Basically Substituted Dioxolanes and Dioxanes

By OLE GISVOLD and H. V. MAULDING, JR.*

The synthesis of a group of basically substituted 1,3-dioxolanes and 1,3-dioxanes is reported. Cyclic acetals and ketals were prepared by the acid catalyzed, azeotropic distillation method, utilizing either a 1,2- or a 1,3-diol and either *p*-nitrobenzaldehyde or *p*-nitroacetophenone as the carbonyl compound, followed by catalytic reduction of the aromatic nitro group to the corresponding primary amine. All members of this series have a *p*-amino-phenyl substituent at position 2 of the dioxolane or dioxane ring in order to conform structurally as closely as possible to the sulfonamide and procaine prototypes. These compounds exhibited no antibacterial action *in vitro*. One compound had local anesthetic activity.

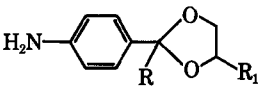
REPLACEMENT OF ESTERS by either substituted or unsubstituted 1,3-dioxolanes and/or 1,3-dioxanes has upon occasion led to effective medicinal agents. Bovet's acetal (1) is one of the most active muscarinic agents ever found. Blicke and co-workers (2–4) produced potent antispasmodics by replacement of the —CHCOO— of adiphenine with basically substituted 1,3-dioxolane and 1,3-dioxane rings. Recently, Hardie and co-workers (5) have reported on the local anesthetic and spasmolytic properties of a series of 4-(2-piperidyl)-1, 3-dioxolanes.

The ester linkage usually found in the procaine prototype is not a necessity as aminoalkyl ethers of the general formula $ArO(CH_2)_3NR_2$ (6) are efficient local anesthetics. Thus it was hoped that dioxolanes and dioxanes of the general formulas (I) and (II) might possess some degree of local anesthetic activity, as they closely resemble procaine and the alkylamino benzoates, with substitution of the ester group by the oxygenated ring representing the major structural modification.

Although there are certain general requirements for anti-*p*-aminobenzoic acid activity these stipulations are not nearly so specific as they may appear at first glance. The structural features requisite for antagonism of PAB are basically: (*a*) a primary aromatic amino group, and (*b*) an electronegatively charged group *para* to the amine (7). Sulfur is not necessary as the sodium *p*-amino-phenyl-arsonate (8) and diaminobenzil (9) are antimetabolites of the acid. As the critical distances between (*a*) the two ring oxygens and (*b*) the ring oxygens and the hydrogens of the primary aromatic amine in the dioxolanes (I) and the dioxanes (II) are quite similar to those stated for sulfanilamide and the *p*-aminobenzoate anion (7) (about 2.4 and 6.8 Å., respectively), it was thought that they might possess some degree of anti-*p*-aminobenzoic acid activity.

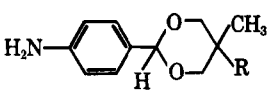
The intermediate halodioxolanes and halodioxanes (Tables I and II) required for the synthesis of the corresponding amino compounds were prepared by condensation of the aldehyde or ketone with glycerol-α-monobromohydrin or 2-methyl-2-bromomethyl-1,3-propanediol (10) in the presence of *p*-toluenesulfonic acid according to the procedure of Salmi (11). The nonhalogenated dioxolanes were prepared in the same manner using the appropriate 1,2-glycol. As it had been found previously that 5-methyl-5-bromomethyl-1,3-dioxanes reacted sluggishly with secondary amines, the bromo dioxane was converted to the iodo derivative (12) so as to obtain the wanted amines.

The 4-aminomethyl-1,3-dioxolanes (Table I) and the 5-methyl-5-aminomethyl-1,3-dioxanes (Table II) were produced by heating the intermediate halo compound, the amine and benzene in a pressure bottle on either a steam bath or in an oven for 6 to 7 days (2–4). In the case of the intermediate amino dioxolanes, these compounds were oils which decomposed on attempted distil-



(I)

R = H, CH_3
R_1 = H, CH_2Ar, CH_2NR_2, CH_2N cyclic alkyl



(II)

R = CH_2NR_2, CH_2N cyclic alkyl

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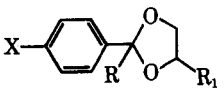
TABLE I—PHYSICAL CONSTANTS OF 1,3-DIOXOLANES



