

PHOTOLYSIS OF TRICLOCARBAN IN DILUTE AQUEOUS AND AQUEOUS ETHANOL SOLUTION

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(Received May 5, 1993; Revised August 9, 1994)

ABSTRACT. The photolysis of Triclocarban, N-(4-chlorophenyl)-N'-(3,4-dichlorophenyl)-urea in dilute aqueous and dilute aqueous ethanol solutions with pyrex filtered light from a mercury arc lamp is discussed. The photolysis products were separated after derivatization with N-methyl-N-trimethylsilyltrifluoroacetamide using gas chromatography. The major photolysis products were identified by mass spectrometry. The major primary photo-reaction is homolytic α -cleavage of the N-CO bond. Possible mechanisms to account for the observed products are proposed. The quantum yield for the loss of Triclocarban under these conditions was estimated to be 0.01.

INTRODUCTION

The halogenated carbanilides Triclocarban (TCC), (N-(4-chlorophenyl)-N'-(3,4-dichlorophenyl)urea, and Halocarban (HC), (N-(4-chlorophenyl)-N'-(4-chloro-3-(trifluoromethyl)phenyl)urea, are among those antimicrobial agents in common use in medicated ("deodorant") soap [1]. The rationale for developing the carbanilide antimicrobial agents, according to Beaver *et al.* [2], was to have new compounds "... more stable to light and less soluble in alkaline soap solutions than the previously described bis- and tris-phenols ...", then in wide use.

A study of the rate of hydrolysis of TCC in acidic, basic and neutral dilute aqueous solutions in the dark and under environmental "sunlight" conditions over a period of thirty days showed that the pseudo first order rate constants obtained in the presence of sunlight were an order of magnitude higher than those obtained in the absence of sunlight ($2.5 \pm 0.1 \times 10^{-3} \text{ day}^{-1}$ versus $3.8 \pm 0.3 \times 10^{-4} \text{ day}^{-1}$ in alkaline solution (0.5 M NaOH)) [3]. The corresponding half-life of TCC under natural sunlight was found to range between 43 and 130 days. The study concluded that, in addition to biodegradation, photohydrolysis is a major degradative pathway for TCC in the environment.

Although the photolysis of triclocarban has not been examined before, the photolysis of the closely related compounds N,N'-diphenylurea and monuron have been investigated. Crosby and Tang [4] examined the effect of sunlight on dilute aqueous solutions of monuron and, using thin layer chromatography, identified *p*-chloroaniline and 4,4'-dichlorocarbanilide

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among the photoproducts. Mazzochi and Rao [5] examined the photochemistry of methanolic solutions of monuron under non-oxygenated conditions employing a low-pressure mercury lamp (254 nm). A photo rearrangement similar to the Photo-Fries reaction of aryl esters and anilides was observed. The rearrangement products identified were 2-amino- and 4-amino-N,N-dimethylbenzamide. Dehalogenation was also observed in these experiments. Schwetlick *et al.* [6] irradiated methanolic solutions of N,N'-diphenylurea with a medium pressure mercury lamp (254 nm). The major products obtained could be explained by a homolytic α -cleavage of the N-CO bond followed by (a) Photo-Fries rearrangement within the solvent cage, or (b) diffusion of the radicals out of the solvent cage and subsequent interaction with the solvent.

The aim of the present work was to identify the major products of photolysis when neutral dilute aqueous and dilute aqueous ethanol solutions of TCC are irradiated with a mercury arc lamp. The products of photolysis were identified using combined gas chromatography mass spectrometry. The major photoproducts identified are shown in Table 1.

RESULTS AND DISCUSSION

Figures 1 and 2 show the chromatograms obtained for TCC irradiated in dilute aqueous ethanol solution, and aqueous solution, respectively. The quantum efficiency for the loss of TCC in dilute aqueous ethanol solution was estimated to be 0.009. This figure agrees with the figure of 4×10^{-3} reported by Schwetlick [7] for carbanilide (N,N'-diphenylurea) when irradiated with 254 nm light.

