mcg./ml. Add the 2.0 mcg./ml. standard solution to alternate cylinders on each plate and the sample to the remaining cylinders. Incubate the plates for at least 48 hours at 30°, read the zones of inhibition, and calculate the concentration of griseofulvin as described for the cylinder plate assay. The lowest concentration of griseofulvin that this method can detect in body fluids is 0.9 mcg./ml.

EXPERIMENTAL

Griseofulvin bulk material, tablets, and suspensions assayed by this cylinder plate or disk method gave results comparable to those obtained using a spectrophotometric method (2) as shown in Table I. Using the described method, standard curves were run using a commercial bulk sample of griseofulvin as a house standard. Four replicate assays of a bulk sample from a different manufacturer were performed on each of three consecutive days. From the results obtained the 95% confidence limits of a single assay of the method described for pharmaceutical preparations were calculated and shown to be ±10.9%. This range can be reduced of course by performing replicate assays. Different commercial preparations were assayed by this procedure and the spectrophotometric method (2). The results summarized in Table I show good agreement.

TABLE I.—GRISEOFULVIN PHARMACEUTICAL PREPARATIONS ASSAYED BY TWO METHODS

Product	Label Potency	Spectrophotometric	Microbial
Bulk	1,000 mcg./mg.	1000	1000
		978	1008
Tablets	250 mg./tablet	250	255
Oral suspension	250 mg./5 ml.	250	250

Experimental studies on the assay in serum were limited because of lack of clinical facilities. However, one male receiving therapy of griseofulvin (250 mg. every 4 hours, total dose 1 Gm./day) for 1 week volunteered to have his serum assayed for griseofulvin. Blood sample was taken 2 hours after a 250 mg. dose of griseofulvin. His serum assayed 0.9 mcg./ml., whereas the serum from a male volunteer receiving no drug was negative.

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Basic 1,3-Dioxolanes

By A. R. PATEL and J. F. ONETO

The preparation of a series of 2-aminomethyl and 4-aminomethyl-1,3-dioxolanes has been described. A selected number of the products were subjected to preliminary pharmacologic evaluation.

IN RECOGNITION of the various structural aspects assigned to muscarine prior to 1942, Fourneau and associates (1) initiated studies on quaternary ammonium compounds which led to the synthesis of 2-methyl-4-dimethylaminomethyl-1,2-dioxolane methiodide. The compound exhibited strong muscarinic activity which decreased with the substitution of bulkier groups for the C-2 methyl moiety.

Subsequently, extensive investigations on the autonomic pharmacodynamics of basic 1,3-dioxolanes and their quaternary derivatives have been reported (2–8). Recently, Hardie and co-workers (9) have reported on the local anesthetic and spasmolytic properties of a series of 4-(2-piperidyl)-1,3-dioxolanes.

The present work was undertaken to prepare basic dioxolanes with additional structural variations for pharmacologic evaluation. The products represent essentially an extension of the Blicke series (5) of 2-aminomethyl and 4-aminomethyl substituted 1,3-dioxolanes.

The intermediate halodioxolanes (Tables I and II) required for the synthesis of the aminodioxolanes were prepared by two general methods: (*a*) condensation of an α-haloketone with a 1,2-glycol or with glycerol-α-monochlorohydrin in the presence of *p*-toluenesulfonic acid according to the procedure of Salmi (10); (*b*) condensation of a ketone with epibromohydrin in the presence of stannic chloride according to the procedure of Bersin and Willfang (11, 12).

The infrared absorption spectra of a number of the halodioxolanes listed in Table I are shown in Table III. The four bands found in the 990–

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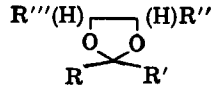
TABLE I.—CONDENSATION PRODUCTS OF α-HALOKETONES WITH 1,2-GLYCOLS[i]



