droxide was refluxed for 4 hr. On cooling, colorless needles separated. These were collected, washed well with water, and recrystallized from 66% ethanol to give 2.3 g. (90%) of the oxetane (XI), m.p. 252° (dec.), $[\alpha]_D^{27}$ +37.8° (pyridine).

Anal. Calcd. for $C_{20}H_{24}N_2O$: C, 77.8; H, 7.9; N, 9.1. Found: C, 77.7; H, 7.9; N, 9.0.

When alkylation of guanidine with I was attempted, the oxetane (XI) was the only product isolated. A solution containing guanidine was prepared by adding 8.0 g. (0.2 mole) of sodium hydroxide to a solution of 28.6 g. (0.32 mole) of guanidine hydrochloride in 200 ml. of 66% ethanol. To this was added 4.0 g. of I and the solution was refluxed for 4.5 hr. On cooling, long colorless needles of the oxetane separated (50% yield). Identification was by m.p., specific rotation and infrared.

Acetoylsis of the oxetane (XI). A solution of 2.2 g. of XI in 25 ml. of glacial acetic acid and 20 ml. of acetic anhydride was refluxed for 1 hr. and the solvents were removed under reduced pressure. The residue was slurried with water, made basic with ammonium hydroxide and the insoluble material was collected, washed well with water, and crystallized twice from 66% ethanol to give 0.76 g. (30%) of 16-methyl-17-acetoxyyohimbane or 16-acetoxymethylyohimbol, m.p. 187–189°, $[\alpha]_D^{27}$ −42.5° (pyridine). The infrared spectrum taken as a Nujol mull showed a sharp peak at 5.80μ with a shoulder at 5.90μ.

Anal. Calcd. for $C_{22}H_{28}N_2O_2$: C, 75.0; H, 8.0; N, 7.9. Found: C, 74.8; H, 7.9; N, 7.5.

16-Methylyohimbol (XII). A. *From the p-toluenesulfonic acid ester of yohimbyl alcohol.* To a mixture of 2.0 g. of lithium aluminum hydride in 40 ml. of dry tetrahydrofuran, a solution of 4.60 g. of I in 120 ml. of tetrahydrofuran was added dropwise with stirring. After the addition, the mixture was refluxed for 4.5 hr. After careful addition of water refluxing was continued for an additional hr. The supernatant liquid was decanted from the inorganic salts and concentrated under reduced pressure. The solid which separated was crystallized from 66% ethanol to give 1.87 g. (63%) of 16-methylyohimbol, m.p. 235° (dec.), $[\alpha]_D^{27}$ −20.4° (pyridine). The infrared spectrum was identical with that of a known sample.[18]

Anal. Calcd. for $C_{20}H_{26}N_2 \cdot {}^1/_2H_2O$: C, 75.2; H, 8.5; N, 8.8. Found: C, 75.0; H, 8.6; N, 8.8.

B. *From the oxetane* (XI). When XI (1.1 g.) was refluxed with lithium aluminum hydride (1.0 g.) in 150 ml. of tetrahydrofuran for 46 hr., 16-methylyohimbol was obtained in 27% yield. Identification was by infrared, m.p., and specific rotation.

16-Methylyohimbone (XIII). A mixture of 1.0 g. of 16-methylyohimbol, 10 g. of aluminum isopropoxide, 50 ml. of dry xylene, and 100 ml. of dry acetone was refluxed for 24 hr. After removal of the acetone under reduced pressure, the xylene solution was extracted with 2*N* sulfuric acid. The acid extract was made strongly basic with sodium hydroxide. The dried precipitate (0.83 g.), m.p. 286° (dec.) was dissolved in benzene and chromatographed over alumina. Elution with 1:1 benzene-chloroform gave 60 mg. of colorless needles, m.p. 293° (dec.), $[\alpha]_D^{27}$ −88° (pyridine). The infrared spectrum, taken as a Nujol mull, showed one band in the carbonyl region at 5.85μ.

Anal. Calcd. for $C_{20}H_{24}N_2O$: C, 77.9; H, 7.9; N, 9.1. Found: C, 78.0; H, 8.1; N, 9.0.

ANN ARBOR, MICH.

(18) We wish to express our appreciation to Professor Paul Karrer for providing a sample of 16-methylyohimbol for comparison.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF TENNESSEE]

Physiologically Active Compounds. III. Hydrochlorides of Amino Esters of Phenylcyclohexylglycolic Acids, of Amides of Benzilic, Phenylcyclohexyl- and Dicyclohexylglycolic, and Phenylcyclohexylacetic Acids; 2-Methylthioethyl Ester Methiodides of Substituted Benzilic Acids

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Fourteen amino ester hydrochlorides of glycolic acids, eight amino ester hydrochlorides of acid amides, and three methyl iodides of thioalkyl esters of substituted benzilic acids have been prepared. In the physiological tests reported, two compounds appear to be more active in experimental animals than atropine in preventing mortality from an anticholinesterase compound; four exhibit pronounced anticholinergic activity, and one, antihistaminic activity. In the cerebral stimulation test, one compound appears to be more active than benactyzine, a commercial product, although it possesses five times the atropine-like activity.

This paper reports a continuation[3] of the syntheses and tests for physiological activity of compounds related to the amino esters of benzilic acids. The ester hydrochlorides of the phenylcyclohexylglycolic acids, which are listed in Table I, were prepared mostly by the partial hydrogenation of the proper benzilic acid derivatives. Since in most of these cases only one of the phenyl groups in the benzilic acid moiety was substituted, it was necessary to determine which of the rings present was hydrogenated. In two cases studied, the 4-methyl- and 3,5-dimethylbenzilic acid derivatives, it was shown that the unsubstituted ring was attacked. Evidence in support of this contention was twofold: (1) An examination of the ultraviolet absorption curves of the half-hydrogenated products given in Fig. 1. It will be observed that (a) the principal

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(3) For paper II see, C. A. Buehler, H. A. Smith, D. M. Glenn, and K. V. Nayak, *J. Org. Chem.*, **23**, 1432 (1958).

