was discarded. A cut weighing 0.56 g. was taken; it distilled at 96–98°, $n^{20}D$ 1.5330. The infrared spectrum showed that this cut was largely N-methyl-2-hydroxymethylpyrrole containing some of the unreacted aldehyde. On the basis of the refractive index, the material was 79% alcohol.

Acknowledgment.—The authors are indebted to Miss C. Brown for the carbon and hydrogen determinations, and to Dr. H. J. Eding for the infrared spectra. The sample of N-methylpyrrole was kindly furnished us by the Electrochemicals Department of E. I. du Pont de Nemours & Co.

DEPARTMENT OF CHEMISTRY
STANFORD RESEARCH INSTITUTE
STANFORD, CALIFORNIA

Preparation of Nicotinic and Isonicotinic Anhydride

BY ANTHONY W. SCHRECKER AND PRISCILLA B. MAURY

RECEIVED JULY 1, 1954

Nicotinic and isonicotinic anhydride were first prepared by reaction of their acid chlorides with their sodium salts.[1] The disadvantages of the original method, which requires vacuum distillation of the acid chlorides, have been emphasized by Badgett,[2] who published a simplified procedure for the preparation of nicotinic anhydride, in which the intermediary nicotinyl chloride was obtained and used *in situ*. His procedure, however, involves the use of nitrobenzene, the last traces of which are not readily removed from the product, and it is furthermore inapplicable to isonicotinic anhydride, which is unstable[1] at the high temperature that must be employed.

More recently, a new procedure for the preparation of nicotinyl chloride has been described,[3] in which oxalyl chloride is substituted for the previously employed[2,4] thionyl chloride. Since hydrogen chloride is not formed under these conditions, nicotinyl chloride is obtained directly, and decomposition by distillation from pyridine[4] or by pyrolysis[2] of the nicotinyl chloride hydrochloride produced in the presence of thionyl chloride becomes unnecessary. Wingfield's procedure is an application of a general reaction discovered by Adams and Ulich,[5] who showed that sodium salts of organic acids react with oxalyl chloride to yield either acid chlorides or acid anhydrides, depending on the molar proportions of the reagents. By modifying Wingfield's procedure in the light of these findings, a very convenient and rapid method for preparing directly both nicotinic and isonicotinic anhydride has been developed in this Laboratory.

Experimental

Nicotinic Anhydride.—To a suspension of 32.24 g. (0.2 mole) of potassium nicotinate, which had been ground to pass a 100-mesh sieve and dried at 135°,[3] in 80 ml. of anhydrous benzene was added, with mechanical stirring and cooling in an ice-bath, 12.69 g. (0.1 mole) of oxalyl chloride in 45 ml. of anhydrous benzene during 20 minutes. The cooling bath was removed after another 15 minutes, and the suspension stirred at room temperature for one hour, then at the refluxing temperature for another hour. It was filtered hot, and the solid washed with boiling benzene. The combined filtrate and washings were concentrated to about 100 ml. and cooled, providing 17.23 g. of colorless prismatic needles, m.p. 123–126° (lit. 122–124°,[1] 122.5–123.5°[2]). The product did not depress the melting point of a sample prepared by Badgett's[2] procedure. Another 2.09 g., m.p. 123°, was obtained from the mother liquor by concentrating and adding hexane, bringing the total yield to 85%.

Isonicotinic Anhydride.—The same procedure was used starting with potassium isonicotinate, except that after removing the ice-bath the suspension was stirred at room temperature for two hours, filtered, and the residue washed first with cold benzene, then extracted with hot benzene. The combined light yellow filtrates were concentrated under reduced pressure to about 100 ml. and diluted with an equal volume of hexane to yield 16.56 g. (73%) of colorless elongated prisms, m.p. 112–114°. Recrystallization from benzene–pentane brought the m.p. to 112.7–113.9°. The analytical sample (same m.p.) was obtained by vacuum sublimation (bath 115°).

Anal. Calcd. for $C_{12}H_8O_3N_2$: C, 63.16; H, 3.53; N, 12.28; sapn. equiv., 114. Found: C, 63.36; H, 3.43; N, 12.47; sapn. equiv., 111.

