[CONTRIBUTION FROM ABBOTT LABORATORIES]

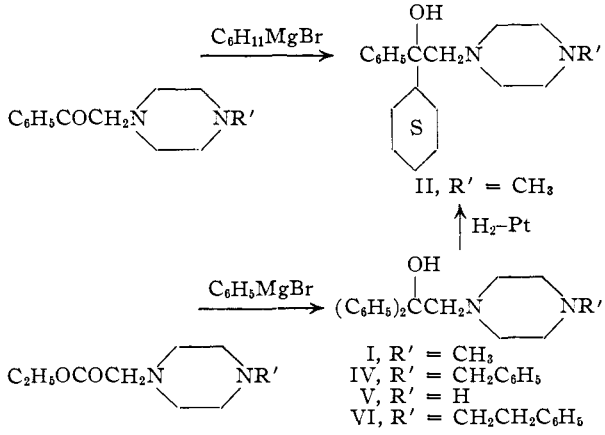
Tertiary Carbinols of the Piperazine Series. I

BY H. E. ZAUGG, R. J. MICHAELS, H. J. GLENN, L. R. SWETT, M. FREIFELDER, G. R. STONE AND A. W. WESTON

RECEIVED DECEMBER 16, 1957

The preparation is reported of basic carbinols of general type A, $C_6H_5C(R)(OH)—X—N\langle\rangle N—R'$, where R is aryl, cyclohexyl or methyl, X is CO or a straight or branched chain alkylene radical, and R' is hydrogen, alkyl or arylalkyl. In several instances the hydroxyl is replaced by other functional groups. Monoquaternary salts and dihydrochlorides of most of the bases are prepared. Of greatest pharmacological interest as gastric antisecretory agents or as drugs for the treatment of parkinsonism, are the compounds where R is phenyl or cyclohexyl, X is methylene and R' is hydrogen or methyl. Compound II (see text) has been resolved and practically all of the desirable physiological activity resides in the levo-rotatory isomer.

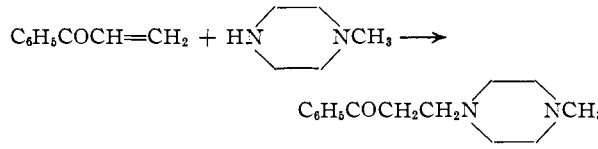
The physiological activity of piperazine derivatives, especially in the field of antihistaminics, is well-known.[1] To date, most piperazines found to be of value possess the two nitrogens of the ring as the sole functional groups. For the purpose of determining general antispasmodic activity as well as more specific action in the gastric antisecretory and antiparkinson areas, piperazines containing the tertiary carbinol group were prepared.



To secure compounds of type A (see Abstract) where R is not phenyl, a 4-substituted-1-phenacylpiperazine was treated with the appropriate Grignard reagent (method A, see Experimental). For the preparation of such compounds containing the cyclohexyl group, either this method using cyclohexylmagnesium bromide or the hydrogenation (method B) of the corresponding diphenylcarbinols (compounds A, R = C_6H_5) could be employed. The diphenylcarbinols where X is methylene (*e.g.*, compounds I and IV) were obtained more readily by the action of phenyl Grignard reagent on a 4-substituted-1-piperazineacetic ester (method D). Hydrogenolysis of the benzyl group of compound IV gave V which could, in turn, be reductively alkylated with phenylacetaldehyde to VI. Compounds of type A where R is varied, X is methylene and R' is methyl are listed in Table I. Those where R is either phenyl or cyclohexyl, X is methylene and R' is varied are given in Table II.

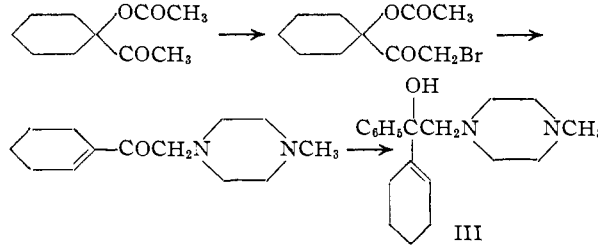
(1) C. Wilson and O. Gisvold, "Textbook of Organic Medicinal and Pharmaceutical Chemistry," 2nd ed., J. B. Lippincott Co., London, 1954, p. 387; see also K. Hamlin, A. Weston, F. Fischer and R. Michaels, THIS JOURNAL, **71**, 2731, 2734 (1949).

The intermediate required for the preparation of compound A (R = C_6H_5, R' = CH_3, X = $-CH_2-CH_2-$) could not be secured by a Mannich-type reaction of 1-methylpiperazine with acetophenone. It was readily obtainable, however, by the addition of 1-methylpiperazine to acrylophenone.



Compound A [R = C_6H_5, R' = CH_3, X = $-(CH_2)_3-$] was prepared by the direct alkylation of 1-methylpiperazine with 4-chloro-1,1-diphenylbutanol. Compounds of type A where R is phenyl, X is varied and R' is methyl, are listed in Table III.

A specific synthesis was employed for the preparation of the Δ^1-cyclohexenylcarbinol III. In the final step phenyllithium rather than the Grignard reagent was used so that 1,2-addition to the carbonyl group would be favored over possible 1,4-addition to the conjugated system. Infrared analysis indicated that this expectation was realized.



Several compounds were prepared in which the hydroxyl group in compound A is replaced. The methyl analogs VII and VIII were obtained by acylation of 1-methylpiperazine with α,α-diphenylpropionyl chloride and then lithium aluminum hydride reduction of the amide group.

