[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

Quaternary Piperazines with Anti-pinworm Activity[1]

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The syntheses and properties of 100 piperazine monoquaternary salts prepared for a study of their anthelmintic activities, and of some related compounds, are reported. Most were prepared by standard methods, but attempts to decarbethoxylate three 1-carbethoxy-4-benzylquaternaries (table, lines 42, 49, 50) led to debenzylation. Anthelmintic activity (*Syphacia obvelata* in the mouse) is discussed briefly as a function of structure.

Consideration of the structures of a number of compounds active in a screening test (*Syphacia obvelata* in the mouse)[2] designed to find substances active against the pinworm of humans, *Enterobius vermicularis*, suggested that two structural features were common to piperazine, gentian violet and several other active series of compounds: all appeared likely to exist largely in the cationic form at physiological acidities,[3] and all had a ring structure near the positive charge. It was thought of interest to prepare some other compounds combining these structural features. The piperazine ring, which occurs in many physiologically active compounds, was therefore given the positive charge induced by quaternization at one nitrogen. It was also anticipated that the well-known tendency of quaternary salts to be poorly absorbed on oral administration would result in negligible systemic toxicity to the host. The high therapeutic index of some of the first compounds prepared led to the synthesis of a large number of diverse piperazine monoquaternaries, whose properties are tabulated.

The thoroughly explored route to unsymmetrical piperazines by alkylation of 1-carbethoxypiperazine[1] was used to prepare most of the compounds. The quaternizations were done in acetone at about room temperature, since some of the higher quaternaries could not be crystallized readily from alcoholic solvents. Further, solvolysis of some halides competed with the slower quaternizations especially in methanol.

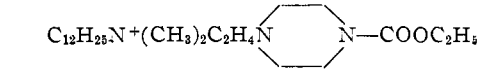
It was convenient to prepare large batches of the 1-carbethoxy-4-alkylpiperazines substituted with the smaller alkyl group and to then quaternize each of these with a number of larger alkyl bromides. In some cases, the alkyl iodides were used as quaternizing agents to speed up the reactions, but they were not as satisfactory since the hydriodides of the starting tertiary amines were sometimes the only isolable products.[4]

The quaternization of 1-carbethoxy-4-propargylpiperazine, *e.g.*, with dodecyl bromide, was so slow as to be essentially unusable. This is, of course, an example of the well-known electron-attracting ability of the ethinyl group. Propargyl bromide was therefore used to prepare quaternaries such as those on lines 38 and 71–79 of the table, and reacted rapidly as anticipated.[5] Indeed, the dipropargyl quaternary was prepared readily (line 76).

To prepare the 1,1-dialkylpiperazinium halides without an amide function at N_4 (lines 1–10 of the table) decarbethoxylation of the corresponding 4-carbethoxy quaternaries by constant-boiling aqueous hydrochloric acid was generally used.[6] The quaternary function at the other nitrogen did not appear to increase the rate of hydrolysis at the carbethoxy group appreciably more than the activation conferred by protonation of a tertiary nitrogen in this strongly acidic medium.

In the case of the attempted acid hydrolysis of 1-carbethoxy-4-methyl-4-benzylpiperazinium chloride and its 4-methyl-4-*p*-chlorobenzyl congener (table, lines 42 and 44), this treatment led to destruction of the quaternary with formation of 1-methylpiperazine (characterized both by benzoylation and by formation of the phenylthiourea) and steam-distillable material resembling the corresponding benzyl halide. The related 1-carbethoxy-4-methyl-4-*p*-anisylpiperazinium chloride (table, line 50) gave what appeared to be a polymer in addition to the 1-methylpiperazine. Raney nickel-catalyzed hydrogenolysis[7] of the 1-nitroso quaternary (table, line 100) was therefore used to prepare 1-methyl-1-benzylpiperazinium chloride.[7,8]

The 1-alkyl-4-amides (other than the carbethoxy compounds) required for preparation of the corresponding quaternaries (table, groups B, C, D, F, G) were in general prepared by the methods previously reported.[9] One exception is the preparation of the compound I, required to determine whether placing the quaternary grouping further from the ring would affect anthelmintic activity.



I

This was prepared from the commercially available aminoethylpiperazine which, on heating with benz-

(1) This paper is No. X on unsymmetrical piperazines from these laboratories. For the previous paper, see R. Baltzly, W. S. Ide and E. Lorz, THIS JOURNAL, **77**, 4809 (1955).

(2) K-F. Chan, *Am. J. Hyg.*, **56**, 22 (1952).