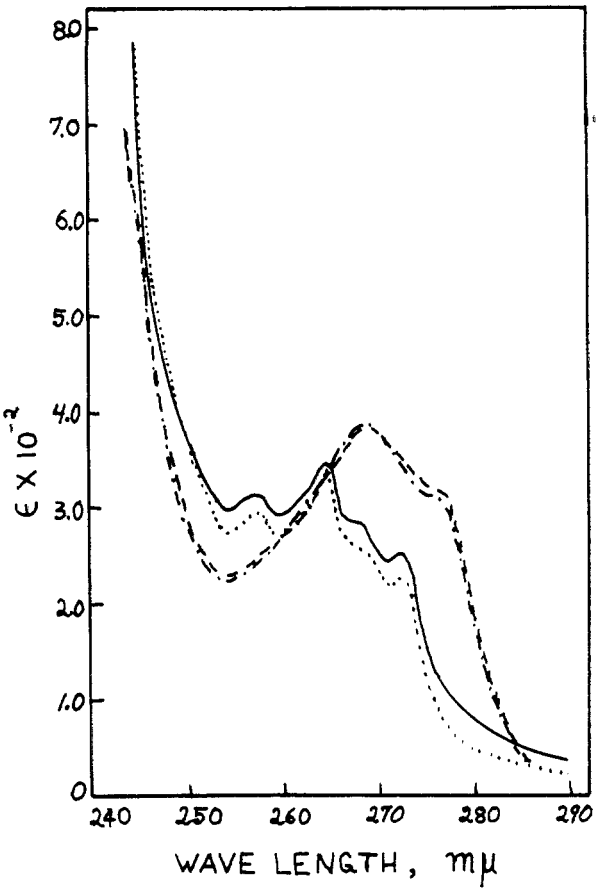
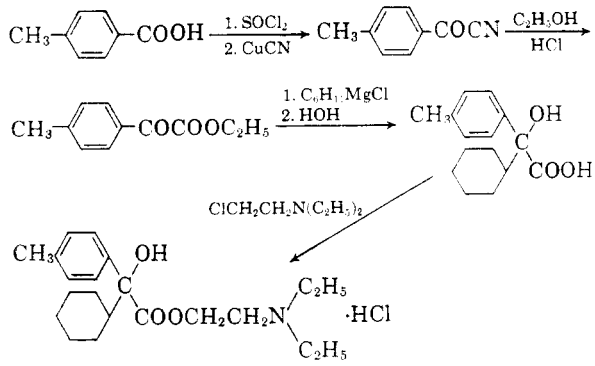


Fig. 1.—Ultraviolet absorption spectra in ethanol of ——— half-hydrogenated 2-diethylaminoethyl 4-methylbenzilate hydrochloride; · · · · synthetic 2-diethylaminoethyl 4-methylphenylcyclohexylglycolate hydrochloride; – – – – half-hydrogenated 2-diethylaminoethyl 3,5-dimethylbenzilate hydrochloride; – · – · – synthetic 2-diethylaminoethyl 3,5-dimethylphenylcyclohexylglycolate hydrochloride.

absorption band for the 3,5-dimethyl ester is greater (269 mμ) than that of the 4-methyl ester (264.5 mμ), (b) the maximum extinction coefficient for the 3,5-dimethyl ester is greater (388.9ε) than that of the 4-methyl ester (348ε) and (c) the 3,5-dimethyl ester gives less fine-band structure than the 4-methyl ester. These facts are best explained on the basis of benzene ring substitution.[4] To put it another way, if the substituted rings had been hydrogenated, the absorption curves would practically be identical since the principal absorption would be due to the benzene rings present. (2) Synthesis of the hydrochlorides of the β-diethylaminoethyl esters of 4-methyl- and 3,5-dimethylphenylcyclohexylglycolic acids. The synthetic ester hydrochlorides were shown to be identical to the half-hydrogenated products by mixed melting points and ultraviolet absorption curves as shown in Fig. 1. The synthetic route used in each case is illustrated with the 4-methyl compound below:



On the basis of the above evidence, it was assumed that, in the half hydrogenation of unsymmetrically substituted benzilic acid esters containing one phenyl group, the phenyl group is hydrogenated in preference to the substituted phenyl group. In Table I, compounds 68, 69, 71, 73, 74 and 75 were assigned the formulas indicated on this basis.

The one-third hydrogenation of the 3-phenyl- and the 4-phenylbenzilic acid ester hydrochlorides produced compounds with satisfactory analyses and melting points, but the ultraviolet absorption curves were of such intensity in comparison to those of related types that a small amount of the isomers may be present. These products, 77 and 78, are listed in Table I.

The methylamides listed in Table II were prepared from the appropriate acid chloride by the method of Krapcho, Turk, and Pribyl.[5] In case the α-hydroxy acid ester was desired, the α-chloro acid chloride was used as starting material and the α-chlorine atom was replaced by an hydroxyl group in the final step. Unfortunately the α-chloro acid chloride could not be prepared from phenylcyclohexylglycolic acid presumably because dehydrohalogenation occurred during the treatment with phosporus pentachloride or thionyl chloride. In addition, no success was achieved in synthesizing the methylamides of phenylcyclohexylglycolic acid by the ester interchange methods mentioned below.

The amides listed in Table II were prepared by the method of Miescher, Meisel, and Hoffmann[6] (82 and 83 from methyl phenylcyclohexylglycolate and 84, 85, and 86 from methyl benzilate followed by hydrogenation). This method gave better yields than that of Phillips.[7]

The 2-methylthioethyl ester methiodides listed in Table III were prepared from the appropriate benzilic acid and 2-chloroethyl methyl sulfide in the presence of sodium ethoxide, followed by treatment of the product with methyl iodide. Unfortunately, of the three methiodides prepared, only the

(4) A. E. Gillam and E. S. Stern, *An Introduction to Electronic Absorption Spectroscopy in Organic Chemistry*, Edward Arnold Ltd., London, 1954, pp. 116–120.

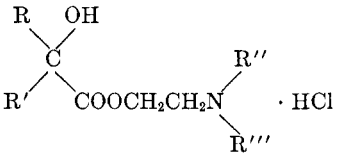
(5) J. Krapcho, C. F. Turk, and E. J. Pribyl, *J. Am. Chem. Soc.*, **77**, 3632 (1955).

(6) K. Miescher, W. Meisel, and K. Hoffmann, U. S. Patent **2,009,114**, July 23, 1935.

(7) A. P. Phillips, *J. Am. Chem. Soc.*, **76**, 1955 (1954).

