Tetrahedron Vol 24. pp. 7 to 11 Pergamon Press. 1968. Printed in Great Britain

REACTIONS OF TRIHALOGENOACETIC ACIDS—VI*

THE REACTION OF TRICHLOROACETIC ACID WITH ENAMINES

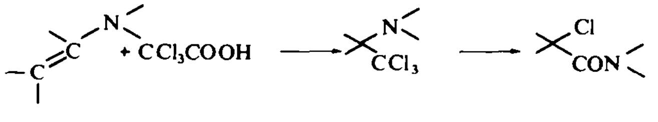
A. Łukasiewicz and J. Lesińka

Institute of Nuclear Research,
Warsaw 91, Dorodna 16, Poland

(Received in the UK 20 March 1967; accepted for publication 5th April 1967)

Abstract—Trichloroacetic acid reacts with various enamines in benzene with evolution of CO_2 and formation of α-(trichloromethyl) amine derivatives. The latter, when heated in ethanol undergo rearrangement to the corresponding α-chloroacylamines.

Trichloroacetic acid reacts with cyclic enamines, yielding trichloromethyl derivatives (A), which in a solvating medium undergo rearrangement to α-chloroacylamines (B).[1]



A B

In the present work the reaction of trichloroacetic acid with various cyclic as well as noncyclic enamines is described in detail.

The reaction was carried out in dry benzene at 18–65° depending on both the reactivity of the components and stability of the reaction products (A).

If the temperature of the reaction is too high the products undergo decomposition with evolution of hydrogen chloride and the evolution of carbon dioxide ceases even before addition of the required amount of trichloroacetic acid is complete.

The products (A) were usually isolated as free amines or in the form of their hydrochlorides but in some cases if they could not be isolated, their products of rearrangement (B) were obtained in an analytically pure form (Table 1).

The amines (A) are very weak bases and are very unstable. In a solvating medium they rearrange very easily to α-chloroacylamines (B). The hydrochlorides of the amines are much more stable and can be stored in a solid state unless as in some cases they are very hygroscopic and then they cannot be obtained analytically pure.

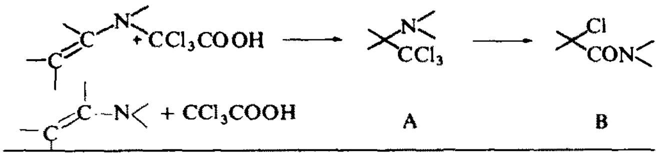
In addition to the examples given in Table 1, trichloroacetic acid was reacted with 1-pyrrolidino-cycloheptene and 1-pyrrolidino-cyclooctene. Although the reaction occurs easily (in the first case at room temperature) the products could not be isolated as either A or B in an analytically pure state.

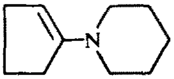
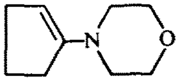
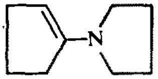
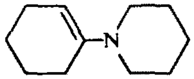
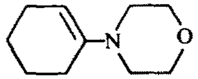
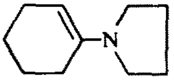
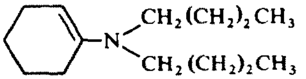
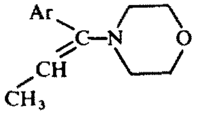
It seems that the stability of the compounds (A) in the case of derivatives of cyclic enamines, depends on size of the ketone ring. The most stable are the cyclopentyl

---

* Part V, A. Lukasiewicz, *Tetrahedron* **23**, 1713 (1967).

TABLE 1. YIELDS OF THE REACTION:



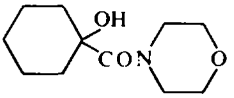
No	Enamine	Reaction products isolated		
		A[a] (B)		Yield %
1		I	A	57·5
2		II[b]	A	80
3		III	A	67
4		IV V	A B	30 + 22
5		VI[b]	A[c]	89
6		IX X	A B	33 + 33
7		XI	B	76
8		XII	B	45

[a] The hydrochloride of the amine.
[b] The compounds II and VI were described by S. Alt and A. Speziale (*J. Org. Chem.* **31**, 1340 (1966).)
[c] The free amine.

derivatives. No marked influence of the size of amine-moiety on the stability of the derivatives A was observed. The morpholine derivatives seem to be more stable than the analogous pyrrolidine or piperidine derivatives. Only in the case of II and VI were crystalline free amines isolated. The amine II may be stored for a few days without marked decomposition. Probably the inductive effect of oxygen in the morpholine ring decreases the interaction of the nitrogen electron pair with the CCl_3 group, making the abstraction of the chlorine more difficult. Failure to obtain the hydrochloride of VI may be due to the same inductive effect (decrease in basicity of the amine).

