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Derivatives of Piperazine. XXXIII. Syntheses of Some Unsymmetrical 1,4-Disubstituted-2-methylpiperazines

C. B. POLLARD, W. M. LAUTER, AND J. G. DUFF

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4-(ω-Hydroxyalkyl)-2-methyl-piperazines were treated with aralkyl and alkyl halides to form twenty-one unsymmetrical 1,4-disubstituted-2-methylpiperazines. Three new 4-(ω-hydroxyalkyl)-2-methylpiperazines were also prepared. A urethane of each of the unsymmetrical 1,4-disubstituted-2-methylpiperazines was prepared. All of the above compounds are now being evaluated pharmacologically.

In the search for compounds having physiological activity, it was considered of interest to synthesize a number of unsymmetrical 1,4-disubstituted-2-methylpiperazines. In this investigation, 1,4-disubstituted-2-methylpiperazines were prepared in which the group in the 1-position was alkyl or aralkyl and the substituent in the 4-position was an ω-hydroxyalkyl.

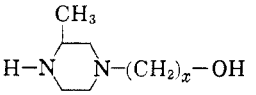
The 4-(ω-hydroxyalkyl)-2-methylpiperazines were prepared by using the method of Kitchen and Pollard[1] wherein excess 2-methylpiperazine reacted with chlorohydrins. The 4-(ω-hydroxyalkyl)-2-methylpiperazines were then treated with an alkyl or an aralkyl halide to give unsymmetrical 1,4-disubstituted-2-methylpiperazines.

The reaction of 2-methylpiperazine with chlorohydrin could give either the 1- or the 4-(ω-hydroxyalkyl)-2-methylpiperazine. Beck, Hamlin, and Weston[2] have demonstrated that monoalkylation of 2-methylpiperazine occurs at the 4-position. It would seem reasonable to assume that the chlorohydrins would react in the same manner.

An urethane of each 1,4-disubstituted-2-methylpiperazine was also prepared. Difficulty in obtaining solid urethanes was encountered. However, in general, 1-naphthyl isocyanate, *p*-chlorophenyl isocyanate, or *p*-ethoxyphenyl isocyanate gave solid urethanes. 1-*n*-Propyl-4-(2-hydroxyethyl)-2-methylpiperazine and 1-isobutyl-4-(2-hydroxyethyl)-2-methylpiperazine failed to give solid urethanes with

TABLE I

DATA ON 4-(ω-HYDROXYALKYL)-2-METHYLPIPERAZINES



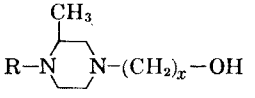
x	Molecular Formula	Molecular Weight	Boiling Point, °/mm. (uncorr.)	n_D^{25}	Yield, %	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
2	$C_7H_{16}N_2O$	144.22	108–110/2	1.4978	77	58.29	58.41	11.19	10.89
3	$C_8H_{18}N_2O$	158.24	119–121/3	1.4932	70	60.72	60.73	11.40	11.42
4	$C_9H_{20}N_2O$	172.27	121–122/1.5	1.4920	60	62.74	62.39	11.70	11.51

(1) L. J. Kitchen and C. B. Pollard, *J. Org. Chem.*, **8**, 338 (1943).

(2) K. Beck, K. Hamlin, and A. Weston, *J. Am. Chem. Soc.*, **74**, 605 (1952).