TABLE I

ESTER HYDROCHLORIDES OF PHENYLCYCLOHEXYLGLYCOLIC ACIDS



No.	R	R′	R″	R‴	Yield, %	M.P.	Analyses Calculated C	Calculated H	Found C	Found H
65	C_6H_5	C_6H_{11}	CH_3	CH_3	47[a]	219–220	63.24	8.25	63.31	8.46
66	C_6H_5	C_6H_{11}	$CH_2(CH_2CH_2)_2CH_2$		47[a]	223–224	66.04	8.45	66.02	8.55
67	C_6H_5	C_6H_{11}	$CH_2(CH_2CH_2)_2CH_2$		24[c]	176–177	60.00	7.78	59.97	8.00
68	2-$CH_3C_6H_4$	C_6H_{11}	C_2H_5	C_2H_5	55[d]	191–193	65.67	8.93	65.97	8.82
69	3-$CH_3C_6H_4$	C_6H_{11}	C_2H_5	C_2H_5	66[d]	187–189	65.67	8.93	65.48	8.51
70	4-$CH_3C_6H_4$	C_6H_{11}	C_2H_5	C_2H_5	75[d]	200–201	65.67	8.93	65.67	9.14
71	2,3-$(CH_3)_2C_6H_3$	C_6H_{11}	C_2H_5	C_2H_5	38[d]	170–172	66.39	9.12	66.01	9.33
72	3,5-$(CH_3)_2C_6H_3$	C_6H_{11}	C_2H_5	C_2H_5	83[d]	217–218	66.39	9.12	66.42	9.21
73	2,4,6-$(CH_3)_3C_6H_2$	C_6H_{11}	C_2H_5	C_2H_5	64[d]	206–207	67.04	9.30	67.19	9.18
74	3,4,5-$(CH_3)_3C_6H_2$	C_6H_{11}	C_2H_5	C_2H_5	85[d]	223–224	67.04	9.30	66.86	9.20
75	2,3,5,6-$(CH_3)_4C_6H$	C_6H_{11}	C_2H_5	C_2H_5	66[d]	204–205	67.66	9.47	68.11	9.73
76	3-$CH_3C_6H_4$	3-$CH_3C_6H_{10}$	C_2H_5	C_2H_5	31[d]	181–182	66.39	9.11	66.06	9.44
77[e]	C_6H_5	3-$C_6H_{11}C_6H_4$	C_2H_5	C_2H_5	34[d]	138–139	70.01	8.14	69.80	8.54
78[e]	C_6H_5	4-$C_6H_{11}C_6H_4$	C_2H_5	C_2H_5	21[d]	148–149	70.01	8.14	70.05	8.36

[a] Based on methyl ester. [b] Methyl bromide. [c] Based on free acid. [d] Based on corresponding ester hydrochloride of benzilic acid. [e] Although the melting point of this compound is reasonably sharp and its analysis is satisfactory, the ultraviolet absorption curve throws some doubt on its purity.

2-methoxy compound was sufficiently stable to be of any practical value.

Tests which are described in a previous paper[8] were made in the Physiology Division of the Directorate of Medical Research in the U. S. Army Chemical Warfare Laboratories at Army Chemical Center, Md., by Drs. John F. O'Leary, Coroline tum Suden, and J. Henry Wills, with the assistance of Messrs. Gerald E. Groblewski and Leonard Carlstrom, to whom we are greatly indebted. The results of the tests are found in Tables IV, V and VI. An examination of these tables shows that:

(1) Two compounds, the diethylaminoethyl ester hydrochloride of 4-methylphenylcyclohexylglycolic acid, 70, and 2-*N*-piperidinoethyl methylbenzilamide hydrochloride, 80, appear to be more active than atropine in preventing mortality from an antichlolinesterase compound. This makes a total of seven of the 77 compounds thus far tested which have shown this result, and 46 more have been equally as effective as atropine.

(2) Of 37 compounds for which tests are reported here dealing with the ability to antagonize the functional effects of acetylcholine and histamine, three (65, 66, 67, all derivatives of phenylcyclohexylglycolic acid) are especially active against acetylcholine, and one (54, the diethylaminoethyl ester hydrochloride of 3,4-dimethyldicyclohexylglycolic acid) is particularly active against histamine. Compounds 65 and 66 are anticholinergic with minimal antihistaminic effectiveness.

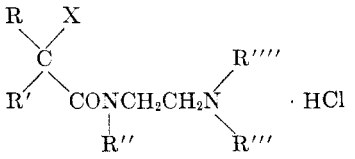
(3) Thirty-seven compounds in addition to the 41 previously tested have now been studied for their effectiveness in changing the diameter of the pupil of the eye. Five of these (67, 68, 70, 81, 83) are active mydriatics, and two (53, 66) are active in producing miosis. Of these seven, three (53, 67, 70) also produced local irritation.

Forty of the compounds, through the courtesy of Dr. Martin L. Black, have been tested by Parke, Davis and Co. for cerebral stimulation on rats. This test is made by the "jiggle cage" method. The compounds are administered either orally or by injection, and the rat is placed in a cage suspended by a spring. The total motion of the cage over a given period of time is integrated and recorded. Compounds of the benactyzine type which are effective cerebral stimulants for rats are of potential usefulness for their tranquilizing action

(8) H. A. Smith, C. A. Buehler, and K. V. Nayak, *J. Org. Chem.*, **21**, 1423 (1956).

TABLE II

AMIDE HYDROCHLORIDES OF BENZILIC, PHENYLCYCLOHEXYLGLYCOLIC DICYCLOHEXYLGLYCOLIC, AND PHENYLCYCLOHEXYLACETIC ACIDS

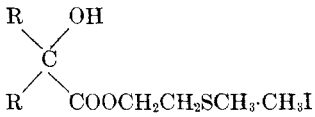


No.	R	R′	R″	R‴	R⁗	X	Yield, %	M.P.	Analyses Calculated C	Calculated H	Found C	Found H
79	C_6H_5	C_6H_5	CH_3	CH_3	CH_3	OH	26[a]	272–274[b]	65.41	7.22	65.28	7.29
80	C_6H_5	C_6H_5	CH_3	$CH_2(CH_2)_3CH_2$		OH	46[a]	226–227[c]	67.94	7.52	68.01	7.28
81	C_6H_5	C_6H_{11}	CH_3	CH_3	CH_3	H	89[d]	206–207	67.34	9.22	67.23	9.38
82	C_6H_5	C_6H_{11}	H	CH_3	CH_3	OH	12[e]	215–216	63.42	8.56	63.70	8.27
83	C_6H_5	C_6H_{11}	H	$CH_2(CH_2)_3CH_2$		OH	18[e]	222–223	66.21	8.73	66.18	8.63
84	C_6H_{11}	C_6H_{11}	H	CH_3	CH_3	OH	29[e]	233–234	62.31	10.17	62.27	10.39
85	C_6H_{11}	C_6H_{11}	H	C_2H_5	C_2H_5	OH	50[e]	231–232	64.06	10.48	63.80	10.43
86	C_6H_{11}	C_6H_{11}	H	$CH_2(CH_2)_3CH_2$		OH	35[e]	260–261	65.17	10.16	65.05	9.96

[a] Based on chloroacid chloride. [b] Krapcho, Turk, and Pribyl, *J. Am. Chem. Soc.*, **77**, 3632 (1955), give 252–253°. [c] Krapcho, Turk, and Pribyl, *loc. cit.*, give 212–214°. [d] Based on acid chloride. [e] Based on methyl ester.

