4-(2-Piperidyl)-1,3-dioxolanes with Local Anesthetic, Spasmolytic, and Central Nervous System Activity[1]

W. R. HARDIE, J. HIDALGO, I. F. HALVERSTADT, AND R. E. ALLEN

Organic Chemistry Department and Pharmacology Department, Cutter Laboratories, Berkeley, California

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A series of 2-(2-piperidyl)-1,4-dioxaspiro[4.5]decanes and 4-(2-piperidyl)-1,3-dioxolanes with alkyl and aryl substituents was synthesized by the acid-catalyzed condensation of (2-piperidyl)-1,2-ethanediol with ketones and acetals. The yields were best when using acetals. Local anesthetic properties, generally with parallel papaverine-like activity, were widely distributed through the series and were most prominent when benzyl substituents were at the 2-position of the dioxolane ring. Several compounds had the unique property of shortening reaction time in the hot-plate test. The spectrum of activities of one structure, 2,2-diphenyl-4-(2-piperidyl)-1,3-dioxolane, led to the separation of its racemates and the resolution of one of them.

Substituted dioxolanes exhibit a variety of effects which include hypnotic and spinal depressant,[2] parasympathomimetic,[3] antispasmodic,[4] central stimulant,[5] and central depressant[6] activities. We have prepared a group of 4-(2-piperidyl)-1,3-dioxolanes with substituents at position 2 (V). One of the structures (V, R_1, R_2 = phenyl) proved to be particularly interesting and was additionally substituted on the piperidine nitrogen with various groups.

The chemistry and those pharmacological properties most widely distributed in the series are described in this report. Additional pharmacological findings have been described elsewhere[7,8] or are to be published.

Chemistry.—The dioxolanes were prepared by the general method of condensing ketones or acetals with vicinal glycols in the presence of an acid catalyst.

The acetals, some not previously reported, were prepared by two methods. Method A, described by Lorette and Howard,[9] was used successfully with several

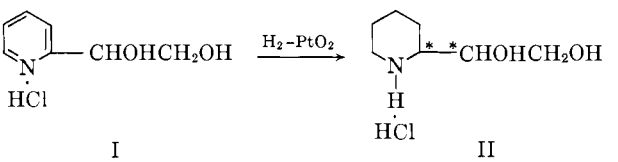
Method A: $R^1R^2CO + 2ROH + CH_3C(OCH_3)_2 \xrightarrow{H^+} R^1R^2C(OR)_2 + CH_3COCH_3 + 2CH_3CH$

aliphatic and mixed ketones (Table I) and with one aromatic ketone, benzophenone, the methylal of which was also readily prepared by reaction with dimethyl sulfite.[10] Neither method A nor dimethyl sulfite could be used successfully to prepare acetals of the substituted aromatic ketones, 4,4′-dimethoxybenzophenone and phenyl 2-thienyl ketone. Method B[11] was used for substituted aromatic ketones and 9-fluorenone. These

Method B: $R^1R^2CO \xrightarrow{PCl_5} R^1R^2CCl_2 \xrightarrow{NaOCH_3} R^1R^2C(OCH_3)_2$

acetals (Table I) were found to be free of ketones, as shown by the absence of infrared absorption in the carbonyl band, except for **5** and **8** which nonetheless gave satisfactory yields of dioxolanes.

The vicinal glycol was obtained by hydrogenating (2-pyridyl)-1,2-ethanediol hydrochloride[12] (I) in water, acetic acid, or methanol using platinum oxide catalyst to give (2-piperidyl)-1,2-ethanediol hydrochloride (II). Rhodium on carbon was also a suitable catalyst.



I II

This glycol (II) has two asymmetric centers (*) resulting in a mixture of two racemates. A portion of the higher melting (β) racemate hydrochloride could be separated from the crude hydrogenation product by fractional crystallization from 2-propanol, but a more practical separation, which gave pure samples of each racemate, was to condense the mixture of glycols with the methylal of benzophenone (method D). The resulting dioxolane racemates were then separated (see Experimental Section) and hydrolyzed to give high recoveries of the glycols.

The compounds in Table II were prepared either by condensation of (2-piperidyl)-1,2-ethanediol hydrochloride (II) with ketones (III) (method C) or by condensation of the glycol with acetals (IV) (method D). Method C was reasonably satisfactory for the 2-(2-piperidyl)-1,4-dioxaspiro[4,5]decanes but was completely inadequate for the 2-substituted 4-(2-piperidyl)-1,3-dioxolanes since aromatic and mixed ketones were quite unreactive with the (2-piperidyl)-1,2-ethanediol hydrochloride. However, their acetals (IV) reacted smoothly by method D to give good yields. 2-Propanol was a good solvent for the condensation and encouraged the separation of crystalline crude products. A very

(1) Portions of this work were presented before the Division of Medicinal Chemistry at the 141st National Meeting of the American Chemical Society, Washington, D. C., March 1962.

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(11) W. Schlenk and E. Bergmann, *ibid.*, **463**, 199 (1928).

(12) F. E. Cislak, U. S. Patent 2,743,277 (1956).

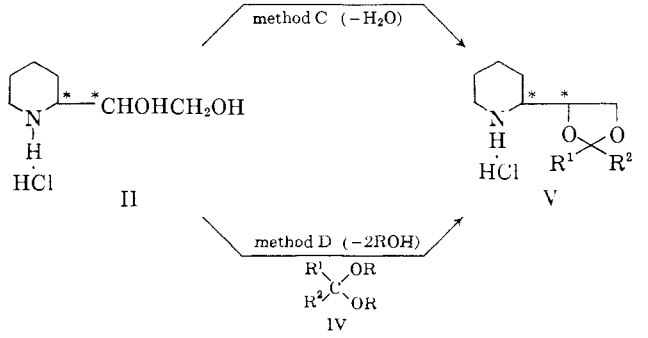
TABLE I

ACETALS

$R^1R^2C(OR)_2$

Compd. no.	R^1	R^2	R	Method	Yield, %	M.p. or b.p. (mm.), °C.[a]	$n^{25}D$	Formula	Carbon, %—Calcd.	Carbon, %—Found	Hydrogen, %—Calcd.	Hydrogen, %—Found
1	CH_3	C_6H_5	C_2H_5	A	57	75 (3)[b]	1.4747					
2	C_2H_5	C_6H_5	C_2H_5	A	56	89–90 (3)[c]	1.4767	$C_{13}H_{20}O_2$	76.22	76.80	10.23	10.11
3	$C_6H_5CH_2$	$C_6H_5CH_2$	C_2H_5	A	44	147–154 (3)	1.5623	$C_{25}H_{28}O_2$	80.72	84.00[e]	9.03	7.98
4	C_6H_5	C_6H_5	CH_3	A	46[d]	107–108[e]						
5	CH_3	$(C_6H_5)_2CH$	C_2H_5	A	43[f]	132–135 (1)	1.5620	$C_{25}H_{28}O_2$	80.72	80.72	9.03	7.88
6	C_6H_5	$C_6H_5CH_2$	C_2H_5	A	21[g]	141–146 (3)						
7	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	C_2H_5	B	69[g,h]	170–172 (1)	1.5302					
8	2-Thienyl	C_6H_5	CH_3	D	24[g,h]	56–59[i]						
9	C_6H_5	4-ClC_6H_4	CH_3	B	63[h]	128 (1)	1.5667	$C_{18}H_{19}ClO_2$	68.57	69.03	5.75	5.75[j]
10	4-ClC_6H_4	4-ClC_6H_4	CH_3	B	55[k]	68.5–70[k]		$C_{18}H_{14}Cl_2O_2$	60.62	60.97	4.75	4.57
11	$C_{12}H_8$[l]		CH_3	B	51[g,h]	86–87.5[m]						

[a] Uncorrected temperature. [b] Lit.[9] b.p. 62° (1 mm.), $n^{25}D$ 1.4752. [c] The carbonyl band was absent from the infrared spectrum and there was a strong aliphatic C–H band at 2950 cm.$^{-1}$, although the carbon analysis indicates the presence of ketone. [d] This methylal was also prepared in 43% yield using dimethyl sulfite.[10] [e] Corrected temperature, lit.[10] m.p. 107.5°. [f] The infrared spectrum indicated some contamination with ketone. [g] This material was not analyzed but did react to give a satisfactory yield of dioxolane. [h] Two-step over-all yield, see method in Experimental Section. [i] Recrystallized from 2-propanol; the melting point was depressed by phenyl 2-thienyl ketone. [j] *Anal.* Calcd.: Cl, 13.50. Found: Cl, 13.51. [k] Recrystallized from 2-propanol. [l] Fluoren-9-ylidene. [m] Recrystallized from benzene, lit.[11] m.p. 87–88°.



slight excess of hydrogen chloride in the reaction mixture would initiate the reaction, especially when method D was employed. The (2-piperidyl)-1,2-ethanediol hydrochloride condensed satisfactorily, either as the α,β racemate mixture or as one of the pure racemates. When a pure racemate of the glycol was used, its racemate assignment was also given to the dioxolane product.

