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REACTIONS OF TRIHALOGENOACETIC ACIDS—III

PREPARATION AND CHEMICAL TRANSFORMATIONS OF N-(1-ARYL-2,2,2-TRIHALOGENOETHYL) AMINES

A. LUKASIEWICZ

The Laboratory of Organic Chemistry Institute of Nuclear Research, Warsaw 9, Poland

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Abstract—A number of sec N-(1-aryl-2,2,2-trihalogenoethyl) amines have been prepared by the reaction of imines with trichloro- and tribromoacetic acids.

Both sec- and t-N-(1-aryl-2,2,2-tribromoethyl) amines when heated in alcohol and treated subsequently with a primary or secondary alkylamine, and then with water, form the corresponding amides of N-alkyl-α-arylglycine. It is suggested that these transformations are connected with the biological activity of trihalogenoaminoethane derivatives.

IN PREVIOUS publications, the reactions of trichloro- and tribromoacetic acids with imines[1] and methylene-bis-amines,[2] and formation of the corresponding sec- and t-N-(1-aryl-2,2,2-trihalogenoethyl) amines (I and II–IV) have been described. As compounds of type I and II–IV exhibit *in vitro* antitumour, fungicidal and antibacterial (antituberculosis) activity, a number of compounds of type II–IV were prepared in order to investigate their biological activity.

$$ArCH = NR + CH_3COOH \dashrightarrow ArCHNHR + CO_2$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\quad |$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\quad CX_3$$

II

$$ArCH = N(CH_2)_nN = CHAr \xrightarrow{2CX_3COOH} ArCHNH(CH_2)_nNHCHAr$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad | \qquad\qquad\quad |$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad CX_3 \qquad\qquad CH_3$$

III

$$+ ArCHNH(CH_2)_nNH_2 \text{ (after hydrolysis)} + CO_2$$
$$\qquad\quad |$$
$$\qquad CX_3$$

IV

Yields of the compounds obtained are given in Table 1. The products were usually

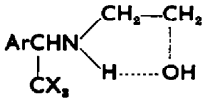
* Results of the biological investigations including the antitumour activity *in vivo* of the 1-aryl-1-alkyl; 1,1-dialkyl-; and 1-aryl-1-alkyl-)-2,2,2-trihalogenoethylamines will be given elsewhere.

[1] A. Lukasiewicz, *Tetrahedron* **20**, 1 (1964).

[2] A. Lukasiewicz, *Tetrahedron* **20**, 1113 (1964).

isolated as hydrochlorides as these are generally stable, although at elevated temperatures they may lose hydrogen chloride and this is responsible for the unsharp melting points of some of the compounds. The hydrochlorides of the amines, II, particularly those with a long alkyl chain lose hydrogen chloride even at room temperature (e.g. 15 and 16, II). The amines, IV, form hydrochlorides soluble in water; and some of these as well as the III hydrochlorides form crystalline hydrates.

The basicity of the amines (II and III) is such that they can be purified by decomposition of the hydrochlorides with benzene–water.[1] In cases where R = C_2H_4OH, the amines (20, 21 and 22 II—Table 1) being more basic the hydrochlorides are soluble and stable in water. The greater basicity of these amines (20–22 II) may be due to intramolecular hydrogen bonding, resulting from an increased electron density at the nitrogen atom:



The difference in basicity of the DL and meso-isomers of the amines, III (n = 2) has been reported.[1] In Table 2 a comparison of the basicity of some amines, III; (n = 2 ÷ 5) is given. The diminishing difference in basicity of both isomers for n > 2 supports the hypothesis[1] that this is due to intramolecular hydrogen bonding depending on the steric conditions of the DL and meso-isomers.

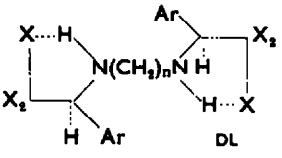


FIG. 1

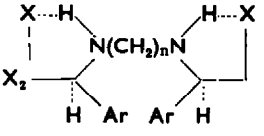
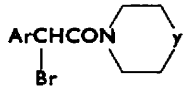


FIG. 2

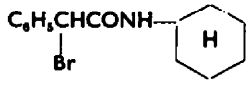
As in the amines, III, there is a tendency towards the conformation presented in Figs. 1 and 2, it may be assumed that the hydrogen bonding is more difficult for the meso-isomer with the vicinity of two aryl groups (n = 2). In compounds where n = 3 and Ar = C_6H_5, the difference disappears[1] (Table 2) but reappears for Ar = *p*—CH_3O—C_6H_4, probably due to an increase in the size of the aryl group. The form with a greater tendency towards hydrogen bonding (DL) should be more basic; thus the length of the alkylene bridge determines the basicity of the meso form. An increase in the length of the bridge results in the disappearance of the less basic form. From Table 2 it follows that compounds with n = 3 and Ar = C_6H_5 are exceptions.

