

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

## Derivatives of Piperazine. XXXII. 1-Aryl-4-(2-hydroxy-3-aryloxypropyl)-piperazines

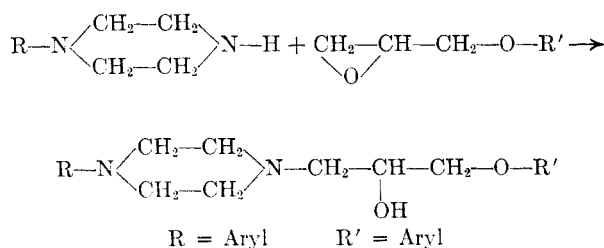
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Fifty-six new 1-aryl-4-(2-hydroxy-3-aryloxypropyl)piperazines have been prepared by the addition of 1-arylpiperazines to 1,2-epoxy-3-aryloxypropanes.

The wide spectrum of pharmacological action of the piperazines, the amino alcohols, and the amino ethers, have made these classes of compounds among the most widely investigated in this field. In view of these activities, a series of new 1-aryl-4-(2-hydroxy-3-aryloxypropyl)piperazines was synthesized.

The synthesis of the series is shown by the general equation



The reaction of amines with epoxides of this type has been shown to yield virtually pure secondary alcohols.<sup>1-4</sup> This structure was substantiated for this series since addition of the piperazines to epichlorohydrin followed by reaction with the sodium phenolate gave products whose infrared spectra, and melting points were identical with materials prepared by the addition of the piperazines to the 1,2-epoxy-3-aryloxypropanes. Pertinent physical and analytical data of the 1-aryl-4-(2-hydroxy-3-aryloxypropyl)piperazines are shown in Table I.

The piperazines used in this work have been previously prepared and described by Pollard, *et al.*<sup>5,6</sup> The aryloxypropane intermediates have also been described in the literature with the exception of 1,2-epoxy-3-(4-methoxyphenoxy)propane. Its preparation and properties are described below.

### EXPERIMENTAL

*Intermediates.* The 1-arylpiperazines were prepared according to Pollard, *et al.*<sup>5,6</sup> The preparation used for the 3-aryloxy-1,2-epoxypropanes was essentially that of Fairbourne, Gibson, and Stevens<sup>7</sup> and is illustrated by the preparation of 1,2-epoxy-3-(4-methoxyphenoxy)propane.

*1,2-Epoxy-3-(4-methoxyphenoxy)propane.* In a five-liter, three-necked flask equipped with mechanical stirrer, addition funnel, and thermometer, were placed 4-methoxyphenol (1000 g., 8.05 moles) and epichlorohydrin (929 g., 10.0 moles). Sodium hydroxide (322 g., 8.05 moles) in 500 g. of water was then added to the stirred mixture at such a rate that the reaction temperature was kept between 70 and 80°. The addition required about 90 min. After the addition was complete, the reaction mixture was heated to 100° for 1 hr., cooled to room temperature, and extracted with benzene. The benzene extract was dried over anhydrous sodium sulfate overnight. Removal of the low boiling materials was then carried out under water-pump vacuum. Distillation of the residue gave 1,2-epoxy-3-(4-methoxyphenoxy)propane (893 g., 51%) boiling at 135-137° at 2.5 mm.

*Anal.* Calcd. for C<sub>10</sub>H<sub>12</sub>O<sub>3</sub>: C, 66.63; H, 6.71. Found: C, 66.60; H, 6.80.

*1-Aryl-4-(2-hydroxy-3-aryloxypropyl)piperazine.* The method of preparation of all of these materials was essentially the same and is given in a general form.

1-Arylpiperazine (0.10 mole) and 1,2-epoxy-3-aryloxypropane (0.10 mole) were mixed in an Erlenmeyer flask. When the reactants were not mutually soluble on mixing for a short time, 50 ml. of 95% ethanol was added to afford complete solution. After standing 24 hr., the reaction was essentially complete. The product at this point was either crystalline or of the consistency of barely molten glass. When crystallization did not occur spontaneously, it was induced by either scratching the container with a glass rod or by seeding with crystalline homologs. The impure crystalline product was then purified by two to five recrystallizations from ethanol, ethanol-benzene, or cyclohexane until the mother liquor obtained was colorless and the product had a melting point range of 1° or less.