Compd.	X	R	R_1	M.p.[a] °C.	Yield, %	Molecular Formula	Anal., %[b] Calcd.	Found
1	NO_2	H	H	89–91[c]	73	$C_9H_9NO_4$[d]	C ...	...
							H ...	...
2	NH_2	H	H	75–79[e]	86	$C_9H_{11}NO_2$[e]	C, 65.43	65.52
							H, 6.71	6.79
3	NO_2	CH_3	H	73–75[c]	77	$C_{10}H_{11}NO_2$	C, 57.41	57.38
							H, 5.30	5.28
4	NH_2	CH_3	H	105–109[c]	44	$C_{10}H_{13}NO_2$	C, 67.02	67.01
							H, 7.31	7.37
5	NO_2	H	CH_2Br	70–106[c, f]	60	$C_{10}H_{10}BrNO_2$	C, 41.70	42.08
							H, 3.47	3.51
6	NO_2	H	$CH_2N(C_2H_5)_2$	165[c, g]	70[h]	$C_{20}H_{23}N_5O_{11}$[g]	C, 47.10	47.03
							H, 4.55	4.61
7	p-$NO_2C_6H_4CH{=}NH$[i]	H	$CH_2N(C_2H_5)_2$	68–78[c]	59	$C_{21}H_{25}N_3O_4$	C, 65.78	65.37
							H, 6.58	6.73
8	NO_2	H	$CH_2NC_5H_{10}$[j]	175–178[k]	73[h]	$C_{16}H_{23}N_2O_4I$[k]	C, 44.24	44.21
							H, 5.33	5.38
9	p-$NO_2C_6H_4CH{=}NH$[i]	H	$CH_2NC_5H_{10}$[j]	90–105[c]	55	$C_{22}H_{25}N_3O_4$	C, 66.81	67.02
							H, 6.37	6.54
10	NO_2	H	$CH_2NC_4H_8O$[l]	173–176[k]	84[h]	$C_{15}H_{21}N_2O_5I$[k]	C, 41.26	41.60
							H, 4.85	4.74
11	NH_2	H	$CH_2NC_4H_8O$[l]	104–114[c]	82	$C_{14}H_{20}N_2O_3$	C, 63.61	63.65
							H, 7.62	7.46
12	NO_2	H	$CH_2N(C_4H_9)_2$	135–137[c, g]	74[h]	$C_{24}H_{31}N_5O_{11}$[g]	C, 50.96	51.06
							H, 5.52	5.36
13	p-$NO_2C_6H_4CH{=}NH$[i]	H	$CH_2N(C_4H_9)_2$	60–64[c]	69	$C_{25}H_{33}N_3O_4$	C, 68.31	68.69
							H, 7.56	7.65
14	p-$NO_2C_6H_4CH{=}NH$[i]	H	$CH_2NC_6H_{12}$[m]	95–104[c]	49	$C_{23}H_{27}N_3O_4$	C, 67.46	67.39
							H, 6.64	6.71
15	NO_2	H	$CH_2C_6H_5$	45–59[c]	61	$C_{16}H_{15}NO_4$	C, 67.35	67.27
							H, 5.30	5.21
16	p-$NO_2C_6H_4CH{=}NH$[i]	H	$CH_2C_6H_5$	108–118[c]	22	$C_{23}H_{20}N_2O_4$	C, 71.12	71.53
							H, 5.19	5.41
17	NO_2	CH_3	$CH_2C_6H_5$	123–135[c]	66	$C_{17}H_{17}NO_4$	C, 68.21	68.27
							H, 5.73	5.82
18	p-$NO_2C_6H_4CH{=}NH$	CH_3	$CH_2C_6H_5$	104.5–109[c]	42	$C_{24}H_{22}N_2O_4$	C, 71.37	71.49
							H, 5.51	5.62

[a] Uncorrected melting points were taken on a Thomas Hoover capillary melting point apparatus. [b] Microanalytical data were provided by the University of Minnesota Microanalytical Laboratory, Minneapolis. [c] Recrystallized from ethanol. [d] *Reference 24.* [e] Previously reported as an oil, (b.p. 150°, 1 mm.), *Reference 25.* [f] Mixture of diastereoisomers. [g] Analyzed as picrate. [h] Yield of base. [i] All primary aromatic amines in this series with the exceptions of compounds 2, 4, and 11 were isolated as p-nitrobenzylidene derivatives due to their instability in the free form. [j] Piperidino. [k] Analyzed as methiodide. [l] Morpholino. [m] 1-Methylpiperidino.

lation and were isolated as picrates or methiodides for analytical purposes.

