ethanol saturated with hydrogen chloride[9] afforded the analytical sample as thin lemon-yellow needles, m.p. 125–126°, which contained no halogen.

Anal. Calcd. for $C_8H_9N_3O_6S$: C, 34.91; H, 3.27; N, 15.27; S, 11.64. Found: C, 35.18; H, 3.27; N, 15.00: S, 11.57.

Both the nature of the solvent and the proportion of zinc oxide used in this preparation are critical. Thus, the above-stated proportion of zinc oxide in 95% ethanol produced only a red gum. Larger proportions of zinc oxide in absolute ethanol gave about 70% yields of IV, but the product had a dark purplish-brown color. Use of absolute ethanol containing no zinc oxide produced a small amount of unidentified white flakes, m.p. 120–121°. With pyridine as solvent, an intractable black product formed immediately. The effect of the varying reflux periods used in these experiments is believed to be slight.

Using pyridine as a solvent, we were unable to effect condensation of I with either 2-chlorothiophene or II. II and I also did not react in absolute ethanol containing zinc oxide.

N-(3,5-Dinitro-2-thienyl)glycine (V). A solution of 0.275 g. (1.00 mmole) of the ethyl ester IV in 12 ml. of concd. hydrochloric acid and 12 ml. of water was boiled, diluted with 20 ml. of water, and then refrigerated to yield 0.235 g. (95%) of V as tiny yellow needles, m.p. 215–217°, with some prior decomposition and sublimation.

Anal. Calcd. for $C_6H_5N_3O_6S$: C, 29.15; H, 2.02. Found: C, 29.64; H, 2.53.

The glycine V was reconverted to IV by saturating its solution in absolute ethanol with dry hydrogen chloride. Concentration and cooling afforded IV as lemon-yellow needles, m.p. 125–126°; no depression when mixed with a sample prepared as described above.

Vesicant properties. Both II and III produced a very persistent skin rash and painful blisters. More than 6 months was required for the irritation to disappear completely, even after treatment with certain cortisone ointments. The person most seriously affected had worked with a large variety of thiophene compounds of other types for several years without any ill effects. In addition to its vesicant properties, III exhibited a potent corrosive action similar to that of the phenols. An acetone solution of III removed the skin in a short time.

Acknowledgment. The authors are indebted to Mr. Jean-Pierre Anselme for repeating and checking the preparations described in this paper.

DEPARTMENT OF CHEMISTRY
FORDHAM UNIVERSITY
NEW YORK 58, N. Y.

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[9] The hydrogen chloride is necessary to remove the color from crude IV.

Syntheses of Some 1-Alkylamino-1,1-di(hydroxymethyl)-2-phenylethanes

B. VITHAL SHETTY AND ALLAN R. DAY[1]

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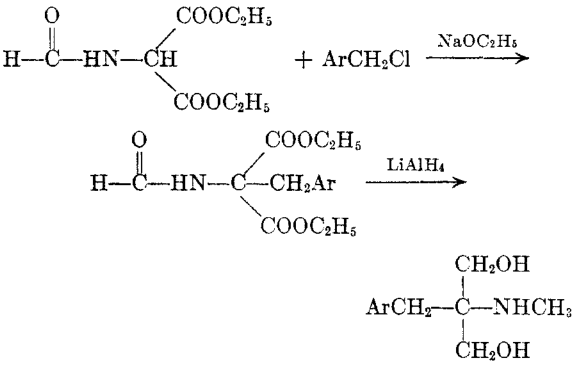
Many derivatives of β-phenylethylamine have been synthesized by earlier investigators with the hope of obtaining physiologically active compounds. In the present study a number of derivatives of β-phenylethylamine, having a trisubstituted carbon atom attached to the amino group, have been synthesized. In all cases the trisubstituted carbon is attached to two hydroxymethyl groups, to a benzyl or a substituted benzyl group and to an alkylamino group. The synthetic steps may be illustrated by the following example:

