δ-LACTONES AND δ-LACTAMS

LXV. Synthesis and Properties of Adducts of 5,6-Disubstituted 2-Pyridones with Dimethyl Acetylenedicarboxylate

N. P. Shusherina, O. V. Slavyanova, G. N. Rodionova, and R. Ya. Levina

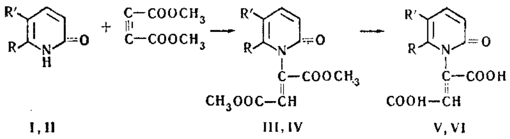
Khimiya Geterotsiklicheskikh Soedinenii, Vol. 6, No. 4, pp. 489-491, 1970

UDC 547.824:542.938

It has been established that the reaction of 5,6-dialkyl-2-pyridones with dimethyl acetylenedicarboxylate leads to esters of 2-ketopyridin-1-ylfuramic acids, which are readily hydrolyzed in the cold by aqueous solutions of alkalis. The ease of hydrolysis of the esters is apparently explained by intramolecular catalysis as a consequent of the nucleophilic participation of the oxygen of the pyridone ring.

In recent years, several attempts to effect the diene synthesis with 2-pyridones [1-3] as dienes have been described. It has been found that 2-pyridones react in the manner of a diene synthesis only when a substituent is present on the hetero atom [3], forming adducts with very low yields (1-10%). 2-Pyridones unsubstituted on the nitrogen atom react with dienophiles in the manner of a Michael condensation [1].

In this work we have studied the reaction to dimethyl acetylenedicarboxylate with 5,6-dialkyl-2-pyridones [4, 5]. (When the present work was completed, a paper [6] on the reaction of acetylenedicarboxylic ester with 2-pyridone and 6-methyl-2-pyridone appeared.) 5,6-Dimethyl- and 5,6-cyclohexano-2-pyridine unsubstituted on the nitrogen atom (I and II) react with acetylenedicarboxylic ester on boiling in xylene in the manner of a Michael condensation with the formation of the adducts III and IV:



R=R'=CH_3 I, III, V; R+R'=$(-CH_2-)_4$ II, IV, VI

The structure of the esters III and IV was confirmed by their IR and PMR spectra. The absence from the IR spectrum of an NH absorption band and the presence of absorption bands of an amide carbonyl (Table 1), and also the PMR spectrum (absence of a NH proton; presence of two vinyl protons in the cis-position with respect to one another, judging from the spin-spin coupling constants, and of an isolated vinyl proton) confirmed that the acetylenedicarboxylic ester has added to the pyridone at the nitrogen atom. We thank L. L. Fedorova and V. N. Babina for obtaining the PMR spectra and assisting in their interpretation. By analogy with literature data [6, 8], the adducts of acetylenedicarboxylic ester with 2-pyridone and other heterocycles may be ascribed the trans configuration, i.e., the structure of 2-oxopyridone-1-ylfumaric acid.

Table 1. IR Spectra* of Compounds II-VI, VIII

Compound	ν, cm⁻¹			
	C=C C—N	C=O (amide)	C=O (ester)	OH, NH
II	1558	1635, 1665	—	2400—3150
III	1538, 1597	1676	1727	—
IV	1542, 1592	1666	1743	—
V	1510, 1562	1635, 1664	1747	2200—3600 (*max* 2600)
VI	1510, 1560	1635, 1660	1748	2670, 3090, 3450 2200—2800, 3425
VIII	1525, 1562	1635, 1662	1715, 1740	2200—3300 (*max* 3160)

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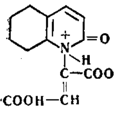
*Taken on a UR-10 spectrophotometer; the samples for the spectra were prepared in the form of tablets with KBr (0.5%) and mulls with paraffin oil.

On being heated above 200°C, the adducts III and IV decomposed into the initial components: 2-pyridones and acetylenedicarboxylic ester (identified by thin-layer chromatography).

