bamates or 1-anilinoalkyl-1,3,3-trimethylureas, were present. These were then characterized by distillation or preparation of the picrate salt.

For the sake of clarity in reading Table IV, the following assignments have been made based on type of compound cyclized:

Method E. Ethyl *N*-(Methylaminoalkyl)carbanilates.

Method F. 1-(Methylaminoalkyl)-3,3-dimethyl-1-phenylureas.

Method G. 1-(2-Anilinoethyl)-1-methylureas.

Method H. 1-(Anilinoalkyl)-1,3,3-trimethylureas.

Cyclization of 1,1 - dimethyl - 3 - (1 - methyl - 2 - methylaminoethyl)-3-phenylurea hydrochloride. Method I. A mixture of 1.0 g. of 1,1-dimethyl-3-(1-methyl-2-methylaminoethyl)-3-phenylurea hydrochloride and 50 ml. of ethyl acetate was heated under reflux for 3 hr., cooled, and filtered. The insoluble material was dimethylamine hydrochloride, 278 mg. (93%). The mother liquor was concentrated to remove volatile material. The residue was an oil, 700 mg. (100%), n_D^{25} 1.565, which gave an infrared absorption spectrum essentially identical to that of analytically pure, distilled 1,4-dimethyl-3-phenyl-2-imidazolidinone. Other experiments indicated that cyclization was complete in 50–60 min.

1,1 - Dimethyl - 3 - (2-methylaminoethyl)-3-phenylurea hydrochloride was cyclized as described above. The cyclization was complete in 3 hr. but incomplete in 2 hr. 1,1-Dimethyl-3-(3-methylaminopropyl)-3-phenylurea hydrochloride and ethyl *N*-(2-methylaminoethyl)carbanilate hydrochloride were recovered (91–97%) unchanged after 18 hr. under reflux in ethyl acetate.

Acknowledgment. We wish to thank Mr. L. Brancone and associates for the microanalyses, Mr. W. Fulmor and co-workers for some of the infrared absorption data, and Dr. H. G. Arlt and associates for the preparation of some of the intermediates.

PEARL RIVER, N. Y.

[CONTRIBUTION FROM THE ORGANIC CHEMICAL RESEARCH SECTION, LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID CO.]

Debenzylation of Tertiary Benzylamines with Ethyl Chloroformate[1]

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When ethyl *N*-(2-benzylmethylaminoethyl)carbanilate (I) (which was desired for testing in our analgesic program[2]) was prepared by the reaction of *N*-benzyl-*N*-methyl-*N'*-phenylethylenediamine (II) with excess ethyl chloroformate under reflux in benzene, a crude product was obtained which distilled over a wide temperature range. Purification by an acid/ether extraction procedure afforded two products. Examination of the infrared absorption spectra showed that both of these compounds had the expected carbonyl band at 5.87 μ, but only one (I) had a band in the 3.6 μ region (3.58 μ). This latter band is a characteristic of secondary and tertiary alkylamines[3] and is generally strong with dialkylbenzylamines. The conclusion that debenzylation had occurred and diethyl *N*-[2-(*N*-carboxy-*N*-methylamino)ethyl]carbanilate (IIIa) had been formed was confirmed by microanalysis. IIIa was also prepared by the reaction of I with ethyl chloroformate. Additional evidence for this structure was obtained by the hydrobromic acid-acetic acid hydrolysis of the analogous diethyl *N*-[2-(*N*-carboxy-*N*-methylamino)ethyl]-*m*-chlorocarbanilate (IIIb) to *N*-(*m*-chlorophenyl)-*N'*-methylethylenediamine (IV) identical to the compound prepared by the reaction of *m*-chloroaniline with 2-chloro-*N*-methylethylamine hydrochloride.

Other compounds, analogous to those described above, have been prepared by these procedures and are characterized in Tables I and II.

The cleavage of tertiary amines by chloroformates has been described in the literature as a means of preparing carbamates,[4] for the opening of tetrahydroisoquinoline ring systems,[5] and in the preparation of derivatives of des-*N*-methylerythromycin.[6] We were unaware of any reference to chloroformates as specific reagents for the debenzylation of tertiary benzylamines, and two additional experiments designed to further study the scope of this reaction, therefore, seemed worthwhile.

