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

Physiologically Active Compounds. IV. Miscellaneous Compounds Related to Aminoethyl Esters of Benzilic Acid

C. A. BUEHLER, H. A. SMITH, K. V. NAYAK,[1] AND T. A. MAGEE[2]

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Six miscellaneous amino ester hydrochlorides, three amino ketone hydrochlorides, and two aminocarbinol hydrochlorides have been prepared. In the physiological tests reported, three compounds appear to be more active in experimental animals than atropine in preventing mortality from an anticholinesterase compound; none of these compounds exhibit the anticholinergic or antihistaminic activity of compounds previously reported.

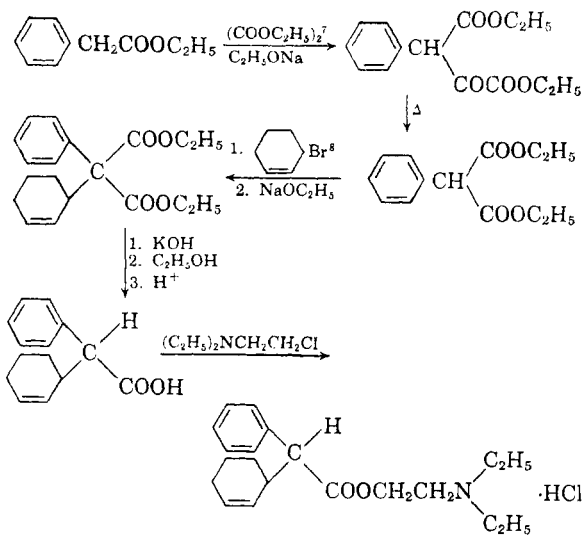
This paper reports additional results[3] on the synthesis and physiological testing of compounds related to the aminoethyl esters of benzilic acid. In the type formula shown in Table I the compounds vary in the R groups, in X, and in Y, as indicated. The eleven hydrochlorides described may be classified into five types: A. Aminoethyl esters containing a substituted hydroxyl or thiol group (Compounds 90, 91, and 92, Table I). B. An aminoethyl ester containing an unsaturated carbocyclic ring (Compound 93, Table I). C. Aminoethyl esters containing a heterocyclic ring (Compounds 94 and 95, Table I). D. Aminoethyl ketones (Compounds 96, 97, and 98, Table I). E. Aminoethylcarbinols (Compounds 99 and 100, Table I).

Synthesis of group A compounds. The free acid of Compound 90 was obtained from benzilic acid by conversion first to diphenylchloroacetic acid by Klosa's method[4] and then to the acid sought by treatment with 2-diethylaminoethanol and potassium carbonate.

Since mercaptodiarylacetic acids appeared to be of interest, several were prepared by the method of Becker and Bistrzycki[5] in which the benzilic acid was treated with phenyl isothiocyanate to give the thiourethan which on hydrolysis gave the mercapto acid. Unfortunately these acids when treated with 2-diethylaminoethyl chloride in isopropyl alcohol did not give the amino esters. A blue solution formed and the evolution of hydrogen sulfide indicated that condensation was occurring between two molecules of the acid. It was also not possible to obtain the mercapto acid ester from the ester hydrobromide of diphenylbromoacetic acid, produced by Klosa's method,[6] by treatment with sodium bicarbonate followed by refluxing with sodium hydrosulfide in acetone.

Since amino esters having free mercapto groups could not be obtained, two were synthesized in which a substituted mercapto group was present. Compound 91 was obtained from chlorodiphenylacetic acid by treatment first with thioacetic acid in benzene and then with 2-diethylaminoethanol. Compound 92 was obtained from the same starting material by treatment with isopropyl mercaptan and calcium carbonate by the method of Klosa,[4] followed by esterification in the usual manner with 2-diethylaminoethanol.

Synthesis of group B compounds. The one amino ester of this group is characterized by containing unsaturated carbocyclic and benzene rings. Compound 93 was synthesized as follows:



Synthesis of group C compounds. The two compounds of this group are characterized by containing heterocyclic and benzene rings. Compound 94 was synthesized from benzfurilic acid obtained from benzfuril. The free acid of Compound 95 was synthesized as follows:

(1) Present address: Steroid Laboratory, Lemuel Shattuck Hospital, Boston 30, Mass.

