Tetrachloro-*bis*-(trifluoromethyl)-benzene.[9]—Chlorination of 238 g. of the dichloro-*bis*-(trifluoromethyl)-benzene obtained above for three hours at 165–215° in the presence of 0.05 g. of aluminum chloride yielded 76 g. of starting material, 55 g. of intermediate fractions (b. p. 180–241°), and finally 31 g. (b. p. 241–244°) which solidified on cooling. Crystallized from ethyl alcohol, it gave colorless crystals, m. p. 47–48°.

Anal. Calcd. for $C_8Cl_4F_6$: Cl, 40.04. Found: Cl, 40.09.

Summary

It has been demonstrated that chlorination of bis-(trifluoromethyl)-benzenes may be effected at elevated temperatures and pressures.

DURHAM, N. C.

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[9] Experiment by Jean B. Bond.

[CONTRIBUTION FROM THE AVERY LABORATORY OF CHEMISTRY OF THE UNIVERSITY OF NEBRASKA]

α-Chloro-β-amino Ketones

BY NORMAN H. CROMWELL AND RONALD A. WANKEL

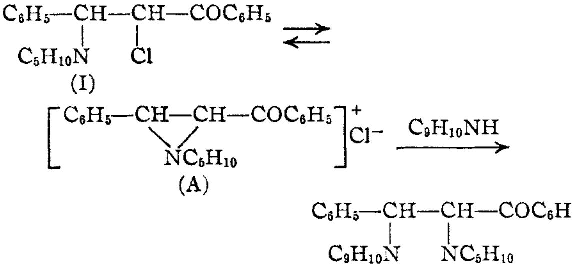
In a previous communication[1] a study was reported concerning the rate of iodine release from acidified potassium iodide solution by α-bromo β-amino ketones prepared from α-bromobenzalacetophenone. These results were compared with those obtained from similar studies with bromobenzylaminobenzylacetophenone hydrobromides prepared by the reactions of 1-benzyl-2-phenyl-3-benzoylethylenimine with wet and dry hydrogen bromide.[1,2] Also recorded was the fact that at room temperature the chlorobenzylaminobenzylacetophenone hydrochlorides, produced by the action of wet or dry hydrogen chloride, gave a slow iodine release. In this latter case no authentic α-halogenated β-amino ketones were available for comparison as had been the case with the bromo series.

Recently considerable interest has been shown in various types of β-chloroethylamines, $\left(\rangle N-\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}-Cl\right)$.[3] β-Halogenated ethylamines seem to owe some of their unusual chemical and physiological properties to the ability of their solutions to form the very reactive quaternary ethyleneimmonium ions.[4]

In the present investigation certain α-chloro β-amino ketones have been prepared for iodine release studies and for pharmacological investigation.

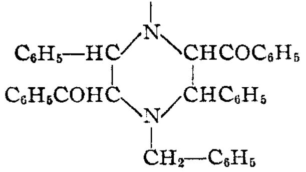
Piperidine, morpholine and tetrahydroisoquinoline each added readily to both α-chlorobenzalacetophenone and α-chlorobenzalacetone to give the desired α-chloro β-amino ketones. Attempts to add benzylamine or dibenzylamine or tetrahydroquinoline to α-chlorobenzalacetophenone were not successful. These α-chloro β-amino ketones, especially the α-chloro-β-aminobenzylacetophenones, proved to be considerably more stable than the corresponding bromo compounds reported in the previous studies.[4]

α-Chloro-β-piperidinobenzylacetophenone (I) was quite stable in absolute alcohol solutions at room temperature, showing little tendency to form the quaternary ethyleneimmonium ion (A), as indicated by the slight reaction of such solutions with silver nitrate after standing fifteen hours. However, this α-chloro β-amino ketone reacted readily with tetrahydroquinoline, as did the analogous bromo ketone,[5] to give a good yield of α-piperidino-β-tetrahydroquinolinobenzylacetophenone.



The hydrochlorides of the α-chloro-β-aminobenzylacetophenones were readily prepared and found to be quite stable in alcohol solution, showing no tendency to rearrange to the β-chloro α-amino ketone hydrochlorides. The hydrochlorides of the α-chloro-β-aminobenzylacetones proved to be too unstable to isolate.

For comparative purposes the reactivity of α,β-dichlorobenzylacetophenone with benzylamine was checked and it was found that the yield of the ethyleneimine ketone was about the same as with dibromo ketones.[6] The molecular weight of this product was determined to eliminate the possibility that this compound might be a piperazine such as



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[1] Cromwell and Caughlan, THIS JOURNAL, **67**, 2235 (1945).