TABLE III

2-METHYLTHIOETHYL ESTER METHIODIDES OF SUBSTITUTED BENZILIC ACIDS



No.	R	Yield, %	B.P., Ester (1 Mm.)	M.P.	Analyses Calculated C	Calculated H	Found C	Found H
87	$2\text{-}CH_3C_6H_4$	37	175–180	61–62	50.85	5.34	50.80	5.61
88	$4\text{-}CH_3C_6H_4$	26	155–160	44–45	50.85	5.34	51.06	5.57
89	$2\text{-}CH_3OC_6H_4$	63	190–194	112–113	47.62	5.00	47.62	5.36

in man. The results of the cerebral stimulation test are given in comparison with benactyzine, the diethylaminoethyl ester hydrochloride of benzilic acid, which is sold commercially as a tranquilizer. The results are given in Table VII. One compound (the dimethylaminoethyl ester hydrochloride of phenylcyclohexylglycolic acid, 65) appears to be slightly more active than benactyzine, although, according to Parke, Davis and Co., it has five times the atropinelike activity; and two compounds, the diethylaminoethyl ester hydrochlorides of 3,4-methylenedioxybenzilic and 2-methylphenylcyclohexylglycolic acids (35, 68), are of approximately equal activity to benactyzine but possess only one fifth to one tenth as great atropinelike activity.

As indicated previously, the same compounds were tested for atropinelike activity. These experiments were performed by administering to an animal (usually a rabbit) a dose of the compound to be studied, and measuring the change in diamater of the eye pupil after a standard time interval. All compounds tested were less active in this respect than atropine. The results, compared to atropine, are given in Table VIII. Benactyzine has one twenty-fifth of the activity of atropine in this test.

TABLE IV

ANTICHOLINESTERASE SCREENING (TEST 1)[a]

(Tests on rabbits with standard 2.0 mg./kg. unless otherwise indicated)

Compared to Atropine		
More active	Equally active	Less active
70	45[b]	68[b]
80	46[c]	78[b]
	65	81[b]
	66	89[b]
	67	
	74	
	82[b]	
	83	
	84	
	85[c]	
	86	

[a] Compounds Nos. 1–25 from Smith, Buehler, and Nayak, *J. Org. Chem.*, **21**, 1423 (1956); Nos. 26–64 from Buehler, Smith, Glenn, and Nayak, *J. Org. Chem.*, **23**, 1432 (1958). [b] Test on rats. [c] Test on rats and rabbits.

EXPERIMENTAL[9]

Methyl phenylcyclohexylglycolate. This ester was obtained by the method of Shacklett[10] as follows: Potassium benzilate was prepared by adding, with stirring, 100 g. of benzilic acid to a solution of 30 g. of potassium hydroxide in 700 ml. of absolute ethanol. After filtering and drying, 107 g. (91%) of an amorphous white solid was obtained. The salt was refluxed for 1 hr. with 30 ml. of methyl iodide in a solution of 500 ml. of butyl carbitol and 80 ml. of water. The reaction mixture, poured into 2.5 l. of water and allowed to cool, gave a light yellow oil, which quickly solidified and which, when removed and dried, was a cream-colored solid weighing 93.5 g. (98%). Two crystallizations from hot ethanol by the addition of water gave snow-white needles, m.p. 76–76.5° (Klinger and Standke[11] give 74–74.5°).

The methyl benzilate obtained above was reduced in approximately 100-g. batches by shaking an acetic acid solution with 0.5 g. of platinum oxide at room temperature under an initial hydrogen pressure of the order of 64 p.s.i. Shaking was continued until about 45% of the amount of hydrogen required for complete hydrogenation was consumed (about 48 hr.). Acetic acid solutions free from the catalyst and containing the partially reduced ester from 475 g. of methyl benzilate were distilled from a pot attached to an 8-ft. Vigreux column equipped with a total reflux-variable take-off distilling head. The acetic acid was removed under reduced pressure produced by a water aspirator while the residue remaining was distilled under about 10 mm. pressure using a vacuum pump. By recovering the phenylcyclohexylglycolic acid present it was shown that from approximately 370 ml. of residue the 245 ml. of distillate which came over after the first 100 ml. had been removed was reasonably pure. Seeding produced white crystals which melted around 40°.

Phenylcyclohexylglycolic acid. This acid was prepared by two methods as follows: (1) By the hydrolysis of the methyl ester using alcoholic sodium hydroxide followed by acidification and crystallization from hot ethanol. The product was white and melted at 160–162° (Smith, Alderman, Shacklett, and Welch[12] gave 167–168°). (2) From benzoyl cyanide by the method of Smith, Alderman, Shacklett, and Welch.[12] This product melted at 158–160°.

β-Aminoester hydrochlorides. These ester hydrochlorides were prepared by two methods: (1) Nos. 65 and 66, Table I, from phenylcyclohexylglycolic acid and the proper β-aminoethyl chloride (β-*N*,*N*-dimethylaminoethyl chloride was produced similarly to the diethyl derivative) as described by Smith, Buehler, and Nayak[8]; (2) Nos. 68–78, Table I, inclusive, by the partial hydrogenation of the benzilic acid ester hydrochlorides:

(a) Catalytic half-hydrogenation of the amino ester hydrochlorides of alkyl substituted benzilic acids. To the acetic acid solutions, as concentrated as possible, of 2 to 3 g. of the hydrochlorides of the 2-diethylaminoethyl esters, as described by Smith, Buehler, and Nayak,[8] 0.4 g. of Adams' platinum catalyst was added. The solution was shaken in a low pressure hydrogenator until the drop in pressure observed was equivalent to 3.4 moles, a slight excess over that required for the half-hydrogenation of one mole of the hydrochloride. After the catalyst was removed and the acetic acid was evaporated *in vacuo*, the residue was digested in hot absolute ethanol, decolorized with Norit, if necessary, and filtered. On cooling, dry ether was added and the precipitate obtained was recrystallized from an ethanol-ether mixture until a sharp melting point was obtained.