Dimethylbenzylamine and 1-benzylpiperidine were each heated under reflux in benzene with 1.5 moles of ethyl chloroformate. After removal of the solvent, the crude reaction mixtures were found to have infrared curves and refractive indices almost identical to those of synthetic mixtures of equal molar quantities of benzyl chloride and the expected carbamate. Gas phase chromatography gave similar results. These data indicated that the benzyl group was preferentially removed as benzyl chloride and that very little cleavage of the methyl groups or the piperidine ring occurred under these conditions.

The debenzylation of tertiary benzylamines can be explained by the intermediate formation of a quaternary urethane salt (V) followed by the loss of the benzyl carbonium ion. Similar mechanisms have been postulated for the cleavage of tertiary amines by carbamates,[4] acids, acid chlorides, acid

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(1) Presented in part at the Frederick F. Blicke Symposium of the Division of Medicinal Chemistry at the 138th National Meeting of the American Chemical Society, New York, N. Y., September 1960.

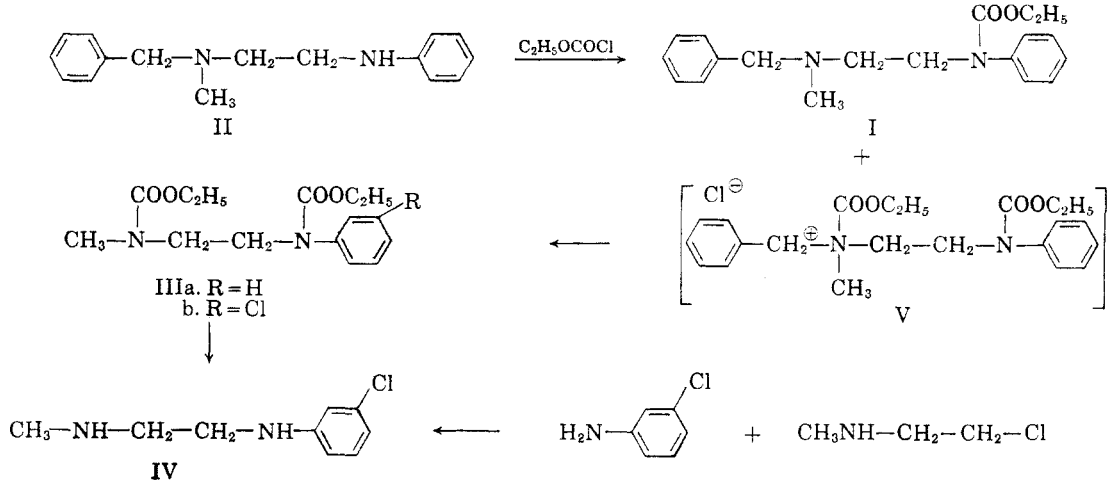
(2) W. B. Wright, Jr., H. J. Brabander, and R. A. Hardy, Jr., *J. Org. Chem.*, 26, 485 (1961).

(3) W. B. Wright, Jr., *J. Org. Chem.*, 24, 1362 (1959).

(4)(a) F. Bayer and Co., Ger. Patent 255,942 (1911); (b) J. A. Campbell, *J. Org. Chem.*, 22, 1259 (1957).

(5)(a) J. Gadamer and F. Knoch, *Arch. Pharm.*, 259, 135 (1921); (b) F. v. Bruchhausen and J. Knabe, *Arch. Pharm.*, 287, 601 (1954).

(6)(a) E. H. Flynn, M. V. Sigal, Jr., P. F. Wiley, and K. Gerzon, *J. Am. Chem. Soc.*, 76, 3121 (1954); (b) E. H. Flynn, H. W. Murphy, and R. E.McMahon, *J. Am. Chem. Soc.*, 77,3104 (1955).



anhydrides, and phosgene.[7] The preferential removal of the benzyl group would be predicted in view of the resonance stabilization of the benzyl carbonium ion.

