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REACTIONS OF TRIHALOGENOACETIC ACIDS—IV

THE REACTION OF TRICHLORO- AND TRIBROMOACETIC ACIDS WITH KETIMINES

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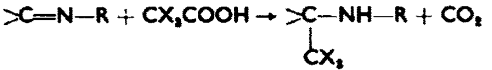
Abstract—The reaction of trichloro- and tribromoacetic acids with some ketimines has been investigated. It has been found that these acids react with the ketimines in an organic solvent with evolution of carbon dioxide and with the formation of α-(trihalogenomethyl)amine derivatives. The compounds obtained, when heated in alcohol undergo transformations, in the presence of water, with the formation of the corresponding α-halogenoacylamines and α-unsaturated acylamines as final products.

In previous publications, the reaction of trichloro- and tribromoacetic acids with Schiff bases[1] and methylenebisamine derivatives[2] has been described. It was found that both these acids also react with ketimines with the evolution of carbon dioxide to form the expected products:


A

$$>C{=}N{-}R + CX_3COOH \rightarrow >\underset{\displaystyle CX_3}{\underset{|}{C}}{-}NH{-}R + CO_2$$

The reaction of various ketimines derived from aliphatic, aromatic and alicyclic amines and aliphatic, alicyclic and aliphaticaromatic ketones with trihalogenoacetic acids has been investigated.

The ketimines were obtained by heating the components in equimolar ratio and removing the water formed as an azeotropic mixture with benzene or toluene, or, according to the method of Reddelien and Meyn (in the presence of $ZnCl_2$).[3]

The reaction of ketimines with trihalogenoacetic acids was carried out in equimolar ratio in dry benzene. The products of the reaction were isolated in the form of hydrochlorides of the amines (Table 1). In the case of the imine derived from an aromatic ketone (benzophenone and amylamine) the expected product of the reaction was not obtained.

The structure of the reaction products has been based on their properties and the results of elementary analyses. The stability of the amines towards mineral acids indicates that the imine bond has disappeared and the CX_3 group has become attached. These amines are weak bases, the hydrochlorides of which easily undergo hydrolysis in the presence of water.[1,2] This property was used for purifying the hydrochlorides. By shaking the hydrochlorides with benzene and water the corresponding free amines pass quantitatively into the benzene phase, from which the pure hydrochloride may be precipitated. This was found to be the best method of purification for the hydrochlorides. All attempts to crystallize the hydrochlorides were

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

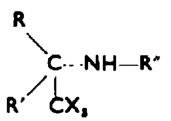
[2] A. Łukasiewicz, *Tetrahedron* **20**, 1113 (1964).

[3] G. Reddelien and O. Meyn, *Ber. Dtsch. Chem. Ges.* **53**, 353 (1920).

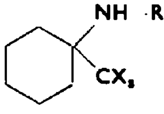
unsuccessful because of the instability of the compounds obtained. The hydrochlorides of the amines in their crystalline form and in non-polar solvents are stable at room temperature, but in solvating media undergo decomposition. The hydrochlorides easily lose hydrogen chloride at elevated temperature and this may account for the varying melting points, depending on the rate of heating.

The free amines are generally very unstable and decompose with the evolution of hydrogen halogenide (some of them even at room temperature) both in solutions and in the crystalline form. The stability of these amines depends on temperature and medium. In order to avoid amine decomposition, the temperature must be carefully controlled during synthesis as the amine stability decreases sharply with increasing temperature.

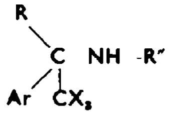
The stability of the compounds A obtained depends on their structure (A$_1$, A$_2$ and A$_3$) and the halogen in the CX$_3$ group. The least stable are the amines II and VII (A$_2$ and A$_1$ type with X = Br) which can not be isolated in the free state. They decompose even at room temperature with evolution of hydrogen bromide, and precipitation of the hydrobromides of the amines. The hydrobromide of the amine II precipitates during synthesis, in spite of the mild conditions of the reaction.



A$_1$



A$_2$



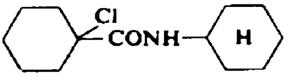
A$_3$

The amine I is the least stable of the trichloromethyl derivatives, although in contrast to II (A$_2$ with X = Br) it may be obtained in analytically pure form.

The compound VIII (A$_3$ type with X = Br) is the most stable and does not undergo decomposition under the conditions of the reaction.