(3) The glycinamide quaternaries of A. J. Rachlin, *et al.*, A.C.S. Div. of Med. Chem. Abstracts, P.5M. (Apr. 8, 1956) also fit this category, as does cyanine dye No. 715 [*cf.* E. Perez-Santiago, J. Oliver-González and C. J. Thillet, *Am. J. Trop. Med. Hyg.*, **2**, 307 (1953)].

(4) E. D. Hughes and U. G. Shapiro, *J. Chem. Soc.*, 1177 (1937), have shown that the ratio of the E_2 elimination to the SN2 hydrolysis of isopropyl iodide in alkaline ethanol–water solution is greater than for isopropyl bromide.

(5) The rapid reactions of propargyl chloride with ethoxide and with radioactive chloride have been reported by C. A. Vernon, *J. Chem. Soc.*, 4462 (1954), and that with ethoxide by L. F. Hatch and V. Chiola, THIS JOURNAL, **73**, 360 (1951). However, the occurrence of side reactions led to inconstancy of the rate, or incomplete reaction. Since the theoretical titer of acetylenic hydrogen is found in the quaternaries readily isolated in excellent yield from our quaternizations with propargyl bromide, it is hoped to measure the rate of this reaction more precisely as time permits.

(6) T. S. Moore, M. Boyle and V. M. Thorne, *J. Chem. Soc.*, 39 (1929).

(7) E. Lorz and R. Baltzly, THIS JOURNAL, **73**, 93 (1951).

(8) Details of this and of the other protecting methods studied will be reported separately.

(9) M. Harfenist, THIS JOURNAL, **76**, 4991 (1954).

