[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, PITMAN-MOORE COMPANY, DIVISION OF ALLIED LABORATORIES, INC.]

Some Ethers Derived from Diethylaminoethyl Benzilate[1]

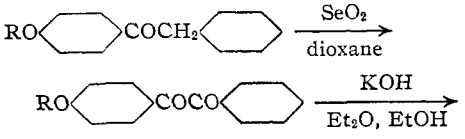
BY EARL R. BOCKSTAHLER AND DONALD L. WRIGHT

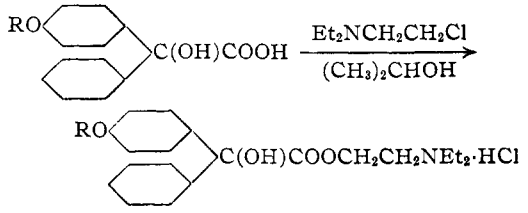
In studies of local anesthetics, it has been demonstrated repeatedly that introducing or varying an alkoxy group on a benzene ring can affect pharmacologic action markedly. For example, the introduction of a butoxy group in one recent instance[2] and of a cyclohexyloxy group in another[3] produced compounds having far greater potency and duration of anesthetic action than was possessed by the ethoxy, methoxy or unsubstituted analogs. Toxicity may or may not be correspondingly altered.

The structural resemblance of the ester type of local anesthetic to antispasmodic aminoalkyl esters suggests that similar enhancement of antispasmodic activity may be possible. Other than scattered instances of methoxy substitution, no data appear to be available in the literature for testing the validity of this conjecture. We therefore undertook the preparation of a homologous series of alkoxy-substituted esters which might be expected to be sufficiently active as antispasmodics to permit judgement on this question.

Diethylaminoethyl benzilate was selected as the parent compound. This substance is known to possess both antispasmodic[4] and local anesthetic[5] as well as mydriatic[6] properties. The 4,4′-dimethoxy derivative has been reported to be inferior to its parent as an antispasmodic.[4] Substitutions which produced the 2,2′-dimethoxy, 3,4,3′,4′-bis-(methylenedioxy), 5,5′-dibromo-2,2′-dimethoxy and 3,3′,4,4′-tetramethoxy derivatives, as ethochlorides, resulted in great reduction or abolition of mydriatic activity.[7]

As a test series, we prepared, as hydrochlorides, ten diethylaminoethyl 4-alkoxybenzilates, in which the number of carbon atoms in the alkyl group was varied from one to seven (Table I). They were obtained from appropriately substituted desoxybenzoins, by the route





For preliminary pharmacological evaluation of these compounds we are indebted to F. H. Schultz, Jr.,[8] W. M. Alexander and W. K. McDonald, of the pharmacology division of this Laboratory, with whose permission we are presenting summarized data. Their results, including additional studies, will be published in detail elsewhere.

As is shown in Table I, the supposition that it would be possible to enhance antispasmodic activity by a suitable choice of alkoxy substituent is not borne out in this series. Activity drops abruptly upon the introduction of a methoxy group, and although some of the later members return to as high a level as the parent compound, none surpass it. A peak is reached with the *n*-amoxy derivative, which possesses activity on the normal gut and against histamine equal to that of the unsubstituted benzilate. Its activity against acetyl-β-methylcholine is two-fifths of that of the parent, and its acute toxicity about half as great.

Enhancement of local anesthetic activity by appropriate alkoxy substitution is clearly apparent, however. A maximum was reached with the *n*-hexyloxy derivative, which produced anesthesia of twenty to thirty minutes duration when applied in 0.01% concentration. At a concentration of 0.25%, which caused temporary irritation (complete recovery by the following day), the duration of anesthesia was approximately three hours.

Because of this favorable finding, nine additional esters containing a variety of nuclear ether substituents were prepared and tested for local anesthetic activity. None was found to surpass the *n*-hexyloxy derivative.

It will be noted that each of the esters except the dibutoxy derivative contains an asymmetric carbon atom. No attempt to resolve these racemic mixtures was made.

Experimental[9,10]

Desoxybenzoins (Table II, A).—The monosubstituted desoxybenzoins, with the exception of the methoxy and

(1) Presented before the Division of Medicinal Chemistry at the 115th meeting of the American Chemical Society at San Francisco, California, March 29, 1949.

