

PYRROCOLINES FROM THE DIENE SYNTHESIS WITH SOME
PYRIDINE BASES AND DIMETHYL
ACETYLENEDICARBOXYLATE

RICHARD H. WILEY AND LOUIS H. KNABESCHUH¹

Received January 15, 1953

Previous studies on the diene reaction of various pyridine bases with dimethyl acetylenedicarboxylate have been described by Diels and Alder and co-workers (1) and by Borrow and Holland (2). This reaction is of unusual interest and value because the studies thus far available (a) indicate its possible utility in the preparation of fused ring systems with a nitrogen bridge-head of both the quinolizine and pyrrocoline types and (b) raise questions of importance in elucidating the mechanism of the diene synthesis.

Preliminary investigation showed that crystalline solids were formed in the reaction of pyridine, 3-picoline, and isoquinoline with dimethyl acetylenedicarboxylate in diethyl ether. With quinoline, 2-picoline, and 2-aminopyridine only tars resulted. Others (1, 2) have reported the isolation of crystalline products from pyridine, quinoline, isoquinoline, 2-picoline, and quinaldine but this is the first time that the reaction with 3-picoline has been observed to give a crystalline product. Because the conditions used for the reaction and the products and yields obtained differ significantly from those previously reported, we have studied the pyridine reaction and the adduct obtained therefrom in detail.

The pyridine adduct obtained in our studies is a white crystalline solid, m.p. 146–147°, and is formed in 20.4% yield on reaction in absolute ether as supplied. This yield is obtained by mixing the reactants at –78° and allowing them to stand at –20° for 20 hours prior to isolation. Experiments given in Table I indicated that the reaction is sensitive to the presence of traces of impurities. For this reason a series of experiments were run to see which of the common ether impurities — water, ethanol, or peroxides — might be responsible for the difficulties involved in reproducing the reaction yields. If these three impurities are carefully removed from the ether, either singly or in groups, none of the crystalline adduct is obtained. In fact, if alcohol- and water-free (sodium-dried), peroxide-free (ferrous sulfate washed) ether is used, the crystalline adduct is obtained, and then in greatly reduced yield, only when ethanol and benzoyl peroxide both are added to the reaction mixture. Although these experiments do not ultimately define the optimum reaction conditions, they do indicate that ethanol is required as a reactant and that peroxide, perhaps as an initiator, is necessary if the crystalline adduct, m.p. 146° is to be obtained. Although previous discussions of the mechanism of the diene reaction have considered both ionic (3–6) and radical (3, 5) mechanisms as possible, these

¹ The authors are indebted to the University of Louisville for a research assistantship in support of one of us (L. H. K.), Taken from a thesis submitted by L. H. K. in partial fulfillment of the requirements for the M.S. degree.