Yields and physical properties of these piperazines are given in Table I.

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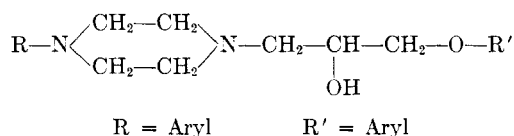
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TABLE I  
DATA ON 1-ARYL-4-(2-HYDROXY-3-ARYLOXYPROPYL)PIPERAZINES



R	R'	Molecular Formula	Molecular Weight	Melting Point	Yield, %	C, % Calcd. Found	H, % Calcd. Found	N, % Calcd. Found
Phenyl	Phenyl	C <sub>19</sub> H <sub>24</sub> N <sub>2</sub> O <sub>2</sub>	276.37	124.5-125	79	73.04 73.30	7.74 7.65	
	2-Chlorophenyl	C <sub>19</sub> H <sub>23</sub> N <sub>2</sub> O <sub>2</sub> Cl	346.85	89-90	75	65.79 65.82	6.68 6.99	
	4-Chlorophenyl	C <sub>19</sub> H <sub>23</sub> N <sub>2</sub> O <sub>2</sub> Cl	346.85	142-143	71	65.79 65.58	6.68 6.85	
	2-Methylphenyl	C <sub>20</sub> H <sub>26</sub> N <sub>2</sub> O <sub>2</sub>	326.43	104-105	91	73.58 73.84	8.03 7.97	
	3-Methylphenyl	C <sub>20</sub> H <sub>26</sub> N <sub>2</sub> O <sub>2</sub>	326.43	89.5-90.2	74	73.58 73.57	8.03 7.99	
	4-Methylphenyl	C <sub>20</sub> H <sub>26</sub> N <sub>2</sub> O <sub>2</sub>	326.43	130.2-130.9	76	73.58 73.70	8.03 8.12	
	1-Naphthyl	C <sub>23</sub> H <sub>26</sub> N <sub>2</sub> O <sub>2</sub>	326.46	105.8-106.5	80	76.21 76.00	7.23 7.19	
	4-Methoxyphenyl	C <sub>20</sub> H <sub>26</sub> N <sub>2</sub> O <sub>3</sub>	342.43	137-138	59	70.14 69.88	7.65 7.45	
2-Chlorophenyl	Phenyl	C <sub>19</sub> H <sub>23</sub> N <sub>2</sub> O <sub>2</sub> Cl	346.85	64-65	51	65.79 65.75	6.68 7.12	
	2-Chlorophenyl	C <sub>19</sub> H <sub>22</sub> N <sub>2</sub> O <sub>2</sub> Cl <sub>2</sub>	381.30	99-100.5	35			7.35 7.53
	4-Chlorophenyl	C <sub>19</sub> H <sub>22</sub> N <sub>2</sub> O <sub>2</sub> Cl <sub>2</sub>	381.30	91.8-92.2	68	59.85 60.06	5.82 5.75	
	2-Methylphenyl	C <sub>20</sub> H <sub>25</sub> N <sub>2</sub> O <sub>2</sub> Cl	360.88	76.7-77.7	41			7.59 7.41
	3-Methylphenyl	C <sub>20</sub> H <sub>25</sub> N <sub>2</sub> O <sub>2</sub> Cl	360.88	64-65	57	66.56 66.71	6.98 7.04	
	4-Methylphenyl	C <sub>20</sub> H <sub>25</sub> N <sub>2</sub> O <sub>2</sub> Cl	360.88	85.9-86.9	42			7.60 7.32