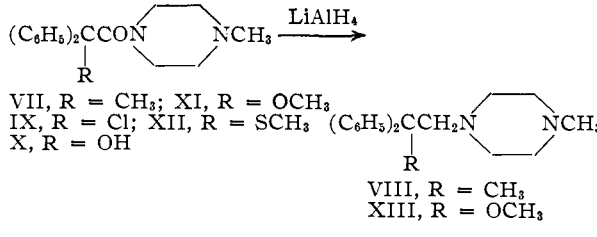


TABLE I

AMINOCARBINOLS OF TYPE $C_6H_5C(OH)(R)CH_2N$⟨piperazine⟩NCH_3

Compound R	Form	M.p.,[a] °C.	Method[b]	Yield, %	Formula	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N	Activity[l]
C_6H_5	Base	83–84	A	53	$C_{19}H_{24}N_2O$	76.99	8.16	9.46	76.85	8.19	9.46	
	2HCl	226–227	D	69	$C_{19}H_{26}Cl_2N_2O$	61.78	7.10	7.59	62.46	6.96	7.68	0.02
	$(CH_3)_2SO_4$	160–162			$C_{21}H_{30}N_2O_6S$	59.69	7.16	6.63	59.40	7.21	6.81	.3
	$C_6H_5CH_2Br$	219–220			$C_{26}H_{31}BrN_2O$	66.80	6.69	5.99	66.94	6.95	5.99	.002
	$2(CH_3)_2SO_4 \cdot H_2O$	135–136			$C_{23}H_{36}N_2O_9S_2 \cdot H_2O$	48.74	6.77	4.94	48.87	6.87	5.16	.1
dl-C_6H_{11}[c]	Base	196–203[d]	A	58	$C_{19}H_{30}N_2O$	75.45	10.00	9.26	75.16	9.76	9.68	
	$2HCl \cdot {}^1/_2H_2O$	239–241[e]	B	94	$C_{19}H_{32}Cl_2N_2O \cdot {}^1/_2H_2O$	59.37	8.65	7.29	59.12	8.38	7.56	.04
	$(CH_3)_2SO_4$	211–212			$C_{21}H_{36}N_2O_6S$	58.85	8.47	6.54	59.35	8.49	6.47	.35
	CH_3I	202–203			$C_{20}H_{33}IN_2O$	54.05	7.48	6.31	53.92	7.30	6.04	.3
	C_2H_5I	232–233			$C_{21}H_{35}IN_2O$	55.02	7.70	6.11	55.86	7.75	5.96	
	$(CH_3)_2CHI \cdot H_2O$	151–153			$C_{22}H_{37}IN_2O \cdot H_2O$	53.87	8.01	5.71	54.03	7.55	6.05	.4
	n-$C_8H_{17}Br \cdot {}^1/_2H_2O$	106–108			$C_{27}H_{47}BrN_2O \cdot {}^1/_2H_2O$	64.26	9.59	5.55	64.59	9.36	5.65	.05
	$HOCH_2CH_2Br$	175–177			$C_{21}H_{35}BrN_2O_2$	59.01	8.25	6.56	59.57	8.15	6.47	.2
d-C_6H_{11}[c]	$2C_4H_{12}O_{12}$[f]	197–199[g]	K		$C_{27}H_{42}N_2O_{13}$	53.81	7.03	4.65	53.99	7.21	4.70	
	2HCl	266[g]			$C_{19}H_{32}Cl_2N_2O$	60.79	8.59	4.27[h]	60.63	8.66	4.50[h]	.0025
	$(CH_3)_2SO_4$	190[g]			$C_{21}H_{36}N_2O_6S$[i]	58.85	8.47	6.54	59.12	8.74	6.51	.0035
l-C_6H_{11}[c]	2HCl	266[g]	K		$C_{19}H_{32}Cl_2N_2O$	60.79	8.59	4.27[h]	60.58	8.42	4.37[h]	.04
	$(CH_3)_2SO_4$	190[g]			$C_{21}H_{36}N_2O_6S$	58.85	8.47	6.54	58.71	8.56	6.38	.70
C_6H_9[j]	2HCl	206–208	C	Poor	$C_{18}H_{30}Cl_2N_2O$	61.12	8.10	7.50	61.16	8.11	7.70	
o-$CH_3C_6H_4$	2HCl	231–233	A	21	$C_{20}H_{28}Cl_2N_2O$	62.66	7.36	7.31	62.72	7.54	7.17	.01
	$(CH_3)_2SO_4$	183–184			$C_{22}H_{32}N_2O_6S$	60.52	7.39	6.42	60.41	7.45	6.25	.04
m-$CH_3C_6H_4$	2HCl	229–230	A	40	$C_{20}H_{28}Cl_2N_2O$	62.66	7.36	7.31	62.48	7.10	7.21	.01
	$(CH_3)_2SO_4 \cdot H_2O$	122–124			$C_{22}H_{32}N_2O_6S \cdot H_2O$	58.13	7.54	6.16	57.88	7.24	6.22	.03
p-$CH_3C_6H_4$	2HCl	232–233	A	37	$C_{20}H_{28}Cl_2N_2O$	62.66	7.36	7.31	62.80	7.18	7.48	.01
	$(CH_3)_2SO_4$	113–115			$C_{22}H_{32}N_2O_6S$	60.52	7.39	6.42	59.87	7.38	6.40	.01
3,4-$(CH_3)_2C_6H_3$	2HCl	228–229	A	26	$C_{21}H_{30}Cl_2N_2O$	63.47	7.61	7.05	63.41	7.88	7.20	< .01
	CH_3I	132–133			$C_{22}H_{31}IN_2O$	56.65	6.70	6.01	55.86	6.72	6.12	.02
m-ClC_6H_4	2HCl	232–233	A	30	$C_{19}H_{25}Cl_3N_2O$	56.51	6.24	6.94	56.71	6.01	6.83	.01
	CH_3I	168–170			$C_{20}H_{26}ClIN_2O$	50.80	5.54	5.93	50.92	5.94	5.79	.2
p-ClC_6H_4	2HCl	229–230	A	30	$C_{19}H_{25}Cl_3N_2O$	56.51	6.24	6.94	56.10	6.25	7.32	.01
	CH_3I	116–117			$C_{20}H_{26}ClIN_2O$	50.80	5.54	5.93	51.02	5.55	5.79	.16
2-C_5H_4N[k]	3HCl	227–228	A	20	$C_{18}H_{26}Cl_3N_3O$	53.12	6.44	10.33	53.53	6.38	10.13	< .01
	$(CH_3)_2SO_4$	183–184			$C_{20}H_{29}N_3O_6S$	56.72	6.90	9.92	56.54	6.94	9.61	.01
CH_3	2HCl	207–208	A	31	$C_{14}H_{24}Cl_2N_2O$	54.72	7.87	9.12	54.80	7.92	9.28	< .001

[a] Uncorrected. [b] See Experimental. [c] Cyclohexyl. [d] Boiling point (4 mm.). [e] The anhydrous salt melts at about 255–256° dec. *Anal.* Calcd. for $C_{19}H_{32}Cl_2N_2O$: C, 60.79; H, 8.59. Found: C, 60.67; H, 8.70. The melting points (with decomposition) of these salts are somewhat variable with the rate of heating. [f] Bis-*d*-tartrate. [g] The melting point (with decomposition) varied ±5° depending on the rate of heating. [h] Oxygen analysis. [i] Calcd.: O, 18.67. Found: O, 18.76. [j] Δ^1-Cyclohexenyl. [k] 2-Pyridyl. [l] Against acetylcholine induced spasm of the isolated rabbit ileum; atropine = 1.

