temperature *in vacuo*, and 35 ml. of a mixture of acetone-free methanol and dioxane (5:2) was added to the residue which contained the *N*-bromomethylphthalimide and some phthaloylglycine. The solution was warmed and then filtered to remove the silver bromide. The pH of the filtrate was adjusted to 6.5 with a saturated solution of NaOH in acetone-free absolute methanol. No attempt was made to isolate the *N*-bromomethylphthalimide.

Labeled N-cyanomethylphthalimide. The labeled nitrile was prepared according to the method of Sakami, *et al.*[7] Sodium cyanide-C^{14}, in 2 ml. of acetone-free absolute methanol, was added to the solution containing the *N*-bromomethylphthalimide. The mixture was shaken and allowed to stand for 6 hr. The nitrile was not isolated.

1-C^{14}-labeled glycine. The solvents containing the labeled *N*-cyanomethylphthalimide were removed *in vacuo* and an acid mixture (22 ml. glacial acetic, 50 ml. 20% HCl) was added to the residue and refluxed for 15 hr. The hydrolysate was cooled in the refrigerator and the insoluble phthalic acid removed by filtration. The filtrate was taken to dryness *in vacuo* at 100° and 25 ml. of concentrated HCl was added. The insoluble sodium chloride was removed and the solution again taken to dryness at 100° *in vacuo*. This procedure was repeated. The residue was finally taken up in a minimal amount of boiling water and 5 volumes of 95% ethanol were added, followed by a small amount of pyridine. The solution was cooled overnight in the refrigerator. The glycine-1-C^{14} was recrystallized twice from an alcohol-water mixture.

Amino acid assay. After recrystallization, the 1-C^{14}-labeled amino acids were chromatographed on paper, located with 0.05% ninhydrin in 1-butanol, and eluted. The activities of the isolated compounds, corrected for self-absorption, were determined in a Tracerlab gas flow counter. The total amount of amino acid was measured by quantitative paper chromatography.[8] Finally, derivatives of the amino acids were prepared and assayed for radioactivity. Within experimental error these derivatives were found to be as radioactive as their amino acid precursors. The results are summarized in Table I.

TABLE I
SYNTHESIS OF 1-C^{14} LABELED AMINO ACIDS

Amino Acid	% Radioactive Yield[a]	Specific Activity $\times 10^4$ counts/minute/mM[b]	Derivative
DL-Alanine	41.3	4.8	Phthaloyl
Glycine	57.5	6.3	Phthaloyl, picrate
DL-Leucine	37.6	2.7	Picrolonate

[a] Calculated on the basis of NaCN-C^{14} used (Activity—2×10^6 counts/minute). [b] Specific activity 39 counts/minute/mM for NaCN-C^{14}.

DISCUSSION

The decreased specific activities of the 1-C^{14} amino acids relative to NaCN-C^{14}, in the presence of the higher yield data, suggest the decarboxylation of the silver phthaloyl derivatives is not stoichiometric. Similar findings were reported for organic acids.[9]

While the data presented in Table I suggest that the procedure may be of practical value, the method is limited to those amino acids which form phthaloyl derivatives. It has been reported that tyrosine, tryptophan, taurine, and serine do not form such derivatives, and thus the procedure would not be applicable to these amino acids.[5] Furthermore, phenylalanine might be expected to undergo bromination in the course of the silver salt decarboxylation step.

Acknowledgment. The author wishes to thank Mrs. Miltza Luper and Mr. Robert C. Nordlie for their excellent technical assistance.

GRAND FORKS, N. D.

(7) Sakami, Evans, and Gurin, *J. Am. Chem. Soc.*, **69**, 1110 (1947).

(8) Awapara, *J. Biol. Chem.*, **178**, 113 (1949).

(9) Stoll and Rouvé, *Helv. Chim. Acta*, **34**, 98 (1951).

[CONTRIBUTION FROM THE WARNER-CHILCOTT RESEARCH LABORATORIES]

1-[(2-Dialkylaminoethoxy)phenyl]-2-amino-1-propanols

ROBERT I. MELTZER AND ARNOLD D. LEWIS

Received December 13, 1956

2-And 4-(2-dimethylaminoethoxy)phenyl- and 2- and 4-(2-diethylaminoethoxy)phenyl-2-amino-1-propanol were synthesized. Derivatives of these compounds, wherein the primary amino group was variously substituted, were also prepared.

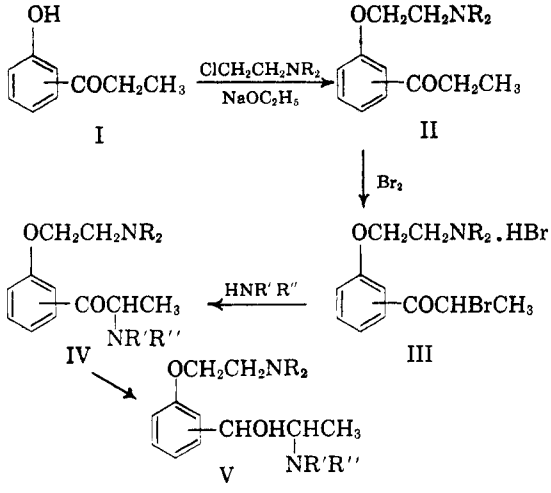
An investigation was undertaken with the object of preparing compounds of the phenethylamine type, having a dialkylaminoalkoxy substituent in the phenyl ring. It was hoped that thereby compounds of pharmacological interest might be attained.

