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REACTIONS OF TRIHALOGENOACETIC ACIDS—II

THE REACTION OF TRICHLORO- AND TRIBROMOACETIC ACIDS WITH METHYLENEBISAMINE DERIVATIVES*

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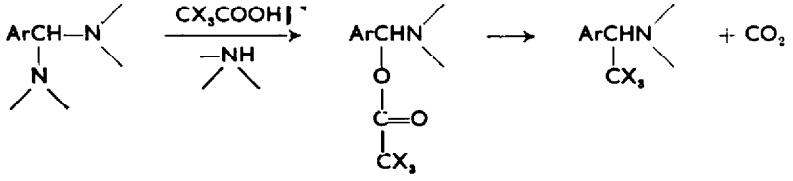
Abstract—Trichloro- and tribromoacetic acids in organic solvents react with aryl derivatives of methylene-bispiperidine and -bismorpholine with evolution of CO_2 and formation of t-N-(1-aryl-2,2,2,-trihalogenoethyl)-amines in good yield. The tribromoethyl derivatives, when heated in alcohol undergo transformations, in the presence of water, with the formation of the corresponding α-aryl-α-bromoacetylamines as final products.

IN A previous publication[2] the reaction of trihalogenoacetic acids with imines, leading to the formation of sec-N-(1-aryl-2,2,2-trihalogenoethyl)-amines was described. The hypothesis was advanced that this reaction—similar to the reduction of imines and methylenebisamines by formic acid[3]—results in decarboxylation of the corresponding esters of α-aminoalcohols.

The reaction of trihalogenoacetic acids with aryl derivatives of methylene-bis-amines, with the formation of the corresponding t-N-(1-aryl-2,2,2-trihalogenoethyl)-amines, probably takes place, according to the mechanism:



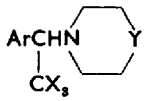
It was found that trichloro- and tribromoacetic acids in an organic solvent react at elevated temperatures with the bisamines (I and II) derived from the aromatic aldehydes and some secondary amines (piperidine and morpholine)

I II

with the formation of the corresponding trihalogenoaminoethane derivatives (III and IV)

* See communication.[1]

[1] A. Łukasiewicz, *Bull. Acad. Polon. Sci., Ser. Sci. Chim.* **11**, 187 (1963).
[2] A. Łukasiewicz, *Tetrahedron* **20**, 1 (1964); *Bull. Acad. Polon. Sci., Ser. Sci. Chim.* **11**, 15 (1963).
[3] A. Łukasiewicz, *Tetrahedron* **19**, 1789 (1963).



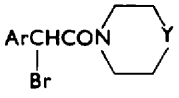
Y = CH_2;O

X = Cl—III, X = Br—IV

The bisamines I and II were obtained by heating the components (one mole of the aldehyde and two moles of the amine) in benzene with simultaneous removal of water. The reactions were carried out in benzene or toluene, using two moles of the acid for one mole of bisamine; the excess acid combining with the amine (piperidine or morpholine) formed. The yields are increased if excess of two moles of acid for one mole of the amine is used. The products III and IV were isolated (generally in good yield—Table 1) as crystalline amines or their hydrochlorides.

The compounds III and IV are weak bases, forming hydrochlorides which undergo hydrolysis in a water–benzene mixture the free amines being extracted quantitatively into the organic layer.[2] The amines can be re-extracted from the organic solution with hydrochloric acid the concentration of which is determined by. the solvent used and the electrophilic nature of the aryl and halogen in the CX_3 group.[2]

The free amines III are stable and can be crystallized without decomposition but the amines IV, when heated in ethanol undergo transformation, in the presence of water to the products V.



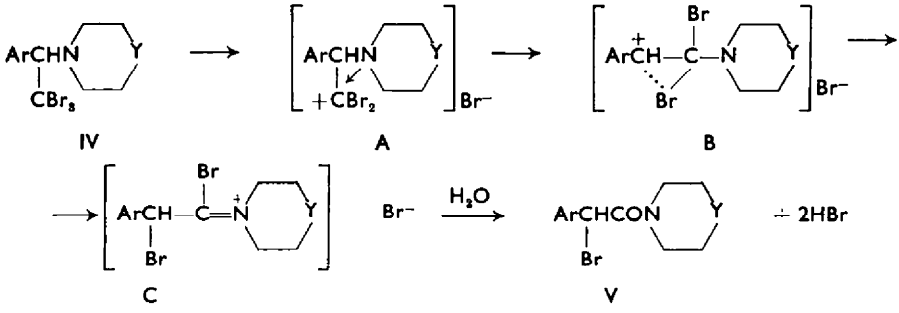
V

By heating the amine IV in anhydrous ethanol and removing the solvent, a syrup insoluble in ether remains which on treatment with water decomposes with evolution of hydrogen bromide and formation of V. Similarly on heating in water containing ethanol, the amines IV transform to the acylamines V.