EXPERIMENTAL

The members of each class of compounds were prepared by essentially the same method, and general procedures are therefore described where possible. Physical constants and analyses are recorded in Tables I and II. Temperatures reported in this paper are uncorrected.

N-Benzyl-N-methyl-N'-phenylethylenediamines. These compounds were prepared by the reaction of *N*-(2-chloroethyl)-*N*-methylbenzylamine hydrochloride with the substituted aniline.[2] Some of the diamine intermediates used have been previously described[2] and are therefore not listed in Table I.

Ethyl N-(2-benzylmethylaminoethyl)carbanilates. A solution of 0.15–0.3 mole of ethyl chloroformate in 50 ml. of benzene was added in the cold to a solution of 0.1 mole of the *N*-benzyl-*N*-methyl-*N'*-phenylethylenediamine in 75 ml. of benzene. The reaction mixture was heated under reflux for 5–18 hr. and then cooled and extracted with 100 ml. of 0.5*N* hydrochloric acid. The aqueous layer was extracted once with ether and the organic layers were combined and set aside (see below). The aqueous layer was made basic by the addition of 50 ml. of 5*N* sodium hydroxide, and the oil which separated was extracted into ether and distilled.

Diethyl N-[2-(N-carboxy-N-methylamino)ethyl]carbanilates. Method A. From N-benzyl-N-methyl-N'-phenylethylenediamines. The organic layers (see above paragraph) were washed with saturated salt solution, dried over magnesium sulfate, and distilled.

Method B. Diethyl N-[2-(N-carboxy-N-methylamino)ethyl] carbanilate (IIIa) *from ethyl N-(2-benzylmethylaminoethyl)-carbanilate* (I). A mixture of 6.3 g. (0.02 mole) of ethyl *N*-(2-benzylmethylaminoethyl)carbanilate, 2.1 ml. (0.022 mole) of ethyl chloroformate, and 20 ml. of benzene was heated at reflux for 18 hr. The cooled reaction mixture was extracted with 25 ml. of 1*N* hydrochloric acid and then with salt solution. The organic layer was dried over magnesium sulfate and distilled.

Preparation of N-methyl-N'-phenylethylenediamine dihydrobromides by hydrolysis of the diethyl N-[2-(N-carboxy-N-methylamino)ethyl]carbanilates. A mixture of 5 g. of the diethyl *N*-[2-(*N*-carboxy-*N*-methylamino)ethyl]carbanilate, 50 ml. of 48% hydrobromic acid, and 50 ml. of acetic acid was heated at reflux for 24 hr. The reaction mixture was concentrated to remove volatile materials, and the residue was recrystallized from ethanol by addition of ether.

Preparation of N-(m-chlorophenyl)-N'-methylethylenediamine (IV) *dihydrobromide from m-chloroaniline and 2-chloro-N-methylethylamine hydrochloride.* A mixture of 97.5 g. (0.75 mole) of 2-chloro-*N*-methylethylamine hydrochloride, 191 g. (1.5 moles) of *m*-chloroaniline, and 500 ml. of toluene was heated at reflux for 16 hr. and cooled. The mixture was stirred with 500 ml. of water and made strongly basic by the addition of 50% sodium hydroxide. The layers were separated and the aqueous layer was extracted with benzene. The organic layers were combined, dried over magnesium sulfate, and distilled *N*-(*m*-Chlorophenyl)-*N'*-methylethylenediamine, b.p. 100–110°/0.3 mm., was obtained in 66% yield.

Anal. Calcd. for $C_9H_{13}ClN_2$: C, 58.5; H, 7.1; Cl, 19.2; N, 15.2. Found: C, 58.3; H, 7.4; Cl, 19.0; N, 15.4.

Two grams of the above base was added to 12 ml. of 2*N* alcoholic hydrogen bromide, and the solution was diluted with ether and cooled. The crystalline product was filtered, washed with ether, and dried in a desiccator. The yield of the dihydrobromide, m.p. 198–200°, was 84%. The mixture melting point with a sample of the product prepared by the hydrolysis of diethyl *N*-[2-(*N*-carboxy-*N*-methylamino)-ethyl]-*m*-chlorocarbanilate was not depressed.