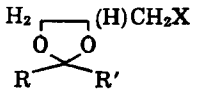
No.	R	R′	R″	R‴	Reflux, Hr.	M.p., °C.	Yield, %	Formula	Analyses, % — Halogen — Calcd.	Found
1[a]	C_6H_5	CH_2Br	H	H	15	59–60	61	$C_{10}H_{11}BrO_2$	32.87	33.01
2	*p*-BrC_6H_4	CH_2Br	H	H	16	82–83	61	$C_{10}H_{10}Br_2O_2$	49.64	49.50
3	*p*-BrC_6H_4	CH_2Br	CH_3	H	9	65–66	48	$C_{11}H_{12}Br_2O_2$	[b]	...
4	*p*-ClC_6H_4	CH_2Br	H	H	22	61 to 62.5	67	$C_{10}H_{10}BrClO_2$	28.79	28.50[c]
5	*p*-ClC_6H_4	CH_2Br	CH_3	H	24	73 to 74.5	50	$C_{11}H_{12}BrClO_2$	[b]	...
6	*p*-ClC_6H_4	CH_2Br	CH_3	CH_3	24	84–89	40	$C_{12}H_{14}BrClO_2$	[b]	...
7[d]	*p*-$CH_3OC_6H_4$	CH_2Br	H	H	12	73.5 to 75	50	$C_{11}H_{13}BrO_3$	29.26	29.46
8	*m*-$NO_2C_6H_4$	CH_2Br	H	H	15	89.5–90.5	62	$C_{10}H_{10}BrNO_4$	27.74	27.82
9	*p*-$NO_2C_6H_4$	CH_2Br	H	H	10	130–133	59	$C_{10}H_{10}BrNO_4$	27.74	27.60
10	*p*-$NO_2C_6H_4$	CH_2Br	CH_3	H	8	126.5 to 128	66	$C_{11}H_{12}BrNO_4$	26.45	26.28
11	*p*-$C_6H_5C_6H_4$	CH_2Br	H	H	15	79.5 to 80	76	$C_{16}H_{15}BrO_2$	25.04	24.92
12	*p*-$C_6H_5C_6H_4$	CH_2Cl	H	H	18	77–78	68	$C_{16}H_{15}ClO_2$	12.91	12.86
13	C_8H_9[e]	CH_2Br	H	H	17	47.5 to 48	65	$C_{12}H_{15}BrO_2$	29.47	29.68
14	C_6H_5	$C(CH_3)_2Br$	H	H	10	74–76	26	$C_{12}H_{15}BrO_2$	29.47	29.24
15	C_6H_5	$C(CH_3)_2Br$	CH_3	H	18	56 to 57.5	22	$C_{13}H_{17}BrO_2$	28.02	27.85
16	C_6H_5	$C(CH_3)_2Br$	CH_3	CH_3	36	91–96	33	$C_{14}H_{19}BrO_2$	26.71	26.62
17	C_6H_5	$C(CH_3)_2Cl$	H	H	7	73.5 to 75	45	$C_{12}H_{15}ClO_2$	15.64	15.71
18	C_6H_5	$C(CH_3)_2Cl$	CH_3	CH_3	24	83.5 to 85	22	$C_{14}H_{19}ClO_2$	13.92	13.82
19[f]	C_6H_5	$CH(Cl)C_6H_5$	H	H	10	74–75	54	$C_{16}H_{15}ClO_2$	12.90	12.65
20	C_6H_5	$C_6H_{10}Br$[g]	H	H	24	119–121	18	$C_{18}H_{19}BrO_2$	25.68	25.48
21	C_6H_5	$C_6H_{10}Cl$[h]	H	H	30	105–106	38	$C_{18}H_{19}ClO_2$	13.29	13.07

[a] Described by Kühn (14). [b] The unanalyzed products were aminated. [c] Analyzed for bromine. [d] Described by Thomae (15). [e] 2,5-Dimethylphenyl. [f] Described by Summerbell and Berger (16). [g] 1-Bromocyclohexyl. [h] 1-Chlorocyclohexyl. All compounds were prepared following the method of Salmi (10). [i] Compounds 2,4, 7, 12, 14, 17, and 19 were recrystallized from methanol, the remainder from ethanol.

1200 cm.$^{-1}$ region are in agreement with the reported observations ascribed by Bergmann and Pinchas (13) as being specific for the C—O—C—O—C grouping. However, Lagrange, and Mastagli (13) have pointed out that many of these bands appear in dioxane derivatives also and that they are not always all present in dioxolanes.

