution) showed no absorption in the carbonyl region but peaks for nitrile (4.46 μ) and epoxide (11.32 μ).

2-Carbamoyl-3,3-diphenyl-1,2-epoxycyclopentane.—A solution of 0.5 g. of the preceding nitrile was treated with 5 ml. of 30% hydrogen peroxide at room temperature. The addition of 10 ml. of 6 *N* sodium hydroxide with shaking caused two layers to separate, however, an exothermic reaction occurred. After the flask had cooled to room temperature the mixture was heated on the steam bath for several min. Cooling in ice followed by the addition of some crushed ice gave white crystals, m.p. 150–151.5°. Recrystallization from methanol did not change the melting point.

Anal. Calcd. for $C_{18}H_{17}NO_2$: C, 77.39; H, 6.14; N, 5.02. Found: C, 77.30; H, 6.12; N, 5.11.

The infrared spectrum ($CHCl_3$ solution) showed absorption due to NH stretching (2.86, 2.96 μ), carbonyl (5.90 μ), and epoxide (11.34 μ).

1-Acetoxy-2-cyano-3,3-diphenylcyclopentene.—Refluxing epoxy nitrile I with dilute sulfuric acid in glacial acetic acid and pouring the reaction mixture on ice gave crystals. Recrystallization from methanol gave a white solid, m.p. 121–122.5°.

Anal. Calcd. for $C_{20}H_{17}NO_2$: C, 79.18; H, 5.65; N, 4.62. Found: C, 79.60, 79.65; H, 6.15, 6.05; N, 4.54.

The infrared spectrum ($CHCl_3$ solution) showed absorption by a conjugated nitrile (4.46 μ), carbonyl (5.72 μ), and C–O stretch (8.10 μ) in acetate. There was no absorption in the epoxide range.

2,2-Diphenyladipamide.—To 100 ml. of 80% sulfuric acid was added 10 g. of 2,2-diphenyladiponitrile and the mixture was heated on the water bath while vigorously stirring for 6 hr. After some cooling, the mixture was poured on ice to give an oil which solidified upon standing, m.p. 196.5–197.5°. The solid was recrystallized from methanol, m.p. 202–203° (lit.[5] 183–185°).

Anal. Calcd. for $C_{18}H_{20}N_2O_2$: C, 72.95; H, 6.80; N, 9.45. Found: C, 73.00; H, 6.92; N, 9.26.

The infrared spectrum (Nujol mull) showed peaks for NH (2.92 μ), bonded NH (3.3–3.25 μ), and carbonyl (5.93 μ). The curve appeared to be changed by crystal effects.

5-Cyano-5,5-diphenylpentanoic Acid.—To 100 ml. of 3:2 dioxane–concentrated hydrochloric acid was added 4 g. of 2,2-diphenyladiponitrile and the mixture was refluxed 48 hr. After cooling, the mixture was poured on ice. The precipitate was filtered and dissolved in 10% sodium hydroxide solution. Upon acidification it gave 4.25 g. (99%) of dry acid, m.p. 187.5–191.5°. After several recrystallizations from methanol, the analytical sample melted at 195.5–197.5° (lit.[5] 182–183°).

Anal. Calcd. for $C_{18}H_{17}NO_2$: C, 77.39; H, 6.14; N, 5.02; neut. equiv., 279. Found: C, 77.35; H, 6.23; N, 4.99; neut. equiv., 280.

The infrared spectrum (Nujol mull) showed no peaks in the NH stretching region, no nitrile peak, but strong carbonyl absorption (5.84 μ).

5-Carbamoyl-5,5-diphenylpentanoic Acid. A.—To 50 ml. of 5:1 concentrated sulfuric acid–acetic acid was added 4.2 g. of crude 5-cyano-5,5-diphenylpentanoic acid and the mixture was refluxed with stirring for 1 hr. Water (8 ml.) was added and heating on the steam bath was continued for 4 hr. The mixture, after partially cooling, was poured on ice and allowed to stand in the refrigerator overnight. The solid was filtered, taken up in sodium hydroxide, acidified, filtered, and recrystallized from a mixture of ethyl acetate–ethanol to give a white solid, m.p. 190.5–191.5° (lit.[5] 183–184°).

B.—Crude 2,2-diphenyladipamide upon basic hydrolysis with 10% potassium hydroxide gave the same compound.

Anal. Calcd. for $C_{18}H_{19}NO_3$: C, 72.70; H, 6.44; N, 4.71; neut. equiv., 297. Found: C, 72.80; H, 6.62; N, 4.64; neut. equiv., 297.

The infrared spectrum (Nujol mull) showed NH stretch (2.90 μ), bonded NH (3.04–3.18 μ), carboxyl carbonyl (5.86 μ), and amide carbonyl (6.09 μ).

