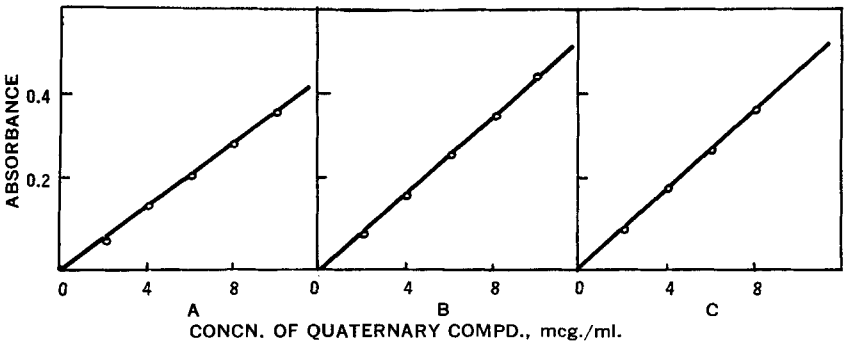

Fig. 2.—Standard curves of quaternary ammonium compound – picric acid complex. Key: A, benzethonium chloride; B, cetylpyridinium chloride; C, benzalkonium chloride.

TABLE I.—ANALYSIS OF KNOWN SAMPLES

Components	Concn.	% Recovered
Benzalkonium chloride	1:5,000	100.2
	1:10,000	99.0
	1:100,000	95.5
Benzethonium chloride	1:5,000	99.5
	1:10,000	100.4
	1:100,000	99.2
Cetylpyridinium chloride	1:1,000	100.2
	1:5,000	100.1
	1:10,000	102.0

the chloroform phase along with the QAC–picric acid complex.

Satisfactory data were obtained under these conditions, and the absorbance of the QAC–picric acid complex was found to be linear with respect to QAC concentration as shown in Fig. 2. These plots were used for determination of the unknown concentration throughout this investigation. The plot of absorbance as a function of concentration of QAC passed through the origin, indicating complete extraction of the QAC–picric acid complex by the chloroform in this procedure.

Table I shows the quantitative recovery of several QAC in the concentration ranges normally employed in pharmaceutical dosage forms. The good reproducibility obtained indicates that this method is reliable even in concentrations as low as 1:100,000. Table II lists data representing an average of three determinations of each dosage form performed on commercial formulations, again indicating the applicability of this method to various preparations.

TABLE II.—ANALYSIS OF COMMERCIAL FORMULATIONS

Items	QAC Concn.	% Recovered
Throat lozenges[a]	Cetylpyridinium chloride, 1:1,500	101 ± .9
Mouthwash[a]	Cetylpyridinium chloride, 1:4,000	103 ± 1.5
OTC soln.[b]	Benzethonium chloride, 0.02%	102 ± 0.5
Benzalkonium chloride ophth. soln.[c]	Benzalkonium chloride, 1:10,000	90 ± 2
Ophth. soln.[d]	Benzalkonium chloride, 0.02%	78 ± 3

[a] The Wm. S. Merrell Co. [b] Wampole Laboratories. [c] College of Pharmacy, University of Iowa. [d] Madland Laboratories.

Although only three QAC and a limited number of commercial formulations were investigated, the data presented do indicate that the method would be adaptable to other QAC and other formulations containing this type preservative.

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Amino Acid Derivatives of Aminosalicylic Acids

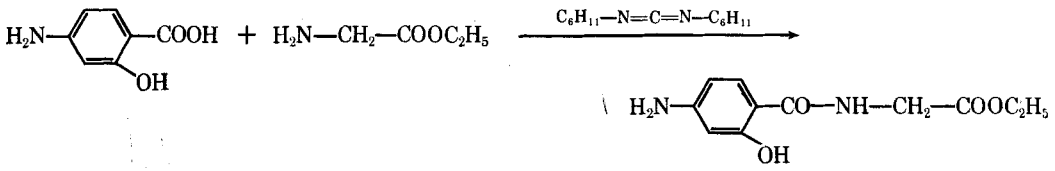
By W. HOEK, J. EBELS, and J. STRATING

A simple method for the synthesis of *p*-aminosalicylglycine ester is given.

To test the antitubercular effect of amino acid derivatives from aminosalicylic acids, Foye and Hull (1) prepared a number of these peptide-like derivatives of 3-, 4-, and 5-aminosalicylic acids with α-amino acids. A simpler method of synthesis became available when Sheehan and Hess (2) introduced dicyclohexyl carbodiimide as a condensation agent for the formation of peptide bonds.

