[CONTRIBUTION FROM THE ORGANIC CHEMISTRY LABORATORIES OF THE UNIVERSITY OF FLORIDA]

Derivatives of Piperazine. XXIII. Addition of 1-Arylpiperazines to α,β-Unsaturated Nitriles and Esters

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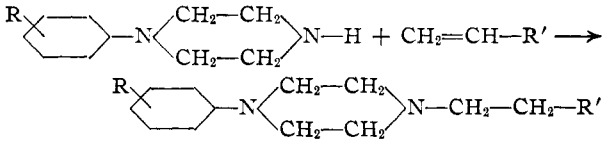
Twenty-four new addition compounds and derivatives of 1-arylpiperazines with acrylonitrile, ethyl acrylate, or *n*-butyl acrylate have been prepared and studied. Crotononitrile, α-methylacrylonitrile, methyl methacrylate and ethyl methacrylate did not react with 1-phenylpiperazine under conditions which were successful with acrylonitrile and unsubstituted acrylate esters. Similarly, methyl and ethyl methacrylates did not react with 1-(2-methylphenyl)-piperazine under conditions which were successful with unsubstituted acrylate esters.

In the course of work in these laboratories on the preparation of physiologically active compounds it became necessary to condense 1-arylpiperazine with acrylonitrile and with ethyl and *n*-butyl acrylate. This paper is a report of these experiments.



R = H, 2-CH_3, 3-CH_3, 4-CH_3, or 3-Cl
R′ = CN, $COOC_2H_5$, $COOC_4H_9$-*n*

The β-aminopropionitriles are best obtained by the addition of secondary amines to acrylonitrile.[2] Likewise, the β-aminopropionates are obtained by the addition of secondary amines to acrylate esters.[3] The mechanism involves a typical 1,4-addition as most workers have assumed.[4,5]

The additions of 1-arylpiperazines and acrylonitrile are effected with about the same ease and without the aid of a catalyst. A noticeable heat is evolved on mixing with acrylonitrile. Similarly, the 1-arylpiperazines reacted readily with ethyl and with *n*-butyl acrylate esters upon heating under reflux.

Attempts to bring about a reaction between crotononitrile or α-methylacrylonitrile and 1-phenylpiperazine under conditions which were successful with acrylonitrile did not succeed. Methyl and ethyl methacrylates did not react with either 1-phenylpiperazine or 1-(2-methylphenyl)-piperazine under conditions which were successful with unsubstituted acrylate esters. This is not surprising in view of the known unreactivity of α-methylacrylonitrile and crotononitrile as compared with acrylonitrile and of the methacrylate esters as compared with unsubstituted acrylate esters.[6,7]

With the exception of 1-(3-chlorophenyl)-4-(2-cyanoethyl)-piperazine, all the nitriles were obtained in excellent yields. Substitution of a methyl or chloro group in the meta position produced high-boiling, viscous liquids. The remaining nitriles reported herein were low-melting solids. The esters, as the hydrochloride salts, were obtained in varying yields.

For the purposes of characterization and physiological testing, the amide and acid derivatives were prepared from the nitrile. The amides were made by hydration of the nitrile in concentrated sulfuric acid; the imino sulfate formed by the addition of the acid to the nitrile was then hydrolyzed. The acids were prepared by alkaline hydrolysis in dilute ethanol. 1-Phenyl-4-(2-cyanoethyl)-piperazine was reduced with lithium aluminum hydride and identified as the phenylurea of 1-phenyl-4-(3-aminopropyl)-piperazine.

Experimental

Detailed directions for the preparation of the compounds reported in this paper are given for only one representative member of each class.

Acrylonitrile.—The product from American Cyanamid Company was distilled and that portion which boiled at 77.3° was used.

Acrylate Esters.—Ethyl acrylate from Carbide and Carbon Chemicals Division of Carbide and Carbon Corporation and *n*-butyl acrylate from Rohm and Haas Company were used without further purification.