The 4-aminomethyl-1,3-dioxolanes (Table IV) were prepared by heating a mixture of the inter-

TABLE II.—4-HALOMETHYL-1,3-DIOXOLANES



No.	R	R′	X	Reflux, Hr.	B.p., °C./mm.	Yield, %
1	*p*-BrC_6H_4	CH_3	Cl	20	115–116/3	86
2	*p*-ClC_6H_4	CH_3	Cl	15	110–111/3	80
3	*p*-$CH_3OC_6H_4$	CH_3	Cl	24	102–104/4	66
4	*p*-$CH_3C_6H_4$	CH_3	Cl	12	110–112/1	59
5	C_6H_5	C_2H_5	Cl	20	106–109/3	75
6	C_6H_5	*n*-C_3H_7	Cl	24	112–114/3	78
7	C_6H_5	$CH(CH_3)_2$	Cl	24	110–112/3	79
8	C_6H_5	$CH(C_2H_5)_2$	Cl	60	108–112/2	45
9	C_6H_5	$CH(C_2H_5)C_4H_9$	Cl	72	130–132/2	59
10	$C_6H_5CH_2$	CH_3	Cl	24	100–104/3	78
11	*p*-$CH_3C_6H_4$	C_6H_5	Cl	36	[a]	...
12	*p*-ClC_6H_4	C_6H_5	Cl	48	[a]	...
13	*n*-C_9H_{19}	CH_3	Br	[b]	117–118/4	71
14	2-C_4H_3S[c]	CH_3	Br	...	100–102/4	87
15[d]	2-C_4H_3S	C_6H_5	Br	...	155–160/2	74
16	$C_6H_5CH_2$	CH_3	Br	...	110–111/3	73
17[d]	$C_6H_5CH_2$	$C_6H_5CH_2$	Br	...	[a]	...
18[d]	*p*-$CH_3C_6H_4$	*p*-$CH_3C_6H_4$	Br	...	[a]	...

[a] The crude products and unanalyzed distilled products were aminated (Table IV). [b] The bromo derivatives, compounds 13–18, were prepared according to the method of Bersin and Willfang (11, 12) which does not involve refluxing. Compounds 1–12 were prepared by the method of Salmi (10). [c] 2-Thienyl. [d] Described by Blicke and co-workers (5).

TABLE III.—INFRARED SPECTRA OF HALOGENATED 1,3-DIOXOLANE DERIVATIVES[a]

No.	1,3-Dioxolanes	Wavenumber (ν), cm.$^{-1}$ 1234–1205	1183–1156	1064–1023	1013–990
1	2-Bromomethyl-2-phenyl-	1220	1169	1042	1000
2	2-Bromomethyl-2-(*p*-bromophenyl)-	1220	1173	1042	1010
3	2-Bromomethyl-2-(*p*-chlorophenyl)-	1220	1162	1039	1013
4	2-Bromomethyl-2-(*p*-methoxyphenyl)-	1215	1169	1030	997
5	2-Bromomethyl-2-(*p*-nitrophenyl)-	1215	1162	1036	1005
6	2-Bromomethyl-2-(*m*-nitrophenyl)-	1227	1177	1044	1002
7	2-Bromomethyl-2-(*p*-phenylphenyl)-	1212	1156	1030	1000
8	2-Chloromethyl-2-(*p*-phenylphenyl)-	1223	1183	1036	1008
9	2-Bromomethyl-2-(2,5-dimethylphenyl)-	1234	1156	1036	990
10	2-(2-Chloroisopropyl)-2-phenyl-	1234	1180	1023	1010
11	2-(α-Chlorobenzyl)-2-phenyl-	1215	1162	1047	1008
12	2-(1-Chlorocyclohexyl)-2-phenyl-	1205	1169	1064	1005

[a] Measured in potassium bromide disks (concentration 0.4%; disk thickness 0.6 mm.) with a Perkin-Elmer model 21 infrared spectrophotometer.

mediate halodioxolane, the amine, and a solvent in a pressure bottle on a steam bath. The periods of heating varied from 2 to 7 days. The products were isolated as hydrochlorides, oxalates, or methiodides.