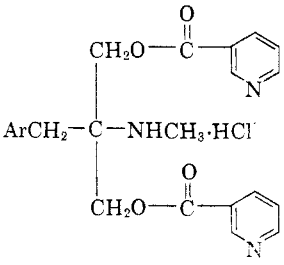


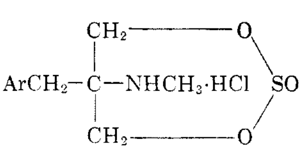
$$\mathrm{H{-}C(=O){-}HN{-}CH(COOC_2H_5)_2} + \mathrm{ArCH_2Cl} \xrightarrow{\mathrm{NaOC_2H_5}} \mathrm{H{-}C(=O){-}HN{-}C(COOC_2H_5)_2{-}CH_2Ar} \xrightarrow{\mathrm{LiAlH_4}} \mathrm{ArCH_2{-}C(CH_2OH)_2{-}NHCH_3}$$

Ar = C_6H_5, 2-$CH_3C_6H_4$, 3-$CH_3C_6H_4$, 4-$CH_3C_6H_4$, 4-$CH_3OC_6H_4$, 4-HOC_6H_4.

In one case the ethylamino group was introduced in place of the methylamino group. Diethyl acetamidomalonate was the starting material for the preparation of the ethylamino compound.

The dinicotinates and the sulfites of most of these compounds were also prepared.





EXPERIMENTAL

Ethyl isonitrosomalonate, I. This compound was prepared by the procedure of Cerchez.[2] The yield was 81%.

Ethyl formamidomalonate, II. Compound I was reduced with zinc dust and formic acid by the method of Conrad and Schulze.[3] The crude yield was 71%. The product was sufficiently pure for the subsequent steps.

Ethyl α-formamido-α-carbethoxy-β-phenylpropionate, III. Compound III was prepared from II by treatment with sodium ethoxide and benzyl chloride.[4] The yield was 96%, m.p. 105–107°.

N-Methyl-1,1-di(hydroxymethyl)-2-phenylethylamine hydrochloride, IV. Lithium aluminum hydride (19.9 g., 0.52 mole) was added to 470 ml. of dry ether and the mixture stirred for 20 min. at room temperature and then for 20 min. while cooling in an ice bath under an atmosphere of dry nitrogen. Then 50 g. (0.17 mole) of compound III, suspended in 250 ml. of dry ether, was added in small amounts during a period of 45 min. while maintaining the temperature below 30°. After the addition was complete, the stirring was continued for 6 hr. The cooled reaction mixture was carefully

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[1] The authors are indebted to the Wyeth Institute for Medical Research for their assistance during this investigation.

[2] V. Cerchez, *Bull. soc. chim. France*, **47**, 1279 (1930).

[3] M. Conrad and A. Schulze, *Ber.*, **42**, 733 (1909).

[4] A. Cohen, E. G. Hughes, and J. A. Silk, British Patent **621,706** (1949).

TABLE I

$$ArCH_2-\overset{\displaystyle CH_2OH}{\underset{\displaystyle CH_2OH}{\overset{|}{\underset{|}{C}}}}-NHR\cdot HCl$$

	Formula	Ar	R	Yield, %	M.P.	C, % Calcd.	C, % Found	H, % Calcd.	H, % Found	N, % Calcd.	N, % Found	Cl, % Calcd.	Cl, % Found
IV	$C_{11}H_{18}ClNO_2$	C_6H_5	CH_3	41	153–155	57.02	56.95	7.77	7.54	6.04	6.22	15.31	15.51
V	$C_{18}H_{22}ClNO$	C_6H_5		13	218–220	67.60	67.70	6.88	6.99	4.38	4.28	11.11	11.14
VI	$C_{12}H_{20}ClNO_2$	o-$CH_3C_6H_4$	CH_3	35	163–165	58.67	58.75	8.14	8.24	5.70	5.87	14.42	14.40
VII	$C_{12}H_{20}ClNO_2$	m-$CH_3C_6H_4$	CH_3	30	117–119	58.67	58.40	8.14	8.40	5.70	5.90	14.42	14.21
VIII	$C_{12}H_{20}ClNO_2$	p-$CH_3C_6H_4$	CH_3	56	157–158	58.67	58.87	8.14	8.22	5.70	5.70	14.42	14.20
IX	$C_{12}H_{20}ClNO_2$	C_6H_5	C_2H_5	15	141–143	58.67	58.52	8.14	8.27	5.70	5.91	14.42	14.27
X	$C_{12}H_{20}ClNO_3$	p-$CH_3OC_6H_4$	CH_3	40	168–170	55.08	55.00	7.65	7.80	5.35	5.65	13.54	13.49
XI	$C_{11}H_{18}ClNO_3$	p-HOC_6H_4	CH_3	33	174–176	53.33	53.19	7.27	7.54	5.65	5.87	14.34	14.53

