[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE COLLEGE OF PHARMACY, UNIVERSITY OF ILLINOIS]

The Behavior of s-Dichloroacetone in Reformatsky Condensations[1]

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Reformatsky condensations were successfully carried out treating *s*-dichloroacetone with ethyl bromoacetate and ethyl α-bromopropionate. The expected products, ethyl β-hydroxy-γ,γ′-dichloroisovalerate and ethyl α-methyl-β-hydroxy-γ,γ′-dichloroisovalerate were obtained when 1,4-dioxane was used as a solvent. These esters were characterized and amino-substituted amides of isovaleric acid prepared from them, using benzylamine, β-phenylethylamine and β-(3,4-dimethoxyphenyl)-ethylamine. The derivatives have been found to possess amebacidal properties by *in vitro* tests.

In the course of an investigation of a synthesis of amebacidal agents structurally related to emetine, we became interested in the behavior of *s*-dichloroacetone in Reformatsky condensation reactions.

The nature and scope of this synthetic reaction have been thoroughly reviewed by Shriner[3] and later developments have been reported by Miller and Nord[4] and Treibs and Leichssenring.[5]

The literature does not reveal any use of this reaction in the condensation of halogenated aliphatic ketones with α- and β-bromoesters, except for Shriner's note, "The reaction follows an abnormal course with halogenated aliphatic ketones. . . ."[3]

Of the numerous attempts along customary lines, to condense *s*-dichloroacetone with ethyl bromoacetate, the only one which yielded traces of what was presumed to be the normal reaction product, employed ethyl ether as a solvent, zinc foil as the condensing agent and iodine as a catalyst; and this only after 21 hours at reflux temperature.

However, when dioxane was used, the reaction proceeded readily, and with this solvent we were able to develop a reaction system in which *s*-dichloroacetone and ethyl bromoacetate condensed to form the normal Reformatsky condensation product, ethyl β-hydroxy-γ,γ′-dichloroisovalerate (I).[6] Identical conditions proved satisfactory for the condensation of *s*-dichloroacetone and ethyl α-bromopropionate, yielding the expected ester, ethyl α-methyl-β-hydroxy-γ,γ′-dichloroisovalerate (II).

In proving the identity of the normal Reformatsky condensation products we sought to prepare derivatives which would be related in some respects to the emetine molecule, have potential amebacidal action, and possibly contribute some data to the structure–activity relationship in amebacidal agents.

We allowed ethyl β-hydroxy-γ,γ′-dichloroisovalerate to react with benzylamine and obtained β,γ-epoxy-γ′-benzylamino-N-benzylisovaleramide (III). Upon reaction with β-(3,4-dimethoxyphenyl)-ethylamine the ester yielded β,γ-epoxy-γ′-[β-(3,4-dimethoxyphenyl)-ethylamino)-N-[β-(3,4-dimethoxyphenyl)-ethyl]-isovaleramide (IV).

Ethyl α-methyl-β-hydroxy-γ,γ′-dichloroisovalerate reacted with β-phenylethylamine to form α-methyl-β-hydroxy-γ,γ′-bis-(β-phenylethylamino)-N-(β-phenylethyl)-isovaleramide (V) and with β-(3,4-dimethoxyphenyl)-ethylamine to yield α-methyl-β-hydroxy-γ,γ′-bis-[β-(3,4-dimethoxyphenyl)-ethylamino]-N-[β-(3,4-dimethoxyphenyl)-ethyl]-isovaleramide (VI).

The formation of an epoxy derivative in the reaction of ethyl β-hydroxy-γ,γ′-dichloroisovalerate (I) and a primary amine, while the closely related ethyl α-methyl-β-hydroxy-γ,γ′-dichloroisovalerate (II) yielded under identical conditions the corresponding hydroxy compound, can be explained on the basis of a greater lability of the hydroxyl-hydrogen atom of the alcohol group. In general, the reactivity of the hydroxyl-hydrogen decreases with an increase in the molecular weight and with the increased branching of the chain of the compound.

A detailed discussion of these principles, supported by experimental evidence, may be found in the publications of Norris and Ashdown,[8] Norris and Cortese[9] and Tronov and Kulev.[10] The latter showed that the hydroxyl-hydrogen activity of *t*-butyl alcohol is considerably greater than that of *t*-amyl alcohol.

