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New Amebacides. IV.[1] The Preparation of Some N-Benzyl-N-(2-carbamylethyl)- and N-Benzyl-N-(2-cyanoethyl)-haloacetamides

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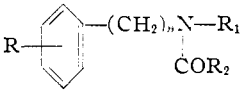
The preparation of a series of N-(2-cyanoethyl)- and N-(2-carbamylethyl)-benzylamines is described. These intermediates have been treated with chloro-, dichloro- and trichloroacetyl chloride to give the corresponding haloacetamides. Many of these amides have been found to possess considerable amebacidal activity when tested in hamsters (*Endameba criceti*).

The present communication deals with the preparation of potential amebacidal agents of the general formula



in which R_1 is $CH_2CH_2CONH_2$ or CH_2CH_2CN; R_2 is CH_2Cl, $CHCl_2$ or CCl_3 and n is 1 or 2. The physical properties of these compounds are described in Tables III and IV.

The benzylamines employed in the present work were prepared either by reductive amination of the appropriate benzaldehyde with alcoholic ammonia or *via* the Delépine reaction from the available benzyl chlorides. Yields in both methods were very satisfactory. Those phenylethylamines which were not available were prepared by reduction of the corresponding phenylacetonitriles with Raney nickel in methanolic ammonia solution.

Carbamylethylation and cyanoethylation of the arylalkylamines were carried out by allowing the amines to stand at room temperature for several days with approximately equimolar quantities of acrylamide or acrylonitrile. The N-(2-cyanoethyl)-benzylamines were vacuum distilled directly to give yields ranging from 70–95% (Table I). The reaction of acrylonitrile with a 50% excess of benzylamine resulted in a quantitative yield of N-(2-cyanoethyl)-benzylamine.[2] For the N-(2-carbamylethyl)-benzylamines (Table II) the best yields were obtained when the products were isolated as the hydrochloride salts. This was accomplished by adding the calculated amount of alcoholic hydrogen chloride in four parts to an acetone solution of the reaction mixture and filtering the product after each addition. In several instances the addition of the last portion of hydrogen chloride resulted in the formation of an intractable gum which was discarded.

An N-substituted propionamide, N-[2-(ethylcarbamyl)-ethyl]-4-isopropylbenzylamine, was prepared by treating N-(2-carbomethoxyethyl)-4-isopropylbenzylamine with anhydrous ethylamine. The dichloroacetamide prepared from this product was obtained as a viscous oil which could not be distilled.

The amides listed in Tables III and IV were prepared from the corresponding amines by treatment with chloroacetyl chloride, dichloroacetyl chloride or trichloroacetyl chloride in the presence of dilute sodium hydroxide solution. An attempt to prepare the trichloroacetamide of the N-(2-cyanoethyl)-4-isopropylbenzylamine using methyl trichloroacetate was unsuccessful[3]; practically all of the starting amine was recovered.

The dichloroacetamides of both the N-(2-cyanoethyl)- and N-(2-carbamylethyl)-benzylamines showed good activity when tested against intestinal amebiasis in hamsters. In general, however, the activities were not in the same range as those found for the N-benzyl-N-(2-hydroxyethyl)-dichloroacetamides.[3] The one exception was the N-(2-carbamylethyl)-N-(2,4-dichlorobenzyl)-dichloroacetamide which was more effective than the corresponding N-(2-hydroxyethyl) compound. Although only a few monochloroacetamide and trichloroacetamide derivatives were investigated the results indicated that for the most part they were much less active as antiamebic agents than the dichloroacetamides. Similarly, it has been found that the homologous N-phenylethyl compounds were much less active than the corresponding N-benzyl derivatives.

