bands at 5.8 μ and 5.9 μ, and strong absorption in the 6.3–6.4 μ region that is indicative of ionized carboxyl groups.

Anal. Calcd. neut. equiv.: 116. Found: 117.

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PITTSBURGH 13, PA.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF VIRGINIA, AND THE RESEARCH AND DEVELOPMENT DIVISION, SMITH KLINE AND FRENCH LABORATORIES]

N-Substituted Derivatives of 2-Phenylcyclopropylamines. Ring-opening Reactions of 2-Phenylcyclopropane Derivatives[1]

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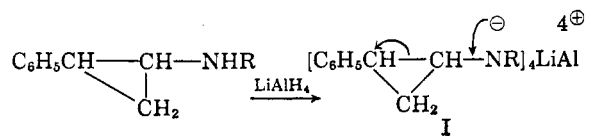
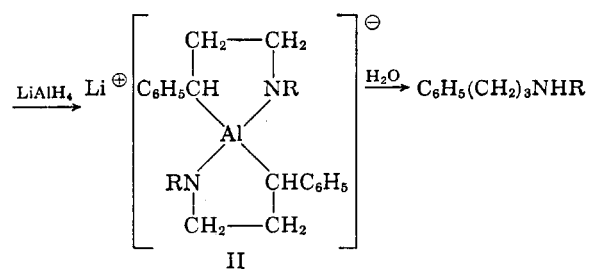
Synthesis of several *N*-substituted derivatives of *trans*-2-phenylcyclopropylamine is described. Several reactions involving opening of the cyclopropane ring, observed in the course of this work, are reported and discussed.

In view of the potent activity[3] of *trans*-2-phenylcyclopropylamine[4] (tranylcypromine, SKF 385) as an inhibitor of monoamine oxidase and as a clinical antidepressant drug, a series of derivatives and analogs was needed to elaborate structure-activity relations. The synthesis and chemistry of some *N*-substituted derivatives of *trans*-2-phenylcyclopropylamine are described in this article.

Initial experiments were directed toward the synthesis of *trans*-*N*-methyl-2-phenylcyclopropylamine. The original report on the synthesis of 2-phenylcyclopropylamine[4] described the preparation of the *N*-methyl derivative by the Decker-Becker method,[5] but several attempts to repeat this procedure were unsuccessful. As an alternate route to this compound, a two-step methylation procedure involving formylation of the amine followed by reduction of the *N*-formyl derivative with lithium aluminum hydride was tried. The formamide was prepared from the amine in almost quantitative yield with either acetic formic anhydride[6] or ethyl formate.[7]

Upon reduction of *trans*-*N*-(2-phenylcyclopropyl)formamide with excess lithium aluminum hydride in ether, the product formed was not the *N*-methyl derivative of *trans*-2-phenylcyclopropylamine. Cleavage of the cyclopropane ring occurred and *N*-methyl-3-phenylpropylamine was obtained. This result had not been anticipated as a variety of cyclopropanecarboxylic acids or their esters[8] and cyclopropyl ketones[9] have been reduced to the corresponding alcohols without affecting the three-membered ring. Further study of this reaction revealed that *trans*-2-phenylcyclopropylamine and its *N*-methyl derivative, prepared by an alternate route (see below), also underwent reduction with ring opening upon treatment with lithium aluminum hydride to form the corresponding 3-phenylpropylamines. A possible mechanism for the hydrogenolysis of these cyclopropane derivatives, resembling a mechanism postulated by Hochstein and Brown[10] for lithium aluminum hydride reduction of cinnamyl alcohol, is outlined below.





In contrast to the derivatives discussed above, *trans*-*N*,*N*-dimethyl-2-phenylcyclopropylamine is stable toward excess lithium aluminum hydride in refluxing ether. This fact is consistent with the proposed mechanism, the first step of which in-

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(2) (a) Smith Kline and French Laboratories. (b) Smith Kline and French Laboratories Post Doctoral Fellow, 1958–1960. (c) Smith Kline and French Laboratories Post Doctoral Fellow, 1960.

(3) R. E. Tedeschi, D. H. Tedeschi, P. L. Ames, L. Cook, P. A. Mattis, and E. J. Fellows, *Proc. Soc. Exptl. Biol. Med.*, 102, 380 (1959).

(4) A. Burger and W. L. Yost, *J. Am. Chem. Soc.*, 70, 2198 (1948).

(5) H. Decker and P. Becker, *Ann.*, 395, 362 (1913).

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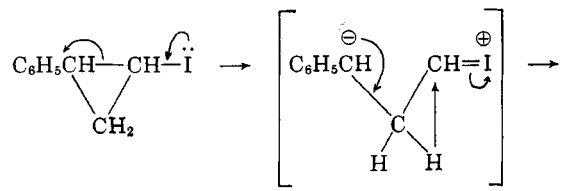
volves removal of a proton from nitrogen by the reducing agent. The route for conversion of the charged species I to the cyclic intermediate II is uncertain; it may involve a cinnamylamine.

