δ-Ethoxy-γ-valerolactone (XIX).—Twenty-five grams (0.15 mole) of XIV was refluxed with 42 g. of sodium hydroxide, dissolved in 350 ml. of water, for 24 hours. During this time ammonia was given off. The solution was then acidified with concentrated hydrochloric acid and refluxed for five hours more. The mixture was then filtered and extracted three times with ether, dried and distilled to yield 8 g. of δ-ethoxy-γ-valerolactone, b.p. 127–129° (14 mm.), $n^{25}D$ 1.4419, yield 36%.

Anal. Calcd. for $C_7H_{12}O_3$: C, 58.31; H, 8.39. Found: C, 58.39; H, 8.45.

α-Cyano-δ-phenoxy-γ-valerolactone (XI).—In a 500-ml. flask equipped as above, 0.25 mole of sodium cyanoacetate was prepared and cooled to 10°. Thirty-seven and five-tenths grams (0.25 mole) of phenyl glycidyl ether was added and the reaction run as above. Most of the alcohol was removed under reduced pressure. Benzene (50 ml.) was added followed by a mixture of 50 ml. of ice and water and 25 ml. of 12 *N* hydrochloric acid. A copious, red precipitate came down which was filtered, washed with benzene and then with water to yield 51.5 g. (53.9%) of fine white crystals, XI, m.p. 136–136.5°.

Anal. Calcd. for $C_{12}H_{11}O_3N$: C, 66.33; H, 5.10; N, 6.44. Found: C, 66.43; H, 5.14; N, 6.47.

α-Carboxy-δ-phenoxy-γ-valerolactone (XII).—Five grams (0.023 mole) of XI was refluxed with 50 ml. of 3 *N* sodium hydroxide for 6 hours during which time evolution of ammonia ceased. The solution was cooled and neutralized in an ice-bath with ice-cold 12 *N* hydrochloric acid. Most of the water was taken off under reduced pressure and the resulting mixture extracted twice with 30-ml. portions of benzene. The benzene extract was dried over anhydrous sodium sulfate and concentrated to about half its volume. The oil which separated crystallized upon rubbing with a benzene–petroleum ether mixture. Yield of XII was 4.2 g. (77.4%), m.p. 93–95° with decomposition.[15] Bromination yielded XIII, melting 156° dec.[15]

Acknowledgment.—The authors wish to thank the Research Corporation for a grant-in-aid supporting this project, and the Shell Chemical Corporation for a generous gift of epichlorohydrin.

HOLLAND, MICHIGAN

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF DEPAUW UNIVERSITY]

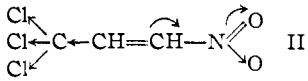
Trichloroaminoalcohols. II. 1,1,1-Trichloro-2-alkoxy-3-aminopropanes

BY IONE THOMPSON, SPIRO LOULOUDES, RICHARD FULMER, FRANCIS EVANS AND HOWARD BURKETT

RECEIVED NOVEMBER 5, 1952

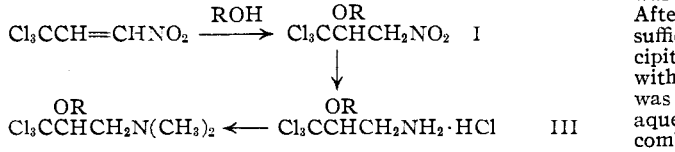
Starting with 1,1,1-trichloro-3-nitropropene, a series of 1,1,1-trichloro-2-alkoxy-3-nitropropanes, the corresponding amines and several of the dimethylamines have been prepared. A few of the latter two types of compounds show marked antispasmodic action.