TABLE I

PROPERTIES OF PIPERAZINE QUATERNARIES

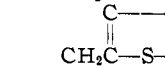
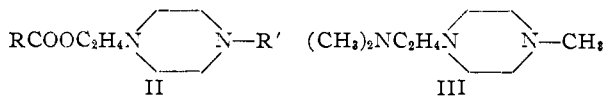
	R	R′	X⁻	M.p., °C.	Recrystn. solvents[a]	Analyses, % Calculated C	Calculated H	Found C	Found H
				A: Compounds of type					
1	CH_3	CH_3	Cl	219–220	W-M	38.51	8.62	38.57	8.79
						Cl^- 37.90		Cl^- 38.19	
2	CH_3	n-C_8H_{17}	Cl	178	A-B-E	Cl^- 24.87		Cl^- 24.87	
3	CH_3	n-$C_{11}H_{23}$	I	175.5–177	A-B-E	I^- 49.73		I^- 50.00	
4	CH_3	n-$C_{12}H_{25}$	Cl	158–159	A-Ac	Cl^- 20.77		Cl^- 20.60	
5	CH_3	n-$C_{13}H_{27}$	Cl	109–120	A-Ac	Cl^- 19.95		Cl^- 19.96	
6	CH_3	n-$C_{14}H_{29}$	Cl	144–145	A-EA-E	Cl^- 19.19		Cl^- 18.83	
7	CH_3	n-$C_{16}H_{33}$	Br	105–108	A-EA	Br^- 32.88		Br^- 33.52	
8	CH_3	$CH_2C_6H_5$	Cl	172–175[c]	A-B-E	Cl^- 27.02		Cl^- 27.12	
9	C_2H_5	n-C_8H_{17}	Cl	188–195	A-B-E	Cl^- 23.68		Cl^- 24.43	
10	C_4H_9	n-$C_{10}H_{21}$	Cl	167.5–168	B-E	Cl^- 19.95		Cl^- 20.23	
11	CH_3	CH_2COOH[b]	Cl	230	W-Ip	36.37	6.98	36.22	7.53
				B: Compounds of type 					
12	CH_3	n-$C_{14}H_{29}$	Br	166.5	Ac-E	Br^- 19.06		Br^- 19.11	
13	CH_3	$CH_2C_6H_5$	Cl	225–226	Ac-E	Cl^- 13.20		Cl^- 13.34	
				C: Compounds of type 					
14	CH_3	CH_3	I	216.5–217.5	AW-A	45.10	5.53	44.83	5.42
15	CH_3	n-C_4H_9	I	140–142	TBW-TB	49.49	6.49	49.08	6.25
16	CH_3	n-$C_{12}H_{25}$	Br	174.5–175.5	Ac-B-E	63.56	9.11	63.72	9.10
17	CH_3	$CH_2C_6H_5$	Cl	116–117	A-AE-E	Cl^- 10.24		Cl^- 10.48	
				D: Compounds of type 					
18	CH_3	n-$C_{12}H_{25}$	Br	192–193	MA	56.01	9.65	56.22	9.99
				E: Compounds of type 					
19	CH_3	CH_3	I	197–199	A-E	34.40	6.10	34.55	6.46
20	CH_3	C_2H_5	Br	170.5–171.5	A-EA-E	42.82	7.72	42.71	7.53
21	CH_3	n-C_3H_7	I	123.5–124.5	A-EA	38.60	6.77	38.58	6.62
22	CH_3	i-C_3H_7	I	178	A-EA	38.60	6.77	38.17	7.04
23	CH_3	n-C_4H_9	I	104–107.5	A-EA-E	40.45	7.07	40.48	7.01
24	CH_3	n-C_5H_{11}	I	131.5–132.5	Ac-EA	42.17	7.35	42.48	7.74
25	CH_3	i-C_5H_{11}	I	133.5–134	A-EA-E	42.17	7.35	42.00	7.11