In other attempts to obtain *N*-substituted 2-phenylcyclopropylamines, we prepared 2-phenylcyclopropyl iodide and studied its reactions with various amines. Although cyclopropyl halides are generally unreactive toward nucleophilic displacement,[11] ethyl 2-bromocyclopropanecarboxylate reacts with potassium *t*-butoxide, *via* a cyclopropene intermediate, to give ethyl 2-(*t*-butoxy)cyclopropanecarboxylate.[12]

2-Phenylcyclopropyl iodide was prepared by the reaction of iodine[13] with silver *trans*-2-phenylcyclopropanecarboxylate. The geometrical configuration of the iodide thus obtained was not determined. Presumably, it is a mixture of isomers, as treatment of both *cis*- and *trans*-isomers of silver 2-methylcyclopropanecarboxylate with bromine has been reported[14] to give an identical 1:2 mixture of *cis*- and *trans*-2-methylcyclopropyl bromides, probably via a common intermediate radical. Proof of the structure of 2-phenylcyclopropyl iodide was accomplished by sodium in liquid ammonia reduction[15] to phenylcyclopropane.

Isomeric cinnamyl iodide was prepared for comparison with 2-phenylcyclopropyl iodide. Cinnamyl iodide is an unstable low-melting solid whereas 2-phenylcyclopropyl iodide is a distillable liquid. The infrared spectra of the two compounds were different, whereas the spectrum of cinnamyl iodide was similar to those of cinnamyl chloride and bromide.

2-Phenylcyclopropyl iodide reacted readily with methylamine, dimethylamine, isopropylamine, and piperidine, at 140°, to give basic products in good yield. The products, however, were not cyclopropylamines, but *N*-substituted cinnamylamines. A possible explanation of these results is that, as formulated below, 2-phenylcyclopropyl iodide thermally rearranged to cinnamyl iodide which reacted with the amine present.



$$[C_6H_5CH{=}CHCH_2I] \xrightarrow{R_2NH} C_6H_5CH{=}CHCH_2NR_2$$

In order to eliminate the possibility of a cyclopropylamine intermediate in the above conversion, *trans*-*N*,*N*-dimethyl-2-phenylcyclopropylamine was treated with dimethylamine in methanol under the same conditions used for formation of *N*,*N*-dimethylcinnamylamine from 2-phenylcyclopropyl iodide. The cinnamylamine was not obtained. Instead, only *N*,*N*-dimethyl-3-phenylpropenylamine was isolated. This enamine was identified by hydrolysis to hydrocinnamaldehyde and by catalytic reduction to *N*,*N*-dimethyl-3-phenylpropylamine. In addition, an infrared spectrum of the product showed a very strong band at 6.05 μ, which may be attributed to the enamine system.[16]

An enamine, 3-phenylpropenylpiperidine, also resulted from treatment of *trans*-*N*,*N*-dimethyl-2-phenylcyclopropylamine with piperidine in methanol. That methanol played a role in these ring-cleavage reactions was shown by an experiment in which *trans*-*N*,*N*-dimethyl-2-phenylcyclopropylamine was heated at 140° with dimethylamine in the absence of methanol. In this instance, the cyclopropylamine derivative was recovered.

When *trans*-*N*,*N*-dimethyl-2-phenylcyclopropylamine was heated at 140° with methanol, in the absence of dimethylamine, a mixture of products, including a large amount of polymeric material, was obtained. The only compound isolated from the mixture was not the enamine, but its reduction product, *N*,*N*-dimethyl-3-phenylpropylamine, obtained in 13% yield. A similar mixture was obtained when a methanolic solution of *trans*-*N*,*N*-dimethyl-2-phenylcyclopropylamine *hydriodide* was heated with dimethylamine at 140°. In this case, *N*,*N*-dimethyl-3-phenylpropylamine (22% yield) and an unidentified tertiary amine, $C_{20}H_{19}N$, (12% yield) were isolated. That *N*,*N*-dimethyl-3-phenylpropenylamine may perhaps first be formed in these reactions and then converted to the saturated amines and other products was indicated by the fact that this enamine, when heated with methanol at 140°, also formed *N*,*N*-dimethyl-3-phenylpropylamine in 16% yield.

A possible mechanism for the observed transformations of *trans*-*N*,*N*-dimethyl-2-phenylcyclopropylamine (III) and enamine, VIa is schematically outlined below.

(8) (a) H. M. Walborsky and F. J. Impastato, *J. Am. Chem. Soc.*, **81**, 5835 (1959). (b) H. M. Walborsky and J. F. Pendleton, *J. Am. Chem. Soc.*, **82**, 1405 (1960). (c) D. B. Denney and E. J. Kupchik, *J. Am. Chem. Soc.*, **82**, 859 (1960). (d) H. Hart and R. A. Martin, *J. Org. Chem.*, **24**, 1267 (1959). (e) J. A. Carbon, W. B. Martin, and L. R. Swett, Am. Chem. Soc. Meeting, April 1958, Abstracts (Medicinal Chemistry). (f) L. I. Smith and S. McKenzie, Jr., *J. Org. Chem.*, **15**, 74 (1950).

(9) (a) J. G. Bennett, Jr., and S. C. Bunce, *J. Org. Chem.*, **25**, 73 (1960). (b) H. M. Walborsky and L. Plonsker, *J. Am. Chem. Soc.*, **83**, 2138 (1961).

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(11) J. D. Roberts and V. C. Chambers, *J. Am. Chem. Soc.*, **73**, 5034 (1951).