Hundreds of phenethylamine derivatives have been prepared for pharmacological testing. Variations in structure have produced compounds with different sympathomimetic properties of clinical interest. Thus, there have been found among these compounds drugs which act as vasoconstrictors, bronchodilators, central nervous system stimulants, analgetics, and uterine contractors.[1] The relationship between activity and structure has been

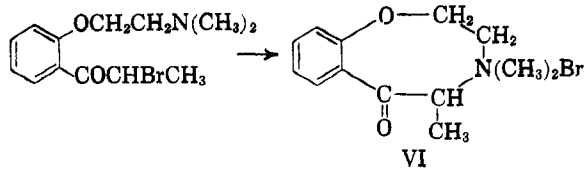
(1) A. Burger, *Medicinal Chemistry*, Vol. I, Interscience Publishers, Inc., New York, N. Y., 1951, pp. 289–349.

satisfactorily established only for the pressor properties of the phenethylamines. The correlation between structure and other sympathometic properties is comparatively rudimentary. It had been noted that the substitution of an alkoxy group in the 2 position of the phenethylamine skeleton resulted in compounds having good bronchodilator properties and poor pressor effects.[2] With this in mind, we decided to introduce dialkylaminoethoxy groups in the 2 position of the phenethylamine structure in the hope of attaining bronchodilators having other physiological effects at a minimum. We considered it would also be of interest to prepare compounds with the dialkylaminoalkoxy side chain in the 4 position both for the purpose of comparison with the *ortho* compounds and for their possible intrinsic interest. Because of the frequent very appreciable difference in pharmacological properties of dimethylamino and diethylamino groups, both the dimethylaminoethoxy and diethylaminoethoxy compounds were desired.

As starting materials, *o*- and *p*-hydroxypropiophenones (I) were chosen. As their sodium salts, these were etherified in alcoholic solution by the use of dimethylaminoethyl chloride and diethylaminoethyl chloride. The yields of the dialkylaminoalkoxypropiophenones (II) made using the former halide were in general poorer than those made using the second halide.



Bromination of *o* - (2 - dimethylaminoethoxy) propiophenone (II, R = methyl) gave the α-bromo product (III, R = methyl) in 50–60% yield. When the base was freed from its hydrobromic acid salt by alkali in the cold, and immediately extracted with ether, there resulted on standing ether-insoluble crystals. This product was water soluble, was not precipitated by alkali, and contained bromine only in the ionic form. Analysis corresponded to that of the compound VI which apparently results by the intramolecular cyclization of *o*-(2-dimethylaminoethoxy)-α-bromopropiophenone.

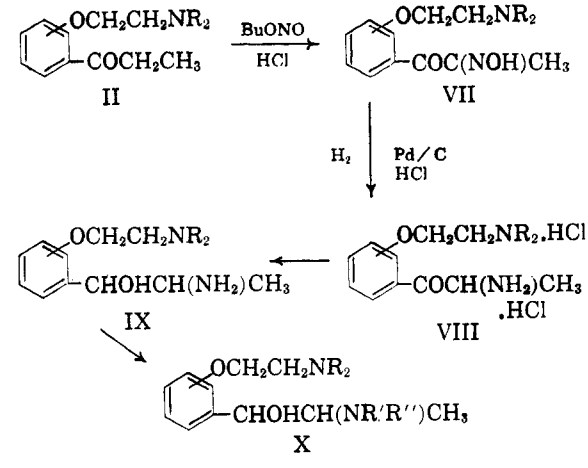


VI

The *o*-(2-dimethylaminoethoxy)-α-bromopropiophenone hydrobromide (III, R = methyl) was allowed to react with large excesses of methylamine, dimethylamine, diethylamine, and morpholine to give the corresponding α-aminoketones (IV). Reduction of the α-dimethylaminoketo and the α-diethylaminoketo compounds gave the corresponding secondary alcohols (V).

All attempted brominations of *p*-(2-dimethylaminoethoxy)propiophenone and *o* and *p*-(2-diethylaminoethoxy)propiophenones gave as the only isolated crystalline compounds the hydrobromides of the starting ketones. Because brominations of this type may be affected by the choice of solvents,[3] the reactions were attempted in chloroform, carbon tetrachloride, water, methanol, ether, and glacial acetic acid, in the presence and the absence of an electric lamp or sunlight, and at low and at elevated temperatures. The failure of these brominations prevented the preparation of the rest of the projected compounds by this method.

A second synthetic route, however, led to the required substances.