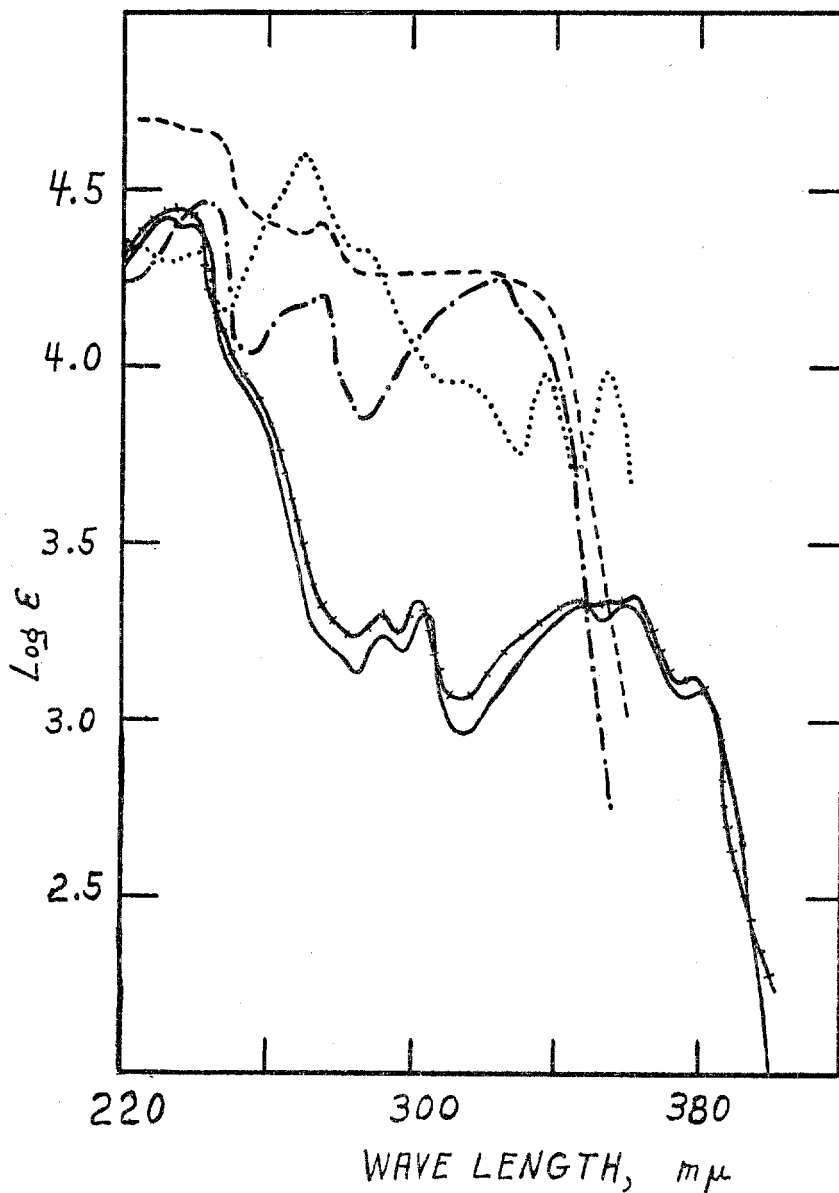
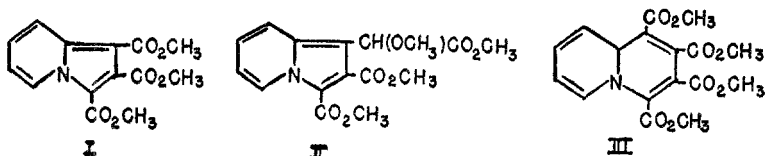


FIG. 1. ULTRAVIOLET ABSORPTION SPECTRA. Pyrrocoline-2-carboxylic acid from pyridine adduct, ———; Pyrrocoline-2-carboxylic acid, synthetic, +++++; 1,2,3-Tricarbomethoxypyrrocoline (pyridine adduct) ---; Trimethyl benzol[*g*]pyrrocoline-1,2,3-tricarboxylate (?) (isoquinoline adduct); β -Picoline adduct, - - - -

three factors—the improved yields at low temperatures, the evidence for peroxide initiation, and the influence of trace impurities — are all consistent with the hypothesis of a free radical mechanism.

The white crystalline pyridine adduct, m.p. 146–147°, has been identified as

1,2,3-tricarbomethoxypyrrocoline (I). Diels and Meyer (1f) obtained a pyridine adduct, m.p. 151°, to which they assigned the structure I, when the addition reaction was carried out in methanol without cooling. At 0° in methanol another product, m.p. 141°, assigned structure II was obtained. Borrows and Holland (2) were unable to obtain I under the stated conditions but did obtain a compound, m.p. 138–139°, which they also thought to be II. Both of these workers (1c, 1d, 2) report the formation of I on oxidation of tetracarbomethoxyquinolizine (III), the adduct obtained from pyridine in ether. Borrows and Holland have