(2) Present address: Diamond Alkali Company, Painesville, Ohio.

(3) For paper III, see H. A. Smith, C. A. Buehler, T. A. Magee, K. V. Nayak, and D. M. Glenn, *J. Org. Chem.*, **24**, 1301 (1959).

(4) J. Klosa, *Arch. Pharm.*, **288**, 42 (1955).

(5) H. Becker and A. Bistrzycki, *Ber.*, **47**, 3152 (1914).

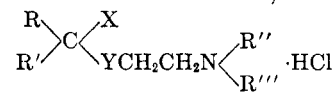
(6) J. Klosa, *Arch. Pharm.*, **288**, 246–52 (1955).

(7) P. A. Levene and G. M. Meyer, *Org. Syntheses*, Coll. Vol. II, 288 (1943).

(8) H. G. Kolloff, J. H. Hunter, E. H. Woodruff, and R. B. Moffett, *J. Am. Chem. Soc.*, **70**, 3862 (1948).

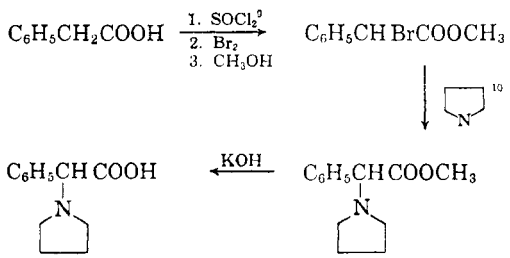
TABLE I

HYDROCHLORIDES OF MISCELLANEOUS ESTERS, KETONES, AND ALCOHOLS



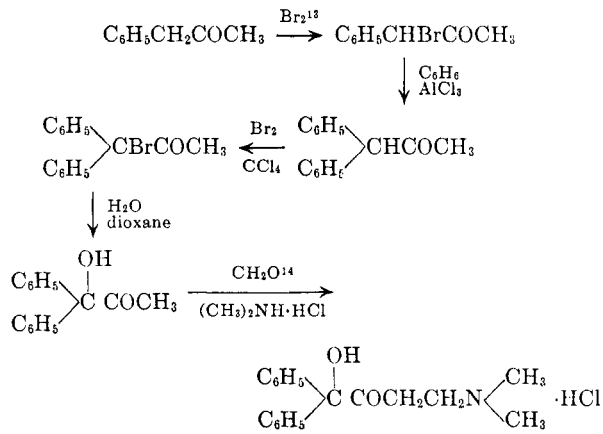
Number	R	R′	R″	R‴	X	Y	Yield, %	M.P.	Calcd. C	Calcd. H	Found C	Found H
90	C_6H_5	C_6H_5	C_2H_5	C_2H_5	$OCH_2CH_2N(C_2H_5)_2$·HCl	COO	87	212–213	62.51	8.07	62.03	8.26
91	C_6H_5	C_6H_5	C_2H_5	C_2H_5	$SCOCH_3$	COO	60	166–167	62.62	6.69	62.27	6.77
92	C_6H_5	C_6H_5	C_2H_5	C_2H_5	$SCH(CH_3)_2$	COO	85	138–139	65.45	7.64	65.28	7.82
93	C_6H_5	C_6H_9[a]	C_2H_5	C_2H_5	H	COO	66	156–157	68.26	8.59	68.10	8.65
94	C_6H_5	C_4H_3O[b]	C_2H_5	C_2H_5	OH	COO	60	146.5–147.5	61.10	6.84	60.94	7.02
95	C_6H_5	C_4H_8N·HCl[c]	C_2H_5	C_2H_5	H	COO	36	177–178	57.29	8.01	57.10	8.09
96	C_6H_5	C_6H_5	CH_3	CH_3	OH	CO	19	163.5–165	67.59	6.93	67.74	6.73
97	C_6H_5	C_6H_{11}	CH_3	CH_3	H	CO	22	181.5–182	69.77	9.11	69.96	8.95
98	C_6H_5	C_6H_{11}	C_5H_{10}[d]		H	CO	25	214–215	72.07	9.22	71.85	9.09
99	C_6H_5	C_6H_5	CH_3	CH_3	H	CHOH	99	175–176	70.68	7.91	70.55	7.57
100	C_6H_5	C_6H_5	CH_3	CH_3	OH	CHOH	95	143–145[e]	67.18	7.52	66.54	7.68

[a] 2-Cyclohexenyl. [b] 2-Furyl. [c] 1-Pyrrolidinyl hydrochloride. [d] Piperidyl. [e] Prepared by Dan M. Glenn of this laboratory.