The probable mechanism governing the rearrangement of compound A to α-chloroacylamines was presented in a previous publication.[1]

In the case of the product VI when the rearrangement occurred in water–ethanol medium, besides the expected compound of the type B (VII), the compound VIII also was isolated.

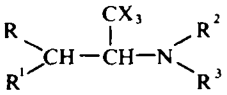


VIII

As chloroacylamine VII was stable on heating in ethanol-HCl medium, it may be assumed that the hydroxyl derivative VIII is formed as the result of hydrolysis of intermediate products, the latter being formed during rearrangement of the amine VI.

As the products (A) formed from enamines and trichloroacetic acid are unstable, the reaction with tribromoacetic acid was not investigated.

It was found that trihalogenoacetic acids also react with enamines derived from aliphatic aldehydes giving good yields of trichloro- and tribromomethyl derivatives of the type:



$$\begin{matrix} R & & CX_3 & & R^2 \\ & \rangle CH- & CH & -N\langle & \\ R^1 & & & & R^3 \end{matrix}$$

X = Cl or Br
NR^2R^3 = morpholine or piperidine rest.

This reaction will be described in a separate publication.

EXPERIMENTAL

Materials. Anhyd trichloroacetic acid (chemical grade) was used. Enamines were prepared by heating the ketones and amines in equimolar ratio or with excess of amine (1-morpholino-1-phenylpropylene) and removing the water formed as an azeotropic mixture with benzene or toluene (1- [di-n-butylamino] cyclohexene; 1-morpholino-1-phenylpropylene). In the case of 1-morpholino-1-phenylpropylene a small amount of toluene *p*-sulphonic acid was necessary.

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

N-[1-(*Trichloromethyl*)*cyclopentyl*] *piperidine hydrochloride* (I). To enamine (3·05 g) obtained from cyclopentanone and piperidine, dissolved in benzene, 3·4 g CCl_3COOH (in benzene) was added slowly at 50°. After the reaction was complete benzene was removed (red.press), anhyd ether was added and I was precipitated with dry HCl in ether (3·5 g), m.p. 112–114° dec. After decomposition by shaking with benzene–water I was reprecipitated as above, m.p. 114–115° dec. (Found: C, 43·25; H, 6·0; N, 4·75. $C_{11}H_{19}NCl_4$ requires: C, 43·0; H, 6·2; N, 4·55%).

On treating I with ethanol-water an oily product was formed (not analyzed).

N-[1-*(Trichloromethyl) cyclopentyl*] *morpholine hydrochloride* (II). To a benzene soln of enamine (4·6 g, b.p. 76–78°/2 mm) obtained from cyclopentanone and morpholine, trichloroacetic acid (4·8 g) in benzene was added dropwise at 55°. The reaction mixture was heated 1·5 hr until evolution of CO_2 ceased).

The solvent was distilled off under red.press and a mixture of anhyd ether and benzene added to the residue (oil). Most of the oil dissolved, and the soln was separated from undissolved oil, some of the solvent was removed under reduced press. (during further evaporation the hydrochloride II was precipitated), a soln of dry HCl in anhyd ether was added and the ppt of II (7·2 g) filtered off (m.p. 116–117° dec).

From the undissolved oil after decomposition with benzene–water and addition of dry HCl in ether 0·25 g of II was additionally obtained. The hydrochloride II was decomposed by shaking with a benzene–water. The benzene layer after removing the solvent afforded a crystalline neutral residue (m.p. 73–74·5°) of the free amine. To the amine dissolved in anhyd ether, a soln of dry HCl in ether was added and the pure hydrochloride II m.p. 116·5–117° dec. filtered off. (Found: C, 39·05; H, 5·5; N, 5·05. $C_{10}H_{17}ONCl_4$ requires: C, 38·85; H, 5·55; N, 4·55%).

N-[1-*(Trichloromethyl)cyclopentyl*] *pyrrolidine hydrochloride* (III). The enamine (4·2 g, b.p. 61°/3 mm), obtained from cyclopentanone and pyrrolidine and 4·8 g trichloroacetic acid (at 40°, procedure as for II) yielded 5·9 g III (m.p. 125–127° dec). After purification (by decomposition with a benzene–water and reprecipitation) the hydrochloride melted at 125–126° dec. (Found: C, 41·25; H, 5·8; N, 4·85. $C_{10}H_{17}NCl_4$ requires: C, 41·0; H, 5·8; N, 4·8%).