Nitrosation of the ketones (II) to isonitrosoketones (VII) was accomplished by the use of butyl nitrite and hydrogen chloride. The amino group in the starting propiophenones (II) made the use of anhydrous ether, the usual solvent, impractical because the amine hydrochloride precipitated completely out of the reaction mixture. By the addition of some alcohol, however, it was possible to get almost quantitative yields. The partially solubilized precipitated aminoketone hydrochloride reacted slowly to give the isonitroso compound which was also insoluble. The end of the reaction could be ascertained by noting the character of the

(2) B. E. Graham and M. H. Kuizenga, *J. Pharmacol. Exptl. Therap.*, **94**, 150 (1948).

(3) A. E. Ardis, R. Baltzly, and W. Schoen, *J. Am. Chem. Soc.*, **68**, 591 (1946).

precipitate. The resulting product in almost quantitative yield was of satisfactory purity for further work.

Reduction of the isonitroso compounds was carried out in two steps.[4] Hydrogenation in alcoholic solution in the presence of palladium on charcoal and of excess hydrogen chloride, gave the diaminoketone dihydrochloride (VIII). This was isolated but not purified, and reduced to the amino alcohol, (IX) in aqueous solution in the presence of fresh catalyst.

Reductive alkylation of the primary amines (IX) using benzaldehyde and hydrogen in the presence of platinum gave the benzylamines (X, R′ = benzyl, R″ = H). In the case of 1-[2-(2-dimethylaminoethoxy)phenyl]-2-amino-1-propanol, the amine was allowed to react with benzaldehyde and the resulting water was removed. Reduction of the reaction product required higher temperature and a longer period, than when the intermediate was not first isolated. This is interesting in view of the findings of other workers that, in the case of ethanolamines, formation of anhydro compounds aided reductive alkylation.[5] The difference may be explicable by assuming that in the presence of water an equilibrium is readily attained among the Schiff's base form, the methylolamine form, and the oxazolidine form, with reduction of all forms taking place. In the absence of water, a slower attainment of equilibrium may result in a greater portion of the reduction taking place *via* less readily reduced forms.

Methylation of the benzyl compounds using formaldehyde and formic acid converted the secondary amines to the tertiary amines (XI, R′ = benzyl, R″ = methyl). The formaldehyde-formic acid method of alkylation was also used to convert the primary amines (IX) obtained by reduction of the isonitroso compounds, to tertiary amines (X, R′ = R″ = methyl). The 1-[2-(2-dimethylaminoethoxy)phenyl]-2-dimethylamino-1-propanol obtained by this procedure was identical with the product obtained *via* the bromoketone intermediate above.

The primary amines (IX) were isopropylated to secondary amines (X, R′ = isopropyl, R″ = H) by reductive alkylation, using acetone and hydrogen in the presence of platinum. Substitution of acetaldehyde for acetone gave a mixture of the monoethylated and diethylated amines which on further ethylation gave the diethylated products (XI, R′ = R″ = ethyl). In the case of the *p*-dimethylaminoethoxy compound, the monoethyl was actually purified. In all other cases the purification of the mixture for attainment of the monoethylated compound was not attempted. The 1-[2-(2-dimethylaminoethoxy)phenyl]-2-diethylamino-1-propanol obtained by the reductive diethylation was the same as the product obtained earlier by reduction of *o*-(2-dimethylaminoethoxy)-α-diethyl aminopropiophenone.

None of the compounds showed pressor activity. Other sympathomimetic properties are under investigation. Melting points, boiling points, analysis, and recrystallization solvents are reported in Table I.

(4) W. H. Hartung, *J. Am. Chem. Soc.*, **53**, 2248 (1931).

(5) E. M. Hancock and A. C. Cope, *J. Am. Chem. Soc.*, 66, 1738 (1944).

EXPERIMENTAL

(2-Dialkylaminoethoxy)propiophenones (II). The dialkylaminoethyl chloride hydrochloride (1 mole) was placed in a separatory funnel with an equal volume of water and ice and an equal volume of benzene. The aqueous layer was made strongly alkaline with alkali and the benzene layer was separated and dried twice briefly over sodium hydroxide pellets. All this was carried out in the cold.

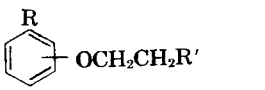
The hydroxypropiophenone (1 mole) was dissolved in 5 times its volume of absolute ethanol in which had previously been dissolved an equivalent of sodium. To this warm solution was added the above benzene solution with stirring. After stirring for at least 1 hr., the solution was kept at reflux for 2 to 4 hr. The solution was filtered and the solvent was removed under vacuum. The residue was taken up in ether and washed with 10% sodium hydroxide to remove unreacted phenol and any quaternary ammonium compounds. From this wash, unreacted phenol could be recovered by acidification. The ether layer was extracted with 6*N* hydrochloric acid and then with concentrated hydrochloric acid. The aqueous extract was made alkaline and extracted with ether. The organic layer was dried over magnesium sulfate and distilled. Yields using dimethylaminoethyl chloride were 30–50% based on starting quantities. As much as 50% of the original starting hydroxypropiophenone could be recovered. Yields using diethylaminoethyl chloride were over 70%.

o-(2-Dimethylaminoethoxy)-α-bromopropiophenone hydrobromide (III, R = methyl). To 241 g. (1.09 mole) of *o*-dimethylaminoethoxypropiophenone in 1200 ml. of methanol was added 174 g. (1.09 mole) of bromine in 1200 ml. of ice cold methanol over a period of 20 min. while keeping the reaction mixture at 10–20° C. and under a 300 watt electric lamp. The reaction mixture was stirred for an additional hour at about 15° and then treated with about 5 ml. of acetone to remove any unreacted bromine. The solvent was then removed on a steam bath until distillation slowed considerably. The residue (about 600 ml.) was cooled and filtered. The product was washed with cold methanol. Further concentration sometimes gave additional material. The yields varied from 30–60% of material melting above 160°. The fully purified product after repeated recrystallization from absolute ethanol melted at 167–168°.