Efforts to prepare 1,1,1-trichloro-2-alkoxy-3-nitropropanes (I) from a reaction between sodium alkoxides and the compound reported to be 1,1,1,2-tetrachloro-3-nitropropane have resulted in failure.[1] However, another approach has been suggested by numerous reports[2,3] of the addition of alcohols to nitroölefins in the presence of the corresponding sodium alkoxide or of the addition of the sodium alkoxide directly to the nitroölefin in an inert solvent. Hence, the previously prepared[1] 1,1,1-trichloro-3-nitropropene (II) was a potentially suitable intermediate. Since the inductive effect of the three chlorine atoms and the electromeric effect of the nitro group should make the middle



II

carbon a more positive center, it was anticipated that alcohols should add across the double bond of II with unusual ease. Indeed, this proved to be true. Warming II with an excess of various alcohols for one to four days afforded I in good yields. One thioether was also prepared.



Reduction of the nitro group of I to give the corresponding 1,1,1-trichloro-2-alkoxy-3-aminopropane hydrochloride (III) was carried out with stannous chloride and hydrochloric acid in yields of 16–65%. The desired product was not obtained from attempts to reduce the nitro group of the thioether.

Methylation of III with formaldehyde and formic acid according to the procedure of Clarke[4] gave 1,1,1-trichloro-2-alkoxy-3-dimethylaminopropane in 30–71% yields for those which were attempted.

Acknowledgment.—The authors thank Eli Lilly and Company for testing these compounds for pharmacological activity and for analysis of a number of them.

Experimental

1,1,1-Trichloro-2-alkoxy-3-nitropropanes. General Procedure.—A solution of 1,1,1-trichloro-3-nitropropene[1] (1 mole) in the alcohol (2 to 4 moles) was kept at 100–120° for 1 to 4 days. After distilling the alcohol, the product was distilled under reduced pressure. Data for these compounds are given in Table I.

1,1,1-Trichloro-2-alkoxy-3-aminopropane Hydrochloride. General Procedure.—The 1,1,1-trichloro-2-alkoxy-3-nitropropane (0.2 mole) was dissolved in 250 ml. of ethanol and heated to reflux. A solution of 292 g. of stannous chloride dihydrate (1.3 moles) in 205 ml. of concd. hydrochloric acid was then added during five minutes with good stirring. After refluxing for six hours, the mixture was cooled and sufficient concd. hydrochloric acid was added to cause precipitation, if necessary. The solid was filtered and mixed with 400 ml. of ether. A 10% solution of sodium hydroxide was added until all the tin hydroxides were dissolved. The aqueous layer was separated and extracted with ether. The combined ether layers were mixed thoroughly with excess concd. hydrochloric acid and the layers separated. The ether was evaporated. In some cases the residue was the major portion of the product. The aqueous acid layer was chilled and the solid filtered. In other cases this was the

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(3) W. J. Seagers and P. J. Elving, THIS JOURNAL, **71**, 2947 (1949).