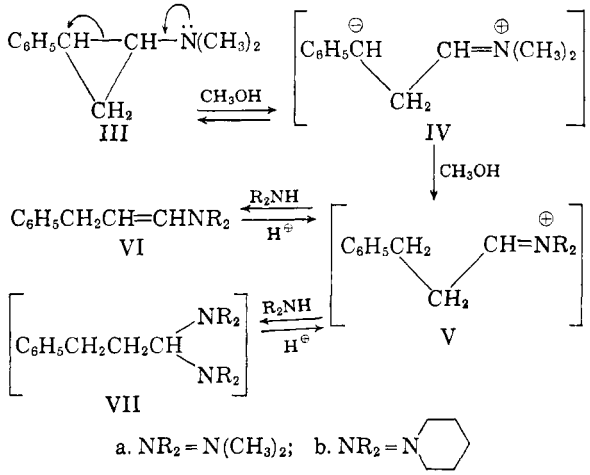
(12) K. B. Wiberg, R. K. Barnes, and J. Albin, *J. Am. Chem. Soc.*, **79**, 4994 (1957).

(13) C. V. Wilson, *Org. Reactions*, **9**, 332 (1957).

(14) D. E. Applequist and A. H. Peterson, *J. Am. Chem. Soc.*, **82**, 2372 (1960).

(15) G. L. Closs and L. E. Closs, *J. Am. Chem. Soc.*, **82**, 5723 (1960).

(16) B. Witkop, *J. Am. Chem. Soc.*, **78**, 2873 (1956).



a. $NR_2 = N(CH_3)_2$; b. $NR_2 =$ N⟨ ⟩

According to this scheme, when III is heated in methanol, ring opening occurs to form species IV which abstracts a proton from the solvent to give Va, in equilibrium with enamine VIa. When dimethylamine or piperidine is present, the equilibrium is shifted in the direction of VI and/or the *gem*-diamino derivative VII, one or both of which are stable under the reaction conditions. In the absence of added amine or in the presence of amine with a strong acid (hydrogen iodide in the case studied) the equilibrium is shifted in the direction of V, and further reaction through this species occurs to yield self-condensation products. Disproportionation of Va or a hydrogen-transfer reaction between Va and VIa or between one of these species and other products leads to the formation of *N*,*N*-dimethyl-3-phenylpropylamine.

The proposed reaction sequence may also account for the observation that *trans*-2-phenylcyclopropylamine, when distilled under 20 mm. pressure, evolved a large amount of ammonia to give a distilland from which, upon acid hydrolysis, hydrocinnamaldehyde was obtained. In this case, according to the scheme above, the cyclopropylamine plays the role of R_2NH, adding to intermediate V, $NR_2 = NH_2$, to form, upon loss of ammonia from the adduct, enamine VI, NR_2 = 2-phenylcyclopropylamino. Hydrolysis of the latter yields hydrocinnamaldehyde.

trans-*N*-Methyl-2-phenylcyclopropylamine was finally prepared by methylation of *trans*-*N*-(2-phenylcyclopropyl)formamide with methyl iodide and sodium hydride[17] followed by acid hydrolysis of the formyl group.

Similar methylation of *trans*-*N*-(2-phenylcyclopropyl)trifluoroacetamide with subsequent hydrolysis of the trifluoroacetamido group gave a better yield of *trans*-*N*-methyl-2-phenylcyclopropylamine. This procedure was also effective for the synthesis of *trans*-*N*-isopropyl-2-phenylcyclopropylamine; however, this compound was obtained more conveniently by condensation of *trans*-2-phenylcyclopropylamine with acetone, followed by catalytic reduction of the isopropylidene derivative.

Pharmacological data for the reported *N*-substituted derivatives of 2-phenylcyclopropylamine will be presented elsewhere.

(17) W. S. Fones, *J. Org. Chem.*, **14**, 1099 (1949).

EXPERIMENTAL[18]

trans-*N*-(*2-Phenylcyclopropyl*)*formamide. Method A.* A mixture of 23.8 g. (0.8 mole) of *trans*-2-phenylcyclopropylamine[4] and 125 ml. of ethyl formate was refluxed for 17 hr. Excess ethyl formate was removed *in vacuo* and the residue was distilled. The distillate, b.p. 134–137°/0.3 mm., weighed 23.1 g. (95.7%) and solidified, m.p. 61–63°. It was recrystallized from toluene to give colorless needles, m.p. 65–66.5°.

Anal. Calcd. for $C_{10}H_{11}NO$: C, 74.51; H, 6.88. Found: C, 74.50; H, 7.15.

Method B. Following directions for the formylation of weakly basic amines[6] using acetic formic anhydride, an almost quantitative yield of *trans*-*N*-(2-phenylcyclopropyl)-formamide, m.p. 65–66.5°, was obtained. A mixture melting point of this material with *trans*-*N*-(2-phenylcyclopropyl)-formamide prepared by Method A was not depressed.