In a preliminary experiment, the compound was obtained in the form of plates, m.p. 103–105° (lit.[1] rhombic prisms, m.p. 103–104°). Subsequent runs yielded the higher-melting polymorphic modification only.

Preparations in which the suspension was refluxed as in the case of nicotinic anhydride gave essentially identical yields and melting points; the product was, however, contaminated with a trace of blue dye, which could be removed by treatment with Norit. The yield was not improved when 0.1 mole of potassium isonicotinate was allowed to react with 0.1 mole of oxalyl chloride to produce isonicotinyl chloride *in situ*, followed by addition of another 0.1 mole of potassium isonicotinate.

LABORATORY OF CHEMICAL PHARMACOLOGY
NATIONAL CANCER INSTITUTE
NATIONAL INSTITUTES OF HEALTH
BETHESDA 14, MD.

---

[1] R. Graf, *Biochem. Z.*, **229**, 164 (1930).

[2] C. O. Badgett, THIS JOURNAL, **69**, 2231 (1947).

[3] H. N. Wingfield, Jr., W. R. Harlan and H. R. Hanmer, *ibid.*, **75**, 4364 (1953).

[4] H. Meyer and R. Graf, *Ber.*, **61**, 2202 (1928).

[5] R. Adams and L. H. Ulich, THIS JOURNAL, **42**, 599 (1920); *cf.* R. Adams, W. V. Wirth and H. E. French, *ibid.*, **40**, 424 (1918).

Allylic Rearrangement of Hexachloropropene-1-C^{14}

BY CALVIN H. SHUFORD, JR., DAVID L. WEST AND H. W. DAVIS

RECEIVED JUNE 12, 1954

Allylic rearrangements of crotyl and methallyl chlorides during reaction have been known for many years. Kundiger and Haney[1] recently reported that 1,1,1-trichloro-2-methyl-2-propene undergoes allylic rearrangement on being heated with thionyl chloride or powdered glass. We wish to report that hexachloropropene also undergoes allylic rearrangement under mild conditions. This conclusion is based on observations with hexachloropropene-1-C^{14} which was synthesized as

$$C^*H_3COOH + C_6H_6 \xrightarrow{PCl_5,\ AlCl_3} C_6H_5COC^*H_3 \xrightarrow{Cl_2} C_6H_5COC^*Cl_3$$

$$\xrightarrow[H_2O]{NaOH} C^*HCl_3 \xrightarrow[AlCl_3]{Cl_2C{=}CCl_2} C^*HCl_2CCl_2CCl_3 \xrightarrow[MeOH]{NaOH} C^*Cl_2{=}CClCCl_3$$

The hexachloropropene was degraded by ozonization, which gave carbon dioxide recovered as barium carbonate and trichloroacetic acid, recovered in most runs as the S-benzylthiuronium salt.

---

[1] D. G. Kundiger and H. N. Haney, THIS JOURNAL, **76**, 615 (1954).

TABLE I

RADIOACTIVITIES OF HEXACHLOROPROPENE AND DEGRADATION PRODUCTS

Hexachloropropene, mc./mole	Before isomerizing treatment				After isomerizing treatment			
	BaCO$_3$		Trichloroacetic acid		BaCO$_3$		Trichloroacetic acid	
	mc./mole	Total, %	mc./mole	Total, %	mc./mole	Total, %	mc./mole	Total, %
0.544	0.379	70 ± 2[a]	0.056[b]	10 ± 2	0.222[c]	41 ± 3	0.262	48 ± 2
.181	.112	62 ± 5	.034[d]	18 ± 5	.079[e]	44 ± 5	....	....
.409	.274	67 ± 1	....	....	.180[e]	44 ± 1	0.194[f]	47
1.05	.789	75 ± 3	.088[d]	8 ± 3	.482[g]	46 ± 3	....	....
0.376	.200	53 ± 1	....	....	.155[g]	41 ± 1	....	....

[a] Estimates based on standard deviation of activity measurements. [b] Aniline salt. [c] After passage through silica gel. [d] S-Benzylthiuronium salt. [e] Fractional redistillation. [f] Sodium trichloroacetate assayed, one determination. [g] Fluorination with SbF$_3$ and SbCl$_5$, ozonolysis of trifluorotrichloropropene.