2,2-Diphenyladipic Acid.—To 200 ml. of 80% sulfuric acid was added 20 g. of 2,2-diphenyladiponitrile and the mixture was heated on the water bath while vigorously stirring for 12 hr. After cooling, the mixture was poured on ice and allowed to solidify. The solid was filtered by suction, washed with water, and dissolved in 200 ml. of 10% potassium hydroxide. After refluxing with stirring for 6 hr., the solution was allowed to cool and was acidified with 1:1 hydrochloric acid. The precipitate was filtered, washed thoroughly with water, and air dried several days, giving 19.7 g. of solid. The solid was dissolved in 150 ml. of glacial acetic acid and treated according to the procedure of Sperber, *et al.*[16] There was obtained 15.7 g. (73%) of white solid, m.p. 174.5–175.5° A sample after several recrystallizations from methanol–water melted at 179–180° (lit.[5] 174–175°); neut. equiv.: calcd., 149; found, 150.

Methyl 2,2-diphenyladipate.—A mixture of 80 g. (0.53 mole) of 2,2-diphenyladipic acid and 150 ml. (1.65 moles) of thionyl chloride was allowed to stand at room temperature overnight. After refluxing for 2 hr. the excess thionyl chloride was removed under reduced pressure. Absolute methanol was added and after refluxing 2 hr., the excess methanol was removed. Complete solidification occurred by allowing the flask to stand in the refrigerator overnight. The crude product melted at 76–77° (lit.[5] 77–78°). A colorless product was obtained by distilling the diester under vacuum, b.p. 160° (0.1–0.2 mm.).

5-Carbomethoxy-2,2-diphenylcyclopentanone.—A vigorously stirred suspension of 1 g. (0.043 g.-atom) of active sodium hydride (added as 2 g. of 50% sodium hydride in oil dispersion) and 100 ml. of xylene was heated under reflux. A solution of 8 g. (0.024 mole) of methyl 2,2-diphenyladipate in 100 ml. of xylene was added dropwise during 1 hr. The mixture was stirred under reflux for 5 hr., cooled, then poured over crushed ice. After acidification with acetic acid, the water layer was discarded. The organic layer was washed with dilute sodium carbonate and water. After removal of the solvent under reduced pressure, the

(19) R. L. Frank and R. R. Phillips, *J. Am. Chem. Soc.*, **71**, 2804 (1949).

(20) L. A. Yanovskaya, A. P. Terentev, and L. I. Belenkii, *Zh. Obshch. Khim.*, **22**, 1594 (1952); *Chem. Abstr.*, **47**, 8032*l* (1953).

residue was dissolved in about 10 ml. of dioxane. A hot, freshly filtered solution of 4 g. (0.02 mole) of cupric acetate in 37 ml. of water was added. The resulting mixture was heated several min. and shaken intermittently while cooling to room temperature. The precipitated copper salt was collected and air dried, weight 7 g. (83%). The copper chelate was not decomposed by shaking with 10% sulfuric acid and only very slightly with 25% sulfuric acid. Shaking with 50% ice cold sulfuric acid and ethyl acetate decomposed most of the copper compound. The organic layer was separated, washed with water and dilute sodium bicarbonate, dried over magnesium sulfate, and filtered. After removing the solvent, the residue was distilled. The distillate collected 163–172° (0.2 mm.) was cloudy and redistillation at 165–170° (0.2 mm.) did not improve the quality of the product.

Anal. Calcd. for $C_{19}H_{17}O_3Cu_{1/2}$: C, 70.15; H, 5.28; Cu, 9.78. Found: C, 70.60; H, 5.49; Cu, 9.48.

Difficulties were also encountered when the cyclization was attempted with metallic sodium or potassium *t*-butoxide in toluene according to established procedures.[21]

5-(2-Diethylaminoethyl)-2,2-diphenylcyclopentanone Hydrochloride.—The cyclization of methyl 2,2-diphenyladipate with sodium hydride in oil was effected as described above. The reaction mixture was cooled in ice while a solution of β-diethylaminoethyl chloride in xylene, prepared according to Meltzer and Lewis,[22] was added. After being stirred at room temperature for 2 hr., the mixture was heated on a boiling water bath for 2 hr. The mixture was cooled, treated with a few ml. of ethanol, and a large volume of water followed by a few drops of acetic acid. The organic layer was separated, and the organic solution was extracted twice with 10% hydrochloric acid. The acid solution was made strongly basic and extracted with ether. After removal of the solvent, the residue was refluxed with 30 ml. of 30% sulfuric acid and 20 ml. of acetic acid for 6 hr. The cooled mixture was poured into ice cold sodium hydroxide and the strongly basic solution was extracted with ether. The ether solution was dried over magnesium sulfate, filtered, and saturated with hydrogen chloride at 0°. The oil which separated crystallized upon standing in the refrigerator overnight. The precipitate was separated and recrystallized three times by dissolving in a minimum amount of absolute ethanol, cooling, and adding anhydrous ether. The pure product (1 g.) melted at 164.5–165.5.

Anal. Calcd. for $C_{25}H_{30}ClNO$: C, 74.27; H, 8.13; Cl, 9.53. Found: C, 74.10; H, 8.43; Cl, 9.65.