The reaction of 1-benzylpiperidine with ethyl chloroformate. A mixture of 7.0 g. (0.04 mole) of 1-benzylpiperidine, 4.8 ml. (0.05 mole) of ethyl chloroformate and 25 ml. of benzene was heated at reflux for 18 hr. The reaction mixture was cooled, diluted with 50 ml. of ether, and stirred for 10 min. with 25 ml. of 2*N* sodium hydroxide. The layers were separated and the aqueous layer was extracted twice with ether. The combined organic layers were extracted twice with 10-ml. portions of 2*N* hydrochloric acid and once with saturated salt solution, dried over magnesium sulfate, and concentrated to a residue of 11.0 g., n_D^{25} 1.491. This represents a 96% yield of benzylchloride and 1-carbethoxypiperidine. An equimolar mixture, n_D^{25} 1.492, of known 1-carbethoxypiperidine and benzyl chloride had an infrared absorption curve very similar to that of the above crude product.

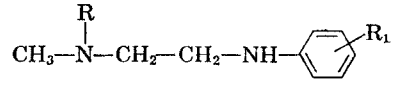
These mixtures and the pure expected products were examined in the Perkin Elmer vaporfractometer (Model 154C). A 1-m. silicone GE SF 96 column at 140° was used. Separation of components was excellent and it was concluded that the crude product was a mixture of about equal molar amounts of benzyl chloride and 1-carbethoxypiperidine.

The reaction of dimethylbenzylamine with ethyl chloroformate. Reaction of 5.4 g. (0.04 mole) of dimethylbenzylamine, 4.8 ml. (0.05 mole) of ethyl chloroformate, and 25 ml. of benzene as described above produced 8.0 g. of crude product.

(7) Methods for the cleavage of tertiary amines have been reviewed in Houben-Weyl, *Methoden der Organischen Chemie*, Thieme, Stuttgart, 1957, Vol. XI, Part 1, p. 985.

TABLE I

N-METHYL-*N'*-PHENYLETHYLENEDIAMINE DERIVATIVES

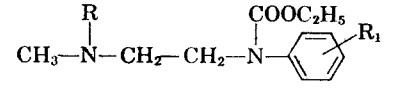


R	R_1	Yield, %[a]	B.p., (mm.)	n_D^{25}	2 HBr M.P.	Formula	Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Bromine Calcd.	Bromine Found	Chlorine Calcd.	Chlorine Found	Nitrogen Calcd.	Nitrogen Found
H	*m*-Cl	69			199–201	$C_9H_{15}Br_2ClN_2$	31.2	30.9	4.4	4.5	46.1	46.4	10.2	10.1	8.1	8.0
H	*p*-Cl	70			206–208	$C_9H_{15}Br_2ClN_2$	31.2	31.4	4.4	4.5	46.1	46.3	10.2	10.6	8.1	8.1
H	*m*-Br	51			205–207	$C_9H_{15}Br_3N_2$	27.6	28.0	3.9	3.6	61.3	61.3			7.2	7.4
H	*m*-OH[b]	30			198–200	$C_9H_{16}Br_2NO$	32.9	32.2	4.3	5.0	48.7	48.3			8.5	8.6
Benzyl	*p*-Cl	44	165–170 (0.2)	1.581		$C_{16}H_{19}ClN_2$	69.9	69.7	7.0	7.3			12.9	13.0	10.2	10.3
Benzyl	*m*-Br	35[c]	180–190 (0.4)	1.600		$C_{16}H_{19}BrN_2$	60.2	59.6	6.0	6.3	25.0	23.4			8.8	8.6
Benzyl	*p*-OCH_3	56[c]	160–170 (0.2)	1.571		$C_{17}H_{22}N_2O$	75.5	74.2	8.2	8.3					10.4	10.2
Benzyl	*m*-CH_3	74	162–165 (0.4)	1.567		$C_{17}H_{22}N_2$	80.3	80.5	8.7	9.0					11.0	11.1

[a] Distilled base or purified salt. [b] Prepared from diethyl *N*-(*N*-carboxy-*N*-methylaminoethyl)-*m*-methoxycarbanilate. [c] Used without further purification.