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TABLE I

OR

$Cl_3CCHCH_2NO_2$

R	Yield, %	B.p., °C.	Mm.	n_D^t	t	d_4^t	t	Nitrogen, % Calcd.	Nitrogen, % Found	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
CH_3	99.0	94	18	1.4822	22	1.414	23	6.29	6.30				
CH_3CH_2	95.2	130	25	1.4725	29	1.334	24	5.92	5.96				
$CH_3CH_2CH_2$	92.5	136	20	1.4725	28	1.326	24	5.59	5.66				
$(CH_3)_2CH$	52.1	105	6	1.4775	20	1.396	20	5.59	5.70				
$CH_3(CH_2)_3$	98.1	101	3	1.4700	29	1.315	25	5.29	5.23				
$(CH_3)_2CHCH_2$	98.1	106	5	1.4693	21	1.310	25	5.29	5.33				
$CH_3(CH_2)_4$	89.0	117	3	1.4703	20	1.286	20	5.03	5.21				
$(CH_3)_2CHCH_2CH_2$	98.3	110	3	1.4680	29	1.308	25	5.03	5.04				
$CH_3(CH_2)_5$	92.2	128	5	1.4670	25	1.240	25	4.79	4.79	36.95	36.68	5.50	5.46
$CH_3CH_2CH_2CH(CH_3)CH_2$	55.4	124	2	1.4695	20	1.216	20			36.95	37.19	5.50	5.70
$(C_2H_5)_2CHCH_2$	62.3	109	1	1.4718	20	1.257	20			36.95	36.98	5.50	5.70
$(CH_3)_2CHCH_2CH(CH_3)$	60.3	101	2	1.4748	20	1.283	20			36.95	37.11	5.50	5.54
$CH_3(CH_2)_6$	90.5	131	2	1.4692	20	1.213	20			39.33	39.62	5.91	6.16
$CH_3(CH_2)_7$	93.0	121	1	1.4690	20	1.189	20	4.37	4.36	41.20	41.66	6.28	6.51
$CH_3(CH_2)_5CH(CH_3)$	60.1	131	2	1.4703	20	1.200	20			41.20	41.41	6.28	6.39
$CH_3(CH_2)_9$	75.0	156	1	1.4651	31	1.140	25	4.02	4.03	44.82	45.14	6.94	7.20
C_6H_{11}	58.5	125	2	1.4998	20	1.342	20			37.24	37.62	4.85	5.14
$C_6H_{11}CH_2$	77.6	127	1	1.4919	20	1.251	20			39.42	39.65	5.28	5.40
$4\text{-}CH_3C_6H_{10}$	38.8	130	2	1.4948	20	1.297	20			39.42	39.33	5.28	5.30
$C_6H_5CH_2CH_2$	87.5	147	1	1.5320	20	1.349	20			42.25	42.46	3.86	4.01
$C_6H_5(CH_2)_3$	77.0	150	1	1.5183	28	1.292	25	4.28	4.31	44.73	44.50	4.32	3.90
$C_6H_5(CH_2)_4$	66.8	167	1	1.5254	20	1.281	20			45.80	45.83	4.68	4.48
$C_6H_5OCH_2CH_2$	14.6	[a]						4.24	4.15	40.21	40.28	3.68	3.85
$CH_3(CH_2)_3$[b]	68.0	138	1	1.5138	23	1.345	25	4.99	4.99	29.98	30.15	4.29	4.40

[a] M.p. 59–60°. [b] This is the thioether.

TABLE II

OR

$Cl_3CCHCH_2NH_2 \cdot HCl$

R	Yield, %	M.p., °C.	Nitrogen (Chlorine), % Calcd.	Nitrogen (Chlorine), % Found	Anticonvulsant action[a] 250 mg./kg.	Anticonvulsant action[a] 400 mg./kg.
CH_3	53	220–230 d.	6.11	6.16	0	0
CH_3CH_2	54	210–213 d.	5.72	5.69	60	60
$CH_3CH_2CH_2$	38	233–238 d.	5.45	5.47	80	100
$(CH_3)_2CH$	28	265–266 d.	(55.39)	(55.60)	0	0
$CH_3(CH_2)_3$	37	195–199 d.	5.14	5.09	60	60
$(CH_3)_2CHCH_2$	65	230–240 d.	5.14	5.16	60	80
$CH_3(CH_2)_4$	38	188–189 d.	(49.81)	(49.84)	40	60
$(CH_3)_2CHCH_2CH_2$	35	172–175 d.	(49.81)	(40.69)	0	60
$CH_3(CH_2)_5$	32	185–190	(47.49)	(47.61)	100	100
$(C_2H_5)_2CHCH_2$	29	187–189 d.	(47.49)	(47.58)	25	75
$(CH_3)_2CHCH_2CH(CH_3)$	17	225–229 d.	(47.49)	(47.48)	20	40
$CH_3(CH_2)_6$	62	158–159	(45.39)	(45.83)	80	100
$CH_3(CH_2)_7$	47	116–117	(43.48)	(43.81)	0	60
$CH_3(CH_2)_5CH(CH_3)$	46	169–171	(43.48)	(43.48)	20	40
$CH_3(CH_2)_9$	47	109–110.5	(39.80)	(39.52)	20	40
C_6H_{11}	64	216–217 d.	(47.71)	(47.81)	0	60
$C_6H_{11}CH_2$	40	206–208 d.	(45.30)	(45.38)	20	80
$4\text{-}CH_3C_6H_{10}$	16	121–122	(45.30)	(45.00)	40	40
$C_6H_5CH_2CH_2$	62	165–166	(44.41)	(44.27)	0	0
$C_6H_5(CH_2)_3$	33	178–179 d.	(42.62)	(42.71)	100	100
$C_6H_5(CH_2)_4$	47	149–150	(40.90)	(40.75)	20	60

