fluoride and 2 ml. of antimony trichloride to give 5.2 g. of trifluorotrichloropropene, b.p. 85–86°. The trifluoride was ozonized in the same way except that the trifluoroacetic acid was not recovered. Results of two fluorinations are given in Table I.

Assays.—These were done by the wet combustion-vibrating reed electrometer method of Neville.[11] It was found that difficulties in operation of the combustion apparatus caused by chlorine attacking the mercury were conveniently overcome by placing in the system a $SnCl_2 \cdot 2H_2O$ absorption tube.

Acknowledgment.—The authors would like to express their appreciation to the United States Atomic Energy Commission and the University of South Carolina Research Fund for financial assistance.

(11) O. K. Neville, *ibid.*, **70**, 350 (1948).

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Homopiperazines Related to Chlorocyclizine

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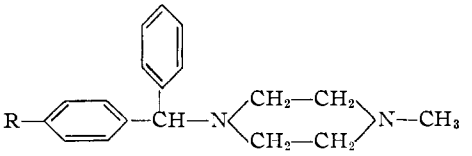
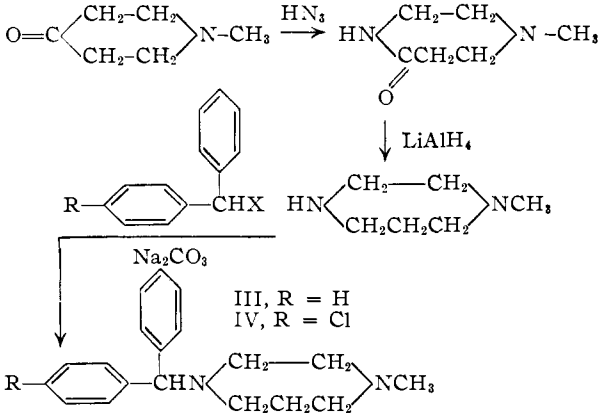
Cyclizine (I) and chlorocyclizine (II) are substituted piperazines[1] which exhibit good antihistaminic activity.[2]



I, R = H
II, R = Cl

To determine the effect of ring enlargement on this property we have synthesized the analogous homopiperazines III and IV by the scheme



III, R = H
IV, R = Cl

In preliminary animal experiments each of these seven-membered ring compounds showed antihistaminic action greater than that of the corresponding piperazine.[3]

Acknowledgment.—We are grateful to Mr. E. F. Shelberg and members of the Microanalytical Department for the analytical results reported.

Experimental

1-Methylhomopiperazine.—A solution of 10.2 g. (0.08 mole) of 1-methyl-5-homopiperazinone[4] in 400 ml. of dry ether was added with stirring under nitrogen to 7.6 g. (0.2 mole) of lithium aluminum hydride in 200 ml. of dry ether during two hours. The mixture was stirred overnight, hydrolyzed by the cautious addition of 25 ml. of water and filtered. The filtrate was dried over potassium carbonate and distilled, yielding 4.5 g. (49%) of product, b.p. 74–75° at 35 mm., $n^{25}D$ 1.4750.

The dihydrochloride salt, prepared in dry ether and crystallized from an ethanol–isopropyl alcohol mixture, melted at 133–136°.

Anal. Calcd. for $C_6H_{16}Cl_2N_2$: C, 38.51; H, 8.62. Found: C, 38.31; H, 8.60.

1-Benzhydryl-4-methylhomopiperazine (III).—To a stirred refluxing mixture of 1.8 g. (0.016 mole) of 1-methylhomopiperazine, 2.1 g. (0.016 mole) of sodium carbonate and 0.1 g. of sodium iodide in 65 ml. of dry toluene there was added, during two hours, 4.5 g. (0.018 mole) of benzhydryl bromide. After two more hours the mixture was cooled and twice extracted with 65 ml. of 2 *N* hydrochloric acid. The combined extracts after washing with ether were made basic with sodium hydroxide, and the oil which separated was extracted by ether. Distillation gave 1.8 g. (41%) of product, a viscous oil which boiled at 155° at 0.3 mm.

Anal. Calcd. for $C_{19}H_{24}N_2$: C, 81.38; H, 8.63. Found: C, 81.12; H, 8.59.

The dihydrochloride salt, m.p. 235°, was prepared and recrystallized in isopropyl alcohol.

Anal. Calcd. for $C_{19}H_{26}Cl_2N_2$: C, 64.58; H, 7.42. Found: C, 65.03; H, 7.19.