The configurations of both A and B forms can be determined by separation of the optical antipodes. In a previous publication[2] the transformations of I (X = Br) which on heating in aqueous ethanol form the acylamines (V) have been described.



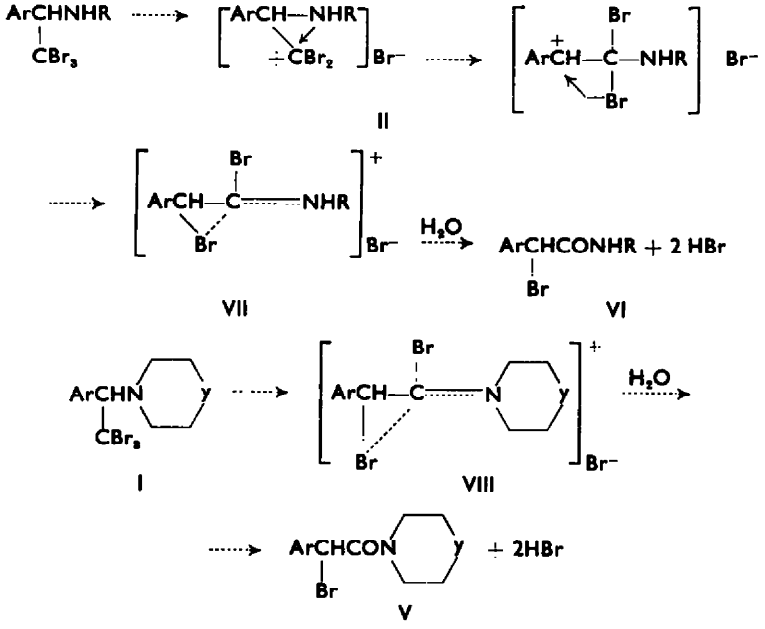
V

The amines, II (X = Br) are more stable than I but they evolve hydrogen bromide on prolonged heating in alcohol. These transformations were investigated for the less stable N-(1-phenyl-2,2,2-tribromoethyl)cyclohexylamine[1] (40, II). On prolonged heating in aqueous ethanol (90%) the acylamine, VI,

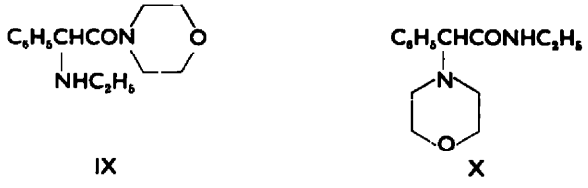


VI

was isolated. This transformation indicates that the rearrangement to α-bromoacylamines in a solvating medium is a general feature of I and II, (X = Br). The mechanism[2] can be represented as follows:

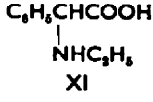


By treating the complex VIII,[2] in anhydrous ethanol with ethylamine and then with water, a compound with analytical data corresponding to IX or X was isolated.



IX X

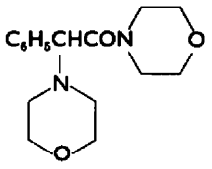
Hydrolysis of this compound yielded an amino acid corresponding to XI and this



XI

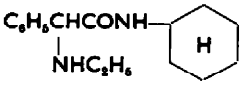
indicates that IX is the main product from the amine (41, I) and ethylamine.

The intermediate VIII from the amine 41 I on treatment with morpholine and water, yields XII.

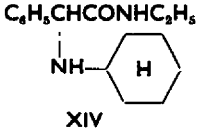


XII

The intermediate VII from the amine (40, II; Ar = C_6H_5 and R = cyclohexyl) with ethylamine and water yields a product with analytical data corresponding to XIII or XIV*.