To present evidence for the presence of the epoxy structure in compounds III and IV, their infrared absorption curves are reproduced in Figs. 1 and 2. Absorption bands in regions believed to be due to the presence of an epoxy group are found in each curve. Both curves show an absorption band in the frequency range 1250–1255 cm.$^{-1}$, the spectral region known to be characteristic of the epoxy group in large molecules.[11] While, in the absorption curve of compound IV, this band might also be attributed to the presence of four methoxy groups, which seem to strengthen the absorption at this frequency, compound III could exhibit this characteristic peak only due to the presence of the epoxy group which is the only ether linkage in the molecule.

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(2) University Fellow, University of Illinois, Chicago Professional Colleges (1951–1952).

(3) R. Adams, *et al.*, "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942.

(4) R. E. Miller and F. F. Nord, *J. Org. Chem.*, **16**, 728 (1951).

(5) W. Treibs and G. Leichssenring, *Ber.*, **84**, 52 (1951).

(6) Arndt, Loewe and Capuano[7] in their investigation of γ-chlorinated acetoacetic esters report to have obtained in one of their distillations a 0.3-g. fraction, containing what was postulated to be principally ethyl β-hydroxy-γ,γ′-dichloroisovalerate. The chlorine analysis for this fraction was reportedly 4.8% below the calculated value for the ester. No further attempts of isolation, purification and characterization were reported.

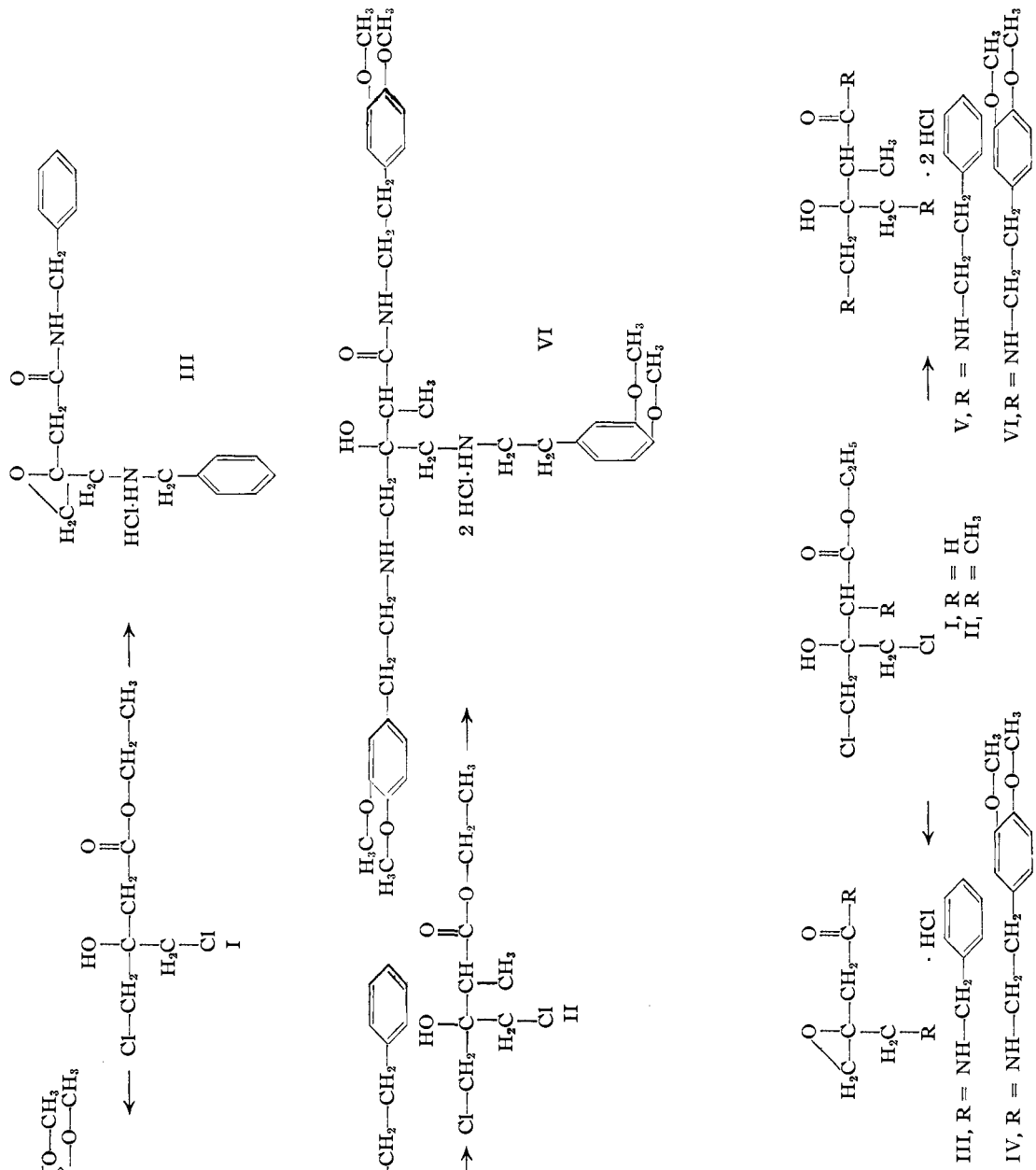
(7) F. Arndt, L. Loewe and L. Capuano, *Rev. faculté sci. univ. Istanbul*, **8A**, 122 (1943).