(b) Catalytic one-third hydrogenation of the amino ester hydrochlorides of phenyl substituted benzilic acids. The ester hydrochloride, 1.5 g., was dissolved in 30 ml. of glacial acetic acid and 0.4 g. of Adams' platinum catalyst was added. A low pressure hydrogenator was employed and 3 moles of hydrogen was consumed in addition to that required to reduce the catalyst. The residue, obtained as above, was digested in 50 ml. of hot ethyl acetate and the undissolved solid was removed by filtration. Cooling the filtrate gave a solid which after two crystallizations from an ethanol-ether mixture gave sharp melting white crystals.

Methyl bromide of phenylcyclohexylglycolic acid, β-N-piperidinoethyl ester (No. 67, Table I). The hydrochloride, 5 g., was converted into the free base with dilute sodium hydroxide. The amino ester was extracted with ether, the solution dried, and the ether removed. To the methanolic solution of the residue was added 10 g. of 25% methyl bromide in methanol. The stoppered flask was allowed to stand at room temperature for several days, after which the methanol was removed and dry ether was added to the flask. A white solid, which melted sharply after two crystallizations from ethanol ether, separated.

4-Methylbenzoyl chloride. *p*-Toluic acid, 95 g., and 70 ml. of thionyl chloride were refluxed on a steam bath for 3 hr. The excess of thionyl chloride was removed by distillation and the residue was distilled under reduced pressure. The liquid distilling over at 57°/0.3 mm. weighed 100.5 g. (93%) (Blicke and Lilienfeld[13] give 117–120°/24 mm., McElvain and Carney,[14] 106°/12 mm.).

4-Methylbenzoyl cyanide. The method is essentially that of Oakwood and Weisgerber.[15] 4-Methylbenzoyl chloride, 27 g., and 26.5 g. of previously dried cuprous cyanide were well mixed and heated under reflux in a Wood's metal bath at 250–260° for 1.5 hr. During heating the flask was removed from the bath about every 15 min. and the contents were thoroughly mixed. Distillation gave a fraction, 15.1 g. (43.5%),

(9) Melting points were determined on an aluminum melting point block equipped with a 76-mm. immersion thermometer.

(10) C. D. Shacklett, "The Catalytic Hydrogenation of Benzilic Acid," Master's thesis, University of Tennessee, Knoxville, May 1947.

(11) H. Klinger and O. Standke, *Ber.*, **22**, 1211 (1889).

(12) H. A. Smith, D. M. Alderman, C. D. Shacklett and C. M. Welch, *J. Am. Chem. Soc.*, **71**, 3772 (1949).

(13) F. F. Blicke and W. M. Lilienfeld, *J. Am. Chem Soc.*, **65**, 2282 (1943).

(14) S. M. McElvain and T. P. Carney, *J. Am. Chem. Soc.*, **68**, 2599 (1946).

(15) T. S. Oakwood and C. A. Weisgerber, *Org. Syntheses*, Coll. Vol. III, 112 (1955).

TABLE V

BLOOD PRESSURE, GUT, AND RESPIRATION EFFECTS (TESTS 2, 3, 4)

No.[a]	Dose, Mg./Kg.	Effect on B.P. Fall in % After: Acetylcholine (2.5 γ)	Effect on B.P. Fall in % After: Histamine (1.5 γ)	Effect of Compound on: Gut	Effect of Compound on: B.p.	Effect of Compound on: Respiration
6	0.5	−6	+14		Slight fall	Brief apnea
12	0.5	+23	0		−12% (coupled beats)	—
13	0.5	+10	+10		−12%	
21	0.5	−20	−33			
23	0.5	+6	−33			
26	0.5	−13	−6			
27	0.5	+4	+7			
31	0.5	−24	+20		—	
32	0.5	−54	−37			
38	0.5	+20	0		−25%	
42	0.5	+5	−25		−14%	
43	0.5	+13	−10		−11%	
45	7.0	−63	−39	−100%	−40%	+ Depth, + rate
46	2.0	−74			None	No effect on rate or depth of respiration
	0.5	−54	−25			
48	0.5	+3	−21		−22%	
50	0.5	+4	0			Brief hypapnea followed by hypernea
52	0.5	+55	+11		−20%	
54	0.5	−20	−83		Slight fall	
57	0.5	+23	0		−26%	
58	0.5	−15	−7		—	
60	0.5	−13	0		Slight fall	
63	0.5	+5	+23		Slight fall	Slight slowing of heart
65	2.0	−93	−18		None	No effect
	0.5	−77				
66	1.0	−78	0	Blocks spontaneous activity and response to acetylcholine and histamine	None	No effect
	1.0	−100	+6			
67	0.5	−100	−40		—	
68	0.5	−38	−20		−25%	
70	0.5	0	+17		Slight fall	
74	0.5	+38	+68		−19%	Slight slowing of heart
78	0.5	+6	−11		None	
80	0.5	+20	0		Slight fall	
81	0.5	+6	0		Slight fall	
82	0.5	0	0	Tonus increase	None	+ Depth, no effect on rate
83	0.5	−15	0			
84	0.5	0	−20		—	
85	6.5	+16	+6	None	None	+ Depth, + rate
86	7.0	−5	0	None	−11%	+ Depth, + rate
89	0.5	0	0			

[a] Compounds Nos. 1–25 from Smith, Buehler, and Nayak, *J. Org. Chem.*, **21**, 1423 (1956); Nos. 26–64 from Buehler, Smith, Glenn, and Nayak, *J. Org. Chem.*, **23**, 1432 (1958).

distilling at 222–224° which solidified on cooling and melted at 50–51° (Soderbaum[16] gives 52°).

Ethyl-4-methylphenylglyoxylate. The method of Claisen[17] was adopted. 4-Methylbenzoyl cyanide, 23 g., in 100 ml. of absolute ethanol was saturated with hydrogen chloride while the temperature was kept below 10°. After the mixture was allowed to stand in the cold room for 8 days, it was poured into a large quantity of water. The ester which separated was extracted three times with ether, and the ether extracts were washed with a dilute solution of sodium bicarbonate, dried, and distilled under reduced pressure. The product, 15.3 g. (50%), boiled at 124–126°/3.5 mm. (Auwers[18] gives 154–156°/18 mm.).