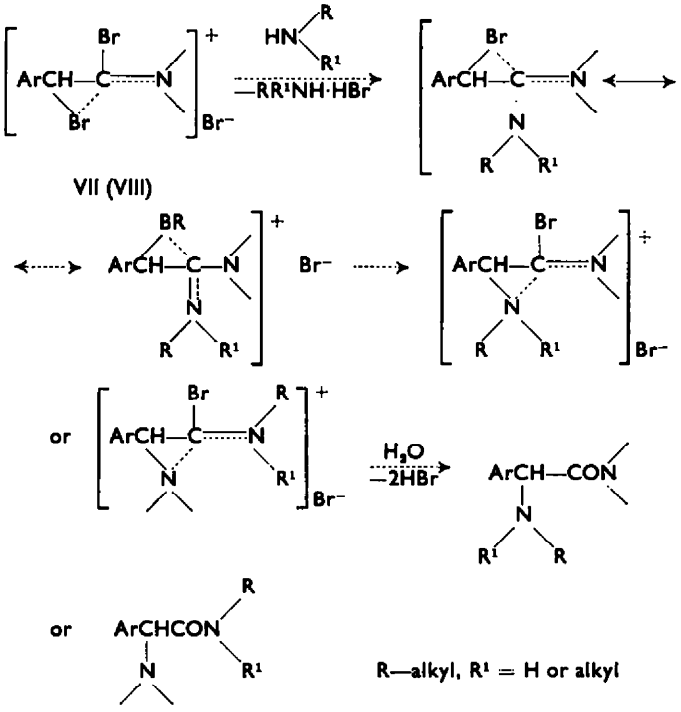
XIII



XIV

The hydrochlorides of the amines IX, XII and XIII–XIV on treatment with alkylamines e.g. ethylamine transform into the free amines. The lower basicity of the amines is due to the amide-carbonyl group.

The compounds IX, XII–XIV from the intermediates VII and VIII probably are formed in accordance with the following mechanism:

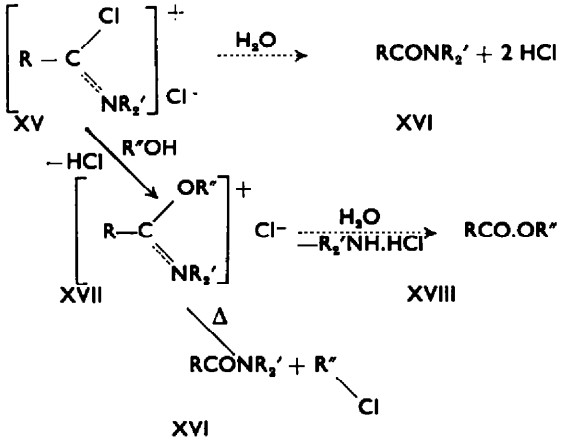


VII (VIII)

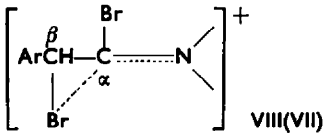
R—alkyl, R^1 = H or alkyl

* Further data concerning the structure XIII–XIV and other compounds of this type will be given in a subsequent publication.

According to this scheme, a primary or secondary amine can be alkylated or acylated by a complex of the type VII or VIII. To determine whether an alkylating or acylating action takes place or predominates detailed investigations are necessary. In the literature[3] the following transformations of the compounds of the type XV are described:



The rearrangement of I in anhydrous ethanol apparently does not lead to the intermediates of the type XVII, since no compounds of the type XVIII are formed.[2] The transformation XVII ⟶ XVI also does not take place as in the reaction giving rise to IX and XII, the acylamine V can not be isolated. Probably the presence of β-bromine in the intermediate VIII (VII) makes the formation of a sufficiently stable intermediate (XVII) impossible because of a shielding effect at the α-position.



VIII(VII)

At the same time, the β-bromine atom in VIII or VII because of its mobility (the possibility of translocation to the α-position) can be replaced by a primary or secondary amine (but not by water). Although the compounds I and II–IV are generally stable, it is probable that while acting biologically, they can undergo the transformations described, the latter being initiated by the liberation of a halogen atom from the CX_3 group. In particular their action on tumour cells can result in the alkylation or acylation of the free amino groups.

The problem of the relation between biological activity and chemical transformation of the trihalogenoaminoethane derivatives is now being investigated.

EXPERIMENTAL

(with the cooperation of Mrs. D. Walkowska)

Materials. Anhydrous trichloroacetic acid and tribromoacetic acid (Fluka) were used. The imines were prepared by heating the components in stoichiometric ratio in benzene[1] and distillation of the products under red. press. (2–3 mm) Hg. The imines from benzaldehyde and methyl- and ethylamine

[3] H. Eilingsfeld, M. Seefelder and H. Weidinger, *Chem. Ber.* **96**, 2671 (1963).