TABLE II

CARBANILIC ACID DERIVATIVES



R	R_1	Yield, %[a]	B.p., (mm.)	n_D^{25}	Formula	Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Halogen Calcd.	Halogen Found	Nitrogen Calcd.	Nitrogen Found
Benzyl	H	62[b]	165–170 (0.4)	1.543	$C_{19}H_{24}N_2O_2$	73.0	73.0	7.7	7.8			9.0	9.0
Benzyl	*p*-Cl	38[b]	170–180 (0.2)	1.550	$C_{19}H_{23}ClN_2O_2$	65.8	66.2	6.7	6.9	10.2	10.8	8.1	8.2
Benzyl	*m*-OCH_3	46[b]	170–175 (0.1)	1.544	$C_{20}H_{26}N_2O_3$	70.2	70.3	7.7	7.8			8.2	8.4
Benzyl	*p*-OCH_3	16[c]	180–190 (0.2)	1.549	$C_{20}H_{26}N_2O_3$	70.2	70.2	7.7	8.0			8.2	8.4
Benzyl	*m*-CH_3	22[c]	176–180 (0.9)	1.541	$C_{20}H_{26}N_2O_2$	73.6	73.9	8.0	8.4			8.6	8.7
$COOC_2H_5$	H	48,[b] 66[d]	142–146 (0.2)	1.509	$C_{15}H_{22}N_2O_4$	61.2	61.2	7.5	7.7			9.5	9.3
$COOC_2H_5$	*p*-Cl	50,[b] 76[c]	158–165 (0.2)	1.516	$C_{15}H_{21}ClN_2O_4$	54.8	54.9	6.4	6.7	10.8	10.3	8.5	8.5
$COOC_2H_5$	*m*-Cl	75[c]	158–163 (0.1)	1.516	$C_{15}H_{21}ClN_2O_4$	54.8	54.9	6.4	6.6	10.8	10.8	8.5	8.5
$COOC_2H_5$	*m*-Br	74[c]	170–175 (0.2)	1.535	$C_{15}H_{21}BrN_2O_4$	48.3	49.8[e]	5.7	5.7	21.4	21.5	7.5	7.1
$COOC_2H_5$	*m*-OCH_3	25[b]	160–165 (0.1)	1.514	$C_{16}H_{24}N_2O_5$	59.2	59.5	7.5	7.5			8.6	8.9
$COOC_2H_5$	*p*-OCH_3	63[c]	168–172 (0.3)	1.508	$C_{16}H_{24}N_2O_5$	59.2	59.3	7.5	7.7			8.6	8.6
$COOC_2H_5$	*m*-CH_3	46[c]	148–152 (0.3)	1.504	$C_{16}H_{24}N_2O_4$	62.3	62.8	7.9	8.0			9.1	8.8

[a] Prepared by Method A, unless otherwise noted. [b] Ethyl chloroformate/amine = 1.5. [c] Ethyl chloroformate/amine = 3.0. [d] Prepared by Method B. [e] Redistillation did not improve analysis.

n_D^{25} 1.479, equivalent to an 81% yield of benzyl chloride and ethyl dimethylcarbamate. This crude mixture was very similar to an equimolar mixture, n_D^{25} 1.475, of known ethyl dimethylcarbamate and benzyl chloride, when examined in the vaporfractometer and by comparison of infrared absorption curves. These compounds were further identified by comparing the infrared absportion curves of the products of fractional distillation with known standards.

Acknowledgment. We are indebted to Mr. L. Brancone and associates for the microanalyses, to Mr. W. Fulmor and coworkers for the infrared absorption data, and to Mr. A. Mistretta for the chromatography.

PEARL RIVER, N. Y.

