STRUCTURE, TAUTOMERISM, AND TRANSFORMATIONS OF β-(3-NITRO-2-PYRIDYL)- AND β-(3-NITRO-4-PYRIDYL)PYRUVIC ACID ESTERS

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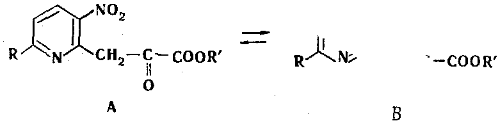
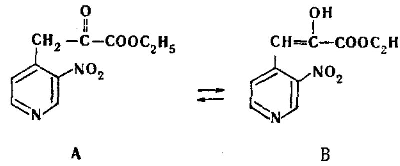
It was shown by means of IR, UV, and PMR spectra that β-(3-nitro-2-pyridyl)pyruvic acid esters are practically completely enolized in the crystal state and in solution; ethyl β-(3-nitro-4-pyridyl)pyruvate has an enol structure in the crystalline state and in pyridine solution, but exists as a mixture of keto and enol forms in low-polarity solvents.

Pyruvic acid esters have a low capacity for transition to the enol form [1]. However, the introduction of electron-acceptor substituents of the nitropyridyl or nitroaryl type into the β-position of these compounds should promote enolization [2, 3]. In fact, there are indications that ester I [4] and 6-methoxy derivative II [5] exist primarily in the hydroxy form. However, more detailed investigations of the structure of these types of substances and of the position of the tautomeric equilibrium in them have not been made.





III

I $R=H$, $R'=C_2H_5$; II $R=OCH_3$, $R'=CH_3$;

We have used the IR, UV, and PMR spectra to examine the structure and tautomerism of esters I-III in the crystalline state and in solution; we also examined some of the chemical transformations of these compounds.

A narrow ν_{CO} band of an ester group at 1725-1745 cm^{-1} and four bands of the stretching vibrations of double bonds are observed in the IR spectra of crystals and solutions (in chloroform and dioxane) of esters I and II (Table 1). Two of the four bands practically coincide with the bands in the spectrum of 6-methoxy-3-nitro-2-methylpyridine (IV) (1593 and 1508 cm^{-1}) and thus are related to the vibrations of the pyridine portion of the molecule, while the higher-frequency band (1613-1643 cm^{-1}) apparently is associated with the presence in esters I and II of a double bond in the side chain of enol form B.

A similar pattern in this region of the IR spectrum is also observed for keto ester III in the crystalline state and in pyridine solutions. In addition, a broad split band at 1707-1735 cm^{-1}, which is evidently

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TABLE 1. UV and IR Spectral Data

Substance	UV spectrum		IR spectrum, ν, cm^{-1}			
	solvent	λ_{max}, nm (ε)	solvent and aggregate state	C=O	C=C	O–H
I	97% alcohol	248 (9100)	Crystals	1725 s	1643s, 1598m, 1563s, 1530 s	
		316 (15200)	$CHCl_3$	1737 s	1625s, 1605 s, 1562 vw, 1535s	
	100% alcohol	249 (8700)	Dioxane	1744 s	1623s, 1605 s, 1560 vw, 1535s	
		316 (15300)				
	Dioxane	249 (9300)	CCl_4^{a}	1735		
		320 (15900)		1745		
II	97% alcohol	274 (8000)	Crystals	1737 s	1613 s,br, 1584s., 1572 s, 1510 s	
		330 (13400)				
		352 (10500)^b	$CHCl_3$	1742 s	1628 vs, 1595 s, 1578s, 1520 m	
	100% alcohol	272 (7700)	Dioxane	1746 s	1625s, 1594s, 1577 m, 1522 m	
		330 (14100)				
		~350 (11400)^b	CCl_4^{a}	1735 s		
	Dioxane	244 (8400)^c				
		272 (8200)^c				
		330 (13800)				
		356 (10900)^b				
III	97% alcohol	267 (6200)	Crystals	1708 s	1655m, 1590 m, 1544 s, 1518 s	2600 m, vbr
		286 (5900)	Pyridine	1723 s	1640 w, 1525 s	
		340 (3650)^b	$CHCl_3$	1735 s	1666 w, 1609 m, 1555 w, 1525 s	3440 m
				1710 m^b		
	100% alcohol	274 (8500)^b				
		290 (9400)	Dioxane	1720 s	1648 w, 1600 s, 1553 w, 1530 s	
		330 (5000)^b		1732 s		
	Dioxane	267 (9300)				
		283 (9000)^b	CCl_4^{a}	1728, 1707		3430 m
		330 (4500)^b				
IV	97% alcohol	272 (5200)^b	Crystals		1593 vs, 1508 m	
		298 (9100)				
V	97% alcohol	246 (6200)	Liquid		1606 s, 1551 m, 1523 s	

Note: ^{a}Because of low solubility, the $\nu_{C=C}$ bands are not observed. ^{b}Shoulder. ^{c}Weakly expressed indistinct maxima.

