ferrous ion. This reaction it must be assumed would be much more rapid than the dissociation of the complex into the ferric ion and riboflavin.

(4) The catalytic decomposition of hydrogen peroxide proceeds simultaneously with the reaction involving hydrogen peroxide and riboflavin. The existence of a lag period may mean that the ferrous ion reacts preferentially with riboflavin, and that consequently the initiation of the decomposition of peroxide depends upon the availability of the ferrous ion. This type of mechanism would indicate that the decomposition of riboflavin proceeds independently of the catalytic decomposition of peroxide or of intermediate products such as ferrates, the formation of which have been demonstrated to attend peroxide decomposition in the presence of iron. This conclusion is supported further by the experiments with catalase and potassium iodide. In these experiments the formation of intermediates leading to an acceleration of the decomposition of peroxides does not lead to a corresponding acceleration of the decomposition of riboflavin but rather to a sharp retardation.

It is clear from the foregoing that the practice in analytical procedures for riboflavin involving the use of peroxides in high concentrations as a reagent for the destruction of interfering pigments is open to criticism. The use of this reagent is justified only in the absence of traces of the ferrous ion and perhaps of other metallic ions.

Summary

Riboflavin which in pure solutions is exceedingly stable to the action of hydrogen peroxide is decomposed rapidly by dilute solutions of this reagent in the presence of traces of the ferrous ion.

The rate of decomposition increases abruptly between 0.18 and 0.36 milligram atom of the ferrous ion per liter.

In the microbiological synthesis of riboflavin by the organism *Clostridium acetobutylicum* a drastic reduction in the yield of riboflavin occurs precisely in this concentration range of the ferrous ion. Added riboflavin is also destroyed in this range, and this suggests that the action of the iron is in part at least destructive rather than inhibitory.

The view that the destruction of riboflavin by the organism *Clostridium acetobutylicum* operates through a peroxide mechanism is supported by experiments in which significant increases in yield of riboflavin are obtained by the use of sodium hydrosulfite and traces of crystalline catalase.

Iodide ion stabilizes riboflavin against the action of hydrogen peroxide *in vitro* and *in vivo* but is inhibitory to the microbiological synthesis of riboflavin. This is explained on the basis of the independent inhibitory action of iodine ion operating through a mechanism in which iodine formed by the action of hydrogen peroxide reacts in the presence of the ferrous ion with the precursors of riboflavin.

Simultaneous with its action on riboflavin, hydrogen peroxide undergoes a thermal decomposition which is catalysed by the ferrous ion. This decomposition is characterized by a lag period during which the greater portion of riboflavin is destroyed.

Ferrous and not ferric ion activates the decomposition of riboflavin.

The use of hydrogen peroxide to destroy interfering pigments in analytical procedures for the determination of riboflavin is justified only in the absence of traces of the ferrous ion and perhaps of other metallic ions.

WASHINGTON, D. C. RECEIVED JANUARY 9, 1946

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, NORTHWESTERN UNIVERSITY DENTAL SCHOOL]

Pressor Amines Containing Nuclear Chlorine and Fluorine[1,2]

BY L. S. FOSDICK, O. FANCHER[3] AND K. F. URBACH[4]

A great number of pressor amines have been synthesized and investigated in the past; however, compounds of this type containing nuclear halogen have received comparatively little attention.

Zeynek[5] reported the preparation of 3,5-dichloro- and 3,5-dibromotyramine. Glynn and Lynell[6] prepared 1-(3,4-dichlorophenyl)-2-aminoethanol for which they reported both decreased activity and toxicity as compared to epinephrine. Edkins and Lynell[7] also synthesized several derivatives of ω-aminoacetophenone containing nuclear bromine and chlorine. Other compounds of this nature previously described include 3-fluorophenethylamine,[8] 3-fluoro-4-hydroxyphenethylamine,[8] *p*-fluorophenethylamine and its N-methyl analog[9] and the *p*-chloro analog of propadrine.[10] Hansen[11] prepared 3-fluoro- and 3-chloro-4-hydroxy-ω-methylaminoacetophenone. He, as well as Edkins and Lynell, was unable to reduce the

(1) This paper represents part of the thesis material submitted by Mr. Fancher and Mr. Urbach at Northwestern University Graduate School.