1-(*p*-Chlorobenzhydryl)-4-methylhomopiperazine (IV).—The method described by Hamlin and co-workers[1] for the corresponding substituted piperazine was used. This afforded a 56% yield of product, an oil boiling at 177° at 0.8 mm., $n^{25}D$ 1.5804.

Anal. Calcd. for $C_{19}H_{23}ClN_2$: N, 8.90. Found: N, 8.82.

The dihydrochloride salt prepared in isopropyl alcohol and recrystallized from ethanol melted at 227–228°.

Anal. Calcd. for $C_{19}H_{25}Cl_3N_2$: C, 58.85; H, 6.50. Found: C, 59.10; H, 6.35.

(1) K. E. Hamlin, A. W. Weston, F. E. Fischer and R. J. Michaels, Jr., THIS JOURNAL **71**, 2731 (1949); R. Baltzly, S. DuBreuil, W. S. Ide and E. Lorz, *J. Org. Chem.*, **14**, 775 (1949).

(2) J. C. Castillo, E. J. De Beer and S. H. Jaros, *J. Pharmacol. Exptl. Therap.*, **96**, 388 (1949); L. W. Roth, R. K. Richards and I. M. Shepperd, *Arch. intern. pharmacodynamie*, **80**, 378 (1949); cyclizine is available under the trade name Marezine, and chlorocyclizine under the names Di-Paralene and Perazil.

(3) Private communication from Dr. L. W. Roth of these laboratories.

(4) S. C. Dickerman and H. G. Lindwall, *J. Org. Chem.*, **14**, 530 (1949).

ABBOTT LABORATORIES
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A New Method for α-Bromination of Carboxylic Acids

BY EDWARD E. SMISSMAN

RECEIVED JULY 6, 1954

An investigation of α-bromination of aliphatic carboxylic acid anhydrides to give α,α′-dibromoanhydrides was conducted in this Laboratory. It was found that acetic anhydride when treated with bromine in the presence of aluminum chloride yielded α,α′-dibromoacetic anhydride. As a preparative method for obtaining α-bromo acids of high molecular weight this method would involve the preparation of anhydrides which are not readily available.

TABLE I

α-Bromo acid	M.p., °C.[a]	B.p. °C.	Mm.	d^{20}_4	Amide	Anilide	Yield, %	Ref.
Acetic	47–49 (50)	100–105	30		86–88 (91)	129–130 (131)	67.6	1
Propionic		200–203 (203.5)	740	1.691 (1.700)		96–97 (99)	76%	2, 8, 9
Butyric		122–126 (127–128)	25 25	1.564 (1.567)	108–110 (112)	95–96.5 (98)	74.7	3, 10
Isobutyric	45–48 (48–49)	110–116 (115)	20 24		146–148 (148)		87	4, 13, 14
Valeric		132–136 (123–124)	25 15	1.381		44–46	85.5	5, 11
Isovaleric		136–140 (150)	25 40	1.459	130–131 (133)		61.1	6, 12
Cyclohexanecarboxylic	59–60 (63)	160–162	18		132–134 (136)		76.5	7

[a] Literature values in parentheses.

In the course of this study, the possibility of forming an anhydride and brominating in one step became the primary objective of the investigation. Aliphatic carboxylic acids were heated with polyphosphoric acid until solution of the acid was effected. Phosphoric acid was added as a diluent for the very viscous polyphosphoric acid. In lieu of the addition of phosphoric acid, several milliliters of water were added to the polyphosphoric acid prior to heating the reaction mixture.

When solution of the carboxylic acid in the polyphosphoric acid was complete, bromine was added slowly to the stirred mixture which, in general, was maintained at a temperature near 100°.

Two methods of isolating the products are feasible. The low boiling bromoacids can be distilled directly from the reaction mixture under reduced pressure. The higher boiling products can be isolated by diluting the reaction mixture with water in order to destroy the polyphosphoric acid. The α-bromoacid can then be extracted from the phosphoric acid solution with chloroform or other organic solvents which are insoluble in phosphoric acid.

The formation of an anhydride as the intermediate in this reaction may be postulated. The acyl phosphate type anhydride and the carboxylic acid anhydride are both possible intermediates. The former anhydride is considered to be the more probable postulate since bromination of butyric anhydride under the same conditions utilized for butyric acid did not give the dibromoanhydride but α-bromobutyric acid as the only product. This would support an assumption that a mixed anhydride was first formed and then destroyed to yield only the brominated acid.

The yields of this reaction, in general, are equivalent to those obtained by the use of red phosphorus and bromine.[1-7]

Acknowledgment.—The author is grateful to the Victor Chemical Co. for experimental quantities of polyphosphoric acid.