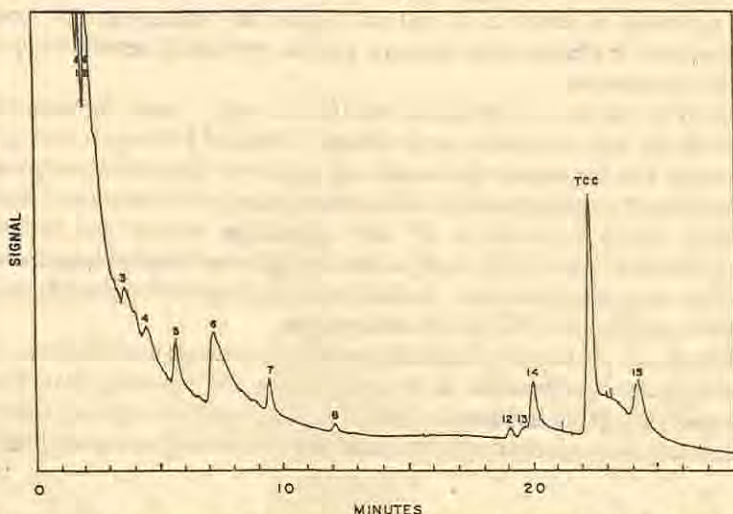


Figure 1. Chromatogram of Triclocarban in ethanol/water (77/23%) irradiated with pyrex filtered mercury arc light after derivatization with MSTFA.

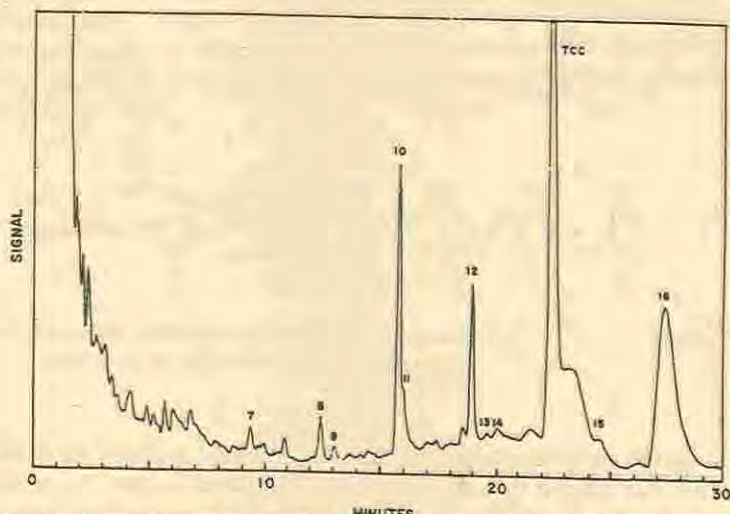


Figure 2. Chromatogram of Triclocarban in water irradiated with pyrex filtered mercury arc light after derivatization with MSTFA.

Table 1. GC retention data of TCC photolysis products.

GC peak	Figure 1		Figure 2		Assignment
	R _T	R _F	R _T	R _F	
1	1.8	0.081			R-N(SiMe ₃)COOEt
2	2.0	0.090			R-N=C=O
3	3.6	0.162	3.6	0.162	R ¹ -N(SiMe ₃)COOEt
4	4.4	0.198	4.4	0.198	R ¹ -N=C=O
5	5.6	0.252	5.6	0.252	R-N(SiMe ₃) ₂
6	7.1	0.320	7.1	0.320	
7	9.4	0.423	9.4	0.420	R ¹ -N(SiMe ₃) ₂
8	12.0	0.541	12.4	0.553	?
9			13.0	0.568	?
10			15.8	0.705	?
11			16.0	0.649	?
12	19.0	0.857	18.9	0.843	
13	19.6	0.883	19.6	0.875	ATCB(TMS) ₃
14	19.9	0.896	20.0	0.893	TCBP(TMS) ₄
TCC	22.2	1.00	22.4	1.00	TCC(TMS) ₂
15	24.2	1.09	24.5	1.093	?
16			27.2	1.222	?

