(25 ml.) for 8 hr. The solution was diluted with water and almost neutralized with hot, saturated barium hydroxide solution. The mixture was centrifuged and the decantate evaporated to dryness under vacuum to yield white crystals of 2-amino-1,7-heptanedioic acid; wt. 0.72 g., (41%) m.p. 221–223° (lit., 225°[24]).

7-Carboxamido-2-ketohexamethylenimine from 7-cyano-2-ketohexamethylenimine. Two grams of 7-cyano-2-ketohexamethylenimine was added to 25 g. of polyphosphoric acid at 65°. After 8 hr., the mixture was hydrolyzed and extracted as described above to yield 7-carboxamido-2-ketohexamethylenimine; wt. 2.05 g. (91%) m.p. 239–241°. On mixing with the product obtained from the Schmidt reaction, no depression of the melting point was observed; m.p. 239–241°.

7-Carboxamido-2-ketohexamethylenimine from 2-cyanocyclohexanone. To a mixture of 12.30 g. (0.1 mole) of 2-cyanocyclohexanone in 192 g. of polyphosphoric acid, 6.80 g. (0.105 mole) of sodium azide was added in small portions over 1 hr. with slow agitation. The mixture was slowly heated at 65° and the temperature maintained at the specified temperature for 8 hr. The reaction mixture was hydrolyzed and the products isolated in the usual manner to yield 12.87 g. (83%) of 7-carboxamido-2-keto-hexamethylenimine; m.p. 238–241°. No trace of the nitrile was detected in the infrared spectrum of the crude product.

Acetanilide from acetophenone. To a mixture of 12.10 g. (0.1 mole) of acetophenone in 225 g. of polyphosphoric acid, 6.80 g. (0.105 mole) of sodium azide was added in small portions over 1 hr. with slow agitation. After stirring at 50° for 7 hr. the mixture was poured over 500 ml. of crushed ice and water. The product was filtered from the solution to yield 13.35 g. (98%) of acetanilide after air drying. The acetanilide was once recrystallized from water; m.p. 113–114° (lit., m.p. 114°[12]).

Phenanthridone from fluorenone. To a mixture of 18.10 g. (0.1 mole) of fluorenone in 350 g. of polyphosphoric acid, 6.80 g. (0.105 mole) of sodium azide was added in small portions over 1 hr. with slow agitation. The temperature was cautiously raised to 70° and maintained at that temperature for 22 hr. with constant stirring. The product was collected on hydrolysis by filtration to yield 17.94 g. (92%) of phenanthridone; m.p. 286–288° (lit., m.p. 293°[25]).

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[CONTRIBUTION FROM THE ORGANIC DIVISION OF THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF FLORIDA]

Derivatives of Piperazine. XXX. Reactions of 1-Arylpiperazines with Epoxides

C. B. POLLARD AND JOAN B. CHRISTIE

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The search for new pharmaceuticals led to the synthesis of 25 new compounds resulting from the reactions of various 1-arylpiperazines with substituted 1,2-epoxides.

Seven of the 1-arylpiperazines used in these syntheses were prepared by the method of Pollard, *et al.*[1,2] The method of Prelog, *et al.*[3–5] proved more satisfactory for the preparation of the alkoxypiperazines. The hydrobromide of 1-(2-methoxyphenyl)-piperazine was reported by Prelog, Driza, and Hanousek.[3] The free amines, 1-(2-methoxyphenyl)-piperazine and 1-(2-ethoxyphenyl)piperazine were prepared in this laboratory by the Prelog method. The acetic acid salts of these amines were prepared for analyses and subsequent identification.

The reactions of ammonia and amines with 1,2-epoxides to form amino alcohols have been thoroughly investigated by Goldfarb,[6] Horne and Shriner,[7] and Wurtz.[8] Krassousky[9] investigated these reactions with unsymmetrical epoxides and obtained secondary amino alcohols. Castro and Noller[10] established that arylamines reacted with epoxides to produce secondary amino alcohols. The experimental work of Boyd and Knowlton,[11] Boyd,[12] and Stephens[13] also confirmed the secondary alcohol formation from these reactions. Kitchen and Pollard[14] showed that piperazine reacts with epoxides to produce mono as well as disubstituted piperazines, both being secondary amino alcohols. In view of the previous work establishing the for-

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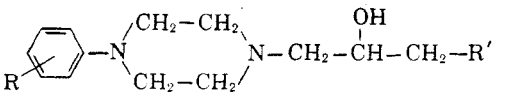
TABLE I