TABLE 1. YIELDS OF THE REACTION:

$$ArCH=N-R + CX_3COOH \rightarrow \underset{\underset{CX_3}{|}}{ArCHNHR} + CO_2$$

(II, III, IV)

Nr	Ar	R	X	II (III, IV)	Yield %
1	2	3	4	5	6
1	C_6H_5	CH_3	Cl	II	53·5
2	C_6H_5	CH_3	Br	II	28
3	C_6H_5	C_2H_5	Cl	II	95·5
4	C_6H_5	C_2H_5	Br	II	74·5
5	C_6H_5	n-C_3H_7	Cl	II	66·5
6	C_6H_5	n-C_4H_9	Cl	II	54·5
7	C_6H_5	iso-C_4H_9	Cl	II	86
8	C_6H_5	iso-C_4H_9	Br	II	89
9	4-CH_3O—C_6H_4	iso-C_4H_9	Cl	II	79
10	4-CH_3O—C_6H_4	iso-C_4H_9	Br	II	77·5
11	C_6H_5	n-C_5H_{11}	Cl	II	76·5
12	4-CH_3O—C_6H_4	n-C_5H_{11}	Br	II	67·5
13	C_6H_5	n-$C_{12}H_{25}$	Cl	II	54
14	C_6H_5	n-$C_{12}H_{25}$	Br	II	44·5
15	C_6H_5	n-$C_{18}H_{37}$	Cl	II	29
16	C_6H_5	n-$C_{18}H_{37}$	Br	II	38·5
17	C_6H_5	CH_2—CH=CH_2	Cl	II	66
18	C_6H_5	CH_2—CH=CH_2	Br	II	81·5
19	4-CH_3O—C_6H_4	CH_2—CH=CH_2	Br	II	53·5
20	C_6H_5	C_2H_4OH	Cl	II	26·5
21	C_6H_5	C_2H_4OH	Br	II	27
22	4-CH_3O—C_6H_4	C_2H_4OH	Cl	II	30
23	4-CH_3O—C_6H_4	cyclohexyl	Cl	II	74
24	4-CH_3O—C_6H_4	cyclohexyl	Br	II	90
25	2-Cl—C_6H_4	cyclohexyl	Cl	II	44·5
26	2-Cl—C_6H_4	cyclohexyl	Br	II	58
27	3-Cl—C_6H_4	cyclohexyl	Cl	II	56·5
28	3-Cl—C_6H_4	cyclohexyl	Br	II	85·5
29	4-Cl—C_6H_4	cyclohexyl	Cl	II	69
30	2-CH_3—C_6H_4	cyclohexyl	Cl	II	31·5
31	2-CH_3—C_6H_4	cyclohexyl	Br	II	33·5
32	C_6H_5	$(CH_2)_2NHCHC_6H_5$ | CCl_3	Cl	III	36·5 *
				+	
33	C_6H_5	$(CH_2)_2NH_2$	Cl	IV	23 *
34	4-CH_3O—C_6H_4	$(CH_2)_2NHCH$—)4-CHO_3—C_6H_4) | CCl_3	Cl	III	27 *
				+	
35	4-CH_3O—C_6H_4	$(CH_2)_2NH_2$	Cl	IV	31
36	C_6H_5	$(CH_2)_4NHCHC_6H_5$ | CCl_3	Cl	III	29 *
				+	
37	C_6H_5	$(CH_2)_4NH_2$	Cl	IV	44
38	C_6H_5	$(CH_2)_5NHCHC_6H_5$ | CCl_3	Cl	III	26·5 *
				+	
39	C_6H_5	$(CH_2)_5NH_2$	Cl	IV	51

* Yields of the reaction: $ArCH=N(CH_2)_nN=CHAr \xrightarrow{2CX_3COOH} \underset{\underset{CCl_3}{|}}{ArCHNH(CH_2)_nNHCHAr}\ \underset{\underset{CCl_3}{|}}{}$ (III)

+ $\underset{\underset{CCl_3}{|}}{ArCHNH(CH_2)_nNH_2}$ (after hydrolysis) (IV)

TABLE 2. A COMPARISON OF THE BASICITY OF SOME AMINES

$$ArCHNH(CH_2)_nNHCHAr \quad (III)^*$$
$$\quad\quad |\quad\quad\quad\quad |$$
$$\quad CCl_3 \quad\quad\quad CCl_3$$

Amine			Conc. of HCl and solvent used			
			0·5N	1·0N		2·0N
Ar	n	Form	ether	benzene	ether	benzene
C_6H_5	2	A	+	+		
		B	−		+	+ (toluene +)
C_6H_5	3	DL + meso	−	+	+	+
4-CH_3O—C_6H_4	3	A	+	+		
		B	−	−	+	+
C_6H_5	4	DL + meso	+	+		
C_6H_5	5	DL + meso	+	+		

[+] The hydrochloride of the amine was precipitated when the solution of the amine was shaken with hydrochloric acid (for n = 5 the aqueous phase was made alkaline; + —the amine was precipitated).

[−] The hydrochloride of the amine was not precipitated.

[*] See Ref. 1.

were prepared by mixing cooled solutions of the reagents in benzene, separation of the water and distillation of the products.