Because of important pharmacological properties of some of the mixed racemates, numerous pure racemates were prepared. α-*dl*-2,2-Diphenyl-4-(2-piperidyl)-1,3-dioxolane hydrochloride[13] (**20**) was of particular interest. This was first separated from the β-racemate by fractional crystallization but was later purified on a substantial scale by the preparation of the DL-tartrate salt. The α,β mixture (method D) was fractionally crystallized from ethanol–methanol which precipitated a portion of the β form. This left a mixture enriched to an estimated 85% of the α form and prevented the coprecipitation of the β racemate in the subsequent precipitation step. The 85:15 mixture of hydrochlorides was treated with aqueous caustic and the free bases were treated with DL-tartaric acid in methanol to give a precipitate of the DL-tartrate salt of the pure α racemate. The free base of the α racemate was also resolved through D- and L-tartrate salts. The tartrates of the *d* and *l* enantiomers were then converted to the hydrochlorides. Larger quantities of the α-*d*[14] (**24**) and α-*l*[15] (**25**) enantiomers were prepared from the pure α racemate. Attempts to resolve the β racemate (**21**) of this compound have not succeeded.

The α racemate **20**, its optical enantiomers **24** and **25**, and the β racemate **21** of 2,2-diphenyl-4-(2-piperidyl)-1,3-dioxolane were the starting materials for the preparation of the nitrogen-substituted compounds in Table II. The method[16] of preparing the acyl derivatives gave better yields when the amount of acyl chloride was increased from 1 to 2 moles/mole of amine. Acyl derivatives were reduced by $LiAlH_4$ to give the corresponding N-alkyl derivatives although this procedure was not successful with the benzoyl derivative. N-Methyldioxolanes were prepared by catalytic hydrogenation in the presence of formaldehyde.[17]

For all compounds in Table II, procedures described in the Experimental Section for the preparation of dioxolanes of one racemate are also illustrative of the preparation of the other racemate of the same structure.

Pharmacology.—The approximate LD_{50} values were determined by intragastric administration of 2% aqueous solutions or suspensions in gum tragacanth to dose groups of five fasted mice. Doses were graduated at 0.3 log interval to a limit of 800 mg./kg. Groups of five mice were employed to determine the time of peak action and the ED_{50} against the seizure pattern induced by a maximal electroshock (MES).[18] Topical local anesthesia was assayed by the rabbit corneal test. The conjunctival sac was instilled with 0.25 ml. of 1% test solution. The disappearance of the blinking reflex upon pitting and stroking the cornea with a blunt probe was considered evidence of local anesthesia. Active compounds were retested in progressive 0.3 log dilutions to provide a comparison of potency with procaine. *In vitro* spasmolysis against $BaCl_2$ was determined in a muscle bath of oxygenated tyrodes solution at 37° using rabbit ileum strips. The test compound was added to the bath and followed in 1 min. by $BaCl_2$. The muscle strip was washed 1 min. later and allowed to rest 5 min. between tests. The ED_{50} values of the test

(13) Dioxadrol.
(14) Dexoxadrol.
(15) Levoxadrol.
(16) W. E. Weaver and W. M. Whaley, *J. Am. Chem. Soc.*, **69**, 515 (1947).
(17) R. E. Bowman and H. H. Stroud, *J. Chem. Soc.*, 1342 (1950).
(18) E. A. Swinyard, *J. Am. Pharm. Assoc., Sci. Ed.*, **38**, 201 (1949).

compound and papaverine were determined and the activity was expressed as their ratio. Analgesic properties were detected by the hot-plate method[19] after an oral dose of one-fourth of the LD_{50}. At the time of peak action (determined in the MES test) groups of ten mice were tested and activity was expressed as the percentage change from mean pretreatment reaction times.

Results.—Many compounds in this series protected the mice against electroshock seizures and several were effective at doses less than one-fourth of the LD_{50}. The most active compound (**18**) had a phenyl substituent at position 2 on the dioxolane and the next most active compounds were both racemates (**28**, **29**) of a structure containing the fluoren-9-ylidene group. There was no correlation between the MES and local anesthetic activity. None of the compounds protected the mice against strychnine- or pentylenetetrazole-induced seizures, but two (**18**, **24**) showed partial protection *vs.* strychnine lethality and heterogeneous protection against pentylenetetrazole-induced seizures.

Many compounds in the series were local anesthetics. Least potent were the spirodecanes (Table II) in which local anesthetic potency was diminished by a chloro substituent and augmented by multiple methyl or phenyl substituents. The 2-substituted dioxolanes (Table II) were also relatively low in potency when a single benzene group was present (**13**, **16**, **17**, **18**, **19**), but the 2,2-diaryldioxolanes were consistently potent. The highest potency was associated with aralkyl substituents (**15**, **31**, **32**). These compounds were 50–80 times as potent as procaine in terms of minimal effective concentrations. The local anesthetic potency associated with the 2,2-diphenyl-4-(2-piperidyl)-1,3-dioxolane (**21**) was not diminished by hydrogenation of the phenyl groups. Activity remained with the introduction of a new basic nitrogen in the side chain attached to the piperidine nitrogen (**51**, **52**, **53**). Converting the piperidine nitrogen to a tertiary amine by methylation (**34**, **37**) had little effect, but propylation (**43**, **44**), benzylation (**47**, **50**), N-oxide formation (**54**, **55**), and quaternization (**38**, **39**) of the basic nitrogen caused a sharp drop in potency.

The spasmolytic activity of these compounds was papaverine-like. The *in vitro* activity against $BaCl_2$ was considerable and was generally parallel to local anesthetic potency. Interestingly, the activity against $BaCl_2$ reached its peak in the α racemate (**14**) of one structure, but the local anesthetic activity was at its maximum in the β racemate (**15**) of the same structure. Although the data are not included in Table II, the *in vitro* anticholinergic activity of these compounds was less than 1% of that of atropine with the notable exception of 2,2-diphenyl-4-(2-piperidyl)-1,3-dioxolane which, when N-methylated (**34**) and quaternized (**39**), was about 25% as active as atropine.

The reaction times on the hot plate were unexpected. A few compounds (**12**, **13**, **29**, **31**) showed a conventional increase in reaction time. On the other hand, the α racemate (**20**) of 2,2-diphenyl-4-(2-piperidyl)-1,3-dioxolane hydrochloride caused an unusual decrease in the reaction time, a property also possessed by certain other α racemates (18, **20**, **40**, **43**, **47**). In those racemates where the separate enantiomers were tested, this property was confined to the α-*d* isomer, such as **24**, which is under clinical investigation. This decrease in reaction time was shown by other α-*d* isomers (**35**, **48**, **57**), but not by their corresponding α-*l* enantiomers (**36**, **49**). The racemates which either decreased or increased reaction time also were highly effective in the maximal electroshock seizure pattern test, although the latter property was not confined to these racemates alone.

(19) N. B. Eddy and D. Leimbach, *J. Pharmacol. Exptl. Therap.*, **107**, 383 (1953).

Experimental Section[20]

Anhydrous 1- and 2-propanol, 1-butanol, 2,2-dimethoxypropane, 1,1-dimethoxy-2-phenylethane, hydratropaldehyde, and the tartaric acids were obtained from commercial sources. Commercial grade ketones were used except for the substituted cyclohexanones supplied by the Dow Chemical Co. 3,5-Dimethylcyclohexanone was prepared by catalytic hydrogenation of commercially available 3,5-dimethylcyclohexenone. Dimethoxyphenylmethane was prepared from benzaldehyde in acidified methanol.[21] We are grateful to Dr. F. E. Cislak of Reilly Tar and Chemical Co. for supplies of (2-pyridyl)-1,2-ethanediol hydrochloride.[22]

Catalytic hydrogenations were done at 4.2 kg./cm.^{2} (60 p.s.i.) of hydrogen in a Parr low-pressure apparatus at room temperature. In the descriptions of product isolations, solvents were evaporated at 15–20-mm. pressure on the steam bath.