1-Arylpiperazines.—1-Phenylpiperazine was prepared by the method of Pollard and MacDowell.[8] 2-Methylphenyl-, 3-methylphenyl-, 4-methylphenyl- and 3-chlorophenylpiperazines were prepared by the method of Pollard and Wicker.[9]

1-Phenyl-4-(2-cyanoethyl)-piperazines.—One hundred and sixty-two grams (1 mole) of 1-phenylpiperazine was placed in a 1-liter, 3-necked flask equipped with thermometer, mechanical stirrer and dropping funnel. The 1-phenylpiperazine was heated to 55°, and 63.5 g. (1.2 moles) of acrylonitrile was slowly added from the dropping funnel. With occasional external cooling the temperature was maintained at 55°. Stirring was continued for 1.5 hours after the addition of acrylonitrile was completed. When cool the reaction mixture was a solid. The solid mass was transferred to a buchner funnel and washed well with water. Three recrystallizations from 95% ethanol gave 139 g. (86%) of the pure nitrile.

1-Phenyl-4-(2-carboxyethyl)-piperazine.—Twenty-one and a half grams (0.1 mole) of 1-phenyl-4-(2-cyanoethyl)-piperazine was heated under reflux with 8.4 g. (0.15 mole) of potassium hydroxide in 250 ml. of 60% ethanol for four hours. The condenser was set for distillation and volatile materials were removed by heating on the steam-bath. The residual solution was cooled and extracted with ether, and the aqueous solution was heated on the steam-bath to remove dissolved ether. The cool aqueous solution was carefully neutralized with dilute hydrochloric acid to precipitate the acid. The acid was filtered with suction and

(1) This paper is abstracted from a portion of a dissertation submitted by R. Robbins to the Graduate Council of the University of Florida in partial fulfillment of the requirements for the degree of Doctor of Philosophy, June, 1951.

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(8) C. B. Pollard and L. G. MacDowell, THIS JOURNAL, **56**, 2199 (1934).

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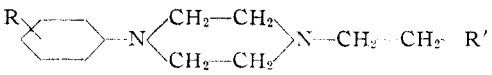
TABLE I

PHYSICAL CONSTANTS AND ANALYTICAL DATA FOR 1,4-SUBSTITUTED PIPERAZINES



R	R′	M.p., °C.[a]	Yield,[b] %	Molecular formula	Nitrogen, % Calcd.	Found
H	CN	71.3–72.1	86	$C_{13}H_{17}N_3$	19.52	19.44
	COOH	187.6–188.6	56.4	$C_{13}H_{18}N_2O_2$	11.96	12.05
	$CONH_2$	170.7–171.6	55.7	$C_{13}H_{19}N_3O$	18.01	17.98
	$COOC_2H_5$	216.2–216.7[c]	48.5	$C_{15}H_{22}N_2O_2 \cdot 2HCl$	8.36	8.36
	$COOC_4H_9$-*n*	211.7–212.2 (dec.)[d]	25.0	$C_{17}H_{26}N_2O_2 \cdot HCl$	8.57	8.39
	$CH_2NHCONHC_6H_5$	126	..	$C_{20}H_{26}N_4O$	16.56	16.52
2-CH_3	CN	78.4–79.4	..[e]	$C_{14}H_{19}N_3$	18.32	18.29
	COOH	221.7–222.7 (dec.)[d]	63.4	$C_{14}H_{20}N_2O_2 \cdot HCl$	9.84	9.91[f]
	$CONH_2$	129.1–129.9	66.6	$C_{14}H_{21}N_3O$	16.99	17.05
	$COOC_2H_5$	200.7–202.2[d]	72.0	$C_{16}H_{24}N_2O_2 \cdot HCl$	8.96	8.97[g]
	$COOC_4H_9$-*n*	212.7–213.7 (dec.)[d]	53.0	$C_{18}H_{28}N_2O_2 \cdot 2HCl$	7.42	7.63
3-CH_3	CN	.....[h]	77.5	$C_{14}H_{19}N_3$	18.32	18.04
	COOH	138.8–139.8[i]	40.4	$C_{14}H_{20}N_2O_2$	11.28	11.02
	$CONH_2$	144.9–145.9	37.0	$C_{14}H_{21}N_3O$	16.99	16.95
	$COOC_2H_5$	196.6–197.2[c]	57.6	$C_{16}H_{24}N_2O_2 \cdot 2HCl$	8.02	8.22
	$COOC_4H_9$-*n*	191.5–192.5[d]	38.2	$C_{18}H_{28}N_2O_2 \cdot HCl$	8.22	8.01
4-CH_3	CN	70.4–71.4	86.0	$C_{14}H_{19}N_3$	18.32	18.14
	COOH	221.2–222.2[d]	42.2	$C_{14}H_{19}N_2O_2 \cdot HCl$	9.84	9.70[j]
	$CONH_2$	191.5–192.5	46.4	$C_{14}H_{21}N_3O$	16.99	16.87
	$COOC_2H_5$	203.2–204.2[c]	25.8	$C_{16}H_{24}N_2O_2 \cdot 2HCl$	8.02	8.05
	$COOC_4H_9$-*n*	201.7–202.7[c]	26.5	$C_{18}H_{28}N_2O_2 \cdot 2HCl$	7.43	7.24
3-Cl	CN	.....[k]	48.7	$C_{13}H_{16}N_3Cl$	16.83	16.80
	COOH	164.4–165.3	62.0	$C_{13}H_{17}N_2O_2Cl$	10.43	10.52
	$CONH_2$	147.5–148.2	59.9	$C_{13}H_{18}N_3OCl$	15.70	15.67