The imines were not analysed. In some cases benzene (toluene) solutions of the imines, obtained after removing the water, were used in the reaction with trihalogenoacetic acids. All m.p. are uncorrected.

N-(1-*Aryl*-2,2,2-*trihalogenoethyl*) *amines* (II)

General procedure. To a benzene or toluene solution of an imine the stoichiometric proportions of trihalogenoacetic acid (in benzene or toluene) was added dropwise at elevated temp. After 1–2 hr, the cooled mixture was shaken with 0·5N HCl and water, the solvent distilled off under red. press. The residue was dissolved in anhydrous ether or ethyl acetate and dry HCl in ether added (procedure A). When no precipitate occurred the solvent was removed and, n-heptane (procedure B) or dry acetone (procedure C) added. The precipitate of the amine (II) hydrochloride was filtered off and dried. The aqueous layer (0·5N HCl) was made alkaline and the amine II when precipitated was extracted with ether, dried and the amine hydrochloride precipitated. The hydrochlorides II were purified by decomposition with benzene–water and reprecipitated as above. Yields of the crude hydrochlorides II are given in Table 1 and m.ps of the purified ones in Table 3.

The amines 20–22 II were isolated as follows: after the reaction was complete part of the solvent was removed, ether added, the mixture shaken with 2N HCl, the acidic layer made alkaline and the crystalline amine filtered off (procedure D). In the case of 22 II, from the acidic layer an oil (*p*-methoxybenzaldehyde) precipited after a few hr, and was removed by extraction with ether. The amines 20–22 II were purified by precipitation from ethanol with water.

The compounds 1–12 and 17–22 (II) were prepared from the distilled imines, 13–16 and 23–31 (II) from crude materials. The reagents used were: n-propyl-, n-butyl-, n-dodecyl-, stearyl- and allylamine (Schuchardt); ethyl- and isobutylamine (B.D.H.); n-amylamine and *p*-chlorobenzaldehyde of (Light); ethanolamine, *o*-chlorobenzaldehyde and *o*-toluylaldehyde (Fluka).

Preparation of the compounds III *and* IV

N,N′-*bis*-(1-*Phenyl*-2,2,2-*trichloroethyl*)-1′,3′-*propylenediamine dihydrochloride* (32 III) *and* N-(1-*phenyl*-2,2,2-*trichloroethyl*)-1′,3′-*propylenediamine dihydrochloride* (33 IV). Benzaldehyde (2·12 g) and 0·74 g propylenediamine (Light) were heated in benzene. After removing the water, 3·4 g CCl_3COOH in benzene was added at 70°. Part of the benzene was removed, ether added and the mixture shaken