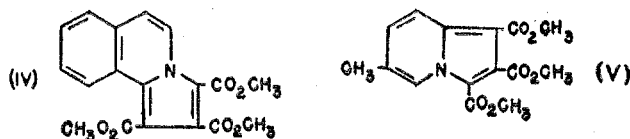
also prepared the pyrrocoline (I) from 2-picoline and bromopyruvic ester. The proof of the structure of I is based on its oxidation to picolinic acid 1-oxide and its hydrolysis to pyrrocoline-2-carboxylic acid. We have repeated and confirmed these degradation reactions and our analytical data support the structure I except for molecular weight determinations, previously unrecorded, which gave values too low. We have observed in further confirmation of this structure that the ultraviolet absorption curves, shown in Figure 1, for the adduct, the pyrrocoline-2-carboxylic acid prepared from the adduct, and the acid prepared by the method of Borrows and Holland are similar. The adduct shows a higher absorption coefficient. The melting point of the adduct, 146°, as obtained in our studies is lower than that reported by Diels and Meyer (1f), 151°. Others (2) have reported similar discrepancies in melting points of products in this series.

An unusual factor in our studies of this reaction is that we have obtained the pyrrocoline adduct in diethyl ether whereas previous workers have obtained the quinolizine III in ether and pyrrocolines in methanol. Our demonstration that the reaction is subject to the influence of traces of impurities, including ethanol, present in ether indicates that successful operation of the reaction requires careful specification of the conditions used.

Unquestionably, more must be known about the relation between reaction conditions and the course of the reaction and about the mechanism by which the carbomethoxy group is lost in formation of the pyrrocoline before a completely satisfactory description of the reaction is possible.

The isoquinoline adduct, m.p. 150–151°, obtained in our studies differs in m.p. from both the previously described isoquinoline adducts, m.ps. 165° and 142°. Our analytical data agree with the values calculated for the benzo[*g*]pyrrocolinetricarboxylic ester (IV) and because of the similarity of the ultraviolet absorption curve, Figure 1, it is believed to have the pyrrocoline structure. The benzo[*g*] structure is preferred to the benzo[*f*] form because of the known tendency of isoquinolines to undergo reactions at the 1,2-bond. The 3-picoline adduct, m.p. 117–119°, might also be assigned a 6- (or 8)-methylpyrrocoline structure (V) on the basis of similarity in method of preparation and confirming

analytical data. Its U.V. curve, also given in Figure 1, is significantly different, however, and for this reason it is believed best to reserve a decision on its struc-



ture until additional data are available. For none of these products have reproducible or confirming molecular weight data been observed.

EXPERIMENTAL²

Dimethyl acetylenedicarboxylate. This ester was prepared in 63% yield by esterification of the acid according to the procedure described previously (7). The acid was prepared from 1,2-dibromosuccinic acid according to a previously described technique (8). The dimethyl ester was fractionated to give a fraction b.p. 49–59°/2 mm.; n_D^{20} 1.4471; sp. gr. $^{20}_4$ 1.45. The ester was redistilled just prior to use in the addition reactions.

Trimethyl pyrrocoline-1,2,3-tricarboxylate (I). The reaction between pyridine and dimethyl acetylenedicarboxylate was studied under a variety of conditions with the results summarized in Table I. The following procedure is typical of that used and gave the maximum yield observed in our studies.

To 6.87 g. (0.048 mole) of dimethyl acetylenedicarboxylate in 100 ml. of diethyl ether (Baker's Purified anhydrous) cooled in a Dry Ice-acetone bath was slowly added with stirring 2.95 g. (0.037 mole) of pyridine (Baker's C. P.). The solution was allowed to remain in the acetone-Dry Ice bath for an hour with shaking from time to time. It was then stored in a refrigerator at -20° for three days. The ether layer was decanted. The residue was washed twice with 20-ml. portions of ether. The combined ether solutions were evaporated to leave a gummy residue which on recrystallization from methanol gave 2.213 g. (20.4%) of adduct, m.p. 146–147°.

Anal. Calc'd for $C_{14}H_{13}NO_6$: C, 57.69; H, 4.47; N, 4.81; Mol. wt., 291.

Found: C, 57.82; H, 4.44; N, 5.02; Mol. wt., 277 (Rast); 268; 272 (cryos.); 149–198 (ebul.).

The adduct is soluble in alcohols, benzene, carbon tetrachloride, ether, pyridine, and hot, dilute acids and bases. It does not take up bromine nor give a Baeyer test for unsaturation. It does not form a crystalline chloroplatinate, perbromide, or nitrate.