N-[1-*(Trichloromethyl)cyclohexyl*] *piperidine hydrochloride* (IV) *and* N-*(1-chlorocyclohexylcarbonyl) piperidine* (V). To a benzene soln of enamine (3·3 g) from cyclohexanone and piperidine 3·4 g CCl_3COOH (in benzene) was added dropwise at 50–60°. After the reaction was complete the mixture was cooled. The ppt formed was filtered off (probably enamine hydrochloride), benzene was removed from the filtrate, dry ether added and then ether with dry HCl, yielding 1·4 g IV, m.p. 74–75·5°. (Found: C, 44·5; H, 6·7; N, 4·6. $C_{12}H_{21}NCl_4$ requires: C, 44·85; H, 6·55; N, 4·35%.) The filtrate was evaporated, n-heptane was added and ether with dry HCl yielding additionally 0·5 g IV (m.p. 74–75°). The filtrate was evaporated again and EtOH with water was added. The mixture became warm and after adding some water the crystalline V was precipitated (1·0 g), m.p. 69–70·5°. (Found: C, 62·85; H, 8·65; N, 6·1, $C_{12}H_{20}ONCl$, requires: C, 62·9; H, 8·75; N, 6·1%).

On treating 0·7 g IV with EtOH–water, the mixture became warm and after a few min V (0·45 g) precipitated.

N-[1-*(Trichloromethyl) cyclohexyl*] *morpholine* (VI). To a benzene soln of enamine (2·1 g, b.p. 86–87°/2 mm) obtained from cyclohexanone and morpholine, trichloroacetic acid (2·1 g) in benzene was added dropwise at 65°. After evolution of gas ceased (1 hr) the turbid reaction mixture was filtered. Evaporation of the solvent under reduced press. gave a crystalline VI (3·2 g) which after crystallization from hexane melted at 74·5–75·5°. (Found: C, 46·4; H, 6·1; N, 5·15. $C_{11}H_{18}ONCl_3$ requires: C, 46·1; H, 6·3; N, 4·9%). The free amine was analysed in spite of its instability, because the attempts to isolate the hydrochloride were unsuccessful

Rearrangement of the amine VI

(a) *In anhydrous ethanol.* The amine VI (1·5 g) was heated in anhyd EtOH (15 ml) under reflux for 15 hr The EtOH was distilled off (red. press.) and to the residue (1·1 g) anhyd ether was added. After filtering (0·2 g of a ppt the properties of which corresponded to morpholine hydrochloride) the soln was washed with water and after drying the ether layer, the solvent was distilled off. The neutral oily residue was dissolved in hexane, filtered through Al_2O_3 and evaporated. The thick oil residue (0·85 g), which partially solidified on long standing in the refrigerator, after crystallization from pet. ether and drying on filter paper melted at 50–52° and was identified as N-(1-chlorocyclohexylcarbonyl) morpholine (VII). (Found: C, 57·4; N, 7·8; N, 6·3. $C_{11}H_{18}O_2NCl$ requires: C, 57·1; H, 7·8; N, 6·05%).

(b) *In ethanol-water mixture.* The product VI (4·0 g) was dissolved in aqueous EtOH. The mixture became warm and after adding water an oil was formed. After a few days EtOH was removed by evaporation (on heating). The residue was extracted with benzene and the benzene soln was dried, filtered through Al_2O_3 and evaporated. The residual oil solidified on standing in the refrigerator and was crystallized from hexane yielding 0·4 g of the solid neutral product (m.p. 139–140·5°) identified as N-(1-hydroxycyclohexylcarbonyl) morpholine (VIII). (Found: C, 61·95; H, 8·7; N, 6·75. $C_{11}H_{19}O_3N$ requires: C, 61·95; H, 8·95; N, 6·55%). The IR spectrum: ν_{max}^{Nujol} cm^{-1} 3340 (OH-tertiary; possible intramolecular hydrogen bonding); 1620 (amide I, tertiary); 1120 (C–N tertiary). The hexane filtrate was evaporated, the residue was dissolved in EtOH and a few drops of water was added. After long standing in the refrigerator the crystalline VII which formed was filtered off (1·7 g).

