STUDIES ON as-TRIAZINE DERIVATIVES. II.[1] A RING-CLEAVAGE REACTION OF 3-TRICHLOROMETHYL-5,6-DIPHENYL-1,2,4-TRIAZINE AND RELATED COMPOUNDS

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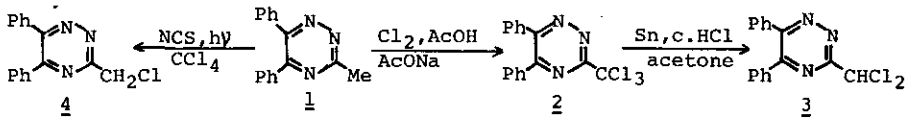
Abstract——3-Chloromethyl- (4), 3-dichloromethyl- (3), and 3-trichloromethyl-5,6-diphenyl-1,2,4-triazine (2) were synthesized from 3-methyl-5,6-diphenyl-1,2,4-triazine (1). The reaction of 4 with sodium ethoxide in ethanol simply afforded the corresponding 3-ethoxymethyl compound. In contrast to this reaction, when 2 and 3 were treated with sodium alkoxide, an unexpected ring-cleavage reaction occurred instead of simple nucleophilic attack to chloromethyl groups. The structure of the products and the reaction mechanism are discussed.

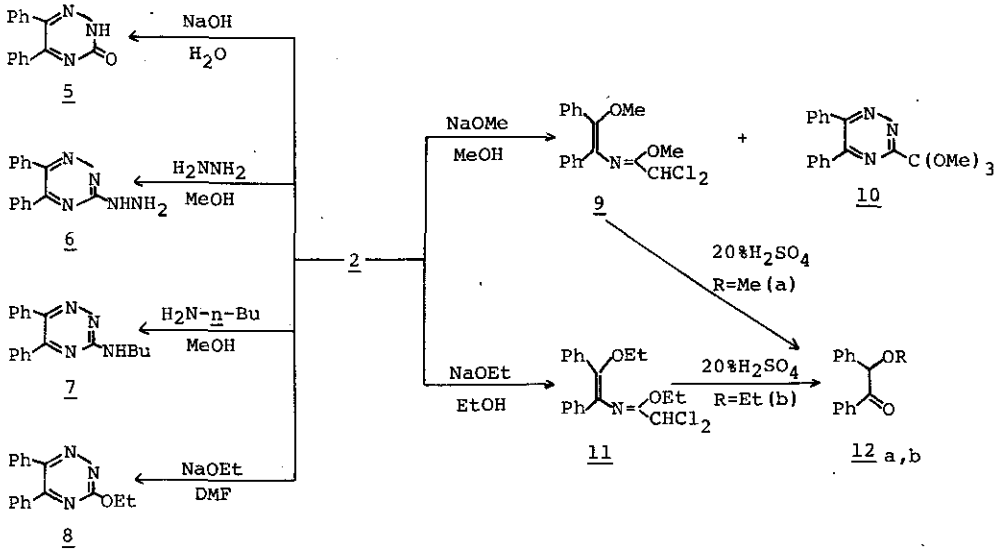
As an extension of our studies on the synthesis of monocyclic diazine derivatives,[2] the synthesis and reaction of 3-trichloromethyl-5,6-diphenyl-1,2,4-triazine (as-triazine) was investigated, because some derivatives of 5,6-diphenyl-as-triazine were reported to have considerable anti-inflammatory effects.[3] In this course, a unique ring-cleavage reaction of as-triazines was occasionally observed, which is the subject of this communication.

When chlorine gas was blown[4] through a warm solution of 3-methyl-5,6-diphenyl-as-triazine (1) and sodium acetate in acetic acid, a side chain chlorination was occurred to give 3-trichloromethyl-5,6-diphenyl-as-triazine (2), $C_{16}H_{10}Cl_3N_3$, mp 132-133°C, in 72 % yield. The reduction of 2 with metallic tin in conc. hydrochloric acid and acetone gave 3-dichloromethyl-5,6-diphenyl-as-triazine (3), $C_{16}H_{11}Cl_2N_3$, mp 143-144°C, in 63 % yield. Further reduction of 3 to 3-chloromethyl-5,6-diphenyl-as-triazine (4) was unsuccessful, but 4 was alternatively obtained by the direct chlorination of 1 with N-chlorosuccinimide under irradiation as pale yellow prisms, $C_{16}H_{12}ClN_3$, mp 95-96°C, in 19 % yield.



Scheme 1

On treatment with aq. sodium hydroxide, 2 and 3 were both transformed into 3-oxo-5,6-diphenyl-2,3-dihydro-as-triazine (5), mp 222-223°C (lit.[5] mp 224-225°C), in 50 and 54 % yields, respectively. In these cases, the corresponding carboxylic acid or carboxaldehyde derivatives were not obtained. Similarly, the reaction of 2 with hydrazine hydrate and n-butylamine gave 3-hydrazino-5,6-diphenyl-as-triazine (6), mp 173-174°C(lit.[1] mp 171-173°C), and 3-n-butylamino-5,6-diphenyl-as-triazine (7), mp 130-131°C(lit.[1] mp 131-132°C), in good yields. These products (6 and 7) were identical with the authentic specimen prepared by previously reported method.[1]