In contrast to the above procedure for the preparation of 4-aminomethyl-1,3-dioxolanes, the preparation of the 2-aminomethyl analogs (Table V) required higher temperatures. For example, when a mixture of 2-bromomethyl-2-phenyl-1,3-dioxolane, morpholine, and benzene was heated in a pressure bottle on the steam bath for 7 days, the starting intermediates were recovered unchanged. The reaction was successfully conducted in the absence of solvent in sealed glass tubes heated at 140–150° for 24 hours. The products were also isolated as hydrochlorides, oxalates, or methiodides.

The condensation of Mannich bases with 1,2-glycols as a direct potential route to 2-aryl-2-(β-aminoethyl)-1,3-dioxolanes was studied. The condensation of β-morpholinopropiophenone hydrochloride with ethylene glycol was carried out with moderate success. Under similar reaction conditions, β-dimethylamino and α-methyl-β-dimethylaminopropiophenone hydrochlorides failed to yield the corresponding dioxolanes.

In preliminary experiments on isolated guinea pig ileum, compounds 1, 3, 5, 6, 8, 19, 22, 26, and 27 (Table IV), compounds 1, 6, and 10 (Table V), and 2-phenyl-2-(β-morpholinoethyl)-1,3-dioxolane hydrochloride exhibited low anticholinergic activity. Significant activity was observed with compound 9 (Table V).

In exploratory experiments on anesthetized dogs, compounds 3, 5, 13, 19, 27, 28, and 30 (Table IV), compounds 6 and 11 (Table V), and 2-phenyl-2-(β-morpholinoethyl)-1,3-dioxolane hydrochloride exhibited weak autonomic activity. Compound 9 (Table V) produced a fall in diastolic pressure and cardiac stimulation at an intravenous dose of 1 mg./Kg. A prolonged duration of action resulted on increasing the dosage to 5 mg./Kg.

EXPERIMENTAL[1]

The procedures used for the synthesis of the intermediate halodioxolanes and the final products are illustrated by the following examples.

2-Phenyl-2-(β-morpholinoethyl)-1,3-dioxolane Hydrochloride.—The compound was prepared according to the procedure of Salmi (10). A mixture of 38.5 Gm. (0.15 mole) of the required Mannich base salt (β-morpholinopropiophenone hydrochloride), 31.0 Gm. (0.5 mole) of ethylene glycol, 0.95 Gm. of *p*-toluenesulfonic acid monohydrate, and 200 ml. of toluene was refluxed for 3 hours in an assembly equipped with a Dean-Stark trap. The reaction mixture was rendered alkaline with 10% aqueous sodium hydroxide. The combined toluene layer and ether extracts of the aqueous phase were washed with water, dried, and concentrated to an oily residue *in vacuo*. Unreacted Mannich base was removed by vacuum distillation (b_3 77–83°). The distillation residue was converted to the hydrochloride with ethereal hydrogen chloride. The yield, after two recrystallizations from absolute ethanol, was 5.5 Gm. (12%), m.p. 220–221°.

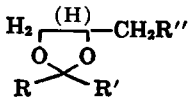
Anal.—Calcd. for $C_{15}H_{22}ClNO_3$: N, 4.67; Cl, 11.83. Found: N, 4.40; Cl, 11.66.

2-Bromomethyl-2-(*p*-phenylphenyl)-1,3-dioxolane.—(Table I, compound 11).—The compound was prepared according to the procedure of Salmi (10). A mixture of 27.5 Gm. (0.1 mole) of *p*-phenylphenacyl bromide, 62 Gm. (1 mole) of ethylene glycol, 0.95 Gm. of *p*-toluenesulfonic acid monohydrate, and 200 ml. of toluene was refluxed for 15 hours. The yield was 24 Gm. (76%), m.p. 79.5 to 80° after recrystallization from ethanol.

2-Benzyl-2-methyl-4-bromoethyl-1,3-dioxolane.—(Table II, compound 16.)—The compound was prepared according to the procedure of Bersin and Willfang (11, 12). A stirred solution of 20 Gm. (0.15 mole) of phenyl-2-propanone and 27.5 Gm. (0.2 mole) of epibromohydrin in 150 ml. of dry carbon tetrachloride was maintained at 0–5° for 2 hours during the dropwise addition of

[1] Melting points were determined on a Fisher-Johns or Nalge melting point apparatus and are uncorrected. Microanalyses are by the Microanalytical Laboratory, Department of Chemistry, University of California, Berkeley.

