The synthetic procedure used was the direct synthesis[4] of the oxazolidinedione from the amine, the α-hydroxy ester in an excess of the reactant, and diethyl carbonate under sodium alkoxide catalysis. Unlike our previous series,[4] the amines herein evaluated, on occasion gave incomplete conversion to the required dione I, with isolation of the intermediate ethyl urethane derived from reaction of the ethyl carbonate with the hetero amine. In one instance (compound 5) the symmetrical bis-urea was also isolated and may have resulted from transient formation of the pyridyl isocyanate,[5,6] followed by reaction with the reactant amine.

Selected compounds in this series proved to be mildly effective as anti-inflammatory agents[7] (compounds 1, 2, 5, 9, 20, 22, 23, and 24). Compounds 9-11, and 23 were effective potentiators of Evipal sleeping time.[8]

(4) S. L. Shapiro, I. M. Rose and L. Freedman, *J. Am. Chem. Soc.*, **81**, 3083 (1959).

(5) S. L. Shapiro, I. M. Rose, and L. Freedman, *J. Am. Chem. Soc.*, **80**, 6065 (1958).

(6) J. W. Baker and D. M. Bailey, *J. Chem. Soc.*, 4652, 4663 (1957).

(7) See S. L. Shapiro, H. Soloway, and L. Freedman, *J. Am. Pharm. Assoc., (Sci. Ed.)*, **46**, 333 (1957), for method of testing.

←— Footnotes to Table I

[a] The following abbreviations are used for the heterocyclic substituent: Py = pyridyl; Pc = picolyl; Im = 2-[1-(2-methyl-2-imidazolinyl)]ethyl; Qn = 3-quinolyl; Pm = 2,6-dimethyl-4-pyrimidyl. [b] The compounds so marked are methiodides of the compounds immediately above. [c] The melting points are uncorrected and were established on a Fisher-Johns melting point block. [d] R.S. = recrystallizing solvent; A = ethyl acetate–hexane; B = ethanol; C = hexane. [e] Yields are based on recrystallized or distilled product. [f] Analyses are by Weiler and Strauss, Oxford, England. [g] After the removal of the formed ethanol of reaction a 13% yield of the ethyl urethane of 2-aminopyridine precipitated, m.p. 105–106°, not depressing the melting point of the authentic urethane prepared from 2-aminopyridine and ethyl chloroformate [R. L. Shriner and R. G. Child, *J. Am. Chem. Soc.*, **74**, 549 (1952), report m.p. 104–105°]. [h] When the mother liquor obtained after filtration of the product was evaporated and the residue recrystallized (hexane) there was obtained 5% yield of the ethyl urethane of 3-aminopyridine, m.p. 90–92° [*J. Am. Chem. Soc.*, **74**, 549 (1952) report m.p. 91–92°]. [i] After the removal of the formed ethanol of reaction 4.2 g. of a mixture of solids, m.p. 120–210° precipitated and was treated with boiling hexane. The hexane insoluble portion proved to be bis(4-methyl-2-pyridyl)urea m.p. 225°. An authentic sample prepared from 2-amino-4-methylpyridine and ethyl chloroformate melted at 228.5° (ethyl acetate). *Anal.* Calcd. for $C_{13}H_{14}N_4O$: C, 64.4; H, 5.8; N, 23.1. Found: C, 64.5; H, 5.1; N, 23.3. The hexane solution on standing gave the ethyl urethane of 2-amino-4-methylpyridine m.p. 128–131°, not depressing the melting point of the authentic urethane (prepared from 2-amino-4-methylpyridine and ethyl chloroformate), m.p. 130–131° (hexane). *Anal.* Calcd. for $C_9H_{12}N_2O_2$: N, 15.6. Found: N, 15.7. [j] A forerun in the distillation 1.6 g. (9%), b.p. 95–97 (0.02 mm.), n_D^{20} 1.5140 gave analyses indicative of impure ethyl urethane of 2-picolylamine. [k] The required initial reactant 2-[1-(2-methyl-2-imidazolinyl)] ethylamine was obtained from the National Aluminate Corp., Chicago, Ill., and was purified by distillation, b.p. 62–80° (0.04 mm.), n_D^{20} 1.5119. [l] A forerun in the distillation, 3.37 g. (19%), b.p. 98–100° (0.08 mm.), n_D^{20} 1.5162 gave analyses indicative of impure ethyl urethane of 2-picolylamine. The oxazolidinedione product boiled 103–104° (0.05 mm.), n_D^{20} 1.5183, and crystallized on standing.