(2) This work was done under a grant from the Abbott Foundation.

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(5) Zeynek, *Z. biol. Chem.*, **114**, 275 (1921).

(6) Glynn and Lynell, *Quart. J. Pharmacol.*, **5**, 480 (1932).

(7) Edkins and Lynell, *ibid.*, **9**, 75 (1936).

(8) Schiemann and Winkelmüller, *J. prakt. Chem.*, **135**, 101 (1932).

(9) Suter and Weston, THIS JOURNAL, **63**, 602 (1941).

(10) Hartung, Munch and Crossley, *ibid.*, **57**, 1091 (1935).

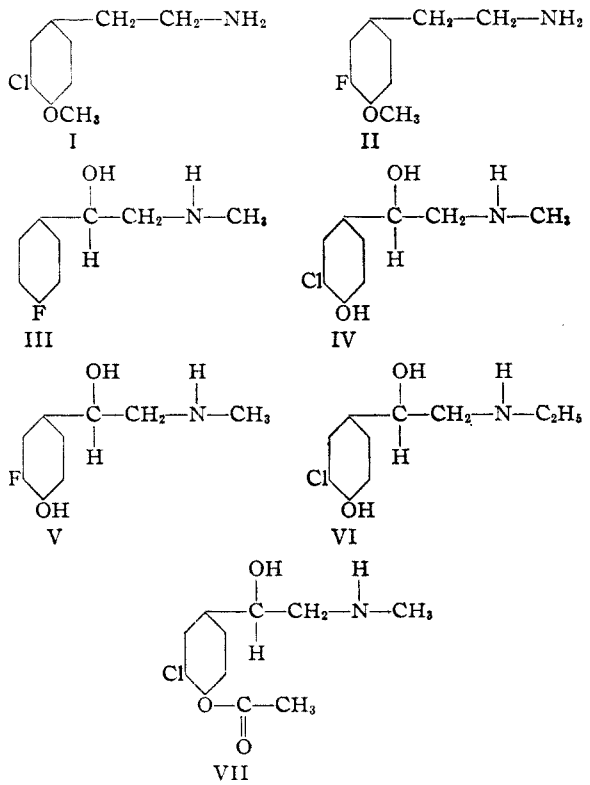
(11) Hansen, *ibid.*, **59**, 280 (1937).

ketones to the secondary alcohols by a variety of methods tried.

In the present investigation 3-chloro- and 3-fluoro-4-methoxyphenethylamine (I, II), 1-(*p*-fluorophenyl)-2-N-methylaminoethanol (III) and 3-chloro and 3-fluoro substituted epinephrine analogs (IV, V, VI, VII) have been prepared.

Preliminary pharmacological data[12] indicate that all of the compounds, with the exception of one (VII), produce vasoconstriction and a rise in blood pressure when injected. The acetylated compound (VII) depresses blood pressure. Of the substituted phenylethylamines, the 3-fluoro compound (II) compares favorably with the 3-chloro analog (I). 1-(*p*-Fluorophenyl)-2-N-methylaminoethanol (III) compares favorably with synephrine as to pressor activity. Compounds IV, V and VI are roughly $^1/_{400}$ as toxic as epinephrine. Pressor activity, however, drops to about the same degree. Duration of action seems to be prolonged in the case of compound VI.

From these experiments we are led to believe that the effect of fluorine in the aromatic ring of a pressor amine compares favorably with chlorine in the same position, but both are inferior to a hydroxy group in this respect. It is hoped that further study of these compounds will be useful in evaluating relative effects of chlorine and fluorine in pharmacodynamically active substances. We intend to extend the chemical work and present more complete pharmacological evaluation in the future.



(12) We are indebted to Dr. C. A. Dragstedt, Northwestern University Medical School, for coöperation on the pharmacological data.