(2-Piperidyl)-1,2-ethanediol Hydrochloride (II).—A solution of 116 g. (0.66 mole) of (2-pyridyl)-1,2-ethanediol hydrochloride[22] in 60 ml. of water, in which was suspended 2 g. of PtO_2, was hydrogenated for a period of 30 hr. or until approximately the theoretical amount of hydrogen was absorbed. The filtered solution was evaporated to a syrup which was diluted with an equal volume of 2-propanol and re-evaporated. This dilution and evaporation was repeated twice, leaving a viscous hygroscopic syrup weighing 120 g.

Anal. Calcd. for $C_7H_{15}NO_2 \cdot HCl$: C, 46.28; H, 8.88; Cl, 19.52; N, 7.71. Found: C, 46.4; H, 8.8; Cl, 19.4; N, 7.9.

A 1% water solution of this material had a low-intensity broad-band ultraviolet absorption spectrum, while a 0.001% water solution of the aromatic starting material had a strong peak at 260 mμ indicating that the hydrogenation was more than 99% complete. A portion of the syrup, dissolved in saturated aqueous potassium carbonate solution containing a small amount of potassium hydroxide, was extracted with chloroform. The solvent was evaporated and the residue was distilled to give the free base of (2-piperidyl)-1,2-ethanediol (59% recovery), b.p. 120–123° (2 mm.), $n^{25}D$ 1.5070.

Anal. Calcd. for $C_7H_{15}NO_2$: C, 57.90; H, 10.41; N, 9.65. Found: C, 58.2; H, 10.1; N, 9.3.

A. α Racemate.—A solution of 305 g. (0.88 mole) of α-*dl*-2,2-diphenyl-4-(2-piperidyl)-1,3-dioxolane hydrochloride (**20**), 5 ml. of concentrated HCl, and 25 ml. of water in 2 l. of methanol was warmed on a steam bath overnight and evaporated at reduced pressure, and the residue was washed with ether. The ether phase was discarded and the residue was dissolved in 150 ml. of butanol and evaporated, crystals forming in the process. After recrystallization from a mixture of 250 ml. of ethanol, 50 ml. of 2-propanol, and 50 ml. of ether, 122 g. (76%) of α-*dl*-(2-piperidyl)-1,2-ethanediol hydrochloride was obtained, melting at 101°.

B. β Racemate.—By the same process, 450 g. of β-*dl*-2,2-diphenyl-4-(2-piperidyl)-1,3-dioxolane hydrochloride (**21**) gave a 90% yield of β-*dl*-(2-piperidyl)-1,2-ethanediol hydrochloride, m.p. 138°, after recrystallization from a mixed solvent of 2 l. of 2-propanol and 300 ml. of methanol.

(20) Melting points were determined on a Fisher-Johns block and are corrected. Elemental analyses were done by Berkeley Analytical Laboratory, Berkeley, Calif., and West Coast Analytical Laboratories, El Cerrito, Calif. Infrared spectra were recorded on a Baird Model 4-55 spectrophotometer using KBr disks for solids and thin layers between disks for liquids. Ultraviolet spectra were recorded on a Cary Model 14 ultraviolet spectrophotometer. Optical rotations were observed using a Gaertner Model L-320 polarimeter.

(21) R. D. Haworth and A. Lapworth, *J. Chem. Soc.*, **121**, 79 (1922).

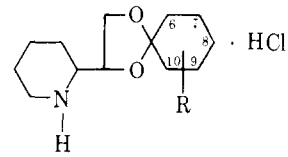
(22) M.p. 120–122°. *Anal.* Calcd. for $C_7H_9NO_2 \cdot HCl$: C, 47.87; H, 5.74; Cl, 20.19; N, 7.98. Found: C, 47.83; H, 5.67; Cl, 19.96; N, 7.99.

TABLE II

4-(2-PIPERIDYL)-1,3-DIOXOLANES

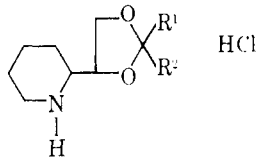
Compd. no.	R	Glycol[a] racemate used	Yield, %	M.p., °C.	Recryst. solvent[b]	Formula	Carbon, % Calcd.	Carbon, % Found

2-(2-Piperidyl)-1,4-dioxaspiro[4.5]decanes (Method C)



1	H	α,β[c]	54	213	A	$C_{13}H_{23}NO_2 \cdot HCl$	59.64	59.50
2[c]	...	α,β	7	210–213	A–B	$C_{14}H_{25}NO_2 \cdot HCl$	60.96	60.83
3	6-CH_3	α,β	26	237–240	C	$C_{14}H_{25}NO_2 \cdot HCl$	60.96	60.62
4	7-CH_3	α,β	8	222–223	A	$C_{14}H_{25}NO_2 \cdot HCl$	60.96	60.80
5	8-CH_3	α,β	30	248	C	$C_{14}H_{25}NO_2 \cdot HCl$	60.96	60.68
6	7-CH_3, 9-CH_3	α,β	22	209–210	A	$C_{15}H_{27}NO_2 \cdot HCl$	62.15	62.04
7	6-C_2H_5	β	10	214	j	$C_{15}H_{27}NO_2 \cdot HCl$	62.15	61.92
8	6-Cl	β	15	224–225	A–D	$C_{13}H_{22}ClNO_2 \cdot HCl$	52.71	52.97
9	8-Cl	α	13	229 dec.	C	$C_{13}H_{22}ClNO_2 \cdot HCl$	52.71	52.65
10	8-Cl	β	47	196–197	A	$C_{13}H_{22}ClNO_2 \cdot HCl$	52.71	53.39
11	8-$C(CH_3)_3$	α	23	254–255	C	$C_{17}H_{31}NO_2 \cdot HCl$	64.22	63.94
12	8-CH_3, 8-C_6H_5	β	3[l]	247–250	E–D	$C_{20}H_{29}NO_2 \cdot HCl$	68.26	68.19

2-Substituted 4-(2-Piperidyl)-1,3-dioxolanes (Method D)



	R^1	R^2							
13	H	$C_6H_5CH_2$	α,β	10	155–163	A–B	$C_{15}H_{21}NO_2 \cdot HCl$	63.48	63.00
14	$C_6H_5CH_2$	$C_6H_5CH_2$	α	64	195	C	$C_{22}H_{27}NO_2 \cdot HCl$	70.67	70.77
15	$C_6H_5CH_2$	$C_6H_5CH_2$	β	71	235	C	$C_{22}H_{27}NO_2 \cdot HCl$	70.67	70.86
16	H	C_6H_5	α,β	43	211	C	$C_{14}H_{19}NO_2 \cdot HCl$	62.33	62.34
17	CH_3	C_6H_5	β	35	231–233	C	$C_{15}H_{21}NO_2 \cdot HCl$	63.48	63.88
18	C_2H_5	C_6H_5	α	55	256	E–A	$C_{16}H_{23}NO_2 \cdot HCl$	64.52	64.60
19	C_2H_5	C_6H_5	β	56	240–241	E–A	$C_{16}H_{23}NO_2 \cdot HCl$	64.52	64.28
20	C_6H_5	C_6H_5	α	50[l]	254–256	C	$C_{20}H_{23}NO_2 \cdot HCl$	69.45	69.48
21	C_6H_5	C_6H_5	β	10[l]	299–301	E	$C_{20}H_{23}NO_2 \cdot HCl$	69.45	69.15
22	C_6H_5	4-ClC_6H_4	α,β	14	257–259	E	$C_{20}H_{22}ClNO_2 \cdot HCl$	63.16	63.34
23	4-ClC_6H_4	4-ClC_6H_4	α,β	4	200–205	A	$C_{20}H_{21}Cl_2NO_2 \cdot HCl$	57.91	58.10
24	C_6H_5	C_6H_5	α-l	72[l]	252–253	A	$C_{20}H_{23}NO_2 \cdot HCl$	69.45	69.47
25	C_6H_5	C_6H_5	α-l	68[l]	251–254	A	$C_{20}H_{23}NO_2 \cdot HCl$	69.45	69.61
26	C_6H_5	2-Thienyl	α	24	211–213	A	$C_{18}H_{21}NO_2S \cdot HCl$	61.43	61.29
27	C_6H_5	2-Thienyl	β	33	276 dec.	E–A	$C_{18}H_{21}NO_2S \cdot HCl$	61.43	61.13
28	Fluoren-9-ylidene		α	48	278 dec.	A	$C_{20}H_{21}NO_2 \cdot HCl$	69.86	69.82
29	Fluoren-9-ylidene		β	31	249–250	E–C	$C_{20}H_{21}NO_2 \cdot HCl$	69.86	69.71
30	C_6H_{11}	C_6H_{11}	β	44[l]	282 dec.	A	$C_{20}H_{33}NO_2 \cdot HCl$	67.10	67.07
31	CH_3	$(C_6H_5)_2CH$	β	35	195–200	C	$C_{22}H_{27}NO_2 \cdot HCl$	70.67	70.59
32	C_6H_5	$C_6H_5CH_2$	α	52	230–234	E–A	$C_{21}H_{25}NO_2 \cdot HCl$	70.08	70.05
33	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	α	76	272 dec.	F	$C_{22}H_{27}NO_4 \cdot HCl$	65.10	64.70