A comparison of the stability of the compounds A obtained reveals that their instability may be due to steric hindrance, causing a state of tension in the molecule. The molecules in which the greatest steric hindrance is present (A$_2$ with R″ = cyclohexyl) decompose most readily. The instability of the tribromomethyl derivatives is probably also due to steric hindrance, in addition to the greater mobility of the bromine atom as compared with that of the chlorine atom. The steric hindrance probably weakens the carbon-halogen bond and, in consequence, the halogen atom is more easily abstracted. The increased stability of the compounds VIII (A$_3$ type) as compared with VII (A$_1$ type) is no doubt due to the stabilizing influence of the aryl group.

The rearrangement of the compounds A in a solvating medium was investigated taking the amine I as an example. Heating the amine I in water containing ethanol (95%) results in a mixture of the compounds IX and X (separated by column chromatography).



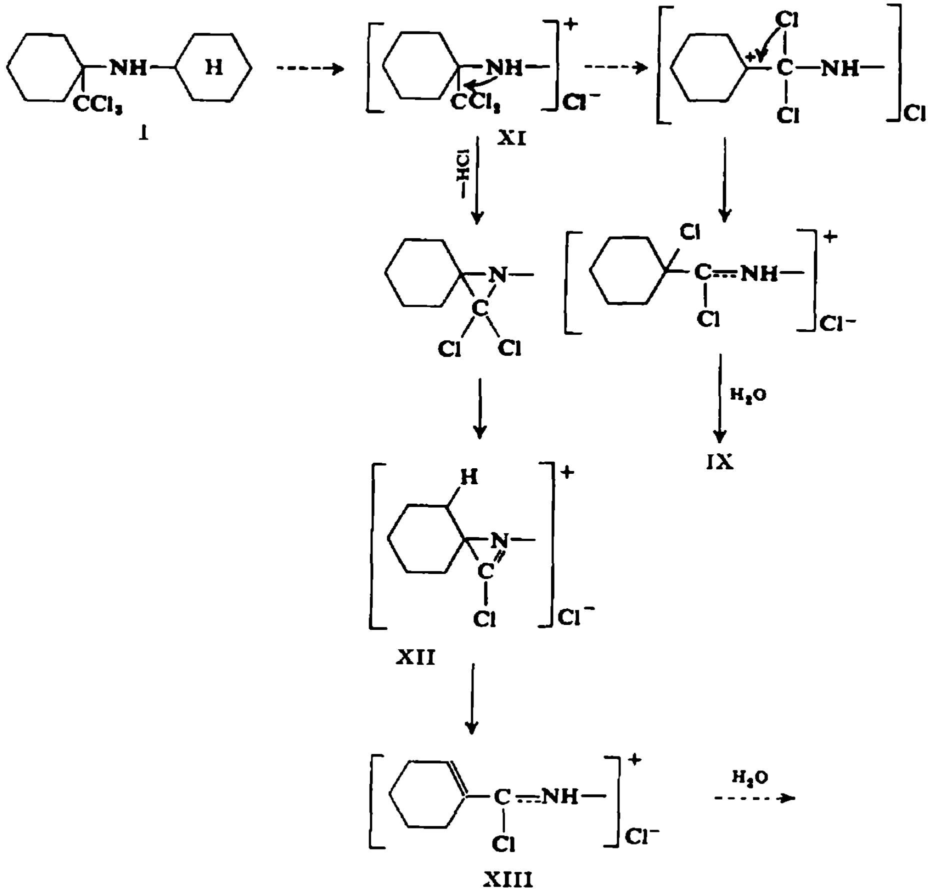
IX

X

Heating of I in anhydrous ethanol yielded, after removal of the alcohol and addition of anhydrous ether to the residue, a crystalline unstable product which on treatment with water transforms immediately into X with evolution of hydrogen chloride. From the ether solution, after decomposing with water, a mixture of IX and X was obtained and separated as above.

The structure of these compounds was based on the results of elementary analyses and the IR spectra.

The mechanism of these transformations is probably as follows:

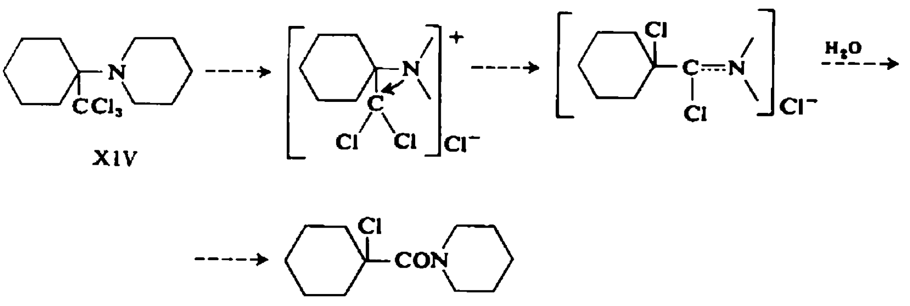


The transformation XI → IX is analogous to that described earlier for N-(1-aryl-2,2,2-tribromoethyl)-amines.[2,4] The scheme for transformation XI → X is supported by following facts:

1. As the crystalline unstable product isolated under anhydrous conditions gives on treatment with water only X, this intermediate must have in its structure a double bond (XIII).