(2) M. B.Moore, *J. Am. Pharm. Assoc.*, **33**, 193 (1944).

(3) S. M. McElvain and T. P. Carney, THIS JOURNAL, **68**, 2592 (1946).

(4) *E. g.*, R. R. Burtner and J. W. Cusic, *ibid.*, **65**, 262 (1943).

(5) *E. g.*, A. Gilman, *et al.*, *J. Pharmacol.*, **74**, 290 (1942).

(6) *E. g.*, F. F. Blicke and C. E. Maxwell, THIS JOURNAL, **64**, 428 (1942).

(7) A. H. Ford-Moore, *J. Chem. Soc.*, 952 (1947).

(8) Present address: Commercial Solvents Corporation, Terre Haute, Indiana.

(9) Analyses by Oakwold Laboratories and Dr. Carl Tiedcke.

(10) Melting points are uncorrected.

TABLE I

2-DIETHYLAMINOETHYL BENZILATE HYDROCHLORIDES

$R(R'C_6H_4)C(OH)COOCH_2CH_2N(C_2H_5)_2 \cdot HCl$

R	R′	Yield, %	M. p., °C.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	LD_{50},[a] mice, i. p. mg./kg.	Local anesthesia,[b] % MAC[d]	Local anesthesia,[b] % MNIC[e]	Spasmolytic index[c] Normal[f]	Spasmolytic index[c] ABMC[g]	Spasmolytic index[c] Histamine[h]
H	H			$C_{20}H_{25}NO_3 \cdot HCl$					112	0.12	0.12	1	1	1
4-$CH_3OC_6H_4$	H	77	169–171	$C_{21}H_{27}NO_4 \cdot HCl$	64.03	63.97	7.16	7.40	75	.1	.1	0.01	0.04	0.2
4-$C_2H_5OC_6H_4$	H	79	173–174	$C_{22}H_{29}NO_4 \cdot HCl$	64.61	65.03	7.40	7.62	155	.25	< .1	.1	.04	.1
4-*n*-$C_3H_7OC_6H_4$	H	68	140–142	$C_{23}H_{31}NO_4 \cdot HCl$	65.45	65.47	7.65	7.91	228	.1	< .05	.1	.04	.5
4-iso-$C_3H_7OC_6H_4$	H	81	161–162	$C_{23}H_{31}NO_4 \cdot HCl$	65.45	65.41	7.65	8.08	143	.05	.05			.33
4-*n*-$C_4H_9OC_6H_4$	H	69	147–148	$C_{24}H_{33}NO_4 \cdot HCl$	66.10	66.18	7.86	8.20	256	.1	< .05	1	.2	1
4-iso-$C_4H_9OC_6H_4$	H	68	140–142	$C_{24}H_{33}NO_4 \cdot HCl$	66.10	65.97	7.86	7.69	136	.05	.05	0.01		0.5
4-*n*-$C_5H_{11}OC_6H_4$	H	79	136–137	$C_{25}H_{35}NO_4 \cdot HCl$	66.73	66.79	8.06	8.24	(230)[i]	.025	.025	1	.4	1
4-iso-$C_5H_{11}OC_6H_4$	H	37	133–135	$C_{25}H_{36}NO_4 \cdot HCl$	66.73	66.58	8.06	8.29	176	.025	.05	.1	.2	0.5
4-*n*-$C_6H_{13}OC_6H_4$	H	71	123–125	$C_{26}H_{37}NO_4 \cdot HCl$	67.30	67.20	8.24	8.61	148	.01	.025	.1	.25	1
4-*n*-$C_7H_{15}OC_6H_4$	H	67	130–132	$C_{27}H_{39}NO_4 \cdot HCl$	67.83	67.76	8.43	8.48	(235)[i]	.025	.025	.1		
4-*n*-$C_8H_{17}OC_6H_4$	H	55	126–127	$C_{28}H_{41}NO_4 \cdot HCl$	68.35	68.30	8.60	8.86	(460)[i]	.5	.25			
4-*n*-$C_{10}H_{21}OC_6H_4$	H	74	124–125	$C_{30}H_{45}NO_4 \cdot HCl$	69.27	68.81	8.92	8.89	[j]	[j]	[j]			
4-$C_6H_5OC_6H_4$	H	75	152–154	$C_{26}H_{29}NO_4 \cdot HCl$	68.49	68.20	6.63	7.24	205	0.1	0.05			0.5
4-$C_6H_5CH_2OC_6H_4$	H	54	147–149	$C_{27}H_{31}NO_4 \cdot HCl$	69.00	68.80	6.86	6.82	175	.05	.05			.25
2,5-$(C_2H_5O)_2C_6H_3$	H	66	151–153	$C_{24}H_{33}NO_5 \cdot HCl$	63.76	63.65	7.58	7.85	153	.05	.1			
3,4-$(C_2H_5O)_2C_6H_3$	H	56	139–140	$C_{24}H_{33}NO_5 \cdot HCl$	63.76	63.81	7.58	7.88	124	.05	.1			
4-*n*-$C_4H_9OCH_2CH_2OC_6H_4$	H	57	116–117.5	$C_{26}H_{37}NO_5 \cdot HCl$	65.05	64.88	7.99	8.29	82	.05	.1			
4-$C_6H_5OCH_2CH_2OC_6H_4$	H	66	128–130	$C_{28}H_{33}NO_5 \cdot HCl$	67.26	66.88	6.85	6.91	(218)[i]	.025	.025	1	0.2	1
4-*n*-$C_4H_9OC_6H_4$	4-*n*-C_4H_9O	61	122–123	$C_{28}H_{41}NO_5 \cdot HCl$	66.20	66.21	8.33	8.38	(172)[i]	.025	.025			