—Hydrogen, %— Calcd.	Found	—Chlorine, %— Calcd.	Found	—Nitrogen, %— Calcd.	Found	Comparative pharmacology: LD_{50}, mg./kg. orally in mice	MES[c] ED_{50}, mg./kg.	Local anesthesia, min. eff. % concn.[d] (proc. = 2)	Bariolytic activity, *in vitro*, rabbit ileum (papav. = 1)	Hot-plate[e] reaction time, % of control
9.24	9.05	13.25	13.53	5.35	5.58	75[g]	>75[h]	1 neg.	<0.3	100
9.50	9.38			5.08	5.29	600	150	2 neg.	<0.5	100
9.50	9.31			5.08	5.01	600	150	1	<0.2	100
9.50	9.76	12.86	12.82	5.08	5.01	600	>150	1	0.3	100
9.50	9.25			5.08	5.04	600	>150	1	0.5	100
9.74	9.77	12.23	12.13	4.83	4.95	500	>125	0.25	1	100
9.74	9.56			4.83	5.01	800	>200	0.5	0.5	100
7.83	7.76	23.94	23.76			800	200	1 neg.	0.3	100
7.83	7.67	23.94	23.78			600 75[g]	>150	0.5 neg.	0.5	100
7.83	8.09	23.94	24.15			800 150[g]	200	0.5 neg.[k]	<0.4	100
10.15	9.44	11.15	11.25	4.41	4.87	600	150	1	1	100
8.59	8.71	10.08	10.32			400	<100	0.25	1	204
7.82	7.67	12.49	12.29	4.94	5.12	300	<80	1	0.3	150
7.55	7.58			3.75	3.73	200 25[g]	>50	0.1	20	100
7.55	7.70			3.75	3.71	200 37.5[g]	>50	0.025	2	100
7.47	7.77			5.19	5.40	75	>20	1	0.5	100
7.81	7.98			4.94	4.97	400	>100	1 neg.	1	100
8.12	8.22			4.70	4.76	600	12.5	1	1	69[m] 82[n]
8.12	8.16			4.70	4.92	600	<75	1	1	126[o]
6.99	7.08	10.25	10.06	4.05	4.14	240	60	0.1	2	63[o]
6.99	6.85			4.05	3.85	600	>100	0.1	1.5	100
6.10	6.50	18.65	18.33	3.68	4.10	400	>100	0.1	3	100
5.35	5.13			3.38	3.19	600	>150	0.25	0.5	100
6.99	6.89	10.25	10.15			340	50	0.1	1	52[p] 70[m]
6.99	6.84	10.25	10.41	4.05	4.22	230	75	0.1	1	100
6.30	6.22			9.12[q]	9.54[q]	400	>50 <100	0.5	3	100
6.30	6.14			9.12[q]	9.34[q]	600	>100	0.1	3	100
6.45	6.69	10.31	10.08			300	<40	0.4	1	100
6.45	6.31	10.31	10.25			300	40	0.4 neg.	1	184
10.14	9.52	9.91	9.51			600	>150	0.1	3	100
7.55	7.60	9.48	9.55			400	50	0.025	1.5	131
7.28	7.22			3.89	4.01	600	75	<0.05	1.5	125
6.95	7.09	8.73	8.65			800	>200	0.3	0.7	95

TABLE II (*Continued*)

Compd. no.	R	Glycol[a] racemate used	Yield, %	M.p., °C.	Recrystn. solvent[b]	Formula	—Carbon, %— Calcd.	Found
		N-Substituted 2,2-Diphenyl-4-(2-piperidyl)-1,3-dioxolanes						
	R³							
34	CH_3	α	9	267–268	E	$C_{21}H_{25}NO_2 \cdot HCl$	70.08	69.97
35	CH_3	α-*d*	80	287 dec.	E	$C_{21}H_{25}NO_2 \cdot HCl$	70.08	69.83
36	CH_3	α-*l*	62	282 dec.	E	$C_{21}H_{25}NO_2 \cdot HCl$	70.08	70.29
37	CH_3	β	49	175–177	A	$C_{21}H_{25}NO_2 \cdot HCl$	70.08	70.38
38	$CH_3 \cdot CH_3I$	α	45	201–204	C	$C_{22}H_{28}INO_2$	56.78	56.46
39	$CH_3 \cdot CH_3I$	β	42	227–228	E	$C_{22}H_{28}INO_2$	56.78	56.93
40	$HOCH_2CH_2$	α	21	208–210	C	$C_{22}H_{27}NO_3 \cdot HCl$	67.76	67.81
41	CH_3CH_2CO	α	82	86–87	D–G	$C_{24}H_{27}NO_3$	75.58	75.61
42	CH_3CH_2CO	β	83	117–119	A	$C_{24}H_{27}NO_3$	75.58	75.28
43	$CH_3CH_2CH_2$	α	98	191–192	D	$C_{23}H_{29}NO_2 \cdot HCl$	71.20	71.25
44	$CH_3CH_2CH_2$	β	60	162–164	A–D	$C_{23}H_{29}NO_2 \cdot HCl$	71.20	71.08
45	$ClCH_2CO$	α	86	120–121	H–G	$C_{22}H_{24}ClNO_3$	68.47	68.37
46	$ClCH_2CO$	β	75	145–146	H	$C_{22}H_{24}ClNO_3$	68.47	68.65
47	$C_6H_5CH_2$	α	35	164–166	A–I	$C_{27}H_{29}NO_2 \cdot HCl$	74.38	74.34
48	$C_6H_5CH_2$	α-*d*	17	191–194	A	$C_{27}H_{29}NO_2 \cdot HCl$	74.38	74.16
49	$C_6H_5CH_2$	α-*l*	19	195–196	A	$C_{27}H_{29}NO_2 \cdot HCl$	74.38	73.83
50	$C_6H_5CH_2$	β	86	202–205	E–I	$C_{27}H_{29}NO_2 \cdot HCl$	74.38	73.30
51	$(C_2H_5)_2NCH_2CO$	α	80	172–173	A–I	$C_{26}H_{34}N_2O_3 \cdot HCl$	68.03	68.47
52	$(C_2H_5)_2NCH_2CO$	β	51	166–167	A–I	$C_{26}H_{34}N_2O_3 \cdot HCl$	68.03	68.22
53	$(C_2H_5)_2NCH_2CH_2$	β	27	160–163	B	$C_{26}H_{36}N_2O_2 \cdot 2HCl$	64.85	64.70
54	CH_3, N-oxide	β	39	190 dec.	C	$C_{21}H_{25}NO_3 \cdot HCl$	67.10	67.20
55	CH_3, N-oxide	α	17	113	B	$C_{24}H_{25}NO_3 \cdot HCl \cdot C_3H_6O$[f]	66.42	65.89
56	$C_6H_5CH_2$, N-oxide	α	19[g]	191	E–B	$C_{27}H_{29}NO_3 \cdot HCl$	71.75	71.65
57	CH_2CHCH_2	α-*d*[i]	28	198–199	A	$C_{23}H_{27}NO_2 \cdot HCl$	71.58	71.52

[a] (2-Piperidyl)-1,2-ethanediol racemates described in Experimental Section. [b] A, 2-propanol; B, acetone; C, ethanol; D, ether; E, methanol; F, dimethyl sulfoxide; G, pentane; H, benzene; I, ethyl acetate. [c] Maximal electroshock seizure in mice, see ref. 18. [d] Rabbit corneal test, see Pharmacology section. [e] One-fourth LD_{50}, oral in mice, see ref. 19. [f] Mixed racemates, see Chemistry section. [g] Intravenous. [h] Intraperitoneal. [i] 2-(2-Piperidyl)-1,4-dioxaspiro[4.6]undecane hydrochloride prepared using cycloheptanone.

