TABLE I

CYANOETHYLATION PRODUCTS OF 2-AMINOETHANETHIOL

pH	Exotherm $^{\circ}_{max}$/min	Product	Yield, %	M.P.[a]
1.5	None	$HCl \cdot H_2NCH_2CH_2SH$[b]	—	69.5–70.3
3.6	36/30	$HCl \cdot H_2NCH_2CH_2SCH_2CH_2CN$	69	81.3–83.1
6.0	52/6	$HCl \cdot H_2NCH_2CH_2SCH_2CH_2CN$	81.4	81.5–83.5
6.8	52/<1	$HCl \cdot H_2NCH_2CH_2SCH_2CH_2CN$	77.8	77.5–78.8
8.8	52/<1	$NCCH_2CH_2SCH_2CH_2NHCH_2CH_2CN \cdot HCl$ $NCCH_2CH_2SCH_2CH_2N(CH_2CH_2CN)_2 \cdot HCl$	82.4[c]	Sirup

[a] All melting points are corrected. [b] Recrystallized from ethanol-ether. [c] Yield calculated as tricyanoethylation product.

ride[6] in 100 ml. of deionized water which had been adjusted to *p*H 6.8 with sodium hydroxide. A strongly exothermic reaction brought the temperature to 52° within 45 sec. After 60 min. the mixture was acidified with hydrochloric acid and vacuum concentrated (90°, 20 mm.) to a sirup. This was treated successively with several portions of ethanol-benzene, with removal of precipitated sodium chloride and further vacuum concentration, to give 50.6 g. (100%) of pale yellow sirup which crystallized on cooling. Recrystallization from ethanol-benzene afforded 38.9 g. (77.8%) of colorless crystals, m.p. 77.5–78.8°.

An analytical sample, m.p. 83.1–83.7°, was obtained after two recrystallizations from ethanol-benzene.

Anal. Calcd. for $C_5H_{11}N_2SCl$: C, 36.03; H, 6.65; N, 16.81. Found: C, 35.96; H, 6.62; N, 16.55.

3-(2-Aminoethylthio)propionic acid hydrochloride. A solution of 33.3 g. (0.2 mole) of 3-(2-aminoethylthio)propionitrile hydrochloride in 50 ml. of concd. hydrochloric acid was heated under reflux for 3 hr. The resulting solution was vacuum concentrated to a sirup which was dissolved in 100 ml. of boiling absolute ethanol. After removal of the precipitated ammonium chloride (9.4 g., 87.8%), the filtrate was again vacuum concentrated. Several successive treatments with ethanol-benzene and, finally, benzene alone gave 36 g. (97.1%) of crude acid, m.p. 116–120°. Recrystallization from ethanol-hexane afforded 27.4 g. (73.8%) of colorless crystals, m.p. 120.5–122.2°.

Analytical material, m.p. 124.7–125.3°, was obtained after two more recrystallizations from ethanol-hexane.

Anal. Calcd. for $C_5H_{12}ClNO_2S$: C, 32.34; H, 6.52; Cl, 19.10. N. 7.55; S, 17.27; Found: C, 32.55; H, 6.72; Cl, 18.83. N, 7.83; S, 17.33.

Hydrolysis of the product from reaction at pH 8.8. A solution of 42.5 g. of the uncrystallizable sirup in 100 ml. of concd. hydrochloric acid was heated under reflux for 4 hr. Upon chilling, 17.9 g. (74.6% of theory for tricyanoethylated product) of ammonium chloride was removed. Vacuum concentration of the filtrate gave 46.9 g. (94.7% of theory for tricarboxylic acid) of uncrystallizable yellow sirup.

Acknowledgment. The authors wish to thank Dr. Julius Kuck and the members of the Microanalytical Laboratory for their contributions.

STAMFORD, CONN.

(6) Obtained from Evans Chemetics, Inc., Waterloo, N. Y.