EXPERIMENTAL

General procedure (Table I). A solution of 0.2 g. of sodium in 4 ml. of ethanol was added to a solution of 0.1 mole of the amine, 0.1 mole of the ethyl α-hydroxy ester and 37 ml. of diethyl carbonate, and the stirred mixture was heated under reflux. When the internal temperature had dropped approximately 20°, the formed ethanol was removed and measured. If the quantity of ethanol was substantially less than theoretical, an additional charge of catalyst was added and the reflux and removal of formed ethanol were repeated as described above. Upon standing, or after removal of most of the diethyl carbonate, the product crystallized and was separated. Liquid products were distilled.

The methiodides were prepared by treating 0.01 mole of the free base with 2 ml. of methyl iodide in 40 ml. of ethanol and were obtained after the reaction mixture had been stored at room temperature for 7 to 10 days.

2-[N-(4-Methyl-2-pyridyl)carbamoyloxy]propionic acid. Alkaline hydrolysis of compound 5 and work-up as previously described[8] afforded the title compound in 68% yield, m.p. 144–148° (ethanol).

Anal. Calcd. for $C_{16}H_{12}N_2O_4$: C, 53.6; H, 5.4; N, 12.5. Found: C, 53.9; H, 5.6; N, 12.8.

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(8) See ref. (1) for method of testing.

Antihypertensive Agents. II. Tropine Quaternaries[1]

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A series of tropine quaternaries (Table I) have been prepared for pharmacological screening. Synthesis was effected by treating a mixture of the quaternizing halide with tropine in a polar solvent such as acetonitrile.[2]

Whereas bis-tropinium salts (compounds 9–12) formed readily, methylene iodide yielded the iodomethyltropinium iodide, suggesting that steric factors prevent two tropinium nitrogens from being linked by a single methylene unit.[3,4]

(1) For Paper I of this series, see S. L. Shapiro, H. Soloway, and L. Freedman, *J. Am. Chem. Soc.*, **80**, 2743 (1958).

(2) C. J. Cavallito, A. P. Gray and E. E. Spinner, *J. Am. Chem. Soc.*, **76**, 1862 (1954).

(3) For a related work see W. C. Davies, E. B. Evans and F. L. Hulbert, *J. Chem. Soc.*, 412 (1939).

(4) The failure for the conversion to the bis-quaternary may be associated with the "neopentyl-like" structure of the iodomethyl quaternary and its relative inactivity in S_N2 reactions, see J. Hine, "Physical Organic Chemistry," McGraw-Hill Book Company, Inc., New York, N. Y., 1956, page 157.

TABLE I

QUATERNARY SALTS OF TROPINE[a]