5-(2-Dimethylaminoethyl)-2,2-diphenylcyclopentanone Hydrochloride.—This compound was prepared as described above for the diethylamino homolog. The white solid melted at 206.5–208.5° dec.

Anal. Calcd. for $C_{21}H_{26}ClNO$: C, 73.25; H, 7.62; Cl, 10.30. Found: C, 73.00; H, 7.59; Cl, 10.55.

5-Dimethylaminomethyl-2,2-diphenylcyclopentanone Hydrochloride.—To 2,2-Diphenylcyclopentanone (1 g.), melted on the steam bath,[23] were added 0.25 g. of paraformaldehyde, 0.25 g. of dimethylamine hydrochloride, and 5 drops of 1:1 hydrochloric acid. The mixture was heated on the steam bath with occasional shaking until complete solidification had occurred. The solid was washed with ether, dissolved in water, filtered, and made basic. The mixture was extracted with isopropyl ether. The ether solution was dried over magnesium sulfate, filtered, and saturated with hydrogen chloride at 0°. The precipitate which formed was separated and after air drying for 12 hr. weighed 0.4 g. It melted at 173°.

Anal. Calcd. for $C_{20}H_{24}ClNO$: C, 72.82; H, 7.33; Cl, 10.75; N, 4.25. Found: C, 72.80; H, 7.50; Cl, 10.85; N, 4.21.

5-Methyl-2,2-diphenylcyclopentanone.—Prepared by cyclization, alkylation, and hydrolysis as described above. The product, b.p. 143° (2 mm.), m.p. 52–54°, was easily recrystallized from methanol. This procedure is better than alkylation of the cyclopentanone.[24] Attempted alkylation with β-dimethylaminoethyl chloride was unsuccessful.

(21) W. S. Johnson, B. Bannister, and R. Pappo, *J. Am. Chem. Soc.*, **78**, 6331 (1956).

(22) R. I. Meltzer and A. D. Lewis, *J. Org. Chem.*, **22**, 615 (1957).

(23) J. M. Sprague and E. M. Schultz, Brit. Patent 733,406; *Chem. Abstr.*, **50**, 7867*e* (1956).

(24) S. Nelson, Ph.D. Thesis, Lehigh University, 1951.

Anorexigenic Agents: Aromatic Substituted 1-Phenyl-2-propylamines

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A number of aromatic substituted 1-phenyl-2-propylamines (Table I) have been prepared by three general routes. The anorectic activities of these compounds are listed in Table IV. Although none are as active as (+)-amphetamine, a number are more potent than phenmetrazine or diethylpropion. The most active compounds are 1-(4-dimethylaminophenyl)-2-propylamine and 1-(3-trifluoromethylphenyl)-2-propylamine. Unexpectedly, 1-(3-trifluoromethylphenyl)-2-propylamine is more potent than 1-(4-trifluoromethylphenyl)-2-propylamine. Both the 3- and 4-trifluoromethylamphetamines depress food intake in the rat and dog without observable central nervous sytem stimulation.

1-Phenyl-2-propylamine (amphetamine)[2] was studied by Alles in 1927.[3,4] Since the initial investigations, dealing with the vasopressor effects of amphetamine in man[5] and the dog,[6] a vast literature on this important sympathomimetic amine has appeared.[3] The majority of these reports are concerned with either more detailed pharmacological studies or clinical applications of this drug.[7]

Although amphetamine has found a number of clinical applications it is most widely used as an adjunct in the treatment of obesity.[8] Concomitant with the anorectic effect are some undesirable side effects, which are related to central nervous system stimulation, such as insomnia, nervousness, and hyperactivity. Some consider that this central sympathomimetic stimulation is the general mechanism by which amphetamine and its congeners depress appetite.[9–11] If this is so then

(1) Presented before the Division of Medicinal Chemistry, 140th National Meeting of the American Chemical Society, Chicago, Ill., Sept. 3, 1961, Abstracts, p. 5-O.

(2) In this report 1-phenyl-2-propylamine (amphetamine) and its derivatives are related to (±)-1-phenyl-2-propylamine, unless stated otherwise.

(3) C. D. Leake, "The Amphetamines," Charles C Thomas, Springfield, Ill., 1958, p. 4.

(4) G. A. Alles, *J. Am. Chem. Soc.*, **54**, 271 (1932); amphetamine was first prepared by L. Edeleano, *Ber.*, **20**, 616 (1887).

(5) G. Piness, H. Miller, and G. A. Alles, *J. Am. Med. Assoc.*, **94**, 790 (1930).

(6) G. A. Alles, *J. Pharmacol. Exptl. Therap.*, **47**, 339 (1933).

(7) L. S. Goodman and A. Gilman, "The Pharmacological Basis of Therapeutics," The Macmillan Company, New York, N. Y., 1958, p. 52.

(8) S. C. Harris, *Ann. N. Y. Acad. Sci.*, **63**, 121 (1955).

(9) W. Modell, *J. Am. Med. Assoc.*, **173**, 1131 (1960).

(10) W. Modell, "Drugs of Choice," The C. V. Mosby Company, St. Louis, Mo., 1960, Chapter 21.