(2-Dialkylaminoethoxy)propiophenone hydrobromides. The free base was dissolved in ether and precipitated with excess hydrogen bromide. The gummy precipitate was recrystallized from absolute ethanol or from 2-propanol.

o-(2-Dimethylaminoethoxy)-α-methylaminopropiophenone hydrochloride (IV.2HCl, R = R′ = methyl, R″ = hydrogen). To 115 g. (3.7 mole) of methylamine in 100 ml. of dry benzene kept at −12 to −17° C. was added 25 g. (0.066 mole) of *o*-(2-dimethylaminoethoxy)-α-bromopropiophenone hydrobromide as a fine powder. The reaction mixture was stirred at 2° C. for 4 hr. and then left overnight at room temperature. Most of the excess methylamine was removed under about 100 mm. in a bath at 40° C. The reaction mixture was then extracted with dilute hydrochloric acid. The acid extract was ether washed, made alkaline, and ether extracted. The ether extract was dried over magnesium sulfate and evaporated to dryness to remove the last traces of methyl-

TABLE I



R′	Position	R	M.p.[a] °C.	Solvent for Recryst.	Calculated C	Calculated H	Calculated X	Found C	Found H	Found X
$N(CH_3)_2$	*o*	$COCH_2CH_3$			70.55	8.65		70.59	8.61	
$N(C_2H_5)_2$	*o*	$COCH_2CH_3$	[b]		72.25	9.30		72.38	9.58	
$N(CH_3)_2$	*p*	$COCH_2CH_3$	39–41[d]		70.55	8.65		70.50	8.40	
$N(C_2H_5)_2$	*p*	$COCH_2CH_3$	[e]		72.25	9.30		72.24	9.05	
$N(CH_3)_2$.HBr	*o*	$COCH_2CH_3$	116.5–117.5	A	51.66	6.67	26.43	51.92	6.87	26.33
$N(C_2H_5)_2$.HBr	*o*	$COCH_2CH_3$	100.5–102.5	A	54.55	7.32	24.20	54.66	7.32	24.05
$N(CH_3)_2$.HBr	*p*	$COCH_2CH_3$	151–152	B	51.66	6.67	26.44	51.87	6.85	26.35
$N(C_2H_5)_2$.HBr	*p*	$COCH_2CH_3$	146–147	B	54.55	7.32	24.20	54.69	7.44	24.20
$N(CH_3)_2$.HBr	*o*	$COCHBrCH_3$	167–168	B	40.97	5.02	41.94	41.14	4.91	41.85
$N(CH_3)_2$.HCl	*o*	$COC(NOH)CH_3$	192–192.5	B	54.44	6.68	12.0[f]	54.65	6.81	12.3[f]
$N(C_2H_5)_2$.HCl	*o*	$COC(NOH)CH_3$	166.5–167.5	B	57.22	7.36	11.26	57.23	7.21	11.25
$N(CH_3)_2$.HCl	*p*	$COC(NOH)CH_3$	216–217	B	54.45	6.68	[g]	54.57	6.52	[g]
$N(C_2H_5)_2$.HCl	*p*	$COC(NOH)CH_3$	177–180	B-C	57.22	7.36	11.26	57.29	7.20	11.26
$N(CH_3)_2$.HCl	*o*	$COCH(CH_3)NHCH_3$.HCl	180–181	A-B	52.01	7.48	21.94	52.22	7.71	21.76
$N(CH_3)_2$.HCl	*o*	$COCH(CH_3)N(CH_3)_2$.HCl	193–195	A	53.44	7.77		53.39	7.58	
$N(CH_3)_2$.HBr	*o*	$COCH(CH_3)N(C_2H_5)_2$.HBr	173–175	A	44.94	6.66	35.18	44.81	6.46	35.08
$N(CH_3)_2$.HBr	*o*	$COCH(CH_3)\overline{NCH_2CH_2OCH_2CH_2}$.HBr	207.5–209	B	43.60	6.03	34.14	43.53	5.85	33.96
$N(CH_3)_2$.HCl	*o*	$CHOHCH(CH_3)NH_2$.HCl	246–247.5[h]	C	50.16	7.77	22.78	49.93	7.93	22.50
$N(C_2H_5)_2$.HCl	*o*	$CHOHCH(CH_3)NH_2$.HCl	197.5–198	B	53.09	8.32	20.90	52.96	8.12	20.78
$N(CH_3)_2$.HBr	*p*	$CHOHCH(CH_3)NH_2$.HBr	109–112[i]	A-B	39.01	6.04	39.94	38.81	6.20	39.61