[a] Dibucaine: 22. Atropine: 300. Papaverine: 117. [b] Dibucaine: MAC, 0.01; MNIC 0.025. [c] Minimum effective concentration of 2-diethylaminoethyl benzilate/M. E. C. of compound being tested. Atropine: normal, 1; ABMC, 2. Papaverine: normal, 0.02; ABMC, 0.0016; histamine, 0.5. [d] Minimum anesthetic concentration; rabbit cornea. [e] Maximum non-irritant concentration; rabbit cornea. [f] Isolated normal rabbit gut. [g] Isolated rabbit gut stimulated by acetyl-β-methylcholine. [h] Isolated guinea pig gut stimulated by histamine. [i] Because of its low solubility, the compound was administered for toxicity determinations in gum acacia suspension. [j] The solubility of the compound, less than 0.01%, was too low for study.

phenoxy, were prepared by refluxing 4-phenylacetylphenol in alcohol or acetone solution with the appropriate bromide or chloride in the presence of potassium carbonate. 4-Phenylacetylphenol was methylated by the use of dimethyl sulfate in aqueous alkaline solution. Phenoxydesoxybenzoin and the two diethoxy derivatives were prepared by Friedel-Crafts reaction of phenylacetyl chloride with appropriate phenol ethers under the usual conditions (aluminum chloride catalyst in carbon disulfide). 4,4′-Di-*n*-butoxydesoxybenzoin was obtained from 4,4′-di-*n*-butoxychalcone according to the scheme described by Rohrmann, Jones and Shonle[11] for lower homologs.

4-*n*-Butoxyacetophenone.—A mixture of 68 g. of 4-hydroxyacetophenone, 72 g. of *n*-butyl bromide, 72.5 g. of potassium carbonate, 8.4 g. of potassium iodide and 25 cc. of 95% ethanol was heated at 75–85° for forty-eight hours. It was then diluted with a little ether and enough water to dissolve the solids. The water layer was discarded. The oil layer was washed with dilute sodium hydroxide solution and with water, dried over sodium sulfate, and distilled, yielding 76 g. (79%) of colorless liquid boiling at 169–170° at 13 mm. *Anal.* Calcd. for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 75.09; H, 8.06.