TABLE II

AMINOCARBINOLS OF TYPE $C_6H_5C(OH)(R)CH_2N$⟨piperazine⟩$N-R'$

Compound R	Compound R'	Form	M.p.,[a] °C.	Method[b]	Yield, %	Formula	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N	Activity[g]
C_6H_5	H	2HCl	247–249	E	96	$C_{18}H_{24}Cl_2N_2O$	60.84	6.81	7.89	61.01	6.54	7.82	0.01
C_6H_{11}[c]	H	$2HCl \cdot {}^1/_2H_2O$	240	B[d]	78	$C_{18}H_{30}Cl_2N_2O \cdot {}^1/_2H_2O$[e]	58.30	8.44	7.57	58.45	8.50	7.61	.005
C_6H_5	C_2H_5	Base	64–65	A	44	$C_{20}H_{26}N_2O$	77.38	8.44	9.03	77.14	8.36	9.03	
		2HCl	214–215			$C_{20}H_{28}Cl_2N_2O$	62.63	7.36	7.31	62.60	7.56	7.19	.01
		$(CH_3)_2SO_4$	145–146			$C_{22}H_{32}N_2O_6S$	60.52	7.39	6.42	60.72	7.28	6.64	.5
C_6H_{11}[c]	C_2H_5	2HCl	235–236	A	17	$C_{20}H_{34}Cl_2N_2O$	61.68	8.80	7.20	60.84	8.93	7.26	.04
		$(CH_3)_2SO_4$	134–135			$C_{22}H_{38}N_2O_6S$	59.70	8.65	6.33	59.07	8.49	6.42	.2
C_6H_5	$CH(CH_3)_2$	Base	95–96	A	48	$C_{21}H_{28}N_2O$	77.73	8.70	8.64	77.39	8.71	8.59	
		2HCl	229–231			$C_{21}H_{30}Cl_2N_2O$	63.47	7.61	7.05	63.57	7.84	6.99	.01
		CH_3I	221–222			$C_{22}H_{31}IN_2O$	56.44	6.70	6.01	57.58	7.00	5.82	.2
C_6H_{11}[c]	$CH(CH_3)_2$	2HCl	254–255	A	20	$C_{21}H_{36}Cl_2N_2O$	62.52	9.00	6.95	62.51	9.12	6.93	.04
		CH_3I	164–166			$C_{22}H_{37}IN_2O$	55.90	7.89	5.93	55.90	7.91	5.73	.4
C_6H_5	$CH_2C_6H_5$	Base	117–119	D	50	$C_{25}H_{28}N_2O$	80.61	7.58	7.52	80.60	7.73	7.49	< .002
		$(CH_3)_2SO_4$	187–188			$C_{27}H_{34}N_2O_6S$	65.03	6.87	5.62	64.87	7.06	5.67	
		CH_3Br	223–224			$C_{26}H_{31}BrN_2O$	66.80	6.69	5.99	66.82	6.91	6.00	
C_6H_5	$CH_2CH_2C_6H_5$	Base	143	F	74	$C_{26}H_{30}N_2O$[f]	80.78	7.82	7.26	80.95	7.95	7.47	
		2HCl	234–236			$C_{26}H_{32}Cl_2N_2O$	67.90	7.02	6.10	67.30	7.07	6.04	

[a] Uncorrected. [b] See Experimental. [c] Cyclohexyl. [d] A 5% rhodium-on-alumina catalyst produced a smoother hydrogenation of the phenyl group than did the platinum oxide catalyst specified in method B. [e] *Anal.* Calcd.: Cl, 19.14; O, 6.55. Found: Cl, 18.65; O, 6.79. [f] *Anal.* Calcd.: O, 4.14. Found: O, 4.42. [g] Against acetylcholine induced spasm of the isolated rabbit ileum; atropine = 1.

Acylation of 1-methylpiperazine by α-chlorodiphenylacetyl chloride gave IX which could be converted to X, XI and XII by treatment with water, methanol and methylmercaptan, respectively. Lithium aluminum hydride reduction of XI produced XIII, but similar treatment of XII led to

TABLE III

COMPOUNDS OF TYPE $(C_6H_5)_2C(R)-X-N$ / NCH_3

Compound R	Compound X	Form	M.p.,[a] °C.	Method[b]	Yield, %	Formula	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N	Activity[i]
CH_3	CO	HCl	232–233	[c]	65	$C_{20}H_{25}ClN_2O$	69.65	7.31	8.12	69.58	7.39	8.16	0.004
		$(CH_3)_2SO_4$	149–150			$C_{22}H_{30}N_2O_5S$	60.80	6.96	6.45	60.97	6.86	6.62	.04
CH_3	CH_2	2HCl	259–260	H	59	$C_{20}H_{28}Cl_2N_2$	65.38	7.68	7.63	65.54	7.80	7.67	.005
		$(CH_3)_2SO_4$	152–153			$C_{22}H_{32}N_2O_4S$	62.83	7.67	6.66	62.88	7.63	6.81	.1
OH	CO	Base	180–182	G	41	$C_{19}H_{22}N_2O_2$	73.52	7.15	9.03	73.42	7.01	9.05	.01
		CH_3Br	284–285			$C_{20}H_{25}BrN_2O_2$	59.26	6.22	6.91	59.09	6.11	7.07	.03
Cl	CO	Base	118–119	G	67	$C_{19}H_{21}ClN_2O$	69.40	6.44	10.78	69.61	6.44	10.83	
OCH_3	CO	Base	118–120	G	85	$C_{20}H_{24}N_2O_2$[d]	74.04	7.46	8.64	74.33	7.23	8.39	
SCH_3	CO	HCl	212–213	G	35	$C_{20}H_{25}ClN_2OS$	63.72	6.69	7.43	63.70	7.17	7.74	
OCH_3	CH_2	2HCl	200–201	H	91	$C_{20}H_{28}Cl_2N_2O$[e]			7.31			7.00	< .005
		$(CH_3)_2SO_4$	155–156			$C_{22}H_{32}N_2O_5S$	60.52	7.39	6.42	60.86	7.60	6.22	.02
$C_5H_{11}N_2$[f]	CO	Base	124–125	G[g]	16	$C_{24}H_{32}N_4O$	73.43	8.22	14.27	73.21	8.17	14.36	
		$2CH_3I \cdot {}^1/_2H_2O$	293–294			$C_{26}H_{38}I_2N_4O \cdot {}^1/_2H_2O$	45.56	5.74	8.17	45.43	5.71	8.76	< .006
OH	$CH(CH_3)$[h]	Base	84–86	A	73	$C_{20}H_{26}N_2O$	77.38	8.44	9.03	77.03	8.68	8.87	
		2HCl	232–235			$C_{20}H_{28}Cl_2N_2O$	62.66	7.36	7.31	62.89	7.21	7.42	.005
		$(CH_3)_2SO_4$	144–145			$C_{22}H_{32}N_2O_5S$	60.52	7.39	6.42	60.23	7.68	6.35	.01
OH	$(CH_2)_2$[h]	Base	116–117	A	26	$C_{20}H_{26}N_2O$	77.38	8.44	9.03	77.35	8.37	9.11	
		2HCl	244–245			$C_{20}H_{28}Cl_2N_2O$	62.66	7.36	7.31	63.86	7.30	7.54	< .005
		$(CH_3)_2SO_4$	181–183			$C_{22}H_{32}N_2O_5S$	60.52	7.39	6.42	61.32	7.12	6.67	.01
OH	$(CH_2)_3$	2HCl	232–233	J	Poor	$C_{21}H_{30}Cl_2N_2O$	63.47	7.61	7.05	63.68	7.67	6.99	.005
		$(CH_3)_2SO_4$	144–145			$C_{23}H_{34}N_2O_5S$	61.31	7.61	6.22	61.76	7.81	6.01	.01