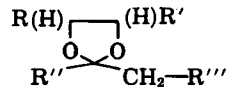
TABLE IV.—4-AMINOMETHYL-1,3-DIOXOLANE SALTS[i]



No.	R	R′	R″ (A,B,C)[a]	M.p., °C.	Yield, %	Formula	Analyses, % C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found	X[b] Calcd.	X[b] Found
1	*p*-BrC_6H_4	CH_3	NC_5H_{10}[c]·A	190–194	36	$C_{16}H_{23}BrClNO_2$	...	...	...	...	3.72	3.86	...	...
2	*p*-BrC_6H_4	CH_3	NC_4H_8O[d]·A	170–173	33	$C_{15}H_{21}BrClNO_3$	...	...	...	...	3.72	3.85	...	...
3	*p*-ClC_6H_4	CH_3	NC_5H_{10}·A	193–196	43	$C_{16}H_{23}Cl_2NO_2$	...	...	...	...	4.22	4.20	21.34	21.30
4	*p*-ClC_6H_4	CH_3	NC_4H_8O·B	204–206	41	$C_{17}H_{22}ClNO_7$	...	...	...	...	3.61	3.72	9.14	9.24
5	*p*-$CH_3OC_6H_4$	CH_3	NC_5H_{10}·C	181–187	56	$C_{18}H_{26}INO_3$	...	...	...	...	3.36	3.42	30.40	30.28
6	*p*-$CH_3C_6H_4$	CH_3	NC_5H_{10}·A	182–185	48	$C_{17}H_{26}ClNO_2$	...	...	...	...	4.49	4.61	11.37	11.59
7	*p*-$CH_3C_6H_4$	CH_3	NC_4H_8O·A	170–174	48	$C_{16}H_{24}ClNO_3$	...	...	...	...	4.46	4.63	11.30	11.41
8	C_6H_5	C_2H_5	NC_5H_{10}·A	197–202	69	$C_{17}H_{26}ClNO_2$	...	...	...	...	4.49	4.58	11.37	11.48
9	C_6H_5	C_2H_5	NC_4H_8O·A	186–189	46	$C_{16}H_{24}ClNO_3$	...	...	...	...	4.46	4.65	11.30	11.30
10	C_6H_5	*n*-C_3H_7	NC_5H_{10}·B	175–180	64	$C_{20}H_{29}NO_6$	63.31	63.21	7.70	7.77	3.69	3.74	...	...
11	C_6H_5	*n*-C_3H_7	NC_4H_8O·B	180–184	69	$C_{19}H_{27}NO_7$	59.83	60.01	7.14	7.07	3.67	3.50	...	...
12	C_6H_5	$CH(CH_3)_2$	NC_5H_{10}·A	220–222.5	61	$C_{18}H_{28}ClNO_2$	...	...	...	...	4.30	4.41	10.88	11.00
13	C_6H_5	$CH(CH_3)_2$	NC_4H_8O·A	204–207	52	$C_{17}H_{26}ClNO_3$	...	...	...	...	4.27	4.25	10.82	10.84
14	C_6H_5	$CH(CH_3)_2$	$N_2C_4H_9$[e]·2A	176–182	54	$C_{17}H_{28}Cl_2N_2O_2$	...	...	...	...	7.71	7.60	19.52	19.27
15	C_6H_5	$CH(C_2H_5)_2$	NC_5H_{10}·B	198–201	34	$C_{22}H_{33}NO_6$	64.84	64.82	8.16	7.94	3.44	3.23	...	...