treated with water to decompose the lithium aluminum compounds and the ether layer then separated. The aqueous layer was extracted with ether and the combined ether extracts were then dried over anhydrous sodium sulfate. The ether was removed under reduced pressure and the residue was dissolved in 300 ml. of dry ether. The ether solution was treated with dry hydrogen chloride and the gummy precipitate so obtained was extracted with dry ether until it solidified. The solid was dissolved in 75 ml. of dry methanol and the solution decolorized with charcoal. Fifty milliliters of dry acetone was then added followed by 300 ml. of dry ether. After standing overnight at −10°, 18 g. of the hydrochloride was obtained.

The dinicotinate of compound IV was prepared by refluxing a solution of 2 g. of nicotinic anhydride[5] and 1 g. of IV in 200 ml. of dry benzene for 28 hr. The mixture was filtered while hot and the residue washed with hot benzene. The benzene filtrate and washings were combined and the benzene removed *in vacuo*. The residue was dissolved in 50 ml. of dry ethanol, decolorized with charcoal, 300 ml. of dry ether added, and the solution then allowed to stand overnight at −10°. The colorless crystals so obtained were dried *in vacuo*, yield 51%, m.p. 189–190°.

Anal. Calcd. for $C_{23}H_{24}ClN_3O_4$: C, 62.51; H, 5.43; Cl, 8.04; N, 9.41. Found: C, 62.29; H, 5.33; Cl, 8.0; N, 9.44.

The hydrochloride of the sulfite of compound IV was also prepared. Eight grams of *N*-methyl-1,1-di(hydroxymethyl)-2-phenylethylamine hydrochloride was thoroughly mixed with 83 ml. of freshly distilled thionyl chloride. The mixture was allowed to stand for the 30 min. The solid was then removed by filtration and washed with petroleum ether (b.p. 30–60°). It was recrystallized from 60 ml. of methanol with the aid of decolorizing carbon. The yield was 62%, m.p. 157–158°.

Anal. Calcd. for $C_{11}H_{16}ClNO_3S$: C, 47.56; H, 5.76; Cl, 12.79; N, 5.04; S, 11.52. Found: C, 47.53; H, 5.80; Cl, 12.60; N, 5.02; S, 11.30.

N-[1,1-Di(hydroxymethyl)-2-phenylethyl]-1,3-dihydroisoindole, V. Ethyl phthalimidomalonate was prepared by the method of Sheehan and Bolhofer.[6] This compound was converted to sodium ethyl phthalimidomalonate by the procedure of Barger and Weichselbaum.[7]

Ethyl benzyl phthalimidomalonate was made by the method reported by Sorensen.[8] The yield was 90%, m.p. 105–106°.

Lithium aluminum hydride (3.5 g., 0.092 mole) was stirred with 200 ml. of dry ether at room temperature for 20 min. and then for 20 min. at 0°, in an atmosphere of nitrogen. Then 10 g. (0.025 mole) of ethyl benzyl phthalimidomalonate dissolved in 150 ml. of dry ether, was added over a period of 30 min. The mixture was stirred and refluxed for 3 hr. It was then cooled and treated carefully with water. The ether layer was separated and the aqueous layer extracted with ether. The combined ether extracts were dried over anhydrous sodium sulfate and the ether removed by distillation. The residue was warmed with 50 ml. of 20% hydrochloric acid and the solution filtered. On cooling, the product (V) separated.

N-Methyl-1,1-di(hydroxymethyl)-2-(2-methylphenyl)ethylamine hydrochloride, VI. Sodium (2.07 g., 0.09 g.-atom) was dissolved in 175 ml. of dry ethanol. To this solution was added 15.0 g. (0.09 mole) of ethyl formamidomalonate with stirring. Then 19.5 g. (0.13 mole) of *o*-methylbenzyl chloride[9] was added over a period of 10 min. with stirring. Stirring

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[5] W. A. Schrecker and B. P. Maury, *J. Am. Chem. Soc.*, **76**, 5803 (1954).