The synthesis of 1-(*p*-fluorophenyl)-2-N-methylaminoethanol (III) followed the general method used by Foldi[13a] and Kharasch[13b] to prepare similar compounds without nuclear fluorine. 3-Fluoro-4-methoxyphenethylamine and 3-chloro-4-methoxyphenethylamine (I, II) were prepared by bromination and subsequent treatment with ammonia of the respective substituted phenethanols. The chlorine and fluorine containing epinephrine analogs (IV, V, VI, VII) were prepared essentially by a method first mentioned in Canadian Patent 318,488 and later extended by Baltzly and Buck.[14,15]

Experimental

***p*-Fluorostyrene.**—Fluorobenzene was prepared according to Balz and Schiemann,[16] brominated, converted to *p*-fluorophenethanol and the corresponding bromide according to Suter and Weston.[17] *p*-Fluorophenethyl bromide (26.5 g.) was added dropwise to fused potassium hydroxide (18 g.) kept at 200° by means of an oil-bath. A mixture of *p*-fluorostyrene, water and the original bromide distilled over when the temperature was raised to 220°. The organic layer was separated, dried over solid potassium hydroxide and distilled under reduced pressure. A few crystals of hydroquinone were added both to the distilling flask and the receiver before the distillation to prevent polymerization. The product obtained was a colorless, sweet-smelling liquid boiling at 58–59° (25 mm.). The yield was 71.5%. The dibromide was prepared as a solid derivative, m. p. 75°, and analyzed.

Anal. Calcd. for $C_8H_7Br_2F$: Br, 56.71. Found: Br, 56.48.

1-(*p*-Fluorophenyl)-1-bromo-2-(N-methyl-*p*-toluenesulfonamido)-ethane.—*p*-Fluorostyrene (12.5 g.) was dissolved in chloroform (50 cc.) and 24 g. of N-bromo-N-methyl-*p*-toluenesulfonamide[13b] was added. The mixture was warmed on a steam-bath to start the reaction and then removed. After the reaction was complete the solvent was removed by distillation *in vacuo*. This left a yellow oil which failed to crystallize. The compound was employed in the subsequent reaction without analysis.

1-(*p*-Fluorophenyl)-1-acetoxy-2-(N-methyl-*p*-toluenesulfonamido)-ethane.—The oil obtained in the previous step (35 g.) was refluxed for four hours with glacial acetic acid (200 cc.) to which had been added 20 g. of anhydrous sodium acetate. The acetic acid was removed and the residue poured into ice water. A heavy oil separated which, after drying in a vacuum desiccator, and solution in alcohol, crystallized slowly when cooled. After filtration the yield could be increased by repeated concentration of the mother liquor; colorless crystals, m. p. 73°. Yield based on *p*-fluorostyrene was 76%.

Anal. Calcd. for $C_{18}H_{20}O_4NSF$: N, 3.84. Found: N, 3.89.

1-(*p*-Fluorophenyl)-1-hydroxy-2-(N-methyl-*p*-toluenesulfonamido)-ethane.—Thirteen grams of the acetate obtained in the preceding reaction was dissolved in absolute alcohol (95 cc.), and 2.2 g. of sodium hydroxide dissolved in 11 cc. of water was added. The mixture was refluxed for thirty minutes, the alcohol was evaporated and water was added to the residue. An oil separated. This was taken up in benzene and the solution concentrated under reduced

(13a) Foldi, *Ber.*, **63**, 2257 (1930).

(13b) Kharasch and Priestley, THIS JOURNAL, **61**, 3425 (1939).

(14) Baltzly and Buck, *ibid.*, **62**, 164 (1940).

(15) Baltzly and Buck, *ibid.*, **65**, 1948 (1943).

(16) Balz and Schiemann, *Ber.*, **60B**, 1186 (1927).

(17) Suter and Weston, THIS JOURNAL, **63**, 602 (1941).

pressure. After standing in a vacuum desiccator for a week the product crystallized in slender yellow needles. Recrystallization from a mixture of benzene and petroleum ether gave a colorless crystalline product; m. p. 95–96°, yield 95%.

Anal. Calcd. for $C_{16}H_{18}O_3NSF$: N, 4.33. Found: N, 4.30.

1-(*p*-Fluorophenyl)-2-N-methylaminoethanol (III).—Three and one-half grams of the hydroxy compound obtained in the last reaction was dissolved in amyl alcohol (100 cc.) and heated to boiling. While the solution was boiling, metallic sodium (6.3 g.) was added in small portions. After all the sodium was dissolved the solution was cooled and treated with water (100 cc.) to decompose sodium amylate. The alcohol layer was separated and extracted with 5% hydrochloric acid. The acid solution was concentrated and extracted with ether to remove residual amyl alcohol. After extraction, solid sodium hydroxide was added to the well cooled aqueous solution. As soon as the solution was alkaline an oil was thrown down which solidified on further cooling. The mixture was extracted with ether, the solvent evaporated and the residue dissolved in 5% hydrochloric acid. When this solution was evaporated to dryness in a vacuum desiccator a brown crystalline compound was obtained. It recrystallizes from absolute alcohol–dry ether as colorless crystals; m. p. 118–121°, yield 77.5%.