(8) J. F. Norris and A. A. Ashdown, THIS JOURNAL, **47**, 837 (1925).

(9) J. F. Norris and F. Cortese, *ibid.*, **49**, 2640 (1927).

(10) B. V. Tronov and L. P. Kulev, *Zhur. Obshchei Khim.*, **4**, 197 (1934); *C. A.*, **29**, 448 (1935).

(11) J. E. Field, J. O. Cole and D. E. Woodford, *J. Chem. Phys.*, **18**, 1298 (1950).



We examined the behavior of these esters toward secondary and tertiary amines. None of the reactions with diethyl-, diisopropyl- and triethylamine yielded the desired reaction products. A reaction of diethylamine with ethyl α-methyl-β-hydroxy-γ,γ′-dichloroisovalerate produced a compound which we failed to identify. Other reactions yielded only the hydrochlorides of diethyl-, diisopropyl- and triethylamine.

We were unable to isolate the normal Reformatsky condensation product from any of the β-bromoester–s-dichloroacetone reaction mixtures.

The treatment of ethyl β-bromopropionate with s-dichloroacetone, under conditions identical with those in the treatment of ethyl bromoacetate, did not result in a spontaneous reaction. On re-

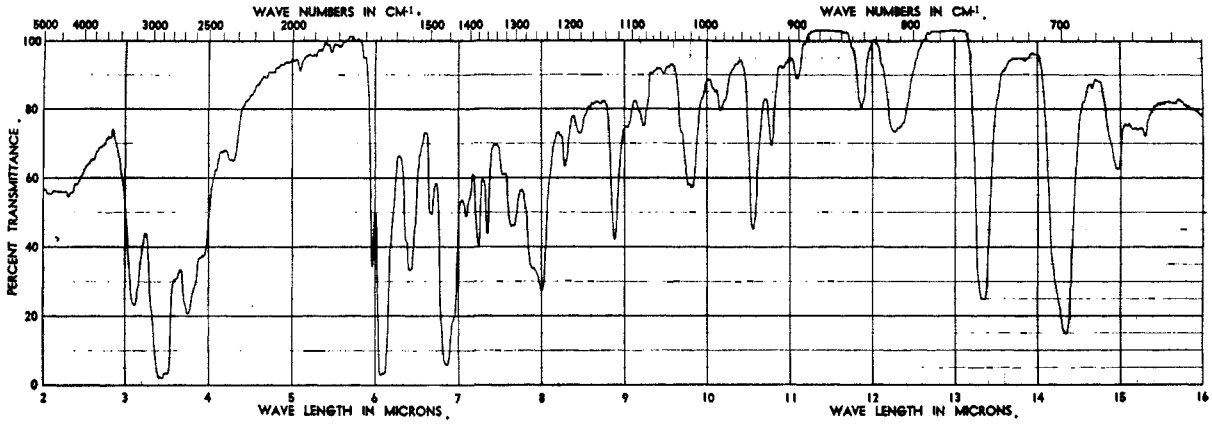


Fig. 1.—Infrared absorption of β,γ-epoxy-γ'-benzylamino-N-benzylisovaleramide hydrochloride (III).