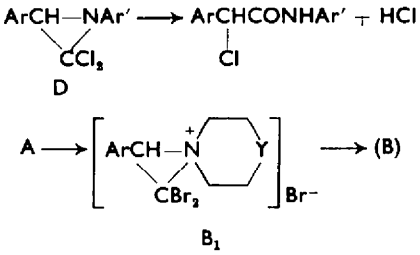
The amines IV are also unstable in nonpolar solvents e.g. concentrated heptane solutions evolve hydrogen bromide at room temperature but dilute solutions require heating.

The course of these transformations is, however, different from that in ethanol because the final products V were not isolated. Some compounds IV are equally unstable in the crystalline form but as hydrochlorides they can be stored without decomposition.[2]

The transformation of the tribromoethyl derivatives IV in ethanol is probably in accordance with the following mechanism:



The hydrolysis of the compound D, described in the literature,[4] is presumably analogous to the transformation A → B, in which the intermediate B_1 is analogous to D:

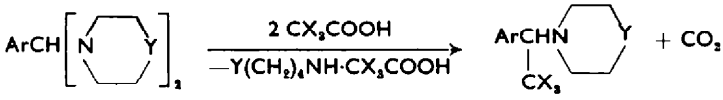


Compound B_1 possessing a three membered ring with a positively charged nitrogen must be very unstable and could exist only momentarily.

The transformation A → B apparently occurs immediately after the abstraction of Br^- (or simultaneously), because in water containing ethanol, the acylamines V are formed, and hydrolysis of the CBr_3 group (amino-acids or their esters should form as a result of hydration of A) does not take place.

It was found that the trihalogenoaminoethane derivatives exhibit *in vitro* fungicidal and antitumor activity,* and, therefore, the rearrangement of the amines IV (A → B type) is especially interesting because of the possible connection between the mechanism of these transformations and biological activity of the derivatives of 2,2,2-trihalogenoethylamines.

TABLE 1. YIELDS OF THE REACTION:



Nr	Ar	Y	X	III(IV)	yield (%)
1	C_6H_5	O	Cl	III	60
2	C_6H_5	O	Br	IV	74
3	C_6H_5	CH_2	Cl	III	86
4	C_6H_5	CH_2	Br	IV	67
5	2-Cl—C_6H_4	CH_2	Cl	III	63
6	3-Cl—C_6H_4	CH_2	Cl	III	68
7	4-CH_3O—C_6H_4	CH_2	Cl	III	62
8	4-CH_3O—C_6H_4	CH_2	Br	IV	72
9	4-NO_2—C_6H_4	CH_2	Cl	III	50
10	2-$C_{10}H_7$ (naphthyl)	CH_2	Cl	III	56

EXPERIMENTAL

Materials. Anhydrous trichloroacetic acid (chemical grade) and tribromoacetic acid (Schuchardt or Fluka) were used. Bisamines were prepared by heating an aromatic aldehyde (one mole) with two moles of an amine (piperidine or morpholine) in benzene and removing the reaction water. In some cases benzene solutions of the bisamines, obtained after removing the water, were used in the reaction with trihalogenoacetic acids. In other cases the crystalline bisamines were isolated (average

* The results of the biological investigations including the antibacterial activity of the 2,2,2-trihalogenoethylamines will be given in a special publication.

[4] A. G. Cook and E. K. Fields, *J. Org. Chem.* **27**, 3686 (1962).

yield above 80%) by removing benzene and addition of a small amount of benzene or ethanol 2:1.* The bisamines were not analysed. All m.ps are uncorrected.

The reaction of bisamines with trihalogenoacetic acids

General procedure. To a benzene (or toluene) solution of a bisamine, trihalogenoacetic acid (in benzene or toluene) was added dropwise (2 moles of the acid for one mole of the bisamine or of an aldehyde, when the bisamine was not isolated) at elevated temp. After the reaction was complete (evolution of gas ceased after 1–1·5 hr), the cooled reaction mixture was washed with 0·5 N HCl and water and the benzene distilled off under red. press.