$N(C_2H_5)_2$	*p*	$CHOHCH(CH_3)NH_2$	70–71	D	67.63	9.84	[j]	67.82	9.82	[j]
$N(CH_3)_2$.HCl	*o*	$CHOHCH(CH_3)N(CH_3)_2$.HCl	216–217	B	53.09	8.32	20.90	52.86	7.83	20.52
$N(C_2H_5)_2$.HCl	*o*	$CHOHCH(CH_3)N(CH_3)_2$.HCl	195–197.5	E-F	55.58	8.78	19.30	55.39	8.49	19.28
$N(CH_3)_2$.HCl	*p*	$CHOHCH(CH_3)N(CH_3)_2$.HCl	255.5–257	B-C	53.09	8.32	20.90	52.82	8.04	20.78
$N(C_2H_5)_2$.HCl	*p*	$CHOHCH(CH_3)N(CH_3)_2$.HCl	229.5–232	B-G	55.58	8.78	19.30	55.77	8.60	19.11
$N(CH_3)_2$.HBr	*o*	$CHOHCH(CH_3)N(C_2H_5)_2$.HBr	216.5–217.5	B-G	44.75	7.07	35.03	45.01	7.10	35.11
$N(C_2H_5)_2$.HBr	*o*	$CHOHCH(CH_3)N(C_2H_5)_2$.HBr	183.5–186	B	47.11	7.49	33.00	47.32	7.21	33.05
$N(CH_3)_2$.HCl	*p*	$CHOHCH(CH_3)N(C_2H_5)_2$.HCl	210–212	A-B	55.58	8.78	19.30	55.35	9.03	19.05
$N(C_2H_5)_2$.HBr	*p*	$CHOHCH(CH_3)N(C_2H_5)_2$.HBr	214–215	B	47.11	7.49	33.00	47.36	7.71	33.08
$N(CH_3)_2$.HCl	*o*	$CHOHCH(CH_3)NHCH_2C_6H_5$.HCl.$3H_2O$	111–113	E-H	52.74	7.97	15.57[k]	52.79	7.89	15.69[k]
$N(C_2H_5)_2$.HBr	*o*	$CHOHCH(CH_3)NHCH_2C_6H_5$.HBr	198–199	B	50.97	6.61	30.84	50.91	6.39	30.56
$N(CH_3)_2$.HCl	*p*	$CHOHCH(CH_3)NHCH_2C_6H_5$.HCl	233–235	B	59.84	7.53	17.67	59.82	7.27	17.83
$N(C_2H_5)_2$.HCl	*p*	$CHOHCH(CH_3)NHCH_2C_6H_5$.HCl	225.5–227	B-C	61.53	7.98	16.51	61.34	7.64	16.25
$N(CH_3)_2$.HCl	*o*	$CHOHCH(CH_3)NHCH(CH_3)_2$.HCl	183–184[l]	A	54.38	8.56	20.07	54.39	8.68	19.76
$N(C_2H_5)_2$.HCl	*o*	$CHOHCH(CH_3)NHCH(CH_3)_2$.HCl	210.5–212	A-B	56.68	8.99	18.59	56.45	8.71	18.40
$N(CH_3)_2$.HBr	*p*	$CHOHCH(CH_3)NHCH(CH_3)_2$.HBr	175.5–176.5[m]	A-B	43.45	6.84	36.1	43.42	6.62	36.1
$N(C_2H_5)_2$.HBr	*p*	$CHOHCH(CH_3)NHCH(CH_3)_2$.HBr	118–121	A	45.97	7.29	33.99	45.78	7.28	34.10
$N(C_2H_5)_2$.HCl	*o*	$CHOHCH(CH_3)N(CH_3)CH_2C_6H_5$.HCl	202–204	A-G	62.29	8.18	15.99	62.17	8.41	15.66
$N(CH_3)_2$.HCl	*p*	$CHOHCH(CH_3)N(CH_3)CH_2C_6H_5$.HCl	196.5–198	A	60.71	7.77	17.01	60.45	7.66	17.04
$N(CH_3)_2$.HCl	*p*	$CHOHCH(CH_3)NHC_2H_5$.HCl	243.5–244.5	B-C	53.09	8.32	20.90	52.28	8.32	20.72

[a] Temperatures are uncorrected. Melting points were taken on a Fisher-Johns melting point block. [b] B.p. 107–9° (0.06 mm.). n_D^{25} 1.5182. [c] B.p. 126–8° (0.5 mm), n_D^{25} 1.5124. [d] B.p. 117° (0.15 mm.), n_D^{25} 1.5303. [e] B.p. 137° (0.4 mm.), n_D^{27} 1.5221. [f] N: calcd., 9.78; found, 9.92. [g] N: calcd., 9.78; found, 9.69. [h] Free base from ether, m.p. 65–66°. [i] Free base from benzene, m.p. 97.5–98°. [j] N: calcd., 10.52; found, 10.46. [k] N: calcd. 6.15, found: 6.15, A-isopropanol, B-ethanol (abs.), C-methanol, D-Skellysolve B, E-1-butanol, F-ethyl acetate, G-ether, H-water. [l] Free base from Skellysolve B, m.p. 72.5–73.5°. [m] Free base from benzene, m.p. 87–87.5°.