The *picrate* of the pyridine adduct was prepared by adding 0.3 g. of the adduct in 10 ml. of 95% ethanol to 10 ml. of a saturated solution of picric acid in 95% ethanol. The solution was heated to boiling and cooled to give 0.49 g. of a crystalline product, m.p. 149–151°. A mixture m.p. with the adduct showed a depression, m.p. 132–135°.

Anal. Calc'd for $C_{20}H_{15}N_4O_{13}$: N, 10.7; Neut. Eq., 524.

Found: N, 10.50, 10.70; Neut. Eq., 493.

Pyrrocoline-2-carboxylic acid. This acid was obtained as follows on aqueous alkaline hydrolysis of the pyridine adduct. To 2.43 g. of the adduct was added a solution of 17.8 g. of potassium hydroxide in 40 ml. of water. The mixture was heated 30 minutes. The solution gave a violet color in a pine splint test indicative of an indole or pyrrocoline structure (1). The solution was diluted, filtered, and acidified to precipitate a white solid. This solid was collected, washed, and dried. On warming with dil. hydrochloric acid, carbon dioxide was evolved. The resulting solution was cooled to precipitate 1.16 g. (87%) of an air-dried solid. Recrystallization from ethanol water gave a light green solid which darkened at 225° and melted at 238–240° and had a neutral equivalent of 164.7 (theory 161). Pyrrocoline-2-car-

² Carbon-hydrogen and nitrogen analyses by Micro Tech Laboratories.

boxylic acid (2) obtained from pyridine and bromopyruvic ester (2) showed the same melting behavior. Mixtures showed no depression of m.p. U.V. absorption curves are given in Figure 1.

Oxidation of pyridine adduct to picolinic acid. The adduct (0.2 g.) was suspended in 2 ml. of acetic acid. A solution of 2 ml. of acetic acid in 4 ml. of 30% hydrogen peroxide was added. The solution was heated on a water-bath for an hour to evaporate to a gummy residue. This residue was taken up in methanol and the solution was cooled to give 0.02 g. of 2-picolinic acid 1-oxide, m.p. 157°. The melting point was not depressed on mixture with a sample of the 1-oxide prepared from a sample of picolinic acid obtained by a previously described process (9).

TABLE I
PYRIDINE-DIMETHYL ACETYLENEDICARBOXYLATE ADDITIONS

MOLES OF REACTANTS		TEMP. (°C./time) ^c	SOLVENT ^d (ml.)	YIELD OF ADDUCT ^e ; g., %
Pyridine ^a	Ester ^b			
0.003	0.002	25-35	Ether (25)	Tar only
.077	.121	0/5 H; 35/0.5 H	Ether (100)	0.95, 4.38
.031	.04	-10 to -20/28 H; 25/24 H	Ether (150)	1.28, 14.1
.037	.048	-78/1 H; -20/3 D	Ether (100) ^f	2.213, 20.4
.004	.006	-78/1 H; -20/3 D	Ether (100) ^g	Trace
.004	.006	-78/1 H; -20/3 D	Ether (100) ^h 0.3 g. abs. ethanol	0.02, —

^a Bakers C.P. Pyridine. ^b Redistilled just before use. ^c H, Hours; D, Days. ^d Baker's Purified anhydrous ether except as noted. ^e M.p. 146-147°C. ^f Similar runs with sodium-dried ether or with sodium-dried ether to which 0.15 g. of absolute ethanol were added gave tars as products from which no crystalline adduct could be isolated. ^g Using ferrous sulfate-washed ether and 0.001 g. of benzoyl peroxide. Similar runs with no benzoyl peroxide; with sodium-dried, ferrous sulfate-washed ether and 0.2 g of 30% aq. hydrogen peroxide; and with sodium-dried, ferrous sulfate-washed ether and benzoyl peroxide gave tars as products from which no crystalline adduct could be isolated. ^h Using sodium-dried, ferrous sulfate-washed ether and 0.001 g. of benzoyl peroxide.