[a] Uncorrected. [b] See Experimental. [c] Method of H. Zaugg and B. Horrom, THIS JOURNAL, **72**, 3004 (1950). [d] *Anal.* Calcd.: O, 9.86. Found: O, 10.12. [e] *Anal.* Calcd.: Cl, 18.50. Found: Cl, 18.33. [f] 1-Methyl-4-piperazyl. [g] The ether was replaced by xylene and the mixture was refluxed for 18 hr. [h] For the corresponding cyclohexyl analog, see under method A in the Experimental section. [i] Against acetylcholine induced spasm of the isolated rabbit ileum; atropine = 1.

cleavage of the thioether group. Properties of these compounds are listed in Table III.

Monoquaternary salts of most of these substituted piperazines were made. For the preparation of the monomethyl piperazinium salts, dimethyl sulfate was preferred to methyl iodide or methyl bromide because of its apparently greater selectivity in forming the monoquaternary salt uncontaminated by the diquaternary salt. However, the quaternary methomethyl sulfates shared with the dihydrochloride salts the inconvenient tendency to formation of hydrates which were just stable enough to render elementary microanalyses difficult. The determination of the location of the quaternary nitrogen atom in these salts is the subject of an accompanying paper.[2]

Compound II was resolved through the bis-*d*-tartrate salt. The *dd*-diastereoisomer proved to be a readily crystallizable solid while the *ld*-form could be obtained only as a thick oil. The fact that the *l*-form of II possesses nearly all of the pharmacological activity (see Table I) shows that practically complete resolution was attained even though the numerically low specific rotations of both the hydrochlorides (±6.2°) and the methomethyl sulfates (±4.4°) might indicate otherwise.

Pharmacology.—The antispasmodic activities of the compounds are listed in the tables in terms of atropine equivalents. The dihydrochlorides of compounds I and V have reached the stage of clinical trial in the treatment of parkinsonism. In dogs, they are highly effective in alleviating the parkinson-like syndrome induced by Tremorine.[3] Both show a relatively low incidence of the usual undesirable atropinic side effects.

The quaternary methomethyl sulfate of the racemic form of compound II has been marketed as a gastric antisecretory agent under the generic name hexocyclium, and the trademark TRAL.[4] A comparison of its activity with the action of other antisecretory agents has been reported elsewhere.[5]

Experimental

Phenacylpiperazines. 1-Methyl-4-phenacylpiperazine.—A solution of 99.5 g. (0.5 mole) of phenacyl bromide in 150 ml. of dry xylene was added dropwise with stirring to a solution of 60 g. (0.6 mole) of 1-methylpiperazine and 60.6 g. (0.6 mole) of triethylamine in 150 ml. of dry xylene heated on the steam-bath. After completion of the addition the mixture was stirred and refluxed for 16 hr. The cooled mixture was filtered to remove triethylamine hydrobromide (91 g., 100%), and the filtrate was extracted with several portions of dilute hydrochloric acid. The combined aqueous extracts were made strongly alkaline with 40% aqueous sodium hydroxide and the resultant oil was taken up in a mixture of ether and benzene and separated. After removal of solvent from the organic layer, the residue was fractionally distilled under reduced pressure to give 90.4 g. (83%) of 1-methyl-4-phenacylpiperazine, b.p. 156–157° (3.5 mm.), m.p. 60–62°. For analysis a sample was recrystallized from Skellysolve B (hexane), m.p. 69–70°.

Anal. Calcd. for $C_{13}H_{18}N_2O$: N, 12.84. Found: N, 12.68.

1-Methyl-4-phenacylpiperazine dihydrochloride, m.p. 250–251° (from methanol). *Anal.* Calcd. for $C_{13}H_{20}Cl_2N_2O$: N, 9.62. Found: N, 9.58.

In like manner, using 1-ethylpiperazine[6] in place of 1-methylpiperazine in the above procedure, **1-ethyl-4-phenacylpiperazine** was prepared in 69% yield, b.p. 170–176° (3.5 mm.), m.p. 46–48° (from cyclohexane).

Anal. Calcd. for $C_{14}H_{20}N_2O$: C, 72.33; H, 8.68; N, 12.06. Found: C, 71.47; H, 8.66; N, 11.72.

Also, using 1-isopropylpiperazine[6] in the above procedure, **1-isopropyl-4-phenacylpiperazine** was obtained in 71% yield, b.p. 173–178° (3.5 mm.), m.p. 34–35° (not recrystallized).

Anal. Calcd. for $C_{15}H_{22}N_2O$: C, 73.13; H, 9.00; N, 11.37. Found: C, 71.70; H, 9.10; N, 11.20.

(2) H. Zaugg and R. Michaels, THIS JOURNAL, **80**, 2768 (1958).

(3) G. Everett, L. Blockus and I. Shepperd, *Science*, **124**, 79 (1956).

(4) Registered trademark of Abbott Laboratories, North Chicago, Ill.

(5) K. Hwang, *Am. J. Gastroenterol.*, **26**, 56 (1956).

(6) H. Stewart, *et al.*, *J. Org. Chem.*, **13**, 134 (1948).

Likewise, replacing phenacyl bromide in the above procedure by α-bromopropiophenone, led to 1-**methyl-4-(α-methylphenacyl)-piperazine** in 87% yield, b.p. 162–164° (3.5 mm.), $n^{25}D$ 1.5362.