Anal. Calcd. for $C_9H_{13}ONFCl$: N, 6.81. Found: N, 7.01.

3-Fluoro-4-methoxyphenethanol.—*o*-Anisidine was converted to 2-fluoro-4-bromoanisole according to Schiemann's procedure.[18,19] This substance (79.5 g.) was dissolved in 150 cc. of dry ether. A small amount of this solution was added to clean magnesium turnings (9.9 g.) and the Grignard reaction induced with a small crystal of iodine. The remainder of the ether solution was slowly dropped in the reaction mixture. When the addition was complete, dry benzene (60 cc.) was added and the mixture allowed to reflux for one hour. The flask was cooled and a solution of 35 g. of ethylene oxide in dry benzene (50 cc.) was added to the Grignard reagent from a dropping funnel cooled by means of an ice–salt-bath. During this addition the temperature was kept below 5°. The mixture was then refluxed for an hour and subsequently decomposed with ice and dilute sulfuric acid. The organic layer was separated, the aqueous layer extracted with ether and the combined ether solutions dried over anhydrous sodium sulfate. Fractionation gave 35 g. of colorless, sweet smelling liquid, boiling at 147–148° (7 mm.); yield 44%; phenylurethan, m. p. 116–117°.

Anal. Phenylurethan calcd. for $C_{16}H_{16}O_3NF$: N, 4.85. Found: N, 4.76.

3-Fluoro-4-methoxyphenethyl Bromide.—The alcohol obtained in the preceding step (30 g.) was dissolved in dry benzene and cooled in a freezing mixture. Phosphorus tribromide (24 g.) was slowly added with stirring. Stirring was continued for thirty minutes after the addition. Subsequently the mixture was heated on a steam-bath until the evolution of hydrogen bromide ceased. The mixture was successively washed with ice water and sodium bicarbonate, 10%, and after separation was dried over calcium chloride and distilled. A 71% yield of a colorless liquid was obtained; b. p. (10 mm.) 139–140°. The product was used in the following step without further characterization.

3-Fluoro-4-methoxyphenethylamine Hydrochloride (II).—The oil (15 g.) obtained in the previous reaction was dissolved in absolute alcohol (500 cc.) and treated with dry ammonia in an ice-bath. The solution was tightly stoppered and kept for ten days at room temperature. The alcohol was removed, the residue dissolved in dry ether, and the solution dried over solid sodium hydroxide. The ether was taken off and the residue dissolved in 5% hydrochloric acid. The solution was evaporated to dryness and crystallized from absolute alcohol-dry ether. A white amorphous product was obtained, m. p. 215–218°, yield 53%.

Anal. Calcd. for $C_9H_{13}ONClF$: N, 6.82. Found: N, 6.89.

3-Chloro-4-methoxyphenethanol.—*o*-Chlorophenol was brominated according to the directions of Raiford and Miller[20] to give a 92% yield of 2-chloro-4-bromophenol. This was methylated with methyl sulfate using the procedure of Ullmann[21] to give 2-chloro-4-bromoanisole. This was dissolved in dry ether and a Grignard reaction was carried out analogous to the one described above in the preparation of 3-fluoro-4-methoxyphenethanol. A 67% yield of a viscous, sweet smelling oil was obtained; b. p. (9 mm.) 165–166°; phenylurethan m. p. 110–111°.

Anal. Phenylurethan calcd. for $C_{16}H_{16}O_3NCl$: N, 4.85. Found: N, 4.52.