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Experimental[4]

4-Butoxybenzylamine.—A 117-g. (0.65 mole) sample of 4-butoxybenzaldehyde in 400 ml. of 13% methanolic ammonia was reduced in the presence of 15 g. of Raney nickel at 70° and at a hydrogen pressure of 1000 p.s.i. The reduction was complete in 5.5 hours. The catalyst was filtered off and the solvent evaporated. Distillation of the resulting oil gave 71 g. (61%) of product, b.p. 95–100° (0.05 mm.), $n^{25}D$ 1.5192.[5]

Anal. Calcd. for $C_{11}H_{17}NO$: N_{AP}, 7.82. Found: N_{AP}, 7.74.

2,4-Dichlorobenzylamine.—A mixture of 195 g. (1 mole) of 2,4-dichlorobenzyl chloride and 155 g. (1.1 moles) of hexamethylenetetramine in one liter of chloroform was refluxed with stirring for 18 hours. The hexamethylenetetramine salt was obtained in 98% yield from the reaction mixture, m.p. 188–191° dec.

Anal. Calcd. for $C_{13}H_{17}Cl_3N_4$: Cl^-, 10.56. Found: Cl^-, 10.42.

The quaternary salt was added to one liter of 6 *N* hydrochloric acid and the mixture steam distilled. After three liters of distillate had been collected the residue was made strongly alkaline with 35% sodium hydroxide solution and extracted with benzene. The benzene solution was dried and the solvent evaporated. Distillation of the resulting oil gave 126 g. (71%) of the product,[6] b.p. 140° (122 mm.), $n^{25}D$ 1.5738.

(1) For previous paper, see THIS JOURNAL, **77**, 5406 (1955).

(2) J. A. King and F. H. McMillan, *ibid.*, **68**, 1468 (1946).

(3) A. R. Surrey, *ibid.*, **76**, 2214 (1954).

(4) All melting points are corrected unless labeled otherwise. The symbol NAP indicates determination of basic nitrogen.

(5) M. Metayer and Ng. Dat-Xuong, *Bull. soc. chim.*, 615 (1954) prepared this compound in a similar manner in 70% yield. Their product was isolated as the hydrochloride salt, m.p. 285°.

(6) Ref. 5. Prepared in 8% yield by reduction of 2,4-dichlorobenzaldehyde with ammonia.

TABLE I

N-(2-CYANOETHYL)-PHENYLALKYLAMINES[a] R—C$_6$H$_4$—(CH$_2$)$_n$NHCH$_2$CH$_2$CN

R	n	Yield, %	B.p. °C.	B.p. Mm.	n^{25}D	Formula	Nitrogen, % Calcd.	Nitrogen, % Found
H	1	100[b]	124	0.9	1.5348	$C_{10}H_{12}N_2$	8.75	8.76[c]
4-CH_3	1	74	123	.7	1.5254	$C_{11}H_{14}N_2$	16.08	15.81
4-$CH(CH_3)_2$	1	91	102	.07	1.5164	$C_{13}H_{18}N_2$	6.92	6.85[c]
4-Cl	1	83	120	.07	1.5407	$C_{10}H_{11}ClN_2$	7.20	7.07[c]
2,4-Cl_2	1	77	158	1	1.5563	$C_{10}H_{10}Cl_2N_2$	6.11	6.09[c]
3,4-Cl_2	1	97	165	0.8	1.5533	$C_{10}H_{10}Cl_2N_2$	12.23	12.13
4-OC_4H_9	1	94	138	.05	1.5158	$C_{14}H_{20}N_2O$	12.06	12.01
2,3-$(OCH_3)_2$	1	73	125	.06	1.5283	$C_{12}H_{16}N_2O_2$	6.36	6.32[c]
3,4-$(OCH_3)_2$	1	79	158	.05	1.5393	$C_{12}H_{16}N_2O_2$	12.72	12.69
3,4-(O_2CH_2)	1	79	127	.03	1.5449	$C_{11}H_{12}N_2O_2$	6.86	6.79[c]
H[d]	2	96	133	.08	1.5248	$C_{11}H_{14}N_2$	8.04	8.18[c]
4-CH_3	2	92	130	.5	1.5210	$C_{12}H_{16}N_2$	7.44	7.42[c]
4-Cl	2	87	110	.03	1.5363	$C_{11}H_{13}ClN_2$	13.42	13.28
2,4-Cl_2	2	65	130	.3	1.5495	$C_{11}H_{12}Cl_2N_2$	11.58	11.58
4-OCH_3	2	88	118	.07	1.5292	$C_{12}H_{16}N_2O$	13.71	13.52
3-OCH_3	2	86	128	.05	1.5285	$C_{12}H_{16}N_2O$	13.71	13.68