A characteristic property of the esters III and IV is their remarkable ease of hydrolysis of cold aqueous 2N caustic soda. As we have described previously for esters of β-2-oxopyridin-1-ylpropionic acids [9], this ease of hydrolysis is apparently due to intramolecular cyclization with the subsequent formation of unsaturated γ- and δ-azlactones with ammonium nitrogen [10], which readily open the lactone ring under the action of alkali, being converted into dicarboxylic acids (V and VI) in quantitative yield. The product of the bromination of the adduct IV (VII, in which the bromine is present (according to the PMR spectrum) in position 3 of the pyridone ring, is converted into the acid (VIII) just as readily.

In the IR spectra (table) of the acids V, VI, and VIII obtained by the hydrolysis of the corresponding esters, there is the absorption characteristic for pyridones in the 1635-1664 cm^{-1} region (amide carbonyl) and strong absorption in the 1510-1525 cm^{-1} region which, with the marked shift of the vibrations of the OH group in the low-frequency direction, indicates a bipolar (betaine-like) structure of the type of VIa. The acids V and VI are not converted into anhydrides under the action of acetic anhydride and acetyl chloride, which permits the assumption of the trans- configuration for them and, consequently, for the initial esters III and IV. On being heated with acetic anhydride to 100°C, the acid VI was recovered unchanged, while above 100°C its complete resinification took place.


VIa

N-Substituted 2-pyridones — N-phenyl- and N-ethyl-5,6-cyclohexano-2-pyridones (IX and X — do not react with acetylenedicarboxylic ester under the conditions described above, nor on being heated in an autoclave at 150-180°C and a pressure of 100-180 atm for 10 hr (for the N-ethylpyridone) and 30 hr (for the N-phenylpyridone).

EXPERIMENTAL

5,6-Cyclohexano-2-pyridone and 5,6-dimethyl-2-pyridone (II and I) were obtained by the chlorination with sulfuryl chloride [5] of the corresponding 5,6-disubstituted 3,4-dihydro-2-pyridones and subsequent dehydrochlorination of the dichlorides formed. Together with the 5,6-dimethylpyridone, 3-chloro-5,6-dimethyl-2-pyridone, subliming at 190°C, was isolated (yield 3%). Found %: C 53.1; H 5.3; N 8.6. C_7H_8NOCl. Calculated %: C 53.3; H 5.1; N 8.9.

N-Phenyl- and N-ethyl-5,6-cyclohexano-2-pyridones (IX and X) were obtained by Acheson and Tasker's method [5] from N-phenyl- and N-ethyl-5,6-cyclohexano-3,4-dihydro-2-pyridones [11]. Compound IX was obtained with a yield of 27%, bp 186-187°C (1 mm), mp 139-140°C (from ethyl acetate), R_f 0.18 (in chloroform; the thin-layer chromatography was carried out on alumina of activity grade II). Found %: C 80.4; H 6.8; N 6.1. $C_{15}H_{15}NO$. Calculated %: C 80.0; H 6.7; N 6.2. Compound X was obtained with a yield of 50%, mp 45-47°C (from petroleum ether with bp 80-100°C). To eliminate traces of the initial dihydropyridone, the material was previously recrystallized repeatedly from ethyl acetate. R_f 0.11 (in chloroform). Found %: C 73.9; H 8.3; N 8.0. $C_{11}H_{15}NO$. Calculated %: 74.5; H 8.5; N 8.0.