Method A. Propylals.—The preparation of 1,1-dipropoxy-1-phenylpropane is illustrative of the preparation of propylals.[9] Propiophenone (140 g., 1.04 moles), 320 g. of 1-propanol, 107 g. of 2,2-dimethoxypropane, 200 ml. of hexane, and 0.2 g. of *p*-toluenesulfonic acid monohydrate were heated in a 2-l. flask fitted with a dropping funnel and a 28-plate Oldershaw distillation column. Distillate was removed from the column at such a rate that the overhead temperature was held at 48–49°. The distillation period was approximately 10 hr. during which 456 ml. of distillate was collected while a total of 280 ml. of hexane was added in three portions through the dropping funnel. The final distillate, collected at a very high reflux ratio, boiled at 64°. The reaction mixture was stabilized by adding 0.2 g. (or sufficient to produce an alkaline reaction) of sodium methoxide, placed in a low-pressure distillation apparatus with a vacuum-jacketed 25-cm. Vigreux column, and stripped of solvents at reduced pressure. The residue was then distilled, and the portion boiling at 86–92° (3 mm.) was redistilled to give 131 g. (53%), b.p. 89–90° (2.5–3 mm.).

Method B. Methylals and Propylals.—In this method the acetals were prepared *via* the dichlorides. Dichlorides were prepared from phenyl 2-thienyl ketone,[23a] 9-fluorenone,[23b] and 4-chlorobenzophenone[23c] according to the literature cited. The preparation of the dichloride of 4,4'-dichlorobenzophenone is not in the literature and illustrates the method. 4,4'-Dichlorobenzophenone (100 g., 0.4 mole) was heated on a steam bath with 120

(23) (a) W. Minnis, *J. Am. Chem. Soc.*, **51**, 2144 (1929); (b) F. E. Ray and C. E. Albertson, *ibid.*, **70**, 1954 (1948); (c) W. W. Kaeding and L. J. Andrews, *ibid.*, **74**, 6192 (1952).

—Hydrogen, %— Calcd.	Found	—Chlorine, %— Calcd.	Found	—Nitrogen, %— Calcd.	Found	Comparative pharmacology: LD50, mg./kg. orally in mice	MES[c] ED50, mg./kg.	Local anesthesia, min. eff. % concn.[d] (proc. = 2)	Bariolytic activity, *in vitro*, rabbit ileum (papav. = 1)	Hot-plate[e] reaction time, % of control
7.28	7.11	9.85	9.38			400 25[g]	100	0.125	5	100
7.28	7.46	9.85	9.81			600 37.5[g]	125	0.25	2	78
7.28	7.21			3.89	3.91	300 75[h]	>75	0.1	1	100
7.28	7.16	9.85	9.70	3.89	4.01	300 75[g]	>75	0.25	4	100
6.06	5.84			3.01	2.80	800 75[h]	>150	0.25 neg.[k]	1	100
6.06	6.06	27.27	27.08	3.01	3.11	600	>150	0.25 neg.[k]	<0.5	100
7.24	6.88	9.09	8.86			600	>75 <150	0.25	3	78[o]
7.45	7.09			3.83	3.93	>800 300[h]	>200	Insol.	Insol.	125
7.45	7.02			3.83	3.92	>800 300[h]	>200	Insol.	Insol.	100
7.80	7.79	9.14	9.15			400	100	2	4	65
7.80	7.71			3.61	3.52	600	>75 <150	2	5	100
6.27	6.06	9.19	9.38			800 400[h]	>200	Insol.	Insol.	100
6.27	6.21	9.19	9.02			800	>200	Insol.	Insol.	100
6.94	6.89	8.13	8.21			600	>75 <150	0.5 neg.[k]	<0.3	65
6.94	6.75	8.13	8.37			>800	120	0.5 neg.[k]	<0.3	65
6.94	6.94	8.13	8.09			>800	200	0.5 neg.[k]	1	100
6.94	7.24	8.13	7.99			>800 400[h]	>200	0.15 neg.[k]	0.3	100
7.69	7.73			6.10	6.34	300	>75	0.25	3	100
7.69	7.64			6.10	6.26	150 12.5[g]	>50	0.1	15	100
7.95	7.68			5.82	6.19	150 10[g]	>37.5	0.1	8	100
6.97	7.15	9.43	9.56			800	200	2 neg.	<0.3	100
7.43	7.48	8.17	8.88	3.23	3.34	600	150	1	<1	75
6.69	6.73	7.84	7.79			600	>150	1 neg.		85
7.31	7.59	9.19	9.12			300	75	1	<1	52

[i] Not recrystallized. [k] Low solubility prevented complete testing. [l] See Experimental Section. [m] 25-mg. dose. [n] 12.5-mg. dose. [o] 75-mg. dose. [p] 50-mg. dose. [q] Sulfur. [r] Crystallized with 1 mole of acetone. [s] Prepared from **47** by the method described for **54** in the Experimental Section. [t] $[\alpha]_D^{22}$ +9.0° (*c* 1, methanol), prepared from **24** by the method described for **50** in the Experimental Section.

ml. of toluene and 91 g. (0.44 mole) of PCl_5 for approximately 6 hr., then allowed to stand several days, and evaporated on the steam bath at 20-mm. pressure. The residue was extracted with benzene, the benzene was evaporated, and the residue was crystallized from 300 ml. of pentane. Evaporation of the mother liquid gave a second crop. The combined crops, 93 g. (76%), melted at 51–53°.

The general procedure[11] for converting dichlorides to ketals is illustrated by the preparation of bis(4-chlorophenyl)dimethoxymethane. Sodium methoxide was formed by slowly adding 180 ml. of dry methanol to 14 g. (0.61 g.-atom) of sodium. The solution was chilled to 0° by an ice bath, and 95 g. (0.31 mole) of bis(4-chlorophenyl)dichloromethane suspended in 230 ml. of chilled dry methanol was added at a rate that allowed the stirred solution to remain below 10°. The mixture was stirred 45 min. and then allowed to warm to room temperature. After refluxing 2 hr., the hot mixture was filtered and the filtrate was concentrated to give two successive crystalline crops which were combined and recrystallized from 2-propanol to give 66 g. (72%) of product, m.p. 68.5–70°.

Method B was modified for the preparation of bis(4-methoxyphenyl)dipropoxymethane. 4,4'-Dimethoxybenzophenone (90 g., 0.37 mole) was dissolved in 350 ml. of benzene, and 94 g. (0.74 mole) of oxalyl chloride was added dropwise during a 2-hr. period of stirring. Following an additional 1 hr. of stirring, the evolution of gases was completed by 1 hr. of reflux and evaporation of all volatile material at reduced pressure. The residue was a red crystalline mass, m.p. 100–105°.[24] This material was dissolved

(24) H. Staudinger, K. Clar, and E. Czako, *Ber.*, **44**, 1645 (1911).

in 300 ml. of dry benzene and added dropwise over a 2-hr. period to a stirred solution of sodium propoxide in 1-propanol at 5°. The latter solution was prepared by carefully adding 450 ml. of dry 1-propanol to 18 g. (0.78 g.-atom) of sodium. After adding the benzene solution, the reaction mixture slowly warmed to room temperature and was filtered. The filtrate was concentrated to an oil which was distilled without fractionation to give 85 g. (67% based on the ketone) of product, b.p. 170–172° (1 mm.).

Method C. Dioxolanes.—The preparation of 2-(2-piperidyl)-1,4-dioxaspiro[4.5]decane hydrochloride (1) is illustrative of the procedure used to make the dioxaspirodecanes appearing in Table II. Cyclohexanone (43 g., 0.44 mole) and 39 g. (0.22 mole) of the mixed racemates of (2-piperidyl)-1,2-ethanediol hydrochloride (II) were dissolved in 150 ml. of 2-propanol and the solution was adjusted to about pH 2 with dry HCl. After standing at room temperature for 3 days, a crystalline precipitate was removed by filtration.[25] The filtrate was heated 2 hr. on the steam bath, and a second precipitate then developed overnight. The combined precipitates (36.9 g., m.p. 220–221°) were washed with a small amount of 2-propanol, and recrystallized from 2-propanol to give 31 g. (54%) of product, m.p. 220–221°.