4,4′-Di-*n*-butoxychalcone.—A mixture of 70.5 g. of 4-*n*-butoxybenzaldehyde, 76 g. of 4-*n*-butoxyacetophenone and 160 cc. of 95% ethanol was added gradually to a solution prepared from 4 g. of sodium and 40 cc. of methanol. After one hour the mixture was chilled thoroughly and filtered. The crystals were washed with water and recrystallized twice from 95% ethanol; yield, 114 g. (82%) of pale yellow crystals, m. p. 90–92°. *Anal.* Calcd. for $C_{23}H_{38}O_3$: C, 78.35; H, 8.01. Found: C, 78.05; H, 8.15.

α,β-Di-4-*n*-butoxyphenyllactic Acid.—To a stirred suspension of 112 g. of 4,4′-di-*n*-butoxychalcone in 600 cc. of 95% ethanol, 500 cc. of acetone and 41 cc. of 25% aqueous sodium hydroxide warmed to 40°, there was added gradually 98 cc. of 30% hydrogen peroxide; the temperature was kept below 45° by external cooling. After standing for one hour, the mixture was chilled and filtered. After one recrystallization from 95% ethanol, the product (63 g.) was suspended in 212 cc. of 95% ethanol and 66 cc. of 25% aqueous sodium hydroxide and boiled under reflux for three hours. The resulting solution was diluted to 2500 cc. with water and filtered. The filtrate was acidified with hydrochloric acid. The product was removed by filtration and recrystallized twice from methanol; yield, 56 g. (47%); m. p. 135–136°. *Anal.* Calcd. for $C_{23}H_{30}O_5$: C, 71.46; H, 7.82. Found: C, 71.89; H, 7.96.

4,4′-Di-*n*-butoxydesoxybenzoin.—To a stirred suspension of 55 g. of α,β-di-*n*-butoxyphenyllactic acid in 155 cc. of glacial acetic acid, there was added in small portions 99 g. of red lead oxide, at such a rate that the temperature of the mixture did not rise above 65°. The mixture was stirred for thirty minutes after addition was complete, then poured into 1500 cc. of water. The resulting precipitate was removed by filtration, washed with dilute alkali and water, and recrystallized from 95% ethanol; yield, 41 g. (85%).

Benzils (Table II, B).—The desoxybenzoin was refluxed for five to eight hours in one or two times its weight of dioxane with 1.1 molecular proportions of selenium dioxide and water. The mixture was then filtered, and the dioxane was removed by evaporation under reduced pressure. The residue solidified spontaneously, or after it had been cooled and rubbed, and was purified by recrystallization from petroleum ether or methyl, ethyl or isopropyl alcohol. Low yields in several instances are indicative, not of failure of the reaction to proceed, but rather of severe losses in recrystallization of low-melting, readily soluble substances.

Benzilic Acids (Table II, C).—A solution of the benzil in ether was allowed to stand[12] with alcoholic potash

(11) E. Rohrmann, H. G. Jones and H. A. Shonle, THIS JOURNAL, **66**, 1856 (1944).

(12) In most cases occasional shaking of the mixture sufficed for good results. A few of the benzils were not completely soluble in the specified amount of ether; in these instances, the mixture was stirred continuously.