[a] N-(2-Cyanoethyl)-furfurylamine is described in the experimental. [b] Lit.[2] 73% yield, b.p. 184–185° (23 mm.). [c] Determination of basic nitrogen. [d] J. Delay, P. Pichart, J. Thuillier and J. P. Marquiset, *Compt. rend. soc. biol.*, **146**, 533 (1952). This compound was listed but not described.

TABLE II

N-(2-CARBAMYLETHYL)-PHENYLALKYLAMINE HYDROCHLORIDES R—C$_6$H$_4$—(CH$_2$)$_n$NHCH$_2$CH$_2$CONH$_2$·HCl

R	n	M.p., °C.	Yield, %	Formula (base)	Analyses, % Chloride Calcd.	Chloride Found	Nitrogen Calcd.	Nitrogen Found
H	1	202–203[a,b]	89	$C_{10}H_{14}N_2O$	16.52	16.42	13.05	13.15
4-CH_3	1	188–190[b,c]	83	$C_{11}H_{16}N_2O$	15.50	15.32		
4-$CH(CH_3)_2$	1	217–218.8[d]	84	$C_{13}H_{20}N_2O$	13.81	13.82	[e]	
4-Cl	1	220.1–221.2	48	$C_{10}H_{13}ClN_2O$	14.24	14.33	11.25	11.26
2,4-Cl_2	1	164.5–166[b]	85	$C_{10}H_{12}Cl_2N_2O$	12.50	12.23		
4-OC_4H_9	1	200–203[b,f]	100	$C_{14}H_{22}N_2O_2$	12.36	12.27		
3,4-$(OCH_3)_2$	1	218.9–220.8	73	$C_{12}H_{18}N_2O_3$	12.90	12.95	10.20	10.42
H	2	181.3–182.7	77	$C_{11}H_{16}N_2O$	15.48	15.28	12.25	12.32

[a] Base boiled at 174° (0.8 mm.), melted at 85–87° (uncor.). [b] Uncorrected. [c] Base melted at 101–103° (uncor.). [d] Base melted at 71–73° (uncor.). [e] *Anal.* Calcd.: C, 60.80; H, 8.24. Found: C, 60.89; H, 8.37. [f] Base melted at 89–91° (uncor.).

Anal. Calcd. for $C_7H_7Cl_2N$: N_{AP}, 7.96. Found: N_{AP}, 7.84.

The hydrochloride melted at 282.1–284.3° (lit.[5] m.p. 275°).

Anal. Calcd. for $C_7H_7Cl_2N$·HCl: Cl^-, 16.69. Found: Cl^-, 16.62.

3,4-Dichlorobenzylamine.—This compound was prepared in a similar manner as above from 3,4-dichlorobenzyl chloride, yield 71%, m.p. 88° (0.5 mm.), n^{25}D 1.5722 (lit.[5] 64% yield by reduction of 3,4-dichlorobenzaldehyde with ammonia, b.p. 139–140° (17 mm.)).

Anal. Calcd. for $C_7H_7Cl_2N$: N_{AP}, 7.96. Found: N_{AP}, 7.77.

The hydrochloride melted at 239.9–241.9° (lit.[5] m.p. 244°).

Anal. Calcd. for $C_7H_7Cl_2N$·HCl: Cl^-, 16.69. Found: Cl^-, 16.47.