TABLE II

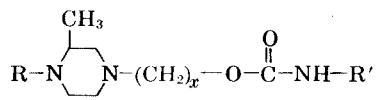
DATA ON UNSYMMETRICAL 1,4-DISUBSTITUTED-2-METHYLPIPERAZINES



R	x	Molecular Formula	Molecular Weight	Boiling Point, °/mm. (uncorr.)	n_D^{25}	Yield, %	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
n-Propyl	2	$C_{10}H_{22}N_2O$	186.30	99–102/1.2	1.4801	45	64.47	64.24	11.91	11.94		
Isopropyl	2	$C_{10}H_{22}N_2O$	186.30	100–101/1.5	1.4812	41	64.47	64.37	11.91	11.61		
Isobutyl	2	$C_{11}H_{24}N_2O$	200.32	112–114/0.6	1.4781	39	65.95	65.66	12.08	11.78	13.99	13.78
t-Butyl	2	$C_{11}H_{24}N_2O$	200.32	84–85/1	1.4570	3	65.95	64.84	12.08	11.88	13.99	13.77
Benzyl	2	$C_{14}H_{22}N_2O$	234.34	178–180/1.5	1.5410	48	71.74	71.46	9.46	9.04	11.96	11.50
Phenethyl	2	$C_{15}H_{24}N_2O$	248.36	162–164/1	1.5342	28	72.54	72.60	9.74	9.49	11.28	11.16
Benzohydryl	2	$C_{20}H_{26}N_2O$	310.43	198–202/1	1.5675	13	77.38	77.21	8.44	8.29	9.03	9.15
n-Propyl	3	$C_{11}H_{24}N_2O$	200.32	117–119/1.5	1.4788	41	65.95	66.42	12.08	12.02	13.99	13.68
Isopropyl	3	$C_{11}H_{24}N_2O$	200.32	114.5–115.5/1.5	1.4824	27	65.95	66.06	12.08	11.86	13.99	13.70
Isobutyl	3	$C_{12}H_{26}N_2O$	214.35	129–133/0.8	1.4738	31	67.23	66.73	12.22	11.79	13.07	12.60
t-Butyl	3	$C_{12}H_{26}N_2O$	214.35	94–99/1	1.4598	7	67.23	67.14	12.22	11.80		
Benzyl	3	$C_{15}H_{24}N_2O$	248.36	176–178.5/2	1.5327	58	72.54	72.63	9.74	9.53	11.28	11.05
Phenethyl	3	$C_{16}H_{26}N_2O$	262.39	189–192/0.6	1.5445	50	73.23	73.03	9.99	10.11	10.68	10.98
Benzohydryl	3	$C_{21}H_{28}N_2O$	324.25	216–221/1	1.5579	16	77.73	77.96	8.70	8.71	8.63	8.14
n-Propyl	4	$C_{12}H_{26}N_2O$	214.35	141–143/1	1.4796	59	67.23	67.09	12.22	11.98	13.07	13.16
Isopropyl	4	$C_{12}H_{26}N_2O$	214.35	132–134/1.5	1.4818	12	67.23	67.24	12.22	12.06	13.07	12.70
Isobutyl	4	$C_{13}H_{28}N_2O$	228.37	137–138/0.6	1.4788	29	68.37	68.56	12.36	12.26		
t-Butyl	4	$C_{13}H_{28}N_2O$	228.37	110–113/1.3	1.4679	8	68.37	68.07	12.36	12.03	12.27	12.08
Benzyl	4	$C_{16}H_{26}N_2O$	262.39	197–200/1	1.5301	51	73.23	72.80	9.99	9.91	10.68	10.72
Phenethyl	4	$C_{17}H_{28}N_2O$	276.41	198–200/1.5	1.5298	67	73.87	74.20	10.21	10.26	10.14	10.25
Benzohydryl	4	$C_{22}H_{30}N_2O$	338.48	226–230/1	1.5628	19	78.06	78.12	8.94	8.76	8.26	7.65