[4] A. Łukasiewicz, *Tetrahedron* 21, 193 (1965).

2. The compound (XIV) obtained from corresponding enamine and trichloroacetic acid[5] (differing from I by the existence of t-nitrogen), in which the formation of the intermediate type XII is not possible undergoes transformation to α-chloroacylamine (XV) only and an unsaturated product is not formed:



XIV

XV

The amine I, when heated in a non-solvating medium gives in the presence of water mainly IX as the final product.

The transformations of the amines A in solvating and non-solvating media are the object of further studies.

EXPERIMENTAL

Materials. Anhydrous trichloroacetic acid (chemical grade) and tribromoacetic acid (Schuchardt or Fluka) were used. Ketimines were prepared by heating the ketones and amines in equimolar ratio and removing the water formed as an azeotropic mixture with benzene or toluene. As this method was unsuccessful in the case of cyclohexanone anil and benzophenone amylamine, the ketimines were obtained according to the Reddelien and Meyn method (in the presence of ZnCl$_2$).[*]

All the ketimines used were purified by vacuum distillation and were not analysed. All m.ps are uncorrected.

The reaction of ketimines with trihalogenoacetic acids

N-*Cycloheyl* (1-*trichloromethylcyclohexylamine*) (I). To a benzene solution of ketimine (1·2 g, b.p. 103°/4 mm), obtained from cyclohexanone and cycloheylamine, trichloroacetic acid (1·1 g) in benzene was added dropwise at 45–50°. After the reaction was complete, the cooled reaction mixture was washed with 0·5 N HCl and water, and the benzene distilled off under red. press. The residue was dissolved in anhydrous ethyl acetate and a solution of dry HCl in ether added and the precipitate of the hydrochloride of the amine (I) filtered off (1·75 g), m.p. 138–140° (dec). The amine (I) was obtained by decomposing the hydrochloride in benzene–water and removing the benzene (red. press.), m.p. 52–52·5 after crystallization from hexane. (Found: C, 52·30; H, 7·1; N, 4·8. $C_{13}H_{22}NCl_3$ requires: C, 52·25; H, 7·4; N, 4·7%.)

N-*Cyclohexyl*(1-*tribromomethyl-cyclohexylamine*)*hydrobromide* (II). To a benzene solution of ketimine (2·8 g) tribromoacetic acid (4·6 g) in benzene was added at 20–25° during stirring with a magnetic bar stirrer. In spite of the mild conditions of the reaction (the reaction mixture was cooled), when evolution of gas ceased (after 0·5 hr), the hydrobromide of the amine (II) was precipitated. This was filtered off and washed with acetone (3·7 g), m.p. 145–147° dec (Found: C, 30·45; H, 4·4; N, 3·1. $C_{13}H_{22}NBr_4$ requires: C, 30·45; H, 4·5; N, 2·75%.)

The benzene was distilled off from the filtrate under red. press. and anhydrous ether added to the residue (oil). After filtering off a small amount of II, the ether solution was saturated with dry HCl but no precipitation occurred. A small amount (0·15 g) of the neutral compound (1-bromo-1-N-cyclohexylcarboxamidocyclohexane) was obtained from the solution and crystallized from pet. ether, m.p. 97–98·5°. (Found: C, 54·4; H, 7·9; N, 4·9. $C_{13}H_{22}NOBr$ requires: C, 54·15; H, 7·65; N, 4·85%.)

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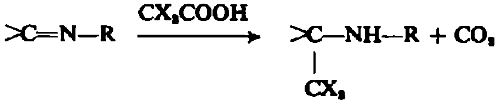
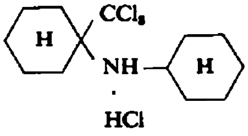
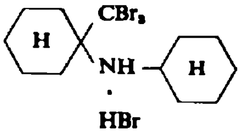
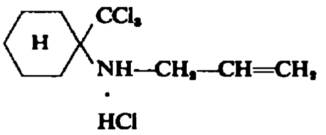
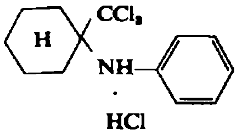
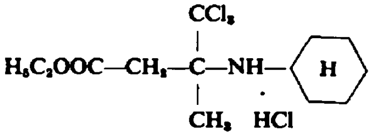
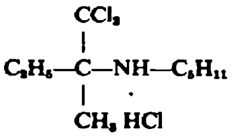
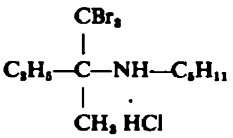
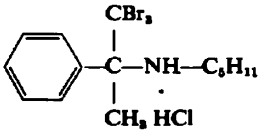
[*] In preparation.