2,4-Dichlorophenethylamine.—A 106-g. (0.57 mole) sample of 2,4-dichlorophenylacetonitrile in 600 ml. of 13% methanolic ammonia was reduced in the presence of 15 g. of Raney nickel at 30° and at a hydrogen pressure of 1000 p.s.i. The reduction was complete in 4 hours. The catalyst was filtered off and the solvent was removed under reduced pressure. The resulting oil was fractionally distilled, 49 g. (45%), b.p. 100–102° (0.3 mm.), n^{25}_D 1.5618 (lit.[7] b.p. 164–165° (15 mm.)).

(7) E. Muller, *Angew. Chem.*, **61**, 179 (1949).

Anal. Calcd. for $C_8H_9Cl_2N$: N_{AP}, 7.37. Found: N_{AP}, 7.28.

N-(2-Cyanoethyl)-2-furfurylamine.—The following is an example of the general procedure employed for the preparation of the N-(2-cyanoethyl)-benzylamines (see Table I).

A mixture of 9.7 g. (0.1 mole) of furfurylamine and 6.4 g. (0.12 mole) of acrylonitrile was allowed to stand at room temperature for one week. After heating on a steam-bath for one-half hour the mixture was distilled and the fraction boiling at 97–99° (0.9 mm.) was collected, 12 g. (80%), n^{25}D 1.4846.

Anal. Calcd. for $C_8H_{10}N_2O$: N, 18.64. Found: N, 18.38.

The reaction time was varied from three to seven days in the preparation of the other 2-cyanoethylamines.

N-(2-Carbamylethyl)-2,4-dichlorobenzylamine Hydrochloride.—The following is an example of the general procedure employed for the preparation of the N-(2-carbamylethyl)-benzylamines (see Table II).

A mixture of 19.4 g. (0.11 mole) of 2,4-dichlorobenzylamine and 9.3 g. (0.13 mole) of acrylamide was warmed gently until solution was complete and then left at room temperature for seven days. The solid mixture was taken up in 500 ml. of acetone and 5 *N* alcoholic hydrogen chloride was added in 5-ml. portions. The precipitate was collected from each fraction before the following portion of acid was added. Fraction (1) 10 g., m.p. 158–163°; (2) 11 g., m.p. 160–162°; (3) 5.5 g., m.p. 153–160°; (4) an intractable gum