Anal. Calcd. for $C_{14}H_{20}N_2O$: C, 72.33; H, 8.68; N, 12.06; O, 6.93. Found: C, 72.78; H, 9.07; N, 11.68; O, 7.30.

β-(1-Methyl-4-piperazino)-propiophenone.—To a cooled solution of 61 g. (0.46 mole) of acrylophenone[7] in 100 ml. of dry toluene was added dropwise with stirring 110 g. (1.1 moles) of 1-methylpiperazine, while keeping the temperature below 50°. The mixture was then heated on the steam-bath for 20 hr. The cooled mixture was extracted with water to remove excess methylpiperazine and the toluene was removed under reduced pressure. The residual oil (70 g., 65%) was distilled *in vacuo* to give β-(1-methyl-4-piperazino)-propiophenone, b.p. 120–126° (3.5 mm.), $n^{25}D$ 1.5392.

Anal. Calcd. for $C_{14}H_{20}N_2O$: C, 72.33; H, 8.68; N, 12.06. Found: C, 73.09; H, 8.70; N, 12.17.

Monohydrochloride, m.p. 173–174° (from ethanol). *Anal.* Calcd. for $C_{14}H_{21}ClN_2O$: C, 62.55; H, 7.88; N, 10.42. Found: C, 63.05; H, 7.90; N, 10.64.

Dihydrochloride, m.p. 195–197° (from methanol). *Anal.* Calcd. for $C_{14}H_{22}Cl_2N_2O$: C, 55.08; H, 7.27; N, 9.18. Found: C, 54.96; H, 7.09; N, 9.15.

Ethyl 1-methyl-4-piperazineacetate, b.p. 119–123° (13 mm.), $n^{25}D$ 1.4597, was prepared in 75% yield by the method of Morren, *et al.*[8]

In a similar manner from 1-benzylpiperazine[9] was obtained in 88% yield, **ethyl 1-benzyl-4-piperazineacetate**, b.p. 176–180° (3 mm.), $n^{25}D$ 1.5173.

Anal. Calcd. for $C_{15}H_{22}N_2O_2$: C, 68.67; H, 8.45; N, 10.68. Found: C, 68.44; H, 8.60; N, 10.96.

1-(2′,2′-Diphenyl-2′-hydroxyethyl)-4-methylpiperazine (I). Method A.—To a cool solution of phenylmagnesium bromide prepared from 0.25 mole each of magnesium and bromobenzene in 200 ml. of dry ether was added, dropwise with stirring, a solution of 29.9 g. (0.137 mole) of 1-methyl-4-phenacylpiperazine in 300 ml. of dry toluene. The ether was removed by distillation and the resulting toluene solution was refluxed for 2.5 hr. After cooling, the reaction mixture was treated dropwise with a solution of 25 g. of ammonium chloride in 100 ml. of water. The toluene layer was separated, the aqueous layer was extracted once with ether and the combined organic extracts were concentrated. The residue was distilled under reduced pressure and after a forerun consisting mainly of unreacted aminoketone, there was obtained 16.5 g. (53%) of carbinol I, b.p. 208–212° (4 mm.), $n^{25}D$ 1.5727. It slowly crystallized, m.p. 70–73° (crude). All of the other compounds reported in the three tables, which were prepared by this method, were obtained by refluxing the Grignard reaction in ether solution for 16 to 18 hr. rather than in toluene for the shorter period.

The dihydrochloride salt of I was prepared from dry hydrogen chloride in an alcoholic ethereal solution. After two recrystallizations from absolute ethanol, it melted at 224–225°.

The quaternary **methomethyl sulfate of I** was prepared by dissolving 2.97 g. (0.01 mole) of the base in dry ether, adding 1.26 g. (0.01 mole) of dimethyl sulfate and allowing the mixture to stand for five days. Filtration of the crystalline product and two recrystallizations from a methanol–ether mixture gave 3.2 g. (76%) of the methomethyl sulfate, m.p. 160–162°. Methyl ethyl ketone was used in place of ether as solvent with equally good results and with the added advantage that the reaction time could be considerably shortened by heating.

Attempts to prepare the corresponding *p*-anisyl, *p*-phenethyl, 3-pyridyl, cyclopentyl, 2-thienyl and *o*-chlorophenylcarbinols by method A failed. Replacing the above phenacylpiperazine by 1-methyl-4-(α-methylphenacyl)-piperazine gave **1-(2′,2′-diphenyl-2′-hydroxyisopropyl)-4-methylpiperazine** in 72% yield, b.p. 210–213° (2.5 mm.), $n^{25}D$ 1.5758, m.p. 84–86° (Table III).

In a similar manner, reaction of cyclohexylmagnesium bromide with β-(1-methyl-4-piperazino)-propiophenone gave **1-(3′-cyclohexyl-3′-hydroxy-3′-phenylpropyl)-4-methylpiperazine**, in a 26% yield, m.p. 105–106° (from ethyl acetate).

Anal. Calcd. for $C_{20}H_{32}N_2O$: C, 75.90; H, 10.19; N, 8.85. Found: C, 76.03; H, 10.42; N, 8.81.

Dihydrochloride, m.p. 251–252° dec. *Anal.* Calcd. for $C_{20}H_{34}Cl_2N_2O$: C, 61.68; H, 8.80; N, 7.20. Found: C, 61.40; H, 9.07; N, 7.18.

Quaternary methomethyl sulfate, m.p. 155–156°. *Anal.* Calcd. for $C_{22}H_{38}N_2O_5S$: C, 59.70; H, 8.65; N, 6.33. Found: C, 59.90; H, 8.72; N, 6.44.

Also, reaction of cyclohexylmagnesium bromide with 1-methyl-4-(α-methylphenacyl)-piperazine according to method A gave a 56% yield of **1-(2′-cyclohexyl-2′-hydroxy-2′-phenylisopropyl)-4-methylpiperazine**, b.p. 193–208° (2.5 mm.), $n^{25}D$ 1.5355.

Anal. Calcd. for $C_{20}H_{32}N_2O$: C, 75.90; H, 10.19; N, 8.85; O, 5.06. Found: C, 75.37; H, 10.28; N, 9.02; O, 5.37.

Dihydrochloride, m.p. 232–233°. *Anal.* Calcd. for $C_{20}H_{34}Cl_2N_2O$: C, 61.68; H, 8.80; N, 7.20. Found: C, 61.45; H, 9.05; N, 7.00.

Quaternary methomethyl sulfate, m.p. 245–246° dec. *Anal.* Calcd. for $C_{22}H_{38}N_2O_5S$: C, 59.70; H, 8.65; N, 6.33. Found: C, 60.21; H, 8.60; N, 6.54.