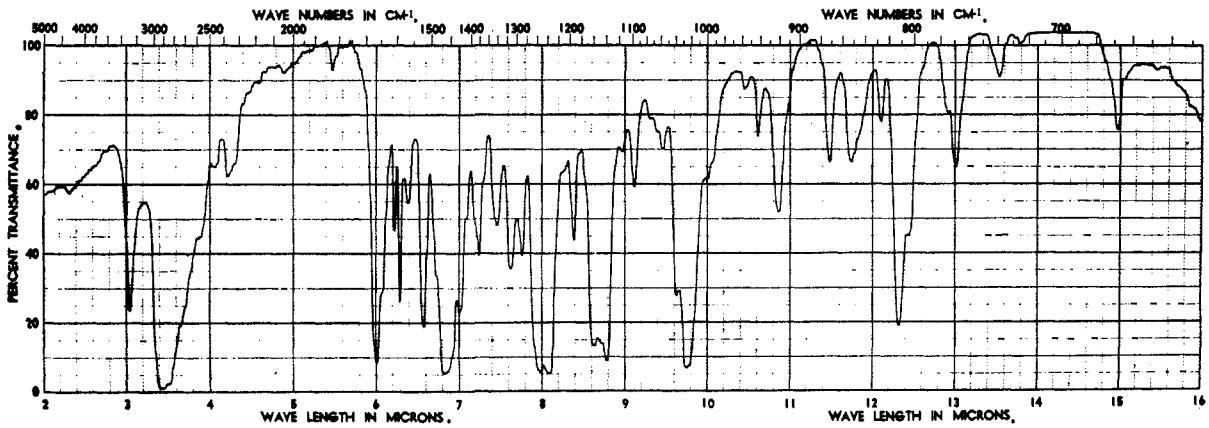


Fig. 2.—Infrared absorption of β,γ-epoxy-γ'-[β-(3,4-dimethoxyphenyl)-ethylamino]-N-[β-(3,4-dimethoxyphenyl)-ethyl] isovaleramide hydrochloride (IV).

fluxing, much of the zinc seemed to enter a reaction, but the reaction mixture yielded only small amounts of a substance of uncertain purity.

In the synthesis of compounds III, IV, V and VI we prepared compounds which are related in some respects to the structure of emetine and exhibit amebacidal activity.

The details of their amebacidal properties, their relative acute toxicity and apparent relationships between the chemical constitution and the amebacidal action of these moieties is discussed in a separate communication.[12]

Experimental

The experiments were carried out in all-glass apparatus.

Ethyl β-Hydroxy-γ,γ'-dichloroisovalerate (I).—Freshly distilled *s*-dichloroacetone (0.3 mole), followed by 0.3 mole of freshly sandpapered zinc foil,[13] 200 ml. of sodium-dried dioxane and 0.3 mole of freshly distilled ethyl bromoacetate were placed in that order in an oven-dried 500-ml. flask, fitted with a reflux condenser, bearing a drying tube. The contents of the reaction flask were thoroughly mixed, a few crystals of iodine added and the mixture allowed to stand for 15–20 minutes at room temperature. Reaction was initiated by cautiously heating with a flame and the rate controlled, as necessary, by cooling in ice-water. After about 45 minutes the reaction was complete. Toward the end of this period the flask was occasionally shaken and the mixture was allowed to cool to room temperature. The reaction mixture was treated with a mixture of 100 ml. of concd. hydrochloric acid and 100 g. of ice. After stirring for 20 minutes 200 ml. of carbon tetrachloride was added and the mixture stirred an additional 20 minutes. After suction filtration the organic layer was separated, the aqueous layer washed twice with 50-ml. portions of carbon tetrachloride and the combined organic layers dried over anhydrous sodium sulfate. The dry solution was filtered and the solvent removed under reduced pressure, finally at 1 mm. using a bath not exceeding 50°.

The residue was taken up immediately in 100 ml. of carbon tetrachloride, allowed to stand for four hours, the solution filtered and the solvent removed under reduced pressure. The residue was treated immediately with 50–80 mg. of hydroquinone and distilled under reduced pressure with a bath temperature not exceeding 145°. The fraction boiling at 40–106° (0.6–1 mm.) was collected. Redistillation of the latter gave a fraction boiling at 82–96° (0.3–0.6 mm.). This distillate yielded upon refractionation a liquid with a slight yellow tint, distilling at 88° (0.3 mm.); d^{20}_4 1.328, $n^{20}D$ 1.4765, yield, 18%.