N-[1-(*Trichloromethyl*)*cyclohexyl*]*pyrrolidine hydrochloride* (IX) *and* N-(1-*chlorocyclohexylcarbonyl*)-*pyrrolidine* (X). To a benzene soln of enamine (1·5 g, 0·01 mol; b.p. 84–85°/3 mm) obtained from cyclohexanone and pyrrolidine, trichloroacetic acid (1·2 g, 0·0075 mol) in benzene was added dropwise at 20°. (For equimolar ratio of components the reaction ceased after adding ~75% of acid). After the reaction was complete, the solvent was evaporated *in vacuo* (without heating) and anhyd ether added to the residual oil. From the ether soln (nearly all the oil dissolved) some of the solvent was removed (red. press.), a soln of dry HCl in anhyd ether was added and a very hygroscopic ppt (IX) quickly filtered off and washed with anhyd ether with addition of a few ml of dry HCl in ether (0·7 g), m.p. is not characteristic (92–100°) and depends on the time of drying. (Found: C, 43·8; H, 6·0; N, 4·9. $C_{11}H_{19}NCl_4$ requires: C, 43·05; H, 6·2; N, 4·6%). (Because of its hygroscopic nature it is very difficult to obtain IX in an analytically pure state.)

The ether filtrate was shaken with water and the solvent distilled off. From the residue after adding EtOH and then water at room temp, X (0·5 g) was precipitated (m.p. 60–63°) which after crystallization from hexane, m.p. 64–65°. (Found: C, 61·25, H, 8·25; N, 6·5. $C_{11}H_{18}ONCl$ requires: C, 61·2; H, 8·4; N, 6·5%). The hydrochloride (IX) decomposes in EtOH–water to X.

N-(1-*Chlorocyclohexylcarbonyl*)*di-n-butylamine* (XI). To a benzene soln of enamine (4·15 g, b.p. 117–118°/5 mm), obtained from cyclohexanone and di-n-butylamine (azeotropic method with toluene for 30 hr), trichloroacetic acid (3·25 g) in benzene was added dropwise at 18–20°. After the reaction was complete, the reaction mixture was washed with 0·25N HCl and water. After drying the benzene layer, evaporation of the solvent under reduced press. (without heating) gave 5·2 g of an orange acidic oil. All attempts to obtain the crystalline amine or hydrochloride were unsuccessful.

The oily product (2·6 g) was dissolved in anhyd EtOH (15 ml) and heated under reflux for 8 hr. The EtOH was distilled off and the residue taken up with hexane. After filtering off a small amount (0·1 g) of a ppt, the hexane soln was washed with water, dried, filtered through Al_2O_3 (activity grade 0·08), and evaporated. The residual oil (2·1 g) after molecular distillation (pot still of Hickman-type) was identified as XI. (Found: C, 65·8; H, 10·35; N, 5·55. $C_{15}H_{28}ONCl$ requires: C, 65·8; H, 10·3; N, 5·1%). The IR spectrum: ν_{max}^{Nujol} cm^{-1} 1635 (Amide I, tertiary); 1125 (C—N tertiary); 680 (C—Cl).

N-(1-*Chloro*-1-*phenyl*-1-*ethyl* ~ acetyl) *morpholine* (XII). The enamine (8·4 g, b.p. 118°/3 mm) obtained from propiophenone and morpholine (azeotropic method with toluene in the presence of small amount of toluene *p*-sulphonic acid for 35 hr) and 6·9 g trichloroacetic acid (at 40–30°, procedure as for XI) yielded 6·1 g of an oily product. All attempts to obtain the hydrochloride in an analytically pure state were unsuccessful.

A soln of the oil in anhyd EtOH (35 ml) was heated under reflux for 8 hr. EtOH was evaporated and the residue was taken up in benzene. After filtering off a ppt (0·05 g) the properties of which corresponded to morpholine hydrochloride the soln was washed with water and after drying the solvent was removed. The neutral oily residue was dissolved in a few ml of EtOH (90%). After a few days a small amount (0·13 g) of neutral ppt (needles) was filtered off (m.p. 125–126° lack of N). From the filtrate the solvent was evaporated and the residual dense oil (4·8 g) after molecular distillation was identified as XII. (Found: C, 62·3; H, 6·3; N, 5·2. $C_{14}H_{18}O_2NCl$ requires: C, 62·75; H, 6·75; N, 5·2%.) The IR spectrum: ν_{max}^{Nujol} cm^{-1} 1640 (amide I, tertiary); 1117 (C—N tertiary), 700 (C—Cl).

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

Acknowledgement—The authors are indebted to Mr. S. Lis for performing the infrared spectrum analysis.

REFERENCE

[1] A. Łukasiewicz and J. Lesińska, *Tetrahedron* **21**, 3247 (1965).