The 2-p-aminophenyl dioxolanes and dioxanes (Tables I and II) were obtained by reduction of the corresponding 2-p-nitro-compounds using platinum oxide as the catalyst (13–15). In all cases where the 2-p-aminophenyl group was present, the compounds showed some degree of instability with the dioxolanes apparently being less stable than the dioxanes. All attempts at salt formation with the reduced substances failed resulting in a yellow polymeric material which was possibly due to the hydrolysis of the acetal or ketal to p-aminobenzyaldehyde and its subsequent Schiff base self-condensation (16, 17).

The Schiff bases were quite easily formed by treatment of the 2-p-aminophenyl-dioxanes and dioxolanes with p-nitrobenzaldehyde (18, 19). They were stable and the only method by which some of the primary aromatic amino compounds could be isolated without decomposition.

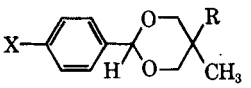
It should be noted that in all cases where the possibility of diastereoisomerism existed in preparation of these compounds it appeared to occur. However, upon preparation of methiodides or picrates from the mixture of isomers a sharp melting point was shown indicative of molecular compound formation (20, 21).

EXPERIMENTAL

The compounds prepared are listed in Tables I and II. The general preparative procedures are illustrated with specific examples.

2-p-Nitrophenyl-5-methyl-5-bromomethyl-1,3-dioxane(II,1)—A mixture of 16.5 Gm. (0.1 mole) of p-nitrobenzaldehyde, 20 Gm. (0.11 mole) of 2-methyl-2-bromomethyl-1,3-propanediol (10),

TABLE II—PHYSICAL CONSTANTS OF 1,3-DIOXANES



Compd.	X	R	M.p.[a] °C.	Yield, %	Molecular Formula	Anal., %[b] Calcd.	Found
1	NO_2	CH_2Br	111–112[c]	46.5[d]	$C_{12}H_{14}NO_4Br$	C, 45.58	45.36
						H, 4.46	4.59
2	NO_2	CH_2I	121.5–124[c]	94	$C_{12}H_{14}NO_4Br$	C, 39.68	40.08
						H, 3.88	4.09
3	NO_2	$CH_2N(C_2H_5)_2$	58–60[c]	64	$C_{16}H_{24}N_2O_4$	C, 62.31	62.29
						H, 7.79	7.89
4	p-$NO_2C_6H_4CH{=}NH$[e]	$CH_2N(C_2H_5)_2$	146–149[c]	48[f]	$C_{23}H_{29}N_3O_4$	C, 67.13	67.20
						H, 7.10	7.25
5	NO_2	$CH_2NC_5H_{10}$[g]	88–89[h]	75	$C_{17}H_{24}N_2O_4$	C, 63.73	63.93
						H, 7.55	7.33
6	NH_2	$CH_2NC_5H_{10}$[g]	122–123[h]	23	$C_{17}H_{26}N_2O_2$	C, 70.34	70.61
						H, 9.05	9.11
7	p-$NO_2C_6H_4CH{=}NH$[e]	$CH_2NC_5H_{10}$[g]	150–153[c]	46	$C_{24}H_{29}N_3O_4$	C, 67.83	67.57
						H, 6.90	7.07
8	NO_2	$CH_2NC_4H_8O$[i]	146–149[c]	39	$C_{16}H_{22}N_2O_5$	C, 59.59	59.51
						H, 6.88	7.05
9	NH_2	$CH_2NC_4H_8O$[i]	129–132[c]	91	$C_{16}H_{24}N_2O_3$	C, 67.73	66.05
						H, 8.27	8.43
10	p-$NO_2C_6H_5CH{=}NH$[e]	$CH_2NC_4H_8O$[i]	184–186[c]	51	$C_{23}H_{27}N_3O_5$	C, 64.93	64.91
						H, 6.39	6.54

[a] Uncorrected melting points were taken on a Thomas-Hoover capillary melting point apparatus. [b] Microanalytical data were provided by the University of Minnesota Microanalytical Laboratory, Minneapolis. [c] Recrystallized from ethanol. [d] A second fraction, m.p. 52–76°, was isolated which gave correct analysis and was presumably the second diastereoisomer. [e] Primary aromatic amines isolated as stable p-nitrobenzylideneanilino-derivatives. [f] Yield based on weight of compd. 3 used in reduction. [g] Piperidino. [h] Recrystallized from methanol. [i] Morpholino.

one crystal of p-toluenesulfonic acid, and 100 ml. of benzene was refluxed (11, 22) for 20 hr. in a flask to which a Dean Stark water trap (23) was attached. The warm mixture was filtered and shaken out three times with 10% sodium carbonate followed by distilled water. The benzene was removed *in vacuo* and the resultant solid dissolved in 350 ml. of ethanol. The precipitate was collected and recrystallized from ethanol yielding 17.0 Gm. (46.5%), m.p. 111–112°.

