sons are not possible. It is possible to give the ranges of estimated values shown in Table I. These estimated relative reactivities are calculated for 35° and 1*M* initial concentrations and are on the same scale as those previously published,[4a] *i.e.*, with the reactivity of ethylmagnesium bromide taken as 100. The only value which is close to the value of 25 reported by Dessy and Salinger[5] for phenylmagnesium bromide in ether is that for experiment No. 6, which is the freshly prepared reagent in ether–tetrahydrofuran. The value calculated from decomposition voltages[15] by use of the empirical logarithmic plot[14] is 4, which is much lower than all values except those for the old reagent in the ether–tetrahydrofuran mixtures.

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[CONTRIBUTION FROM MELLON INSTITUTE]

Ozonolysis of Acenaphthene

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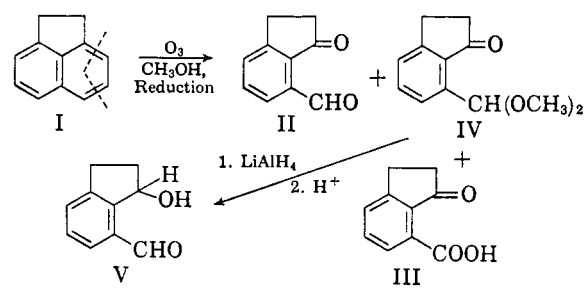
The ozonolysis of acenaphthene with two molecular equivalents of ozone was conducted in the participating solvents, methanol and *t*-butyl alcohol. By reduction of the primary ozonolysis products, 7-formyl-1-indanone was obtained as the major product along with a low yield of 1-indanone-7-carboxylic acid. The dimethyl acetal of 7-formyl-1-indanone was also prepared and characterized. Lithium aluminum hydride reduction of the acetal gave a good yield of material believed to be 7-formyl-1-indanol.

Previous work in this laboratory on the ozonolysis of acenaphthylene[1c] indicated that the use of excess ozone (more than one molecular equivalent) resulted in attack upon the naphthalene nucleus. It seemed of interest, therefore, to determine how the parent compound, acenaphthene, would behave when exposed to the action of ozone. The ozonolysis of acenaphthene has recently been reported by Copeland and associates.[2] By using two molecular equivalents of ozone and an oxidative work-up, which was not further described, they obtained a 24% yield of hemimellitic acid. No other products were identified. Our previous experience in the ozonolysis of fluoranthene[3] and Bailey's excellent work on the ozonolysis of naphthalene[4] indicated that 7-substituted derivatives of 1-indanone might be obtained from the ozonolysis of acenaphthene by using mild work-up procedures. To avoid the formation of unstable ozonides, methanol and *t*-butyl alcohol were used as participating solvents.

DISCUSSION

I. The ozonolysis reaction. It was anticipated that ozone would attack acenaphthene (I) at two bonds of one of the aromatic rings. The fact that ozone absorption was quantitative until almost two molecular equivalents of ozone were absorbed indicated the actual occurrence of such a reaction. A sharp decrease then occurred in ozone absorption. Such an attack would split off two carbon atoms from the aromatic nucleus and leave an indane skeleton substituted at the 1- and 7- positions. Research was directed toward determining ozonolysis conditions and work-up procedures that would yield optimum quantities of 7-formyl-1-indanone (II) and 1-indanone-7-carboxylic acid (III). These products, as well as the dimethyl acetal of 7-formyl-1-indanone (IV), were isolated, the isolation being dependent on the solvent used for ozonolysis and the method of work-up used.



I II IV V III

Reduction of the product of the ozonolysis of acenaphthene in methanol was attempted to obtain a satisfactory yield of 7-formyl-1-indanone. When potassium iodide was the reducing agent, a mixture of 7-formyl-1-indanone and its dimethyl acetal was obtained. It was necessary to conduct the ozonolysis at a reduced temperature (−20° was effective) and to start the reduction while the solution was still cold to prevent undesirable side

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reactions. To increase the solubility of the acenaphthene at this low temperature, a mixture of carbon tetrachloride and methanol (3:1) was used. The use of carbon tetrachloride also facilitated separation of the aldehyde and acetal from inorganic reduction products.

Ordinarily when a mixture of aldehyde and acetal are obtained, conversion to a single product by hydrolysis of the acetal can be easily accomplished. However, in the hydrolysis of the above acetal, the method of hydrolysis must be carefully chosen because 7-formyl-1-indanone readily condenses with itself in the presence of mineral acid. By using very dilute hydrochloric acid and mixing in a blender so that the oily acetal was finely dispersed, a 52% yield of fair-quality 7-formyl-1-indanone was quickly obtained.