R = -PhCl, R¹ = -PhCl₂

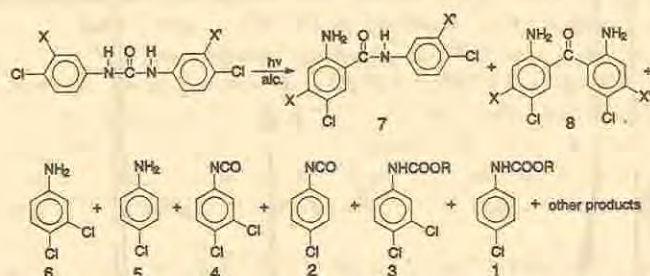
ATCB(TMS)₃ = *o*-amino-*m,p,p'*-trichlorobenzanilide, tri-TMS derivative

TCBP(TMS)₄ = *o,o'*-diamino-*m,p,p'*-trichlorobenzophenone, tetra-TMS derivative

TCC(TMS)₂ = Triclocarban di-TMS derivative

The photolysis of TCC in 77% ethanol irradiated with Pyrex filtered UV light from a medium pressure mercury lamp may be represented as shown in Scheme 1. The products obtained resemble those reported by Schwetlick *et al.* [6] for N,N'-diphenylurea and suggest that the primary photochemical process involves a homolytic α -cleavage of the N-CO bond. Possible secondary reactions leading to the observed products are:

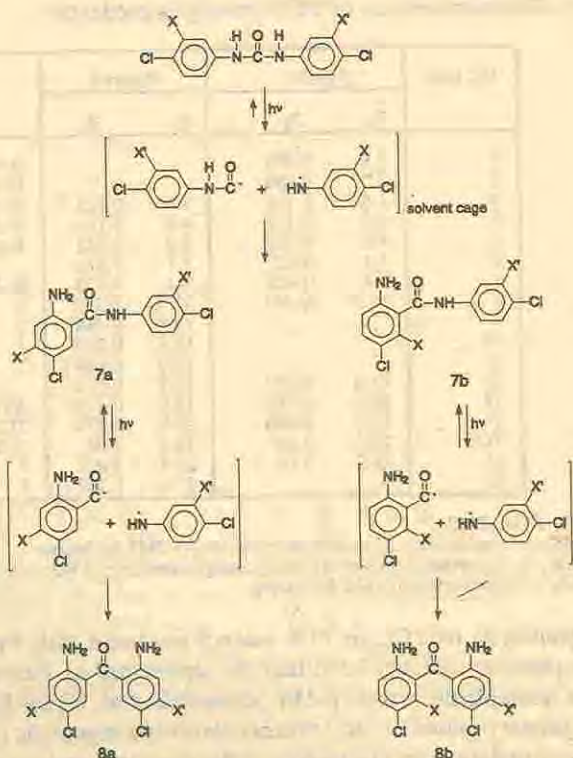
A. Solvent-cage recombination of the radicals leading to Photo-Fries rearrangement products: The products expected from this reaction are the 2-aminotrichlorobenzanilides 7. Two isomers of 7 are possible as illustrated in Scheme 2. However, only one broad peak was



Scheme 1.

TCC photolysis products when irradiated with pyrex filtered UV radiation in 77:23 ethanol/water mixed solvent.

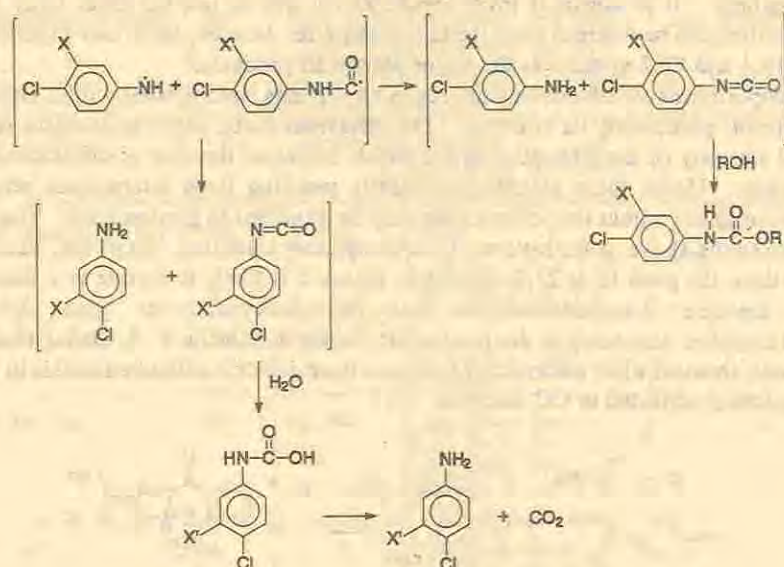
obtained in the GC chromatogram of standard 7 synthesized as described in the Experimental section. This may suggest that the less sterically hindered isomer, 7a, is formed in much greater yield than the sterically hindered isomer 7b. The benzanilides themselves undergo further Photo-Fries rearrangement to give 2,2'-diamino-4-(or -6-)5,5'-trichlorobenzophenone (8) as shown in Scheme 2. These reactions were reported previously in the case of N,N'-diphenylurea [6].