1-(2′-Cyclohexyl-2′-hydroxy-2′-phenylethyl)-4-methylpiperazine (II) by Hydrogenation of (I). Method B.—A solution of 11.0 g. (0.03 mole) of the recrystallized dihydrochloride of I in 30 ml. of water was treated with 0.33 g. of platinum oxide catalyst and hydrogenated at 55–60° under 30 pounds pressure. The reaction was complete in 4 hr. The warm solution was filtered and concentrated to dryness under reduced pressure. The residue was taken up in 125 ml. of hot absolute ethanol, filtered and cooled. There was obtained 10.6 g. (94%) of II dihydrochloride, m.p. 239–241°. Best results in this hydrogenation were obtained with pure I. With highly purified I, a catalyst percentage as low as 2% could be used successfully.

1-(2′-Δ¹-Cyclohexenyl-2′-hydroxy-2′-phenylethyl)-4-methylpiperazine (III). From 1-Acetylcyclohexyl Acetate. Method C.—A solution of 14.7 g. (0.08 mole) of 1-acetylcyclohexyl acetate[10] in 15 ml. of glacial acetic acid was treated in one portion with a solution of 12.8 g. (0.08 mole) of bromine in 20 ml. of glacial acetic acid followed by four drops of a 30% solution of hydrogen bromide in acetic acid. After stirring for 45 min. at 40° under an atmosphere of nitrogen, the mixture was diluted with 200 ml. of ether and then poured onto crushed ice. The mixture was neutralized by the careful addition of cold 40% aqueous sodium hydroxide followed by excess saturated sodium bicarbonate solution. Separation of the ether, drying and removal of the ether followed by distillation of the residue gave 17.7 g. of a colorless liquid boiling over the range 103–125° (0.8 mm.). This is probably a mixture of 1-bromoacetylcyclohexyl acetate and 1-bromoacetylcyclohexene. It darkened on standing.

This bromo derivative was dissolved in 50 ml. of dry xylene and added dropwise with stirring over a period of 15 min. to a solution of 20.2 g. (0.202 mole) of 1-methylpiperazine in 75 ml. of xylene. The mixture was stirred and refluxed for 15 hr., cooled and treated with 50 ml. of water. The product was extracted from the organic layer by means of dilute hydrochloric acid, and the extract was made strongly alkaline with 40% aqueous sodium hydroxide. The resulting precipitated oil was taken up in ether, dried, and distilled to give two fractions, b.p. 136–138° (1 mm.) (3.6 g.), and b.p. 144–168° (1 mm.) (1.7 g.). The first fraction analyzed more closely for the unsaturated 1-methyl-4-tetrahydrophenacylpiperazine than for the corresponding cyclohexyl acetate from which it would derive.

Anal. Calcd. for $C_{13}H_{22}N_2O$: C, 70.21; H, 9.97; N, 13.05. Found: C, 68.65; H, 10.18; N, 13.62.

Both fractions (5.3 g.) were combined, dissolved in 50 ml. of dry ether, and added dropwise with stirring to a cooled solution of phenyllithium previously prepared in the usual way from 11.3 g. (0.072 mole) of bromobenzene, 1.0 g. (0.144 mole) of lithium and 100 ml. of dry ether in an atmosphere of dry nitrogen. After stirring and refluxing for 2 hr., the mixture was treated dropwise with 50 ml. of water and the ether was separated. Drying and removing the ether left an oily residue which did not crystallize. It was

(7) F. Blicke and J. Burckhalter, THIS JOURNAL, **64**, 451 (1942).

(8) Morren, *et al.*, *Bull. soc. chim. Belge*, **59**, 228 (1950); *C. A.*, **45** 6210 (1951).

(9) Cymerman-Craig, *et al.*, *Australian J. Chem.*, **9**, 403 (1956).

(10) G. Stacy and R. Mikulec, *Org. Syntheses*, **35**, 1 (1955).

converted to a salt by means of ethereal hydrogen chloride. Three recrystallizations from methanol gave 1.3 g. of the dihydrochloride of III, m.p. 206–208°. It was characterized by microanalysis (see Table I) of the elements and by close correspondence of its infrared spectrum with that of the dihydrochloride of compound I.

1-(2′,2′-Diphenyl-2′-hydroxyethyl)-4-benzylpiperazine (IV) by Reaction of Phenyl Grignard Reagent with 1-Benzyl-4-piperazineacetic Ester. Method D.—A solution of 1.05 moles of phenylmagnesium bromide in 350 ml. of dry ether was treated with 250 ml. of dry benzene and the ether was removed by distillation. To the resulting benzene solution was added dropwise with stirring a solution of 69 g. (0.263 mole) of ethyl 1-benzyl-4-piperazineacetate in 100 ml. of dry benzene. The mixture was stirred and refluxed for 16 hr. The cooled stirred reaction mixture was then treated dropwise with a solution of 100 g. of ammonium chloride in 300 ml. of water. After removal of the magnesium salts by filtration and washing the filter cake with ether, the organic layer was worked up as in method A. From the ether–benzene extract was obtained 49.3 g. (50%) of IV, m.p. 116–119°. One recrystallization from 95% ethanol gave analytically pure product, m.p. 117–119° (see Table II).

Compound I (Table I) was prepared from 1-methyl-4-piperazineacetic ester in a similar manner in a 69% yield using, however, a 5:1 rather than the above 4:1 molar ratio of Grignard reagent to ester. Attempts to use thienylmagnesium bromide in this reaction failed to produce any isolable dithienylcarbinol. Using toluene in place of benzene as solvent led to negligible improvement.

1-(2′,2′-Diphenyl-2′-hydroxyethyl)-piperazine (V) by Hydrogenolysis of the 4-Benzyl Derivative. Method E.—A solution of 18.6 g. (0.05 mole) of 1-(2′,2′-diphenyl-2′-hydroxyethyl)-4-benzylpiperazine in 200 ml. of 50% aqueous ethanol containing 0.1 mole of hydrochloric acid was treated with 2.0 g. of 5% palladium–charcoal catalyst and hydrogenated for 2 hr. at 25 pounds pressure. The catalyst was removed by filtration and the filtrate was concentrated to dryness under reduced pressure. The residue was taken up in hot 95% ethanol and allowed to cool. A first crop gave 14 g. and a second gave 3 g. of the dihydrochloride of V, m.p. 247–249°, yield 96%. It could be converted to a solid free base, m.p. 138–139°.