Other attempts were made to prepare amino esters containing heterocyclic rings. Neither methylphenyl-(1-pyrrole) acetate (method of Potts and Saxton[11]) nor phenyl-(2-pyridyl)glycolic acid (from corresponding benzil) were obtained pure. The intermediate, ethyl benzo[b]thiophene-3-glyoxylate, was obtained in a pure state by the method of Martin and Avakian,[12] but neither the 3-methylphenyl[benzo[b]thiophene-3]glycolic acid nor the 3,5-dimethylphenyl[benzo-[b]-thiophene-3]glycolic acid could be obtained in crystalline form by the method[3] previously reported. The gums obtained did not give the desired esters.

Synthesis of group D compounds. These compounds differ from those previously discussed in that they are ketones rather than esters. Compound 96 was synthesized by the sequence:



The proper ketone for the synthesis of Compounds 97 and 98 was obtained from the acid chloride and dimethylcadmium by the method of Cason.[15] Then a second modified Mannich reaction was employed. Under the most favorable conditions, the yields in this final step were low.

Synthesis of group E compounds. Compounds 99 and 100 were obtained by the catalytic hydrogenation of the appropriate ketones. In the case of 100, the proper aminoalkylhydroxy ketone hydrochloride was obtained from the appropriate aminoalkyl ketone hydrochloride.

Physiological tests. Tests which are described in a former paper[16] were made in the Physiology Division of the Directorate of Medical Research in the U. S. Army Chemical Research and Development Laboratories at Army Chemical Center, Md., by Drs. John F. O'Leary, Caroline tum Suden, and J. Henry Wills, with the assistance of Messrs. Gerald E. Groblewski, Leonard Carlstrom,

(9) J. Klosa, *Arch. Pharm.*, **285**, 332 (1952); *Chem. Abstr.*, **48**, 2705f (1954).
(10) J. Klosa, *Arch. Pharm.*, **285**, 401 (1952); *Chem. Abstr.*, **48**, 8756b (1954).
(11) K. T. Potts and J. E. Saxton, *J. Chem. Soc.*, 2642 (1954).
(12) G. J. Martin and S. Avakian, U. S. Patent **2,550,017** (April 24, 1951).
(13) C. L. Stevens and C. T. Lenk, *J. Org. Chem.*, **19**, 538 (1954).
(14) H. E. Zaugg, M. Freifelder, and B. W. Horrom, *J. Org. Chem.*, **15**, 1191 (1950).
(15) J. Cason, *J. Am. Chem. Soc.*, **68**, 2078 (1946).
(16) H. A. Smith, C. A. Buehler, and K. V. Nayak, *J. Org. Chem.*, **21**, 1423 (1956).

and Miss Lea Somers, to whom we are greatly indebted. The results of the tests are found in Tables II, III, and IV. An examination of these tables shows that

TABLE II

ANTICHOLINESTERASE SCREENING (TEST 1)[a]

Compared to Atropine		
More Active	Equally Active	Less Active
90	93	92
91	94	98[b]
95	96	99[b]
		100[b]

[a] Tests on rabbits with standard 2.0 mg./kg. unless otherwise indicated. [b] Test on rats.

(1) Three compounds, the diethylaminoethyl ester hydrochlorides of diphenyl(2-diethylaminoethoxy)acetic acid, 90, of diphenylthioacetoxyacetic acid, 91, and of phenyl(1-pyrrolidine) hydrochloride acetic acid, 95, appear to be more active than atropine in preventing mortality from an anticholinesterase compound. This makes a total of ten of the 88 compounds thus far tested which have given this result.