Scheme 2.

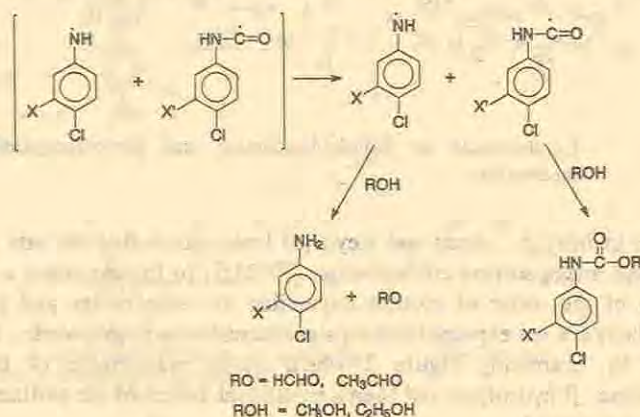
Solvent cage recombination of the primary diradical pair to give Photo-Fries rearrangement products.

B. Disproportionation of the cage radicals to give chloro (or dichloro) aniline and dichloro (or chloro) phenylisocyanate. Subsequent interaction of the isocyanate with the solvent yields 4-chloro or 3,4-dichlorophenylethylurethane when the solvent is ethanol. In aqueous solution, the disproportionation reaction can be expected to yield mainly the anilines and carbon dioxide as shown in Scheme 3.



Scheme 3. Disproportionation of the cage radicals.

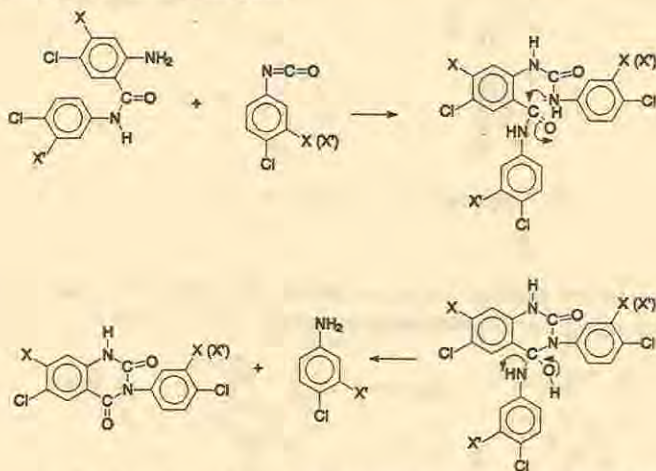
C. Diffusion of the radicals out of the solvent cage and subsequent interaction with the solvent to yield anilines and chlorophenylethylurethanes as shown in Scheme 4.



Scheme 4. Diffusion of the Primary diradical pair out of the solvent cage and subsequent interaction with the solvent.

When dilute aqueous solutions of TCC are irradiated the product mixture is different from that obtained for ethanolic solutions. From the discussions above it might be expected that the proportion of anilines in the photolysis mixture will increase when TCC is irradiated in dilute aqueous solutions as a result of out-of-solvent-cage interactions which should yield mainly anilines. It is apparent from Figure 2 that this is not the case. Only traces of 4-chloroaniline can be inferred from the chromatogram. Instead, three new products appear at 15.8, 19.1 and 27.2 minutes as the major photolysis products.

The proportion of out-of-solvent-cage reactions depends, among other things, on the nature of the solvent, particularly its viscosity. The behaviour noted above is probably due to the increased viscosity of the aqueous solution which decreases the rate of diffusion out of the solvent cage. Under these conditions products resulting from interactions between the photolysis products within the solvent cage may be expected to predominate. The products giving rise to the above peaks have not been completely identified. However, based on GC retention data, the peak 16 at 27.2 minutes in Figure 2 is likely to be due to a condensation product between 2-aminobenzamide and phenylisocyanate to give 2,4-dioxo-3-phenylquinazoline, according to the mechanism shown in Scheme 5. A similar peak at 27.2 minutes was obtained when phenylisocyanate was heated with 2-aminobenzamide in methanol and the mixture subjected to GC analysis.