R
|
TrN$^+$ X$^-$

No.	R	X	M.p., °C.[b]	Rs[c]	Yield,[d] %	Formula	Analyses,[e] % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
1	n-$C_{12}H_{25}$—	Br	211–213	A–B	58	$C_{20}H_{40}BrNO$					3.6	3.8
2	C_8H_{15}—[f]	Br	182–185	B–C	49	$C_{16}H_{30}BrNO$	57.8	57.9	9.1	8.9		
3	$C_6H_5(CH_2)_2$—	Br	217–220	A	84	$C_{17}H_{26}BrNO$	60.0	60.4	7.7	7.8	4.1	3 8
4	$(C_6H_5)_2CH$—	Cl	195–197	A	9	$C_{21}H_{26}ClNO$	73.3	73.4	7.6	7.7	4.1	4.1
5	$HC{\equiv}CCH_2$—	Br	243–245	A	57	$C_{11}H_{18}BrNO$	50.8	51.0	7.0	7.2	5.4	5.3
6	ICH_2—	I	203–206	D	31	$C_9H_{17}I_2NO$[g]	26.4	26.2	4.2	4.1	3.4	3.4
7	$IC{\equiv}CCH_2$—[h]	Cl	212	A	12	$C_{11}H_{17}ClINO$					4.1	4.1
8	[i]	Cl	>300	A	32	$C_{14}H_{32}Cl_2N_2O$	53.3	53.4	10.2	10.4	8.9	9.2
9	$—CH_2CH{=}CHCH_2—$[j]	2Cl	>300	D	37	$C_{20}H_{36}Cl_2N_2O_2$	59.0	59.1	8.9	8.9	6.9	6.9
10	$—CH_2C{\equiv}CCH_2—$[j]	2Cl	260–263	A	21	$C_{20}H_{34}Cl_2N_2O_2$[k]					6.9	6.9
11	$—(CH_2)_5—$[j]	2Br	>300	D	30	$C_{21}H_{40}Br_2N_2O_2$	49.2	49.2	7.9	7.7	5.5	5.9
12	$—(CH_2)_6—$[j]	2Br	282–285	B–D	22	$C_{22}H_{42}Br_2N_2O_2$	50.2	49.8	8.0	7.9	5.3	5.5
13	CH_3COCH_2—	Cl	246–247	C	47	$C_{11}H_{20}ClNO_2$	56.5	56.5	8.6	8.5	6.0	6.1
14	$C_6H_5COCH_2$—	Cl	220–223	C	41	$C_{16}H_{22}ClNO_2$	65.0	65.2	7.5	7.8	4.7	4.8
15[n]	H H	Cl	258–260	A	58	$C_{10}H_{19}ClN_2O_2$	51.2	51.2	8.2	8.1	11.9	11.8
16[n]	CH_3— CH_3—	Br	242–243	E	57	$C_{12}H_{23}BrN_2O_2$	46.9	47.2	7.5	7.0	9.1	9.2
17[n]	$—(CH_2)_4—$	Br	241	A	61	$C_{14}H_{25}BrN_2O_2$	50.5	50.5	7.6	7.4	8.4	8.2
18[n]	i-C_5H_{11}— H	Cl	183–184	G	33	$C_{15}H_{29}ClN_2O_2$	59.1	59.2	9.6	9.1	9.2	9.6
19[n]	[l] H	Br	246–248	C–F	52	$C_{13}H_{31}BrN_2O_2$	55.8	55.6	8.1	7.9	7.2	7.4
20[n]	$C_6H_5CH_2$— H	Cl	196–197	E	32	$C_{17}H_{25}ClN_2O_2$	62.9	62.8	7.8	7.7	8.6	8.7
22[n]	$C_6H_5CHCH_3$— H	Br	198–199	C–F	47	$C_{13}H_{27}BrN_2O_2$					7.3	7.4
23[n]	$C_6H_5CH_2$— i-C_3H_7—	Br	169–172	F–G	35	$C_{20}H_{31}BrN_2O_2$	58.4	58.3	7.6	7.2	6.8	7.3
24[n]	$C_6H_5CH_2CHCH_3$—[m] H	Cl	204–207	H	49	$C_{19}H_{29}ClN_2O_2$	64.7	64.7	8.3	8.2	7.9	7.6
25[n]	C_6H_5— H	Cl	175–178	C	39	$C_{16}H_{23}ClN_2O_2$	61.8	61.8	7.5	7.4	9.0	9.2
26[n]	p-Cl—C_6H_4— H	Cl	247–248	C	44	$C_{16}H_{22}Cl_2N_2O_2$	55.7	56.0	6.4	6.4	8.1	7.9

[a] The formula for the tropine base has been shown as TrN. [b] Melting points are uncorrected and have been taken on a Fisher-Johns melting point block. [c] Recrystallization solvent: A—ethanol; B—isopropyl ether; C—isopropyl alcohol; D—methanol; E—acetonitrile; F—hexane; G—ether; H—ethyl acetate. [d] Yields are based on recrystallized product. [e] Analyses were performed by Weiler and Strauss, Oxford, England. [f] C_8H_{15}— is 2-cyclohexylethyl-. [g] Calcd.: I, 62.1. Found: I, 62.4. [h] The reactant 3-chloro-1-iodopropyne-1 was obtained from the Dow Chemical Company. [i] R = $—CH_2CH_2N(C_2H_5)_2 \cdot HCl$. [j] Ditropinium quaternary salt. [k] An acceptable CH analysis was not obtained. [l] R_1 = (2,5-endomethylenecyclohexyl)methyl. [m] Derived from d-α-methylphenethylamine. [n] R = $R_1R_2NCOCH_2$—; R_1 and R_2 shown under R column.

Pharmacology. All of the compounds were evaluated for hypotensive response following procedures previously described.[5] A 3+ response was noted on administration of compounds 14, 15, 20 and 25, while compounds 3, 24 and 26 showed 2+ hypotension. Each of the 3+ compounds also showed a potentiating effect on adrenalin and complete ganglionic block. Compound 26 inhibited adrenalin and showed a ganglionic block, compound 3 resembled the 3+ responders, and compound 24 was without effect on adrenalin.

In the carbamido series (compounds 15–26) it is of interest that hypotensive activity was associated with the compounds R_1, R_2 = H, and R_1 = aralkyl or aryl and R_2 = H. Other structural modifications such as those found in compounds 16, 17, 18, 19, 22 and 23 were associated with loss of hypotensive activity.

EXPERIMENTAL[6]

N-(Iodomethyl) tropinium iodide (Compound 6, Table I). Tropine (5.6 g., 0.04 mole) and 5.3 g. (0.02 mole) of diiodomethane were dissolved in 30 ml. of acetonitrile and maintained at 20° for 5 days.

The formed crystals were separated to give 5.0 g. (62%), m.p. 198–202°.

The same compound was obtained from 1:1 molar ratios of the reactants at 20°, or when the reaction mixture above was heated for 0.5 hour under reflux. The reaction of tropine with penta-erythrityl tetrabromide failed with no evidence of quaternization after 50 hr. under reflux in acetonitrile.