amine. The residue was taken up in ether and treated with dry hydrogen chloride to complete the precipitation. The gummy residue was crystallized from 2-propanol and purified from 1:1 2-propanol–ethanol. The yield of pure product was 1.7 g. (7%).

o-(2-Dimethylaminoethoxy)-α-N-morpholinopropiophenone hydrobromide (IV.2HBr, R = methyl, NR′R″ = morpholine). To 800 g. (9.2 moles) of dried, distilled morpholine was added with stirring and keeping the temperature below 35°, 100 g., (0.26 mole) of *o*-(2-dimethylaminoethoxy)-α-bromopropiophenone hydrobromide. The reaction was stirred for 6 hr., heated to 90° and stirred overnight while allowing the solution to cool to room temperature. Addition of a liter of ether precipitated the morpholine hydrobromide which was removed by filtration. The remaining morpholine was removed by distillation under 1 mm. from a bath at 50° C. The residue was taken up in ether, washed with water, dried over magnesium sulfate, and treated with ethereal hydrogen bromide to complete precipitation. The yield of crystalline material melting at 204–5° was 60% of theory. Recrystallization from ethanol raised the melting point to 207.5–209°.

o-(2-Dimethylaminoethoxy)-α-diethylaminopropiophenone hydrobromide (IV.2HBr, R = methyl, NR′R″ = $N(C_2H_5)_2$. To 475 g. (15 moles) of diethylamine was added with stirring 76.2 g. (0.2 mole) of finely powdered *o*-(2-dimethylaminoethoxy)-α-bromopropiophenone hydrobromide. The temperature of the reaction mixture rose from 25 to 28°. Stirring was continued overnight. The reaction mixture was then filtered to remove the diethylamine hydrobromide and the filtrate distilled to recover the excess diethylamine. Last traces of diethylamine were removed on a water bath (45° C) at 1 mm. pressure. The residue was taken up in 200 ml. anhydrous ether and gaseous HBr added to the Congo Red endpoint. The hydrobromide precipitated as a sticky hygroscopic solid. This was then recrystallized to give a 33% yield of pure product.

o-(2-Dimethylaminoethoxy)-α-dimethylaminopropiophenone hydrochloride (IV.2HCl, R = R′ = R″ = methyl). To a solution of 60 g. (1.33 moles) of dry dimethylamine in 300 ml. of absolute ethanol kept at below 10° C. was added a hot solution of 90 g. (0.24 mole) of *o*-dimethylaminoethoxy-α-bromopropiophenone hydrobromide in 900 ml. of absolute ethanol. Stirring was continued until room temperature was attained and for an additional 2 hr. The alcohol was removed by distillation. The residue was taken up in 200 ml. of 5*N* ammonium hydroxide and 300 ml. of ether. The ether layer, after drying over magnesium sulfate, was distilled. Redistillation gave a fraction boiling at 127–130°/0.6 mm. This was dissolved in 2-propanol and treated with dry hydrogen chloride. The precipitate was purified by recrystallization from 2-propanol.

1-[2-(2-Dimethylaminoethoxy)phenyl]-2-diethylamino-1-propanol dihydrobromide (V.2HBr, R = methyl, R′ = R″ = ethyl). This was obtained by reduction of *o*-(2-dimethylaminoethoxy)-α-diethylaminopropiophenone dihydrobromide in water solution at 100° and at 1000 lbs. pressure in the presence of 10% palladium on charcoal. Filtration and evaporation to dryness gave a white solid which was purified by recrystallization from an ethanol-ether mixture.

1-[2-(2-Dimethylaminoethoxy)phenyl]-2-dimethylamino-1-propanol dihydrochloride. (V.2HCl, R = R′ = R″ = methyl). This was prepared by reduction of *o*-(2-dimethylaminoethoxy)-α-dimethylaminopropiophenone dihydrochloride in aqueous solution at 100° and at 1000 lbs. pressure in the presence of 10% palladium on charcoal. Filtration and evaporation to dryness gave an oil which was crystallized from ethanol.

Cyclization of o-(2-Dimethylaminoethoxy)-α-bromopropiophenone. To a solution of 76 g. of *o*-(2-dimethylaminoethoxy)-α-bromopropiophenone hydrobromide in 500 ml. of water and ice, overlayered by 4 l. of ether, was added 100 ml. of 20% sodium hydroxide while stirring vigorously. The layers were separated as quickly as possible. The aqueous layer was washed once with ether. The combined ether layers were dried over magnesium sulfate for a few minutes and gravity filtered. The whole operation took about 20 min. The clear filtrate became cloudy in less than 5 min. After 5 days, filtration yielded 37.5 g. of crystals melting over 200°. Recrystallization from propanol-methanol mixture in the presence of Darco gave crystals m.p. 202–204°. This material is soluble in water and in alkali and analysis agreed with that for 1,8-dimethyl-5,6-benzo-1,3-azoxycyclooctan-7-one methobromide.