2-p-Nitrophenyl-4-diethylaminomethyl-1,3-dioxolane (I, 6)—A solution of 14.4 Gm. (0.05 mole) of 2-p-nitrophenyl-4-bromomethyl-1,3-dioxolane and 14.6 Gm. (0.20 mole) of diethylamine in 50 ml. of benzene was heated in a pressure bottle on a steam bath for 6 days (2–4). The diethylamine hydrobromide was removed by filtration and the solvent and excess diethylamine evaporated. The resultant oil was taken up into 100 ml. of benzene followed by extraction with 10% citric acid. The acidic extracts were neutralized with solid sodium carbonate. The oily amine was again dissolved in benzene and the preceding acid-base extraction repeated twice more. The amine was taken up in ether and dried with anhydrous sodium sulfate. Upon evaporation of the ether 9.9 Gm. (70%) of a yellow oil, n_D^{21} 1.5262, was obtained which was found to decompose on attempted distillation (0.5 mm.). A picrate (m.p. 165°) was prepared for analysis by adding dropwise an ethanolic solution of picric acid to a solution of the amine in ethanol.

2-p-Aminophenyl-4-(1-piperidylmethyl)-1,3-dioxolane (Not Isolated)—A solution of 2.1 Gm. of 2-p-nitrophenyl-4-(1-piperidylmethyl)-1,3-dioxolane in 50 ml. of absolute ethanol with 100 mg. of platinum oxide (13) was reduced on the Parr hydrogenator (15) at 30 lb. pressure and the shaking stopped when the calculated amount of hydrogen had been taken up. The catalyst was removed by filtration, the solvent removed *in vacuo*, and the pale yellow oil used immediately for preparation of the Schiff base. All attempts at salt preparation failed.

2-[4-(N-4'-Nitrobenzylideneanilino)]-4-(1-piperidylmethyl)-1,3-dioxolane (I, 9)—An equimolar quantity of p-nitrobenzaldehyde (995 mg.) was added to the 2-p-aminophenyl-4-(1-piperidylmethyl)-1,3-dioxolane obtained from the preceding step and the mixture heated under reduced pressure on a water bath (18, 19). After 15 min. the oil had turned bright orange. It was removed from the water bath and refluxed for 20 min. with 10 ml. of ethanol. The Schiff base began to crystallize as bright gold needles on cooling to room temperature and on recrystallization from absolute ethanol yielded 1.5 Gm. (55%), m.p. 90–105°.

2-p-Aminophenyl-4-(4-morpholinomethyl)-1,3-dioxolane(I, 11)—A solution of 6.35 Gm. of 2-p-nitrophenyl-4-(4-morpholinomethyl)-1,3-dioxolane in 30 ml. of absolute ethanol with 100 mg. of platinum oxide (13) was reduced on the Parr hydrogenator (15) at 30 lb. pressure until hydrogen uptake ceased (about 10 min.). The resulting mixture was filtered through a sintered-glass filter to remove catalyst and the filtrate placed in the deep freeze. After 2 weeks a white crystalline precipitate was noted which was removed and recrystallized three times from absolute ethanol, yielding 4.8 Gm. (82.5%) of small white plates, m.p. 104–114°. The infrared spectrum showed the presence of a primary aromatic amino group.

MICROBIOLOGY AND PHARMACOLOGY

These series of compounds were subjected to microbiological screening on *E. coli*, *S. aureus*, two

species of Mycobacteria, *S. cerevisiae*, *C. albicans*, and *G. candidum*. None showed appreciable inhibition of any test organisms at concentrations of 100 mcg./ml.

None of the compounds had surface anesthetic activity when tested in the rabbit's eye.

Intracutaneous injection of a 0.25% solution of compound 13 (Table I) in guinea pigs caused anesthesia of 30 min. duration.