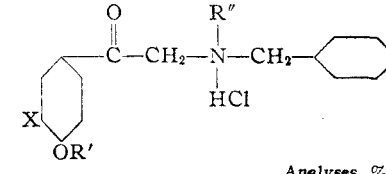
3-Chloro-4-methoxyphenylethylamine Hydrochloride (I).—This compound was obtained by converting the alcohol prepared in the previous reaction into the bromide and subsequent treatment with dry ammonia in the manner already described under the preparation of its fluoro analog. 3-Chloro-4-methoxyphenethyl bromide was obtained as an oil in 62% yield; b. p. (9 mm.) 162–165°. The hydrochloride of 3-chloro-4-methoxyphenethylamine is an amorphous white powder melting at 192–195°. The yield based on the bromide was 50%.

Anal. Calcd. for $C_9H_{13}ONCl_2$: N, 6.31. Found: N, 6.27.

Chlorine and Fluorine Substituted Epinephrine Analogs.—These compounds were all prepared by treating appropriately substituted ω-chloroacetophenones with N-monoalkylbenzylamines and subsequent catalytic debenzylation and reduction, following essentially the method previously mentioned.[14,15] The preparation of 1-(3-chloro-4-hydroxyphenyl)-2-N-methylaminoethanol (IV) is given as an example. The constants of the other analogs and intermediary alkylbenzylaminoacetophenones are summarized in Tables I and II.

TABLE I

SUBSTITUTED ω-(N-ALKYLAMINOBENZYL)-ACETOPHENONES (HYDROCHLORIDES)



X	R′	R″	M. p., °C.	Yield, %	Analyses, % N calcd.	N found
Cl	H	Methyl	211–213	70–80	4.29	4.25
Cl	H	Ethyl	207–208	50–55	4.12	4.15
Cl	—C(=O)—CH₃[a]	Methyl	212–214	80	3.81	3.62
F	H	Methyl	225–230	70	4.52	4.61

[a] This compou d was obtained from the acetylated 3-chloro-4-hydroxy-ω-chloroacetophenone. The free phenol was acetylated with acetic anhydride and a few drops of concentrated sulfuric acid. The yield was quantitative. Recrystallized from alcohol, 3-chloro-4-acetoxy-ω-chloroacetophenone was obtained as a pale yellow, lachrymatory powder melting at 81–82°.

3-Chloro-4-hydroxy-ω-N-methylbenzylaminoacetophenone Hydrochloride.—3-Chloro-4-hydroxy-ω-chloroacetophenone was prepared by the Fries rearrangement of *o*-chlorophenyl chloroacetate previously prepared by Hansen.[11] It was found that chloroacetylation of *o*-chlorophenol with chloroacetyl chloride and recrystallization of the ω-chloroacetophenone with benzene instead of toluene

(18) Schiemann, *Z. physik. Chem.*, **A156**, 397 (1931).

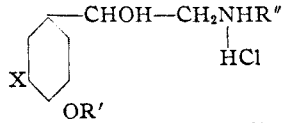
(19) Schiemann, *et al.*, *J. prakt. Chem.*, **143**, 18 (1935).

(20) Raiford and Miller, THIS JOURNAL, **55**, 2125 (1933).

(21) Ullmann, *Ann.*, **327**, 114 (1903).

TABLE II

SUBSTITUTED EPINEPHRINE ANALOGS (HYDROCHLORIDES)



X	R′	R″	M. p., °C.	Yield, %	Analyses, % N calcd.	N found
Cl	H	Methyl	196–200	95	5.88	5.67
Cl	H	Ethyl	208–211	90	5.55	5.52
Cl	—C(=O)—CH₃	Methyl	202–204	97	5.00	4.85
F	H	Methyl	[a]	85	6.32	6.02

[a] This compound was obtained as a hard glass which failed to crystallize. It softened between 60–70°.

after the decomposition of the aluminum complex raised the yield of this intermediary product. 3-Chloro-4-hydroxy-ω-chloroacetophenone (0.1 mole) was added as a powder to methylbenzylamine (0.2 mole) dissolved in 500 cc. of dry dioxane. The mixture was shaken at room temperature for several hours or until crystals of methylbenzylamine hydrochloride were seen to form and then left to stand tightly stoppered for one to two days. The methylbenzylamine hydrochloride was removed by filtration on a suction flask and washed with dioxane. To the combined filtrates absolute alcohol, saturated with dry hydrogen chloride, was added, whereupon an oil was thrown out. The addition of the alcoholic hydrogen chloride was stopped as soon as the oil began to redissolve. A small quantity of dry ether was added and the mixture left in the icebox. The oil usually solidified within 24 hours. The tertiary amine hydrochloride was dissolved in methanol, refluxed for ten minutes with activated charcoal and precipitated by the addition of dry ether.[22] A colorless crystalline product was obtained.