4-Methylphenylcyclohexylglycolic acid. Magnesium turnings, 1.98 g., were covered with sodium-dried ether and 1.5 to 2 g. of pure chlorocyclohexane was added. On adding a crystal of iodine, heat was applied with a steam bath with-

(16) H. A. Soderbaum, *Ber.*, **25**, 3462 (1892).

(17) L. Claisen, *Ber.*, **12**, 629 (1879).

(18) K. Auwers, *Ber.*, **44**, 600 (1911).

TABLE VI

EYE EFFECTS[a,b] (TESTS 5, 6)

Mydriasis					Miosis		Local Irritation, Active
Active	Moderately active	Least active	No definite effect		Active	Moderately active	
67	6	19	10	51	53	22	19
68	65		12	52	66	47	47
70	85		13	54		82	53
81	86		21	58			67
83	89		23	63			70
			24	66			78
			29	74			
			34	78			
			38	80			
			48	84			
			50				

[a] Compounds Nos. 1–25 from Smith, Buehler, and Nayak, *J. Org. Chem.*, **21**, 1423 (1956); Nos. 26–64 from Buehler, Smith, Glenn, and Nayak, *J. Org. Chem.*, **23**, 1432 (1958). [b] No compound produced local anesthesia.

TABLE VII

TESTS FOR CEREBRAL STIMULATION

Compared to Benactyzine				
More active	Equally active	Less active	No activity	
65	35[a]	2	6	25
	68	3[a]	7	28
		4	8	29
		5	9	30
		10	11	33
		45	12	34
		69	15	37
		71	16	
		79	17	42
			18	76
			20	77
			21	82
			22	84
			24	85

[a] Lethal in doses of 50 mg./kg. or greater.

TABLE VIII

TESTS FOR ATROPINELIKE ACTIVITY

Compared to Atropine (Dose, 25 Mg./Kg.)						
1/5	1/25	1/125	1/250	1/500 or less	None	
65	45[a]	4	2	6	7	28
	68[a]	71	3[a,b]	8	9	29
	69	79	5	10	12	30
			35	11	15	33
			82	21	16	34
				24	17	37
				76	18	42
					20	77
					22	84
					25	85

[a] Dose, 12.5 mg./kg. [b] Produced convulsions when tested in dosage of 25 mg./kg.

out stirring and these conditions were maintained for 5 to 10 min. after the iodine color had disappeared. Once the reaction had started, more dry ether and the remainder of the chlorocyclohexane—total was 9.63 g.—in ether was added. Stirring and refluxing were then continued for another 40 min. The Grignard reagent thus prepared was added dropwise to a solution of 10.4 g. of ethyl 4-methylphenylglyoxylate in dry ether. The mixture was then refluxed for 1 hr. after which it was poured into a mixture of crushed ice and dilute sulfuric acid. The organic layer was separated and the aqueous layer was extracted a few times with ether. The total ester recovered weighed 8.9 g. (60%), b.p. 155–158°/3 mm. Hydrolysis of this product with sodium hydroxide in a mixture of water and ethanol followed by acidification gave 5.2 g. (65%) of the acid, white crystals, m.p. 189–190°.

Anal. Calcd. for $C_{15}H_{20}O_3$: C, 72.57; H, 8.12. Found: C, 72.66; H, 8.04.

2-Diethylaminoethyl 4-methylphenylcyclohexylglycolate hydrochloride. The ester, 0.7 g., prepared from the above acid, 0.5 g., by treatment with the chloramine as already described, was obtained in a yield of 93.5%, m.p. 202–203°.

Anal. Calcd. for $C_{21}H_{34}NO_3Cl$: C, 65.67; H, 8.93. Found: C, 65.54; H, 9.00.

3,5-Dimethylbromobenzene. 2,4-Dimethylaniline, purified as described by Shacklett,[19] 159 g., and 1250 ml. of concentrated hydrochloric acid were mixed and then cooled, with stirring, to 5 to 10°. A solution of 70 ml. of bromine in 125 g. of 48% hydrobromic acid and 125 g. of concentrated hydrochloric acid was added slowly, with stirring, while the temperature was kept below 20°. After being heated to 50 to 70° until the color of bromine had disappeared, the mixture was cooled below 0° by the addition of ice. A solution of 109 g. of sodium nitrite in 300 ml. of water and ice was added, with vigorous stirring and with the addition of ice to keep the temperature near 0 to 5°, until the amine was completely diazotized (starch-potassium iodide paper test). Cold solutions of 526 g. stannous chloride in 3 l. of water and 1313 g. of sodium hydroxide in 2 l. of water were mixed and after cooling to 0° with ice, the diazotized solution was added slowly with vigorous stirring and allowed to stand overnight. Steam distillation of the organic layer yielded another organic layer which was washed successively with dilute sulfuric acid, water, dilute sodium hydroxide, and water. It was then dried and distilled *in vacuo*. 3,5-Dimethylbromobenzene, 136 g. (56%) boiling at 70°/6 mm. (Fieser and Heymann[20] give 88–89°/12 mm.) was obtained.

3,5-Dimethylbenzoic acid. A Grignard reagent from 12.16 g. of magnesium in 250 ml. of dry ether and 85 g. of the bromobenzene in ether was gently poured into a slurry of

(19) C. D. Shacklett, "A Study of the Kinetics of the Catalytic Hydrogenation of Certain Substituted Benzilic Acids," doctoral dissertation, University of Tennessee, 1951, p. 133.

(20) L. F. Fieser and H. Heymann, *J. Am. Chem. Soc.*, **64**, 380 (1942).

Dry Ice in dry ether. Working up the reaction mixture in the usual manner gave 46.5 g. (67.5%) which when crystallized from ethanol melted at 169–170° (Heilbron and Bunbury[21] give 170°; Fisher and Windaus,[22] 166–167°).

3,5-Dimethylbenzoyl chloride. This acid chloride was prepared by the same method as the 4-methyl derivative above. The acid, 33.5 g. gave 33.5 g. (89%) of the acid chloride, b.p. 90°/3.5 mm. (Weiler[23] gives 109.5°/10 mm.).

3,5-Dimethylbenzoyl cyanide. The method is analogous to that described for 4-methylbenzoyl cyanide above. The acid chloride, 10 g., yielded 5.8 g. (61.5%) of the cyanide, m.p. 61–62°.