Anal. Calcd. for $C_7H_{12}O_3Cl_2$: Cl, 33.01; M_D, 47.43. Found: Cl, 32.88; M_D, 45.72.

The compound decomposed gradually on standing, releasing hydrogen chloride. In the determination of its physical constants, analysis and preparation of its derivatives, it was used immediately after distillation. It was soluble in organic solvents, very slightly soluble in water. Contact with skin should be avoided because of its irritating action.

Ethyl α-Methyl-β-hydroxy-γ,γ'-dichloroisovalerate (II).—This ester was prepared according to the method described

(12) W. Balamuth and A. Lasslo, *Proc. Soc. Exp. Biol. Med.*, **80**, 705 (1952).

(13) We found that other forms of zinc caused considerable difficulty. The findings of Natelson and Gottfried[14] seem to agree with our observations. The zinc metal foil, which we used, had a thickness of 0.06 mm. It was thoroughly sandpapered with No. 1 sandpaper, immediately before the reaction, then cut into squares not exceeding 1 cm. on a side. The zinc metal foil was furnished through the courtesy of J. T. Baker Chemical Company, Phillipsburg, N. J.

(14) S. Natelson and S. P. Gottfried, THIS JOURNAL, **61**, 970 (1939).

in the synthesis of I, using ethyl α-bromopropionate. The first distillate was dried, redistilled, b.p. 76–116° (1.5–2 mm.), and then refractionated. The fraction 101–108° (0.8–1.3 mm.), was collected, and yielded upon refractionation a liquid distilling at 98° (1 mm.); d^{20}_4 1.264, $n^{20}D$ 1.4852, yield, 11%.

Anal. Calcd. for $C_8H_{14}O_3Cl_2$: Cl, 30.95; M_D, 52.05. Found: Cl, 30.74; M_D, 51.92.

Other properties of this ester resembled closely those of I.

β,γ-Epoxy-γ'-benzylamino-N-benzylisovaleramide Hydrochloride (III).—Freshly distilled I (0.02 mole) and 0.2 mole of freshly distilled benzylamine were placed in a 200-ml. flask, 0.2 g. of ammonium chloride added, and the flask attached to a condenser. The contents were thoroughly mixed and the mixture heated in an oil-bath for 4–5 hours at 140–150°, with occasional shaking. After cooling, the reaction mixture was treated with equal volumes (100 ml.) of ether and a 10% solution of sodium carbonate. The aqueous layer was drawn off and extracted twice with 50-ml. portions of ether. The ether extracts were combined and dried over anhydrous sodium sulfate. The dry solution was filtered and the solvent removed under reduced pressure. The pressure was further reduced with an oil pump and unreacted benzylamine distilled off, using a bath not exceeding 140°. The residue was washed by decantation with petroleum ether to remove traces of benzylamine and the petroleum ether removed completely under reduced pressure. To the residue an absolute alcoholic solution of hydrogen chloride was added gradually until the solid completely dissolved. The solution was then reduced to three-fourths of its original volume under reduced pressure (aspirator), without applying heat. If crystallization failed to occur at this point, precipitation of the product was induced by adding gradually anhydrous ether to the ice-cooled solution. The precipitate was filtered off and dried thoroughly under reduced pressure, using no heat. It was recrystallized from absolute alcohol; if no spontaneous crystallization occurred, it was induced with anhydrous ether or petroleum ether. The product was recrystallized twice. White, needle-like microcrystals melting at 193° were obtained, yield 36%.

Anal. Calcd. for $C_{19}H_{23}O_2N_2Cl$: C, 65.80; H, 6.68; N, 8.08; Cl, 10.23. Found: C, 66.35; H, 6.92; N, 7.91; Cl, 10.56.

The compound was very soluble in water, soluble in alcohol, insoluble in ether and petroleum ether.