(2) None of the eleven compounds for which tests are reported here was as effective in antagonizing the functional effects of acetylcholine and histamine as some of those reported previously.

(3) Three additional compounds (91, 94, and 95) were effective in changing the diameter of the pupil of the eye, while four (92, 93, 96, and 100) produced local irritation.

EXPERIMENTAL[17]

Diphenylchloroacetic acid. This acid was prepared by Klosa's method[4] in which 150 g. of benzilic acid gave 98 g. of the chloro acid. One crystallization from a benzene-ligroin mixture produced crystals melting at 120–122° (Klosa[4] gives 124–125°).

Diphenyl(2-diethylaminoethoxy) acetic acid. The method was essentially that of Klosa[6] in which 5 g. of the chloro acid, 14 g. of 2-diethylaminoethanol in 30 ml. of benzene, and 4 g. of previously dried potassium carbonate were refluxed with stirring for 36 hr. The solvent and excess 2-diethylaminoethanol were removed by distillation under reduced pressure, after which the reaction product was extracted with ether. To this extract, decolorized by boiling with Norit, ethanol saturated with dry hydrogen chloride was added and a solid separated. Crystallization several times from an ethanol-ether mixture gave 5.3 g. of white crystals, m.p. 176–178° (Klosa[6] gives 180–182°).

TABLE III

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

No.	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
90	2.5	+16	+44	Slight tonus increase	−62	0
91	2.5	+27	+18	Slight tonus increase	−6	0
92	2.5	−17	−14	Tonus increase	−17	0
93	2.5	−37	0	Blocks spontaneous activity	−90 then +12	− Depth
94	2.5	−43	−29	Blocks spontaneous activity	0	− Depth
95	2.5	0	0	Slight tonus decrease	0	0
96	2.5	−12	+75		Slight rise	
98	2.5	−27	0		−12	
99	0.5	−14	0		Slight fall	
100	2.5	+ 6	−25			

TABLE IV

EYE EFFECTS (TESTS 5, 6)

Mydriasis				
Active	Moderately Active	Least Active	No Definite Effect	Local Irritation Active
91	98	90	99	92
94		92		93
95				96
				100

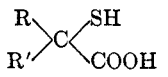
The mercaptodiarylacetic acids which were prepared are listed in Table V. These acids were prepared by a method similar to that of Becker and Bistrzycki.[5] The preparation of mercaptodiphenylacetic acid, which is typical, follows.

Diphenylcarboxymethyl-N-phenylthiocarbamate. Benzilic acid, 22.8 g., was mixed thoroughly in an ice bath with 16.9 g. of phenyl isothiocyanate in 20 ml. of glacial acetic acid until the temperature fell to 0°. Concentrated sulfuric acid, 10 ml., was then added with stirring and the mixture was kept in the ice bath for 3 more hr. and then at room temperature for 20 hr. Upon introduction into ice water the crude carbamate separated, 39.4 g., practically a quantitative yield. Two crystallizations from methanol-water gave

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

TABLE V

MERCAPTODIARYLACETIC ACIDS



R	R′	Yield, %	M.P.	Calcd. C	Calcd. H	Found C	Found H
C_6H_5	C_6H_5	88	148–149[a]				
3-$CH_3C_6H_4$	3-$CH_3C_6H_4$	80	102–103	70.56	5.92	70.55	5.74
2-$CH_3OC_6H_4$	2-$CH_3OC_6H_4$	86	138–139.5	63.14	5.30	63.00	4.95

[a] Becker and Bistrzycki[5] give 147.5–149°.

a m.p. of 138–139° (Becker and Bistrzycki[5] give 140.5° dec.; Schoberl[18] gives 146–147° dec.).

Anal. Calcd. for $C_{21}H_{17}NO_3S$: C, 69.41; H, 4.72. Found: C, 69.52; H, 4.77.

Mercaptodiphenylacetic acid. The carbamate, 10 g., was saponified with potassium hydroxide in water and ethanol and there was recovered 6.6 g. of the acid. Crystallized from 50% acetic acid, it weighed 5.9 g. (88%) and melted at 148–149° (Becker and Bistrzycki[5] give 147–149°; Schoberl[18] gives 150–152°).