[CONTRIBUTION FROM THE RADIUM INSTITUTE OF THE UNIVERSITY OF PARIS]

Some Homologs of α,α-Dimethyl-β-phenethylamine

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Received August 18, 1959

A number of homologs of α,α-dimethyl-β-phenethylamine bearing substituents on the aromatic nucleus have been synthesized, starting from the corresponding benzyl chlorides, for investigation of their sympatho-mimetic activity. α,α-Dimethyl-β-(2-chlorophenyl)propionamide has been found to undergo Hofmann degradation to the corresponding symmetrical urea.

β-Arylethylamines containing a quaternary carbon atom *alpha* to the amine radical are interesting sympatho-mimetic substances with a wide range of secondary activities. The naphthyl derivatives, for instance, also possess local anesthetic properties greater than that of cocaine,[1] and *N*-methyl-α,α-dimethyl-β-phenethylamine is a valuable nasal shrinker causing no cerebral stimulation.[2]

It was deemed of interest to prepare a number of new β-arylethylamines for biological investigation, especially those bearing alkyl or halogen substituents on the aromatic nucleus. Recently, α,α-dimethyl-β-(3,4-dimethylphenethyl)amine was prepared in the course of a study of the Bischler-Napieralski reaction;[3] we now record the synthesis of two of its position isomers, starting from the chloromethylation-products of *m*- and *p*-xylene. These underwent Haller condensation[4] with isobutyrophenone in the presence of sodium amide to

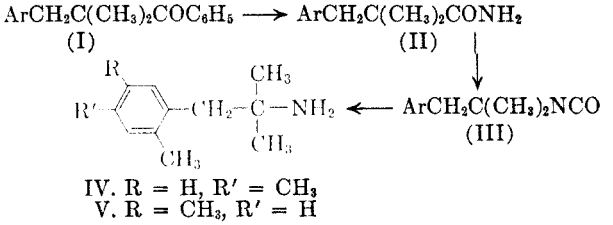
(1) P. Cagniant, C. Mentzer, and N. P. Buu-Hoï, *Bull. Soc. Chim. France*, **10** [5], 145 (1943).

(2) *Cf.* A. Burger, *Medicinal Chemistry*, Interscience Publishers Inc., New York, 1951, p. 311.

(3) N. P. Buu-Hoï, C. T. Long, and N. D. Xuong, *J. Org. Chem.*, **23**, 12 (1958).

(4) A. Haller, *Bull. Soc. Chim. France*, **31**, [4], 1073 (1902).

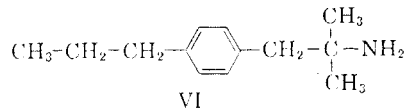
the corresponding α,α-dimethyl-β-*m*- and α,α-dimethyl-β-*p*-xylylpropionylbenzene of general formula I; sodium amide cleavage of these tertiary ketones afforded α,α-dimethyl-β-*m*- and α,α-dimethyl-β-*p*-xylylpropionamide (general formula II), which in turn underwent Hofmann degradation[5] to yield α,α-dimethyl-β-*m*- and α,α-dimethyl-β-*p*-xylylethyl isocyanate (general formula III).



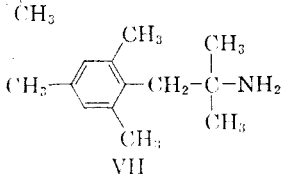
IV. R = H, R′ = CH_3
V. R = CH_3, R′ = H

These esters were readily hydrolyzed by hydrochloric acid to α,α-dimethyl-β-(2,4-dimethylphenethyl)amine (IV) and α,α-dimethyl-β-(2,5-dimethylphenethyl)amine (V).

Two higher homologs of these bases, namely α,α-dimethyl-β-*p*-propylphenethylamine (VI) and α,α-dimethyl-β-(2,4,6-trimethylphenethyl)amine (VII)



VI



VII

were prepared similarly, starting from the chloromethylation-products of propylbenzene and mesitylene. However, a similar synthesis with *o*-chlorobenzyl chloride as starting material was unsuccessful, as the Hofmann degradation of the corresponding propionamide led, not to the expected amine, but to the symmetrical urea (VIII). The formation of this compound is clearly due to a quick reaction between the isocyanate liberated and the amine resulting from its hydrolysis; an earlier example of such a reaction was recorded by Mentzer.[6]

[*o*-Cl-$C_6H_3CH_2C(CH_3)_2NH$]$_2$CO
VIII

The amines described herein are undergoing biological investigation, and results will be reported elsewhere.