Anal. Calcd. for $C_{10}H_9NO$: C, 75.43; H, 5.70. Found: C, 75.32; H, 5.70.

Ethyl 3,5-dimethylphenylglyoxylate. This ester was prepared similarly to the 4-methyl ester described above. The cyanide, 7 g., gave 4.2 g. of ester boiling at 130°/4.5 mm. It gives a positive test with 2,4-dinitrophenylhydrazine.

3,5-Dimethylphenylcyclohexylglycolic acid. This acid was prepared through the use of the Grignard reagent as described for the 4-methylphenyl derivative above. Ethyl 3,5-dimethylphenylglyoxylate, 6.4 g., gave 1.6 g. (18%) of the ester boiling at 170°/4.5 mm. The latter on hydrolysis yielded 0.6 g. (41.5%) of the acid, m.p. 170–171°.

Anal. Calcd. for $C_{16}H_{22}O_3$: C, 73.26; H, 8.46. Found: C,73.21; H, 8.66.

2-Diethylaminoethyl 3,5-dimethylphenylcyclohexylglycolate hydrochloride. By the usual manner 0.5 g. of the acid produced 0.48 g. (63.5%) of the ester, m.p. 217–218°.

Anal. Calcd. for $C_{22}H_{36}ClNO_3$: C, 66.39; H, 9.12. Found: C, 66.74; H, 9.10.

2-N,N-Dialkylaminoethyl methylamines. These amines were prepared by the methods of Kermack and Wight[24] and Damiens,[25] the latter method being the more successful.

α,α-Diphenyl-α-chloracetylchloride. This acid chloride was prepared by the method of King and Holmes.[26] Benzilic acid, 20 g., gave 11 g. (46%) of the acid chloride, white crystals, m.p. 47–49° (King and Holmes[26] give 48.5–49.5°; Billman and Hidy,[27] 50–51°).

Phenylcyclohexylacetyl chloride. Phenylcyclohexylacetic acid, 43.6 g., with thionyl chloride gave 40 g. (85%) of a yellow liquid, b.p. 136–139°/3 mm. (Venus-Danilova and Bol'shukin[28] give 157–158°/10 mm.).

Hydrochlorides of 2-N,N-dialkylaminoethyl methylamides of substituted glycolic and acetic acids. These compounds, 79, 80, and 81 (Table II) were prepared from the acid chlorides above and the appropriate methyl amine by the method of Krapcho, Turk, and Pribyl.[5] The preparation of 2-*N*-piperidinoethyl methylbenzilamide hydrochloride which is typical, will be described. A solution of 2.3 g. of α,α-diphenyl-α-chloroacetyl chloride in 6 ml. of hexane and 4 ml. of benzene was maintained at 20–30° during the dropwise addition of 1.18 g. of 2-*N*-piperidinoethyl methylamine in 2 ml. of benzene. A heavy white precipitate formed during the addition and at the end the mixture was stirred for 1 hr. at room temperature (solution soon resulted), refluxed for another hour and cooled and treated with water. The organic layer was extracted with dilute hydrochloric acid, after which the original aqueous layer and the aqueous extracts were combined, washed with ether and heated on a steam bath for 10 min. to hydrolyze the α-chloro group. The aqueous solution was made strongly basic and extracted with ether. The dried ethereal solution, cooled in an ice bath, was saturated with hydrogen chloride to give 1.5 g. (47%) of a white solid, m.p. 215–217°. Recrystallization from an ethanolic solution by adding anhydrous ether and chilling elevated the melting point to 226–227° (Krapcho, Turk, and Pribyl[5] give 212–214°).

Anal. Calcd. for $C_{22}H_{29}ClN_2O_2$: C, 67.94; H, 7.52. Found: C, 68.01; H, 7.28.

2-N,N-Dialkylaminoethylamines. These amines were obtained commercially with the exception of 2-*N*-piperidinoethylamine which was prepared by the method of von Alphen[29] in which 100 g. of 1,5-dibromopentane gave 32 g. (58%) of the amine, b.p. 187–189° (von Alphen[29] gives 187°).

Hydrochlorides of 2-N,N-dialkylaminoethylamides of glycolic acids. Compounds 82 and 83 (Table II) were prepared by the method of Miescher, Meisel, and Hoffmann[6] while 84, 85, and 86 (Table II) were prepared by the same method from the methyl benzilate followed by reduction. The preparation of 2-*N*-piperidinoethyl dicyclohexylglycolamide hydrochloride (86) which is typical is given below.

A mixture of 11.0 g. of methyl benzilate and 10.1 g. of 2-*N*-piperidinoethylamine was refluxed for 2 hr., after which the reaction mixture was dissolved in ether and extracted three times with dilute hydrochloric acid. The combined aqueous extracts were made basic and an oil which quickly solidified separated to give 6.2 g. (41%) of an orange solid. Crystallization from ethanol produced a white solid, m.p. 115–116°. The hydrochloride prepared by saturating an ethereal solution of the free amine with hydrogen chloride melted at 203–204° (Phillips[7] gives 201–202°). Complete hydrogenation of the hydrochloride in acetic acid using Adams' platinum catalyst at room temperature gave 6 g. (35%) of a white solid, m.p. 260–261°.

Anal. Calcd. for $C_{21}H_{39}ClN_2O_2$: C, 65.17; H, 10.16 Found: C, 65.05; H, 9.96.

2-Hydroxyethyl methyl sulfide. To 47.9 g. of sodium in 1000 ml. of absolute ethanol, 100 g. of methyl sulfide was added and the solution was heated to boiling. Heating was then discontinued and 302 g. of ethylene chlorohydrin was added dropwise with stirring over a 2-hr. period. As much of the alcohol as possible was removed by distillation on a steam bath, and cooling caused large amounts of sodium chloride to crystallize. The salt was removed by filtration and washed with two 100-ml. portions of 95% ethanol, after which the combined filtrate and washings were concentrated on a steam bath under reduced pressure and the residue was distilled *in vacuo* to give 140 g. (76%) of a liquid, b.p. 68–70°/20 mm. (Windus and Schildneck[30] give 68–70°/20 mm.).

2-Chloroethyl methyl sulfide. The procedure of Kirner and Windus[31] was employed. 2-Hydroxyethyl methyl sulfide, 140 g., gave 133 g. (71%) of a liquid, b.p. 54–56°/30 mm. (Kirner and Windus[31] give 54–56°/30 mm.).