Lithium aluminum hydride reduction of trans-2-phenylcyclopropylamine and N-substituted derivatives. (a) *trans-2-Phenylcyclopropylamine.* To a suspension of 3.8 g. (0.1 mole) of lithium aluminum hydride in 200 ml. of dry ether was added dropwise a solution of 6.7 g. (0.5 mole) of *trans*-2-phenylcyclopropylamine[4] in 50 ml. of ether. After stirring and refluxing 12 hr., the mixture was cooled, and while stirring 4 ml. of water, followed by 4 ml. of 2*N* sodium hydroxide and 12 ml. of water, was added dropwise. The precipitated solid was filtered and the filtrate was concentrated to leave a colorless oil. The oily residue was dissolved in a small volume of ethanol and the solution was adjusted to *p*H 5 with ethereal hydrogen chloride. After recrystallization from ethanol-ether the yield of colorless crystals, m.p. 219–221°, was 7.2 g. (85%). These crystals did not depress the melting point of an authentic sample of 3-phenylpropylamine hydrochloride,[19] m.p. 218°.[20]

(b) *trans*-*N*-(*2-Phenylcyclopropyl*)*formamide.* Reduction of *trans*-*N*-(2-phenylcyclopropyl)formamide with 2 mole equivalents of lithium aluminum hydride in refluxing ether gave a 95.5% yield of *N*-methyl-3-phenylpropylamine, b.p. 125–127°/32 mm., n_D^{26} 1.5100. A *hydrochloride*, prepared in ethanol-ether, recrystallized from acetone as leaflets, m.p. 144.5–145.5°.

Anal. Calcd. for $C_{10}H_{16}ClN$: C, 64.68; H, 8.69. Found: C, 64.80; H, 8.73.

A mixture melting point of this salt with an authentic sample of *N*-methyl-3-phenylpropylamine hydrochloride,[21] m.p. 145.5–146°, gave no depression.

(c) *trans*-*N*-*Methyl*-*2*-*phenylcyclopropylamine. trans*-*N*-Methyl-2-phenylcyclopropylamine was treated with 2 mole equivalents of lithium aluminum hydride as described in (a). The product was converted to a hydrochloride, m.p. 145–146°, as described in (b). A mixture melting point of this material with an authentic sample of *N*-methyl-3-phenylpropylamine hydrochloride, m.p. 145.5–146°, was not depressed. (d) *trans*-*N*,*N*-*Dimethyl*-*2*-*phenylcyclopropylamine.*[4] *trans*-*N*,*N*-Dimethyl-2-phenylcyclopropylamine[4] was treated with 2 mole equivalents of lithium aluminum hydride in

(18) Melting points are uncorrected. Microanalyses by Mrs. Doris Rolston and co-workers of the Analytical and Physical Chemistry Section, Smith Kline and French Laboratories, and by Mrs. Dolores Ellis of the University of Virginia.

(19) J. v. Braun and H. Deutsch, *Ber.*, **45**, 2188 (1912).

(20) J. Tafel, *Ber.*, **22**, 1854 (1889).

(21) A. C. Cope and S. M. McElvain, *J. Am. Chem. Soc.*, **53**, 1587 (1931).

ether as described in (a). Starting material was recovered in quantitative yield.

2-Phenylcyclopropyl iodide. A solution of 48.7 g. (0.3 mole) of *trans*-2-phenylcyclopropanecarboxylic acid[4] and 13 g. (0.315 mole) of sodium hydroxide in 300 ml. of water was adjusted to *p*H 6.8 with dilute nitric acid. After filtration, a solution of 50.7 g. (0.3 mole) of silver nitrate in 100 ml. of water was added to the stirred filtrate over a period of 30 min. The mixture was allowed to stand at room temperature overnight. The precipitated silver salt was filtered, washed twice with 50 ml. of water, twice with 25 ml. of ethanol, and dried *in vacuo* over phosphorus pentoxide to give 78.6 g. (98%) of colorless crystals of silver *trans*-2-phenylcyclopropanecarboxylate. From a suspension of 17.7 g. (0.066 mole) of silver *trans*-2-phenylcyclopropanecarboxylate in 4.1 l. of carbon tetrachloride, 100 ml. of solvent was distilled under dry nitrogen. Dry iodine (33.5 g., 0.132 mole) was added and the mixture was stirred and refluxed for 2 hr. The mixture was filtered and the filtrate was decolorized with 200 ml. of 1*N* sodium sulfite solution. The organic layer was washed with 50 ml. of 2*N* sodium carbonate solution, 2*N* hydrochloric acid, and five 50-ml. portions of water. The solution was dried with sodium sulfate at 0° in the dark, solvent was removed *in vacuo* and the residual orange oil was distilled. The yield of almost colorless oily 2-phenylcyclopropyl iodide, b.p. 80–81°/0.4 mm., was 10.3 g. (64.3%).

Anal. Calcd. for C_9H_9I: C, 44.29; H, 3.72. Found: C, 44.91; H, 3.91.

Infrared spectrum (*film*) (μ). 3.30(s), 5.15(w), 5.45(w), 5.58(w), 5.74(w), 5.98(w), 6.24(s), 6.90(s), 7.00(m), 7.75(w), 8.10(s), 8.26(s), 8.50(s), 8.65(w), 9.13(m), 9.31(m), 9.60(m), 9.72(m), 10.05(w), 10.30(m), 10.82(m), 11.35(m), 11.82(w), 12.20(s), 13.77(m), 14.40(s).

