blue liquid on melting or when dissolved in solvents. The identity of an isonitroso compound was shown beyond reasonable doubt by a "normal" molecular weight together with lack of color and by solubility in alkali.

Summary

1. The action of ethyl nitrite on certain ketones using aqueous hydrogen chloride, acetyl chloride and dry hydrogen chloride as catalysts has been studied. The results are expressed in tabular form.

2. Certain new compounds prepared are listed in Table IV.

STATE COLLEGE, PENNSYLVANIA

RECEIVED JULY 12, 1935

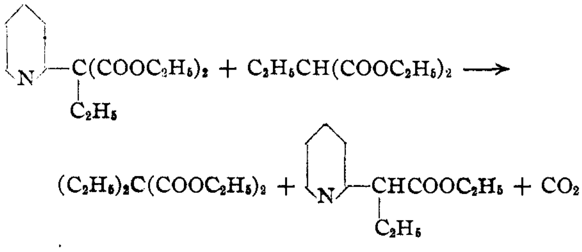
[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

Ethyl-2-pyridylmalonic Ester

BY L. A. WALTER AND S. M. MCELVAIN

The observation that the presence of a pyridine nucleus in certain types of therapeutic agents definitely lowers the intravenous toxicities of these substances[1] suggested the preparation and pharmacological evaluation of some pyridyl substituted barbituric acids. The first work along this line was directed toward the preparation of 5-ethyl-5-(2-pyridyl)-barbituric acid. Although it has not been possible to obtain this barbituric acid by the condensation of urea with the corresponding malonic ester, the preparation and properties of the ethyl-2-pyridylmalonic ester seem to be of sufficient interest to report.

This ester was prepared by the reaction of 2-bromopyridine with sodio-ethylmalonic ester in the absence of alcohol. When the reaction was carried out in alcoholic solution practically all of the bromopyridine which reacted was converted into 2-ethoxypyridine. Even in the absence of alcohol the yield of the pyridyl substituted malonic ester was not high (19%). Considerable amounts of ethyl α-(2-pyridyl)-butyrate and diethylmalonic ester were obtained as by-products of the reaction. These products apparently were the result of the alkylation of ethylmalonic ester by the ethyl-2-pyridylmalonic ester, thus



All attempts to condense ethyl-2-pyridylmalonic ester with urea either by means of dry or alcoholic sodium ethoxide were unsuccessful. The reaction product was in each case α-(2-pyridyl)-butyramide. Thus the behavior of this pyridyl substituted malonic ester parallels that which has been observed[2] for diphenylmalonic ester. It appears, therefore, that the 2-pyridyl group when substituted in a malonic ester approaches the effectiveness of two phenyl groups in promoting the cleavage of the ester. When compared to a single phenyl group the 2-pyridyl group is certainly very much more effective in increasing the sensitivity of the malonic ester to cleavage. For example, it was found that after refluxing for one hour with alcoholic sodium ethoxide, ethyl phenylmalonic ester suffered alcoholysis to ethyl carbonate and the corresponding acetic ester to the extent of 31% while under the same conditions ethyl-2-pyridylmalonic ester underwent alcoholysis to the extent of 93%.

The unusual labilizing effect of the 2-pyridyl group on the carbethoxy group of this pyridylmalonic ester is probably associated with the 2-linkage. It is well known that certain pyridine substituents, such as methyl, halogen, etc., are most reactive when they are in the 2-position. In the 4-position they are somewhat less reactive, while in the 3-position they are least reactive and resemble more closely the corresponding benzene derivatives in their behavior. It would be reasonable to expect, therefore, that a 3-pyridylmalonic ester, when it is made, will be found to have a resistance to alcoholysis comparable to that of a monophenyl substituted malonic ester and consequently be the most promising intermediate for the preparation of a 5-pyridylbarbituric acid.

---

[1] Strong and McElvain, THIS JOURNAL, **55**, 816 (1933); Snell and McElvain, *ibid.*, **56**, 1612 (1934).

[2] Dox and Thomas, *ibid.*, **45**, 1811 (1923); Cope and McElvain, *ibid.*, **54**, 4319 (1932).