TABLE III

DATA ON URETHANES OF UNSYMMETRICAL 1,4-DISUBSTITUTED-2-METHYLPIPERAZINES



R	x	R′	Molecular Formula	Molecular Weight	Melting Point, °, (corr.)	Yield, %	Carbon, %		Hydrogen, %		Nitrogen, %	
							Calcd.	Found	Calcd.	Found	Calcd.	Found
n-Propyl	2	1-Naphthyl	$C_{21}H_{29}N_3O_2$	355.46	[a]	77	70.95	70.60	8.22	8.48	11.82	11.90
Isopropyl	2	*p*-Ethoxyphenyl	$C_{19}H_{31}N_3O_3$	349.46	75–77	66	65.27	65.37	8.94	9.10	12.02	12.60
Isobutyl	2	1-Naphthyl	$C_{22}H_{31}N_3O_2$	369.49	[b]	95					11.37	11.66
t-Butyl	2	*p*-Chlorophenyl	$C_{18}H_{28}N_3O_2Cl$	353.88	134–135	98	61.09	60.73	7.97	7.83	11.87	12.04
Benzyl	2	*p*-Chlorophenyl	$C_{21}H_{26}N_3O_2Cl$	387.90	83.5–84.5	82	65.02	64.75	6.76	6.59	10.83	10.90
Phenethyl	2	*p*-Ethoxyphenyl	$C_{24}H_{33}N_3O_3$	411.52	69–70	97	70.08	70.01	8.08	7.74	10.21	10.40
Benzohydryl	2	1-Naphthyl	$C_{31}H_{33}N_3O_2$	479.59	142–143	63	77.63	77.49	6.93	7.03	8.79	8.85
n-Propyl	3	1-Naphthyl	$C_{22}H_{31}N_3O_2$	369.49	81–82	77	71.51	71.09	8.46	8.35		
Isopropyl	3	1-Naphthyl	$C_{22}H_{31}N_3O_2$	369.49	99–100	58	71.51	71.29	8.46	8.32		
Isobutyl	3	1-Naphthyl	$C_{23}H_{33}N_3O_2$	383.51	70–71	94	72.49	72.95	8.67	8.57	10.95	11.55
t-Butyl	3	*p*-Chlorophenyl	$C_{19}H_{30}N_3O_2Cl$	367.91	129.5–130.5	77	62.02	61.26	8.22	7.75	11.42	11.12
Benzyl	3	1-Naphthyl	$C_{26}H_{31}N_3O_2$	417.53	81–82	82	74.68	74.79	7.27	7.48	9.95	10.07
Benzyl	3	*p*-Chlorophenyl	$C_{22}H_{28}N_3O_2Cl$	401.93	75–75.5	94	65.74	65.71	7.02	7.01		
Phenethyl	3	1-Naphthyl	$C_{27}H_{33}N_3O_2$	431.55	89–89.5	77	75.14	74.96	7.71	7.77		
Benzohydryl	3	*p*-Chlorophenyl	$C_{28}H_{32}N_3O_2Cl$	478.02	123–125	94	70.35	70.43	6.75	6.67	8.79	8.30
n-Propyl	4	*p*-Ethoxyphenyl	$C_{21}H_{35}N_3O_3$	377.51	58.5–59.5	77	66.81	66.76	9.32	9.06	11.13	11.10
Isopropyl	4	*p*-Chlorophenyl	$C_{19}H_{30}N_3O_2Cl$	367.91	84–85	60	62.02	61.68	8.22	8.11	11.42	10.80
Isobutyl	4	*p*-Chlorophenyl	$C_{20}H_{32}N_3O_2Cl$	381.94	78–79	92	62.89	63.08	8.45	8.36	11.00	10.80
t-Butyl	4	*p*-Chlorophenyl	$C_{20}H_{32}N_3O_2Cl$	381.94	97–98	75	62.89	62.85	8.45	8.33	11.00	10.95
Benzyl	4	*p*-Ethoxyphenyl	$C_{25}H_{35}N_3O_3$	425.55	83–85	94	70.56	70.31	8.29	8.29	9.87	10.10
Phenethyl	4	1-Naphthyl	$C_{28}H_{35}N_3O_2$	445.58	95.5–96.5	69	75.48	75.53	7.92	7.81	9.43	9.54
Benzohydryl	4	*p*-Chlorophenyl	$C_{29}H_{34}N_3O_2Cl$	492.04	98–99.5	95	70.78	70.81	6.96	7.05	8.54	8.35

[a] Freezing point, 23° (uncorr.). [b] Freezing point, 25–26° (uncorr.).

the above isocyanates. Difficulty was encountered in obtaining satisfactory analyses on compounds containing the isobutyl and the *t*-butyl radicals. Repeated purifications did not improve the analyses.

EXPERIMENTAL

A general procedure is given for the preparation of each type of compound. Physical and analytical data are listed in Tables I, II, and III.

2-Methylpiperazine was purchased from the Wyandotte Chemical Corporation.

Chlorohydrins. Tetramethylene chlorohydrin was prepared by the method of Starr and Hixon.[3] Trimethylene chlorohydrin and ethylene chlorohydrin were purchased from the Eastman Kodak Company.

Alkyl and aralkyl halides. With the exception of benzohydryl chloride, alkyl and aralkyl bromides were used. They were purchased from the Eastman Kodak Company.

4-(ω-Hydroxyalkyl)-2-methylpiperazines. 2-Methylpiperazine (2.8 moles) was dissolved in 500 ml. of ethanol. The chlorohydrin (1.0 mole) was added and the mixture was shaken well. The mixture was then refluxed for 2 hr. Potassium hydroxide (1.1 moles) was added and after heating for 0.5 hr., approximately half of the ethanol was removed by distillation. The reaction mixture was cooled and filtered. The remainder of the ethanol and the unreacted 2-methylpiperazine were then removed by distillation. The 4-(ω-hydroxyalkyl)-2-methylpiperazines were then distilled using reduced pressure.