	1-Naphthyl	C <sub>23</sub> H <sub>25</sub> N <sub>2</sub> O <sub>2</sub> Cl	396.91	124-124.6	75	69.60 69.69	6.35 6.20	
	4-Methoxyphenyl	C <sub>20</sub> H <sub>25</sub> N <sub>2</sub> O <sub>3</sub> Cl	376.88	93-94	65	63.73 63.55	6.69 6.68	
3-Chlorophenyl	Phenyl	C <sub>19</sub> H <sub>23</sub> N <sub>2</sub> O <sub>2</sub> Cl	346.85	85-86	68	65.79 65.69	6.68 6.51	
	2-Chlorophenyl	C <sub>19</sub> H <sub>22</sub> N <sub>2</sub> O <sub>2</sub> Cl <sub>2</sub>	381.30	97-98	68	59.85 60.01	5.82 5.67	
	4-Chlorophenyl	C <sub>19</sub> H <sub>22</sub> N <sub>2</sub> O <sub>2</sub> Cl <sub>2</sub>	381.30	109-109.7	72	59.85 59.87	5.82 5.74	
	2-Methylphenyl	C <sub>20</sub> H <sub>25</sub> N <sub>2</sub> O <sub>2</sub> Cl	360.88	94-95	71	66.56 66.26	6.98 6.62	
	3-Methylphenyl	C <sub>20</sub> H <sub>25</sub> N <sub>2</sub> O <sub>2</sub> Cl	360.88	80.5-81.5	62	66.56 66.47	6.98 7.01	
	4-Methylphenyl	C <sub>20</sub> H <sub>25</sub> N <sub>2</sub> O <sub>2</sub> Cl	360.88	92-93	61	66.56 66.87	6.98 7.01	
	1-Naphthyl	C <sub>23</sub> H <sub>25</sub> N <sub>2</sub> O <sub>2</sub> Cl	396.91	123-124	66	69.60 69.91	6.35 6.38	
	4-Methoxyphenyl	C <sub>20</sub> H <sub>25</sub> N <sub>2</sub> O <sub>3</sub> Cl	376.88	106.5-107.5	70	63.73 63.57	6.69 6.79	
4-Chlorophenyl	Phenyl	C <sub>19</sub> H <sub>23</sub> N <sub>2</sub> O <sub>2</sub> Cl	346.85	130.8-131.4	69	65.79 65.89	6.68 6.68	
	2-Chlorophenyl	C <sub>19</sub> H <sub>22</sub> N <sub>2</sub> O <sub>2</sub> Cl <sub>2</sub>	381.30	111.5-112.5	79	59.85 60.17	5.82 6.05	
	4-Chlorophenyl	C <sub>19</sub> H <sub>22</sub> N <sub>2</sub> O <sub>2</sub> Cl <sub>2</sub>	381.30	154-155	53	59.85 59.88	5.82 5.98	
	2-Methylphenyl	C <sub>20</sub> H <sub>25</sub> N <sub>2</sub> O <sub>2</sub> Cl	360.88	93-94	48	66.56 67.02	6.98 6.98	
	3-Methylphenyl	C <sub>20</sub> H <sub>25</sub> N <sub>2</sub> O <sub>2</sub> Cl	360.88	106.3-106.6	67	66.56 66.67	6.98 7.22	
	4-Methylphenyl	C <sub>20</sub> H <sub>25</sub> N <sub>2</sub> O <sub>2</sub> Cl	360.88	144-145	50	66.56 66.75	6.98 7.23	

