

REACTION OF α -TRIHALOMETHYLBENZHYDROLS
WITH SULFURIC ACID - HYDROGEN AZIDE

A. Kalir and D. Balderman

Department of Organic Chemistry, Israel Institute for Biological Research,
Sackler Medical School, Tel-Aviv University, Ness Ziona 70400, Israel.

ABSTRACT

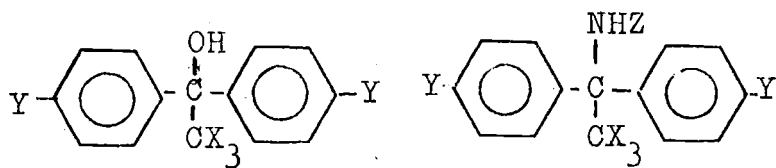
α -Trifluoromethyl-4,4'-dichlorobenzhydrol (1, X = F, Y = Cl) reacted with sulfuric acid - sodium azide to give the azide 3, which was reduced to the desired benzhydramine 2. In identical conditions Kelthane (IX = Y = Cl) behaved differently and gave a compound of an unknown structure.

None of the compounds prepared showed any appreciably insecticidal potency.

The DDT molecule underwent many structural modifications in order to prepare active compounds. Introduction of the α -hydroxy group yielded Kelthane, I, X=Y=Cl, a well known miticide. The present work was aimed at the preparation and screening of the corresponding α -amino derivatives.

α -Trihalomethylbenzhydrols, 1 react with nitriles e.g. acetonitrile, in the presence of concentrated sulfuric acid (Ritter reaction) to produce N-(2,2-diaryl-1,1,1-trihaloethyl) acetamides, 2, Z=CH₃CO. Attempts to deacylate the amides to the α -trihalomethylbenzhydramines, 2, Z=H did not succeed (Kaluszyner et al., 1963). 2,2-Diphenylcarbinol, Ic, Y=H gives with sodium azide in sulfuric acid the azide 3c, Y=H (Ege and Sherk, 1953). In view of the easy reducibility of azides to amines (Grundmann, 1963) we decided to apply this method for the preparation of free amines.

מכון ויצמן למדע
המחלקה לכימיה אורגנית
תל אביב 61000



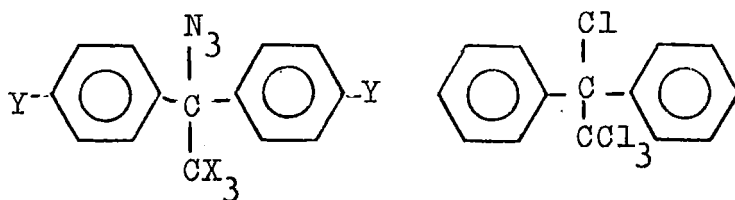
1

2

a, X = F

b, X = Cl

c, X = H



3

4

4,4'-Dichloro- α -trifluoromethylbenzhydrol, 1a, Y=Cl yielded the corresponding azide 3a identified by its strong IR peak at 2100 cm^{-1} . The azide was reduced to the amine 2a, X=Cl, Z=H. The amine was acetylated to the known acetamide, 2a, Y=Cl, Z=CH₃CO (Kaluszynier et al., 1963). When this reaction was applied to the trichloromethyl derivative 1b, Y=Cl (Kelthane) a compound, m.p. $138-140^\circ\text{C}$ was isolated. This compound contained nitrogen and its elemental analysis corresponded to C₁₄H₁₀Cl₅N. A compound having this formula and the same m.p. - namely α -trichloromethyldichlorobenzylaniline ClC₆H₄CH(CCl₃)NHC₆H₄Cl has been reported recently (Hirwe et al., 1972). We prepared this compound by refluxing the Schiff base ClC₆H₄CH = NC₆H₄Cl with excess of trichloroacetic acid in xylene (the starting material was recovered unchanged when toluene was used). The mixed m.p. was depressed, and IR and NMR spectra of the two compounds were different. In particular the peak at 5.0 of the benzylic hydrogen found in benzylaniline was absent in the NMR spectra of our reaction product, and its structure is under investigation.

From reaction between 2,2-diphenyl-1,1,1,2-tetrachloroethane 4 (Bergmann and Kaluszynier, 1958) and sodium azide in dimethylformamide only 1,1-dichloro-2,2-diphenylethylene was isolated.

Toxicity. Neither the amine 2b, Y=Cl, Z=H, nor the amides 2a, and 2b, Y=Cl, Z=CH₃CO showed any appreciable toxicity when tested against house flies.

Experimental

4,4'-Dichloro- α -trifluoromethylbenzhydrazide, 3a, Y=Cl

Sodium azide (30 g. 0.48 mole) was added to 250 ml of cold concd. sulfuric acid. 32.1 g (0.1 mole) or 4,4'-dichloro- α -trifluoromethylbenzhydrol (Kaluszyner et al., 1955) (the product contained some 4,4'-dichlorodiphenyl) was added with stirring to the above mixture at 0°. The color turned yellow. After additional 6 hr. of stirring the mixture was poured into ice-water, the acid was neutralized, and the organic material was extracted with benzene. The benzene extract was concentrated leaving 35 g of an oily residue. TLC (neutral alumina-benzene) of the residue showed the presence of dichlorodiphenyl and traces of the starting benzhydrol.