Diphenylthioacetoxyacetic acid. A hot solution of 9.9 g. of diphenylchloroacetic acid in 20 ml. of benzene was treated dropwise with 3 g. of commercially available thiolacetic acid. The mixture was stirred, and a slow stream of nitrogen was introduced to sweep out the hydrogen chloride formed. After refluxing for 5 hr., also in an atmosphere of nitrogen, the solvent was removed by distillation under reduced pressure, and the residue on crystallization from carbon tetrachloride gave 10 g. of white crystals, m.p. 157–158°.

α-(Isopropylthio)diphenylacetic acid. A modification of Klosa's method[4] was employed. A mixture of 10 g. of diphenylchloroacetic acid, 4 g. of reagent grade calcium carbonate, and 50 ml. of 2-propanethiol was refluxed for 30 hr. with continuous stirring. Upon reduction of the volume of the filtrate by evaporation under reduced pressure and cooling with ice, 10.5 g. of the acid separated, m.p. 118–122°.

Ethyl phenylacetate. Phenylacetic acid, 204 g., was esterified with 700 ml. of absolute ethanol and 9 ml. of concd. sulfuric acid by refluxing for 18 hr. to give 205 g. (83%) of the ester, b.p. 89°/3 mm.

Diethyl phenylmalonate. By Levene and Meyer's method[7] 175 g. of ethyl phenylacetate gave 185 g. of diethyl phenylmalonate, b.p. 115–116°/0.8 mm.

3-Bromocyclohexene. Cyclohexene, 304 ml., was brominated with *N*-bromosuccinimide by the method of Ziegler and co-workers[19] to give 73 g. (57%) of the bromo derivative, b.p. 72–74°/30 mm. (Crossley[20] gives 74°/28 mm.).

Diethyl phenyl-Δ²-cyclohexenylmalonate. By the method of Kolloff and co-workers[8] 70.8 g. of diethyl phenylmalonate gave 55 g. (58%) of the unsaturated ester, b.p. 158–159° (0.8 mm.) (Kolloff and co-workers[8] give 126°/0.07 mm.).

Phenyl-Δ²-cyclohexenylacetic acid. The unsaturated ester, 55 g., again by the method of Kolloff and co-workers,[8] produced 34.5 g. (92%) of the free acid, m.p. 117–119.5° (Kolloff and co-workers[8] give 120–122°).

Benzfurilic acid. Benzfuril, 2 g., was converted into benzfurilic acid, 1 g. (47%), m.p. 102–104.5° (Fischer[21] gives 108° dec.) by Fischer's method.

Methyl α-bromo-α-phenylacetate. Phenylacetic acid, 68 g., gave 88 g. (77%) of the bromoacetate, b.p. 82–86°/0.5 mm. (Klosa[9] gives 136–140°/8 mm.) by Klosa's method.[9]

Phenyl(1-pyrrolidinyl)acetic acid. The method[10] was similar to that employed by Klosa. The bromo ester, 9.16 g. in 50 ml. of pure benzene, was refluxed with 10 ml. of pyrrolidine for 6 hr., after which it was allowed to stand overnight with continuous stirring at room temperature. Subsequently the mixture was stirred and refluxed for another 4 hr., and then it was cooled and extracted twice with 2*N* aqueous hydrochloric acid solution. After washing with ether, the aqueous solution was made alkaline and the precipitate obtained was extracted thrice with ether and dried with anhydrous magnesium sulfate. Since the crude ester, 7.5 g., obtained on evaporation of the ether could not be distilled under reduced pressure, it was dissolved in 85 ml. of methanol and refluxed for 2.5 hr. with 6 g. of potassium hydroxide in 60 ml. of water. The solution, after being diluted with water and heated on the steam bath to remove methanol, was cooled, filtered, and treated with dilute hydrochloric acid until faintly acidic to litmus. The residue obtained on evaporation was treated with benzene and evaporated again to remove any water present. Extraction twice with boiling ethanol gave a solution which produced crystals when it was evaporated to a small volume, decolorized with Norit, treated with dry ether, and allowed to stand in the cold room. Crystallization twice from isopropyl alcohol gave 4.8 g. of the acid (55%) melting with decomposition at 215.5–217°.