TABLE I (Continued)

R	R'	Molecular Formula	Molecular Weight	Melting Point	Yield, %	C, % Calcd. Found	H, % Calcd. Found	N, % Calcd. Found
	1-Naphthyl	C <sub>23</sub> H <sub>25</sub> N <sub>2</sub> O <sub>2</sub> Cl	396.91	125.3-126	53	69.60 69.70	6.35 6.40	
	4-Methoxyphenyl	C <sub>20</sub> H <sub>25</sub> N <sub>2</sub> O <sub>2</sub> Cl	376.88	143.5-144.5	68	63.73 63.90	6.69 6.50	
2-Methylphenyl	Phenyl	C <sub>20</sub> H <sub>25</sub> N <sub>2</sub> O <sub>2</sub>	326.42	83.6-84.6	48			8.58 8.68
	2-Chlorophenyl	C <sub>20</sub> H <sub>25</sub> N <sub>2</sub> O <sub>2</sub> Cl	360.88	83-84	42			7.60 7.65
	4-Chlorophenyl	C <sub>20</sub> H <sub>25</sub> N <sub>2</sub> O <sub>2</sub> Cl	360.88	94-95	20	66.56 66.72	6.98 7.26	
	2-Methylphenyl	C <sub>21</sub> H <sub>25</sub> N <sub>2</sub> O <sub>2</sub>	340.45	80.8-82.3	38			8.23 8.29
	3-Methylphenyl	C <sub>21</sub> H <sub>25</sub> N <sub>2</sub> O <sub>2</sub>	340.45	57.1-58.6	36			8.23 8.30
	4-Methylphenyl	C <sub>21</sub> H <sub>25</sub> N <sub>2</sub> O <sub>2</sub>	330.45	75.8-76.3	45			8.23 8.19
	1-Naphthyl	C <sub>24</sub> H <sub>29</sub> N <sub>2</sub> O <sub>2</sub>	376.48	84.8-85.2	41	76.56 76.31	7.50 7.63	
	4-Methoxyphenyl	C <sub>21</sub> H <sub>25</sub> N <sub>2</sub> O <sub>3</sub>	356.45	100-100.5	52	70.76 70.53	7.92 8.03	
3-Methylphenyl	Phenyl	C <sub>20</sub> H <sub>25</sub> N <sub>2</sub> O <sub>2</sub>	326.43	83.5-84.2	55	73.58 73.53	8.03 7.91	
	2-Chlorophenyl	C <sub>20</sub> H <sub>25</sub> N <sub>2</sub> O <sub>2</sub> Cl	360.88	79.9-80.5	48	66.56 66.20	6.98 6.77	
	4-Chlorophenyl	C <sub>20</sub> H <sub>25</sub> N <sub>2</sub> O <sub>2</sub> Cl	360.88	113.8-114.1	59	66.56 66.19	6.98 7.05	
	2-Methylphenyl	C <sub>21</sub> H <sub>25</sub> N <sub>2</sub> O <sub>2</sub>	340.45	81-82	41	74.08 73.97	8.29 8.29	
	3-Methylphenyl	C <sub>21</sub> H <sub>25</sub> N <sub>2</sub> O <sub>2</sub>	340.45	77-77.8	58	74.08 73.51	8.29 8.26	
	4-Methylphenyl	C <sub>21</sub> H <sub>25</sub> N <sub>2</sub> O <sub>2</sub>	340.45	92.7-93	58	74.08 73.75	8.29 8.26	
	1-Naphthyl	C <sub>24</sub> H <sub>29</sub> N <sub>2</sub> O <sub>2</sub>	376.48	96.2-96.8	70	76.56 76.38	7.50 7.70	
	4-Methoxyphenyl	C <sub>21</sub> H <sub>25</sub> N <sub>2</sub> O <sub>3</sub>	356.45	100-100.5	62	70.76 70.53	7.92 8.03	
4-Methylphenyl	Phenyl	C <sub>20</sub> H <sub>25</sub> N <sub>2</sub> O <sub>2</sub>	326.43	119-119.5	70	73.58 73.69	8.03 8.14	
	2-Chlorophenyl	C <sub>20</sub> H <sub>25</sub> N <sub>2</sub> O <sub>2</sub> Cl	360.88	87-87.5	55	66.56 66.36	6.98 7.05	
	4-Chlorophenyl	C <sub>20</sub> H <sub>25</sub> N <sub>2</sub> O <sub>2</sub> Cl	360.88	137.8-138.6	55	66.56 66.69	6.98 7.11	
	2-Methylphenyl	C <sub>21</sub> H <sub>25</sub> N <sub>2</sub> O <sub>2</sub>	340.45	97.3-97.8	56	74.08 73.76	8.29 8.61	
	3-Methylphenyl	C <sub>21</sub> H <sub>25</sub> N <sub>2</sub> O <sub>2</sub>	340.45	85.6-86.5	57	74.08 74.06	8.29 8.27	
	4-Methylphenyl	C <sub>21</sub> H <sub>25</sub> N <sub>2</sub> O <sub>2</sub>	340.45	126-126.7	56	74.08 73.93	8.29 8.35	
	1-Naphthyl	C <sub>24</sub> H <sub>29</sub> N <sub>2</sub> O <sub>2</sub>	376.48	106.8-107.3	57	76.56 76.47	7.50 7.56	
	4-Methoxyphenyl	C <sub>21</sub> H <sub>25</sub> N <sub>2</sub> O <sub>3</sub>	356.45	130-131	63	70.76 70.69	7.92 7.97	