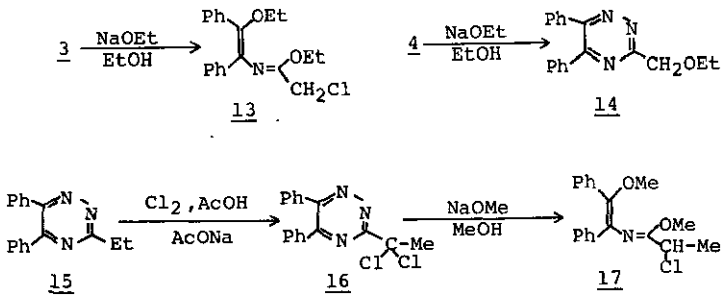
Scheme 2

In contrast to the above results, when 2 was treated with sodium alkoxide in alcohol, an abnormal reaction occurred, and the formation of the expected alkoxyl derivatives[6] was not observed. Namely, the reaction of 2 with sodium methoxide in boiling methanol afforded colorless needles, $C_{18}H_{17}Cl_2NO_2$, (9) , mp 71-71.5°C, in 30% yield, together with a small amount of the ortho ester, 2-trimethoxymethyl-5,6-

diphenyl-as-triazine (10), $C_{19}H_{19}N_3O_3$, mp 127-128°C.

The hydrolysis of 9 with dilute sulfuric acid gave α-methoxybenzyl phenyl ketone (12a, R=Me) which was identical with an authentic specimen[7] prepared by the methylation of benzoin with thionyl chloride and methanol. This finding suggested the structure of the main product (9) to be 1-methoxy-2-(2,2-dichloro-1-methoxyethylidene)amino-1,2-diphenylethane as shown in Scheme 2. This structure is also supported by the following spectral data. The ^{1}H-NMR spectrum of 9: δ($CDCl_3$) 3.48 (3H,s), 3.88 (3H,s), 6.27 (1H,s), 7.13-7.80 (10H,m). The ^{13}C-NMR spectrum of 9: δ ($CDCl_3$) 54.8 (q), 58.2 (q), 60.0 (d), 127.6 (d), 128.0 (d), 128.6 (s), 129.1 (d), 133.7 (s). The reaction of 2 with sodium ethoxide gave the same type ethoxyl derivative (11), $C_{20}H_{21}Cl_2NO_2$, liquid, whose ^{1}H-NMR spectrum is in good agreement with the open-chain structure.

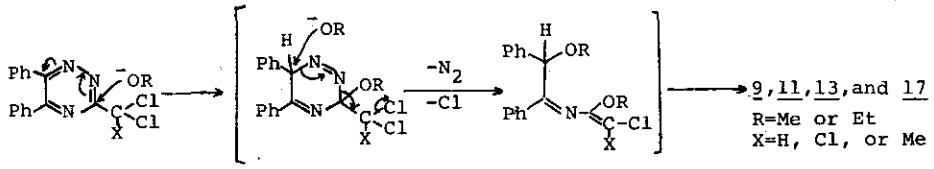
The ring-cleavage reaction of this type seems to require the presence of two chlorine atoms at the 3-methyl group. In fact, 3-dichloromethyl-5,6-diphenyl-as-triazine (3) and 3-(α,α-dichloroethyl)-5,6-diphenyl-as-triazine (16), which was prepared by the chlorination of 3-ethyl-5,6-diphenyl-as-triazine (15), were converted to the compounds 13 and 17, respectively, while the reaction of 4 with sodium ethoxide in boiling ethanol gave 3-ethoxymethyl-5,6-diphenyl-as-triazine (14), $C_{18}H_{17}N_3O$, mp 87-88°C, as usual.



Scheme 3

We have no experimental evidence regarding the mechanism of this ring-opening reaction, but the addition of various nucleophiles to as-triazine rings are frequently reported.[8] Furthermore Grabowski et al.[9] reported that the reaction of 2-trichloromethylpyrazine with three equivalents of sodium methoxide in refluxing methanol gave 2-dimethoxymethyl-5-methoxypyrazine as a main product.

They suggested the addition of methoxide ion to the pyrazine ring at the initial stage of the reaction.



Scheme 4

Thus, it seems to be reasonable to propose the reaction pathway, which is based on the 1,4-addition of the alcohol to the 3- and 6-position of 5,6-diphenyl-3-dichloro (or trichloro)methyl-as-triazine, as illustrated in Scheme 4.

REFERENCES AND NOTES

1. Part 1: S. Konno, M. Yokoyama, A. Kaite, I. Yamatsuta, S. Ogawa, M. Mizugaki, and H. Yamanaka, Chem. Pharm. Bull., 1982, 30, 152.
2. T. Sakamoto and H. Yamanaka, Heterocycles, 1981, 15, 583.
3. H. R. Sullivan, W. M. Miller, D. G. Stark, and P. G. Wood, Xenobiotica, 1981, 11, 9.
4. H. Bredereck, W. Jentzsch, and G. Morlock, Chem. Ber., 1960, 93, 2405: This paper has provided a convenient method for the synthesis of 4-trichloromethylpyrimidine using chlorination of 4-methylpyrimidine with chlorine gas.
5. H. Bilts, Ber., 1905, 38, 1417.
6. When 2 was allowed to react with powdered sodium ethoxide in warm dimethylformamide, 3-ethoxy-5,6-diphenyl-as-triazine (8) was obtained, although the yield was poor.
7. E. Fischer, Ber., 1893, 26, 2413; H. Mueller, H. J. Traencker, H. Habetz, and H. Pelster, Ger. Offen., 2,420,474(Chem. Abstr., 1976, 84, 30476b).
8. W. W. Paudler and J. Lee, J. Org. Chem., 1971, 36, 3921; J. Daunis and C. Pigière, Bull. Soc. Chim. France, 1973, 2493; T. Sasaki, K. Minamoto and K. Harada, J. Org. Chem., 1980, 45, 4587, 4594.
9. E. J. J. Grabowski, E. M. Tristram, R. Tull, and P. I. Pollak, Tetrahedron Lett., 1968, 5931.

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