[a] Per cent. protection against electroshock in rats at dose level given.

TABLE III

OR

$Cl_3CCHCH_2N(CH_3)_2$

R	Yield, %	B.p., °C.	Mm.	n_D^t	t	d_4^t	t	Nitrogen, % Calcd.	Nitrogen, % Found	Anticonvulsant action[a] 250 mg./kg.	Anticonvulsant action[a] 400 mg./kg.
CH_3	56	64	4	1.4650	31	1.239	25	6.35	6.52	0	0
CH_3CH_2	67	93	14	1.4607	25	1.190	25	5.93	6.00	..	...
$CH_3CH_2CH_2$	66	111	17	1.4589	32	1.161	25	5.63	5.49	60	80
$CH_3(CH_2)_3$	66	122	25	1.4556	31	1.131	25	5.33	5.14	40	60
$(CH_3)_2CHCH_2$	61	125	26	1.4596	31	1.138	25	5.33	5.51	..	...
$(CH_3)_2CHCH_2CH_2$	30	106	4	1.4590	25	1.175	25	5.06	5.18	60	100
$CH_3(CH_2)_5$	71	108	3	1.4600	27	1.080	25	4.82	4.85[b]	60	60
$C_6H_5(CH_2)_3$	43	154[d]	3					4.62	4.52[c]	40	80

[a] Per cent. protection against electroshock in rats at dose level given. [b] Calcd. for $C_{11}H_{22}ONCl_3$: C, 45.46; H, 7.62 Found: C, 45.71; H, 7.66. [c] Calcd. for $C_{14}H_{20}ONCl_3$: C, 51.80; H, 6.16. Found: C, 52.10; H, 6.14. [d] M.p. 125–127°.

major portion of the product. In either event, the combined solids were recrystallized from ethanol–concd. hydrochloric acid. Data for these compounds, including pharmacological properties are given in Table II.

1,1,1-Trichloro-2-alkoxy-3-dimethylaminopropane. General Procedure.—A slight excess of 5% sodium hydroxide was added to the 1,1,1-trichloro-2-alkoxy-3-aminopropane hydrochloride (0.20 mole). After separating the aqueous layer, a solution of formalin (0.22 mole) in 90% formic acid (0.50 mole) was added to the resultant amine. After standing for 15 minutes, the mixture was heated in an oil-bath at 130° for five hours. Concentrated hydrochloric acid (0.22 mole) was added and the mixture was evaporated to dryness under reduced pressure with warming on the steam-bath. The residue was dissolved in water. The solution was decolorized and made basic with ammonium hydroxide. Extraction with ether, drying over magnesium sulfate and removal of the ether left an oily residue which was distilled under reduced pressure. Data for these compounds are presented in Table III.

GREENCASTLE, INDIANA

[CONTRIBUTION FROM THE CHEMISTRY DIVISION OF THE OAK RIDGE NATIONAL LABORATORY]

The Rates and Migration Ratios Observed in the Unimolecular and Bimolecular Reactions of 2-Phenyl-2-(*p*-tolyl)-ethyl Tosylate and Related Compounds[1]

BY JOHN G. BURR, JR.