Scheme 5. Condensation of 2-aminobenzamide and phenylisocyanate: a possible mechanism.

Significance of hydrolysis. Audu and Heyn [3] have shown that the rate of hydrolysis of TCC in either the mixed solvent ethanol-water (77/23%) or in pure water is extremely slow with half lives of the order of months depending on temperature and pH. Therefore, hydrolysis products are not expected to be a significant factor in this work. This is borne out experimentally by examining Figure 2 which shows only traces of the 4-chloro- or 3,4-dichloroaniline. If hydrolysis had been a significant source of the anilines, large amounts would have been expected.

Table 2. Significant fragments in the mass spectra of the TMS derivatives of TCC and degradation products

	Parent substance	MW	Ions	<i>m/z</i> (intensity %)	Fragmentation path
1	R-N(SiMe ₃)COOEt	271	M ⁺ - 72 M ⁺ -72-15	199 (39.9), 200 (6.0), 201 (14.6), 202 (2.1) 183 (1.72), 184 (100), 185 (15.0), 186 (36.1), 187 (7.7)	Loss of Si(CH ₃) ₃ Loss of Si(CH ₃) ₃ and CH ₃
2	R-N=C=O	153	M ⁺	152 (3.4), 153 (100), 154 (9.5), 155 (34.1), 156 (3.0)	
3	R ¹ -N(SiMe ₃)COOEt	305	M ⁺ -15 M ⁺ -72	trace 232 (0.9), 233 (33.6), 234 (6.0), 253 (23.3) 236 (3.4)	Loss of CH ₃ Loss of Si(CH ₃) ₃
4	R ¹ -N=C=O	187	M ⁺	187 (100), 188 (8.6), 189 (64.8), 190 (5.6), 191 (10.7)	
5	R-N(SiMe ₃) ₂	271	M ⁺ -72 M ⁺ -72-15	199 (40.5), 200 (6.5), 201 (14.7), 202 (2.2) 184 (100), 185 (15.5), 186 (36.2), 187 (6.0)	Loss of Si(CH ₃) ₃ Loss of Si(CH ₃) ₃ and CH ₃
6	R ¹ -N(SiMe ₃) ₂	305	M ⁺ -72 M ⁺ -72-15	232 (1.3), 233 (29.9), 234 (6.1), 235 (23.0), 236 (3.9) 217 (2.6), 218 (90.5), 219 (13.8), 220 (58.2), 221 (8.6)	Loss of Si(CH ₃) ₃ Loss of Si(CH ₃) ₃ and CH ₃
7	ATCB tri-TMS	530	M ⁺ -37 M ⁺ -88-35 M ⁺ -271 M ⁺ -153	349 (trace) ^a 334 (trace) 187 (19.0), 189 (17.2) 218 (3.9)	Loss of HCl and H Loss of OSi(CH ₃) ₃ and Cl Loss of R-N(SiMe ₃) ₂ Loss of R-N=C=O
8	TCBD tetra-TMS	602	[M-35- 3(15)]	262 (15.3), 263 (7.8), 264 (11.3)	Loss of HCl and 3 methyl groups
9	TCC di-TMS	458	M ⁺ -15 M ⁺ -35-30 M ⁺ -89-72 M ⁺ -89-72- 35	445 (trace) 394 (2.2) 296 (2.2) 261 (1.3), 262 (100), 263 (16.0), 264 (65.2), 265 (10.7)	Loss of CH ₃ Loss of Cl and CH ₃ Loss of OSi(CH ₃) ₃ and Si(CH ₃) ₃ Loss of OSi(CH ₃) ₃ , Si(CH ₃) ₃ and Cl

R = -PhCl, R¹ = -PhCl₂ATCB(TMS)₃ = *o*-amino-*m,p,p'*-trichlorobenzanilide, tri-TMS derivativeTCBP(TMS)₄ = *o,o'*-diamino-*m,p,p'*-trichlorobenzophenone, tetra-TMS derivativeTCC(TMS)₂ = Triclocarban di-TMS derivative

EXPERIMENTAL

General. Mps were determined on a Gallenkamp capillary apparatus. IR spectra were recorded on a Perkin-Elmer 180 Grating infrared spectrophotometer. UV-VIS spectra were

recorded on a Beckman Model 124 spectrophotometer. Microanalysis were done by Quelp Chemical Laboratories Ltd., Ontario, Canada.