Proof of structure of 2-phenylcyclopropyl iodide. 2-Phenylcyclopropyl iodide was reduced to phenylcyclopropane by the general method of Closs and Closs.[15] A solution of 2.2 g. (0.009 mole) of 2-phenylcyclopropyl iodide in 5 ml. of anhydrous ether was added to a solution of 0.5 g. (0.022 g.-atom) of sodium in 15 ml. of liquid ammonia at −70°. After stirring the mixture for 0.5 hr., excess ammonia was allowed to evaporate. The residue was extracted with ether and the ethereal extracts were concentrated to leave an orange oil. Distillation gave 1.1 g. of colorless oil, b.p. 74–75°/32 mm.; n_D^{20} 1.5280. Literature[22] b.p. 79–80°/37 mm.; n_D^{20} 1.5285. Infrared spectra of phenylcyclopropane prepared by the method described by Hammond and Todd[23] and the product prepared by the above procedure were identical.

Cinnamyl iodide. To a solution of 17.9 g. (0.12 mole) of sodium iodide in 250 ml. of acetone was added 15.2 g. (0.1 mole) of 3-chloropropenylbenzene. The mixture was allowed to stand at room temperature for 1.5 hours, then it was filtered and the filtrate was concentrated *in vacuo* to give 23.1 g. (95%) of a yellow crystalline solid, m.p. 53–55°. For analysis, a small sample was recrystallized from ether, m.p. 56.5–57.5°. The product gradually decomposed to a dark oil on standing at room temperature; however, it was stable at 0°.

Anal. Calcd. for C_9H_9I: C, 44.29; H, 3.72. Found: C, 44.41; H, 3.81.

Infrared spectrum (Nujol mull) (μ). 3.45(s), 6.21(w), 6.78(m), 6.90(s), 7.10(w), 7.32(s), 7.60(w), 7.72(m), 8.30(w), 8.55(w), 8.80(s), 8.93(m), 9.40(m), 9.60(w), 9.80(w), 10.02-(w), 10.22(m), 10.40(s), 11.00(w), 11.52(w), 12.68(m), 13.35-(s), 14.52(s).

Reaction of 2-phenylcyclopropyl iodide with amines. (a) *Methylamine.* A mixture of 1.1 g. (0.0045 mole) of 2-phenylcyclopropyl iodide, 4.0 ml. of methanol, and 7.5 g. (0.25 mole) of methylamine was heated in a sealed tube at 100° for 97 hr. The solvent was evaporated and the residual oil was dissolved in ether. The ethereal solution was extracted with 2*N* hydrochloric acid. The acid extracts were made alkaline and the mixture was extracted with ether. After drying, the ether extracts were concentrated and the residual oil was distilled. The yield of colorless distillate, b.p. 136–140°/29 mm., was 0.42 g. (63%). A *hydrochloride*, prepared in ether, melted at 152.5–153° after recrystallization from acetone.

Anal. Calcd. for $C_{10}H_{14}ClN$: C, 65.39; H, 7.68. Found: C, 65.20; H, 7.85.

A mixture melting point of this sample with *N*-methylcinnamylamine hydrochloride[24] was not depressed.

(b) *Isopropylamine.* A methanolic solution of 2-phenylcyclopropyl iodide was treated with isopropylamine in the same manner described in (a) and gave 63% of a colorless oil, b.p. 69–72°/0.3 mm. A *hydrochloride* was prepared in the usual way; it was recrystallized from absolute ethanol, m.p. 237–238°. The infrared spectrum showed a strong absorption at 10.3 μ (*trans*-olefin) indicating the product was *N*-isopropylcinnamylamine hydrochloride.

Anal. Calcd. for $C_{12}H_{18}ClN$: C, 68.07; H, 8.57; N, 6.62. Found: C, 68.28; H, 8.95; N, 6.94.

(c) *Piperidine.* Treatment of a methanolic solution of 2-phenylcyclopropyl iodide with piperidine in the same manner described in (a) gave a 36% yield of a colorless oil, b.p. 84–95°/0.2 mm. The *hydrochloride*, prepared in ether, recrystallized from acetone as needles, m.p. 210–211°. An infrared spectrum (strong 10.3 μ absorption) indicated the product was *N*-cinnamylpiperidine hydrochloride.

Anal. Calcd. for $C_{14}H_{20}ClN$: C, 70.72; H, 8.48. Found: C, 70.43; H, 8.38.

(d) *Dimethylamine.* 2-Phenylcyclopropyl iodide (2.44 g., 0.01 mole) was heated in a sealed tube with 11.2 g. (0.25 mole) of dimethylamine and 8.0 g. (0.25 mole) of methanol at 135–140° for 26 hr. The product, 1.13 g. (70%) of a colorless oil, b.p. 135–139°/10 mm., was isolated in the same manner described in (a). A *hydrochloride* was prepared in the usual way; it crystallized from ethyl acetate as fine needles, m.p. 192–193°. The melting point of this salt was not depressed by mixture with an authentic sample of *N,N*-dimethylcinnamylamine hydrochloride, m.p. 190.5–191°.[25]

Reaction of trans-N,N-dimethyl-2-phenylcyclopropylamine with dimethylamine in methanol. A solution of 2.4 g. (0.015 mole) of *trans*-*N,N*-dimethyl-2-phenylcyclopropylamine, 16.9 g. (0.375 mole) of dimethylamine, and 12.0 g. (0.375 mole) of methanol was heated in a sealed tube at 135–140° for 26 hr. The pale yellow solution was concentrated *in vacuo* at 30°. Distillation of the residual oil gave 1.7 g. (71%) of a colorless liquid, b.p. 58–60°/0.6 mm.; n_D^{25} 1.5300.