TABLE 3

Compound II	Temperature of the reaction °C	procedure	m.p. °C	analysis: Found C	Found H	Found N	Formula	Required (%) C	Required (%) H	Required (%) N
1	2	3	4	5	6	7	8	9	10	11
1	70–75	A	227 dec.	38·85	3·85	5·6	$C_9H_{11}NCl_4$	39·25	4·0	5·1
2	70	A	186 dec.	26·85	2·65	3·4	$C_9H_{11}NClBr_3$	26·4	2·7	3·4
3	70	A	195–196·5 dec.	41·65	4·4	5·0	$C_{10}H_{13}NCl_4$	41·5	4·5	4·85
4	50	A	182·5 dec.	28·45	2·95	3·45	$C_{10}H_{13}NClBr_3$	28·45	3·1	3·3
5	70	A	206 dec.	44·2	5·15	4·7	$C_{11}H_{15}NCl_4$	43·55	4·95	4·6
6	70	A	203·5 dec.	45·4	5·35	4·5	$C_{12}H_{17}NCl_4$	45·45	5·35	4·4
7	70–75	A	179–180·5 dec.	45·5	5·25	4·45	$C_{12}H_{17}NCl_4$	45·45	5·35	4·4
8	40	A	176–177 dec.	31·65	4·0	3·4	$C_{12}H_{17}NClBr_3$	32·0	3·8	3·1
9	70	A	158–159 dec.	45·5	5·4	4·3	$C_{12}H_{19}ONCl_4$	44·95	5·5	4·05
10	40	A	164–166 dec.	31·95	4·35	3·1	$C_{12}H_{19}ONClBr_3$	32·45	3·95	2·9
11	70–75	A	163–165 dec.	47·45	5·75	4·45	$C_{13}H_{19}NCl_4$	47·15	5·75	4·25
12	40	A	144–145 dec.	34·6	4·4	2·95	$C_{14}H_{21}ONClBr_3$	34·0	4·25	2·85
13	70–75	B	94–95 (softened at 86°)	55·85	7·9	3·25	$C_{20}H_{33}NCl_4$	55·95	7·7	3·25
14	50–55	B	94–95·5 dec.	43·05	5·8	2·7	$C_{20}H_{33}NClBr_3$	42·7	5·85	2·5
15	75	A	105–107	60·85	8·85	3·35	$C_{26}H_{45}NCl_4$	60·8	8·75	2·75
16	45	B	100–102	47·85	6·75	2·5	$C_{26}H_{45}NClBr_3$	48·3	6·95	2·5
17	70–75	A	189·5–190·5 dec.	44·05	4·3	4·7	$C_{11}H_{13}NCl_4$	43·85	4·3	4·65
18	50	A	172 dec.	30·55	3·2	3·25	$C_{11}H_{13}NClBr_3$	30·4	3·0	3·2
19	50	A	176–177 dec.	31·4	3·25	3·05	$C_{12}H_{15}ONClBr_3$	31·05	3·25	3·0
20	75	D	74·5–75*	44·8	4·5	5·1	$C_{10}H_{12}ONCl_3$	44·8	4·5	5·2
21	70	D	105–106*	30·05	3·05	3·55	$C_{10}H_{12}ONBr_3$	29·85	3·0	3·5
22	90	D	68·5–69·5*	44·55	4·95	5·05	$C_{11}H_{14}O_2NCl_3$	44·3	4·7	4·7
23	70–75	C	192–193·5 dec.	48·7	5·95	3·85	$C_{15}H_{21}ONCl_4$	48·25	5·65	3·75
24	45	A	179–180·5 dec.	36·05	4·05	2·95	$C_{15}H_{21}ONClBr_3$	35·55	4·15	2·75
25	100	A	179–181 dec.	45·0	4·8	3·8	$C_{14}H_{18}NCl_5$	44·55	4·75	3·7
26	70	A	85·5–86·5*	35·55	3·6	3·55	$C_{14}H_{17}NClBr_3$	35·45	3·6	2·95
27	100	A	175–176 dec.	44·6	4·6	4·15	$C_{14}H_{18}NCl_5$	44·55	4·75	3·7
28	75	A	166–167 dec.	33·35	3·55	2·8	$C_{14}H_{18}NCl_2Br_3$	32·95	3·55	2·75
29	100	A	190–192 dec.	44·65	5·0	4·05	$C_{14}H_{18}NCl_5$	44·55	4·75	3·7
30	100	A	187·5–188·5 dec.	50·8	5·95	4·2	$C_{15}H_{21}NCl_4$	50·4	5·9	3·9
31	90	C	88–89*	39·8	4·25	3·55	$C_{15}H_{20}NBr_3$	39·65	4·4	3·1

* M.p. and analysis refer to free amine.

with 2N HCl. The precipitate of 32 III was filtered off (2·2 g), the aqueous phase made alkaline, the precipitated oil extracted with ether, dried, the ether removed and anhydrous ethanol and dry HCl in ether added. The precipitate of 33 IV (0·85 g) was filtered off and dried, m.p. 195·5° dec. The analysis corresponds to monohydrate*. (Found: C, 35·4; H, 5·05; N, 7·85; $C_{11}H_{19}ON_2Cl_5$ requires: C, 35·5; H, 5·1; N, 7·55%). The 32 III was crystallized from ethanol (with HCl), m.p. 192·5° dec. The analysis corresponds to the dihydrate. (Found: C, 38·3; H, 4·45; N, 4·85 $C_{19}H_{36}O_2N_2Cl_8$ requires: C, 38·15; H, 4·35; N, 4·7%).

The 32 III dihydrate was decomposed with benzene–water and reprecipitated from anhydrous ethanol with dry HCl in ether, m.p. 191–192° dec. The analysis corresponds to the monohydrate. (Found: C, 39·55; H, 4·25. $C_{19}H_{34}ON_2Cl_8$ requires: C, 39·3; H, 4·15%). The hydrates 32 III and 33 IV lose water of crystallization on heating.