Procedure A. To the residue, after removal of benzene, ethanol 2:1 was added and the precipitate of the amine (III or IV) filtered off and dried.

Procedure B. The residue was dissolved in ethyl acetate and a solution of dry HCl in ethyl acetate (or in anhydrous ether) added and the precipitate of the corresponding hydrochloride filtered off.

Procedure C. The residue was dissolved in ether, the solution shaken with HCl (1:3), the acidic layer made alkaline, the precipitate of the amine filtered off, washed with ethanol (2:1) and dried. The hydrochlorides of the amines can also be obtained by addition of conc. HCl in ethanol to the residue, evaporation to dryness (under red. press.) and addition of dry acetone (procedure D).

N-(1-*Phenyl*-2,2,2-*trichloroethyl*)-*morpholine* (1 III)

The bisamine (2·62 g, m.p. 96–98°) obtained from benzaldehyde and morpholine was heated with trichloroacetic acid (3·25 g) in benzene (20 ml) at 60°. After cooling, the morpholine trichloroacetate was filtered off, the filtrate washed with 0·5 N HCl, with water and the benzene distilled off. Following the procedure A, 1·75 g 1 III was obtained, m.p. 76–77° and purified by precipitation from alcohol with water. (Found: C, 48·7; H, 4·65; N, 4·7. $C_{12}H_{14}ONCl_3$ requires: C, 48·9; H, 4·7; N, 4·75%).

N-(1-*Phenyl*-2,2,2-*tribromoethyl*)-*morpholine* (2 IV)

From 1·4 g bisamine and 3·2 g tribromoacetic acid (in benzene at 40–50°), 1·7 g 2 IV was obtained. The product was purified by precipitation from ethanol with water, m.p. 120–121° (Found: C, 33·85; H, 3·2; N, 3·75. $C_{12}H_{14}ONBr_3$ requires: C, 33·65; H, 3·25; N, 3·25%).

N-(1-*Phenyl*-2,2,2-*trichloroethyl*)-*piperidine* (3 III)

The benzylidene-bispiperidine (3·25 g) and trichloroacetic acid (4·1 g) were heated in benzene (25 ml) at 60° (no ppt. formed) yielding 3·14 g amine 3 III (procedure A), m.p. 48·5–49·5° after precipitating from alcohol with water. (Found: C, 53·2; H, 5·65; N, 5·15. $C_{13}H_{16}NCl_3$ requires: C, 53·4; H, 5·5; N, 4·8%).

N-(1-*Phenyl*-2,2,2-*tribromoethyl*)-*piperidine* (4 IV)

From 5·2 g benzylidene-bispiperidine and 12·0 g tribromoacetic acid (in benzene at 40°) following the procedure B, 5·7 g hydrochloride of the amine 4 IV was obtained. The amine 4 IV was obtained by decomposition of the hydrochloride with a benzene–water mixture, removal of the benzene (red. press.) and adding ethanol 2:1; m.p. 79–80° after precipitating from ethanol with water. (Found: C, 36·7; H, 4·1; N, 3·3. $C_{13}H_{16}NBr_3$ requires: C, 36·6; H, 3·75; N, 3·3%). The free amine (4 IV) when stored (in dark) decomposes partially with the formation of amine hydrobromide. From conc. solutions in heptane after a few days a brown precipitate formed (in dark at room temp), from which the amine (4 IV) hydrobromide was isolated. On heating the precipitate is quickly formed.

N-(1-o-*Chlorophenyl*-2,2,2-*trichloroethyl*)-*piperidine* (5 III)

The bisamine (4·5 g, m.p. 62–64°) from *o*-chlorobenzaldehyde (Schuchardt) and piperidine and trichloroacetic acid (5·0 g) were heated in benzene at 70°. Following the procedure B, 3·43 g of the hydrochloride of the amine 5 III was obtained. By decomposition of the hydrochloride (a benzene–water mixture), the amine 5 III was obtained, m.p. 44–45° by precipitation from ethanol with water. (Found: C, 47·9; H, 4·6; N, 4·35. $C_{13}H_{15}NCl_4$ requires: C, 47·7; H, 4·6; N, 4·3%).

* 2 parts ethanol: 1 part water.