26	CH_3	n-C_6H_{13}	I	115–117.5	A-EA-E	43.75	7.61	43.87	7.49
27	CH_3	n-C_7H_{15}	Br	161–162	A-EA-E	51.27	8.89	50.75	8.81
28	CH_3	n-C_8H_{17}	Br	183–184	A-EA-E	52.59	9.10	52.67	9.10
29	CH_3	n-C_9H_{19}	I	107–108.5	A-EA	47.91	8.30	48.04	7.92
30	CH_3	n-$C_{10}H_{21}$	Br	203.5–204.5	Ac-EA	54.95	9.48	54.75	9.44
31	CH_3	n-$C_{11}H_{23}$	Br	198.5–199	Ac-EA	56.01	9.65	55.79	10.02
32	CH_3	n-$C_{12}H_{25}$	Br	216	D	56.99	9.81	56.56	10.08
33	CH_3	n-$C_{13}H_{27}$	Br	215.5–218.5	D	Br^- 18.36		Br^- 18.75	
34	CH_3	n-$C_{14}H_{29}$	Br	203–203.5	A-EA-E	57.98	10.36	57.51	10.12
35	CH_3	n-$C_{15}H_{31}$	Br	201–202.5	Ac-EA; N-EA	59.63	10.23	59.30	10.32
36	CH_3	n-$C_{16}H_{33}$	Br	219–221	D	60.40	10.35	60.58	10.44
37	CH_3	$C_9H_{18}CH{=}CH_2$	I	111–113	EA	50.48	8.22	50.44	8.16
38	CH_3	$CH_2C{\equiv}CH$	Br	151–152	A-EA	45.37	6.58	45.52	6.78
39	CH_3	$CH_2CH_2C{\equiv}CH$	Tos[d]	146–148	Ac-E	57.63	7.12	57.74	7.08
40	CH_3	$CH_2C{\equiv}C{-}C_4H_9$	Br	123–125	Ac-B-E	Br^- 22.92		Br^- 22.48	
41	CH_3	C_5H_5	I	137.5–138.5	A-Ac-E	I^- 33.81		I^- 34.23	
42	CH_3	$CH_2C_6H_5$	Cl	185.5–186.5	A-EA-E	Cl^- 11.66		Cl^- 11.87	
43	CH_3	$CH_2C_6H_4Cl(2)$	Cl	165–167.5	Ac-E	Cl^- 10.65		Cl^- 10.60	
44	CH_3	$CH_2C_6H_4Cl(4)$	Cl	189	A-Ac-E	54.04	6.62	54.34	6.70
45	CH_3	$CH_2C_6H_3Cl_2(2,4)$	Cl	178.3–179	A-B-E	Cl^- 9.64		Cl^- 9.21	
46	CH_3	$CH_2C_6H_3Cl_2(3,4)$	Cl	170–171	Ac-E	Cl^- 9.64		Cl^- 9.62	
47	CH_3	$CH_2C_6H_4CH_3(2)$	Br	200.5–202.5	A-Ac-E	Br^- 22.38		Br^- 22.63	
48	CH_3	$CH_2C_6H_4CH_3(3)$	Br	176–178	A-EA-E	Br^- 22.38		Br^- 22.32	
49	CH_3	$CH_2C_6H_4CH_3(4)$	Br	189–190	A-B-E	Br^- 22.38		Br^- 22.59	
50	CH_3	$CH_2C_6H_4OCH_3(4)$	Cl	189	N-EA	58.55	7.68	58.45	7.92
51	CH_3	$(CH_2)_2C_6H_5$	I	194.5–195.5	A-EA-E; W	I^- 31.40		I^- 31.42	
52	CH_3	$(CH_2)_3C_6H_5$	Br	138.5–139.5	N-Ac-E	Br^- 21.52		Br^- 21.81	
53	CH_3	$CH_2CH{=}CHC_5H_5$[e]	Cl	157–158	Ac-EA-E	Cl^- 10.92		Cl^- 10.87	
54	CH_3		Cl	164–165	A-EA-E	Cl^- 11.64		Cl^- 11.62	