N,N′-*bis*-(1-p-*Methoxyphenyl*-2,2,2-*trichloroethyl*)-1′,3′-*propylenediamine* (34 III) *and* N-(1-p-*methoxy*-2,2,2-*trichloroethyl*)-1′,3′-*propylenediamine dihydrochloride* (35 IV). From 2·7 g *p*-methoxybenzaldehyde, 0·72 g propylenediamine and 3·4 g CCl_3COOH (in benzene, at 70°), 35 IV (1·2 g) and 34 IIIA (0·92 g) were obtained. By extraction with 1:3 HCl, the 34 IIIB hydrochloride (1·0 g) was obtained. Decomposition of the hydrochlorides with benzene–water yielded 34 IIIA (0·7 g), m.p. 97–98·5° from ethanol 95%. (Found: C, 46·1; H, 4·3; N, 5·8. $C_{21}H_{24}O_2N_2Cl_6$ requires: C, 45·9; H, 4·35; N, 5·75%) and 0·8 g 34 IIIB, m.p. 72–73° from 95% ethanol. (Found: C, 45·9; H, 4·35; N, 5·75%) were obtained. The hydrochloride 35 IV (very hygroscopic) melted above 100° dec. (Found: C, 37·2; H, 5·45; N, 7·25; $C_{12}H_{19}ON_2Cl_5$ requires: C, 37·5; H, 4·95; N, 7·3%).

N,N′-*bis*-(1-*Phenyl*-2,2,2-*trichloroethyl*)-1′,4′-*tetramethylenediamine dihydrochloride* (36 III) *and* N-(1-*phenyl*-2,2,2-*trichloroethyl*)-1′,4′-*tetramethylenediamine dihydrochloride* (37 IV). From 4·24 g benzaldehyde, 1·76 g tetramethylenediamine (Schuchardt) and 6·5 g CCl_3COOH (in toluene, at 90–95°) 36 III (3·5 g) and 37 IV (3·43 g) were obtained. The hydrochloride 36 III was purified by decomposition with benzene–water and by reprecipitation of the hydrochloride from anhydrous ethanol with HCl in ether, m.p. 231–232° dec. The analysis corresponds to the monohydrate. (Found: C, 41·9; H, 4·65; N, 4·8. $C_{20}H_{26}ON_2Cl_8$ requires: C, 41·8; H, 4·55; N, 4·85%). On heating the hydrate 36 III loses water of crystallization. The hydrochloride 37 IV was purified by dissolving in water (a small amount of an oil was removed by extraction with ether), addition of alkali and reprecipitation of the hydrochloride from anhydrous ethanol with HCl in ether, and by drying *in vacuo*, m.p. 206–207·5° dec. On heating above 100° a liquid condensed on the walls of the tube. The analysis corresponds to a combination of 37 IV with ethanol; 37 IV $\frac{1}{2}C_2H_5OH$. (Found: C, 39·7; H, 5·6; N, 6·9; $C_{18}H_{32}O_{0.5}N_2Cl_5$ requires: C, 39·9; H, 5·6; N, 7·15%). After heating *in vacuo* at 100° and treating with HCl in ether the compound was again analysed. (Found: C, 39·3; H, 5·5; N, 7·3; $C_{18}H_{19}N_2Cl_5$ requires: C, 39·15; H, 5·15; N, 7·6%).

N,N′-*bis*-(1-*Phenyl*-2,2,2-*trichloroethyl*)-1′,5′-*pentamethylenediamine dihydrochloride* (38 III) *and* N-(1-*phenyl*-2,2,2-*trichloroethyl*)-1′,5′-*pentamethylenediamine dihydrochloride* (39 IV). From benzaldehyde (4·24 g) and pentamethylenediamine (2·05 g, Schuchardt) and CCl_3COOH (6·5 g, in toluene, at 90°) a mixture of 38 III and 39 IV (8·1 g) was obtained from the acidic layer by addition of alkali. The mixture of hydrochlorides was shaken with benzene–water. From the benzene layer, 38 III (3·1 g) and from the aqueous layer 39 IV (4·3 g) were obtained by precipitation from anhydrous ethanol with HCl in ether. The 38 III melted at 217·5–218·5° dec. (Found: C, 43·25; H, 4·45; N, 4·8; $C_{21}H_{26}N_2Cl_8$ requires: C, 42·7; H, 4·4; N, 4·75%).

The analysis of 39 IV corresponds to a combination with water and ethanol; 39 IV·H_2O·$\frac{1}{2}C_2H_5OH$, m.p. 181–182°; on heating above 100° a liquid condensed on the walls of the tube. (Found: C, 39·9; H, 6·05; N, 6·55; $C_{18}H_{30}O_{1.5}N_2Cl_5$ requires: C, 39·7; H, 6·15; N, 6·6%). After heating *in vacuo* at 100° and treating with HCl in ether the compound was again analysed. (Found: C, 40·3; H, 5·7; N, 7·15; $C_{18}H_{21}N_2Cl_5$ requires: C, 40·85; H, 5·5; N, 7·4%).

Rearrangement of N-(1-*phenyl*-2,2,2-*tribromoethyl*)*cyclohexylamine* (40 II)[1]

1. N-(α-*Bromo*-α-*phenylacetyl*)-*cyclohexylamine* (VI). The hydrochloride, 40 II (3·0 g) was shaken with benzene–water, the benzene removed, 10 ml ethanol (90%) added and the solution refluxed for

* The formation of the hydrates of some hydrochlorides III and IV when precipitated from anhydrous ethanol with dry HCl in ether can be caused by the presence of small amounts of water in the ether–HCl solution.