1-(2′,2′-Diphenyl-2′-hydroxyethyl)-4-(2″-phenylethyl)-piperazine (VI). Method F.—A suspension of 3.55 g. (0.01 mole) of 1-(2′,2′-diphenyl-2′-hydroxyethyl)-piperazine dihydrochloride (V) in a mixture of 75 ml. of ethanol and 5 ml. of water was treated with 1.68 g. (0.02 mole) of anhydrous sodium acetate and 4 ml. (excess) of a 50% alcoholic solution of phenylacetaldehyde. After several hours of shaking, 0.4 g. of a 5% palladium–charcoal catalyst was added and the mixture was hydrogenated at 50–60° and 25 pounds pressure until reaction was complete (5–6 hr.). The catalyst was removed by filtration and the filtrate was concentrated to dryness under reduced pressure. The residue, treated with a mixture of benzene and water, was made alkaline with sodium hydroxide solution and the benzene layer was separated. The benzene was dried over anhydrous magnesium sulfate, filtered, and treated with 0.02 mole of alcoholic hydrogen chloride. The precipitated dihydrochloride of VI weighed 3.5 g. (74%), m.p. 234–236°. The free base could also be isolated as a solid, m.p. 143° (see Table II).

Substituted Diphenylacetylpiperazines. 1-Benzilyl-4-methylpiperazine (X). Method G.—A solution of 11.7 g. (0.117 mole) of 1-methylpiperazine in 50 ml. of dry ether was added dropwise to a stirred solution of 15.5 g. (0.0585 mole) of α-chlorodiphenylacetyl chloride[11] in 150 ml. of dry ether. After standing at room temperature overnight, enough water was added to dissolve precipitated salts, and the aqueous layer was drawn off. The ether layer was extracted with one portion of dilute hydrochloric acid and the combined aqueous extracts were made alkaline with 40% aqueous sodium hydroxide solution. The liberated base was taken up in chloroform, separated, and the chloroform was removed by distillation. Three recrystallizations of the solid residue (m.p. 164–170°) from ethanol gave 7.5 g. (41%) of **1-benzilyl-4-methylpiperazine (X)**, m.p. 180–182° (Table III).

When the above procedure was modified by filtering off precipitated salts, washing the cake well with dry ether (instead of treating with water), combining all ether extracts and concentrating them to a small volume, a 67% yield of **1-(α-chlorodiphenylacetyl)-4-methylpiperazine (IX)**, m.p. 118–119°, was obtained.

Refluxing this chloride overnight in excess methanol, cooling, removing the crystallized hydrochloride by filtration and converting to the free base with alkali gave an 85% yield of **1-(α-methoxydiphenylacetyl)-4-methylpiperazine (XI)** m.p. 118–120°.

Heating a mixture of 40 g. (0.12 mole) of 1-(α-chlorodiphenylacetyl)-4-methylpiperazine, 71 g. (1.5 moles) of methyl mercaptan and 200 ml. of isopropyl alcohol in a bomb at 60° for 12 hr. gave a 35% yield of **1-(α-methylthiodiphenylacetyl)-4-methylpiperazine (XII)** isolated as the hydrochloride, m.p. 212–213° (from methanol–ether).

1-(2′,2′-Diphenylpropyl)-4-methylpiperazine. Method H.—A solution of 0.0328 mole (as the free base) of 1-(2′,2′-diphenylpropionyl)-4-methylpiperazine (VII) in 100 ml. of dry ether was added dropwise to a stirred suspension of 2.5 g. (0.0656 mole) of lithium aluminum hydride in 50 ml. of dry ether. After stirring and refluxing for 18 hr., the mixture was cooled and treated dropwise with 15 ml. of water followed by 25 ml. of 3% hydrochloric acid. The product was isolated in the usual way in the form of the dihydrochloride, m.p. 259–260° dec. (7.0 g., 59%) (see Table III).

Reduction of 1-(α-methoxydiphenylacetyl)-4-methylpiperazine (XI) in the same way gave 1-(2′,2′-diphenyl-2′-methoxyethyl)-4-methylpiperazine (XIII) in 91% yield. However, attempted reduction of the corresponding methylthio ether XII was unsuccessful. Cleavage of the methylthio group resulted.

1-(4′,4′-Diphenyl-4′-hydroxybutyl)-4-methylpiperazine. Method J.—To 25 g. (0.25 mole) of 1-methylpiperazine was added with stirring and in one portion 24.9 g. (0.1 mole) of crude 4-chloro-1,1-diphenylbutanol.[12] After stirring the mildly exothermic reaction for one hr. without external heating, the mixture was heated on the steam-bath for an additional hour. The cooled reaction mixture was then diluted with 100 ml. of water, made alkaline with ammonium hydroxide, and the resulting oil was taken up in ether, separated and dried. Filtration and removal of the ether by distillation gave an oil which could not be crystallized. The dihydrochloride was then prepared by treatment with excess dry hydrogen chloride in isopropyl alcohol. Three recrystallizations of this salt from ethanol followed by three more from methanol gave 1.9 g. of the dihydrochloride, m.p. 232–233° (Table III). The quaternary methomethyl sulfate was also prepared in the usual manner (see method A).

Resolution of 1-(2′-Cyclohexyl-2′-hydroxy-2′-phenylethyl)-4-methylpiperazine (II). Method K.—A solution of 95 g. (0.314 mole) of II (liquid free base) in 50 ml. of warm methanol was added to 100 g. (0.666 mole) of *d*-tartaric acid dissolved in 250 ml. of hot methanol. After heating to boiling, the precipitated salt was brought into solution by the addition of 1500 ml. of hot methanol. The solution was filtered and allowed to stand undisturbed for 48 hr. The mother liquor was decanted from the solid product which was then sucked dry on a sintered glass funnel and washed with 100 ml. of methanol. The dried material weighed 67 g., m.p. 189–191° dec. A second crop (13.3 g., m.p. 187–192°) was obtained by concentrating the mother liquor to 300 ml. and allowing to stand for 36 hr. The mother liquor was saved for isolation of the *l*-isomer. The combined crops (80.3 g.) were dissolved in 1500 ml. of boiling methanol, the solution was filtered, concentrated to a volume of 700 ml., seeded and allowed to stand for 48 hr. Filtering and washing with methanol gave 49 g., m.p. 194–196° dec. One more recrystallization from a minimum quantity of methanol gave 27.0 g. of ***d*-II-bis-*d*-tartrate**, m.p. 197–199° dec., $[\alpha]^{25}D$ + 15.4° (*c* 0.05 g./ml., H_2O) (see Table I for further data).