Method D. Dioxolanes.—The 2-substituted dioxolanes appearing in Table II were prepared by the reaction of aromatic ketals with (2-piperidyl)-1,2-ethanediol hydrochloride. The procedure is illustrated, except for minor variations in reaction time and quantities of solvent, by the preparation of 2,2-diphenyl-4-(2-piperidyl)-1,3-dioxolane hydrochloride. 2-Propanol (2-l.) and 1436 g. (7.9 moles) of the mixed racemates of (2-piperidyl)-1,2-ethanediol hydrochloride were heated and stirred in a 5-l. flask equipped with a thermometer. When the temperature reached 80°, 2012 g. (8.8 moles) of dimethoxydiphenylmethane was added, followed by 1 g. of dry HCl in a few milliliters of 2-propanol. A rapid reaction ensued with evolution of methanol vapors and the development of a heavy precipitate. After a few minutes methanol evolution subsided and the mixture was then heated and stirred for 2 hr. and filtered warm on a suction funnel. The filter cake was washed successively with 2-l. portions of solvent, four times with ether and three times with 2-propanol, to give 2042 g. (75%) of crude product, m.p. 234–238°.[26] The mother liquor was concentrated by one-third and gave a second crop of 119 g., m.p. 238°.

Racemate Separation. 2,2-Diphenyl-4-(2-piperidyl)-1,3-dioxolane Hydrochloride. A. β Racemate (21).—A 680-g. (1.97 moles) portion of crude 2,2-diphenyl-4-(2-piperidyl)-1,3-dioxolane hydrochloride prepared by method D was dissolved in 6.8 l. of absolute ethanol and 2 l. of methanol at reflux, and the solution was allowed to stand for 3 days at 25° when it was decanted from approximately 170 g. of crystals. A saturated solution of the crystals (8% w./v.) in hot methanol gave a 50% weight recovery of pure β racemate, m.p. 301°.

B. α Racemate (20).—The decanted mother liquor from a crystallization of crude α racemate was evaporated to a dry powder and 660 g. (1.9 moles) was suspended in 800 ml. of 10% aqueous NaOH. The suspension was vigorously stirred with successive portions of 800 and 500 ml. of ether, the solid phase disappearing during the first equilibration, and the combined extracts were dried ($MgSO_4$) and evaporated to 586 g. of oil. The oil was dissolved in 2.2 l. of methanol to which was rapidly added 177 g. (1.05 moles) of DL-tartaric acid monohydrate in 1.5 l. of methanol while stirring. Precipitation began immediately and the mixture was allowed to stand quietly at room temperature for 2.5 hr. when it was filtered and the filter cake was washed four times with 250-ml. portions of methanol and dried to give 506 g. of DL-tartrate salt, m.p. 222–228°. This was stirred in a mixture of 1.6 l. of 10% aqueous NaOH and 2 l. of ether until the solid had disappeared. The aqueous phase was re-extracted with two successive 500-ml. portions of ether and the combined extracts were dried ($MgSO_4$). Evaporation of the ether gave 401 g. of oil which was dissolved in 1.25 l. of methanol, and 350 ml. of dry ether containing 48 g. of dry HCl was added rapidly with stirring. This solution was quickly diluted with 2.5 l. of dry ether. After standing 40 min., the precipitate was filtered, washed twice with 400-ml. portions of 3:1 dry ether–methanol and then 500 ml. of dry ether to give 416 g. of the α racemate, m.p. 248–253°.

Resolution of α Racemate (20). A. *d* Enantiomer (24).—Compound **20** (24.4 g., 0.071 mole) was converted to the free base by the extraction procedure described in the preceding section (B) and the residual oil (21.5 g., 0.069 mole) was dissolved in 80 ml. of methanol and stirred while rapidly adding a solution of 5.83 g. (0.039 mole) of D-(+)-tartaric acid in 80 ml. of methanol. After standing for 2.5 hr., the solution was filtered and the precipitate was washed with 30-ml. portions of methanol leaving 11.4 g. of tartrate salt, m.p. 241–244°. The filtrate was set aside for purification of the *l* enantiomer. A portion (9 g., 0.012 mole) of the tartrate salt was decomposed by suspension in 40 ml. of 10% aqueous NaOH and extracted into three successive 50-ml. portions of ether. The combined extracts were dried ($MgSO_4$) and evaporated to an oil which was taken up in 22.5 ml. of methanol and acidified to pH 3 with 3.5 *M* ethereal HCl. After 2 hr., the mixture was filtered and washed three times with 15-ml. portions of 3:1 ether–methanol and dried to give 7.0 g. (72%), m.p. 248–256°, of α-*d* enantiomer, $[\alpha]^{25}D$ +33.9° (*c* 2, methanol).

B. *l* Enantiomer (25).—The filtrate retained above was evaporated to 16.2 g. of residue which was converted to the free base by suspending it in 25 ml. of 20% aqueous NaOH and equilibrating it with four successive 50-ml. portions of ether. The combined extracts were dried ($MgSO_4$) and evaporated to an oil, which was treated, as described in A above for the preparation of the *d* isomer, by dissolving it in 45 ml. of methanol and then adding 3.39 g. (0.023 mole) of D-(−)-tartaric acid in 45 ml. of methanol. Of this 10.1 g. of precipitated tartrate salt, 8.5 g. was converted, *via* the free base, to the hydrochloride, 7.01 g. (68%), m.p. 248–254°, of the α-*l* enantiomer, $[\alpha]^{25}D$ −34.5° (*c* 2, methanol).

4-(1-Methyl-2-piperidyl)-2,2-diphenyl-1,3-dioxolane Hydrochloride. A. β Racemate (37).—Compound **21** (23 g., 0.07 mole) dissolved in 250 ml. of methanol was mixed with 34 g. of 37% aqueous formalin and 2 g. of 10% palladium on carbon. The mixture was hydrogenated until absorption stopped (6 hr.) and filtered. The filtrate was evaporated to an oil which was diluted with 2-propanol and re-evaporated several times until it crystallized. The crystals were washed with ether and recrystallized twice by dissolving in 2-propanol and diluting with ether to give 11.8 g. (49%) of product, m.p. 175–177°. An additional 6.0 g., m.p. 166–171°, was obtained from the mother liquor.

B. α Racemate (34).—By the procedure described in section A above, 34.5 g. (0.1 mole) of **20** was reductively N-methylated. The filtered reaction mixture was evaporated to a white powder, stirred with 100 ml. of water, and refiltered to give 24.2 g. of crude **34**. This was recrystallized three times from methanol and twice from 50% methanol–water to give 3.1 g. (9%), m.p. 267–268°, of α racemate.

C. α-*l* Enantiomer (36).—Compound **25** (20 g., 0.058 mole) was reductively methylated as described in section A above and the crude product was recrystallized from methanol to give 13 g. (62%) of product, m.p. 282° dec., $[\alpha]^{25}D$ −30.7° (*c* 1, methanol).

D. α-*l* Enantiomer (35).—By the procedure described in section A above, **24** (25 g., 0.072 mole) was methylated to give 22.5 g. (87%) of product, m.p. 287° dec., $[\alpha]^{25}D$ +31.8° (*c* 1, methanol).

α-*dl*-4-[1-(2-Hydroxyethyl)-2-piperidyl]-2,2-diphenyl-1,3-dioxolane Hydrochloride (40).—A suspension of 69 g. of **20** in 100 ml. of 10% aqueous NaOH was stirred vigorously with three successive 150-ml. portions of benzene (the solid phase disappeared during the second extract) and the extracts were combined and dried (K_2CO_3). Evaporation of the solvent gave 59.5 g. of oily free base. A portion of this oil (15.4 g., 0.044 mole) was dissolved in 50 ml. of 1:1 methanol–water and then mixed with 25 ml. of methanol containing 2.2 g. (0.05 mole) of ethylene oxide. The mixture was placed in a glass pressure flask in a steam bath, heated at 100° for 16 hr., and then evaporated to an oil which was diluted with benzene and re-evaporated to a dry oil. This was taken up in dry benzene and treated with 1.14 g. (0.03 mole) of dry HCl in 25 ml. of 2-propanol which precipitated a crop of 5.8 g. The mother liquor was evaporated and the amorphous residue was washed with dry ether and then triturated with 2-propanol to give more crystals. The combined crystal crops were recrystallized from ethanol–ether and then from ethanol to give 4.2 g. (21%) of product, m.p. 208–210°.

(25) Those reaction mixtures which gave meager precipitates were diluted with ether before the work-up to facilitate crystallization of the crude product.

(26) Quantitative infrared analysis on this crude product indicated that the α and β racemates were present in 3:2 ratio. The analytical method will be published by Dr. Dale Robertson of Arapahoe Chemicals, Inc., Boulder, Colo., and Dr. H. N. Beniams of Cutter Laboratories.