Anal. Calcd. for $C_{11}H_{15}N$: C, 81.93; H, 9.38. Found: C, 81.76; H, 9.53. The product was identified as *N,N*-dimethyl-3-phenylpropenylamine by its infrared spectrum, conversion to cinnamaldehyde 2,4-dinitrophenylhydrazone and catalytic reduction to *N,N*-dimethyl-3-phenylpropylamine. An infrared spectrum of the above product showed a strong absorption at 6.05 μ; this may be attributed to an enamine system.[16]

The product was converted to a *2,4-dinitrophenylhydrazone*, m.p. 147–149°, in the usual way.[26] A mixture melting point of this derivative with hydrocinnamaldehyde 2,4-dinitrophenylhydrazone, m.p. 149°[26] was not depressed.

A mixture of 0.5 g. (0.003 mole) of *N,N*-dimethyl-3-phenylpropenylamine, 10 mg. of platinum oxide, and 20 ml. of ethanol was shaken under a hydrogen atmosphere until

(22) F. H. Case, *J. Am. Chem. Soc.*, **56**, 715 (1934).

(23) G. S. Hammond and R. W. Todd, *J. Am. Chem. Soc.*, **76**, 4081 (1954).

(24) H. Emde and M. Franke, *Arch. Pharm.*, **247**, 333 (1909).

(25) J. F. Bunnett, J. L. Marks, and H. Moe, *J. Am. Chem. Soc.*, **75**, 985 (1953); F. E. King and D. Holmes, *J. Chem. Soc.*, 164 (1947).

(26) R. L. Shriner and R. C. Fuson, *The Systematic Identification of Organic Compounds*, Third Ed., Wiley, New York, 1948.

an equivalent of hydrogen was absorbed. The mixture was filtered and the filtrate concentrated to give a colorless liquid. An ethanolic solution of the oil was treated with an excess of picric acid to yield fine yellow needles, m.p. 101–103°, after recrystallization from ethanol. Admixture of these crystals with *N,N*-dimethyl-3-phenylpropylamine picrate, m.p. 103°,[27] caused no melting point depression.

Reaction of trans-N,N-dimethyl-2-phenylcyclopropylamine with piperidine in methanol. A solution of 4.8 g. (0.03 mole) of *trans-N,N*-dimethyl-2-phenylcyclopropylamine and 64 g. (0.75 mole) of piperidine in 24 g. (0.75 mole) of methanol was heated in a sealed tube at 140° for 38 hr. Excess piperidine and methanol were removed *in vacuo* at 50°. The residual oil was fractionated to give 1.1 g. (23%) of unchanged *trans-N,N*-dimethyl-2-phenylcyclopropylamine, b.p. 45–50°/0.15 mm. and 2.6 g. (44%) of 3-phenylpropenylpiperidine as a colorless liquid, b.p. 112–115°/0.15 mm., $n_D^{24.8}$ 1.5451.

Anal. Calcd. for $C_{14}H_{19}N$: C, 83.53; H, 9.51. Found: C, 83.21; H, 9.48.

An infrared spectrum of the product had a strong band at 6.05 μ (enamine).

Treatment of trans N,N-dimethyl-2-phenylcyclopropylamine with dimethylamine. A solution of 4.8 g. (0.03 mole) of *trans-N,N*-dimethyl-2-phenylcyclopropylamine and 16.9 g. (0.375 mole) of dimethylamine was heated in a sealed tube at 140° for 26 hr. Evaporation of dimethylamine followed by distillation of the residual oil gave 4.5 g. of *trans-N,N*-dimethyl-2-phenylcyclopropylamine.

Reaction of trans-N,N-dimethyl-2-phenylcyclopropylamine in methanol. A solution of 4.8 g. (0.03 mole) of *trans-N,N*-dimethyl-2-phenylcyclopropylamine in 20 g. (0.62 mole) of methanol was heated in a sealed tube at 140° for 26 hours. After removal of excess methanol, the residual oil, which contained a large amount of polymeric material, was distilled to give 0.65 g. (13.5%) of a colorless liquid, b.p. 50–53°/0.3 mm. A *picrate* of this oil was prepared in ethanol. The yellow crystals melted at 97–99° and the melting point was not depressed by mixture with an authentic sample of *N,N*-dimethyl-3-phenylpropylamine picrate.[27]