[2] Cromwell, Babson and Harris, *ibid.*, **65**, 312 (1943).

[3] For example, the nitrogen mustards, Gilman and Philips, *Science*, **103**, 409 (1946); N,N-dibenzyl-β-chloroethylamine, Nickerson and Goodman, *Federation Proc.*, Feb., 1946, p. 195; N-benzohydryl-β-chloroethylamines, Cromwell and Fitzgibbon, THIS JOURNAL, **70**, 387 (1948).

[4] Cromwell and Cram, *ibid.*, **65**, 301 (1943); Cromwell, *Chem. Rev.*, **38**, 118 (1946).

[5] Cromwell, THIS JOURNAL, **63**, 2984 (1941).

[6] Cromwell, *ibid.*, **69**, 258 (1947).

TABLE I

PHYSICAL AND ANALYTICAL DATA FOR α-CHLORO β-AMINO KETONES

α-Chlorobenzylacetophenones	No.	M. p., °C.	Yield, %	Formula	Chlorine, % Calcd.	Chlorine, % Found
β-Piperidino	(I)	124	75	$C_{20}H_{22}ONCl$	10.82	10.64
Hydrochloride	(II)	142	90	$C_{20}H_{23}ONCl_2$	19.47	19.36
β-Morpholino	(III)	127	74	$C_{19}H_{20}O_2NCl$	10.75	10.68
Hydrochloride	(IV)	148	93	$C_{19}H_{21}O_2NCl_2$	19.36	19.27
β-Tetrahydroisoquinolino	(V)	95	69	$C_{24}H_{22}ONCl$	9.43	9.28
Hydrochloride	(VI)	114	91	$C_{24}H_{23}ONCl_2$	17.20	17.01
α-Chlorobenzylacetones						
β-Piperidino	(VII)	57	55	$C_{15}H_{20}ONCl$	13.34	13.12
β-Morpholino	(VIII)	65	66	$C_{14}H_{18}O_2NCl$	13.24	13.04
β-Tetrahydroisoquinolino	(IX)	76	45	$C_{19}H_{20}ONCl$	11.30	11.09

TABLE II

RELEASE OF IODINE BY CHLORO KETONES IN THIRTY MINUTES AT 26° (0.200 G. SAMPLES)

Halogenated ketone	0.0300 M $Na_2S_2O_3$, ml. used	0.0300 M $Na_2S_2O_3$, ml. required	Per cent. reaction
(III)	1.93	40.40	4.78
(V)	1.35	35.48	3.52
(VI)	0.97	32.38	3.03

As shown in Table II, these various α-chloro β-amino ketones released iodine slowly from acidified potassium iodide solutions at room temperature. At elevated temperatures these compounds reacted with such solutions much more rapidly and at a constant rate. (See Fig. 1 and Table III.) It was also found that the reaction products of 1-benzyl-2-phenyl-3-benzoylethylenimine with wet or dry hydrogen chloride[2] released no iodine under such conditions, and thus both must still be assumed to be β-chloro-α-benzylaminobenzylacetophenone hydrochloride, as was previously decided.[1] This constitutes a method of differentiating between α-chloro β-amino ketones and the very similar β-chloro α-amino ketones.

TABLE III

RELEASE OF IODINE BY CHLORO KETONES AT 66° (0.100 G. SAMPLES)

Sample	Reaction time in minutes	0.0300 M $Na_2S_2O_3$, ml. used	0.0300 M $Na_2S_2O_3$, ml. required	Per cent. reaction
(I)	20	19.89	20.34	97.8 ± 3.0
(II)	20	18.16	18.34	99.0
	15	16.48	18.34	89.9
	10	10.91	18.34	59.4
	5	5.70	18.34	31.1
(III)	20	19.69	20.20	97.4
(IV)	20	17.43	18.20	95.8
	15	16.90	18.20	92.9
(V)	20	16.95	17.74	95.6
(VI)	20	15.86	16.18	98.0
	15	12.94	16.18	80.0
(IX)	20	20.23	21.24	95.2
β-Chloro-α-benzylaminobenzylacetophenone hydrochloride	30[a]	0.00	17.14	0.0
	30[b]	0.00	17.14	0.0
α-Chlorobenzalacetophenone	20	1.36	27.34	5.0
Morpholine	30	0.00	...	0.0
Blank	30	0.00	...	0.0

[a] From 1-benzyl-2-phenyl-3-benzoylethylenimine and aqueous hydrogen chloride. [b] Using dry hydrogen chloride in benzene, see ref. 2.