TABLE III

N-(2-CYANOETHYL)-N-PHENYLALKYL-HALOACETAMIDES[a] R—C$_6$H$_4$—(CH$_2$)$_n$NCH$_2$CH$_2$CN, COR′

R	n	R′	Yield, %	M.p., °C.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
4-CH(CH$_3$)$_2$	1	CH$_2$Cl	67	62.1–66.2	C$_{15}$H$_{19}$ClN$_2$O	64.61	64.38	6.87	7.10	Cl, 12.71	12.65
2,4-Cl$_2$	1	CH$_2$Cl	42	68.5–69.9	C$_{12}$H$_{11}$Cl$_3$N$_2$O	47.16	47.25	3.63	3.63	9.16	9.14
3,4-(OCH$_3$)$_2$	1	CH$_2$Cl	78	74.4–79.1	C$_{14}$H$_{17}$ClN$_2$O$_3$	56.64	56.55	5.77	5.42	Cl, 11.96	12.25
H	1	CHCl$_2$	93	77.0–79.5	C$_{12}$H$_{12}$Cl$_2$N$_2$O	53.15	53.02	4.46	4.63	Cl. 26.15	26.26
4-CH$_3$	1	CHCl$_2$	74	80.1–83.7	C$_{13}$H$_{14}$Cl$_2$N$_2$O	54.74	54.43	4.95	5.26	9.83	9.93
4-CH(CH$_3$)$_2$	1	CHCl$_2$	83	107.9–111.6	C$_{16}$H$_{18}$Cl$_2$N$_2$O	57.52	57.79	5.79	5.52	Cl, 22.64	22.34
4-Cl	1	CHCl$_2$	82	*b*	C$_{12}$H$_{11}$Cl$_3$N$_2$O	47.16	47.06	3.63	3.60	Cl, 34.80	34.67
2,4-Cl$_2$	1	CHCl$_2$	48	116.7–118.4	C$_{12}$H$_{10}$Cl$_4$N$_2$O			Cl,[c] 20.86	20.60	8.24	8.25
3,4-Cl$_2$	1	CHCl$_2$	84	90.2–92.9	C$_{12}$H$_{10}$Cl$_4$N$_2$O			Cl,[c] 20.86	20.95	8.24	8.23
4-OC$_4$H$_9$	1	CHCl$_2$	65	93.9–95.5	C$_{16}$H$_{20}$Cl$_2$N$_2$O$_2$	55.99	56.20	5.87	6.12	8.16	8.12
2,3-(OCH$_3$)$_2$	1	CHCl$_2$	95	70.8–73.2	C$_{14}$H$_{16}$Cl$_2$N$_2$O$_3$	50.77	51.05	4.87	5.19	8.46	8.33
3,4-(O$_2$CH$_2$)	1	CHCl$_2$	88	90.9–93.9	C$_{13}$H$_{12}$Cl$_2$N$_2$O$_3$	49.55	49.77	3.84	3.76	8.89	8.82
H	2	CHCl$_2$	87	59.7–61.6	C$_{13}$H$_{14}$Cl$_2$N$_2$O	54.74	55.00	4.95	5.18	Cl, 24.86	25.49
4-CH$_3$	2	CHCl$_2$	79	64.3–68.0	C$_{14}$H$_{16}$Cl$_2$N$_2$O	56.20	56.29	5.39	5.46	9.37	9.31
4-Cl	2	CHCl$_2$	86	89.9–93.9	C$_{13}$H$_{13}$Cl$_3$N$_2$O	48.85	48.63	4.10	3.96	Cl[c], 22.19	22.24
2,4-Cl$_2$	2	CHCl$_2$	69	92.3–95.6	C$_{13}$H$_{12}$Cl$_4$N$_2$O	44.10	43.79	3.42	3.37	7.92	7.87
3-OCH$_3$	2	CHCl$_2$	86	*d*	C$_{14}$H$_{16}$Cl$_2$N$_2$O$_2$	53.35	53.86	5.12	4.75	8.89	8.83
4-OCH$_3$	2	CHCl$_2$	92	56.5–>66°	C$_{14}$H$_{16}$Cl$_2$N$_2$O$_2$	53.35	53.20	5.12	5.25	8.89	8.84
4-CH(CH$_3$)$_2$	1	CCl$_3$	86	47.1–50.2	C$_{15}$H$_{17}$Cl$_3$N$_2$O	51.82	51.97	4.93	4.94	Cl, 30.60	30.50
4-Cl	1	CCl$_3$	91	84.8–86.9	C$_{12}$H$_{10}$Cl$_4$N$_2$O	42.38	42.55	2.97	3.17	8.24	8.29
3,4-Cl$_2$	1	CCl$_3$	92	94.8–98.7	C$_{12}$H$_9$Cl$_5$N$_2$O			Cl, 47.33	47.48	7.48	7.55

[a] N-(2-Cyanoethyl)-N-furfuryldichloroacetamide is described in the experiment. [b] B.p. 180–185° (0.03 mm.), solidified on standing. [c] Determination of readily hydrolyzable chlorine. [d] Obtained as an impure oil, a sample of which decomposed on distillation.