[6] J. C. Sheehan and W. A. Bolhofer, *J. Am. Chem. Soc.*, **72**, 2786 (1950).

[7] G. Barger and T. E. Weichselbaum, *Org. Syntheses*, **Coll. Vol. II**, 384 (1943).

[8] S. P. L. Sorensen, *Centrl.*, **II**, 33 (1943).

[9] K. Kindler and E. Yehlhaar, *Archiv. Pharm.*, **274**, 385 (1936).

and refluxing were continued for 1 hr. The mixture was filtered while hot and the residue was washed with hot alcohol. The alcohol was removed under reduced pressure and the product, ethyl α-formamido-α-carbethoxy-β-2-methylphenylpropionate, was recrystallized from acetone-water, yield 68%, m.p. 92–94°.

Anal. Calcd. for $C_{16}H_{21}NO_5$: C, 62.54; H, 6.84; N, 4.56. Found: C, 62.60; H, 7.03; N, 4.67.

This product was reduced to compound VI with lithium aluminum hydride by the procedure used for making compound IV.

The corresponding sulfite was prepared as described for compound IV. The yield was 65%, m.p. 164–165°.

Anal. Calcd. for $C_{12}H_{18}ClNO_3S$: C, 49.39; H, 6.17; Cl, 12.17; N, 4.80; S, 10.97. Found: C, 49.30; H, 6.15; Cl, 12.40; N, 4.79; S, 10.89.

The corresponding dinicotinate, prepared by the method described for compound IV, melted at 193–194°, yield 38%.

Anal. Calcd. for $C_{24}H_{26}ClN_3O_4$: C, 63.22; H, 5.71; Cl, 7.79; N, 9.22. Found: C, 63.01; H, 6.05; Cl, 7.6; N, 8.92.

N-Methyl-1,1-di(hydroxymethyl)-2-(3-methylphenyl)ethylamine hydrochloride, VII. Ethyl α-formamido-α-carbethoxy-β-3-methylphenylpropionate was prepared by the procedure used for making α-formamido-α-carbethoxy-β-phenylpropionate except that *m*-methylbenzyl chloride was used in place of benzyl chloride. The yield was 84%, m.p. 94–96°.

Anal. Calcd. for $C_{16}H_{21}NO_5$: C, 62.54; H, 6.84; N, 4.56. Found: C, 62.50; H, 6.81; N, 4.76.

Ethyl α-formamido-α-carbethoxy-β-3-methylphenylpropionate was reduced with lithium aluminum hydride to compound VII.

The dinicotinate of VII was prepared in 38% yield, m.p. 185–186°.

Anal. Calcd. for $C_{24}H_{26}ClN_3O_4$: C, 63.22; H, 5.71; Cl, 7.79; N, 9.22. Found: C, 63.20; H, 5.88; Cl, 7.72; N, 9.37.

The sulfite of VII was prepared in 65% yield, m.p. 148–149°.

Anal. Calcd. for $C_{12}H_{18}ClNO_3S$: C, 49.39; H, 6.17; Cl, 12.17; N, 4.80; S, 10.97. Found: C, 49.26; H, 6.42; Cl, 12.20; N, 5.13; S, 10.75.

N-Methyl-1,1-di(hydroxymethyl)-2-(4-methylphenyl)ethylamine hydrochloride, VIII. Ethyl α-formamido-α-carbethoxy-β-4-methylphenylpropionate was prepared by the method used for making ethyl α-formamido-α-carbethoxy-β-phenylpropionate except that *p*-methylbenzyl chloride was used in place of benzyl chloride. The yield was 93%, m.p. 135–136°.

Anal. Calcd. for $C_{16}H_{21}NO_5$: C, 62.54; H, 6.84; N, 4.56. Found: C, 62.63; H, 7.26; N, 4.79.

Ethyl α-formamido-α-carbethoxy-β-4-methylphenylpropionate was reduced with lithium aluminum hydride to compound VIII.

The sulfite of VIII was prepared in 65% yield, m.p. 156–157°.