α-dl-**2,2-Diphenyl-4-(1-propionyl-2-piperidyl)-1,3-dioxolane** (**41**).—A mixture of 150 ml. of ethylene dichloride, 50 ml. of 40% aqueous NaOH, and 30.0 g. (0.087 mole) of **20** was stirred vigorously for approximately 1.5 hr. until all the solid phase had dissolved. The reaction mixture was then chilled in an ice–salt bath to −5° and with continued stirring a solution of 16 g. (0.17 mole) of propionyl chloride in 50 ml. of ethylene dichloride was added dropwise during a period of 1 hr., while the reaction mixture was held at −5–0°. Stirring was continued as the bath slowly rose to room temperature and the aqueous phase was separated and extracted with fresh solvent. The combined solvent extracts were washed with dilute HCl, dried (K_2CO_3), and evaporated to an oil which was crystallized three times from ether by adding pentane to give 26 g. (82%) of product, m.p. 86–87°.

α-dl-**2,2-Diphenyl-4-(1-propyl-2-piperidyl)-1,3-dioxolane Hydrochloride** (**43**).—Lithium aluminum hydride (3.75 g., 0.1 mole) was suspended in 200 ml. of absolute ether in a 2-l. flask fitted with a condenser, stirrer, and dropping funnel and flushed with dry nitrogen. While stirring, a solution of 26 g. (0.071 mole) of **41** in 900 ml. of dry ether was added during a period of 4 hr. at a rate which gave a slight reflux. Stirring was continued overnight and then 25 ml. of water was carefully added and a white precipitate formed. The ether phase was decanted and evaporated to an oil which was diluted with 300 ml. of benzene, and 4.0 g. of dry HCl in 10 ml. of 2-propanol was added. The acidic solution was evaporated at reduced pressure and a small amount of ether was added to the residue which then crystallized to give 27 g. (98%), m.p. 191–192°.

β-dl-**4-(1-Chloroacetyl-2-piperidyl)-2,2-diphenyl-1,3-dioxolane** (**46**).—A suspension of 72 g. (0.21 mole) of **20** in 250 ml. of 20% aqueous NaOH was stirred vigorously with 400 ml. of ethylene dichloride until the solid phase had been dissolved. The stirred mixture was then cooled to 0° and 45 g. (0.40 mole) of chloroacetyl chloride in 100 ml. of ethylene dichloride was added dropwise, during a period of 1.5 hr. After an additional hour of stirring, the mixture gradually warmed to room temperature and the phases were separated. The aqueous phase was extracted twice with small portions of ethylene dichloride and the combined solvent phases were dried (K_2CO_3), evaporated to an oil, redissolved in 250 ml. of dry benzene, and chilled to give 59 g. (73%) of product, m.p. 145–146°.

α-dl-**4-(1-Diethylaminoacetyl-2-piperidyl)-2,2-diphenyl-1,3-dioxolane Hydrochloride** (**51**).—A solution of diethylamine (24 g., 0.33 mole) and 32 g. (0.083 mole) of **45** in 100 ml. of dry benzene was refluxed for 3 hr. After standing at room temperature for several days, the precipitate was filtered off and the filtrate was evaporated to an oil which was taken up in dry benzene and treated with 3 g. (0.082 mole) of dry HCl in 17 ml. of 2-propanol. The solvent was removed and the amorphous residue was diluted with ethyl acetate. A chalky precipitate formed which was separated and recrystallized from 2-propanol by dilution with ethyl acetate to give 30.5 g. (80%) of product, m.p. 172–173°.

β-dl-**4-[1-(2-Diethylaminoethyl)-2-piperidyl]-2,2-diphenyl-1,3-dioxolane Dihydrochloride** (**53**).—Compound **52** (19.0 g., 0.041 mole) was suspended in 50 ml. of 12% aqueous NaOH and extracted three times with 100-ml. portions of ether and the combined extracts, dried over barium oxide, were evaporated to a residue, which was taken up in 100 ml. of anhydrous ether. Following the reduction procedure used for the preparation of **43**, this ether solution was added to a suspension of 1.28 g. (0.034 mole) of $LiAlH_4$ in 100 ml. of ether and reduced. The reaction product was dissolved in benzene and treated with 1.2 g. of HCl in 2-propanol. A small precipitate was discarded and the filtrate was evaporated to a residue which crystallized when it was refluxed with benzene. It was recrystallized from 2-propanol–ethyl acetate and then from acetone to give 2.6 g. (13%) of **53**, melting at 160–163°.

4-(1-Benzyl-2-piperidyl)-2,2-diphenyl-1,3-dioxolane Hydrochloride. A. *α* **Racemate** (**47**).—The free base of **20** was prepared by equilibrating a suspension of 36 g. (0.1 mole) of the hydrochloride in 100 ml. of 20% aqueous NaOH with three successive portions of benzene. The combined extracts, dried over K_2CO_3, were concentrated to 250 ml. and treated with 8.5 g. (0.05 mole) of benzyl bromide at room temperature. After 2 days a precipitate was removed. The filtrate was refluxed for 2 hr. to give a small additional precipitate which, together with the first crop, weighed 20.4 g. (0.052 mole, calculated as the hydrobromide of the starting material). The filtrate was acidified by careful addition of dry HCl in a small amount of 2-propanol and then concentrated to a hard glass which was triturated with dry ether to give a chalky precipitate. Several recrystallizations from 2-propanol–ether acetate and one from ethyl acetate containing a trace of 2-propanol gave 7.6 g. of product (35% based upon benzyl bromide), m.p. 164–166°.

B. *β* **Racemate** (**50**).—The free base of **21**, prepared as in section A above (18.5 g., 0.06 mole), was dissolved in 100 ml. of ethanol together with 4.9 g. (0.029 mole) of benzyl bromide, allowed to stand several hours, and refluxed 4 hr. The precipitate of 11.4 g. was removed and the filtrate was evaporated to an oil of 11.0 g. which was diluted with benzene and treated with 1.0 g. (0.027 mole) of dry HCl in a small amount of 2-propanol, to give a precipitate of 10.8 g. (86% based on benzyl bromide), m.p. 202–206°. Recrystallization from methanol–ethyl acetate gave 6.9 g. of **50**, m.p. 202–205°.

C. *α-d* **Enantiomer** (**48**).—Compound **24** (34.6 g., 0.1 mole) was dissolved in 200 ml. of methanol and the free base was liberated by the addition of 5.4 g. (0.1 mole) of sodium methoxide. After filtering, the solution was evaporated to an oil and dissolved in 100 ml. of benzene containing 21.4 g. (0.125 mole) of benzyl bromide and 27.6 g. (0.2 mole) of K_2CO_3. The mixture was stirred at room temperature for 16 hr. and equilibrated with water, and the benzene phase combined with an ether extract of the aqueous phase was dried (K_2CO_3) and evaporated to an oil. The oil was taken up in dry benzene and treated with 22 ml. of 2-propanol containing 3.5 g. (0.1 mole) of dry HCl. The solvent was then evaporated and the residue was diluted with dry ether. The precipitate which separated was recrystallized twice from methanol–ethyl acetate and twice from 2-propanol to give 7.5 g. (17%) of **48**, m.p. 191–194°, $[\alpha]^{25}D$ +16.7° (*c* 2, methanol).

D. *α-l* **Enantiomer** (**49**).—Using the same procedure as in section C above starting with **25**, *α-l*-4-(1-benzyl-2-piperidyl)-2,2-diphenyl-1,3-dioxolane hydrochloride was prepared, 8.5 g. (19%), m.p. 195–196°, $[\alpha]^{25}D$ −16.6° (*c* 2, methanol).

8-Methyl-8-phenyl-2-(2-piperidyl)-1,4-dioxaspiro[4.5]decane Hydrochloride (**12**).—A solution of 500 g. (3.72 moles) of hydratropaldehyde in 2.5 l. of methanol was stirred under nitrogen, cooled to 3°, and treated in 3 min. with a cold, freshly prepared solution of 4.0 moles of sodium methoxide in 2.5 l. of methanol. The temperature was maintained at 0 ± 2° during the next 2 hr. while a solution of 287 g. (4.10 moles) of methyl vinyl ketone in 2 l. of methanol was added with good stirring. After warming to room temperature overnight, the solution, still under nitrogen, was heated at 60° for 5 hr. It was cooled slightly, acidified to pH 6 with 250 ml. of glacial acetic acid, and the solvents were evaporated. The saline precipitate was dissolved by the addition of 700 ml. of water, and the mixture was extracted with three 700-ml. portions of ether. These were united, washed with two 150-ml. portions of water, and concentrated on a steam bath. The residue was refluxed with 250 ml. of benzene under a Dean–Stark trap to remove 25 ml. of water and then distilled to yield 438.5 (63%) of 4-methyl-4-phenyl-2-cyclohexen-1-one, b.p. 114–115° (1 mm.), $n^{24}D$ 1.5600.