Reaction of trans-N,N-dimethyl-2-phenylcyclopropylamine hydroiodide with dimethylamine in methanol. A solution of 4.34 g. (0.015 mole) of *trans-N,N*-dimethyl-2-phenylcyclopropylamine hydriodide (prepared by addition of aqueous 50% hydriodic acid to an ethanol-ether solution of *trans-N,N*-dimethyl-2-phenylcyclopropylamine; m.p. 116–118°), 16.9 g. (0.375 mole) of dimethylamine and 12.0 g. (0.375 mole) of methanol was heated in a sealed tube at 140° for 26 hr. The solution was concentrated *in vacuo* to leave a semisolid residue containing a considerable amount of polymeric material. The residue was suspended in 50 ml. of water. The mixture was made alkaline with 10*N* sodium hydroxide solution and extracted with ether. After drying, the combined ether extracts were evaporated. The resulting oil was fractionated to give 0.53 g. (22%) of a colorless oil, b.p. 48–50°/0.2 mm. and 0.80 g. of a viscous yellow oil, b.p. 165–180°/0.2 mm. A *picrate* of the lower boiling fraction was prepared in ethanol; it melted at 98–100° and did not depress the melting point of a sample of *N,N*-dimethyl-3-phenylcyclopropylamine picrate.[27] The higher boiling fraction crystallized after standing at room temperature for 24 hr. After recrystallization from hexane, 0.3 g. (12.5%) of colorless needles, m.p. 90–93°, were obtained.

Anal. Calcd. for $C_{20}H_{19}N$: C, 87.87; H, 7.01; N, 5.12. Found: C, 87.70; H, 6.60; N, 5.48.

A *hydrochloride* of the above material was prepared by adjusting an ethanolic solution to *p*H2 with ethereal hydrogen chloride. The colorless prisms melted at 168–170°.

Anal. Calcd. for $C_{20}H_{20}ClN$: C, 77.53; H, 6.51; N, 4.52. Found: C, 77.63; H, 6.44; N, 4.76.

An infrared spectrum of this hydrochloride showed a strong tertiary ammonium absorption at 4.15 μ.

Reaction of N,N-dimethyl-3-phenylpropenylamine in methanol. A solution of 4.8 g. (0.03 mole) of *N,N*-dimethyl-3-phenylpropenylamine in 12.0 g. (0.375 mole) of methanol was heated in a sealed tube at 140° for 26 hr. Solvent was removed *in vacuo* and the residue was distilled to give 0.76 g. (15.8%) of a colorless oil, b.p. 48–50°/0.2 mm. A *picrate*, m.p. 101–103°, was prepared in ethanol. A mixture melting point with *N,N*-dimethyl-3-phenylpropylamine picrate[27] was not depressed.

Degradation of 2-phenylcyclopropylamine. A 2-kg. sample of *trans*-2-phenylcyclopropylamine was partially distilled at *ca.* 20 mm. The operation was discontinued when a large amount of ammonia was evolved. The still residue was partially dissolved in 2*N* hydrochloric acid and the insoluble material was extracted with benzene. The organic extract was dried and concentrated. Distillation of the residual oil gave a pale yellow liquid, b.p. 53–54°/0.7 mm.; n_D^{25} 1.5190.

Treatment of this material with 2,4-dinitrophenylhydrazine in the usual way[28] gave orange crystals, m.p. 159–162°.

Anal. Calcd. for $C_{15}H_{14}N_4O_4$: C, 57.32; H, 4.49; N, 17.83. Found: C, 57.28; H, 4.62; N, 18.06.

The pale yellow liquid was also converted to a *semicarbazone*,[26] m.p. 126–129°.

The following constants have been reported for hydrocinnamaldehyde: n_D^{20} 1.5167; 2,4-dinitrophenylhydrazone, m.p. 149°[26]; semicarbazone, m.p. 127.[26]

The infrared spectrum of an authentic sample of hydrocinnamaldehyde was nearly identical with the unknown liquid and the retention time of the authentic sample when chromatographed in the vapor phase was identical with the unknown compound.

trans-N-(2-Phenylcyclopropyl)trifluoroacetamide. To 13.3 g. (0.1 mole) of *trans*-2-phenylcyclopropylamine was added slowly, and with cooling, 63 g. (0.3 mole) of trifluoroacetic anhydride. The mixture was refluxed for 2 hr., and excess reagent was removed *in vacuo*. The residue crystallized from ethyl acetate to give 16.1 g. (97%) of fine needles, m.p. 96–98°.

Anal. Calcd. for $C_{11}H_{10}F_3NO$: C, 57.64; H, 4.40. Found: C, 57.61; H, 4.58.

trans-N-Methyl-2-phenylcyclopropylamine. (a) *From trans-N-(2-phenylcyclopropyl)trifluoroacetamide.* To a solution of 12.6 g. (0.055 mole) of *trans-N*-(2-phenylcyclopropyl)-trifluoroacetamide in 500 ml. of tetrahydrofuran was added, under nitrogen, 1.32 g. (0.055 mole) of sodium hydride, and the mixture was refluxed for 1 hr. After cooling, methyl iodide (35.5 g., 0.25 mole) was added and the mixture was refluxed under a Dry-Ice condenser for 6 hr. Addition of another 3.5 g. (0.025 mole) of methyl iodide was followed by refluxing for another 12 hr. Solvent was removed *in vacuo* and the residue was shaken for 17 hr. with a mixture of 30 ml. of 2*N* sodium hydroxide and 100 ml. of ethanol. Solvent was again removed in a vacuum, and the residue was dissolved in 2*N* hydrochloric acid. The solution was made alkaline and the mixture was extracted with ether. The ether extracts were dried and the solvent was removed at 20° under reduced pressure. Distillation of the residual oil gave 6.09 g. (83%) of a colorless liquid, b.p. 50.5–64°/0.3 mm. A *hydrochloride* was prepared in ether; it recrystallized from acetone as colorless prisms; m.p. 112–113°.