DATA CONCERNING COMPOUNDS HAVING THE GENERAL FORMULA



Empirical Formula	R	Yield, %	M.P., °C. (Corr.)	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
			R′ = –S–						
$C_{19}H_{24}N_2OS$	H	28.9	95–96	69.47	7.36		69.10	7.52	
$C_{19}H_{24}Cl_2N_2OS$	*o*-Cl·HCl	18.0	158–161	57.14	6.06		56.85	6.03	
$C_{19}H_{23}ClN_2OS$	*m*-Cl	28.0	121.5–122.5	62.87	6.39		62.84	6.25	
$C_{19}H_{23}ClN_2OS$	*p*-Cl	20.5	119–120	62.87	6.39		62.56	6.62	
$C_{20}H_{27}ClN_2OS$	*o*-CH_3·HCl	13.4	174–176	63.39	7.18		63.04	7.19	
$C_{20}H_{26}N_2OS$	*m*-CH_3	24.8	109.1–109.6	70.15	7.65		69.80	7.68	
$C_{20}H_{26}N_2OS$	*p*-CH_3	18.1	99–101	70.15	7.65		70.11	7.47	
$C_{20}H_{26}N_2O_2S$	*o*-OCH_3	27.8	92–93	67.01	7.31		67.14	7.34	
$C_{21}H_{28}N_2O_2S$	*o*-OC_2H_5	32.0	100–101	67.71	7.58	7.52	67.86	7.61	7.55
			R′ = –$(CH_2)_8CH_3$						
$C_{22}H_{38}N_2O$	H	31.4	78.3–79.3	76.25	11.06	8.09	76.03	11.32	8.00
$C_{22}H_{37}ClN_2O$	*m*-Cl	15.7	65.7–66.7	69.37	9.79	7.36	69.16	9.43	7.20
$C_{22}H_{37}ClN_2O$	*p*-Cl	23.6	84.5–85.5	69.37	9.79	7.36	69.60	9.83	7.65
$C_{23}H_{40}N_2O$	*m*-CH_3	13.9	63.7–64.7	76.61	11.18	7.77	76.71	11.20	7.75
$C_{23}H_{40}N_2O$	*p*-CH_3	24.4	74.8–75.8	76.61	11.18	7.77	76.40	11.19	7.80
			R′ = –O– (2-OCH_3)						
$C_{20}H_{25}ClN_2O_3$	*o*-Cl	31.9	60.6–61.6	63.74	6.69	7.44	63.76	6.62	7.05
$C_{20}H_{25}ClN_2O_3$	*m*-Cl	53.0	67.7–68.7	63.74	6.69	7.44	64.00	7.03	7.45
$C_{20}H_{25}ClN_2O_3$	*p*-Cl	29.2	75.8–76.8	63.74	6.69	7.44	64.07	6.99	7.45
$C_{21}H_{28}N_2O_3$	*p*-CH_3	53.0	93–94	70.76	7.92	7.86	70.90	8.10	7.95
			R′ = –O– (3-OCH_3)						
$C_{20}H_{26}N_2O_3$	H	40.3	99–101	70.17	7.66	8.18	70.11	7.59	7.75
$C_{20}H_{26}Cl_2N_2O_3$	*o*-Cl·HCl	8.7	179–180	58.11	6.34	6.78	58.60	6.65	6.70
$C_{20}H_{25}ClN_2O_3$	*m*-Cl	57.8	74.8–75.8	63.74	6.69	7.44	63.30	6.59	7.75
$C_{20}H_{25}ClN_2O_3$	*p*-Cl	42.7	85.9–87.9	63.74	6.69	7.44	63.60	6.69	7.29
$C_{21}H_{29}ClN_2O_3$	*o*-CH_3·HCl	36.4	168.2–170.2	64.17	7.44		64.06	7.51	
$C_{21}H_{28}N_2O_3$	*m*-CH_3	50.8	71.2–72.2	70.75	7.92	7.86	70.40	7.45	7.94
$C_{21}H_{28}N_2O_3$	*p*-CH_3	37.9	69.7–71.7	70.75	7.92	7.86	70.30	7.70	8.06

mation of secondary amino alcohols, structure studies were considered unnecessary in this project.

EXPERIMENTAL

1-(2-Ethoxyphenyl)piperazine monohydrobromide. Two moles (624 g.) of bis(β,β′-bromoethyl)amine hydrobromide and 1500 ml. of methanol were placed in a 3-l. flask. Two moles (274.18 g.) of freshly distilled *o*-phenetidine were added slowly. The mixture was refluxed for 10 hr. using an efficient, water-cooled condenser. One mole (106 g.) of sodium carbonate was added and refluxing was continued for 10 hr. The original volume was reduced by one half by distillation of methanol. Cooling the solution produced crystals of 1-(2-ethoxyphenyl)piperazine monohydrobromide. Neut. equivalent: calcd., 287.15; found, 285.00.

1-(2-Ethoxyphenyl)piperazine. One mole (287.15 g.) of 1-(2-ethoxyphenyl)piperazine monohydrobromide was slurried in 200 ml. of water and then neutralized with 40% sodium hydroxide. The oil which formed was removed and distilled under water-pump vacuum to remove water. Distillation at 0.08 mm., 112–114° (uncorr.) gave a 26% yield of the free amine.

1-(2-Ethoxyphenyl)piperazinium acetate. Three and one-tenth grams (0.05 mole) of glacial acetic acid was added dropwise with stirring to 10.32 g. (0.05 mole) of 1-(2-ethoxyphenyl)piperazine dissolved in acetone. The precipitated salt was recrystallized four times from acetone and ethanol. M.p. 113.1–114.1° (corr.); yield, 28%.