Anal. Calcd. for $C_{13}H_{14}O$: C, 83.83; H, 7.58. Found: C, 83.37; H, 7.56.

A mixture of 83.7 g. (0.45 mole) of 4-methyl-4-phenyl-2-cyclohexenone and 2 g. of 5% palladium on carbon in 120 ml. of ethyl acetate was hydrogenated to completion in 2 hr. The catalyst was filtered off and the filtrate was concentrated to give a crystalline residue which was dissolved in 250 ml. of warm glacial acetic acid, mixed with 220 ml. of water, and cooled to give an oil which crystallized. After standing overnight at −7°, the crystals were filtered, washed quickly with two 50-ml. portions of cold 50% acetic acid and two 50-ml. portions of cold 25% acetic acid, and dissolved in 125 ml. of ether. This was washed with a little dilute K_2CO_3 solution and then with water and concentrated on a steam bath. The oil was allowed to crystallize and was dried (P_2O_5) to give 54.5 g. of 4-methyl-4-phenylcyclohexanone (64%), m.p. 41–43.5°.

Anal. Calcd. for $C_{13}H_{16}O$: C, 82.94; H, 8.54. Found: C, 82.78; H, 8.30.

A mixture of 20 g. (0.11 mole) of *β-dl*-(2-piperidyl)-1,2-ethanediol hydrochloride and 20.7 g. (0.11 mole) of 4-methyl-4-phenylcyclohexanone in 100 ml. of 2-propanol was acidified by the addition of 0.01 mole of 4.2 *M* dry HCl in ether. The solution was refluxed for 4 hr. and let stand overnight. The solvent was then distilled and the syrupy residue was refluxed in 100 ml. of benzene under a Dean–Stark trap for 95 hr. until 1.7 ml. of water had been collected. The solvent was evaporated and the crystalline

residue was recrystallized four times from 1:2 methanol-ether to give 3.07 g. (8%), m.p. 247–250°.

Material from the mother liquors (17.5 g.), despite repeated crystallizations from various solvents, melted at 202–219°. We were unable to show this material to be different from the 3.07-g. fraction by elemental analyses, mixture melting point, infrared absorption, or thin layer chromatography, and its configuration at the spiro carbon remains in doubt.

β-*dl*-2,2-Dicyclohexyl-4-(2-piperidyl)-1,3-dioxolane Hydrochloride (30).—Compound **21** (17.3 g., 0.05 mole) was suspended in aqueous caustic and extracted into ether, and the ether was evaporated to give an oil. The oil was dissolved in 110 ml. of cold glacial acetic acid and 3 g. of 5% rhodium on alumina and hydrogenated for 26 hr. while the hydrogen pressure dropped 1.13 kg./cm.² (calcd. 0.88 kg./cm.²). The mixture was filtered and the solvent was distilled at reduced pressure leaving a residue which was neutralized with 50 ml. of 8% NaOH and extracted with ether. The combined extracts were dried ($MgSO_4$), filtered, and evaporated to an oil which crystallized on contact with dry ether. The 12 g. of crude product was dissolved in 200 ml. of ether and its hydrochloride was precipitated by adding 1.36 g (0.037 mole) of dry HCl in 24 ml. of 2-propanol. Recrystallization from 2-propanol gave 7.8 g. (44%) of product, m.p. 282° dec.

β-*dl*-4-(1-(Methyl-2-piperidyl)-2,2-diphenyl-1,3-dioxolane N-Oxide Hydrochloride (54).—Compound **27** (10 g., 0.028 mole) was suspended in aqueous caustic and extracted into ether, and the ether was evaporated to give an oil which was taken up in 100 ml. of methanol containing 14 ml. of 30% H_2O_2 in water. The reaction mixture stood for 2 weeks at +2° while a precipitate developed. The solvent was removed and the residue was taken up in 50 ml. of methanol, stirred with 100 mg. of PtO_2 until no further bubbles developed, and then filtered. Removal of the solvent gave a white solid which was recrystallized from ethyl acetate containing a trace of methanol. It was redissolved in fresh, dry methanol-ethyl acetate and treated with 0.7 g. of dry HCl in 5 ml. of 2-propanol to precipitate the hydrochloride, which was recrystallized from 75 ml. of butanol containing a trace of methanol and then from ethanol to give 4.2 g. (40%) of product, dec. pt. 190°.

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Notes

3-Indolylsuccinimides and 3-(3-Pyrrolidinyl)indoles

Y. G. PERRON, W. F. MINOR, M. E. BIERWAGEN,[1] S. A. RIDLON, AND M. H. PINDELL

Research Division, Bristol Laboratories, Division of Bristol-Myers Company, Syracuse, New York 13201

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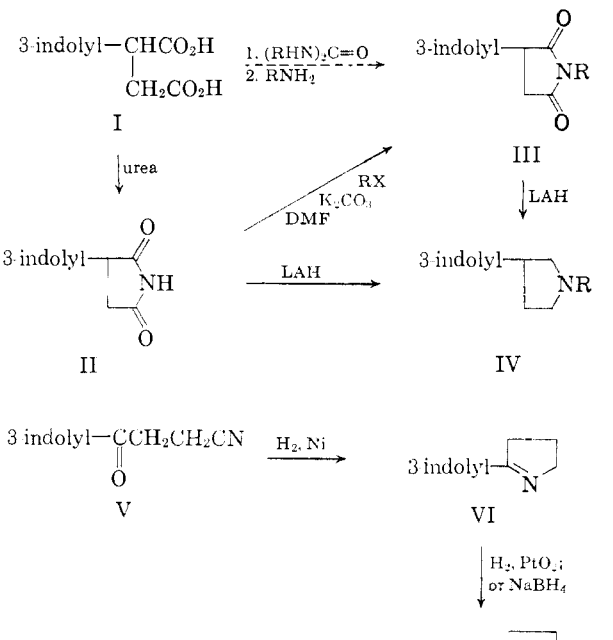
In a previous publication[2] we reported that 3-indolesuccinic acid (I) could be converted to 3-indolesuccinimide (II) by fusion with urea. Treatment of I with 1,3-dimethyl- and 1,3-diethylureas under the same conditions has given N-methyl- and N-ethyl-3-indolylsuccinimides (III, Scheme I). The same products have also been obtained by the reaction of 3-indolesuccinimide with methyl and ethyl iodides, respectively, in the presence of potassium carbonate in dimethylformamide. The reaction of potassium 3-indolesuccinimide with ethyl iodide in dimethylformamide gave N-ethyl-3-indolylsuccinimide in good yield.

Other N-substituted 3-indolylsuccinimides were prepared by the reaction of 3-indolesuccinic acid with amines in refluxing toluene, with azeotropic removal of the water formed. N-(2-Morpholinoethyl)-, N-(3-morpholinopropyl)-, and N-[2-(2-pyridyl)ethyl]-3-indolylsuccinimides were prepared in this manner (Scheme I) and are recorded in Table I.

Reduction of the N-substituted 3-indolylsuccinimides[3] with lithium aluminum hydride in dioxane or tetrahydrofuran produced the corresponding 3-(1-substituted 3-pyrrolidinyl)indoles[3] (IV, Table II). In some cases these products could not be obtained in pure form and are not reported here.

An approach to the synthesis of 3-(2-pyrrolidinyl)-indoles seemed possible through a procedure analogous

SCHEME I



to that of Burckhalter and Short,[4] who hydrogenated β-aroylpropionitriles over Raney nickel catalyst to produce 2-arylpyrrolidines. Therefore, 3-(β-cyanopropionyl)indole[5] was hydrogenated in methanol over Raney nickel catalyst until hydrogen absorption had ceased. The uptake corresponded to 2 moles and the product was identified as 2-(3-indolyl)-1-pyrroline (VI), analogous to the 2-aryl-1-pyrrolines obtained by Burckhalter and Short when the hydrogenations of β-aroylpropionitriles were interrupted after the absorption of 2 moles of hydrogen. This compound was converted to the

(1) To whom inquiries concerning this manuscript should be addressed.
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