Anal. Calcd. for $C_{12}H_{18}ClNO_3S$: C, 49.39; H, 6.17; Cl, 12.17; N, 4.80; S, 10.97. Found: C, 49.68; H, 6.45; Cl, 12.15; N, 4.96; S, 10.81.

N-Ethyl-1,1-di(hydroxymethyl)-2-phenylethylamine hydrochloride, IX. Ethyl acetamidomalonate was the starting material for this preparation. Otherwise the procedure was similar to that used for making compound IV.

N-Methyl-1,1-di(hydroxymethyl)-2-(4-methoxyphenyl)ethylamine hydrochloride, X. Ethyl α-formamido-α-carbethoxy-β-4-methoxyphenylpropionate[4] was reduced with lithium aluminum hydride to compound X.

The dinicotinate of X melted at 172–173°, yield 33%.

Anal. Calcd. for $C_{24}H_{26}ClN_3O_5$: C, 61.08; H, 5.51; Cl, 7.52; N, 8.90. Found: C, 61.13; H, 5.56; Cl, 7.6; N, 8.95.

The corresponding sulfite melted at 167–168°, yield 73%.

Anal. Calcd. for $C_{12}H_{18}ClNO_4S$: C, 46.82; H, 5.85; Cl, 11.54; N, 4.55; S, 10.40. Found: C, 46.93; H, 5.82; Cl, 11.45; N, 4.68; S, 10.55.

N-Methyl-1,1-di(hydroxymethyl)-2-(4-hydroxyphenyl)ethylamine hydrochloride, XI. One gram of compound X was refluxed in 2 ml. of 48% hydrobromic acid and 5 ml. of acetic acid for 20 min. On diluting with 20 ml. of water a dark gummy material separated. The gum was washed with dilute sodium hydroxide solution and then with water. The residue was dissolved in ether, the solution dried and treated with dry hydrogen chloride. The hydrochloride, which was quite hygroscopic, was recrystallized from propanol and dry ether.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF PENNSYLVANIA
PHILADELPHIA 4, PA.

Synthesis of *N*-(2-Hydroxyethyl)-*N'*-(4-pentenyl)ethylenediamine

E. F. CLUFF AND H. F. MCSHANE, JR.

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As an intermediate for the preparation of a certain polyurethane elastomer[1] the substituted ethylenediamine (I) was required in a state of high purity. Diamine syntheses involving alkylation reactions usually give mixtures which contain difficultly separable tertiary amine isomers. The latter materials act as chain terminating agents in polycondensation reactions and prevent the attainment of high molecular weight. Consequently the synthetic route shown in the flowsheet was chosen to provide a diamine of unequivocal structure.

Aminolysis of dimethyl oxalate (II) with *N*-(2-hydroxyethyl)ethylenediamine (III) provided crystalline *N*-(2-hydroxyethyl)piperazine-2,3-dione (IV) in 20–35% yield. This reaction has been shown to be general for many *N*-substituted ethylenediamines.[2] The present reaction most likely proceeds through the formation and subsequent breakdown of a linear polyamide. As the temperature was slowly raised to about 180°, an essentially quantitative yield of alcohol was obtained, and the reaction mass became increasingly more viscous. At this point, the product was insoluble in alcohol and no piperazinedione (IV) could be isolated. Increasing the temperature above 180° to about 220° produced a marked viscosity reduction in the reaction mass which was then alcohol soluble and deposited crystals of IV.

Conversion of IV to the monopotassium salt proceeded smoothly in refluxing *t*-butyl alcohol. The salt was not isolated but was alkylated directly with 1-bromo-4-pentene to provide the crystalline disubstituted piperazinedione (V) in 70% yield. Hydrolysis of V with aqueous-alcoholic potassium hydroxide provided an excellent yield of *N*-(2-hydroxyethyl) - *N'* - (4 - pentenyl)ethylenediamine (I). That alkylation of the piperazinedione (IV) had occurred on nitrogen and not on hydroxyl

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(1) E. F. Cluff and E. K. Gladding, Proceedings International Rubber Conf., Washington, D. C., 1959, p. 543.

(2) J. L. Riebsomer, *J. Org. Chem.*, **15**, 68 (1950).