Sulfur dioxide, the other reducing agent that was found effective, offers two advantages over potassium iodide. It is considerably cheaper and its use facilitates isolation of 1-indanone-7-carboxylic acid as a by-product. It was necessary to add pyridine to the reaction mixture prior to introduction of the sulfur dioxide, but the role of pyridine has not been fully explored. With this process, 70% yields of crude dimethyl acetal of 7-formyl-1-indanone were consistently obtained. In addition, 1-indanone-7-carboxylic acid was isolated in about 7% yield. Obtaining a satisfactory product from hydrolysis of the crude acetal was difficult. The most successful hydrolysis yielded 72% of 7-formyl-1-indanone melting from 77 to 95°. This is a 51% over-all yield of crude keto aldehyde. Attempts to recrystallize the crude keto aldehyde obtained from this procedure resulted in a low recovery of good quality product. With other reducing agents, efforts to obtain 7-formyl-1-indanone or its acetal by reduction of the ozonolysis products resulted in either intractable gums or high-melting, insoluble solids, which are believed to be condensation products of the keto aldehyde and/or its acetal.

By analogy with the ozonolysis of fluoranthene,[3] treatment of acenaphthene in aqueous *t*-butyl alcohol with two molecular equivalents of ozone might be expected to yield, upon hydrolysis, 7-formyl - 1 - indanone and 1 - indanone - 7 - carboxylic acid. Acetal formation would not be expected to occur. After such an ozonolysis, neutralization with very dilute aqueous base and removal of solvent by distillation gave a 48% yield of 7-formyl-1-indanone, but attempted recrystallization of this product led to a very low recovery of keto-aldehyde of good quality. None of the keto acid was obtained, but instead, the remaining product was an unidentified, high-melting solid designated compound A. This product is believed to be a condensation product of 7-formyl-1-indanone with itself and/or with 1-indanone-7-carboxylic acid. Although the yield and purity of products from these procedures are not high, the products are new, and other convenient methods for their synthesis are not available.

II. Reactions of ozonolysis products. The literature on 1-indanone indicates why 7-formyl-1-indanone is difficult to handle. On being heated in the presence of acid, 1-indanone will condense with itself to form a dimer and then a trimer with loss of water. Indanone also condenses with aldehydes in the presence of acid or base.[5] Substitution of a formyl group on the indanone nucleus, therefore, makes it very susceptible to self-condensation in the presence of acid or base. The fact that the dimethyl acetal and 1-indanone-7-carboxylic acid are also formed during ozonolysis further complicates the reaction, for these compounds also have a reactive 1-indanone site and can condense with the aldehyde or with each other to give a variety of condensation products.

Not only is 7-formyl-1-indanone readily subject to self-condensation, but, like 1-formyl-9-fluorenone, is also resistant to mild oxidation to the corresponding acid. As with the fluorenone derivative,[3] treatment of the ozonolysis product with excess ozone or ozone-catalyzed oxidation of the keto aldehyde failed to give any significant yield of the acid. Peracetic acid oxidation, which worked well for preparation of 9-fluorenone-1-carboxylic acid, quickly led to the formation of a high-melting condensation product of 7-formyl-1-indanone.

The only reaction in which 7-formyl-1-indanone performed satisfactorily was the peroxide-catalyzed conversion to the dimethyl acetal. This method of catalyzing acetal formation, developed in our laboratory,[3] produced an 85% yield of high quality product.

Because the indanones are so readily condensed, it was thought that conversion to 1-indanol derivatives might result in more stable products. Reduction of the dimethyl acetal of 7-formyl-1-indanone and hydrolysis produced an 85% yield of 7-formyl-1-indanol (V). However, this product also appears to be unstable, for, although the product formed derivatives, attempts to purify the derivatives resulted in decomposition. The high-melting product designated compound A, which is formed on ozonolysis in aqueous *t*-butyl alcohol and direct isolation, was degraded by oxidation. Treatment with excess alkaline permanganate resulted in a mixture of products from which a 22 weight per cent yield of hemimellitic acid was isolated as the monosodium salt. This provides presumptive evidence that the indane skeleton is present and may help to explain the hemimellitic acid isolated by Copeland and associates.[2]

EXPERIMENTAL

The acenaphthene used in this work was commercial material having a melting point of 94° and an estimated 99 to 100% purity. The methanol, *t*-butyl alcohol, and carbon

tetrachloride were reagent grade materials. All melting points are uncorrected. Infrared spectra were determined with a Perkin-Elmer Infracord Model 137 infrared spectrophotometer fitted with a sodium chloride prism. Elemental analyses were performed by the Mellon Institute Microanalytical Laboratory. Other reagents mentioned were of the purest quality obtainable. The ozonator and accessory equipment have been described previously.[5]