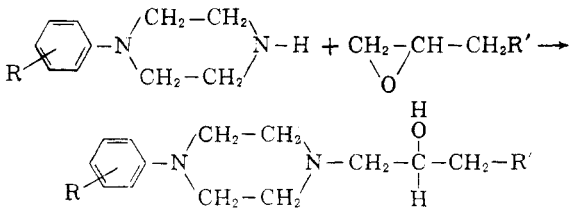
Anal. Calcd. for $C_{14}H_{22}N_2O_3$: C, 63.14; H, 8.35; N, 10.52. Found: C, 63.35; H, 8.56; N, 10.32.

1-(2-Methoxyphenyl)piperazine was prepared in the same manner as 1-(2-ethoxyphenyl)piperazine. B.p., 130–133° at 0.1 mm. (uncorr.).

1-(2-Methoxyphenyl)piperazinium acetate was prepared in the same manner as the 1-(2-ethoxyphenyl)piperazinium acetate. M.p., 128.3–129.3° (corr.).

Anal. Calcd. for $C_{13}H_{20}N_2O_3$: C, 61.88; H, 7.99; N, 11.10. Found: C, 61.90; H, 8.01; N, 10.90.

Reactions of 1-arylpiperazines with 1,2-epoxides. The various 1-arylpiperazines were treated with various 1,2-epoxides, illustrated by the general equation:



The 1-arylpiperazine (0.10 mole) was thoroughly mixed with the 1,2-epoxide in an Erlenmeyer flask, and allowed to stand for from one to two days. Either a crystalline solid or a viscous liquid, which showed no tendency to flow, was formed. In some cases crystallization was induced by scratching the flask or by seeding. Purification of these products was extremely difficult. Ethanol proved to be the best crystallizing solvent for all the reported products except 1-(2-chlorophenyl)-4-[2-hydroxy-3-(2-methoxyphenoxy)propyl] piperazine. It was crystallized from freshly distilled ethyl ether. The omissions of certain members of series result from the fact that analytical samples of these members could not be obtained. Data concerning the new compounds prepared are given in Table I.

The 1,2-epoxydodecane was obtained from the Becco Chemical Division of Food Machinery Chemical Corp. The 1,2-epoxy-3-aryloxypropanes were prepared by Dr. Jaime B. Fernandez using the method of the Shell Development Co.[15]

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[CONTRIBUTION FROM JOHN HARRISON LABORATORY OF CHEMISTRY, UNIVERSITY OF PENNSYLVANIA]

A Procedure for Phthaloylation under Mild Conditions

AJAY K. BOSE,[1] FRANCES GREER,[2] AND CHARLES C. PRICE

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By allowing phthalic anhydride to react with a number of amino acids and related primary amines in refluxing nonpolar solvents in the presence of triethylamine and separating the water formed, the phthalimide derivative may be prepared in good yield and without racemization. Phthaloylation without racemization may also be carried out in *N*,*N*-dimethylformamide medium.

Sheehan, Chapman, and Roth[3] have shown that phthaloylation by the fusion of an amino acid with phthalic anhydride can lead to racemization if the reaction temperature is higher than 150°. More recently it has been reported[4] that some substituted amino acids like *N*-benzylcysteine undergo racemization if the fusion temperature exceeds 110°. Baker and co-workers[5] have reported a mild two-step process for phthaloylation which involves the preparation of a phthalamic acid in the first step and its cyclization *via* a mixed anhydride in the second step. Evidently this process is suitable only for those amino compounds which do not also possess a free carboxyl group. Balenović and Gašpert[4] have developed a two-step procedure applicable to amino acids which involves the cyclization of a phthalamic ester obtained by the reaction of an amino acid with *o*-carbethoxythiobenzoic acid.

We wish to report here a one-step process for phthaloylation that avoids high temperature.

This phthaloylation procedure consists in treating one equivalent of phthalic anhydride with an amino compound in a refluxing solvent (*e.g.*, toluene or benzene) in the presence of triethylamine, a water separator being used to remove the water formed in the reaction. In the phthaloylation of an amino acid the best yield is obtained when the quantity of triethylamine used is about one-tenth of an equivalent.

Using this method ethyl phthalimidoacetate was obtained from glycine ethyl ester hydrochloride in 96% yield when toluene was the reaction medium. When, however, a water separator was not used the yield was reduced to 50%; the rest of the glycine ester was presumably in the form of the corresponding phthalamic acid because on standing in a dilute hydrochloric acid solution, this material was slowly converted to ethyl phthalimidoacetate. Drefahl and Fischer[6] have recently reported that mineral acids catalyze the dehydration of some phthalamic acids to phthalimide derivatives in the presence of an excess of water.

Due to the instability of aminoacetonitrile to heat, the fusion method is unsuitable for the phthaloylation of this compound. However, by treating aminoacetonitrile bisulfate with phthalic anhydride and triethylamine in benzene medium, phthal-

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