1-Substituted-4-(2-hydroxyalkyl)-2-methylpiperazines. 4-(ω-Hydroxyalkyl)-2-methylpiperazine (0.60 mole) was dissolved in 175 ml. of absolute ethanol. To this solution was added the aralkyl or the alkyl halide (0.60 mole). The reaction mixture was refluxed 6 to 10 hr. Sodium bicarbonate (0.75 mole) was added, the ethanol was removed by distillation, and 300 ml. of water was added. The reaction mixture was extracted with ether. The ether extracts were dried over anhydrous sodium sulfate and then filtered. After the removal of the ether, the products were distilled using reduced pressure.

Urethanes of 1-substituted-4-(ω-hydroxyalkyl)-2-methylpiperazines. The isocyanate (0.05 mole), dissolved in 20 ml. of hexane, was added to a solution of the 1-substituted-4-(ω-hydroxyalkyl)-2-methylpiperazine (0.05 mole) in 20 ml. of hexane. The two were mixed well and allowed to stand at room temperature. The solid urethanes were filtered and recrystallized from hexane or heptane. The oils were washed with hexane.

(3) D. Starr and R. Hixon, *J. Am. Chem. Soc.*, **56**, 1595 (1934).

GAINESVILLE, FLA.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MICHIGAN STATE UNIVERSITY]

The Reaction of Some Organomagnesium Iodides with 1,2-Epoxypropane

FRANCIS E. EVANS[1,2] AND RALPH C. HUSTON[3]

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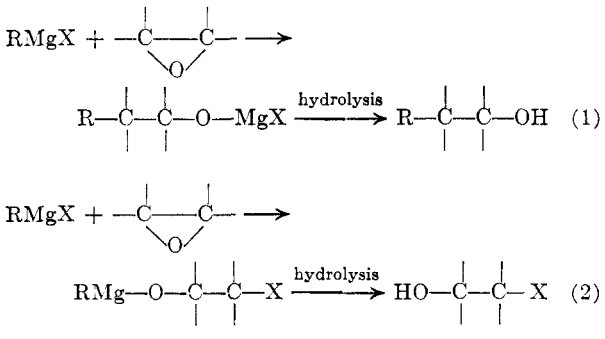
Several Grignard reagents prepared by the reaction of an organic iodide with magnesium in the presence of anhydrous ether were treated with one and two molar equivalents of 1,2-epoxypropane to give an alcohol and an iodohydrin. In all cases, the yield of the iodohydrin was greater than that of the expected alcohol. Only when two molar equivalents of epoxide were present was the yield of alcohol significant. The reaction of the dioxane soluble portion of the Grignard reagent (R_2Mg) with two molar equivalents of epoxide to yield an alcohol was also investigated.

It has been shown[4-6] that the reaction of a Grignard reagent with an epoxide occurs in such a manner that either the organo-magnesium bond or the magnesium-halide bond may be attacked by the epoxide (1,2). The resulting products are mixtures of an alcohol and a halohydrin.



When Grignard reagents obtained from organic chlorides,[5] bromides,[6] and iodides[4] were treated with epoxyethane (ethylene oxide) in equimolar quantities the products were predominately the expected alcohols, indicating mainly reaction at the organo-magnesium bond. Halohydrin, presumably formed by reaction at the magnesium-halide bond, was produced in all cases, but in surprisingly increased yields when Grignard reagents prepared from iodides were used. The yield of both the expected alcohol and the halohydrin were increased when the reaction was carried out between two moles of epoxyethane and one mole of the Grignard reagent.

(1) Abstracted from a thesis submitted by Francis E. Evans in partial fulfillment of the requirements for the degree of Doctor of Philosophy, Michigan State University, March 1955.

(2) Present address: Research and Development Department, National Aniline Division, Allied Chemical Corp., Buffalo, N. Y.

(3) Deceased, April, 1954.

(4) R. C. Huston and A. A. Agett, *J. Org. Chem.*, **6**, 123 (1941).

(5) R. C. Huston and C. C. Langham, *J. Org. Chem.*, **12**, 90 (1947).

(6) R. C. Huston and H. M. D'Arcy, *J. Org. Chem.*, **18**, 16 (1953).