I. Ozonolysis of acenaphthene in methanol–carbon tetrachloride. A suspension of acenaphthene (15.4 g., 0.10 mole) in 150 ml. of carbon tetrachloride and 50 ml. of methanol was treated with approximately 2.3 weight % ozone (in oxygen) at a flow rate of 102 l. per hr. at −20° for 192 min. Under these conditions, 9.6 g. (0.20 mole) of ozone was passed into the reaction mixture. After being flushed with oxygen to remove unchanged ozone, the colorless solution was reduced as follows:

A. Reduction with potassium iodide. The cold reaction mixture was poured into a solution of potassium iodide (30 g., 0.18 mole) in 100 ml. of water and 20 ml. of glacial acetic acid. The mixture was cooled in a water bath at about 10° and stirred for 30 min. The liberated iodine was then reduced with 200 ml. of 20% aqueous sodium thiosulfate solution. The carbon tetrachloride layer was separated, washed with water, and evaporated to dryness on a steam bath under an air blast. The tacky residue, weighing 12.0 g., was mixed with very dilute hydrochloric acid (240 ml. of 0.3% solution) in a blender. A precipitate quickly formed and was filtered, yielding 8.4 g. (52.5% yield) of crude 7-formyl-1-indanone, which melted at 82–91°. Recrystallization from *n*-heptane raised the melting point to 92–93°. The infrared spectrum showed a doublet carbonyl band at 5.85 μ and 5.95 μ.

Anal. Calcd. for $C_{10}H_8O_2$: C, 74.98; H, 5.03. Found: C, 74.76; H, 5.23.

B. Reduction with sulfur dioxide. The cold reaction mixture from an ozonization was transferred to an 800-ml. beaker immersed in an ethanol–Dry Ice bath at −20°. Pyridine (8 ml., 7.8 g., 0.10 mole) was added, and sulfur dioxide from a generating flask was bubbled into the stirred solution over a 25-min. period. The sulfur dioxide was generated by dropwise addition of 6 ml. of sulfuric acid to a suspension of 20 g. of *meta* sodium bisulfite in 20 ml. of water. The generating flask was heated to 50° on a steam bath. Under these conditions, 12.2 g. (0.19 mole) of sulfur dioxide was used, an allowance being made for the solubility of sulfur dioxide in water. The reaction mixture was flushed with a stream of air for 30 min. Then 200 ml. of water was added with stirring and was followed by 100 ml. of sodium carbonate (10% solution). The carbon tetrachloride layer was separated, washed with two 25-ml. portions of water, and evaporated to dryness. The oil obtained weighed 14.4 g. (70% yield) and was identified as crude dimethyl acetal of 7-formyl-1-indanone. Its infrared spectrum showed a single carbonyl band at 5.9 μ and a band at 7.5 μ which apparently is characteristic of methyl ethers. The crude oil was estimated to be of above 80% purity by comparison of its infrared spectrum with that of an authentic sample. The aqueous layer was acidified with 12 ml. of hydrochloric acid and extracted with two 100-ml. portions of benzene. The benzene was partially evaporated and *n*-heptane was added to the hot solution, which yielded 1.2 g. (6.8% yield) of 1-indanone-7-carboxylic acid on cooling. When the acid was recrystallized from ethyl acetate, it melted at 159.5–161.5°. The infrared spectrum showed a strong hydroxyl band at 3.9 μ and carbonyl bands at 5.8 μ and 6.1 μ.

Anal. Calcd. for $C_{10}H_8O_3$: C, 68.18; H, 4.57; neut. equiv., 176. Found: C, 67.90; H, 4.88; neut. equiv., 177.

II. Ozonolysis of acenaphthene in aqueous t-butyl alcohol. A suspension of acenaphthene (15.4 g., 0.10 mole) in 350 ml. of *t*-butyl alcohol and 50 ml. of water was treated with approximately 2.3 weight % ozone (in oxygen) at a flow rate of 102 l. per hr. at 5° for 192 min. Under these conditions, 9.6 g. (0.20 mole) of ozone was passed into the reaction mixture. The reaction mixture was then flushed with oxygen and transferred to a 2-l. flask. Sodium bicarbonate (800 ml. of 0.7% solution) was added, and the alcohol was removed by distillation to a head temperature of 95°. The resultant precipitate was filtered, dried, and then extracted with three 50-ml. portions of chloroform. The combined chloroform extracts were evaporated to dryness, yielding 7.7 g. (48.2% yield) of crude 7-formyl-1-indanone. The infrared spectrum of this product was identical with that of a pure sample of 7-formyl-1-indanone and showed a doublet carbonyl band at 5.85 μ and 5.95 μ. The purity of the crude product was estimated to be above 90%. Distillation of the aqueous filtrate to one half of its original volume yielded a solid, which was filtered and combined with the chloroform-insoluble fraction. This unidentified, high-melting solid, designated as compound A, weighed 6.7 g. (43.5 weight % yield). Recrystallization from *N,N*-dimethylformamide produced a yellow solid that melted at 291–297° dec.