TABLE IV

N-(2-CARBAMYLETHYL)-N-PHENYLALKYL-HALOACETAMIDES R—C$_6$H$_4$—(CH$_2$)$_n$NCH$_2$CH$_2$CONH$_2$, COR′

R	n	R′	Yield, %	M.p., °C.	Formula	Analyses, % Chlorine Calcd.	Chlorine Found	Nitrogen Calcd.	Nitrogen Found
4-CH(CH$_3$)$_2$	1	CH$_2$Cl	82	78.3–80.7	C$_{15}$H$_{21}$Cl$_3$N$_2$O$_2$	11.95	11.85	9.44	9.64
4-Cl	1	CH$_2$Cl	91	101.2–102.8	C$_{12}$H$_{14}$Cl$_3$N$_2$O$_2$	24.51	24.60	9.69	9.76
H	1	CHCl$_2$	46	83.9–89.2	C$_{12}$H$_{14}$Cl$_3$N$_2$O$_2$	*c*		9.69	9.78
4-CH$_3$	1	CHCl$_2$	98	118.3–120.9	C$_{13}$H$_{16}$Cl$_3$N$_2$O$_2$	23.38	23.30	*d*	
4-CH(CH$_3$)$_2$	1	CHCl$_2$	93	68.1–71.1	C$_{15}$H$_{20}$Cl$_3$N$_2$O$_2$	21.41	21.40	8.46	8.54
4-Cl	1	CHCl$_2$	78	99.0–101.2	C$_{12}$H$_{13}$Cl$_3$N$_2$O$_2$	32.87	33.10	8.66	8.71
2,4-Cl$_2$	1	CHCl$_2$	60[a]	124.7–127.0	C$_{12}$H$_{12}$Cl$_4$N$_2$O$_2$	39.61	39.55	*e*	
4-OC$_4$H$_9$	1	CHCl$_2$	25[a]	89.4–91.3	C$_{16}$H$_{22}$Cl$_2$N$_2$O$_3$	*f*		7.76	7.75
3,4-(OCH$_3$)$_2$	1	CHCl$_2$	89	157.2–159.4	C$_{14}$H$_{18}$Cl$_2$N$_2$O$_4$	20.30	20.00	8.24	7.92
H	2	CHCl$_2$	95	111.6–120.3	C$_{13}$H$_{16}$Cl$_2$N$_2$O$_2$	23.38	23.70	9.24	9.03
H	1	CCl$_3$	78	111.7–113.6	C$_{12}$H$_{13}$Cl$_3$N$_2$O$_2$	32.87	33.15	8.66	8.74
4-Cl	1	CCl$_3$	88	143–145[b]	C$_{12}$H$_{12}$Cl$_4$N$_2$O$_2$	39.61	39.40		
4-OC$_4$H$_9$	1	CCl$_3$	40	113.0–114.5	C$_{16}$H$_{21}$Cl$_3$N$_2$O$_3$	26.89	26.27	7.08	7.02
H	2	CCl$_3$	83	106–107.5[b]	C$_{13}$H$_{15}$Cl$_3$N$_2$O$_2$			8.30	7.93

[a] Some material lost during purification. [b] Uncorrected. [c] *Anal.* Calcd.: C, 49.97; H, 4.85. Found: C, 50.25; H, 5.20. [d] *Anal.* Calcd.: C, 51.50; H, 5.32. Found: C, 51.81; H, 5.67. [e] *Anal.* Calcd.: C, 40.24; H, 3.38. Found: C, 40.29; H, 3.27. [f] *Anal.* Calcd.: C, 53.19; H, 6.14. Found: C, 53.34; H, 6.12.

which was discarded. The solid fractions were combined (26.5 g. total, 85%) and recrystallized from isopropyl alcohol to give a product melting at 164.5–166° (uncor.).

The reaction time was varied from five to ten days for the preparation of the other 2-carbamylethylamines. The bases were obtained either directly from the reaction mixture by recrystallization from an appropriate solvent (benzene, benzene–Skellysolve A, isopropyl alcohol, etc.) or from the hydrochlorides by neutralization and extraction.

N-(2-Carbomethoxyethyl)-4-isopropylbenzylamine.—With stirring and occasional cooling (temperature <35°) 43 g. (0.5 mole) of methyl acrylate was added to 60 g. (0.4 mole) of 4-isopropylbenzylamine. After standing four days at room temperature the excess methyl acrylate was removed under reduced pressure and the mixture distilled. The fraction boiling at 115–135° (0.3 mm.), n^{25}D 1.5030, was collected, 75 g. (80%).