TABLE I (*continued*)

	R	R′	X⁻	M.p., °C.	Recrystn. solvents[a]	Analyses, % Calculated C	Calculated H	Found C	Found H
				E: Compounds of type $C_2H_5OOCN\overset{+}{\underset{}{\square}}NRR'\cdot X^-$					
55	CH_3	$CH_2C(=O)SC=C$	Br	138–145	A-EA	Br⁻ 22.88		Br⁻ 22.68	
56	CH_3	$CH_2C(=O)-C_6H_5$	Br	172.5–175	N-EA	51.78	6.24	51.53	6.04
57	CH_3	CH_2COOCH_3	Cl	143–145	M-Ac-E	47.05	7.54	46.60	7.36
58	CH_3	$CH_2COOC_2H_5$	Cl	145.5–146.5	A-B-EA-E	48.89	7.86	48.68	7.90
59	CH_3	$CH_2COOC_{12}H_{25}$	Cl	113.5–116	M-B-E	Cl⁻ 8.15		Cl⁻ 8.26	
60	CH_3	$CH(CH_3)COOC_{12}H_{25}$	Cl	75–77	Ac-E	Br⁻ 16.20		Br⁻ 16.25	
61	C_2H_5	C_2H_5	I	154–156	A-B-EA	38.60	6.77	38.35	7.04
62	C_2H_5	n-C_8H_{17}	I	106–109	Ac-E	47.88	8.27	48.29	8.55
63	C_2H_5	$CH_2C_5H_5$	Cl	133.5–134.5	N-Ac-E	Cl⁻ 11.34		Cl⁻ 11.14	
64	C_4H_9	n-$C_{10}H_{21}$	I	155.5–156.5	A-EA	52.18	8.98	52.55	8.92
65	$CH_2CH=CH_2$	n-C_8H_{17}	Br	154.5–155.5	Ac-E	Br⁻ 20.42		Br⁻ 20.58	
66	$CH_2CH=CH_2$	n-$C_{10}H_{21}$	Br	169	Ac-E	Br⁻ 19.50		Br⁻ 19.21	
67	$CH_2CH=CH_2$	n-$C_{12}H_{25}$	Br	177–177.5	Ac-E	Br⁻ 17.86		Br⁻ 18.05	
68	$CH_2CH=CH_2$	$CH_2CH=CH_2$	Br	172–173	A-Ac-E	Br⁻ 25.04		Br⁻ 25.00	
69	$CH_2CH=CH_2$	$CH_2CH=CH_2$	Cl	154–158	A-Ac-E	Cl⁻ 12.91		Cl⁻ 12.88	
70	$CH_2CH=CH_2$	$CH(CH_3)COOC_2H_5$	Br	114.5–116	A-B-E	Br⁻ 21.08		Br⁻ 21.23	
71	$CH_2C\equiv CH$	n-C_8H_{17}	Br	125–126	Ac-EA-E	Br⁻ 20.52		Br⁻ 20.85	
72	$CH_2C\equiv CH$	n-$C_{10}H_{21}$	Br	125–127	Ac-EA	Br⁻ 19.15		Br⁻ 19.10	
73	$CH_2C\equiv CH$	n-$C_{11}H_{23}$	Br	140.5–142.5	Ac-EA	Br⁻ 18.53		Br⁻ 18.36	
74	$CH_2C\equiv CH$	n-$C_{12}H_{25}$	I	87–91	EA-B-E	I⁻ 25.78		I⁻ 25.23	
75	$CH_2C\equiv CH$	$CH_2CH=CH_2$	Br	166–167	A-Ac-E	Br⁻ 25.20		Br⁻ 24.80	
76	$CH_2C\equiv CH$	$CH_2C\equiv CH$	Br	193.3–194.3	A-B	0.635%[f]		0.641%[f]	
77	$CH_2C\equiv CH$	$CH_2C\equiv C-C_4H_9$	Br	119–121	Ac-EA-E	Br⁻ 21.57		Br⁻ 21.58	
78	$CH_2C\equiv CH$	C_5H_5	Br	174.5–175.5	AW-Ac-E	Br⁻ 22.62		Br⁻ 22.77	
79	$CH_2C\equiv CH$	$CH_2C_5H_5$	Cl	165–165.5	A-EA-E	63.39	7.12	63.31	7.05
80	$CH_2CH_2C\equiv CH$	n-C_8H_{17}	Tos[d]	178–181	Ac-EA	N	5.65	N[g]	5.38
81	$CH_2CH_2C\equiv CH$	n-$C_{10}H_{21}$	Tos[d]	193.5–195.5	Ac-EA	64.33	9.05	64.09	9.19
82	$CH_2C_6H_5$	$CH_2C(=O)SC=C$	Br	163.5–166.5	A-B-E	Br⁻ 18.79		Br⁻ 18.71	
83	$CH_2CH_2C_6H_5$	n-$C_{12}H_{25}$	I	111–114	EA-E	I⁻ 22.71		I⁻ 22.22	
84	$CH_2CH_2C_6H_5$	$CH_2C_6H_5$	Cl	181.5–183	A-EA-E	Cl⁻ 9.12		Cl⁻ 9.13	
85	OCH_3	n-$C_{12}H_{25}$	I	142–143.5	Ac-E	I⁻ 26.20		I⁻ 26.30	
86	CH_2CH_2OH	n-$C_{15}H_{33}$	Br	100–101	Ac	Br⁻ 15.76		Br⁻ 15.70	
				F: Compounds of type $H_2NCON\overset{+}{\underset{}{\square}}NRR'\cdot X^-$					
87	CH_3	CH_3	I	232.5–233.5	W-A-Ac	I⁻ 44.50		I⁻ 44.31	
88	CH_3	CH_3	Cl	247–247.5	M-Ac	Cl⁻ 18.31		Cl⁻ 18.55	
89	CH_3	$CH_2C_6H_5$	Cl	203[h]	A-Ac	57.91	7.48	58.15	7.82
				G: Compounds of type $(CH_3)_2NC(=O)-N\overset{+}{\underset{}{\square}}NRR'\cdot X^-$					
90	CH_3	CH_3	I	213–214	A-Ac-E	I⁻ 40.51		I⁻ 40.42	
91	CH_3	n-C_4H_9	I	136–137	A-Ac-E	40.57	7.38	40.51	7.26
92	CH_3	n-$C_{12}H_{25}$	Br	187–190	D	Br⁻ 19.02		Br⁻ 19.07	
93	CH_3	$CH_2C_6H_5$	Cl	175	A-Ac	Cl⁻ 11.91		Cl⁻ 11.59	
				H: Compounds of type $(C_2H_5)_2NC(=O)-N\overset{+}{\underset{}{\square}}NRR'\cdot X^-$					
94	CH_3	n-$C_{10}H_{21}$	Br	158–163	Ac-E	Br⁻ 19.00		Br⁻ 18.97	
95	CH_3	n-$C_{12}H_{25}$	Br	167–169	Ac-EA	Br⁻ 17.81		Br⁻ 17.71	
96	CH_3	n-$C_{14}H_{29}$	Br	169–174	Ac-EA	Br⁻ 16.78		Br⁻ 17.39	
				I: Compounds of type $ONN\overset{+}{\underset{}{\square}}NRR'\cdot X^-$					
97	CH_3	CH_3	I	219–223	N-E	I⁻ 46.78		I⁻ 45.95	
98	CH_3	CH_3	Cl	257	M-Ac	Cl⁻ 19.72		Cl⁻ 19.96	
99	CH_3	n-$C_{12}H_{25}$	I	182.5–183	A-EA	48.07	8.52	47.97	8.40
100	CH_3	$CH_2C_6H_5$	Cl	197	A-EA-E	56.40	7.09	56.30	7.20
						Cl⁻ 13.86		Cl⁻ 14.11	