20 hr. The solvent was distilled off, ethanol 2:1 added, the precipitate VI (0·45 g) filtered off and washed with n-heptane. From the filtrate the hydrochloride 40 II (0·48 g) was recovered. After crystallization from n-heptane with ethyl acetate, VI melted at 136–137°. (Found: C, 57·1; H, 6·2; N, 4·8. $C_{14}H_{18}ONBr$ requires: C, 56·75; H, 6·1; N, 4·75%).

2. *Amide of α-phenyl-N-alkylglycine* (XIII–XIV). The amine, 40 I from its hydrochloride (5·0 g) was refluxed in anhydrous ethanol (15 ml) for 20 hr (no moisture). Part of the solvent was distilled off, excess $C_5H_5NH_2$ in benzene and 0·5 ml water added, the solvent removed (red. press.), anhydrous ether added and the precipitate of $C_5H_5NH_2 \cdot HBr$ filtered off. From the filtrate a hydrochloride was precipitated with dry HCl in ether and was treated with ether–water, water from the aqueous phase was evaporated and to the residue anhydrous ethanol with ether added, yielding the hydrochloride XIII–XIV (0·7 g), m.p. 223–226° from anhydrous ethanol. (Found: C, 64·6; H, 8·25; N, 9·4; $C_{16}H_{28}ON_2Cl$ requires: C, 64·85; H, 8·45; N, 9·45%).

To a solution of the hydrochloride in aqueous ethanol, excess $C_5H_5NH_2$ in benzene was added, the solvent removed, anhydrous ether added and a precipitate of $C_5H_5NH_2 \cdot HCl$ filtered off. The solvent was removed from the filtrate, n-heptane added and XIII–XIV filtered off, m.p. 102·5–103·5°. (Found: N, 10·6; $C_{16}H_{24}ON_2$ requires: N, 10·75%).

Rearrangement of N-(1-*phenyl*-2,2,2-*tribromoethyl*)-*morpholine*[2] (41 I)

1. N-(α-*Phenyl*-α-N'-*ethylaminoacetyl*)*morpholine* (IX). The amine, 41 I (2·0 g) freshly prepared by decomposition of the hydrochloride 41 I, was refluxed in anhydrous ethanol for 4 hr, part of the solvent removed, and excess $C_5H_5NH_2$ in benzene and 0·5 ml water added. Following the procedure described, the hydrochloride IX (0·9 g) was obtained, m.p. 242–244° dec. from anhydrous ethanol. (Found: C, 59·35; H, 6·85; N, 10·35; $C_{14}H_{21}O_2N_2Cl$ requires: C, 59·15; H, 7·05; N, 9·9%).

By treating the hydrochloride IX with $C_5H_5NH_2$, the amine IX was obtained, m.p. 60–61°. (Found: N, 11·35; $C_{14}H_{20}O_2N_2$ requires: N, 11·3%). The amine IX is soluble in water.

N-*Ethyl*-α-*phenylglycine* (XI). The hydrochloride IX (1·8 g) was heated under reflux in 20% HCl for 20 hr, the solution evaporated, dilute NH_4OH added to pH = 7 and the precipitated XI filtered off (0·75 g). The compound XI was crystallized from water. (Found: C, 66·55; H, 7·35; N, 7·95; $C_{10}H_{13}O_2N$ requires: C, 67·0; H, 7·25; N, 7·8%). From the filtrate after crystallization, XI was obtained by evaporating part of the solvent. (Found: C, 66·9; H, 7·4; N, 7·95%). The compound XI decomposes on heating above 240° and is soluble in dil. NaOH and HCl solutions.

2. N-(α-*Phenyl*-α-N'-*morpholine-acetyl*)*morpholine hydrochloride* (XII). From the amine, 41 I (2·0 g) and morpholine (excess), XII (0·87 g) was obtained, m.p. 254° (dec.) from anhydrous ethanol. (Found: C, 58·7; H, 6·95; N, 8·7; $C_{16}H_{22}O_3N_2Cl$ requires: C, 58·9; H, 7·05; N, 8·6%).

Determination of the basicity of the amines III

The amine was examined by dissolving 0·1 g in 2 ml ether or benzene and shaking with HCl (2 ml) for 15 min. If no precipitate formed, the aqueous phase was made alkaline. The results are presented in Table 2.

The elementary analyses were carried out by the Department of Organic Chemistry, Warsaw University.

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