TABLE II

INTERMEDIATE COMPOUNDS

No.	R	R′	A. Desoxybenzoins, $RCOCH_2C_6H_4R'$ Yield, %	M. p., °C.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
1	4-$CH_3OC_6H_4$	H	83	74–76	$C_{15}H_{14}O_2$			[a]	
2	4-$C_2H_5OC_6H_4$	H	81	103–104	$C_{16}H_{16}O_2$			[b]	
3	4-*n*-$C_3H_7OC_6H_4$	H	73	94–95[c]	$C_{17}H_{18}O_2$	80.30	79.86	7.13	7.42
4	4-iso-$C_3H_7OC_6H_4$	H	77	105.5–106.5	$C_{17}H_{18}O_2$			[d]	
5	4-*n*-$C_4H_9OC_6H_4$	H	93	84.5–85.5	$C_{18}H_{20}O_2$			[d]	
6	4-iso-$C_4H_9OC_6H_4$	H	47	94–94.5[e]	$C_{18}H_{20}O_2$	80.58	80.64	7.51	7.62
7	4-*n*-$C_5H_{11}OC_6H_4$	H	90	73.5–74.5	$C_{19}H_{22}O_2$	80.81	81.02	7.85	8.16
8	4-iso-$C_5H_{11}OC_6H_4$	H	65	64.5–65.5	$C_{19}H_{22}O_2$	80.81	81.18	7.85	8.22
9	4-*n*-$C_6H_{13}OC_6H_4$	H	59	76–77.5	$C_{20}H_{24}O_2$	81.04	81.22	8.16	8.32
10	4-*n*-$C_7H_{15}OC_6H_4$	H	88	70–71.5	$C_{21}H_{26}O_2$	81.25	81.00	8.44	8.36
11	4-*n*-$C_8H_{17}OC_6H_4$	H	88	69.5–70.5	$C_{22}H_{28}O_2$	81.54	80.47	8.71	8.62
12	4-*n*-$C_{10}H_{21}OC_6H_4$	H	79	70–71	$C_{24}H_{32}O_2$	81.76	81.05	9.16	9.15
13	4-$C_6H_5OC_6H_4$	H	74	88–89[f]	$C_{20}H_{16}O_2$	83.33	81.49	5.55	5.66
14	4-$C_6H_5CH_2OC_6H_4$	H	73	134.5–136	$C_{21}H_{18}O_2$			[g]	
15	2,5-$(C_2H_5O)_2C_6H_3$	H	39	51–52	$C_{18}H_{20}O_3$	76.01	75.72	7.09	7.53
16	3,4-$(C_2H_5O)_2C_6H_3$	H	48	89–91	$C_{18}H_{20}O_3$	76.01	76.24	7.09	6.93
17	4-*n*-$C_4H_9OCH_2CH_2OC_6H_4$	H	52	40–41	$C_{20}H_{24}O_3$	76.89	77.02	7.74	8.01
18	4-$C_6H_5OCH_2CH_2OC_6H_4$	H	71	123.5–124.5	$C_{22}H_{20}O_3$	79.48	79.46	6.06	5.90
19	4-*n*-$C_4H_9OC_6H_4$	4-*n*-C_4H_9O	32[h]	121–122	$C_{22}H_{28}O_3$	77.61	77.89	8.29	8.31

No.	B. Benzils, $RCOCOC_6H_4R'$ Yield, %	M. p., °C.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	C. Benzilic acid, $R(R'C_6H_4)C(OH)COOH$ Yield, %	M. p., °C.	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
1	65	61.5–63	$C_{15}H_{12}O_3$		[i]			48	147.5–149		[j]		
2	43	69.5–70.5	$C_{16}H_{14}O_3$	75.58	75.67	5.54	5.84	27	112–114	70.58	71.23	5.92	5.90
3	60	102–103	$C_{17}H_{16}O_3$	76.11	76.11	6.01	5.96	32	103–104	71.32	70.91	6.34	6.50
4	6	30–31	$C_{17}H_{16}O_3$	76.11	76.26	6.01	6.62	(15)[k]	120–122	71.32	71.63	6.34	6.72
5	52	58–59	$C_{18}H_{18}O_3$	76.59	77.08	6.43	6.24	30	85–86	72.00	72.29	6.71	6.44
6	69	68.5–69.5	$C_{18}H_{18}O_3$	76.59	76.20	6.43	6.60	39	87–89	72.00	72.00	6.71	6.96
7	20	37–38	$C_{19}H_{20}O_3$	77.00	77.41	6.80	6.55	23	90–91	72.58	72.41	7.05	6.66
8					Not obtained crystalline								
9	91	51.5–52.5	$C_{20}H_{22}O_3$	77.38	77.03	7.15	7.40	15	62–64	73.17	73.28	7.37	7.68
10	96	55–56	$C_{21}H_{24}O_3$	77.75	77.87	7.46	7.77	65	90–91	73.66	73.89	7.65	8.02
11	5	37–38	$C_{22}H_{26}O_3$	78.08	78.34	7.74	8.00	(6)[k]	68–69	74.13	73.86	7.92	8.00
12	14	37–38	$C_{23}H_{30}O_3$	78.64	78.50	8.25	8.04	40	75–77	74.95	74.59	8.39	8.54
13	69	66–67	$C_{20}H_{14}O_3$	79.46	79.53	4.67	4.22	53	127–129	75.00	74.80	5.04	5.62
14	72	95–96	$C_{21}H_{16}O_3$	79.74	79.78	5.10	4.90	73	119–120	75.42	75.43	5.42	5.28
15	76	124–126	$C_{18}H_{18}O_4$	72.48	72.66	6.08	6.44	63	111–113	68.35	68.45	6.37	6.73
16	72	122–123	$C_{18}H_{18}O_4$	72.48	72.54	6.08	5.97	71	123–124	68.35	68.24	6.37	6.22
17	88	68–69	$C_{20}H_{22}O_4$	73.51	73.70	6.80	6.56	70	81–83	69.75	69.81	7.02	7.00
18	72	106–107	$C_{22}H_{18}O_4$	76.27	76.62	5.36	5.65	60	139.5–141	72.50	72.98	5.53	5.35
19	76	88–89	$C_{22}H_{26}O_4$	74.55	74.46	7.40	7.36	63	88–90	70.97	71.26	7.58	7.96