Twenty-four grams of this salt was converted to the free base by dissolving in water and treating with excess aqueous 20% sodium hydroxide solution. The precipitated oil was taken up in ether, washed three times with water, once with saturated brine, and dried over anhydrous magnesium sulfate. After filtering, the ethereal solution was treated with a slight excess of a solution of hydrogen chloride in isopropyl alcohol. The precipitated dihydrochloride was recrystallized from a methanol–isopropyl alcohol mixture to give

(11) J. Billman and P. Hidy, THIS JOURNAL, **65**, 760 (1943).

(12) P. Barrett and S. Wilkinson, British Patent 683,950; *C. A.*, **48**, 2112 (1954).

11.7 g., m.p. 256–258° dec. Analysis indicated contamination by tartaric acid so that the above transformation through the free base was repeated once more to give 8.44 g. of *d*-II **dihydrochloride**, m.p. 266° dec., $[\alpha]^{25}D$ +6.2° (*c* 0.05 g./ml., H_2O) (Table I).

To isolate the *l*-isomer, the mother liquor, remaining after isolation of the second crop from the original crystallization, was evaporated to dryness at room temperature to give a yellow semi-solid residue. This was taken up in a minimum quantity of boiling methanol and refrigerated for several days after seeding with *d*-II bis-*d*-tartrate. The precipitated material was removed by filtration and the filtrate was concentrated to a volume of 75–100 ml. This was refrigerated again for several days, but only a trace of solid precipitated. After filtering, the filtrate was evaporated to dryness to yield a semi-solid product which was extracted four times by decantation with boiling isopropyl alcohol. The combined extracts were filtered and concentrated to give 29.4 g. of a viscous yellow oil which consisted largely of *l*-II **bis-*d*-tartrate**. This material was treated in exactly the same way as described above for the 24 g. of *d*-II bis-*d*-tartrate. There was obtained, in this way, 3.05 g. of *l*-II-**dihydrochloride**, m.p. 266° dec., $[\alpha]^{25}D$ −6.2° (*c* 0.05 g./ml., H_2O) (Table I).

Treatment of the free base obtained from *d*-II dihydrochloride with dimethyl sulfate in methyl ethyl ketone in the usual manner (method A) gave *d*-II **methomethyl sulfate**, m.p. *ca.* 190° dec., $[\alpha]^{22}D$ +4.42° (*c* 0.05 g./ml., H_2O).

Similarly, from *l*-II dihydrochloride was obtained *l*-II **methomethyl sulfate**, m.p. *ca.* 190° dec., $[\alpha]^{22}D$ −4.45° (*c* 0.10 g./ml., H_2O) (see Table I).

Acknowledgment.—The authors wish to thank Dr. G. M. Everett, Dr. K. Hwang, Mr. L. E. Blockus and Miss I. M. Shepperd for the pharmacological data. Extended and more detailed results will be published by them elsewhere. The infrared determinations were carried out by Mr. W. Washburn and the microanalyses under the direction of Mr. E. F. Shelberg.

NORTH CHICAGO, ILLINOIS

[CONTRIBUTION FROM ABBOTT LABORATORIES]

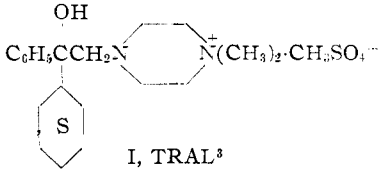
Tertiary Carbinols of the Piperazine Series. II. The Site of Quaternization

BY HAROLD E. ZAUGG AND RAYMOND J. MICHAELS

RECEIVED DECEMBER 16, 1957

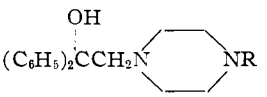
By a system of alternate introduction of benzyl and methyl groups, by hydrogenolytic removal of benzyl from a methylated 1-benzyl-4-piperazine-ethanol derivative, and by unequivocal synthesis of the alternate position isomer, it has been demonstrated that 1-(2′,2′-diphenyl-2′-hydroxyethyl)-4-methyl(and benzyl)-piperazine (II and III) and the cyclohexyl analog quaternize at the 4-position. The possibility of the occurrence of geometric isomerism in 1,4-substituted piperazines is discussed. An incidental anomaly indicating a cationic influence on anionic exchange with IR-45 resin is noted.

In the first paper of this series[1] the preparation was reported of a number of monoquaternary salts of unsymmetrically 1,4-disubstituted piperazines. The ambiguity arising from the uncertain position of the quaternary center remained unresolved. Baltzly, Ide and Lorz,[2] in a study of benzylhydrylpiperazines, assumed, on the basis of steric and known electronic effects, that quaternization of their compounds occurred at the nitrogen atom (called terminal, in this discussion) not attached to the benzhydryl group. Their assumption was reinforced by the inability of their compounds to form diquaternary salts. However, in our series of piperazinecarbinols,[1] the demonstrated capacity to form diquaternary salts shows that the nitrogen atom (called central, in this discussion) attached to the bulkier group can quaternize. Because one of our quaternary salts I has shown clinical usefulness, it seemed desirable to identify unequivocally the particular nitrogen atom involved in salt formation even though the assumptions of the previous workers[2] seem quite reasonable.



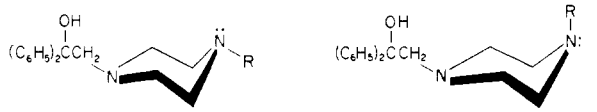
I, TRAL[3]

In the accompanying paper[1] it was reported (see Tables I and II) that the quaternary salt obtained from II by the action of methyl bromide melted at 223–224°, whereas the quaternary salt obtained from III by the action of benzyl bromide melted at 219–220°. Although their mixed melting point was intermediate between these two values and their infrared spectra (KBr pellet) were essentially identical, thus indicating terminal quaternization,



II, R = $CH_2C_6H_5$
III, R = CH_3

there still remained the possibility that this small difference in melting point could be due to the presence of a different ratio of two possible geometric isomers in the two salts. If, in II and III, different equilibria between the two possible conformations, a and b, were to result from the difference in bulk between methyl and benzyl, then different ratios of the two possible geometric isomers of the salts obtained by terminal quaternization would be expected, provided that the large group on the central nitrogen were to maintain a stable conforma-



tion with respect to the ring. That such isomerism about the nitrogen atom actually does occur in the more rigid tropine ring system, has been shown by Zeile and Schulz.[4] However, their stereoisomeric

(1) H. Zaugg, *et al.*, THIS JOURNAL, **80**, 2763 (1958).

(2) R. Baltzly, W. Ide and E. Lorz, *ibid.*, **77**, 4809 (1955).

(3) Registered trademark of Abbott Laboratories, North Chicago, Ill.

(4) K. Zeile and W. Schulz, *Ber.*, **88**, 1078 (1955).