EXPERIMENTAL

The experimental work was done with Miss O. Roussel.

Preparation of intermediates. m- and *p*-Xylene were chloromethylated according to the method of von Braun and Nelles,[7] as was propylbenzene (prepared by Kishner-Wolff reduction of propiophenone), which gave a 40% yield of *p-propylbenzyl chloride*, b.p. 205–207°, n_D^{24} 1.5534. Bert[8] reported the preparation of this compound without giving any data. The chloromethylation of mesitylene was performed according to Vavon and Bolle.[9]

Condensation of benzyl chlorides with isobutyrophenone. A solution of isobutyrophenone (0.1 mole) in 225 ml. of anhydrous toluene was refluxed with sodium amide (0.15 mole) for 10 hr.; after cooling, the substituted benzyl chloride (0.1 mole) was added, and refluxing was continued for 18 more hr. After cooling, the reaction mixture was treated with water and acidified with acetic acid, the toluene layer was decanted, washed with water, and dried over sodium sulfate, the solvent was removed, and the residue was vacuum-fractionated. Thus were obtained, in the form of pale yellow oils:

α,α-dimethyl-β-m-xylylpropionylbenzene (70% yield), b.p. 215–217°/25 mm., n_D^{26} 1.5629.

Anal. Calcd. for $C_{19}H_{22}O$: C, 85.7; H, 8.3. Found: C, 85.7; H, 8.2.

α,α-dimethyl-β-p-xylylpropionylbenzene (60% yield), b.p. 197–200°/13 mm., $n_D^{19.5}$ 1.5699.

Anal. Calcd. for $C_{19}H_{22}O$: C, 85.7; H, 8.3. Found: C, 85.9; H, 8.2.

α,α-dimethyl-β-(p-propylphenyl)propionylbenzene (40% yield), b.p. 210–212°/18 mm., n_D^{22} 1.5628.

Anal. Calcd. for $C_{20}H_{24}O$: C, 85.7; H, 8.6. Found: C, 85.4; H, 8.4.

α,α-dimethyl-β-(2,4,6-trimethylphenyl)propionylbenzene (52% yield), b.p. 226–228°/17 mm., n_D^{22} 1.5775.

Anal. Calcd. for $C_{20}H_{24}O$: C, 85.7; H, 8.6. Found: C, 85.3; H, 8.4.

α,α-dimethyl-β-o-chlorophenylpropionylbenzene (60% yield), b.p. 217°/17 mm., n_D^{23} 1.5902.

Anal. Calcd. for $C_{17}H_{17}OCl$: C, 74.9; H, 6.3. Found: C, 74.8; H, 6.2.

Haller cleavages of the propiophenones. A solution of ketone (0.1 mole) in 135 ml. of anhydrous toluene was refluxed with sodium amide (0.15 mole) for 24 hr., and the cooled reaction mixture was treated with water. The toluene solution was decanted, washed with water, and dried over sodium sulfate, the solvent was distilled off, and the residue was vacuum-fractionated. The following substances were obtained:

α,α-dimethyl-β-m-xylylpropionamide (60% yield), b.p. 205°/21 mm., needles (from petroleum ether), m.p. 56°.

Anal. Calcd. for $C_{13}H_{19}NO$: C, 76.1; H, 9.3; N, 6.8. Found: C, 76.2; H, 9.0; N, 7.0.

α,α-dimethyl-β-p-xylylpropionamide (85% yield), b.p. 196–198°/15 mm., leaflets (from petroleum ether), m.p. 60°.

Anal. Calcd. for $C_{13}H_{19}NO$: C, 76.1; H, 9.3; N, 6.8. Found: C, 75.9; H, 9.1; N, 6.9.

α,α-dimethyl-β-p-propylphenylpropionamide (45% yield), b.p. 206–208°/18 mm., n_D^{24} 1.5644, leaflets (petroleum ether), m.p. 43°.