[a] Ney, *Ber.*, **21**, 2450 (1888). [b] C. Torres, *Añales soc. españ. fís. Quím.*, **24**, 82 (1926), (*C. A.*, **20**, 2158 (1926)). [c] Valette, note *d*, gives m. p. 65–66°. [d] M. Valette, *Bull. soc. chim.*, **47**, 289 (1930). [e] Valette, note *d*, gives m. p. 62°. [f] E. R. Bockstahler, Thesis, Yale University, 1934. [g] W. D. McPhee and E. S. Erickson, THIS JOURNAL, **68**, 624 (1946). [h] Calcd. from 4,4′-di-*n*-butoxychalcone. [i] A. McKenzie, E. M. Luis, M. Tiffeneau and P. Weill, *Bull. soc. chim.*, **45**, 414 (1929). [j] E. Christie, A. McKenzie and A. Richtie, *J. Chem. Soc.* 153 (1935). [k] Calcd. from the desoxybenzoin; crude benzil was used.

at room temperature until rearrangement appeared complete, usually overnight. For each 0.1 mole of benzil, 320 cc. of ether, 8 g. of potassium hydroxide and 64 cc. of 95% ethanol were employed. The mixture was then extracted with water, and the extract acidified with hydrochloric acid, which precipitated the benzilic acid. Some unreacted benzil could occasionally be recovered from the ether layer; the recorded yields allow for this.

Our experience is in agreement with the statement of Ford-Moore[6] that "there is a strong tendency for the acid to separate in an obstinately gummy form." Even the purified acids crystallized extremely slowly, sometimes requiring several days for recrystallization, and the freshly precipitated crude products sometimes had to stand for several months before crystallization began spontaneously or after rubbing. The acids were recrystallized from benzene, petroleum ether or mixtures of the two.

2-Diethylaminoethyl Benzilate Hydrochlorides.—Equimolecular quantities of the benzilic acid and freshly distilled 2-diethylaminoethyl chloride were mixed in isopropyl alcohol (about 4 cc. for each gram of acid used), and refluxed for eight hours. The crude products crystallized from the cooled mixture directly or after dilution with ether. For purification, they were redissolved in a small volume of methanol, and isopropyl ether was added gradu-

ally until a permanent precipitate began to form. This, a high-melting impurity, was removed by filtration. The filtrate was diluted further with ether, and the desired product separated. Occasionally it was necessary to repeat this process several times to obtain a constant, sharply-melting product.

Summary

Ten new diethylaminoethyl 4-alkoxybenzilates have been prepared in the form of hydrochlorides and screened for antispasmodic potency. None possesses greater activity than diethylaminoethyl benzilate itself; the *n*-amoxy derivative is approximately as active as the latter, and has half its acute toxicity.

These and nine additional new diethylaminoethyl benzilate hydrochlorides containing various nuclear ether substituents have also been screened for local anesthetic potency. The *n*-hexyloxy derivative is the most active of the series.