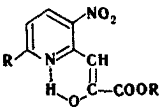
TABLE 2. Chemical Shifts of the Protons of Ester III (δ, ppm)

Solvent	2-H		5-H		6-H		CH_2	=CH	OCH_2		CH_3	
	A	B	A	B	A	B	A	B	A	B	A	B
$CDCl_3$	9,40	9,14	7,30	8,24	8,80	8,77	4,59	7,00	4,41	4,43	1,39	1,39
CD_3COCD_3	9,32	9,14	7,66	8,86	8,90	8,79	4,82	6,91	4,41	4,36	1,41	1,41
CD_3OD	9,00	9,04	7,58	8,44	8,68	8,63	—	—	4,23	4,60	1,41	1,37
CD_3COOD	9,40	9,18	7,63	8,49	8,92	8,81	—	—	4,41	4,46	1,40	1,37
C_5D_5N			8,08		8,71			7,16		4,17		1,05
CD_3SOCD_3	9,30	9,04	7,60	8,35	8,45	8,40	4,61	6,77	4,20	4,21	1,50	1,50

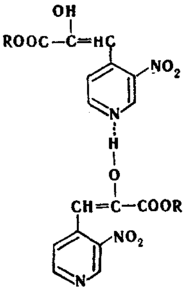
associated with the stretching vibrations of the two carbonyl groups of form A – the ester and ketone carbonyl groups – appears in the spectra of solutions of it in $CHCl_3$, CCl_4, and dioxane in the region of the stretching vibrations of double bonds. It should be noted that the frequencies of the stretching vibrations of these groups in methyl pyruvate have very close values [6].

Thus an examination of the IR spectral data shows that I and II in the crystalline state and in solutions have enol structure B, while III in chloroform, dioxane, and carbon tetrachloride exists as a mixture of the ketone and enol forms but exists as the enol in pyridine.

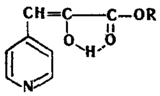
The ν_{OH} bands in the high-frequency region of the spectra of esters I and II cannot be followed. This is characteristic for compounds with a chelate hydrogen bond, for which one should observe a shift in the ν_{OH} band to the low-frequency region and a decrease in its intensity. The ring nitrogen atom and the hydroxyl group (C) can participate in the formation of this sort of hydrogen bond with closing of a six-membered ring for I and II. An intramolecular hydrogen bond with the participation of the nitro group is unlikely, inasmuch as in this case one must assume the development of an eight-membered ring. If the nitro groups did participate in the formation of intramolecular hydrogen bonds, the character of the absorption in the ν_{OH} region would be practically identical for all of the investigated compounds (I-III). In fact, the spectra in this region for esters I and II, for which the ν_{OH} bands are practically unobserved, differ from the spectrum of ester III, in which a band at 2600 cm^{-1} appears for crystals, while a distinct band at 3430-3440 cm^{-1} appears for solutions. The possibility of an intramolecular bond with the participation of the hydroxyl group and ring nitrogen atom in ester III is excluded. The presence of a ν_{OH} band at 3430 cm^{-1} in the spectrum of a solution of III can therefore be explained by intramolecular interaction of the OH and CO groups with the formation of a five-membered ring (E). The retention of the low frequency when the solution is diluted markedly confirms the intramolecular character of this bond. The broad absorption bands at 2600 cm^{-1} in the spectra of crystals of III can be assigned with great probability to intermolecular interactions of compounds of the D type.



C



D



E

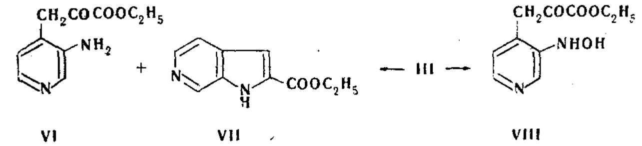
The UV spectral data are in agreement with the above-described structure of the compounds. Thus, for example, the UV spectra of esters I-III differ appreciably from the spectra of methoxy derivative IV and 3-nitro-4-methylpyridine (V), respectively, with respect to the presence of longer-wave absorption and the considerable increase in the intensity of the maxima. This indicates elongation of the conjugation chain in the molecule and confirms the enol structure of the compounds under consideration. In contrast to esters I and II, the spectra of which in various solvents remain practically unchanged, an appreciable decrease in the intensity of the absorption maximum at 267 nm with an increase in the polarity of the solvent (Table 1) is observed in the spectra of ester III. The absence of absorption above 250-270 nm in the spectrum of nitro pyridine V – a model compound for ketone form IIIA – indicates the presence of two tautomeric forms in solutions of III; the percentage of the hydroxy form is reduced as the polarity of the solvent increases.

A signal at 7.52 ppm, which corresponds to the CH= proton in the CH=C(OH)COOR grouping, and the signal of the proton of a hydroxyl group at 13.8 ppm are observed in the PMR spectrum of I (in $CDCl_3$). Such a weak-field position of the signal of the OH group is an additional confirmation of a very strong chelate intramolecular hydrogen bond. Similar data were obtained for II.