TABLE 1. YIELDS AND CONDITIONS (TEMP) OF THE REACTION



$$>C=N-R \xrightarrow{CX_3COOH} \underset{\displaystyle CX_3}{>C}-NH-R + CO_2$$

No.	Reaction product	Yield %	Temp °C
I		78	45
II		46	25
III		48	55
IV		45	70
V		43	75
VI	 $C_2H_5-\underset{CH_3}{\overset{CCl_3}{C}}-NH-C_6H_{11} \cdot HCl$	40	55
VII	 $C_2H_5-\underset{CH_3}{\overset{CBr_3}{C}}-NH-C_6H_{11} \cdot HCl$	50	28
VIII		48	45

N-*Allyl*(1-*trichloromethylcyclohexylamine*)*hydrochloride* (III). The imine (1·8 g, b.p. 83–85° 1–2 mm), obtained from cyclohexanone and allylamine, and 2·3 g trichloroacetic acid (at 50–55°, procedure as for I) yielded 1·8 g III. The product was purified by decomposition with a benzene–water mixture and reprecipitation of the hydrochloride, m.p. 141–143° dec. (Found: C, 41·4; H, 5·8; N, 4·85. $C_{10}H_{17}NCl_4$ requires: C, 41·0; H, 5·8; N, 4·8%.)

N-*Phenyl*(1-*trichloromethylcyclohexylamine*)*hydrochloride* (IV). The imine (5·6 g, b.p. 116°/4 mm) from cyclohexanone and aniline and trichloroacetic acid (5·4 g) was heated in benzene at 70° yielding (procedure as above) 4·7 g IV, m.p. 127–129° dec. (Found: C, 47·55; H, 5·2; N, 4·5. $C_{13}H_{17}NCl_4$ requires: C, 47·45; H, 5·2; N, 4·25%.) The free amine obtained by decomposition of the hydrochloride with a benzene–water mixture, crystallized from hexane, m.p. 64·5–65·5°. (Found: C, 53·6; H, 5·6; N, 5·1. $C_{13}H_{16}NCl_3$ requires: C, 53·35; H, 5·5; N, 4·8%.)

3-(*Trichloromethyl*)-3-(N-*cyclohexylamine*)*ethyl butyrate hydrochloride* (V). The imine (2 g, b.p. 101–102°/1 mm) obtained from ethyl acetoacetate and cyclohexylamine was heated with trichloroacetic acid (1·6 g) in benzene at 75°. The residue, after washing with 0·25 N HCl and with water, and after evaporation of benzene (red. press.), was dissolved in anhydrous ether with a few drops of acetone and a solution of dry HCl in ether added and the precipitate (V) filtered off (1·5 g), m.p. 111–112° dec. (Found: C, 42·45; H, 6·3; N, 3·75. $C_{13}H_{23}O_2NCl_4$ requires: C, 42·5; H, 6·25; N, 3·8%.)

N-(1-*Ethyl*-1 *methyl*-2,2,2-*trichloroethyl*)*amylamine hydrochloride* (VI). The imine (4·2 g, b.p. 45–47°/4–5 mm) obtained from methylethyl ketone and n-amylamine and 4·8 g trichloroacetic acid (in benzene at 55°) yielded 3·5 g VI (precipitated from anhydrous ether with HCl in ether). After purifying by decomposition with a benzene–water mixture and reprecipitation as above, VI melted at 134–135° dec. (Found: C, 40·8; H, 6·95; N, 4·85. $C_{10}H_{21}NCl_4$ requires: C, 40·45; H, 7·15; N, 4·7%.)

N-(1-*Ethyl*-1-*methyl*-2,2,2-*tribromoethyl*) *amylamine hydrochloride* (VII). To the benzene solution of imine (0·95 g) tribromoacetic acid (1·99 g) in benzene at 28–30° was added. After the reaction was complete, part of the benzene was distilled off under red. press. (during evaporation the hydrobromide is precipitated). A solution of dry HCl in anhydrous ether with a small amount of ethyl acetate was added to the residual benzene solution and the precipitate of VII (1·4 g) filtered off. After purification (by decomposition with a benzene–water and reprecipitation) the hydrochloride melted at 143–145 dec. (Found: C, 28·0; H, 4·8; N, 3·3. $C_{10}H_{21}NCl\,Br_3$ requires: C, 27·9; H, 4·9; N, 3·25%.)