Anal. Calcd. for $C_{13}H_{18}BrO_2N$: C, 52.01; H, 6.04; N, 4.67; Br, 26.6. Found: C, 52.05; H, 6.08; N, 4.66; Br, 26.7.

o-Dialkylaminoethoxy-α-isonitrosopropiophenone hydrochloride (VII). Into a solution of 0.6 mole of (2-dialkylaminoethoxy)propiophenone in 550 ml. absolute ethanol-ether (2:5) solution was passed 0.8 mole of hydrogen chloride while stirring vigorously and cooling with an ice bath. To the resulting thick semi-solid mixture was added with stirring, 0.9 mole of butyl nitrite at such a rate as to cause and maintain very gentle refluxing. Stirring was continued at room temperature for about 2.5 hr. after addition was completed. The appearance of the precipitate changed during this time to a heavier and more granular looking material. The reaction mixture was filtered, washed with ethanol-ether and dried. The yield of product thus obtained was almost quantitative, of sharp melting point and satisfactory for reduction.

1-[(2-Dialkylaminoethoxy)phenyl]-2-amino-1-propanol (IX). The reduction of 0.38 mole of isonitroso compound as its hydrochloride was carried out in 1 liter of absolute alcohol containing 1.15 moles of additional hydrogen chloride in the presence of 11 g. of 10% palladium on charcoal and under about 1000 lbs. hydrogen pressure. After the theoretical hydrogen uptake for reduction of the isonitroso was completed, the reaction mixture was evaporated to dryness. The catalyst may or may not have been removed first. The residue was taken up in water to make a liter of solution. Another 11 g. of catalyst was added and reduction was continued. After the theoretical hydrogen uptake for the reduction of carbonyl, the solution was filtered and evaporated to dryness. The residue was recrystallized from the appropriate solvent.

In the case of the *p*-dimethylaminoethoxy isomer it was sometimes necessary to heat the reaction mixture to about 100° during the second reduction in order to expedite it. Instead of evaporating the aqueous reduction mixture to dryness, it was concentrated, made alkaline with 50% sodium hydroxide, and extracted with benzene. Concentration of the benzene gave the crystalline free base. Recrystallization from benzene gave a melting point of 96–97.8°. The base in ether solution was converted to its hydrobromide using gaseous hydrogen bromide.

In the case of the *o*-diethylaminoethoxy isomer it was advisable to heat during both reductions. On concentration of the aqueous reduction, the concentrated solution was made alkaline with 50% sodium hydroxide and extracted with ether. Hydrogen chloride in ether converted the base to its salt.

In the case of the *p*-diethylaminoethoxy isomer the aqueous reduction mixture was made alkaline with 50% sodium hydroxide and extracted with benzene. The dried benzene extract on concentration gave the crystalline base. We were unable to get a non-hygroscopic salt.

The over-all yields for the reductions were 40–70%.

1-[(2-Dialkylaminoethoxy)phenyl]-2-benzylamino-1-propanol. (X, R′ = benzyl, R″ = hydrogen). To the suspension obtained by reducing 200 mg. of platinum oxide in 25 ml. of absolute ethanol was added 10 mmoles of the primary amine and 11 mmoles of freshly distilled benzaldehyde in 50 ml. of absolute ethanol. After shaking with hydrogen until the theoretical amount of hydrogen was taken up, the reaction mixture was filtered. An excess of concentrated hydrochloric or hydrobromic acid was added and crystalli-

zation was induced by seeding, scratching, and/or concentration.

In the case of the *o*-dimethylaminoethoxy isomer, the ethanol mother liquor was evaporated and replaced by 1-butanol before addition of the concentrated hydrochloric acid. The reduction in the case of this isomer took about 3 hr. at room temperature for 20 mmoles. The following variation increased the temperature and time required for the reaction. The amine and benzaldehyde were mixed in 50 ml. of benzene. After 2 hr., the water which separated was removed by magnesium sulfate and the benzene was removed under vacuum. Absolute ethanol was added and also removed under vacuum. The ethanol was replaced and the solution added to the reduced catalyst as above. At room temperature there was practically no hydrogen uptake at atmospheric pressure or at 50 lbs. pressure. At about 60–75°, several hours were required.

1-[(2-Dialkylaminoethoxy)phenyl]-2-benzylmethylamino-1-propanol (*X*, *R′* = *benzyl*, *R″* = *methyl*). In a manner similar to the methylation of the primary amine to give the dimethylamine, the benzylamine was methylated using formic acid and formaldehyde.

1-[(2-Dialkylaminoethoxy)phenyl]-2-dimethylamino-1-propanol (*X*, *R′* = *R″* = *methyl*). A solution of 20 mmoles of the primary amine base, 200 mmoles of 98–100% formic acid and 250 mmoles of formaldehyde as its 40% aqueous solution, was kept in a bath at 120° for about 3 hr. and at 145° for about the same length of time. To the reaction mixture was added 6 ml. of concentrated hydrochloric acid. The residue obtained on evaporation to dryness on a steam bath under vacuum was taken up in concentrated hydrochloric acid and again evaporated to dryness. The residue was now crystallized and recrystallized from the appropriate solvent.