Anal. Calcd. for $C_{14}H_{21}ON$: C, 76.7; H, 9.7; N, 6.4. Found: C, 76.5; H, 9.4; N, 6.3.

α,α-dimethyl-β-(2,4,6-trimethylphenyl)propionamide (60% yield), b.p. 207–208°/12 mm., n_D^{24} 1.5569.

Anal. Calcd. for $C_{14}H_{21}ON$: C, 76.7; H, 9.7; N, 6.4. Found: C, 76.8; H, 9.6; N, 6.7.

α,α-dimethyl-β-o-chlorophenylpropionamide (40% yield), b.p. 193–195°/14 mm., colorless prisms (cyclohexane), m.p. 76°.

Anal. Calcd. for $C_{11}H_{14}ONCl$: C, 62.4; H, 6.7. Found: C, 62.3; H, 6.6.

Hofmann degradation of the propionamides. An ice cold solution of potassium hypobromite (prepared from 25 g. of potassium hydroxide and 11 g. of bromine in 100 ml. of water) was shaken with the propionamide (0.05 mole) until two phases had formed (15 min.); the reaction product was

(5) *Cf.* M. Montagne and M. Casteran, *Compt. rend.*, 191, 139 (1930).
(6) C. Mentzer, *Compt. rend.*, **213**, 581 (1941).
(7) J. von Braun, *Ber.*, **67**, 1094 (1934).
(8) L. Bert, *Compt. rend.*, **186**, 373 (1928).
(9) G. Vavon and C. Bolle, *Compt. rend.*, **204**, 1826 (1937).

then taken up in ether, the ethereal solution washed with a few ml. of water and dried over sodium sulfate, the ether distilled, and the residue vacuum-fractionated. The following isocyanates were obtained, as colorless, pleasant-smelling oils:

α,α-dimethyl-β-m-xylylethyl isocyanate (46% yield), b.p. 151–152°/20 mm., n_D^{22} 1.5158.

Anal. Calcd. for $C_{13}H_{17}NO$: N, 6.9. Found: N, 6.5.

α,α-dimethyl-β-p-xylylethyl isocyanate (51% yield), b.p. 149–151°/20 mm., n_D^{22} 1.5172.

Anal. Calcd. for $C_{13}H_{17}NO$: N, 6.9. Found: N, 6.6.

α,α-dimethyl-β-(p-propylphenyl)ethyl isocyanate (47% yield), b.p. 145–147°/13 mm., n_D^{22} 1.5108.

Anal. Calcd. for $C_{14}H_{19}NO$: N, 6.5. Found: N, 6.2.

α,α-dimethyl-β-(2,4,6-trimethylphenyl)ethyl isocyanate (49% yield), b.p. 146–149°/13 mm.

Anal. Calcd. for $C_{14}H_{19}NO$: N, 6.5. Found: N, 6.2.

Hydrolysis of the isocyanates. The isocyanates (0.1 mole) were hydrolyzed by stirring on a water bath with a large excess of concd. hydrochloric acid (400 ml.), the reaction being manifest by a more or less rapid evolution of carbon dioxide. When this had terminated, the mixture was boiled until a totally limpid liquid was obtained; on cooling, water (250 ml.) was added, the liquid was made basic with 30% aqueous sodium hydroxide, and the reaction product was taken up immediately in ether. The ethereal solution was then washed with a minimum of water and dried over sodium sulfate, the solvent was removed, and the residue was vacuum-fractionated. The yields ranged from 30 to 88%. The following amines were obtained, as colorless oils, together with their hydrochlorides (prepared by saturating with hydrogen chloride a solution of the amine in ether, and crystallization of the precipitate from ethanol + benzene):

α,α-dimethyl-β-(2,4-dimethylphenethyl)amine (IV), b.p. 132–133°/22 mm., n_D^{20} 1.5231.

Anal. Calcd. for $C_{12}H_{19}N$: C, 81.3; H, 10.8; N, 7.9. Found: C, 81.3; H, 10.6; N, 7.9.

Hydrochloride, colorless needles, m.p. 209° (sublimation above 170°).

Anal. Calcd. for $C_{12}H_{20}ClN$: Cl, 16.6; N, 6.6. Found: Cl, 16.8; 6.8.