General preparation of thioesters. The acid,[8] 0.05 mole, was dissolved in a solution of sodium ethoxide, prepared from 0.05 mole of sodium and 50 ml. of absolute ethanol, and 0.055 mole of 2-chloroethyl methyl sulfide was added after refluxing for 4 hr., the sodium chloride was removed by filtration and the ethanol by distillation under reduced pressure. The ester of boiling point given in Table III was recovered by distillation *in vacuo*.

General preparation of methiodides. Compounds 87, 88, and 89 (Table III) were obtained by allowing the appropri-

(21) I. Heilbron and H. M. Bunbury, "Dictionary of Organic Compounds," Vol. II, Oxford University Press, New York, 1953, p. 284.

(22) E. Fischer and A. Windaus, *Ber.*, **33**, 1971 (1900).

(23) M. Weiler, *Ber.*, **32**, 1910 (1899).

(24) W. O. Kermack and T. W. Wight, *J. Chem. Soc.*, 1421 (1935).

(25) R. Damiens, *Ann. chim.*, **6**, 835 (1951).

(26) F. E. King and D. Holmes, *J. Chem. Soc.*, 164 (1947).

(27) J. H. Billman and P. H. Hidy, *J. Am. Chem. Soc.*, **65**, 760 (1943).

(28) E. I. Venus-Danilova and A. I. Bol'shuken, *J. Gen. Chem. (U.S.S.R.)*, **7**, 2823 (1937); *Chem. Abstr.*, **32**, 2925 (1938).

(29) J. von Alphen, *Rec. trav. chim.*, **56**, 529 (1937).

(30) W. Windus and P. R. Schildneck, *Org. Syntheses*, **Coll. Vol. II**, 345 (1943).

(31) W. R. Kirner and W. Windus, *Org. Syntheses*, **Coll. Vol. II**, 136 (1943).

ate ester to stand with an equal volume of methyl iodide in a closed vessel in the absence of light until crystals formed. Washing with dry ether and crystallization from absolute ethanol gave pure salts. It was necessary to store these compounds in a dark area to reduce decomposition.

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[CONTRIBUTION FROM THE DEPARTMENTS OF CHEMISTRY AND MICROBIOLOGY, UNIVERSITY OF PENNSYLVANIA]

Some Derivatives of Glycineamidine[1]

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Phthalimidoacetonitrile has been converted through an imidoester to some derivatives of glycineamidine. The reactions of phthalimidoacetonitrile and ethyl phthalimidoacetate with ammonia under different conditions have been studied.

The discovery that formylglycineamidine ribotide is an intermediate in the biosynthesis of purines[2] prompted us to attempt the preparation of glycineamidine and derivatives which might serve as replacements or antagonists in biological systems. After our work was initiated, the preparation of glycineamidine dihydrobromide was reported by Mengelberg.[3]

The starting point of our synthesis was phthalimidoacetonitrile (I), which has been prepared in the past by the reaction of potassium phthalimide and chloroacetonitrile,[4] by the dehydration of phathalimidoacetamide,[5] and by the interaction of sodium cyanide and phthalimidomethyl-trimethyl ammonium iodide.[6] We found it convenient to prepare I by the phthaloylation[7] of the readily available aminoacetonitrile bisulfate[8] in pyridine or toluene. A shorter route involves the reaction of methyleneaminoacetonitrile[9] with phthalic anhydrate in refluxing *N*,*N*-dimethylformamide leading to a 64.5% yield of I.

Although earlier efforts have been reported unsuccessful,[4] we were able to convert phthalimidoacetonitrile (I) in 89% yield to the imidoester hydrochloride II using dioxane as the reaction medium. Since then the preparation of phthalimidoacetimido methyl ester hydrochloride has been reported[10] using benzene as the solvent.

When II was dissolved in cold water, a clear solution was obtained which almost immediately started to deposit a crystalline solid which was identified as *N*-phthaloylglycine ethyl ester (VIII). When II was maintained in the molten condition for a few minutes, it was converted into phthalimidoacetamide (IX), which was directly obtained from I by reaction with either concentrated sulfuric acid or with a basic solution of hydrogen peroxide. These observations are in accord with the imidoester structure for II.

When II was treated with an alcoholic solution of ammonia, a compound was obtained which, on the basis of its analysis and infrared spectrum, has been assigned the phthalamidoamidine structure III. Phthalimido compounds are known to give phthalamido compounds on reaction with ammonia.[10] This structure is supported by the observation that on treatment with a mixture of acetic and hydrobromic acids, III affords a compound to which the phthalimidoamidine structure IV has been assigned on the basis of its analysis and infrared spectrum.

When the amido amidine III is added to water a clear solution is first obtained which in the course of a few minutes starts to deposit a compound V which is insoluble in water and the usual organic solvents, but is soluble in dilute acid and alkali. The infrared spectrum of V indicates the lack of the phthalimido grouping and the presence of a salt like structure. The analysis corresponds to the formula $C_{10}H_{11}O_3H_3 \cdot H_2O$. One mole of water could be removed only after very intensive drying. Two plausible structures, V and XI, can be written to correspond to $C_{10}H_{11}N_3O_3$. A comparison with an authentic sample of (*o*-carboxamido)benzamidoacetamide

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(1) Supported in part by U.S.P.H.S. Grant CY-2714 and CY-2790.

(2) B. Levenberg and J. M. Buchanan, *J. Am. Chem. Soc.*, **78**, 504 (1956).

(3) M. Mengelberg, *Ber.*, **89**, 1185 (1956).

(4) A. Sonn and S. Falkenheim., *Ber.* **55**, 2975 (1922); Y. Chi and S. Tshien, *J. Am. Chem. Soc.*, **64**, 90 (1942).

(5) E. Radde, *Ber.*, **55**, 3174 (1922).

(6) R. O. Atkinson, *J. Chem. Soc.*, 1329 (1954).

(7) A. K. Bose, F. Greer and C. C. Price, *J. Org. Chem.*, **23**, 1335 (1958).

(8) W. K. Auslow and H. King, *Org. Syntheses*, **Coll. Vol. I**, 298 (1943).

(9) R. Adams and W. D. Langley, *Org. Syntheses*, **Coll. Vol. I**, 355 (1943).

(10) P. E. Peterson and C. Niemann, *J. Am. Chem. Soc.*, **79**, 1389 (1957).