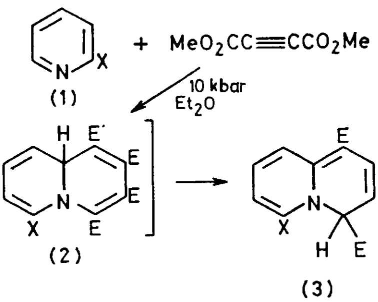
High-pressure Reaction of 2-Halogenopyridines with Dimethyl Acetylenedicarboxylate

By Kiyoshi Matsumoto* and Yukio Ikemi-Kono
(*Department of Chemistry, College of Liberal Arts and Sciences, Kyoto University, Kyoto* 606, *Japan*)
and Takane Uchida
(*Department of Chemistry, Faculty of Education, Fukui University, Fukui* 910, *Japan*)

Summary 2-Bromo-, 2-chloro-, and 2-fluoro-pyridines, whose nucleophilicities are not high enough for them to attack dimethyl acetylenedicarboxylate at atmospheric pressure, react with the latter under high-pressure (10 kbar) at room temperature to give 1 : 2 adducts (from the bromo- and chloro-pyridines) (9a*H*- and 4*H*-quinolizines) or a 1 : 3 adduct (from the fluoro-pyridine).

Various types of products have been obtained in the reactions of acetylene-carboxylic esters with nitrogen-containing heterocyclic compounds.[1] These reactions, however, are limited to heterocycles whose nucleophilicities are high enough for them to attack the esters; reaction does not take place with 2-fluoro- (pK_a −0·44),[2] 2-chloro- (pK_a 0·72),[3] 2-bromo- (pK_a 0·90),[3] or 2-cyano-pyridine (pK_a −0·26)[3] in boiling benzene, acetonitrile, or even dimethylformamide, while pyridine (pK_a 5·17), and 2-methyl- (pK_a 5·97), 2-ethyl- (pK_a 5·97), 2-methoxy- (pK_a 3·28), 3-cyano- (pK_a 1·45), and 4-cyano-pyridine (pK_a 1·90)† react at room temperature to produce the corresponding quinolizines and/or indolizines.[3,4] These reactions have been suggested to proceed by nucleophilic attack of the nitrogen heterocycle on the ester to form a dipolar intermediate which combines with a second molecule of the ester giving a 1,5-dipolar intermediate, followed by intramolecular cyclization to yield the product. Although this mechanism has not been definitely established, a net volume contraction (which would lead to a rate acceleration on application of pressure) is expected for a reaction involving charge separation in the transition state or the conversion of two or three molecules into a single molecule.[5]



E = CO_2Me

a; X=F
b; X=Cl
c; X=Br

Thus, to investigate the effect of pressure, an ethereal solution of equimolar quantities of 2-chloropyridine (**1b**)

---

† Taken from A. Albert, *Phys. Methods Heterocyclic Chem.*, 1963, **1**, 1. Although nucleophilicity and basicity do not always vary in the same way, the latter can be usually employed as a measure of the former in a series of structurally similar compounds.

and dimethyl acetylenedicarboxylate (DMAD) in a 10 ml Teflon pressure-vessel was kept under a hydrostatic pressure of 10 kbar at room temperature for 7 days. After removal of solvent and unchanged reactants *in vacuo*, the black residue was chromatographed on Florisil to give the 4*H*-quinolizine (**3b**)‡ (5·3% yield; yellow crystals; m.p. 139—140 °C).[6] The analogous reaction of 2-bromopyridine (**1c**) with DMAD produced, in addition to the 4*H*-quinolizine (**3c**)‡ (2·3% yield; m.p. 135—136 °C), the 9a*H*-quinolizine (**2c**)‡ (3·9% yield; yellow crystals; m.p. 114—115 °C).

The high-pressure reaction of 2-fluoropyridine (**1a**) with DMAD gave an orange 1:3 adduct, m.p. 76—78 °C (2·3% yield), the structure of which has not yet been established.

In conclusion, the use of high-pressure is valuable in those cases where a reactant is not nucleophilic enough to induce addition reactions at atmospheric pressure.

This work was supported by a Grant-in-Aid for Developmental Scientific Research from the Ministry of Education. We thank Professor H. Ozasa for his interest and encouragement.

(*Received*, 15*th March* 1978; *Com.* 283.)

---

‡ Analytical and spectroscopic data (mass, i.r., ^{1}H and ^{13}C n.m.r.) are in accord with the assigned structure.

[1] R. M. Acheson, *Adv. Heterocyclic Chem.*, 1963, **1**, 125; M. V. George, S. K. Khetan, and R. K. Gupta, *ibid.*, 1976, **19**, 279; R. M. Acheson and G. Procter, *J.C.S. Perkin I*, 1977, 1924, and earlier papers.

[2] K. Matsumoto, unpublished observations.

[3] R. M. Acheson and D. A. Robinson, *J. Chem. Soc.* (*C*), 1968, 1630.

[4] R. M. Acheson, R. S. Feinberg, and J. F. M. Gagan, *J. Chem. Soc.*, 1965, 948; R. M. Acheson, A. R. Hands, and M. J. Woolven, *ibid.*, 1963, 2082; L. M. Jackman, A. W. Johnson, and J. C. Tebby, *ibid.*, 1960, 1579.

[5] K. E. Weale, 'Chemical Reactions at High Pressures,' E. & F. N. Spon, Paris, 1967; W. J. le Noble, *Progr. Phys. Org. Chem.*, 1967, **5**, 207; For recent examples of high-pressure organic reactions, see W. G. Dauben and A. R. Kozikowski, *J. Amer. Chem. Soc.*, 1974, **96**, 3664; W. G. Dauben and H. O. Krabeenhoft, *ibid.*, 1976, **98**, 1992; *J. Org. Chem.*, 1977, **42**, 282; Y. Okamoto and K. I. Lee, *J. Amer. Chem. Soc.*, 1975, **97**, 4015; G. Holan, J. J. Evans, and M. Linton, *J.C.S. Perkin I*, 1977, 1200; J. A. Gladysz, S. J. Lee, J. A. V. Tomasello, and Y. S. Yu, *J. Org. Chem.*, 1977, **42**, 4170.

[6] For ^{13}C n.m.r. data of similar adducts from alkylpyridines, see P. J. Abbott, R. M. Acheson, U. Eisner, D. J. Watkin, and J. R. Carruthers, *J.C.S. Perkin I*, 1976, 1269.