Experimental

The procedures described below are representative of those employed in the preparation of the acids listed in Table I. With the butyric and valeric acids, the reaction mixture was heated to 100–120° during the addition of bromine and with butyric anhydride no diluent was used. A larger excess of bromine might be required if efficient condenser action is not obtained.

Preparation of α-Bromoacetic Acid.—In a 50-ml. 3-neck round-bottom flask were placed 6 g. (0.1 mole) of acetic acid, 10 ml. of polyphosphoric acid (PPA) and 1 ml. of H_2O. The flask was fitted with a condenser, a dropping funnel and a mechanical stirrer. The mixture was heated with stirring for 45 minutes. The acetic acid became miscible with the PPA and the solution turned a light yellow. Eighteen and seven-tenths grams (0.117 mole) of bromine was then added dropwise with stirring while the reaction mixture was maintained at 80–100°. The addition required 1 hour and the mixture was allowed to stir for an additional two hours until the evolution of hydrogen bromide from the condenser had ceased. The reaction mixture was transferred to a distilling flask and the volatile material removed *in vacuo*. The fraction distilling 100–105° (30 mm.) was collected. This material was redistilled and solidified upon cooling.

Preparation of α-Bromocyclohexanecarboxylic Acid.—In a 100-ml., 3-neck round-bottom flask fitted with a condenser, stirrer and addition funnel were placed 50 ml. of PPA and 12.8 ml. (12.82 g., 0.10 mole) of cyclohexane carboxylic acid. The mixture was stirred and heated for 10 minutes at 120°. The solution turned a bright yellow after 5 minutes but did not become clear. Sixteen milliliters (49.6 g., 0.275 mole) of bromine was added dropwise to the stirred solution. Hydrogen bromide evolved immediately. Heating and stirring was continued for four hours. Fifty milliliters of water was added dropwise to decompose the PPA. The excess bromine was removed *in vacuo* and the reaction mixture was extracted with two 100-ml. portions of benzene. The benzene extracts were combined and dried over anhydrous Na_2SO_4. The benzene was removed *in vacuo* and the red viscous oil remaining was distilled. A clear colorless sirupy liquid, b.p. 160–162° (18 mm.) which solidified on cooling was obtained, m.p. 59–60° (lit. 63°), yield 15.7 g. (76.5%).

Preparation of α,α'-Dibromoacetic Anhydride.—Two and seventeen-hundredths grams (0.0212 mole) of acetic anhydride was placed in a 50-ml. erlenmeyer and 5 ml. of car-

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(3) E. Fischer and A. Mouneyrat, *Ber.*, **33**, 2387 (1900).
(4) J. Volhard, *Ann.*, **242**, 161 (1887).
(5) K. von Auwers and G. Wegener, *J. prakt. Chem.*, [2] **106**, 245 (1923).
(6) C. S. Marvel, *Syntheses*, **20**, 106 (1940).
(7) O. Aschan, *Ann.*, **271**, 265 (1892).
(8) M. Weinig, *ibid.*, **280**, 248 (1894).
(9) L. Ramberg, *ibid.*, **370**, 238 (1909).
(10) W. H. Perkin, *J. Chem. Soc.*, **65**, 429 (1894).
(11) P. A. Levene, T. Mori and L. A. Mikeska, *J. Biol. Chem.*, **75**, 344.
(12) B. Schleicher, *Ann.*, **267**, 116 (1892).
(13) J. J. Sudborough and L. L. Lloyd, *J. Chem. Soc.*, **75**, 479 (1899).
(14) A. Michael, *Ber.*, **34**, 4043 (1901).

bon tetrachloride was added. To this mixture was added 0.5 ml. of dry bromine and 0.200 g. (0.0015 mole) of aluminum chloride. The bromine color disappeared. One milliliter of dry bromine was added and the $AlCl_3$ went into solution. On standing overnight the bromine color disappeared and the $AlCl_3$ settled out. This procedure was repeated until the bromine color remained. The solution was filtered through glass wool and the excess bromine and carbon tetrachloride removed *in vacuo*. The residue was distilled. The fraction boiling 153–155° (25 mm.) was collected; yield 3.19 g. of a clear, colorless liquid, b.p. 270–271° (atm.) (lit. 275° (740 mm.)) (57.9%).

One gram of the preceding liquid was heated on a steam-bath with 3 ml. of water for 15 minutes. The water was evaporated and on cooling a white crystalline material solidified, m.p. 48–49°. This material gave no depression of melting point when admixed with authentic α-bromoacetic acid.