RECEIVED APRIL 17, 1953

The first-order acetolysis rates and the bimolecular rates of reaction with alkoxide ion of 2,2-diphenylethyl tosylate, 2-phenyl-2-(*p*-tolyl)-ethyl tosylate and of 2,2-di-(*p*-tolyl)-ethyl tosylate have been determined. The rates of the acetolyses have been found to stand in the respective ratios of 1.00/1.62/8.32. The bimolecular reaction rates have been found to stand in the respective ratios of 1.00/0.62/0.38. The use of 2-phenyl-2-(*p*-tolyl)-ethyl-1-C^{14} tosylate showed that the rearrangement of the *p*-tolyl group in the first-order reaction was 71.2% (migration ratio of *p*-tolyl to phenyl of 2.47), and in the second-order reaction was less than 2%. Thus the successive substitution of methyl groups in the para positions of the diphenylethanol system produces a *non-linear increase in the rates of first order acetolysis, but a linear decrease in the rates of bimolecular reaction.* The linear decrease in the rates of the bimolecular reaction indicates that the inductive effect of the substituted benzhydryl radical is a linear function of the number of *p*-methyl substituents. The non-linear increase in the rates of the first-order reaction considered together with the relative migrations of phenyl and *p*-tolyl group do not present a consistent picture. It does indicate that the anchimeric ability of a group in these rearrangements is affected by the nature of the non-migrating group. The various rate constants presented here reflect the effect of a unique structure variation upon the relative rates of both unimolecular and bimolecular types of reaction.

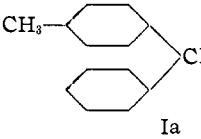
Introduction

The migration ratios observed in the Wagner-Meerwein rearrangement of several substituted 2,2-diphenylethanols-1-C^{14} were recently reported.[2] The results obtained were discussed in terms of the neighboring group type of participation of the aryl groups in this acid-catalyzed dehydration–rearrangement. Measurement of this type of participation can be obtained only from kinetic or stereochemical data, and since our results for the 2,2-diphenylethanols were obtained under conditions precluding any measurements of rates or stereochemistry we could at that time only indicate the possibility that the migration aptitudes of substituted aryl groups would be related to the rearrangement rates of the compounds containing these groups. It has seemed important to us to carry out one of these rearrangements under conditions where simultaneous indication of migratory aptitude and the rate of rearrangement could be obtained.

Since the diphenylethanol system, containing at most one center of asymmetry, is not amenable to stereochemical analysis, it was hoped that the acetolyses of the substituted 2,2-diphenylethyl tosylates would show relative rates indicating the relative anchimeric abilities of the substituted phenyl groups. This acetolysis has been shown[3] to produce stilbene from 2,2-diphenylethyl tosylate, indicating complete rearrangement. Our work also indicates stilbenes to be the only product.

Results

Such a kinetic analysis has now been accomplished for one such system: 2-phenyl-2-(*p*-tolyl)-ethyl tosylate (I), and the related compounds, 2,2-diphenylethyl tosylate (II) and 2,2-di-(*p*-tolyl)-ethyl tosylate (III). The relative migrations of phenyl and *p*-tolyl were observed in the acetolysis of 2-phenyl-2-(*p*-tolyl)-ethyl-1-C^{14} tosylate (Ia).



Ia

$(C_6H_5)_2CHCH_2OTs$

II

$(p\text{-}CH_3C_6H_4)_2CHCH_2OTs$

III

These compounds have been prepared and solvolyzed in glacial acetic acid. Their rates of acetolysis are recorded in Table I. At least two independent determinations of each rate were made and in general the agreement was excellent. Four independent determinations were made of the rate for the solvolysis of 2-phenyl-2-(*p*-tolyl)-ethyl tosylate since the rate constant for this compound tended to rise a little during each run. It was not a serious trend, however, and is reflected chiefly in a somewhat inferior precision for the constant. The data for a typical run on each compound are reported in Table II.

For reasons which will become apparent in the following section, it was found desirable to measure the rate of reaction of these same three esters in a

(1) This document is based upon work performed under contract Number W-7405-eng-26 for the Atomic Energy Commission at the Oak Ridge National Laboratory.

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