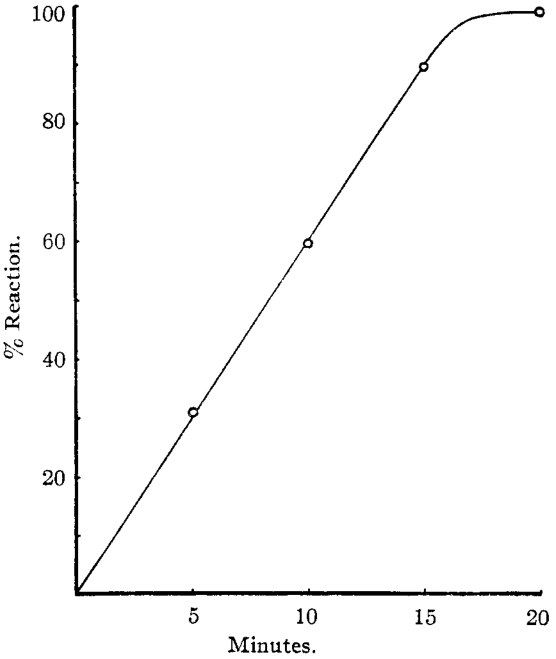

Fig. 1.—Rate of iodine release by (II) at 66°.

Nevertheless, further proof that certain ones of these reaction products of ethylene imine ketones with hydrogen halides actually are β-halogeno α-amino ketone hydrohalides seems to be required. Their very slow reaction with an acidified solution of potassium iodide could conceivably be the result of their being the least reactive of the two possible racemates of the α-halogeno β-amino ketone hydrohalide. This possibility is being investigated.

Experimental[7]

α,β-Dichloro Ketones.—These compounds were prepared by the methods given by Goldschmidt,[8] using an efficient gas–liquid reaction tower, as described by Degering.[9] The yield of α,β-dichlorobenzylacetophenone was the same as previously reported, but the yield of α,β-dichlorobenzylacetone was considerably lower, although the reaction was repeated several times. In a typical experiment, 40 g. (0.274 mole) of benzalacetone was dissolved in 50 ml. of chloroform, cooled to 5° and placed in the glass tower of the chlorination apparatus.[9] Tank grade chlorine gas was bubbled into the solution for one hour. The chloroform was evaporated under reduced pressure to leave an oily solid residue which on recrystallization from absolute alcohol gave 20 g. (33.6% yield) of α,β-dichlorobenzylacetone, m. p. 92–93°. Evaporation of the absolute alcohol solution and vacuum distillation of the residual oil gave 20 g. of α-chlorobenzalacetone, described below.

α-Chlorobenzalacetone.—This compound was obtained in an 83% yield according to the method given by v. Auwers and Brink.[10] The resulting yellow oil distilled at 140–141° at 5 mm. and solidified on cooling in an ice-bath. Recrystallization from petroleum ether (b. p. 60–70°) by cooling to 0° gave large, colorless crystals, m. p. 20–21°.

α-Chlorobenzalacetophenone.—This unsaturated chloroketone was prepared in a 75% yield by the method of v. Auwers and Hügel.[11] The golden yellow oil distilled at 195–200° at 5 mm. and solidified on cooling in an ice-bath. Recrystallization from petroleum ether gave large, colorless crystals, m. p. 29–30°.

Addition of Amines to the α-Chloro Unsaturated Ketones.—Five grams of the α-chloro unsaturated ketone was dissolved in 5 ml. of dry ether and the solution cooled to 0°. A cold solution of an equal molecular amount of the amine in 2 ml. of dry ether and 2 ml. of petroleum ether was added all at once. In five to ten minutes the solution became a solid mass. After standing in the ice-bath for one hour the colorless solid was filtered and washed with petroleum ether. These products were recrystallized by dissolving them in warm petroleum ether and then cooling the solutions to 0°. In this way the α-chloro β-amino ketones (I), (III), (V), (VII), (VIII) and (IX) were prepared (see Table I).

When 0.5 g. of (I) was dissolved in 10 ml. of absolute alcohol and allowed to stand at room temperature for fifteen hours, only a slight precipitate of silver chloride resulted upon addition of alcoholic silver nitrate. The chloro amino ketones (I), (III) and (V) were stable at room temperature for several months, while (VII), (VIII) and (IX) decomposed upon standing for twenty-four hours at room temperature.

Attempts to add benzylamine, or dibenzylamine, or tetrahydroquinoline to α-chlorobenzalacetophenone at various temperatures ranging from −40 to 40° were unsuccessful.