3-Picoline-dimethyl acetylenedicarboxylate adduct. This adduct was obtained using the procedure described for the pyridine adduct from 4.58 g. (0.032 mole) of the ester in 100 ml. of ether and 1.15 g. (0.012 mole) of 3-picoline (Distillation Products, 90-95% grade). On recrystallization from methanol 1.08 g. of a yellow crystalline solid, m.p. 117-119.5° was obtained.

Anal. Calc'd for $C_{15}H_{15}NO_6$: C, 59.01; H, 4.92; N, 4.59; Mol. wt. 305.

Found: C, 59.06; H, 4.98; N, 4.82; Mol. wt. (cryos.), 266.

*Trimethyl benzo[*g*]pyrrocoline-1,2,3-tricarboxylate (IV) (?)*. This adduct was obtained using the procedure described for the pyridine adduct. From 3.43 g. (0.024 mole) of the ester in 100 ml. of ether at -80° and 1.65 g. (0.012 mole) of isoquinoline there was obtained 0.61 g. of a yellow, crystalline solid, m.p. 149-151°. Additional recrystallization from methanol gave a white solid, m.p. 150-151°. This solid does not absorb bromine in carbon tetrachloride or reduce permanganate.

Anal. Calc'd for $C_{15}H_{15}NO_6$: C, 63.34; H, 4.39; N, 4.10; Mol. wt., 341.

Found: C, 63.36; H, 4.64; N, 3.62; Mol. wt. (cryos.), 270.

Ultraviolet absorption data. Ultraviolet absorption measurements were made with a Beckman DU photoelectric spectrophotometer using 1.00-cm. silica cells and hydrogen and tungsten discharge lamps as light sources. In all measurements 95% ethanol was used as

solvent. The pyridine adduct (pyrrocoline) showed absorption maxima at 243, 270, and 320 $m\mu$; the isoquinoline adduct at 240, 269, 337, and 354 $m\mu$; the 3-picoline adduct at 275 $m\mu$.

SUMMARY

The diene addition reaction between pyridine bases and dimethyl acetylenedicarboxylate gives crystalline products from pyridine, 3-picoline, or isoquinoline when the reaction is run in ether at -78° . Yields of up to 20.4% of the pyridine adduct have been obtained. The pyridine adduct has been identified as 1,2,3-tricarbomethoxypyrrrocoline for which additional characterization data are reported. The isoquinoline adduct also has the properties of a pyrrocoline and is assigned the structure trimethyl benzo[*g*]pyrrrocoline-1,2,3-tricarboxylate. A 3-picoline adduct not previously reported has been obtained under similar conditions but does not have the absorption characteristics of a pyrrocoline.

LOUISVILLE 8, KY.

LITERATURE REFERENCES

- (1) DIELS AND ALDER AND CO-WORKERS, (a) *Ann.*, **486**, 211 (1931); (b) **490**, 267 (1931); (c) **498**, 1, 16 (1932); (d) **505**, 103 (1933); (e) **510**, 87 (1934); (f) **513**, 129 (1934); (g) **516**, 45 (1935); (h) **519**, 140 (1935); (i) **525**, 73 (1936); (j) **530**, 68, 87 (1937).
- (2) BORROWS AND HOLLAND, (a) *J. Chem. Soc.*, 672 (1947); (b) *Chem. Revs.*, **42**, 618 (1948).
- (3) DEWAR, *Electron Theory of Organic Chemistry*, Oxford University Press, London, 1949, p. 150-156.
- (4) KLOETZEL, *Org. Reactions*, **4**, 8-9 (1948).
- (5) WATERS, *Physical Aspects of Organic Chemistry*, D. van Nostrand Co., New York, 1950, p. 425, 511.
- (6) PRICE, *Reactions at Carbon-Carbon Double Bonds*, Interscience Publishers, Inc., New York, 1946, p. 49.
- (7) JEFFREY AND VOGEL, *J. Chem. Soc.*, 678 (1948).
- (8) ABBOTT, ARNOLD, AND THOMPSON, *Org. Syntheses*, Coll. Vol. II, 10 (1943).
- (9) SINGER AND McELVAIN, *Org. Syntheses*, **20**, 79 (1940).