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Nitration of Benzo[c]cinnoline

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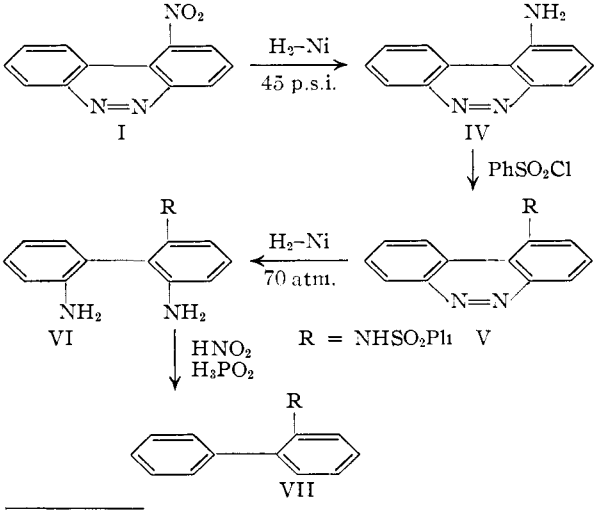
Although the compound benzo(c)cinnoline has been known for some time, all reported derivatives have been made indirectly. The formation of two monoaminobenzo(c)cinnolines by reduction of the appropriate mononitrobenzo(c)cinnoline-6-oxide prepared by nitration of benzo(c)cinnoline-5-oxide with fuming nitric acid has been reported.[3] Although these mononitro and monoamino compounds were identified by reduction to triaminobiphenyl and cyclized to aminocarbazoles, dipole measurements have raised considerable doubt concerning the structure proof.[4]

Nitration of benzo(c)cinnoline with mixed sulfuric and nitric acids at 30° gave a mixture from which three compounds (I, II and III) could be isolated with difficulty. Nitration with potassium nitrate and sulfuric acid generally gave the same products as nitration with mixed acids, but the yields were not as high. In the course of these nitrations, it was found that the nitric acid, whether used as such or formed from a salt, must be fairly pure for the best yields and easiest separation of products. As nitration conditions were made milder in order to make isolation easier, compound III no longer was formed. Compound III is most likely either a dinitrobenzo(c)cinnoline or a mononitro product formed by nitration at a less reactive center. Either of these reactions would be expected to occur under more strenuous conditions.

Nitration with mixed acids at 0–5° gave a mixture of I and II in 57.7 and 12.1% yield, respectively. These compounds, whose elemental analyses correspond to that expected for a mononitro derivative, were best isolated by extraction in a Soxhlet extractor. The major isomer, melting at 160–161°, was removed first by extraction with Skellysolve B. Two recrystallizations from ethanol were usually sufficient to purify this isomer. Occasionally the compound must be treated with Norite in acetone to remove the last of a red impurity which occurs in the nitration. The minor isomer, melting at 230°, was extracted with ethanol. This isomer, being much less soluble, was purified by washing with hot ethanol.

Again, effort was made to nitrate under milder conditions. However, nitration of benzo(c)cinnoline did not occur with a mixture of nitric and acetic acids even at 80° for four hours.

The major nitration product was identified by conversion to a known monosubstituted biphenyl. By taking advantage of the fact that the azo group of benzo(c)cinnoline is stable to stannous chloride and hydrochloric acid, sodium hydrosulfite, Raney nickel and low pressure hydrogen, hydrogen and platinum, and sodium amalgam and alcohol, a nitro group may be reduced without disturbing the benzo(c)cinnoline nucleus. In fact, the first three named reagents have been used to convert the nitro compound, I, to its corresponding amine, IV. This amine was protected during the following reactions by conversion to its benzenesulfonamide, V. The azo group of the sulfonamide was reduced to the expected diamine VI with Raney nickel and hydrogen at 70 atmospheres.[3] Deamination of the diamine was accomplished by allowing the tetrazonium salt formed by reaction of the diamine with nitrous acid to stand in hypophosphorous acid. This work was patterned after a reported deamination of substituted diaminobiphenyls.[5] The 2-benzenesulfonamidobiphenyl, VII, which resulted from these reactions, was compared with the benzenesulfonamide of authentic 2-aminobiphenyl.



(1) Department of Chemistry, University of Kentucky, Lexington, Kentucky.

(2) National Science Foundation Fellow, 1952–1953.

(3) F. King and T. King, *J. Chem. Soc.*, 824 (1945).

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(5) S. Ross and I. Kuntz, THIS JOURNAL, **74**, 1297 (1952).