REFERENCES

(1) Fourneau, E., Bovet, D., Bovet, F., and Mentezin, G., *Bull. Soc. Chim. Biol.*, **26**, 516(1944).
(2) Blicke, F. F., and Anderson, F. E., *J. Am. Chem. Soc.*, **74**, 1733(1952).
(3) Blicke, F. F., and Schumann, E. L., *ibid.*, **74**, 2613 (1952).
(4) Blicke, F. F., and Milleson, H. E., *ibid.*, **77**, 32(1955).
(5) Hardie, W. R., Halverstadt, I. F., and Allen, R. E., Abstracts of Papers, Am. Chem. Soc., 141st meeting, March 1962, p. 2N.
(6) Ing, H. R., and Ormerod, W. E., *J. Pharm. Pharmacol.*, **4**, 21(1952).
(7) "Selective Toxicity," Albert, A., 2nd ed., John Wiley & Sons, New York, N. Y., 1960, p. 51.
(8) Hirsch, J., *Science*, **96**, 1942(1942).
(9) Kuhn, R., Moeller, E., and Wendt, G., *Ber.*, **76**, 1044(1943).
(10) Barbiere, J., and Matti, J., *Bull. Soc. Chim.*, **5**, 1565 (1938).
(11) Salmi, E. J., and Kyrki, K., *Suomen Kemistilehti*, **19B**, 97(1946); through *Chem. Abstr.*, **41**, 5480c(1947).
(12) Blicke, F. F., and Schumann, E. L., *J. Am. Chem. Soc.*, **76**, 1226 (1954).
(13) Adams, R., Cohen, F. L., and Rees, O. W., *ibid.*, **49**, 1093(1927).
(14) Adams, R., and Hiers, R. S., *ibid.*, **49**, 1099(1927).
(15) Gilman, H., and Blatt, A. H., "Organic Synthesis," Coll. vol. I, 2nd ed., John Wiley & Sons, New York, N. Y., 1956, p. 240.
(16) Tipston, R. S., *J. Med. Chem.*, **6**, 217(1963).
(17) Rabjohn, N., "Organic Synthesis," Coll. vol. IV, John Wiley & Sons, New York, N. Y., 1963, p. 32.
(18) Hantzsch, A., and Schwab, O., *Ber.*, **34**, 282(1901).
(19) Gilman, H., and Blatt, A. H., "Organic Synthesis," Coll. vol. I, John Wiley & Sons, New York, N. Y., 1956, p. 80.
(20) Belleau, B., and Triggle, D. J., *Can. J. Chem.*, **40**, 1201(1962).
(21) Belleau, B., and Puranen, J., *J. Med. Chem.*, **6**, 325 (1963).
(22) Salmi, E. J., Ulla-Maija, T., and Louhenkurbi, P., *Suomen Kemistilehti*, **20B**, 1(1947); through *Chem. Abstr.*, **42**, 537g(1948).
(23) Dean, E. W., and Stark, D. D., *J. Ind. Eng. Chem.*, **12**, 485(1920).
(24) Hibbert, M., and Carter, N. M., *J. Am. Chem. Soc.*, **50**, 3374(1928).
(25) McQueen, D. M., and Woodward, D. W., U. S. pat. 2,481,434 (1949).

Keyphrases

1,3-dioxolanes, basically substituted—synthesis
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Azeotropic distillation reaction—acid catalyzed
Microbiological screening
Anesthesia, local—screening

Dissolution Rates in Surfactant Solutions Under Stirred and Static Conditions

By M. GIBALDI, S. FELDMAN, R. WYNN, and N. D. WEINER*

The dissolution rate of benzoic acid was determined in water and solutions of polyoxyethylene (23) lauryl ether by the rotating disk and static disk methods. The results under stirred and static conditions substantially deviated from the Noyes-Whitney equation. Dissolution rates in surfactant solutions were much less than anticipated on the basis of solubilization data. The ratios of dissolution rate in surfactant solution to that in pure solvent were found to be significantly greater under static conditions as compared to the ratios determined under stirred conditions, suggesting a possible change in dissolution mechanism. Certain aspects of dissolution rate theory are explored to explain this unusual phenomenon.

THE INFLUENCE of interacting colloids such as polymers or micellar aggregates on drug solubility has been investigated extensively and the literature contains numerous reports concerning drug solubilization in colloidal systems. However, only a limited amount of information is available on the influence of solubilization on dissolution rate.

Taylor and Wurster (1) found significant increases in both the solubility and dissolution rate of various forms of prednisolone in 0.1% solutions of sodium lauryl sulfate. Since this concentration is considerably below the critical micelle concentration (CMC) and since the extent of solubiliza-

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