Anal. Calcd. for $C_{10}H_{14}ClN$: C, 65.39; H, 7.68. Found: C, 65.39; H, 7.59.

(b) *From trans-N-(2-phenylcyclopropyl)formamide.* Alkylation of *trans-N*-(2-phenylcyclopropyl)formamide was accomplished in the same manner as described above (a) for the trifluoroacetamide derivative. In this case, the intermediate *trans-N*-methyl-*N*-(2-phenylcyclopropyl)formamide (17.5 g., 0.1 mole) was refluxed with 300 ml. of 6*N* hydrochloric acid for 20 hr. The solution was concentrated *in vacuo*. The residue was dissolved in water and the mixture was extracted with ether. The aqueous layer was made alkaline and the mixture was extracted with ether. The combined ethereal extracts were dried and concentrated. Distillation of the residual oil gave 10.8 g. (73%) of *trans-N*-methyl-2-phenylcyclopropylamine.

(27) C. Mannich and G. Heilner, *Ber.*, 55, 356 (1922).

trans-N-Isopropyl-2-phenylcyclopropylamine hydrochloride. A mixture of 13.3 g. (0.1 mole) *trans*-2-phenylcyclopropylamine and 7.0 g. (0.12 mole) of acetone in 300 ml. of benzene was stirred at room temperature for 1 hr. and then refluxed azeotropically for 1.5 hr. The solution was concentrated *in vacuo*. The residual oil was dissolved in 100 ml. of ethanol and 0.3 g. of platinum oxide was added. The mixture was hydrogenated at room temperature under 50 p.s.i. of hydrogen. After 1 hr., the mixture was filtered and the filtrate concentrated. The yellow oil was converted to a *hydrochloride* in ethanol. Two recrystallizations from butanone gave 17.9 g. (85%) of colorless crystals, m.p. 155–157°.

Anal. Calcd. for $C_{12}H_{18}ClN$: C, 68.07; H, 8.57. Found: C, 67.98; H, 8.52.

trans-N-Isopropyl-2-phenylcyclopropylamine was also prepared in 70% yield from *trans-N*-(2-phenylcyclopropyl)-trifluoroacetamide and isopropyl iodide in the same manner as described for the preparation of *trans-N*-methyl-2-phenylcyclopropylamine from the trifluoroacetamide derivative.

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Products from the Reaction of 2-Bromo-4′-phenylacetophenone with Powdered Sodium Hydroxide in Ether

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Under heterogeneous conditions 2-bromo-4′-phenylacetophenone reacts with powdered sodium hydroxide in anhydrous ether to give *p*-phenylbenzoic acid (4%) and neutral polymerization products which could not be identified. Addition of 0.5% water to the reaction medium increases the yield of *p*-phenylbenzoic acid to 22% and also gives *p*-phenylmandelic acid (12%) and *p*-phenylacetophenone (8%). Careful exclusion of ether peroxides from the reaction medium and use of a nitrogen atmosphere markedly decreases the quantities of *p*-phenylbenzoic and *p*-phenylmandelic acids and increases the quantity of *p*-phenylacetophenone formed. Increase in the amounts of added water up to a maximum of 5%, at which point the reaction medium becomes homogeneous, results in almost complete quenching of the reaction and recovery of a high per cent of unchanged starting material.

Acidic products containing the same number of carbon atoms[3–7] and containing fewer carbon atoms,[5,8] have been reported from reactions of nucleophilic bases with α-halo ketones containing no enolizable α′-hydrogen atoms *via* quasi-Favorski rearrangements and cleavage processes, respectively. The present paper reports the results of investigations into the nature of the products obtained from the reaction of 2-bromo-4′-phenylacetophenone with sodium hydroxide in ether under heterogeneous conditions.

The experimental results summarized in Table I were obtained from the reaction of 2-bromo-4′-phenylacetophenone (I) with approximately a two-fold excess of solid sodium hydroxide in ether with variations in conditions as indicated. Each run was agitated vigorously with a Morton Hi-Speed stirrer for ten hours at room temperature. Preliminary experiments using anhydrous ether indicated that the yield of crude acid approached a maximum in ten hours. The sodium hydroxide was added as pellets which were pulverized in a few minutes by the action of the stirrer.

The reaction of I with powdered sodium hydroxide in anhydrous ether using normal precautions against moisture yielded a small amount of *p*-phenylbenzoic acid (II) as the only acidic product. Approximately one half of the starting material was recovered unchanged. The identity of the *p*-phenylbenzoic acid was rigorously established by means of ultraviolet spectra, equivalent weights, and by mixed melting point determinations involving the isolated acid and its *p*-phenylphenacyl derivative with synthetic *p*-phenylbenzoic and 4-biphenylacetic acids and their *p*-phenylphenacyl derivatives, respectively. The isolated acid and the synthetic *p*-phenylbenzoic acid showed absorption maxima in the ultraviolet at about 271 mμ with similar extinction coefficients, while the 4-biphenylylacetic acid showed an absorption maximum at 252 mμ with a much lower extinction coefficient.

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