Anal. Calcd. for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37. Found: C, 70.01; H, 7.55.

Ethoxalyl chloride. By the method[22] of Southwick and Seivard, 156 g. of potassium ethyl oxalate gave 81 g. of the acid chloride, b.p. 132–134° (Southwick and Seivard[22] give 133–135°).

Ethyl benzo[b]thiophene-3-glyoxylate. By the method[12] of Martin and Avakian, 13.4 g. of benzothiophene gave 7.5 g. (32%) of the glyoxylate, b.p. 144–146°/0.5 mm. (Martin and Avakian[12] did not report the boiling point).

Anal. Calcd. for $C_{12}H_{10}O_3S$: C, 61.52; H, 4.30. Found: C, 61.55; H, 4.52.

The 2,4-dinitrophenylhydrazone melted at 199–201°.

Anal. Calcd. for $C_{18}H_{14}N_4O_6S$: C, 52.17; H, 3.41. Found: C, 52.37; H, 3.63.

Ester hydrochlorides. The acids were converted into the ester hydrochlorides (Compounds 90–95) by the method described in a former paper.[16]

1,1-Diphenylpropanone-2. By Schultz and Mickey's method[23] 148 g. of phenylacetone gave 117.5 g. of the white ketone, m.p. 58–60° (Schultz and Mickey[23] give 60–61°).

1,1-Diphenyl-1-bromopropanone-2. By Stevens and Lenk's method,[13] 34 g. of the ketone gave 30 g. (64%) of crude ketone, a light tan solid, m.p. 49–50° (Stevens and Lenk[13] give 55–56°).

1,1-Diphenyl-1-hydroxypropanone-2. The crude bromo ketone, 30 g., in 430 ml. of 1,4-dioxane and 100 ml. of water

(18) A. Schoberl, *Ber.*, **70**, 1191 (1937).

(19) K. Ziegler, A. Spaeth, E. Schaaf, W. Schumann, and E. Winkelmann, *Ann.*, **551**, 80 (1942).

(20) A. W. Crossley, *J. Chem. Soc.*, **85**, 1422 (1904).

(21) E. Fischer, *Ann.*, **211**, 232 (1882).

(22) P. L. Southwick and L. L. Seivard, *J. Am. Chem. Soc.*, **71**, 2535 (1949).

(23) E. M. Schultz and S. Mickey, *Org. Syntheses*, **29**, 38 (1949).

was refluxed for 3 hr. After removing the solvents by distillation under reduced pressure, the residue was dissolved in petroleum ether (b.p. 66–75°). Chilling in a Dry Ice bath and vigorously stirring produced 20 g. (84%) of the hydroxy ketone. Crystallization of a portion from ligroin gave white needles, m.p. 58–60° (Stevens and Sherr[24] give 66–67°; Temnikova[25] gives 65–66°). A mixed melting point of our product with an authentic sample showed no appreciable depression.

1,1-Diphenyl-1-hydroxy-4-dimethylaminobutanone-2 hydrochloride (Compound 96). This ketone hydrochloride was prepared by a modification of Zaugg, Freifelder, and Horrom's procedure[14] for the Mannich reaction. A mixture of 5.3 g. of 1,1-diphenyl-1-hydroxypropanone-2, 2.4 g. of dimethylamine hydrochloride, and 1.6 g. of paraformaldehyde in 30 ml. of *n*-octyl alcohol was refluxed for 10 min. Then an additional 1.6 g. of paraformaldehyde was added in small portions over a 30-min. period with continued refluxing. Concentrated hydrochloric acid, 0.3 ml., was added and the mixture was refluxed for an additional 5 min., after which it was extracted with water and dilute hydrochloric acid. The combined extracts were made basic with sodium carbonate and the oil which separated was extracted with two portions of ether. After washing the combined extracts with water until the washings became neutral, they were dried and saturated with hydrogen chloride while being cooled in an ice bath. A white solid, 1.2 g. (19%) separated. Two crystallizations from ethanol by adding anhydrous ether gave a melting point of 163.5–165°.

Phenylcyclohexylacetyl chloride. Phenylcyclohexylacetic acid, 43.6 g., with 60 ml. of thionyl chloride gave 40 g. (85%) of the acid chloride, b.p. 136–139°/3 mm.