Experimental

Ethyl-2-pyridylmalonic Ester.—To a suspension of 13.6 g. (1 mol) of sodium ethoxide in 100 cc. of absolute ether was added 38 g. (1 mol) of diethyl ethylmalonate. The mixture was warmed until the solid material had dissolved and then the ether and alcohol were removed under diminished pressure. To the remaining sodio-ethylmalonic ester 50 g. of 2-bromopyridine[3] was added and the mixture heated, with stirring, in an oil-bath at 140–150° for thirty hours. The reaction mixture then was treated with 150 cc. of ether and the ethereal solution washed with water and dried. Distillation of this solution gave the following products: 2 g. of 2-ethoxypyridine, b. p. 66° (25 mm.); 30 g. of 2-bromopyridine, b. p. 92–93° (25 mm.); 15 g. of a mixture of ethyl and diethyl malonic esters, b. p. 108–114° (25 mm.); 9 g. of ethyl α-(2-pyridyl)-butyrate, b. p. 97–98° (2 mm.), d_4^{25} 1.0330, n_D^{25} 1.4873; 9 g. of ethyl-2-pyridylmalonic ester, b. p. 136–137° (2 mm.), d_4^{25} 1.0950, n_D^{25} 1.4849.

Anal. Ethyl α-(2-pyridyl)-butyrate. Calcd. for $C_{11}H_{15}O_2N$: C, 68.35; H, 7.83. Found: C, 68.20; H, 7.94. Diethyl ethyl-2-pyridylmalonate. Calcd. for $C_{14}H_{19}O_4N$: C, 63.35; H, 7.37. Found: C, 63.10; H, 7.39.

An attempt was made to prepare ethyl-2-pyridylmalonic ester by reaction of 2-bromopyridine with an alcoholic solution of sodio-ethylmalonic ester. From a run using 53 g. of 2-bromopyridine the only reaction product isolated was 20 g. (49%) of 2-ethoxypyridine. This compound was found to boil at 66° (25 mm.) and 160–161° (740 mm.); mercuric chloride derivative,[4] m. p. 152–153; hydrochloride, m. p. 90–91°.

Anal. Hydrochloride. Calcd. for $C_7H_{10}ONCl$: Cl, 22.21. Found: Cl, 22.17.

Reaction of Ethyl-2-pyridylmalonic Ester with Urea and Sodium Ethoxide.—To a solution of 7.9 g. of sodium ethoxide in 50 cc. of absolute alcohol was added 3.3 g. of urea and 7.5 g. of ethyl-2-pyridylmalonic ester. This solution was heated in a sealed tube at 100° for seven hours. After this time the alcoholic solution was diluted with 50 cc. of water and treated with the exact quantity of acetic acid necessary to react with the sodium ethoxide used. The alcohol then was removed under diminished pressure and the remaining aqueous solution extracted with ether. This ether extract was evaporated and the residue washed with petroleum ether to remove any unreacted ester. The tar-like material remaining was recrystallized from 25 cc. of water and gave 0.1 g. of crystals which after several recrystallizations from hexone melted at 188°. This material was shown not to be a barbituric acid by its elementary analysis.

The aqueous mother liquor from this crystallization together with the original aqueous solution was concentrated and from them was obtained 3.8 g. (80%) of α-(2-pyridyl)-butyramide, m. p. 125–126°. This same amide resulted from the ammonolysis of ethyl α-(2-pyridyl)-butyrate.

Anal. Calcd. for $C_9H_{12}ON_2$: C, 65.81; H, 5.85. Found: C, 65.79; H, 5.73.

When the ethyl-2-pyridylmalonic ester was heated with urea and dry sodium ethoxide the principal product of reaction was likewise the α-(2-pyridyl)-butyramide.

Alcoholysis of Ethyl-2-pyridylmalonic Ester and of Ethylphenylmalonic Ester.—A 3.0736-g. sample of each of these substituted malonic esters was refluxed for one hour with 50 cc. of absolute alcohol containing 1.2 g. of sodium ethoxide. The alcohol and any diethyl carbonate then was distilled off under diminished pressure and condensed by passing through a spiral surrounded by an ice-salt mixture. The residue remaining in the reaction flask was washed with ether to remove any unreacted malonic ester. The alcohol and ethyl carbonate, which previously had been distilled off, together with a small amount of water, were added to the residue and the resulting alkaline solution refluxed for thirty minutes. The solution was then acidified with sulfuric acid and the carbon dioxide evolved absorbed in ascarite and weighed. The carbon dioxide obtained from ethyl 2-pyridylmalonic ester weighed 0.4730 g. (92.7%) while that obtained from ethyl phenylmalonic ester amounted to 0.1548 g. (30.8%).

Summary

The preparation and properties of ethyl-2-pyridylmalonic ester are described.

Madison, Wisconsin

Received July 19, 1935

---

[3] Craig, This Journal, **56**, 231 (1934).

[4] Von Pechmann and Baltzer [*Ber.*, **24**, 3148 (1891)] report the b. p. of this compound as 156° and the m. p. of its mercuric chloride derivative as 141°.