Isomerization occurred when the hexachloropropene was treated chromatographically on silica gel and on heating at 120° for 4–5 hours during fractional distillation. Isomerization also occurred in the presence of the fluorinating agents antimony trifluoride and antimony pentachloride. The results are summarized in Table I. The agreement of the barium carbonate activity percentages after the various treatments suggests strongly that the material has been equilibrated completely in each case.

The degradation of the hexachloropropene was somewhat troublesome in that only 80–90% of the activity was accounted for. After experimentation with various derivatives of trichloroacetic acid, with the assay procedure, with the decomposition of the ozonide, and further purification[2] of the hexachloropropene, it was concluded that carbon dioxide was being produced to some extent from an unlabeled position during the ozonolysis process. Partial abnormal rearrangement of the "molozonide" as has been observed with many oxygen and nitrogen compounds[3] would produce such results.

Furthermore, the fact that the hexachloropropene was isomerized on being subjected to a prolonged redistillation, accounts for the failure to achieve complete labeling in the 1-position, some rearrangement having occurred during the original distillation.

Experimental

Acetophenone-methyl-C^{14}.—The method used was essentially that of Ullmann and Bleier.[4] Approximately 1 mc., 85 mg., of sodium acetate-2-C^{14} (Tracerlab, Inc.) was allowed to equilibrate with 12 g. of glacial acetic acid. The acid was then added dropwise to a stirred mixture of 46 g. of phosphorus pentachloride and 60 g. of benzene. Aluminum chloride, 80 g., was added and the mixture refluxed 30 minutes. The reaction mixture was added to ice (900 g.) and hydrochloric acid (100 g.), the organic layer separated and washed with aqueous sodium hydroxide. After drying and distilling off the benzene, the acetophenone-methyl-C^{14} was collected at 90–91° (20 mm.), 18 g. (75%) being obtained. This was diluted with unlabeled acetophenone to give material with an activity of 1.05 mc./mole, assayed as the 2,5-dinitrophenylhydrazone.

Chloroform-C^{14}.—This was prepared by a procedure based on the work of Aston and co-workers[5] and similar to a preparation of chloroform-*d* by Boyer, *et al.*[6] The acetophenone-methyl-C^{14} (41 g.) was dissolved in 175 ml. of glacial acetic acid and chlorine passed in with stirring until no more reaction occurred. Then anhydrous sodium acetate (88 g.) was added and chlorine passed in at 105–110° until reaction ceased. The trichloro compound was washed with water, and cleaved by adding to it with stirring at 55–60° aqueous sodium hydroxide (25 g. of NaOH in 140 ml. of water). The chloroform-C^{14} which distilled was dried over calcium chloride and redistilled from aluminum chloride. The yield of chloroform-C^{14}, activity assumed to be 1.05 mc./mole, was 31.5 g. or 78%.

Hexachloropropene-1-C^{14}.—Chloroform-C^{14} (31.5 g.) was condensed with 43.5 g. of tetrachloroethylene, 20 g. of aluminum chloride catalyst, by the method of Prins.[7] The crude heptachloropropane was dehydrohalogenated by adding with stirring 10.5 g. of sodium hydroxide dissolved in 65 ml. of methyl alcohol. The hexachloropropene-1-C^{14} was washed with water, dried with calcium chloride and distilled at 120–121° at 50 mm. The yield was 33.9 g. or 51.5% (based on chloroform).

This material could not be satisfactorily assayed directly by the wet combustion method and a 1-g. sample was converted to trichloroacrylic acid for this purpose, by hydrolysis with warm concd. sulfuric acid. After recrystallization from carbon disulfide, the trichloroacrylic acid had m.p. 76–77° and an activity of 1.05 mc./mole.

One sample of labeled hexachloropropene (0.544 mc./mole) was treated chromatographically with silica gel for the purpose of further purification. The compound (15 ml.) was poured on a column of 200-mesh silica gel (Davidson, #922-08-08-226) 1-cm. in diameter and 40 cm. long and eluted with methanol. The first five fractions had $n^{24}\text{D}$ 1.5478[8] and were considered on the basis of their infrared spectra to be quite pure. Ozonolysis as described below of a sample of this purified material gave barium carbonate having an activity of 0.222 mc./mole showing that the hexachloropropene had been isomerized.