Materials. Triclocarban was obtained from Pfaltz and Bauer, Inc., Stamford, Conn., and used without further purification. All other compounds were reagent grade chemicals.

Solvents. Ultra-pure water (from a Millipore Q water system), ethanol (USP grade), methanol, acetonitrile, acetone and dichloromethane (spectroscopic grade).

Cuvette. 15 ml cylindrical with quartz windows. The cuvette, and all other glassware, were subjected to sequential rinsing with spectro grade acetone, acetonitrile and methanol, and drying in the oven at 110° prior to use.

Photolysis tank. 30 x 10 x 25 cm molded borosilicate 1 cm thick glass TLC tank with glass cover. The tank was cleaned with No-Chromix solution (Godax Laboratories, Inc., N.Y.) and rinsed several times with ultra pure water prior to use.

Mercury lamp. 250 watt, type 37-5KE (Sylvania Electric Products Inc., Manchester, New Hampshire) and operated with a Jefferson mercury-lamp ballast, indoor constant voltage type, 227-1 871.

Gas chromatography. Gas-liquid chromatography was carried out on a 5' x 1/4" o.d. glass column, 2 mm i.d., containing 3% Dexsil 400 on 100-120 mesh Supelcoport (Supelco, Inc., Bellefonte, PA), using a Varian Aerograph GC series 1520c equipped with flame-ionization detector. All determinations were made with temperature programming between 128° and 248° at 6°/min. Nitrogen (prepurified grade) was employed as the carrier gas. The injection port and detector were maintained at 210° and 270°, respectively.

Mass spectra. A MAT 44 Varian Quadrupole GC-MS spectrometer at 70 eV, interfaced with a PDP 1134 computer was used.

Experimental procedure

Samples in alcohol/water mixed solvent were irradiated using the 15 ml cuvette. Each time 13.0 ml of a 7.6×10^{-3} molar solution of TCC were irradiated. The cuvette was stoppered throughout the irradiation period and the solution was neither stirred nor agitated. These solutions were sufficiently concentrated to allow derivatization and GC separation without further concentration steps. The derivatization prior to GC separation was carried out using MSTFA, N-methyl-N-trimethylsilyltrifluoroacetamide, (Pierce Chemical Co., Rockford, IL).

Aqueous samples were irradiated using the photolysis tank. Four liters of ultrapure water were added to the clean tank, then 1.00 ml of a stock solution of TCC in acetonitrile was added by means of a syringe resulting in a solution 6.18×10^{-8} molar with respect to TCC. (Preliminary studies had shown the solubility of TCC in water to be of the order of 6×10^{-7} mol/L at room temperature). The glass cover was put in place and the solution was allowed to equilibrate for about 10 minutes before starting the irradiation. After the irradiation the solution was extracted and concentrated by the resin polymer (XAD-2) method [8]. All extraction glassware was cleaned with the No-Chromix solution and rinsed with ultrapure water prior to use. Glassware used in the concentration steps was similarly cleaned and

rinsed, followed by rinsing with spectro grade methanol and dichloromethane, then dried in the oven at 110° prior to use. Dichloromethane was employed as eluting solvent. The solution was concentrated to a final volume of 1.0 ml. A blank extraction was performed on the resin column following sample extractions.

Derivatization and gas chromatography. 50 - 300 μ l were transferred to a 300- μ l Reacti-vial and the solvent evaporated to almost dryness using a gentle stream of dry prepurified grade of nitrogen. After closing the vial to avoid entry of air, 50 μ l MSTFA were injected into the vial and the mixture was incubated in the oven at 90° for 90 min. One or 2 μ l of the silylated samples were drawn for injection into the GC. Standard samples of TCC, as well as of degradation standards were similarly treated.

Chemical actinometry. The quantum efficiency for the loss of TCC was estimated using decafluorobenzophenone in isopropanol as secondary actinometer as described by Filipescu *et al.* [9]. The spectrum of decafluorobenzophenone in the near-UV region is very similar to that of TCC, the respective molar absorptivities are 3182 (290 nm) for decafluorobenzophenone, and 3548 (295 nm) for TCC. The estimation of the quantum efficiency for the photodegradation of TCC was based on the assumption that for equal volumes of sample and actinometer solution irradiated with identical beam geometry, the intensity of the light beam incident just within photolysis cell front window is approximately equal for the solution of the sample and the actinometer substance.