[a] Recrystallization solvents were: A = absolute ethanol; AW = 95% ethanol; Ac = acetone; B = benzene; D = dioxane (purified); E = absolute ether; EA = ethyl acetate; Ip = isopropyl alcohol; M = methanol; MA = methyl acetate; N = nitromethane; TB = *t*-butyl alcohol; TBW = 2% water in TB; W = water. [b] Prepared by hydrolysis of the 1-carbethoxy esters, lines 57 and 58. [c] Hydrate had m.p. 116°. [d] Tos = *p*-toluenesulfonate. [e] Assumed, but not proved to have been produced without allylic rearrangement. [f] Acetylenic H by method given in S. Siggia, "Quantitative Organic Analysis *via* Functional Groups," John Wiley and Sons, Inc., New York, N. Y., 1949, p. 55. The compound puffs on attempted microanalysis by standard methods for C and H. [g] Kjeldahl nitrogen, performed by Mrs. R. Purdey. [h] M.p. 215° on rapid heating.

aldehyde, gave the Schiff base. On treatment of this with ethyl chlorocarbonate, it was carbethoxylated to the unstable carbethoxy Schiff base hydrochloride which, on steam distillation of the crude reaction mixture, lost its benzal group to give 1-(2'-aminoethyl)-4-carbethoxypiperazine hydrochloride. Dimethylation (Clarke–Eschweiler) and quaternization of the resulting tertiary amine led to the desired quaternary. Details of these reactions are given in the Experimental section. That quaternization occurs on the side-chain nitrogen is indicated on the basis of analogy to previous work[10] which in-



II III

dicates that the piperazines II quaternize preferentially at N–R' and that only the bis-quaternary is produced on refluxing III with methanolic methyl iodide.[11]

The amine oxide methiodide (table, line 85) was prepared by quaternization of the oxide produced readily by hydrogen peroxide treatment of 1-carbethoxy-4-*n*-dodecylpiperazine as given in the Experimental section.

Anthelmintic Activity.—Results of the anthelmintic tests will be published in detail elsewhere. They may be summarized in part as showing that a maximum in therapeutic index occurs in the mouse at about the 4-methyl-4-tridecyl- or tetradecylpiperazinium halides. To a first approximation, the position of this maximum is independent of the amide substituent. Of these N-1-amide substituents, the carbethoxy and the diethylcarbamyl groups seem to be best[12] while the 1-nitroso and, surprisingly, the 1-carbamyl quaternaries are inactive (groups F and I). Compound 34, the best of this series, is comparable to piperazine in therapeutic index in these tests.

Activities of 1-methyl quaternaries in which the other 1-substituent is unsaturated, aryl, aralkyl or heterocyclic follow no obvious order. The therapeutic indices of those few quaternaries in which the 1-methyl group was replaced by larger groups seem lower than those of the corresponding 1-methyl quaternaries.

Acknowledgment.—We thank Mr. Samuel W. Blackman for the carbon–hydrogen analyses reported here, and Mr. Ernest Magnien for preparation of certain of the intermediates.

Experimental

Analyses for Halides.—Chlorides were determined by the exceptionally convenient method using phenosafranin as adsorption indicator in dilute nitric acid solution. Bromides and occasionally iodides were also done by this method when a spot test indicated its applicability, otherwise by use of eosin as adsorption indicator or by the Volhard titration.

Melting Points.—These normally occurred with decomposition and frequently were a function of the rate of heating, which therefore was maintained at 3°/min.

1-Carbethoxy-4-dodecylpiperazine-4-oxide.—Fifteen grams (0.13 mole) of 30% hydrogen peroxide was added to a solution of 27 g. (0.083 mole) of 1-carbethoxy-4-*n*-dodecylpiperazine in 116 ml. of glacial acetic acid maintained at about 40°. An equal amount of peroxide was added after 24 hr., and the solution was kept for 3.5 more days. Only a faint positive test with iodide–starch was obtained at this time. The solution was evaporated to a small volume on the steam-bath at 20 mm. pressure, made strongly basic with excess of saturated aqueous potassium carbonate and the resulting oil extracted with two portions of ether. The ethereal solution was dried over magnesium sulfate and concentrated and the residue crystallized from acetone–Skellysolve B. Three crops totaling 23 g. were taken and recrystallized from acetone–Skellysolve A to give 17 g. (two crops), m.p. 139.5°.

Anal. Calcd. for $C_{19}H_{38}N_2O_3$: C, 66.63; H, 11.18. Found: C, 66.95; H, 11.33.

1-Dodecylpiperazine-1-oxide.—A solution of 12 g. (0.035 mole) of the carbethoxypiperazine oxide was heated under reflux with 120 ml. of water containing 12 g. (0.07 mole) of barium hydroxide for 3 hr. Barium ion was removed from the solution by passing in an excess of carbon dioxide and then boiling the solution briefly (*cf.* ref. 9). Evaporation *in vacuo* of the filtrate from this operation gave 8 g. of white solid, which was recrystallized readily from acetone–Skellysolve B to give 5.2 g., m.p. *ca.* 68.5°. This was hygroscopic and apparently light-sensitive and so was converted to the dihydrochloride, m.p. 153–159°.

Anal. Calcd. for $C_{16}H_{36}N_2OCl_2$: Cl^-, 20.62. Found: Cl^-, 20.52.