For a research project of the Laboratory of Pharmacotherapy and Pharmaceutical Compounding, University of Groningen, involving the estimation of *p*-aminosalicylic acid and its metabolites

Received June 7, 1965, from the Department of Organic Chemistry, Rijks-Universiteit Groningen, The Netherlands. Accepted for publication July 14, 1965.



Scheme I

(one of them is the prepared derivative) in blood serum as a consequence of the application of *p*-aminosalicylic acid derivatives to patients, the availability of *p*-aminosalicylglycine ester was necessary.

This compound, which is only described by Foye and Hull (1) as its benzyl ether derivative, can easily be obtained from 4-aminosalicylic acid (PAS) and aminoacetic ethyl ester by using dicyclohexylcarbodiimide as a condensing agent (3). (Scheme I.)

The desired amine, isolated as its hydrochloric acid salt, is a hygroscopic but stable compound. The product gave a correct elemental analysis and showed a positive test for an aromatic amine (coupling of the diazonium salt with β-naphthol).

Chromatography on Whatman No. 4 paper, with butanol–acetic acid–water, showed one spot with $R_f = 0.5$. Some tailing, probably due to hydrolysis of the hydrochloric acid salt, was observed.

It is clear that this method can in principle be extended to the preparation of other amino acid esters.[1]

[1] One of the referees pointed out that the 5-aminosalicylic acid derivatives are rapidly converted to quinonimines and that suitable protection should be taken in this series.

EXPERIMENTAL

To a solution of 7.3 Gm. (0.071 mole) of aminoacetic ester and 10.7 Gm. (0.070 mole) of *p*-aminosalicylic acid in a mixture of 45 ml. of dimethylformamide and 20 ml. of acetonitrile, 18 Gm. (0.085 mole) of dicyclohexylcarbodiimide was added. After 24 hr., the reaction mixture was acidified with 2 ml. of acetic acid and the precipitated dicyclohexylurea filtered off; yield, 11.3 Gm. = 70%.

The filtrate was immediately treated with an excess of absolute ether saturated with gaseous hydrochloric acid. After decanting the supernatant liquid, the residue was dissolved in absolute ethanol and precipitated with absolute ether. After drying in vacuum over potassium hydroxide, 12.0 Gm. (63%) of a slightly colored product was collected which softened at about 90° and decomposed at about 110°.

Anal.—Calcd. for $C_{11}H_{14}N_2O_4$: C, 48.09; H, 5.51; Cl, 12.90. Found: C, 48.1; H, 5.9; Cl, 13.1.

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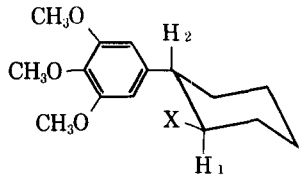
cis- and *trans*-2-(3,4,5-Trimethoxyphenyl)cyclohexylamine

By WILLIAM F. TRAGER* and ALAIN C. HUITRIC

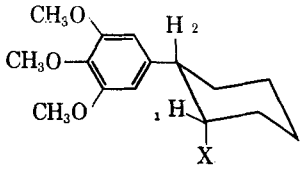
trans- and _cis_-2-(3,4,5-Trimethoxyphenyl)-cyclohexylamine have been prepared for evaluation of psychotropic activity. The synthesis and characterization by NMR spectroscopy are reported.

TRANS- and *cis*-2-(3,4,5-trimethoxyphenyl)cyclohexylamine (III and IV) were obtained by catalytic hydrogenation in acetic acid of *trans*- and *cis*-2-(3,4,5-trimethoxyphenyl)nitrocyclohexane (I and II), respectively, prepared by the general scheme previously reported for the synthesis of *cis*- and *trans*-2-arylnitrocyclohexanes (1).

The NMR spectra were determined with a Varian HR-60 spectrometer at 23° with tetramethylsilane as internal reference. Deuterated chloroform was used as solvent for the nitro compounds, and tetrachloroethylene was used for the amines. The spectra of the four compounds are consistent with structures in which the cyclohexane ring is in a chair conformation with the aromatic group in an equatorial orientation. The NMR signals of H-1 and H-2 in



I, X = NO_2
III, X = NH_2



II, X = NO_2
IV, X = NH_2

Received May 19, 1965, from the College of Pharmacy, University of Washington, Seattle.
Accepted for publication June 15, 1965.
This investigation was supported in part by grant MH 11034-01 from the National Institute of Mental Health, U. S. Public Health Service, Bethesda, Md.
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