N-(1-m-*Phenyl*-2,2,2-*trichloroethyl*)-*piperidine hydrochloride* (6 III)

m-Chlorobenzaldehyde (1·4 g) and 1·7 g piperidine were heated in benzene. After removing the water, the benzene was distilled off, the residue (oil) dissolved in toluene and 3·25 g trichloroacetic acid (in toluene) added at 85°. Following the procedure D, 2·47 g 6 III was obtained, m.p. 161° dec. (Found: C, 43·25; H, 4·4; N, 4·3. $C_{13}H_{16}NCl_5$ requires: C, 42·95; H, 4·4; N, 3·85%).

N-(1-p-*Methoxyphenyl*-2,2,2-*trichloroethyl*)-*piperidine hydrochloride* (7 III)

From 2·72 g *p*-methoxybenzaldehyde, 3·5 g piperidine and 6·5 g trichloroacetic acid (in benzene at 60°) following the procedure B, 4·47 g 7 III was obtained. The product was purified by decomposition with a benzene–water mixture and by again precipitating the hydrochloride, m.p. 161–162° dec. (Found: C, 46·7; H, 5·35; N, 3·9. $C_{14}H_{19}ONCl_4$ requires: C, 46·8; H, 5·3; N, 3·9%).

N-(1-p-*Methoxyphenyl*-2,2,2-*tribromoethyl*)-*piperidine* (8 IV)

From 2·72 g *p*-methoxybenzaldehyde, 3·5 g piperidine and 12·0 g tribromoacetic acid (in benzene, at 40°), 7·1 g hydrochloride of the amine 8 IV was obtained (procedure B), m.p. 127–128° dec. The amine 8 IV was obtained by decomposition the hydrochloride with a benzene–water mixture, m.p. 90·5–92·5° after precipitation from alcohol with water. (Found: C, 37·4; H, 3·95; N, 3·2. $C_{14}H_{18}ONBr_3$ requires: C, 36·85; H, 3·95; N, 3·05%).

N-(1-p-*Nitrophenyl*-2,2,2-*trichloroethyl*)-*piperidine* (9 III)

The bisamine (3·05 g, m.p. 79·5–81·5°) from *p*-nitrobenzaldehyde (Schuchardt) and piperidine and trichloroacetic acid (3·25 g) were heated in benzene (20 ml) yielding 1·7 g 9 III (procedure C), m.p. 73–74° after precipitating from ethanol with water. (Found: C, 46·2; H, 4·4; N, 8·7. $C_{13}H_{13}O_2N_2Cl_3$ requires: C, 46·2; H, 4·45; N, 8·3%).

N-(1-β-*Naphthyl*-2,2,2-*trichloroethyl*)-*piperidine* (10 III)

From 1·57 g β-naphthaldehyde (Light), 1·7 g piperidine and 3·25 g trichloroacetic acid (in benzene, at 70°), 1·92 g 10 III was obtained (procedure C), m.p. 127·5–129° from ethanol. (Found: C, 59·65; H, 5·25; N, 4·1. $C_{17}H_{16}NCl_3$ requires: C, 59·65; H, 5·25; N, 4·1%).

Rearrangement of the amines IV

1. The amine 2 IV (0·5 g) was heated in anhydrous ethanol (5 ml) for 4 hr, part of the ethanol distilled off (red. press., pH of alcohol ~7) and water added. The precipitated α-phenyl-α-bromoacetylmorpholine (11 V; 0·25 g) was filtered off (the filtrate highly acidic) and purified by crystallization from heptane with a small amount of ethyl acetate, m.p. 103–104°. (Found: C, 50·7; H, 5·0; N, 5·55. $C_{12}H_{14}O_2NBr$ requires: C, 50·7; H, 4·95; N, 4·95%). Compound 11 V forms no hydrochloride on treating with dry HCl in an ether solution.

2. The amine 2 IV (0·5 g) was heated for 4 hr in water containing alcohol (~90% ethanol). Following the above procedure, 0·2 g 11 V was obtained. From the filtrate no crystalline products (except small amounts of a precipitate the properties of which corresponded to morpholine hydrobromide) were isolated.

3. The amine 4 IV (0·6 g) was heated in anhydrous ethanol for 4 hr. The solvent was distilled off and anhydrous ether was added (the oil remained insoluble). When water was added the oil decomposed and dissolved in the ether. The ether layer was dried (the water layer being acidic), the ether removed and heptane added; the precipitate of α-phenyl-α-bromoacetylpiperidine (0·3 g) was crystallized from heptane, m.p. 70–71° (Found: C, 55·45; H, 5·55; N, 5·05; $C_{13}H_{16}ONBr$ requires: C, 55·3; H, 5·65; N, 4·95%).

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

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