1-(2'-Benzalaminoethyl)-piperazine.—Addition of 116 g. (1.1 moles) of freshly purified benzaldehyde in a thin stream during four minutes to a well-stirred 129 g. (1 mole if pure) of 2-aminoethylpiperazine (Carbide and Carbon Chemical Co., Inc., "95%") led to spontaneous evolution of steam from the mixture. The remaining water was distilled off at the water-pump until the bath temperature reached 160°. The remaining amber oil was distilled retaining fractions boiling at 140° at 0.2 mm. to 180° at 0.1 mm., totaling 187 g. Redistillation gave 133.5 g. boiling at 130–133° at 0.005 mm. A hard pitch was found as the boiler residue of both distillations, presumably a result of thermal decomposition of the Schiff base. The titration curve of the distillate showed only one inflection point between *p*H 11.5 and 1.5, on titration with hydrochloric acid.

Anal. Calcd. for $C_{13}H_{19}N_3$: equiv. wt., 108.5. Found: equiv. wt., 115.

1-Carbethoxy-4-(2'-aminoethyl)-piperazine.—One hundred grams (0.94 mole) of redistilled ethyl chlorocarbonate was added during 20 minutes to a stirred, cooled solution of 127 g. (0.59 mole) of 1-(2'-benzalaminoethyl)-piperazine in 1 l. of absolute ethanol maintained at 20°. After an additional 0.75 hr. of stirring, the solvent was distilled off at the water-pump, finally on a steam-bath. Distillation of 700 ml. of water from the residue at the water-pump (85% of theory of benzaldehyde was recovered) and similar distillation of 1.1 l. of 1.2 *N* HCl was followed by recrystallization of the residual oil from absolute ethanol by addition of carbon tetrachloride to faint turbidity at 40°. From 77 g. of crude product there was obtained after three recrystallizations 28.2 g. of white solid, m.p. 157.5–158.5.

Anal. Calcd. for $C_9H_{21}N_3O_2Cl_2$: Cl^-, 25.68. Found: Cl^-, 25.70.

1-Carbethoxy-4-(2'-dimethylaminoethyl)-piperazine.—Twenty grams (0.072 mole) of 1-carbethoxy-4-(2'-aminoethylpiperazine) dihydrochloride and 4.3 g. (0.041 mole) of sodium carbonate were added to 38 ml. of 98–100% formic acid, and half of 45 ml. of 38% formaldehyde was added to the mixture. It was then heated under reflux for 6 hr., treated with the rest of the formaldehyde and again refluxed for 6 hr. The reaction mixture was then acidified with 25 ml. of concentrated hydrochloric acid and evaporated on a steam-bath at the water-pump. The residue was dissolved in water, the water saturated with potassium carbonate with cooling and the resulting oil taken into 2 portions of ether. Removal of the ether, acidification with ethanolic hydrogen chloride and dilution with ether gave a white solid. This was recrystallized by addition of acetone to its solution in hot 10% aqueous ethanol. It sublimed when heated over 240° and had m.p. 282–285 when rapidly heated on a hot-stage. The yield was quantitative.

(10) W. S. Ide, E. Lorz and R. Baltzly, THIS JOURNAL, **76**, 1122 (1954).

(11) Personal communication from Dr. A. P. Phillips.

(12) Compare the results of anti-filarid tests reported by S. Kushner, *et al.*, *J. Org. Chem.*, **13**, 144 (1948).

Anal. Calcd. for $C_{11}H_{25}N_3O_2Cl_2$: Cl^-, 23.41. Found: Cl^-, 23.50.

2-(4'-Carbethoxypiperazino)-ethyldimethyldodecylammonium Bromide (I).—The hydrochloride of the dimethyl tertiary base (above) was converted to the base by excess of aqueous potassium carbonate and subsequent ether extraction and treated with a 100% excess of *n*-dodecyl bromide in acetone at 40° for 19 days. The *extremely hygroscopic* solid produced by dilution with ether was recrystallized twice from ethyl acetate, m.p. 67°.

Anal. Calcd. for $C_{23}H_{48}N_3O_2Br$: Br^-, 16.71. Found: Br^-, 16.58.

The picrate had m.p. 124° (mixed m.p. depression with picric acid).

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[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

Protecting Groups in the Synthesis of Unsymmetrical Piperazines[1]

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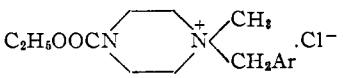
Methods for removing various groups useful in protecting one of the two nitrogens of substituted piperazines were studied using piperazine quaternaries with the following N-substituting protective groups: carbethoxyl (removal by aqueous barium hydroxide), acetyl (removal by acid), nitroso (removal by hydrogenolysis catalyzed by Raney nickel) and nitroso with an equivalent of carbamyl (removal of nitroso as nitrous acid, destroyed by the carbamyl function). The relative utility of these methods is briefly considered.