N-(1-*Phenyl*-1-*methyl*-2,2,2-*tribromoethyl*)*amylamine hydrochloride* (VIII). The imine (2 g, b.p. 100–105°/1–3 mm) obtained from acetophenone and n-amylamine was heated with tribromoacetic acid (3·1 g) in benzene at 45°. The mixture was washed with 0·5 N HCl and with water, and the residue after evaporating the benzene (red. press.) was dissolved in a mixture of anhydrous ether and ethyl acetate with a few drops of acetone and a solution of dry HCl in ether added and the precipitated VIII filtered off (2·3 g) m.p. 138–140° dec unchanged after purification. (Found: C, 35·3; H, 4·4; N, 3·1. $C_{14}H_{21}NClBr_3$ requires: C, 35·15; H, 4·4; N, 2·95%.)

Rearrangement of the amine I

1. *In anhydrous ethanol.* The amine I (3·7 g) was heated in anhydrous EtOH (40 ml) for 3 hr. The EtOH was distilled off (red. press., the alcohol being acidic) and to the residue anhydrous ether (25 ml) was added. The precipitate (0·6 g; unstable product evolving HCl) was filtered off, and after decomposition with water, 0·4 g of the neutral compound X (1-cyclohexene-1-N-cyclohexylcarboxamide) was isolated, m.p. 117–118° and after crystallization from hexane, 117·5–118·5°. (Found: C, 75·6; H, 10·15; N, 6·75. $C_{13}H_{21}NO$ requires: C, 75·35; H, 10·15; N, 6·75%.) The IR spectrum: $\nu_{max}^{CCl_4}$ cm^{-1} 3418 (NH group), ν_{max}^{Nujol} cm^{-1} 1657 (amide carbonyl), 1612 (C═C bond), 1539 (amide II).

The ether filtrate was shaken with water. The ether layer was dried (the water layer being acidic) and the solvent was evaporated. From the neutral solid residue (2·1 g) after crystallization from hexane 0·24 g of the compound X was isolated. The residue (1·7 g) was separated by column chromatography (Al_2O_3, activity grade 0·09). The two components were isolated. The first fraction with hexane as eluent (0·45 g) m.p. 87–89° (88–89·5° after crystallization from pet. ether) was identified as 1-chloro-1-N-cyclohexylcarboxamidocyclohexane (IX), (Found: C, 64·25; H, 9·3; N, 5·75, $C_{13}H_{22}NOCl$ requires: C, 64·05; H, 9·1; N, 5·75%.) The IR spectrum: $\nu_{max}^{CCl_4}$ cm^{-1} 3420 (NH group), ν_{max}^{Nujol} cm^{-1} in the region 1676–1663 (amide carbonyl), 1530–15 (amide II), 738 (C–Cl). The second fraction with benzene as eluent gave 1·1 g of the compound X.

2. *In water containing alcohol* (~95% EtOH). The amine I (4·8 g) was heated in water containing EtOH (50 ml) for 4 hr. The EtOH was distilled off (red. press., the alcohol being acidic) and to the residue anhydrous ether was added. After filtering the solution, a precipitate was obtained (0·25 g) the properties of which corresponded to cyclohexylamine hydrochloride. Ether was removed from the filtrate (red. press., the ether being acidic) and the solid residue (3·2 g) was dissolved in benzene. The benzene solution was washed with water and after drying the benzene layer, the solvent was distilled off. From the residue, following the above procedure (1), 0·55 g IX and 1·6 g X were obtained.

3. *In anhydrous benzene*. The amine I (2·3 g) was heated in anhydrous benzene (20 ml) for 80 hr. The benzene was distilled off (red. press.) and to the residue a mixture of anhydrous ether and ethyl acetate (5:1) was added. To the filtrate after filtering off a small amount of the hydrochloride of the amine I, a solution of dry HCl in anhydrous ether was added and the hydrochloride of the undecomposed amine I (0·7 g) was filtered off. The solvent was distilled off from the filtrate and the residue (oil) dissolved in EtOH and the compound IX precipitated with water (0·6 g, m.p. 87·5–89°). The filtrate after evaporation of the EtOH was shaken with benzene. The benzene layer was dried and the solvent was removed. The residue (0·5 g) was separated by column chromatography (following the procedure 1) and the two components IX (0·2 g) and X (0·15 g) were isolated.

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

Acknowledgement—The authors are indebted to Mr. W. Stachowicz for performing the infrared spectrum analysis.