recrystallized from hot dilute hydrochloric acid but it was best to cause slow deposition of the salt from the dilute acid at room temperature on standing. After several recrystallizations in this way, it was further recrystallized from ethanol-toluene and then formed a nearly white crystalline powder. The best material, on heating, began to turn orange at 210–215° with melting at 228–234° to an orange-brown melt.

Anal. Calcd. for $C_{16}H_{16}NO_2Cl$: C, 66.32; H, 5.53. Found: C, 66.69; H, 5.80.

DL-*β*-(*1-Fluorenyl*)*alanine.* The hydrochloride could be converted to the free amino acid by extraction with ammonium hydroxide and acidification with acetic acid. This tended to form a pink product, especially if heated. It was found preferable to acidify a very dilute solution of the hydrochloride in dilute potassium hydroxide with acetic acid so that the amino acid slowly deposited at room temperature. In this way, a nearly white crystalline product was formed. On heating, the best sample began to turn orange at 210–212° and melted 221–230° to an orange-brown melt.

Anal. Calcd. for $C_{16}H_{15}NO_2$: C, 75.89; H, 5.93. Found: C, 76.04; H, 5.96.

Reaction with ninhydrin. The amino acid was suspended in dilute acetic acid and treated with an excess of ninhydrin and heated. A greenish-gray solution was formed at first which became dark blue-gray on further heating. On boiling a few minutes, a purple solution was produced with dark blue-gray particles (from undissolved amino acid) in suspension.

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UNIVERSITY OF CALIFORNIA SCHOOL OF MEDICINE
BERKELEY, CALIF.

Preparation of *N*-Substituted Glycines. II. *N*-(3,5-Dinitro-2-thienyl)glycine[1,2a]

JACK M. TIEN AND I. MOYER HUNSBERGER[2b]

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Our interest in *N*-heteroaryl derivatives of the sydnone ring system[3] led us to attempt the preparation of an *N*-thienylsydnone. As no *N*-thienylglycines have been reported in the literature, we first attempted to prepare *N*-2-thienylglycine by condensation of 2-chlorothiophene with glycine ethyl ester hydrochloride (I); however, only unchanged chlorothiophene was isolated. The more reactive 2-bromo-5-nitrothiophene (II) also failed to condense with I. Finally, the hitherto unreported 2-bromo-3,5-dinitrothiophene (III) was prepared in high yield by nitration of 2-bromo-5-nitrothiophene with mixed acid at low temperature. After considerable difficulty the condensation of III with I was effected by heating in absolute ethanol containing a rather carefully regulated amount of zinc oxide. In this way the ethyl ester (IV) of *N*-(3,5-dinitro-2-thienyl)glycine, m.p. 125–126°, was obtained in good yield. Acid hydrolysis of IV then afforded the desired *N*-(3,5-dinitro-2-thienyl)glycine (V). Esterification of V regenerated IV.

All attempts to nitrosate both the glycine (V) and its ethyl ester (IV) were unsuccessful; methods specifically designed for nitrosating weakly basic amines gave only unchanged starting material. As 3,5-dinitro-2-thienol[4] is a much stronger acid than 2,4-dinitrophenol, it seems likely that IV and V also are weaker bases than the corresponding benzene derivatives. Apparently, two nitro groups on the thiophene ring exert effects comparable to three nitro groups on the benzene ring. In this connection it is noteworthy that V separated as the free base from aqueous hydrochloric acid and that IV did not form a hydrochloride salt in absolute ethanol saturated with dry hydrogen chloride.

Further work in this series was abandoned because of the extremely potent vesicant action of both II and III (see Experimental).

EXPERIMENTAL[5]

2-Bromo-3,5-dinitrothiophene (III).[6] Concentrated sulfuric acid (45 ml.) and 60 ml. of yellow fuming nitric acid (sp. gr. 1.49–1.50)[7] were mixed at −5°. The mixed acid was kept at −5° (ice-salt bath) while 14.6 g. (0.070 mole) of II[8] was added portionwise (stirring) during 25 min. After about 10 min. a pasty mass had formed. The ice-salt bath was replaced by a water bath, and stirring was continued for another 25 min. The yellow slurry was poured onto chipped ice to yield 17 g. (96%) of III as a pale yellow crystalline powder, m.p. 135–136°. Recrystallization from hot ethanol afforded colorless plates of unchanged m.p.