1-Phenyl-1-cyclohexylpropanone-2. Cason's method[15] was employed. To dimethylcadmium, from 2.9 g. of magnesium turnings, excess methyl iodide, and 11 g. of anhydrous cadmium chloride, in a hot solution of benzene was added in about 2 min., without external heating, 26 g. of phenylcyclohexylacetyl chloride in 30 ml. of benzene. The solution was refluxed for 5 hr. and then the complex formed was decomposed with ice and dilute sulfuric acid. The combined benzene extracts were washed with water, 5% aqueous sodium carbonate, then with water again, and dried over anhydrous magnesium sulfate. Distillation gave a clear yellow liquid, b.p. 124–150°/4 mm. This material was redistilled through a modified Claisen head to give 11.7 g. (49%) of a clear yellow liquid, b.p. 132–136°/2.5 mm.

The oxime melted at 123–124°.

Anal. Calcd. for $C_{15}H_{21}NO$: C, 77.87; H, 9.15. Found: C, 78.27; H, 9.10.

The 2,4-dinitrophenylhydrazone melted at 155–156°.

Anal. Calcd. for $C_{21}H_{24}N_4O_4$: C, 63.62; H, 6.10. Found: C, 63.52; H, 6.15.

1-Phenyl-1-cyclohexyl-4-dimethylaminobutanone-2 hydrochloride (Compound 97). In this case Wilson and Kyi's modification[26] of the Mannich reaction was employed. A solution of 8 g. of the ketone, 4.9 g. of dimethylamine hydrochloride, 1.8 g. of paraformaldehyde, 8 drops of concd. hydrochloric acid, and 25 ml. of absolute ethanol was refluxed for 16 hr. Upon pouring the cool solution into anhydrous ether, 8.5 g. of a white solid, m.p. 159–161°, was obtained. For purification the hydrochloride was converted into the free base and then back to the hydrochloride again. In this way 2.5 g. of white crystals melting at 177–178° was obtained. A purer sample obtained by crystallization twice from ethanol-ether gave a m.p. of 181.5–182°.

1-Phenyl-1-cyclohexyl-4-piperidinobutanone-2 hydrochloride (Compound 98). This compound, m.p. 214–215°, was also prepared by Wilson and Kyi's modification[26] of the Mannich reaction.

1,1-Diphenyl-4-dimethylamino-2-butanol hydrochloride (Compound 99). This alcohol hydrochloride was prepared from the ketone hydrochloride (obtained from 1,1-diphenylpropanone-2 by Wilson and Kyi's procedure[26] in 45% yield) by low pressure hydrogenation using Adams' platinum catalyst. The final product melted at 175–176°.

1,1-Diphenyl-1-hydroxy-4-dimethylaminobutanone-2 hydrochloride. 1,1-Diphenyl-4-dimethylaminobutanone-2 hydrochloride (prepared by Wilson and Kyi's method[26]), 7.5 g. in 100 ml. of water, was made basic with aqueous potassium hydroxide. The solution was extracted with two 100-ml. portions of carbon tetrachloride, and the combined extracts were dried over anhydrous magnesium sulfate. To the solution at −15° was added 3.5 g. of bromine and the mixture was allowed to stand at −15° for 1 hr., after which the solvent was removed under reduced pressure. The residue, dissolved in 100 ml. of dioxane and 30 ml. of water, was refluxed for 3 hr. and the solvent was again removed under reduced pressure. The solution of the residue in 300 ml. of dilute aqueous potassium hydroxide was extracted with two 100-ml. portions of ether and the combined ethereal extracts were dried with anhydrous magnesium sulfate. When dry hydrogen chloride was passed through this solution, 1 g. of a solid (12%) separated. Crystallization five times from ethanol-ether, using Norit A, gave white crystals, m.p. 163–164° (Zaugg, Freifelder, and Horrom[14] give 163.5–165°).

1,1-Diphenyl-1-hydroxy-4-dimethylamino-2-butanol hydrochloride (Compound 100). Catalytic hydrogenation of the corresponding ketone gave the dihydroxy compound, m.p. 143–145°.

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