N-(Carbamidomethyl)tropinium chloride (Compound 15, Table I). A solution of 4.2 g. (0.03 mole) of tropine, 5.6 g. (0.06 mole) of α-chloroacetamide and 60 ml. of acetonitrile was maintained at 20° for 5 days. Filtration yielded 4.7 g. of product, m.p. 232–237°. An additional 1.4 g. was obtained by addition of ether to the filtrate.

N-Methyl-α-chloroacetanilide.[7] The following preparation is typical of the synthesis of compounds of the α-haloacetamides.

A solution of 11.8 g. (0.11 mole) of *N*-methylaniline in 75 ml. of acetonitrile was slowly added to a cooled solution of 5.7 g. (0.05 mole) of chloroacetyl chloride in 25 ml. of acetonitrile. After 48 hr. at 20°, the *N*-methylaniline hydrochloride was separated and the filtrate evaporated. Trituration of the residue with ether gave 8.8 g. (96%) of crude product, which recrystallized (hexane) melted 69–70°.

The constants of most of the α-haloacetamides were in substantial agreement with values reported in the literature. The following amides have not been previously reported: *N*-benzyl-*N*-*i*-propyl-bromacetamide, b.p. 124–136° (0.2 mm.); *N*-α-phenethyl-bromacetamide, m.p. 82–83° (hexane); *N*-(2,5-endomethylenecyclohexyl)methyl-bromacetamide, b.p. 104–130° (0.04 mm.).

Analyses were N Calcd./N Found, respectively, 5.2/5.1, 5.8/6.0, 5.7/5.6.

(5) (a) For evaluation of hypotensive effect see Ref. 1; (b) for evaluation of effect on adrenalin and ganglionic block see S. L. Shapiro, H. Soloway, E. Chodos and L. Freedman, *J. Am. Chem. Soc.*, **81**, 203 (1959).

(6) Data given in the tables are not reproduced in this section. Representative examples of the synthetic work are given.

(7) Reported by W. A. Jacobs and M. Heidelberger, *J. Biol. Chem.*, **21**, 105 (1915), m.p. 70°.

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Bis(5-hydroxymethyl-1-naphthyl)disulfide

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Although preparations of bis(hydroxyalkyl-aryl) disulfides, including those of bis(2-hydroxymethylphenyl)disulfide,[1a,b,c] bis(4-hydroxylmethyl phenyl) disulfide,[1c] and bis(4-β-hydroxyethyl-1-naphthyl) disulfide[2] have been reported previously, an example of a bis(hydroxymethyl-naphthyl)disulfide was hitherto unknown. Since the aforementioned known disulfides have been evaluated as chain transfer agents for free radical polymerization systems,[1b,1c,2] it seemed worthwhile to evaluate a compound of the latter type in such a system.

This paper reports the preparation of such a disulfide, namely bis(5-hydroxymethyl-1-naphthyl)-disulfide (VI) by the following procedure: A sample of 5-acetoxymethyl-1-nitronaphthalene (II) was prepared in two steps from 1-nitronaphthalene by the method of Short and Wang[3] *via* chloromethylation and acetolysis, and hydrolyzed to the known carbinol (III) (99%) with alcoholic alkali. The overall yield of III obtained from 5-chloromethyl-1-nitronaphthalene (I) by this two step method was much greater (65%) than that which we obtained by hydrolyzing the chloride directly to the carbinol with aqueous sodium carbonate by Short's procedure[3] (12%). Compound III was catalytically reduced to 5-hydroxymethyl-1-naphthylamine (IV), an orange compound, m.p. 107.2–108.4° (94%) with Raney nickel, converted to a crude form of 5-hydroxymethyl-1-thionaphthol (V) *via* the xanthate method, and oxidized to the corresponding disulfide (VI), a tan compound, m.p. 196.1–197.1°.

EXPERIMENTAL[4]

5-Hydroxymethyl-1-nitronaphthalene (III). This compound was prepared by alkaline hydrolysis of 5-acetoxymethyl-

(1) (a) A. Reichert and K. Crämer, *Ber.*, **61**, 2555 (1928); (b) A. J. Costanza, R. J. Coleman, R. M. Pierson, C. S. Marvel, and C. King, *J. Polymer Sci.*, **17**, 319 (1955); (c) R. M. Pierson, A. J. Costanza, and A. H. Weinstein, *J. Polymer Sci.*, **17**, 221 (1955).

(2) A. H. Weinstein, R. M. Pierson, B. Wargotz, and T. F. Yen, *J. Org. Chem.*, **23**, 363 (1958).

(3) W. F. Short and H. Wang, *J. Chem. Soc.*, 991 (1950).

(4) All melting points are corrected.