16	C_6H_5	$CH(C_2H_5)_2$	NC_4H_8O·B	194–197	34	$C_{21}H_{31}NO_7$	61.60	61.71	7.63	7.51	3.42	3.27	...	...
17	C_6H_5	$CH(C_2H_5)C_4H_9$	NC_5H_{10}·B	140–144	45	$C_{24}H_{37}NO_6$	66.18	65.90	8.56	8.38	3.22	3.17	...	...
18	C_6H_5	$CH(C_2H_5)C_4H_9$	NC_4H_8O·B	145–147	46	$C_{23}H_{35}NO_7$	63.14	62.98	8.06	7.97	3.20	3.12	...	...
19	*n*-C_9H_{19}	CH_3	$N(C_2H_5)_2$·A	137–139	30	$C_{18}H_{36}ClNO_2$	...	...	...	...	4.17	4.45	10.55	10.29
20	$C_6H_5CH_2$	CH_3	NC_5H_{10}·B	128–131	59	$C_{19}H_{27}NO_6$	62.45	62.18	7.45	7.56	3.83	3.57	...	...
21	$C_6H_5CH_2$	CH_3	NC_4H_8O·B	137–140	48	$C_{18}H_{25}NO_7$	58.84	58.96	6.86	6.81	3.81	3.53	...	...
22	*p*-ClC_6H_4	C_6H_5	NC_5H_{10}·A	182–192	58	$C_{21}H_{25}Cl_2NO_2$	...	...	...	...	3.55	3.56	17.98	17.89
23	*p*-ClC_6H_4	C_6H_5	NC_4H_8O·A	181–185	52	$C_{20}H_{23}Cl_2NO_3$	...	...	...	...	3.53	3.70	17.89	18.05
24	*p*-$CH_3C_6H_4$	C_6H_5	NC_5H_{10}·A	190–195	11	$C_{22}H_{28}ClNO_2$	...	...	...	...	3.75	3.86	9.48	9.30
25	*p*-$CH_3C_6H_4$	C_6H_5	NC_4H_8O·B	182–184	33	$C_{23}H_{27}NO_7$	64.32	64.35	6.34	6.39	3.26	3.15	...	...
26	*p*-$CH_3C_6H_4$	*p*-$CH_3C_6H_4$	$N(C_3H_7)_2$·C	133–134	45	$C_{25}H_{36}INO_2$	...	...	...	...	2.75	2.85	24.91	24.66
27	*p*-$CH_3C_6H_4$	*p*-$CH_3C_6H_4$	NC_4H_8O·A	209–212	58	$C_{22}H_{29}ClNO_3$	...	...	...	...	3.59	3.66	9.09	9.03
28	2-C_4H_3S[f]	CH_3	$N(C_2H_5)_2$·B	140–143	25	$C_{15}H_{23}NSO_6$	...	...	...	...	4.06	3.78	9.28	9.52
29	2-C_4H_3S	CH_3	NC_4H_8O·B	129–131	62	$C_{15}H_{21}NSO_3$	...	...	...	...	3.90	4.13	8.92	8.60
30	2-C_4H_3S	C_6H_5	NC_4H_8O·C[g]	194–197	...	$C_{19}H_{24}INSO_3$[h]	...	...	...	...	2.96	2.91	26.81	26.60
31	2-C_4H_3S	C_6H_5	NC_5H_{10}·B	186–191	67	$C_{21}H_{25}NSO_6$	60.12	59.78	6.01	6.05	3.34	3.37	7.64	7.44

