Reactions of Picryl Ether with Amino Compounds

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The cleavage of phenyl ether linkage, either in acidic or alkaline medium, has been achieved only under vigorous conditions. In this respect, ammonolysis of picryl ether was proved to be an exceptional case. Picryl ether (TNP-OC_2H_5* m. p. 77.5~78.5°C[1]; TNP-OC_6H_5 m. p. 151~152°C[2]) gave picramide (m. p. 187~188°C; λ_{max} mμ ($\varepsilon \times 10^{-4}$): 325 (1.14), 415 (0.86)) and *N*-methylpicramide (m. p. 109~110°C; λ_{max} mμ ($\varepsilon \times 10^{-4}$): 346 (1.60) with a marked shoulder at 418 mμ) only by dissolving the ether into hydrated ethanol solution of ammonia (7.5 N) and methylamine (5 N), at room temperature, respectively. The results of spectrophotometric investigation[3], as illustrated in Fig. 1, indicated that the ammonolysis of picryl ether proceeded almost immediately with quantitative yield.

The most remarkable fact was different behaviors of the both picryl ethers with dimethylamine; thus the phenyl ether gave *N*, *N*-dimethylpicramide (m. p. 137~138°C[4]; λ_{max} mμ ($\varepsilon \times 10^{-4}$): 380 (1.38)) immediately, while the ethyl ether did not even after 24 hr. under the conditions described in Fig. 1. With the use of excess amounts of dimethylamine (Tokyo Chemical Industry Co., Ltd.; Guaranteed Reagent), there was observed some formation of *N*-methylpicramide, presumably being originated from the contaminated methylamine.

Reaction of the same type occurred in much less alkaline medium (pH 8), and not only with amine but also with amino acid. Thus equimolar mixtures of glycine and picryl ethyl ether and of proline and picryl phenyl ether in borate buffer (pH 8.0) at room temperature gave TNP-glycine (m. p. 161°C; λ_{max} mμ ($\varepsilon \times 10^{-4}$): 340 (1.25)[5]) and TNP-proline (m. p. 164~165°C; λ_{max} mμ ($\varepsilon \times 10^{-4}$); 362 (1.29)[5]) with excellent yield, respectively. Some typical results on the reaction in analytical scale are summarized in Fig. 2, together with those of

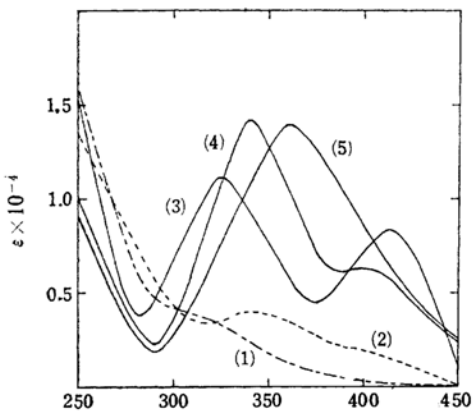

Fig. 1. Aminolysis of picryl phenyl ether (1) TNP-OC_6H_5 in N/10 HCl in 50% ethanol TNP-OC_6H_5 was previously dissolved into (2) N NaOH, (3) 7.5 N NH_3, (4) 5 N CH_3NH_2 and (5) 3.6 N $(CH_3)_2NH$, in 50% ethanol, and the mixture was acidified with HCl exactly after 1 min. Final concentrations were 1.0×10^{-4} M in all cases. The spectra (3), (4) and (5) were just the same as those of picramide, *N*-methyl- and *N*, *N*-dimethylpicramide of 1.0×10^{-4} M, respectively. The spectrum (2) indicated some formation of picric acid under the action of alkali.

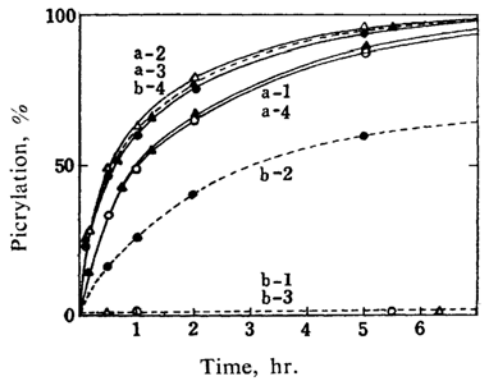

Fig. 2. Picrylation of glycine (——) and proline (----)
1) with TNP-OC_2H_5 (—○—)
2) with TNP-OC_6H_5 (—●—)
3) with TNP-SO_3H (—△—)
4) with TNP-Cl (—▲—)

The initial concentrations of amino acid and picryl compounds were 1.0×10^{-4} M in an equi-volume mixture of M/15 borate buffer (pH 8.0) and ethanol.

The picrylations of glycine (a) and proline (b) were estimated from the increment of optical density at 340 mμ and at 360 mμ respectively (see Fig. 1).

* TNP is an abbreviation for picryl (2, 4, 6-trinitrophenyl).

1) C. Willgerodt, *Ber.*, **12**, 1277 (1879).
2) C. Willgerodt, ibid., **12**, 1278 (1879).
3) The details of procedure were described in K. Satake, M. Tanaka and H. Shino, *J. Biochem.*, **50**, 6 (1961).
4) van Romburgh, *Rec. trav. chim.*, **2**, 105 (1883).

trinitrophenylations with TNP-Cl[5] and TNP-SO_3H[5,6] under the similar conditions.

It will be of interest that picryl ether is a powerful trinitrophenylating agent even under physiological condition. The ether as well as the chloride, a well-known trinitrophenylating reagent of protein, has been already reported to produce allergic dermatitis and to produce an antibody which reacts with TNP-protein on their repeated contact with skin[7]. The facts described in this paper will explain why picryl ether is a precursor of antigenic TNP-protein in vivo.

The details on trinitrophenylation of protein with picryl ether will be described elsewhere.

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5) T. Okuyama and K. Satake, *J. Biochem.*, **47**, 454 (1960).
6) K. Satake, T. Okuyama, M. Ohashi and T. Shinoda, ibid., **47**, 654 (1960).
7) I. A. Brownie and W. K. Cumming, *Biochem. J.*, **40**, 640 (1946); P. G. H. Gell, *Brit. J. Exptl. Path.*, **25**, 174 (1944).