According to the PMR spectral data, III exists in two tautomeric forms. Thus in acetone, in addition to the signal of the olefinic proton of the enol form at 6.90 ppm, one observes a signal at 4.82 ppm of the CH_2 group of the ketone form (Table 2); the ratio of tautomer A to B is ~2 : 1. A mixture of two tautomeric forms is also observed in $CDCl_3$, but in this case the ratio of A to B is ~4 : 1. In CD_3OD and CD_3COOD solutions the CH and CH_2 signals, as a result of rapid deuterium exchange, do not appear. However, the doubling of the other signals in the spectra attests to the presence of both tautomeric forms with ketone to enol ratios of 3 : 1 and 1.5 : 1, respectively. The enol form predominates in $CD_3SO_2CD_3$ (1 : 5), while the keto form is practically absent in pyridine.

We have shown that, in contrast to β-(3-nitro-2-pyridyl)pyruvic acid esters, in which Reissert reductive cyclization is readily realized by hydrogenation with palladium under normal conditions [7], in the case of ethyl β-(3-nitro-4-pyridyl)pyruvate the transition from hydrogenation in an autoclave [8] to milder conditions is accompanied by the formation of uncyclized ethyl β-(3-amino-4-pyridyl)pyruvate (VI).

The development, in addition to ethyl 6-azaindole-2-carboxylate (VII), of aminopyridine VI may be associated with the existence of starting ester III in solution as two tautomeric forms with commensurable amounts of both tautomers.



Cyclization of amino ester VI to azaindole derivative VII is accomplished with great difficulty on prolonged refluxing in xylene. This makes it possible to assert that ester VI is not an intermediate in the Reissert synthesis of azaindoles.

It is also interesting to note that the reduction of amino ester III on a nickel catalyst in pyridine does not go to completion but is interrupted at the step involving hydroxylamino derivative VIII.

EXPERIMENTAL

The IR spectra of mineral oil pastes or solutions in chloroform, dioxane, and carbon tetrachloride were recorded with a Perkin-Elmer 457 spectrometer. The UV spectra of solutions were obtained with an EPS-3 spectrophotometer. The PMR spectra were recorded with JNM-4H-100 and C-60HL spectrometers with tetramethylsilane as the internal standard.

Hydrogenation of Ethyl β-(3-Nitro-4-pyridyl)pyruvate (III). A) A solution of 1.5 g of $PdCl_2$ in 10 ml of 18% hydrochloric acid was added to a solution of 2 g (8 mmole) of III in 150 ml of alcohol, and hydrogenation was carried out at a pressure of 20-30 cm (water gauge). After the calculated amount of hydrogen had been absorbed, the catalyst was removed by filtration, and the solvent was vacuum evaporated to give 1.2 g of a substance, which, according to thin-layer chromatography (TLC), was a mixture of ethyl 6-azaindole-2-carboxylate (VII) and ethyl β-(3-amino-4-pyridyl)pyruvate (VI) [Al_2O_3 with methanol as the mobile phase and development with iodine vapors; R_f 0.8 for ester VII, and R_f 0 for ester VI]. The mixture was crystallized from 60 ml of ethyl acetate to give 0.7 g (44%) of ester VII with mp 212-213°. The ethyl acetate solution was evaporated to give 0.5 g (29%) of ester VI as yellow crystals with mp 147-149° (from benzene). The substance was quite soluble in alcohol and chloroform, was crystallized from benzene, acetone, and ethyl acetate, and was only slightly soluble in water. Found: C 57.5; H 5.4; N 13.5%. $C_{10}H_{12}N_2O_3$. Calculated: C 57.6; H 5.7; N 13.5%.

B) A 5 g sample of Raney nickel was added to a solution of 1 g (4 mmole) of ester III in 100 ml of pyridine, and the ester was hydrogenated at 20-30 cm (water gauge) until hydrogen absorption ceased. The catalyst was removed by filtration, the solvent was vacuum evaporated, and the residue (0.75 g) was crystallized from ethyl acetate and alcohol to give 0.23 g (24%) of ethyl β-(3-hydroxylamino-4-pyridyl)pyruvate (VIII) with mp 181° (from alcohol). The white substance was quite soluble in acetone but only slightly soluble in ether, benzene, chloroform, alcohol, and water. Found: C 53.6; H 5.5; N 12.2%. $C_{10}H_{12}N_2O_4$. Calculated: C 53.5; H 5.4; N 12.5%.

Ethyl 6-Azaindole-2-carboxylate (VII). A 0.15 g sample of calcined potassium carbonate was added to a solution of 0.6 g (3 mmole) of ester VI in 30 ml of xylene, and the mixture was refluxed for 6 h. The xylene solution was filtered, and the filtrate was vacuum evaporated to give 0.15 g (27%) of ester VII with mp 212-214° (from ethyl acetate) [8].

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