III. Reactions of acenaphthene ozonolysis products. A. Preparation of the dimethyl acetal of 7-formyl-1-indanone. Recrystallized 7-formyl-1-indanone (1.0 g.), methanol (25 ml.), and Becco 40% peracetic acid (3 drops) were refluxed for 3 hr. in a 100-ml. flask. Aqueous sodium bicarbonate (25 ml. of 7% solution) was added, and the methanol was removed by distillation to a head temperature of 100°. The brown, oily residue was extracted with 15- and 10-ml. portions of chloroform. The chloroform was heated with activated charcoal and filtered through a Celite bed. The chloroform was evaporated under vacuum, yielding 1.1 g. (85% yield) of the dimethyl acetal of 7-formyl-1-indanone. The infrared spectrum showed a single carbonyl band at 5.9 μ and a band at 7.5 μ, which apparently is characteristic for methyl ethers.

Anal. Calcd. for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84; OCH_3, 30.09. Found: C, 69.56; H, 6.97; OCH_3, 29.92.

B. Reduction of the dimethyl acetal of 7-formyl-1-indanone. Lithium aluminum hydride (1.4 g., 0.037 mole) in ether (200 ml.) was stirred in a 1-l., three neck flask equipped with reflux condenser, dropping funnel, and mechanical stirrer. A solution of crude dimethyl acetal of 7-formyl-1-indanone (7.8 g., 0.038 mole) was added dropwise to the flask over a 1-hr. period. After the mixture was stirred for an additional 30 min., the excess lithium aluminum hydride was destroyed by careful addition of ethyl acetate until bubbling ceased. Sulfuric acid (100 ml. of 1:4 by volume aqueous solution) was added, and stirring was continued for an additional 1 hr. The mixture was filtered, and the ether layer was separated, water washed, and evaporated to dryness. The dark, viscous oil weighed 5.2 g. (85% yield, calculated as crude 7-formyl-1-indanol). The infrared spectrum showed a hydroxyl band at 2.6 μ and a carbonyl band at 5.9 μ. The compound formed a precipitate with 2,4-dinitrophenylhydrazine. Attempts to obtain an analytically pure sample of this compound or its derivative were unsuccessful.

C. Oxidation of unknown compound A. A 2.5-g. portion of compound A was mixed with potassium hydroxide (10 g. of 87% purity) and water (125 ml.) in a 500-ml. flask and was refluxed 1 hr. Potassium permanganate (12 g.) was added and the mixture was refluxed for 16 hr. The precipitated manganese dioxide was removed by filtration. The pale yellow filtrate was acidified to a *p*H of 1 with hydrochloric acid and evaporated to dryness. The organic acids were extracted from the residue with acetone (100 ml.). Evaporation of the acetone yielded a tacky residue, which was dissolved in water. Careful addition of sodium hydroxide to a *p*H of 4 caused a precipitate to form. This precipitate was 0.6 g. (24 weight % yield) of crude monosodium hemimellitate. The product was recrystallized from a solution of water and ethyl acetate. The infrared spectrum showed acid hydroxyl bands at 3.8 μ and 4.1 μ, carbonyl

(5) Beilstein's *Handbuch der Organischen Chemie*, Vol. VII, 1st ed., Verlag von Julius Springer, Berlin, 1925, p. 360.

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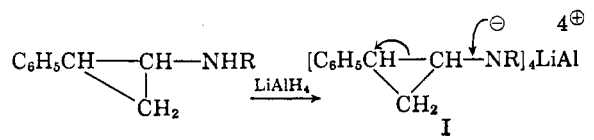
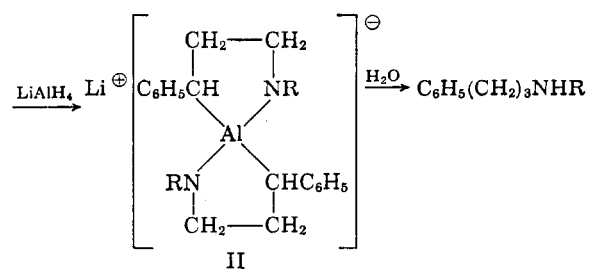
Synthesis of several *N*-substituted derivatives of *trans*-2-phenylcyclopropylamine is described. Several reactions involving opening of the cyclopropane ring, observed in the course of this work, are reported and discussed.

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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