Eighteen new benzilic acids, eighteen new benzils and eleven new desoxybenzoins were prepared as intermediates.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUQUESNE UNIVERSITY]

Relative Chloromethylation Rates of Some Aromatic Compounds[1]

BY H. HARRY SZMANT AND JOSEPH DUDEK

Apparently the only extensive study of relative chloromethylation rates of aromatic compounds is that of Vavon, Bolle and Calin[2]; the conclusions of that study are the only ones quoted in authoritative reviews of the chloromethylation reaction.[3] In this paper we wish to point out certain errors in the results of Vavon and co-workers, and to present what we believe to be more nearly correct relative chloromethylation rates of certain compounds studied by these authors. The rates for a few compounds not previously studied are also reported.

The chloromethylation reaction (I) is accompanied by several competitive reactions (II–IV). The situation may be illustrated with the chloromethylation of benzene.

$$C_6H_6 + CH_2O + HCl \longrightarrow C_6H_5CH_2Cl + H_2O \quad (I)$$

$$C_6H_5CH_2Cl + C_6H_6 \longrightarrow C_6H_5CH_2C_6H_5 + HCl \quad (II)$$

$$2C_6H_5CH_2Cl \longrightarrow C_6H_5CH_2C_6H_4CH_2Cl + HCl, \text{ etc.} \quad (III)$$

$$C_6H_5CH_2Cl + C_6H_5CH_2C_6H_5 \longrightarrow C_6H_5CH_2C_6H_4CH_2C_6H_5 + HCl, \text{ etc.} \quad (IV)$$

The course of the chloromethylation reaction can be followed by determining ionic chlorine at certain time intervals. However, the various side reactions liberate ionic chlorine from the initial chloromethylated product; hence to evaluate the chloromethylation rate, one must determine the rate of loss of chloride during the initial period of the reaction before the initial chloromethylation product has accumulated. In arriving at the relative chloromethylation rates in this study we have arbitrarily chosen to compare the time intervals required for the loss of ten per cent. of the initial ionic chlorine. In most of the cases studied, a linear relationship between the rate of chloride loss and elapsed time persisted to the point chosen for the comparison. In a few cases where the curve tended to bend ahead of time, the initial slope was extrapolated to the point chosen for the comparison. The relative chloromethylation rates obtained in this study are listed in Table I, together with the values obtained by Vavon and co-workers. Typical graphs showing per cent. loss of ionic chlorine with time are given in Figs. 1 and 2.

TABLE I

RELATIVE RATES OF CHLOROMETHYLATION

	Compound	$t_{10\%}$[a]	Relative rate[b]	Relative rate[c] of Vavon and co-workers
1	Benzene	9.2	1.0	1
2	Toluene	3.0	3.1	3
3	*n*-Butylbenzene	3.2	2.9	..
4	*t*-Butylbenzene	3.3	2.8	..
5	*p*-Xylene	5.7	1.6	2
6	Mesitylene	0.7	13	600
7	Diphenylmethane	12	0.77	..
8	Bromobenzene	19	0.48	..
9	Diphenyl sulfide	10.5	0.88	..
10	Diphenyl ether	6.1	1.5	100
11	Anisole	0.4	23	1334
12	*p*-Methyl cresyl ether	1.25	7.4	1200

[a] Time (in minutes) required for a 10% decrease in initial chloride concentration. [b] Relative rate ($t_{10\%}$ of benzene)/($t_{10\%}$ of compound). [c] Relative rates reported in ref. 2.

Experimental

All chloromethylation experiments were carried out by allowing 0.1 mole of the aromatic starting material, 0.11 mole of paraformaldehyde and 9 ml. of concd. hydrochloric acid (equivalent to 0.11 mole hydrogen chloride) to react in 125 ml. of glacial acetic acid. In order to avoid any reaction at temperatures other than the desired one, all the formaldehyde, hydrochloric acid and 100 ml. of the acetic acid were heated with stirring in the reaction flask until the desired temperature (85°) was reached, and then (at zero time) the preheated mixture of the compound under study was added in 25 ml. of acetic acid. Samples (2 ml.) were withdrawn from the reaction mixture at desired intervals

(1) Presented at the San Francisco meeting of the American Chemical Society, March, 1949.

(2) Vavon, Bolle and Calin, *Bull. soc. chim.*, **6**, 1025 (1939).

(3) Fuson and McKeever, in "Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1942, Vol. I, p. 66.