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

Stereospecific Synthesis of A Reserpine Analog[1a,b]

PAUL B. LE VINE AND JAMES E. GEARIEN

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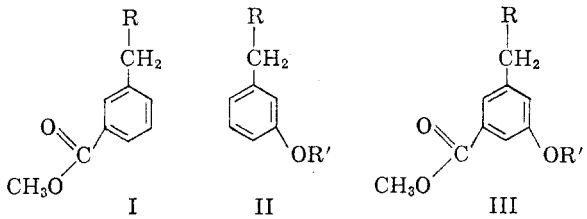
The stereospecific synthesis of *cis*-*N*-(3-hydroxycyclohexylmethyl)-β-phenylethylamine hydrochloride is described. This compound may be considered to be an analog of reserpine which contains ring E and a part of rings C and D of the naturally occurring alkaloid. The substituents on the cyclohexyl ring have similar configuration to those found in the reserpine molecule.

The discovery by Miller and Weinberg[2] that the γ-diethylaminopropyl ester of 3,4,5-trimethoxybenzoic acid possesses tranquillizing properties may indicate that the indole ring system of the reserpine molecule is not necessary for its pharmacological activity. Earlier attempts in this laboratory to prepare reserpine analogs[3] without the indole ring system resulted in three series of compounds that were devoid of biological activity. These compounds, which may be considered to contain the E ring and a portion of the D and C rings of the reserpine molecule were methyl 3-(*N*-substituted aminomethyl)benzoates (I), 3-(*N*-substituted aminomethyl)phenylacetates (*II*), and methyl 3-acetoxy-5-(*N*-substituted aminomethyl)benzoates (III).



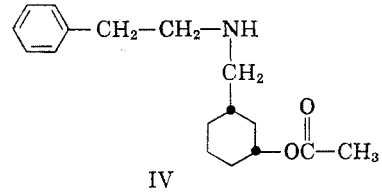
I II III

R = Piperidino or diethylamino
R′ = Acetyl, benzoyl or 3,4,5-trimethoxybenzoyl

While these compounds resemble a portion of the reserpine molecule, the ring is aromatic, while the E ring of reserpine is not. Furthermore, the substituents on the ring of the synthetic compounds are planar with the ring while the substituents on the E ring of reserpine have been shown to be present in the *cis* configuration. Since the carbon to carbon bonds of the aliphatic chain of β-diethylaminopropyl-3,4,5-trimethoxybenzoate possess free rotation, the compound could assume any spacial arrangement necessary for tranquillizing activity.

In order to evaluate the importance of stereochemical configuration upon the pharmacological activity of reserpine analogs of this type, it appeared desirable to investigate possible synthetic approaches to reserpine analogs similar to compound II in which the ring is cyclohexyl and whose substituents are in the *cis* configuration.

This report describes the stereospecific synthesis of *cis*-*N*-(3-acetoxycyclohexylmethyl)-β-phenylethylamine hydrochloride (IV).



IV

For this synthesis it appeared logical to utilize as the starting compound the lactone of 3-hydroxycyclohexanecarboxylic acid. This compound not only possessed the proper configuration but had functional groups capable of undergoing the necessary chemical reactions without inversion or epimerization. The desired lactone was prepared by heating *cis* 3-hydroxycyclohexanecarboxylic acid. 3-Hydroxycyclohexanecarboxylic acid was conveniently synthesized from 3-hydroxybenzoic acid which was prepared by the fusion of 3-sulfobenzoic acid with sodium hydroxide.[4] The catalytic hydrogenation of this compound to 3-hydroxycyclohexanecarboxylic acid with Raney Nickel at high temperatures and pressures has been reported to yield

(1)(a) Presented at the Frederick F. Blicke Symposium of the Division of Medicinal Chemistry at the 138th National Meeting of the American Chemical Society, New York, N. Y., September, 1960. (b) This paper comprises a portion of a thesis presented by Paul B. LeVine in partial fulfillment of the requirements for the M.S. degree at the University of Illinois.

(2) F. M. Miller and M. S. Weinberg, Abstract of Papers, 130th Meeting, American Chemical Society, Atlantic City, N. J., Sept. 16–21 (1956).

(3) F. A. Turner and J. E. Gearien, *J. Org. Chem.*, 24, 1952 (1959).

(4) D. A. Shirley, *Preparation of Organic Intermediates*, p. 251, Wiley, New York, 1951.