Anal. Calcd. for C$_{14}$H$_{21}$NO$_2$: N$_{AP}$, 5.95. Found: N$_{AP}$, 5.92.

The fraction boiling at 135–155° (0.3 mm.), n^{25}D 1.4990, was also collected, 12 g. Its analysis is near that calculated for N,N-bis-(2-carbomethoxyethyl)-4-isopropylbenzylamine.

Anal. Calcd. for C$_{18}$H$_{27}$NO$_4$: N$_{AP}$, 4.36. Found: N$_{AP}$, 4.70.

N-[2-(Ethylcarbamyl)-ethyl]-4-isopropylbenzylamine.—A mixture of 23.5 g. (0.1 mole) of N-(2-carbomethoxyethyl)-4-isopropylbenzylamine, 45.1 g. (1.0 mole) of anhydrous ethylamine and 50 ml. of ethanol was left stoppered at room temperature for five days. The solvent and excess ethyl-

amine were removed under reduced pressure and the resulting viscous red oil was distilled. The fraction that boiled at 135–148° (1 μ), $n^{25}D$ 1.5204, weighed 21 g. (85%).

Anal. Calcd. for $C_{15}H_{24}N_2O$: N_{AP}, 5.62. Found: N_{AP}, 5.64.

N-(2-Cyanoethyl)-N-(4-isopropylbenzyl)-dichloroacetamide.—The following is an example of the general procedure employed for the preparation of the haloacetamides (see Tables III and IV).

A mixture of 20.2 g. (0.1 mole) of N-(2-cyanoethyl)-4-isopropylbenzylamine, 125 ml. of a 1 *N* sodium hydroxide solution and 100 ml. of ethylene dichloride was cooled to 0° in an ice–salt bath. A solution of 14.7 g. (0.1 mole) of dichloroacetyl chloride in 50 ml. of ethylene dichloride was then slowly added with stirring (temperature <5°). After the addition was complete, stirring was continued while the mixture was allowed to warm to room temperature. The organic layer was separated, washed with 2 *N* hydrochloric acid and with water and filtered with charcoal. The solvent was removed under reduced pressure and the resulting solid, 26 g. (83%), was recrystallized once from isopropyl alcohol, m.p. 107.9–111.6°.

N-(2-Cyanoethyl)-N-(2-furfuryl)-dichloroacetamide. The procedure here was the same as above. The product was a brown non-distillable oil, that was dried at 60–70° (0.05 mm.) for 2 hours. The yield was 77%.

Anal. Calcd. for $C_{10}H_{10}Cl_2N_2O_2$: C, 45.99; H, 3.86; N, 10.73. Found: C, 45.44; H, 4.16; N, 10.58.

The haloacetamides of the 2-carbamylethylamines were prepared in the same manner as above. Two molar equivalents of base were employed when the starting material was the amine hydrochloride.

N-[2-(Ethylcarbamyl)-ethyl]-N-(4-isopropylbenzyl)-dichloroacetamide.—This compound was prepared from N-[2-(ethylcarbamyl)-ethyl]-4-isopropylbenzylamine. The product, a viscous red oil, was dried for one hour at 70° (0.3 mm.), (89%).

Anal. Calcd. for $C_{17}H_{24}Cl_2N_2O_2$: Cl, 19.73; N, 7.80. Found: Cl, 19.60; N, 7.65.

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[CONTRIBUTION FROM THE WALKER LABORATORY OF THE RENSSELAER POLYTECHNIC INSTITUTE]

Derivatives of Aromatic Sulfinic Acids. II. The Reaction of Thionyl Chloride with Sulfinic Esters[1,2]

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Esters of aromatic sulfinic acids react with thionyl chloride as do sulfurous esters to give the sulfinyl chloride and the alkyl chlorosulfinate. In the absence of added chloride ion, the reaction is slow. By the use of *l*-menthyl *l*-*p*-toluenesulfinate it has been shown that the reaction is first order in ester and first order in added chloride ion. Trace impurities of the thionyl chloride, probably mainly hydrogen chloride, also affect the rate.