Anal. Calcd. for $C_4HN_2O_4BrS$: Br, 31.59; S, 12.67. Found: Br, 31.51; S, 12.53.

This compound was very soluble in acetone, chloroform, dioxane, and petroleum ether; it was soluble in ether but insoluble in benzene, water, and concentrated or dilute hydrochloric acid.

Ethyl ester (IV) *of N-(3,5-dinitro-2-thienyl)glycine.* A hot solution of 6.3 g. (0.045 mole) of I in 450 ml. of absolute ethanol was treated with 11.0 g. (0.0435 mole) of III and 1.40 g. (0.0172 mole) of zinc oxide. The reagents were added alternately and in about six equal portions, a given portion not being added until the preceding one had dissolved. The yellow solution was refluxed in a hot water bath for 2 hr. On cooling, the solution deposited 9.80 g. (82%) of crude IV as yellow to brown needles. Recrystallization from hot

(1) Paper I: J. M. Tien and I. M. Hunsberger, *J. Am. Chem. Soc.* **77**, 6696 (1955).

(2) (a) Supported, in part, by a research grant (CY-2962) from the National Cancer Institute of the Public Health Service and by the U. S. Air Force under Contract No. AF 18(603)-127, monitored by the Air Force Office of Scientific Research of the Air Research and Development Command. Reproduction in whole or in part is permitted for any purpose of the United States government. (b) To whom all inquiries should be sent: Department of Chemistry, University of Massachusetts, Amherst, Mass.

(3) J. M. Tien and I. M. Hunsberger, *J. Am. Chem. Soc.*, **77**, 6604 (1955).

(4) C. D. Hurd and K. L. Kreuz, *J. Am. Chem. Soc.*, **74**, 2965 (1952).

(5) All combustion analyses were performed by Schwarzkopf Microanalytical Laboratories, Woodside, N. Y.

(6) This procedure is similar to that used[4] for nitrating 2-chloro-5-nitrothiophene.

(7) Red fuming nitric acid produced virtually identical results.

(8) V. S. Babasinian, *J. Am. Chem. Soc.* **57**, 1764 (1935).

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.

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FORDHAM UNIVERSITY
NEW YORK 58, N. Y.

(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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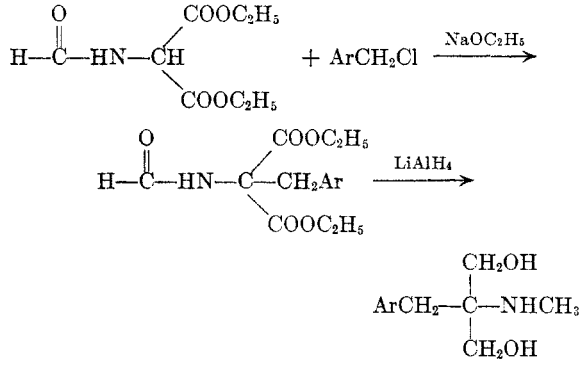
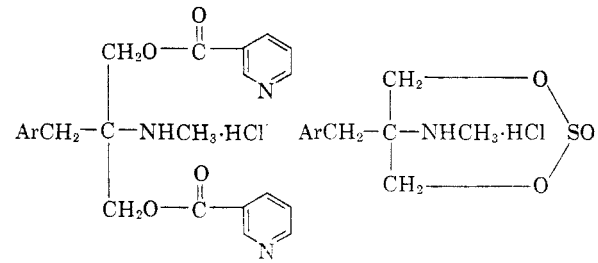
Many derivatives of β-phenylethylamine have been synthesized by earlier investigators with the hope of obtaining physiologically active compounds. In the present study a number of derivatives of β-phenylethylamine, having a trisubstituted carbon atom attached to the amino group, have been synthesized. 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:



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

(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).