Syntheses in the field of unsymmetrical piperazines are based to a considerable extent on the mono-carbethoxylation of piperazine[2] to protect one nitrogen, although the direct preparations of other mono-amides, and even of alkyl and aralkyl piperazines,[3] have been reported.

The carbethoxy group may be removed either by heating the carbethoxypiperazines with constant-boiling (approx. 6 *N*) aqueous hydrochloric acid at its boiling point (approx. 110°) for two to three days or much more rapidly, as would be anticipated on theoretical grounds, by heating them with alkali.[2,4]

The requirement of protective groups other than carbethoxy became urgent when attempts to hydrolyze the unsymmetrical 1-carbethoxy-4-methyl-4-benzylpiperazinium chlorides (I)[1] by the hydrochloric acid method led to loss, not only of the carbethoxyl, but also of the benzyl group.[5] Further,



I, Ar = C_6H_5, *p*-Cl-C_6H_4, *p*-$CH_3OC_6H_4$-

the acid-catalyzed decarbethoxylation of 1-carbethoxy-4-methyl-4-propargylpiperazinium chloride gave a product containing an impurity of lower halide content, which could not be removed by repeated crystallization.

Although it was felt that the basicity required for saponification of the carbethoxyl group might lead to decomposition of the quaternaries, the rate of the saponification of the propargyl quaternary (I for Ar put C≡CH) by aqueous barium hydroxide was studied. At about 50°, an excess of 0.4 *N* aqueous barium hydroxide gave 85% hydrolysis of the carbethoxyl function (by acidimetric titration of aliquots) in 1 hr. The decarbethoxylated 1-methyl-1-propargylpiperazinium chloride isolated in fair yield after 140 min. under reflux or remaining overnight at 50° was moderately pure and readily gave analytically pure product on recrystallization, although each recrystallization was accompanied by great loss of material.

Theoretical considerations indicated that acid hydrolysis of a 1-acylpiperazine should be rapid, especially under conditions in which the 4-nitrogen, if not quaternized, would be protonated. As anticipated, the de-acetylations of the test substances 1-acetyl-4,4-dimethylpiperazinium chloride and 1-acetyl-4-methyl-4-benzylpiperazinium chloride had been completed (titration) after 30–40 minutes at 95° in the presence of two equivalents of 2 *N* hydrochloric acid and, indeed, were about half completed after four days at room temperature. Hydrolysis of the carbethoxy group of the 1-carbethoxy-4,4-dimethyl quaternary, in contrast, was undetectable after 24 hr. at 95°, in the presence of the same excess of acid. Although the hydrolysis mixture of the acetylmethylbenzyl quaternary had a faint odor resembling benzyl chloride (or alcohol), the appropriate de-acetylated quaternary was isolated in excellent yield from it as well as from the dimethyl analog.

The Raney nickel-catalyzed hydrogenolysis of the nitroso group[6] from 1-nitroso quaternaries was studied with 1-nitroso-4-methyl-4-dodecylpiperazinium iodide which readily gave an 86% yield of analytically pure de-nitrosated quaternary. The corresponding 1-nitroso-4-methyl-4-benzylpiperazinium chloride absorbed the theoretical amount of hydrogen rapidly, and then absorption nearly stopped. Yields averaging 75% were obtained, but the product was contaminated by nickel ion. This was removed by treatment of the reduction filtrate

(1) This is paper No. 11 in a series on unsymmetrical piperazines from these laboratories. For the preceding paper, see M. Harfenist, THIS JOURNAL, **79**, 2211 (1957).

(2) T. S. Moore, M. Boyle and V. M. Thorne, *J. Chem. Soc.*, 39 (1929).

(3) *Cf.* R. Baltzly, THIS JOURNAL, **76**, 1164 (1954), and references given there.

(4) M. Harfenist, *ibid.*, **76**, 4991 (1954).

(5) A related reaction, the spontaneous loss of the 4-methoxybenzhydryl group from 1-(4'-methoxybenzhydryl)-4-methylpiperazine dihydrochloride has been reported by R. Baltzly, S. DuBreuil, W. S. Ide and E. Lorz, *J. Org. Chem.*, **14**, 775 (1942). However, the *p*-methoxy group appeared to be necessary for decomposition under these mild conditions, even though a benzhydryl group should be lost more readily than the benzyl group present in the compounds reported here.

(6) E. Lorz and R. Baltzly, THIS JOURNAL, **73**, 93 (1951).