The reactions of esters of sulfurous acid with acid chlorides and anhydrides illustrate the behavior of alkyl sulfites as mild alkoxylating agents.[3] Thionyl chloride, thionyl bromide,[3a] sulfuryl chloride,[3b,c] alkyl chlorosulfonates,[3b-d] phosphorus pentachloride,[3a] acyl halides and organic acid anhydrides[3b] have been used as alkoxide acceptors.

Esters of the aromatic sulfinic acids differ from the sulfites in having an aryl group attached to sulfur instead of one of the alkoxyl groups. It seemed of interest, in view of the fact that the covalence of sulfur is the same in these two classes of compounds, to determine whether or not the aromatic sulfinic esters would undergo a reaction comparable to that of the sulfurous esters.

Methyl benzenesulfinate and methyl *p*-toluenesulfinate, indeed, react smoothly at room temperature to yield the sulfinyl chloride and methyl chlorosulfinate in good yield.

$$ArSO_2CH_3 + SOCl_2 \longrightarrow ArSOCl + CH_3OSOCl$$

A trace of tetraethylammonium chloride added to the reactants[4] causes the reaction to become violent, and at the same time the methyl chlorosulfinate is decomposed to methyl chloride and sulfur dioxide.

This reaction of the sulfinic esters may proceed in a manner similar to that of the alkyl sulfites.[4] Since the sulfur of these esters is asymmetric, optically active esters can be used in a kinetic study of the reaction. *l*-Menthyl *l*-*p*-toluenesulfinate[5] was used for kinetic measurements since the change in optical activity of the solution of reactants could be followed as the reaction took place at the asymmetric sulfur.

In nitrobenzene as a solvent at 25°, there was no detectable change in rotation of 0.08 *M* ester with 0.12 *M* thionyl chloride over a period of 1 hr. However, with tetraethylammonium chloride added to the two reactants to the extent of 0.0009–0.02 *M*, the rate-of-change in rotation became easily measurable. Typical results are those of Fig. 1 which illustrate the strict linearity for a period of over two half-lives of a first-order plot of the rotation. These also demonstrate the marked dependence of the rate on added chloride ion; this dependence on chloride ion concentration of the pseudo-first-order rate constant for the first twelve runs of Table I is presented graphically in Fig. 2. The water content, as determined by Karl Fischer titrations, of the tetraethylammonium chloride solution in nitrobenzene and of the nitrobenzene used as a solvent for the kinetic runs was not demonstrably different from zero (<0.001 *M*).[6] Yet to exclude the possibility that a species other than the quaternary chloride was the active catalyst, the additional reagents in amounts listed in

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(2) Paper I in this series, H. F. Herbrandson, R. T. Dickerson, Jr., and J. Winstein, THIS JOURNAL, **76**, 4046 (1954).

(3) (a) P. Carré and D. Libermann, *Bull. soc. chim. France*, **53**, 1050 (1933); (b) R. Levaillant, *Ann. chim.*, **6**, 461 (1936); (c) C. M. Suter and H. L. Gerhart, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 111; (d) C. Barkenbus and J. J. Owen, THIS JOURNAL, **56**, 1204 (1934).

(4) P. D. Bartlett and H. F. Herbrandson, *ibid.*, **74**, 5971 (1952).

(5) H. Phillips, *J. Chem. Soc.*, **127**, 2552 (1925). The diastereoisomer of this compound, *l*-menthyl *d*-*p*-toluenesulfinate, which differs only in the configuration of the sulfur, never has been obtained optically pure.

(6) This determination was kindly made by Dr. Andrew A. Laurene.