1-(3-Chloro-4-hydroxyphenyl)-2-N-methylaminoethanol Hydrochloride (IV).—The substituted acetophenone (0.05 mole) prepared in the preceding step was dissolved in absolute methanol (250 cc.) A little platinum black was added as catalyst and the mixture was subjected to hydrogen at 45 lb. pressure and room temperature. The reduction was usually complete in eight to twelve hours. The catalyst was removed, the solvent evaporated under reduced pressure and the residue dried over phosphorus pentoxide in a vacuum desiccator. A hard glass formed which could be crystallized from absolute methanol by adding a sufficient amount of dry ether. The product consists of colorless crystals which are soluble in water and hot acetone as well as methanol.

Summary

1. The preparation of a number of chlorine and fluorine containing analogs of epinephrine, synephrine and phenylethylamines has been described.

2. All of these compounds, with the exception of one which acts as a depressor, have pressor activity.

3. The toxicity of these compounds is much less than that of epinephrine.

(22) In the preparation of some of the other alkylbenzylaminoacetophenones some alkylbenzylamine came through. The hydrochlorides were subsequently separated by fractional precipitation.

CHICAGO, ILLINOIS RECEIVED JANUARY 14, 1946

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF CALIFORNIA AT LOS ANGELES]

Cyclopropane Derivatives. II. The Electric Moments of Some Alicyclic Compounds

BY MAX T. ROGERS AND JOHN D. ROBERTS[1]

There is considerable evidence that compounds in which a cyclopropane ring is located adjacent to an unsaturated linkage, such as a carbonyl group or double bond, exhibit many of the physical and chemical properties characteristic of substances containing conjugated double bonds. For example, the absorption spectrum of a double bond conjugated with a cyclopropane ring is shifted toward longer wave lengths, the shift being somewhat less than that observed for conjugated double bonds[2,3,4,5] and a detailed investigation of three type reactions showed that a cyclopropane ring conjugated with a carbonyl group behaved in a manner not fundamentally different from the corresponding α,β-unsaturated carbonyl compounds.[6]

Since conjugation usually has a considerable effect on electric dipole moment, we have determined the electric moments of cyclopropyl chloride, cyclopropylidene chloride and cyclopropyl cyanide for comparison with those of the corresponding cyclopentyl compounds in which conjugation was expected to be unimportant. The moments of some other cyclopentyl derivatives which have not been reported previously were also determined.

Experimental Part

Materials

Benzene.—Reagent benzene was stirred with concentrated sulfuric acid, washed with potassium hydroxide solution, then with water, and dried over calcium chloride. The material was fractionally crystallized twice, dried and distilled over sodium, d^{25}_4 0.87341.

Carbon tetrachloride was purified by the method of Fieser.[7]

Cyclopropyl and cyclopropylidene chlorides prepared in a previous investigation[8] were fractionated before use: monochloride: b. p. 43°, $n^{25}D$ 1.4079, d^{25}_4 0.9899; dichloride: b. p. 75°, $n^{25}D$ 1.4380, d^{25}_4 1.2109.

Cyclopropyl cyanide was prepared by the method of Schlatter[9]; b. p. 65° (75 mm.), $n^{25}D$ 1.4188, d^{25}_4 0.8908.

Cyclopentyl chloride.—To a solution of 272 g. of anhydrous zinc chloride in 190 g. of concentrated hydrochloric

(1) Present address: Converse Memorial Laboratory, Harvard University, Cambridge 38, Mass.

(2) Carr and Burt, THIS JOURNAL, **40**, 1590 (1918).

(3) Klotz, *ibid.*, **66**, 88 (1944).

(4) Roberts and Green, *ibid.*, **68**, 214 (1946).

(5) Rogers, unpublished results.

(6) Kohler and Conant, THIS JOURNAL, **39**, 1404 (1917).

(7) Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., New York, N. Y., 1941, p. 365.

(8) Roberts and Dirstine, THIS JOURNAL, **67**, 1281 (1945).

(9) Schlatter, "Organic Syntheses," **23**, 20 (1943).