β,γ-Epoxy-γ'-[β-(3,4-dimethoxyphenyl)-ethylamino]-N-[β-(3,4-dimethoxyphenyl)-ethyl]-isovaleramide Hydrochloride (IV).—The reaction was carried out in the same type of apparatus and under the conditions described in the synthesis of III, using 0.07 mole of freshly distilled I, 0.50 mole of freshly distilled β-(3,4-dimethoxyphenyl)-ethylamine[15] and 1.0 g. of ammonium chloride. Upon cooling it formed a crystalline cake, which was *liquefied* with a 10% solution of sodium carbonate and transferred gradually to a separatory funnel. The viscous dark brown liquid was drawn off and washed twice with large volumes of distilled water. The substance was then dissolved in 300 ml. of absolute alcohol and filtered. The alcohol was removed under reduced pressure (aspirator). The residue was heated in an oil-bath at 150° for 10 minutes at 0.3 mm. pressure, cooled, and washed by decantation twice with anhydrous ether to remove possible traces of unreacted amine. The ether was removed completely under reduced pressure. An absolute alcohol solution of hydrogen chloride was added gradually with agitation to the remaining semi-solid mass, until it was completely dissolved. This material was slow to dissolve and after a short time a crystalline precipitate began to appear, even before all of it had dissolved. The suspension was concentrated under reduced pressure, without heating, to three-fourths of its original volume. The crystalline precipitate was then immediately filtered off, dried under reduced pressure, without heating, and recrystallized thrice from either absolute or 95% alcohol. The needle-like crystals with a grayish tint melted at 191.5°, yield 10%.

Anal. Calcd. for $C_{29}H_{35}O_6N_2Cl$: N, 5.66; Cl, 7.16. Found: N, 5.59; Cl, 7.04.

The compound exhibited similar solubilities to those of III.

α-Methyl-β-hydroxy-γ,γ'-bis-(β-phenylethylamino)-N-(β-phenylethyl)-isovaleramide Dihydrochloride (V).—The procedure in the preparation of this compound was the same as for the synthesis of IV using 0.07 mole of freshly distilled II, 0.50 mole of β-phenylethylamine and 1.0 g. of ammonium chloride. Most of the unreacted amine was removed during the distillation at 0.3 mm. pressure using an oil-bath kept at 140–142°. Petroleum ether was used to wash the cooled residue from this distillation since ether dissolved the product. Crystals of the dihydrochloride did not appear in the acid–alcohol solution. The crude salt, contaminated with β-phenylethylamine hydrochloride, was precipitated from the concentrated solution by the slow addition of anhydrous ether. The product obtained at this point was purified by dissolving it in a minimum volume of hot absolute alcohol, charcoaling, filtering, and, after cooling, adding sufficient anhydrous ethyl acetate to produce a faint but permanent cloud. Upon standing overnight crystals of the hydrochloride of β-phenylethylamine were precipitated. These were removed by filtration. To the filtrate anhydrous ether was added gradually until a cloudiness was produced. Upon standing the desired product precipitated and after drying under reduced pressure, without heating, was recrystallized several times by the same process. The compound was a white microcrystalline powder melting at 152–153°, yield 8%.

Anal. Calcd. for $C_{30}H_{41}O_2N_3Cl_2$: N, 7.69; Cl, 12.97. Found: N, 7.79; Cl, 13.18.

The compound exhibited similar solubilities to those of III. It was slightly soluble in propylene chloride and ethyl acetate.

α-Methyl-β-hydroxy-γ,γ'-bis-[β-(3,4-dimethoxyphenyl)-ethylamino]-N-[β-(3,4-dimethoxyphenyl)-ethyl]-isovaleramide Dihydrochloride (VI).—The procedure in the synthesis and purification of this compound was the same as for the synthesis of IV, using 0.07 mole of freshly distilled II, 0.50 mole of β-(3,4-dimethoxyphenyl)-ethylamine and 1.0 g. of ammonium chloride. The crystallization of the compound was accomplished by the process described in the preparation of compound V. The purification was somewhat less tedious since no perceptible quantity of the hydrochloride of β-(3,4-dimethoxyphenyl)-ethylamine appeared during the crystallization. The white microcrystalline powder melted at 140–141°, yield 6%.

Anal. Calcd. for $C_{36}H_{53}O_8N_3Cl_2$: N, 5.78; Cl, 9.76. Found: N, 5.72; Cl, 9.61.

The compound had solubility characteristics similar to those of V.

Acknowledgment.—The authors wish to thank Drs. E. E. Smissman and H. S. Gutowsky for the infrared analyses.

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(15) Furnished to us through the courtesy of Monsanto Chemical Company, St. Louis, Missouri.