A sample distilled at 135-137° (0.25 mm), n_D^{20} 1.5620 contained about 90% of the azide.

Anal. Calcd. for C₁₄H₈Cl₂F₃N₃: C, 48.6; H, 2.30; Cl, 20.5; F, 16.5; N, 12.10.

Found: C, 51.1; H, 2.8; Cl, 20.4; F, 15.0; N, 10.6.

IR (neat) - 2130 cm⁻¹(strong).

4,4'-Dichloro- α -trifluoromethylbenzhydrazylamine, 2a, Y=Cl

The foregoing crude azide in 50 ml of isopropanol was reduced over Raney-nickel. The solution was filtered, concentrated, and treated with concd. HCl. The solid product could not be recrystallized, so dil. NaOH was added, and the base extracted with benzene. The solvent was removed, and the amine (10 g) distilled at 150-152° (0.5 mm); n_D^{18} 1.5610.

Anal. Calcd. for C₁₄H₁₀Cl₂F₃N : C, 55.8; H, 2.9; Cl, 20.6; N, 4.1.

Found: C, 55.2; H, 3.2; Cl, 21.8; N, 4.3.

IR (neat) - 3280 cm⁻¹. The peak at 2130 cm⁻¹ disappeared.

NMR (CCl₄), 7.12 (q 8H, arom); 2.0 (2H, NH₂).

Heating with acetic anhydride gave a crystalline derivative, m.p. 210-212°, identical with 2a, X=Cl, Z=CH₃CO prepared earlier (Kaluszyner et al., 1963).

Reaction of 4,4'-dichloro- α -trichloromethylbenzhydrol with sulfuric acid hydrogen azide.

The benzhydrol, 1b, Y=Cl (18.6 g, 0.05 mole) was added at -5° to a mixture prepared from 150 ml of concd. sulfuric acid and 6.5 g (0.1 mole) of sodium azide. After the addition was completed the mixture was stirred 24 hr. at room temperature, and worked up as described before.

The crude product was recrystallized from ether-petrol ether to give 5.0 g of crystals, m.p. $138-140^{\circ}$.

Anal. Calcd. for $C_{14}H_{10}Cl_5N$: C, 45.5; H, 2.7; Cl, 48.0; N, 3.8.

Found: C, 46.3; H, 2.7; Cl, 46.9; N, 3.6.

NMR (CCl_4), 7.12 (d); 7.02 (d); 6.5 (d). No peak could be detected at 4.96. This peak was present in the spectrum of $ClC_6H_4CH(CCl_3)NHC_6H_4Cl$ prepared according to Hirwe et al., 1972.

Reaction of 2,2-diphenyl-1,1,1,2-tetrachloroethane, 4 with sodium azide

A solution of 10 g (0.15 mole) of sodium azide in 10 ml water was added to 15 g (0.04 mole) of 4 in 100 ml dimethylformamide, and stirred 5 hr. at $120-130^{\circ}$. The solution was diluted with water, the organic product extracted with benzene, and concentrated. The oily residue was dissolved in dichloroethane, washed with ammonia, and the solvent removed, leaving a solid (8 g), that was recrystallized from petrol ether, m.p. $74-76^{\circ}$.

This product was identified as slightly impure 1,1-dichloro-2,2-diphenylethylene.

Anal. Calcd. for $C_{14}H_{10}Cl_2$: C, 67.5; H, 4.1; Cl, 28.4

Found: C, 68.1; H, 4.0; Cl, 27.7.

Acknowledgement

We thank Prof. A.S. Tahori and his coworkers for the toxicological screening.

REFERENCES

- Bergmann, E.D. and Kaluszyner, A. 1958. Di(*p*-chlorophenyl) trichloromethylcarbinol and related compounds. J. Org. Chem. 23: 1306-1308.
- Ege, S.N. and Sherk, K.W. 1953. The formation of azides in the reaction of hydrogen azide with diarylethylenes. J. Amer. Chem. Soc. 75: 354-357.
- Grundmann, C. 1965. Methoden zum Herstellung und Umwandlung von organischen Azidoverbindungen. Houben-Weyl Methoden der Organischen Chemie, Vol. X/3. G. Thieme, Stuttgart, pp.822-823.
- Hirwe, A.S., Metcalf R.L. and Kapoor I.P., 1972. α -Trichloromethylbenzylanilines and α -trichloromethylbenzyl phenyl ethers with DDT-like insecticidal action. J. Agr. Food Chem. 20: 818-824.
- Kaluszyner, A., Reuter, S. and Bergmann, E.D. 1955. Synthesis and biological properties of diaryl-(trifluoromethyl)-carbinols. J. Amer. Chem. Soc. 77: 4164-4168.
- Kaluszyner, A., Blum, S. and Bergmann, E.D., 1963. The Ritter reaction of tertiary trihalomethylcarbinols and related substances. J. Org. Chem. 28: 3588-3590.