α,α-dimethyl-β-(2,5-dimethylphenethyl)amine (V), b.p. 118°/15 mm., $n_D^{21.5}$ 1.5246.

Anal. Calcd. for $C_{12}H_{19}N$: C, 81.3; H, 10.8; N, 7.9. Found: C, 81.3; H, 10.8; N, 7.9.

Hydrochloride, m.p. 230°.

Anal. Calcd. for $C_{12}H_{20}ClN$: Cl, 16.6; N, 6.6. Found: Cl, 16.5; N, 6.4.

α,α-dimethyl-β-p-propylphenethylamine (VI), b.p. 123–125°/14 mm., n_D^{22} 1.5182.

Anal. Calcd. for $C_{13}H_{21}N$: C, 81.6; H, 11.1; N, 7.3. Found: C, 81.4; H, 10.9; N, 7.1.

Hydrochloride, m.p. 217° (sublimation above 166°).

Anal. Calcd. for $C_{13}H_{22}ClN$: Cl, 15.6; N, 6.2. Found: Cl, 15.5; N, 6.0.

α,α-dimethyl-β-(2,4,6-trimethylphenethyl)amine (VII), b.p. 130–131°/14 mm.

Anal. Calcd. for $C_{13}H_{21}N$: C, 81.6; H, 11.1; N, 7.3. Found: C, 81.6; H, 10.9; N, 7.2.

Hydrochloride, m.p. 214° (sublimation above 175°).

Anal. Calcd. for $C_{13}H_{22}ClN$: Cl, 15.6; N, 6.2. Found: Cl, 15.8; N, 5.9.

N,N'(α,α-dimethyl-β-o-chlorophenethyl)urea (VIII). This compound was obtained as the sole product from the hydrolysis of the corresponding isocyanate, and crystallized from benzene in shiny colorless prisms, m.p. 224°.

Anal. Calcd. for $C_{21}H_{26}Cl_2N_2$: C, 64.1; H, 6.7; N, 7.1. Found: C, 64.1; H, 6.8; N, 7.0.

Acknowledgment. The authors thank the "Institut de Sérothérapie Hémopoïétique" and Dr. D. Sénac (Paris) for financial help.

PARIS (V^e), FRANCE

[CONTRIBUTION FROM THE ORGANIC CHEMICALS DIVISION, ST. LOUIS RESEARCH DEPARTMENT, MONSANTO CHEMICAL CO.]

N-Substituted Glycinate and Alaninate Esters

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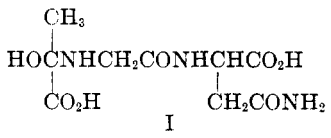
Received October 23, 1959

N-Substituted glycinate and α- and β-alaninate esters were prepared as possible antimetabolites for the control of *Fusarium* wilt diseases. Some qualitative results are presented on the relative ease of displacement of the α-halogen atom and aminolysis of the ester group in the reaction of haloacetate esters with primary aliphatic amines.

The pathogenicity of *Fusarium lycopersici* has been attributed to one of its metabolic products, lycomarasmin (I). Tomato wilt, an important economic plant disease, is caused by this organism. The toxic effects of I are also reproduced by the synthetic peptide serylglycylasparatic acid and reversed by serylglycylglutamic acid.[1]



I

Since lycomarasmin is a tripeptide composed of asparagine, glycine, and α-hydroxyalanine units, it was felt that antimetabolites for the control of wilt diseases[2] might be found in *N*-substituted glycinates and alaninates. These amino acid derivatives might prevent the formation of the toxic agent, lycomarasmin. Growth inhibition of the fungus would also result if the biosynthesis of the tripeptide were essential to the *Fusarium* organism.

N-Substituted glycinates have been prepared by the alkylation of amines with haloacetates,[3] by reductive alkylation of aldehydes and ketones with

(1) J. W. Foster, *Chemical Activities of Fungi*, Academic Press Inc., New York, N. Y., 1949, p. 494.

(2) *Plant Diseases, The Year Book of Agriculture*, U. S. Dept. of Agriculture, Washington, D. C., 1953.