1-[2-(2-Dimethylaminoethoxy)phenyl]-2-dimethylamino-1-propanol (*V or X*, *R* = *R′* = *R″* = *methyl*) was also obtained, as described above, *via o*-(2-dimethylaminoethoxyphenyl)-α-bromopropiophenone hydrobromide.

1-[(2-Dialkylaminoethoxy)phenyl]-2-isopropylamino-1-propanol (*X*, *R′* = *isopropyl*, *R″* = *hydrogen*). To a suspension obtained by reducing 200 mg. of platinum oxide in 25 ml. of alcohol was added a day-old solution of 20 mmoles of the primary amine and 25 mmoles of acetone. After uptake of the theoretical quantity of hydrogen, the reaction mixture was concentrated to dryness. In all but the *p*-diethylaminoethoxy isomer (an oil), solid free bases were obtained as residues. The residues were dissolved in the solvent from which the salt was to be recrystallized and the appropriate hydrogen halide was added.

1-[(2-Dialkylaminoethoxy)phenyl]-2-diethylamino-1-propanol (*X*, *R′* = *R″* = *ethyl*). To a solution of 20 mmoles of the primary amine in 50 ml. of absolute ethanol was added 20 mg. of platinum oxide and 50 mmoles of freshly distilled acetaldehyde while keeping the reaction flask in an ice bath. Hydrogen was introduced with shaking at atmospheric pressure and temperature until no further hydrogen uptake occurred. An additional 50 mmoles of acetaldehyde was added and reduction again continued until cessation of hydrogen uptake. The catalyst was removed by filtration. The residue obtained on evaporation of the filtrate, was taken up in 2-propanol and made acid to Congo Red with hydrogen bromide or hydrogen chloride. The resulting solid was recrystallized.

1-[2-(2-Dimethylaminoethoxy)phenyl]-2-diethylamino-1-propanol (*V or X*, *R* = *methyl*, *R′* = *R″* = *ethyl*) was prepared in this way, and also as described above *via o*(2-dimethylaminoethoxyphenyl)-α-bromopropiophenone hydrobromide.

1[4-(2-Dimethylaminoethoxy)phenyl]-2-ethylamino-1-propanol dihydrochloride (*X.2HCl*, *R* = *methyl*, *R′* = *ethyl*, *R″* = *hydrogen*). This was prepared in the same way that *1*-[4-(2-dimethylaminoethoxy)phenyl]-2-diethylamino-1-propanol was prepared except that the second reduction in the presence of acetaldehyde was omitted. Repeated recrystallization from ethanol-methanol solvent gave 25–30% yield of product which showed no primary amine by Van Slyke analysis and analyzed as expected for the monoethylated product.

MORRIS PLAINS, N. J.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, PURDUE UNIVERSITY]

Beckmann Rearrangement of Some Cyclic Sulfone Ketoximes[1]

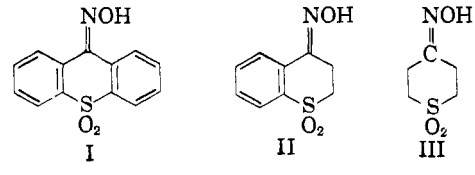
WILLIAM E. TRUCE AND JOHN A. SIMMS[2]

Received December 17, 1956

The ease of rearrangement of thiaxanthone 5,5-dioxide oxime (I), 4-thiachromanone 1,1-dioxide oxime (II), and tetrahydro-1,4-thiapyrone 1,1-dioxide oxime (III) was found to be III ≫ II ≅ I. The rearrangement product of I was characterized by independent synthesis.

It has been show that some heterocyclic ketoximes undergo the Beckmann rearrangement to give the expected lactams.[3-5] However, all of the ketoximes previously examined had the ketoxime function separated from the hetero atom by saturated carbon atoms. It was felt that an appreciable change in reactivity might result if the hetero atom was conjugated with the oxime group.

Therefore, the three cyclic sulfone ketoximes, thiaxanthone 5,5-dioxane oxime (I), 4-thiachromane 1,1-dioxide oxime (II), and tetrahydro-1,4-thiapyrone 1,1-dioxide oxime (III), were prepared and the conditions necessary for their rearrangement were determined.



I II III

(1) Taken from Mr. Simms' Ph.D. Thesis, Purdue University, 1956.

(2) Dow Chemical Company Fellow, 1954–1955.

(3) S. C. Dickerman and H. G. Lindwall, *J. Org. Chem.* **14**, 534 (1949).

(4) I. N. Nazarov and A. I. Kuznetsova, *Bull. Acad. Sci. (USSR), Div. Chem. Sci.*, 455–60 (1953) (English translation).

(5) C. Barkenbus, J. F. Diehl, *et al.*, *J. Org. Chem.* **20**, 871–4 (1955).