Determinations were made using the 15 ml cuvette. Exactly 13.0 ml of 3.140×10^{-3} M decafluorobenzophenone and 7.639×10^{-3} M TCC solution were employed. The solutions were irradiated for 5.0 and 65.0 hr, respectively. The quantum efficiency for the loss of TCC was estimated to be 0.009.

Identification of photoproducts. Identification of photoproducts was based on GC retention data of authentic standards as well as on MS data obtained when the photolysate was subjected to combined GC-MS analysis (see Table 2). Authentic standards for products 1, 3, 7, 8 and 9 were synthesized in this laboratory for verification of their identity. Standards for 2, 4, 5 and 6 were obtained from a commercial supplier (Aldrich, WI).

Synthesis of degradation standards

2-Amino-3',4',5-trichlorobenzanilide. This compound was prepared from 5-chloro-2-nitrobenzoic acid and 3,4-dichloroaniline as starting materials. The 5-chloro-2-nitrobenzoic acid was refluxed with SOCl_2 to yield 5-chloro-2-nitrobenzoyl chloride [10]. The 5-chloro-2-nitrobenzoyl chloride was converted to 2-nitro-3',4',5-trichlorobenzanilide by reacting it with 3,4-dichloroaniline [2]. The 2-nitro-3',4',5-trichlorobenzanilide was then reduced to 2-amino-3',4',5-trichlorobenzanilide by refluxing with $\text{Na}_2\text{S}_2\text{O}_4$ [11]. The product was recrystallized once from ethanol-water and gave a mp of 158-160° (Lit. [12] mp 160-161°). The IR spectrum showed the characteristic N-H stretching band at 3500-3300 cm^{-1} , C=O stretching band at 1650 - 1500 cm^{-1} , and C-Cl stretching band at 800-600 cm^{-1} .

N-p-chlorophenylethylurethane and N-3,4-dichlorophenylethylurethane [13]. The urethanes were prepared by condensing the appropriate aniline with ethyl chlorocarbonate. To a solution of 2.17 g (0.02 mole) of ethyl chlorocarbonate in 15 ml benzene was added with stirring at 10° 0.02 mole of the aniline and 0.02 mole of triethylamine in 20 ml benzene. The

mixture was allowed to stand for 3 hr. After filtering, the crystalline solid product was recrystallized once from cyclohexane.

2,2'-Diamino-4,4',5'-trichlorobenzophenone. This compound was synthesized from *m*-chlorobenzoyl chloride and *o*-dichlorobenzene as starting materials. The first-step involved preparation of 3,3',4-trichlorobenzophenone from the *m*-chlorobenzoyl chloride and *o*-dichlorobenzene [14, 15]. The 3,3',4-trichlorobenzophenone obtained was reduced to 3,3',4-trichlorodiphenylmethane by the modified Clemensen reduction using zinc amalgam, hydrochloric acid and toluene [16]. The 3,3',4-trichlorobenzophenone was in turn converted to 2,2'-dinitro-4,5,5'-trichlorodiphenylmethane by nitration using a mixture of KNO_3 and H_2SO_4 [15]. The 2,2'-dinitro-4,5,5'-trichlorodiphenylmethane obtained was then oxidized to 2,2'-dinitro-4,5,5'-trichlorobenzophenone using chromic and glacial acetic acids [17, 18]. The dinitro compound was then reduced at $70^\circ\text{--}90^\circ$ with SnCl_2 [19]. The 2,2'-diamino-4,5,5'-trichlorobenzophenone obtained was recrystallized from ethanol to give yellow crystals, mp 101° . The IR spectrum showed the characteristic N-H stretching band at $3500\text{--}3300\text{ cm}^{-1}$, C=O stretching band at $1650\text{--}1600\text{ cm}^{-1}$ and C-Cl stretching band at $800\text{--}600\text{ cm}^{-1}$.

ACKNOWLEDGEMENT

The loan of the gas chromatograph by the U.S. Air Force Hanscom Base Laboratory is gratefully acknowledged.

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