Hydrochlorides of α-Chloro β-Amino Ketones.—Five grams of the α-chloro-β-aminobenzylacetophenone was dissolved in 150 ml. of dry ether and 50 ml. of pure acetone and cooled to 10°. A cold saturated solution of dry hydrogen chloride in dry ether was added slowly with stirring until no further precipitation took place. The colorless solid product was filtered and recrystallized by dissolving in about 40 ml. of alcohol followed by the addition of 120 ml. of dry ether. In this way the hydrochlorides (II), (IV) and (VI) were prepared.

A 0.5-g. sample of (II) was dissolved in 25 ml. of absolute alcohol and allowed to stand at room temperature for forty-eight hours. Addition of 50 ml. of dry ether to this solution gave 0.48 g. of a compound identical with (II) (same m. p. and rate of iodine release).

The hydrochlorides of the α-chloro-β-aminobenzylacetones (VII), (VIII) and (IX) decomposed almost immediately upon isolation from the ether–acetone solutions to give the starting secondary amine hydrochlorides, and thus were not studied.

Reaction of Tetrahydroquinoline with (I).—Three grams (0.00915 mole) of (I) was dissolved in 5 ml. of absolute alcohol and 2.43 g. (0.0183 mole) of tetrahydroquinoline added. This solution was warmed for five minutes on a steam-bath and allowed to stand for forty-eight hours at room temperature. The light yellow product was filtered, washed with water and recrystallized from chloroform and alcohol to give 1.59 g. (41% yield) of yellow crystals, m. p. 166–167°, identical with α-piperidino-β-tetrahydroquinolinobenzylacetophenone,[5] as indicated by a mixed melting point experiment.

Reaction of α,β-Dichlorobenzylacetophenone with Benzylamine.—Nine grams (0.33 mole) of the dichloroketone was mixed with 10 ml. of alcohol and 6 ml. of benzene. This mixture was cooled in an ice-bath and then treated with 10.6 g. (0.097 mole) of benzylamine. Following the previously described procedure,[6] 2.3 g. (23% yield) of a compound, m. p. 107°, identical with 1-benzyl-2-phenyl-3-benzoylethylenimine[2] was obtained.

Mole Weight Determination.—Using 8–12% solutions in benzene and the cryoscopic method, calcd. for $C_{22}H_{19}NO$: 313. Found: 300, 316.

The Determination of Active Chlorine. (a) Reaction with Potassium Iodide at 26°.—Following the directions previously described,[1] the results given in Table II were obtained.

(b) **Reaction with Potassium Iodide at 66°.**—A mixture of 5 ml. of dry acetone, 5 ml. of absolute alcohol, 0.6 ml. of 3 *N* hydrogen chloride in absolute alcohol, and 16 ml. of 0.2 *N* potassium iodide in 50% absolute alcohol–acetone was brought to reflux temperature in a water-bath. A 0.100-g. sample of the chlorine compound was then dropped into this solution to dissolve immediately. After allowing the solution to reflux for the stated length of time, the flask was removed from the water-bath and 50 ml. of ice-cold water, along with 2 ml. of freshly prepared 2% starch solution was added immediately. The solution was then titrated rapidly with 0.0300 molar sodium thiosulfate until the color changed from blue to colorless (see Table III and Fig. 1).

Summary

1. Piperidine, morpholine and tetrahydroisoquinoline have been found to add readily to both α-chlorobenzalacetophenone and α-chlorobenzalacetone. The stability and reactivity of the resulting α-chloro β-amino ketones have been compared with that of the analogous α-bromo β-amino ketones.

2. The rates of reaction of chloro amino ketones with acidified potassium iodide solution have been studied, and a method of differentiating α-chloro β-amino ketones from β-chloro α-amino ketones proposed.

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[7] All m. p.'s were observed using a strong glass and obtained by placing the sample in the bath about 10° below the m. p. and heating at the rate of 3° per minute. Total chlorine determinations were made by the hydrogen jet method of Caldwell, *Ind. Eng. Chem., Anal. Ed.*, **7**, 38 (1935), and Winter, *ibid.*, **15**, 571 (1943), with the assistance and advice of H. Armin Pagel, Department of Chemistry, University of Nebraska.

[8] Goldschmidt, *Ber.*, **28**, 1532, 2540 (1895).

[9] Degering, *Ind. Eng. Chem.*, **24**, 181 (1932).

[10] v. Auwers and Brink, *J. prakt. Chem.*, **133**, 154 (1932).

[11] v. Auwers and Hügel, *ibid.*, **143**, 157 (1934).