[a] A = hydrochloride; B = oxalate; C = methiodide. [b] Halogen or sulfur. [c] Piperidino. [d] Morpholino. [e] Piperazino. [f] 2-Thienyl. [g] The corresponding oxalate melted at 188–191°. [h] Calcd.: S, 6.77. Found: S, 6.60. [i] Reaction time: compounds 3, 19, 24, 27, 28—2 days; 26—2.5 days; 1, 12, 20—4 days; 22—4.5 days; 5—5 days; 10, 11, 13, 17, 18, 23, 25—7 days; all other compounds—6 days. Compounds 1–3, 8, 9, 19, 22–24, and 27 were recrystallized from isopropanol, the remainder from absolute ethanol.

TABLE V.—2-AMINOMETHYL-1,3-DIOXOLANE SALTS[j]



No.	R	R′	R″	R‴	M.p., °C.	Yield, %	Formula	Analyses, % N Calcd.	N Found	X,[a] Calcd.	X,[a] Found
1	H	H	C_6H_5	$N_2C_4H_9$[b]·2HCl	250[i]	23	$C_{14}H_{22}Cl_2N_2O_2$	8.72	8.68	22.07	21.89
2	H	H	*p*-BrC_6H_4	NC_5H_{10}[c]·HCl	224–227	48	$C_{15}H_{21}BrClNO_2$	3.86	3.98	...	...
3	H	CH_3	*p*-BrC_6H_4	$NC_5H_{10}·C_2H_2O_4$[d]	154–157	47	$C_{15}H_{24}BrNO_6$	3.26	3.30	18.57	18.82
4	H	H	*p*-ClC_6H_4	NC_5H_{10}·HCl	208–213	67	$C_{15}H_{21}Cl_2NO_2$	4.40	4.55	22.28	22.02
5	H	H	*p*-ClC_6H_4	NC_4H_8O·[e]HCl	200–205	38	$C_{14}H_{19}Cl_2NO_3$	4.37	4.49	22.15	22.08
6	H	CH_3	*p*-ClC_6H_4	NC_5H_{10}·HCl	189–191	80	$C_{16}H_{23}Cl_2NO_2$	4.20	4.18	21.34	21.24
7	CH_3	CH_3	*p*-ClC_6H_4	NC_5H_{10}·HCl	208–214	74	$C_{17}H_{25}Cl_2NO_2$	4.05	4.11	20.48	20.50
8	H	H	*p*-$C_6H_5C_6H_4$	$NC_5H_{10}·C_2H_2O_4$	179–180	30	$C_{23}H_{27}NO_6$[f]	3.39	3.50	...	...
9	H	H	*p*-$C_6H_5C_6H_4$	$NC_5H_{10}·CH_3I$	222–224	...	$C_{22}H_{28}INO_2$	...	...	27.27	27.60
10	H	H	*p*-$C_6H_5C_6H_4$	$NC_4H_8O·C_2H_2O_4$	195–198	42	$C_{22}H_{25}NO_7$[g]	3.37	3.08	...	...
11	H	H	C_8H_9[h]	$NC_5H_{10}·CH_3I$	219–223	31	$C_{18}H_{28}INO_2$	3.36	3.50	30.41	30.22
12	H	CH_3	C_8H_9	$NC_5H_{10}·CH_3I$	185–188	57	$C_{19}H_{30}INO_2$	3.25	3.35	29.42	29.38

[a] Halogen. [b] Piperazino. [c] Piperidino. [d] Oxalate. [e] Morpholino. [f] Calcd. C, 66.81; H, 6.58. Found: C, 66.98; H, 6.76. [g] Calcd.: C, 63.60; H, 6.07. Found: C, 63.30; H, 5.89. [h] 2,5-Dimethylphenyl. [i] With decomposition. [j] Compounds 2 and 5 were recrystallized from absolute ethanol-ether; 4, 6, and 7 from isopropanol; the remainder from absolute ethanol.

5.2 Gm. of stannic chloride in 50 ml. of carbon tetrachloride. The product was purified by distillation (b_3 110–111°).

2 - Methyl - 2 - (*p* - tolyl) - 4 - piperidinomethyl-1,3-dioxolane Hydrochloride.—(Table IV, compound 6.)—A solution of 11.5 Gm. (0.05 mole) of 2-methyl-2-(*p*-tolyl)-4-chloromethyl-1,3-dioxolane and 42.5 Gm. (0.5 mole) of piperidine in 50 ml. of benzene was heated in a pressure bottle on a steam bath for 6 days. The mixture was treated with 10% aqueous sodium hydroxide. The combined benzene layer and ether extract of the aqueous phase was concentrated *in vacuo*. The residue was converted to the hydrochloride and recrystallized from absolute ethanol. The yield was 7.5 Gm. (48%), m.p. 182–185°.

2 - (*p* - Phenylphenyl) - 2 - piperidinomethyl-1,3-dioxolane Methiodide.—(Table V, compound 9.)—A mixture of 11 Gm. (0.04 mole) of 2-bromomethyl-2-(*p*-phenylphenyl)-1,3-dioxolane and 8.5 Gm. (0.1 mole) of piperidine was heated at 150° in a sealed glass tube for 24 hours. The mixture was made alkaline with 10% aqueous sodium hydroxide and extracted with ether. The solvent and unreacted amine were removed *in vacuo*. Excess methyl iodide was added to an ether solution of the residue and allowed to stand at room temperature for 24 hours. The product was recrystallized from absolute ethanol, m.p. 222–224°.

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