Ozonolysis.—One-ml. samples of the halogenated olefins dissolved in 60 ml. of carbon tetrachloride were ozonized for 2 hours at room temperature in an apparatus similar to that described by Smith, Greenwood and Hudrlik.[9] The ozonized solution was added dropwise with stirring to 50 ml. of 4% sulfuric acid in water, nitrogen being used to sweep the carbon dioxide into barium hydroxide solution. The barium carbonate was washed and dried for assay. The trichloroacetic acid was extracted from the water with ether, the ether evaporated and the acid converted to the S-benzylthiuronium salt. In the case of the hexachloropropene described above, the results were: barium carbonate, 0.789 mc./mole; S-benzylthiuronium salt, 0.088 mc./mole. On the basis of conclusions stated above, this represents approximately 92% labeling in the 1-position. Results with other samples are shown in Table I.

Fluorination of Labeled Hexachloropropene.—The procedure of Whaley and Davis[10] was used. Sixteen grams of hexachloropropene was treated with 32.5 g. of antimony tri-

---

[2] Infrared analysis showed the presence of a small amount of oxygen containing material. It was in removal of this chromatographically with silica gel that isomerization was observed.

[3] J. E. Leffler, *Chem. Revs.*, **45**, 399 (1949).

[4] F. Ullmann and H. Bleier, *Ber.*, **35**, 4273 (1902); see also H. J. Scheifele, Jr., and D. F. DeTar, *Org. Syntheses*, **32**, 8 (1952).

[5] J. G. Aston, J. D. Newkirk, J. Dorsky and D. M. Jenkins, THIS JOURNAL, **64**, 1413 (1942).

[6] W. M. Boyer, R. B. Bernstein, T. L. Brown and V. H. Dibeler, *ibid.*, **73**, 770 (1951).

[7] H. J. Prins, *Rec. trav. chim.*, **54**, 249 (1935). For such a small scale preparation, the short reaction time as originally used by Prins was found to be much better than the procedure given by M. W. Farlow, *Org. Syntheses*, **17**, 58 (1937).

[8] P. Fritsch, *Ann.*, **297**, 312 (1897), gives $n^{20}\text{D}$ 1.5091 which the present authors believe to be in error.

[9] L. I. Smith, F. L. Greenwood and O. Hudrlik, *Org. Syntheses*, **26**, 63 (1946).

[10] A. M. Whaley and H. W. Davis, THIS JOURNAL, **70**, 1026 (1948).

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).

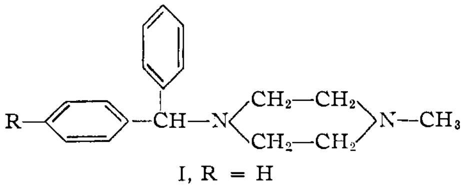
DEPARTMENT OF CHEMISTRY
UNIVERSITY OF SOUTH CAROLINA
COLUMBIA, SOUTH CAROLINA

Homopiperazines Related to Chlorocyclizine

BY ARMIGER H. SOMMERS, R. J. MICHAELS, JR., AND ARTHUR W. WESTON

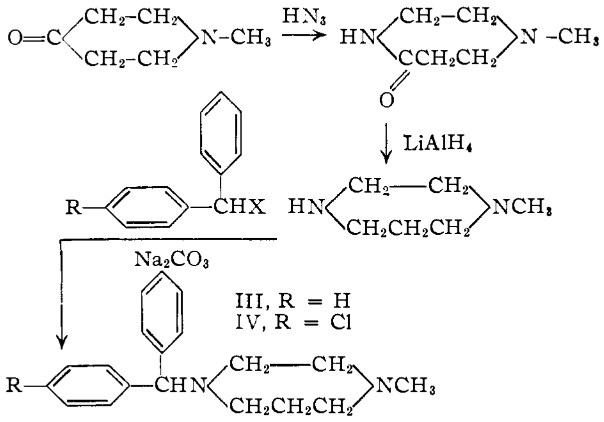
RECEIVED JULY 6, 1954

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
NORTH CHICAGO, ILLINOIS

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.