[a] All melting points are corrected. [b] Yields of nitriles and esters are based upon the 1-arylpiperazines; yields of acids and amides are based upon the nitriles. [c] Dihydrochloride. [d] Monohydrochloride. [e] Crude yield was quantitative. [f] *Anal.* Cl: Calcd., 12.45%; found, 12.42%. [g] *Anal.* Cl: calcd., 11.32%; found, 11.52%. [h] B.p. 197–199°C. (1.3 mm.) (cor.); $n^{25}D$ 1.5580; d^{25}_{25} 1.052. [i] Softens at 120°. [j] *Anal.* Cl: calcd., 12.45%; found, 12.49%. [k] B.p. 210.6–212.6° (1.3 mm.) (cor.); $n^{25}D$ 1.5762; d^{25}_{25} 1.168.

washed well with water. Two recrystallizations from water gave 12.1 g. (56.4%) of pure acid.

1-(2-Methylphenyl)-4-(2-carbamylethyl)-piperazine.—Ten grams of 1-(2-methylphenyl)-4-(2-cyanoethyl)-piperazine was dissolved in 40 ml. of concentrated sulfuric acid. This mixture heated spontaneously. After standing for five minutes at 90–100° the reaction mixture was cooled and poured into 200 ml. of ice-cold water. The aqueous solution was made basic with a solution of sodium hydroxide. The amide was filtered with suction and after two recrystallizations from 10% ethanol yielded pure white crystals.

1-(4-Methylphenyl)-4-(2-carbethoxyethyl)-piperazine Dihydrochloride.—A mixture of 17.6 g. (0.1 mole) of 1-(4-methylphenyl)-piperazine and 20.0 g. (0.2 mole) of ethyl acrylate in 25 ml. of anhydrous benzene was heated under reflux for 18 hours. The cool reaction mixture was extracted three times with 3 *N* hydrochloric acid (200 ml.). The acid solution was basified with potassium carbonate solution and then extracted three times with ether. The ether solution was dried with anhydrous potassium carbonate. An excess of methanolic hydrogen chloride was added to the dry, filtered ether solution from which the dihydrochloride of the ester precipitated. Three recrystallizations from anhydrous methanol gave 4.55 g. (25.8%) of pure white crystals.

1-Phenyl-4-(3-phenylcarbamidopropyl)-piperazine.—Thirty-three and eight-tenths grams (0.1 mole) of 1-phenyl-4-(2-cyanoethyl)-piperazine was added slowly to an ethereal solution of one-tenth mole of lithium aluminum hydride at reflux. After one hour the product was hydrolyzed according to the procedure of Amundsen and Nelson.[10] The solid was filtered and discarded. The ether solution was evaporated to give 1-phenyl-4-(3-aminopropyl)-piperazine. This compound was not purified, but the yield was approximately 85%. One-twentieth mole of 1-phenyl-4-(3-aminopropyl)-piperazine was dissolved in benzene and $^1/_{20}$ mole of phenyl isocyanate was added. The mixture was boiled 20 minutes, cooled and crystallized. Recrystallization from benzene gave a pure product.

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(10) L. H. Amundsen and L. S. Nelson, THIS JOURNAL, **72**, 242 (1951).