Reaction of 2-pyridones with dimethyl acetylenedicarboxylate. A solution of 0.06 mole of a 2-pyridone and 0.06-0.07 mole of acetylenedicarboxylic ester in 50 ml of xylene was boiled for 5 hr (if toluene or benzene was used instead of xylene, the time of heating had to be increased to 12 hr). The solvent was distilled off in vacuum and the residue, a dark partially crystallizing oil, was recrystallized, with solid carbon dioxide cooling, first from petroleum ether (bp 80-100°C) and then from ether. The bright yellow crystalline substance was chromatographed in a thin layer of Al_2O_3 (R_f 0.15 in chloroform), and when the initial pyridone was present as an impurity (R_f 0-0.02) the product was freed from it by washing its ethereal solution with 4 N HCl. Dimethyl 5,6-cyclohexano-2-oxopyridin-1-yl-fumarate (IV), yield 60%, mp 108-109°C (from ether). PMR spectrum: multiplet of a cyclohexane ring (δ 2.10 ppm), two singlets of the protons of a methoxycarbonyl group (δ 3.69 and 3.82 ppm), two doublets and a singlet in the region of vinyl protons (doublets with δ 6.20 and 7.01 ppm, J = 10.5-11 Hz, singlet δ 7,07 ppm). Found %: C 61.5; H 5.9; N 5.1. $C_{15}H_{17}NO_5$. Calculated %: C 61.8; H 5.9; N 4.8. Dimethyl 5,6-dimethyl-2-oxopyridin-1-ylfumarate (III), yield 31%, mp 98-99°C (from ether). Found %: C 58.7; H 5.8; N 5.1. $C_{13}H_{15}NO_5$. Calculated %: C 58.9; H 5.7; N 5.3. Dimethyl 3-bromo-5,6-cyclohexano-2-oxopyridin-1-ylfumarate (VII). At room temperature 0.26 ml (5 m) of bromine was added dropwise to a solution of 1.45 g (5 m) of IV in 30 ml of ether or chloroform. After the solvent had been distilled off in vacuum, the residue (a viscous oil) was treated with water in the cold and was then recrystallized from ether (with solid carbon dioxide cooling). This gave 1.15 g (70%) of product with mp 139-141°C. R_f 0.22 (in chloroform). In the region of vinyl protons, the PMR spectrum has two singlets with δ 6.98 and 7.33 ppm. Found %: C 48.9; H 4.5; N 3.9. $C_{15}H_{16}NO_5Br$. Calculated %: C 48.7; H 4.4; N 3.8.

5,6-Dialkyl-2-oxopyridin-1-ylfumaric acids. Some 0.5 g of one of the esters III, IV, and VII was boiled with 3 ml of 2 N aqueous caustic soda (its complete dissolution was instantaneous), the solution was acidified with conc. HCl, and the crystals of the dicarboxylic acid (V, VI, or VIII) were filtered off, recrystallized from water, and dried in vacuum at 70°C.

5,6-Dimethyl-2-oxopyridin-1-ylfumaric acid (V, monohydrate) was obtained in quantitative yield, mp 145-147°C. Found %: C 51.6; H 5.2; N 5.7. $C_{11}H_{11}NO_5 \cdot H_2O$. Calculated %: C 51.8; H 5.1; N 5.5.

5,6-Cyclohexano-2-oxopyridin-1-ylfumaric acid (VI, monohydrate) was obtained in quantitative yield, mp 165-166°C. Found %: C 55.4; H 5.3; N 5.0. $C_{13}H_{13}NO_5 \cdot H_2O$. Calculated %: C 55.5; H 5.4; N 5.0. An attempt to sublime the acid at 200°C led to its decomposition. When the monohydrate of the acid was heated in vacuum over P_2O_5 at 110°C for 60 hr, the anhydrous acid, VI, with mp 190-191°C was obtained. Found %: C 58.8; H 5.2; N 5.2. $C_{13}H_{13}NO_5$. Calculated %: C 59.3; H 5.0; N 5.3.

3-Bromo-5,6-cyclohexano-2-oxopyridin-1-ylfumaric acid (VIII). Yield 85%, mp 213-214°C. Found %: C 45.9; H 3.8; N 4.4. $C_{13}H_{12}NO_5Br$. Calculated %: C 45.6; H 3.5; N 4.1.

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26 June 1968

Moscow State University