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OXIDATION REACTIONS OF AZINES. 4.* CONJUGATION OF 4-ARYL-1,2,5,6-TETRAHYDROPYRIDINES WITH COMPOUNDS CONTAINING AN ACTIVATED METHYL GROUP. SYNTHESIS AND STRUCTURE OF 2-ACYLMETHYLENE- AND 2-NITROMETHYLENE-1,2,5,6-TETRAHYDROPYRIDINES

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A novel $C_{sp}^3-C_{sp}^3$ oxidative conjugation with compounds containing an activated methylene group has been described in the case of 1-alkyl-4-aryl-1,2,5,6-tetrahydropyridines. It was shown that treatment of the indicated Δ^3-piperidines with methyl ketones or nitromethane in the presence of $KMnO_4$ gives their 2-acylmethylene- or 2-nitromethylene derivatives respectively.

We have previously shown that oxidation of 1-alkyl-4-aryl-1,2,5,6-tetrahydropyridines in water-acetonitrile and $KMnO_4$ gives the corresponding β,γ-dihydroxy-α-piperidone [2] or 1,2,5,6-tetrahydro-α-pyridone [1]. Exchange of acetonitrile for acetone (with other reaction conditions the same) alters the reaction course. The oxidative ketohydroxylation basically becomes an oxidative conjugation (formally $C_{sp}^3-C_{sp}^3$) of acetone with the allylamine fragment in the starting piperidine leading to formation of the 2-acetylmethylenetetrahydropyridine system. We have briefly reported this previously [3]. Only the oxidative conjugation of indoxyl to form indigo, which is accelerated in basic medium [4], shows some similarity to the indicated reaction. A further example known to us of the conjugation of 4a,9-diaza-1,2,4a,9a-tetrahydrofluorene with nitromethane and a number of methylene active compounds in the presence of MnO_2 [5] is, however, based on the oxidation of an aniline fragment to para-quinoneimine which then undergoes nucleophilic conjugation with CH acids (formally $C_{sp}^2-C_{sp}^3$) conjugation).

In this work we have studied a possible broadening of the scope of oxidative conjugation (in the presence of $KMnO_4$) in a series of CH active compounds (acetone, acetophenone, 2-acetylthiophene, and nitromethane) with 4-aryl-1,2,5,6-tetrahydropyridines (Ia-d). The latter have a methyl or ethyl group on the nitrogen atom, since their N-unsubstituted analog undergoes complete tarring in this reaction. The reaction of the indicated reagents gives 4-acylmethylene (IIa-e) and 2-nitromethylene-4-aryl-1,2,5,6-tetrahydropyridines (IIIf, g), characterized by their ^1H and ^{13}C NMR spectra (see Tables 1 and 2).

In the case of the oxidative conjugation of piperidines Ia, b with acetone, it was found that lengthening of the alkyl chain at the nitrogen atom did not have a significant effect on the reaction course. In both cases, a high yield of 2-acetylmethylene-1-methyl- (IIa) or 2-acetylmethylene-1-ethyl-4-([2.2]paracyclophan-4-yl)-1,2,5,6-tetrahydropyridine (IIb) respectively was obtained. The introduction of the acetonylidene substituent into one of the heterocycle α-positions was readily confirmed chemically by aromatization of IIa, b via heating with sulfur. The PMR spectrum of the pyridine obtained (III) shows three signals, the multiplicity and chemical shifts of which unambiguously point to the aromatization of the heterocycle and

*For communication 3, see [1].

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TABLE 1. Parameters for Compounds Synthesized*

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	R_f (ether)	IR spectrum, ν, cm^{-1}	Mass spectrum, m/z, (I, %)	Yield, %
		C	H	N					
IIb	$C_{26}H_{29}NO$	83.83 84,10	7.92 7,82	4.13 3,77	Oil	0,42	1690	$[M]^+$ 371 absent, $[M - C_3H_4]^{+\cdot}$ 331(10), $[M - C_4H_5]^{+\cdot}$ 319(3), $[M - CH_2COCH_3]^{+\cdot}$ 315(100), 104(70)	70
E-IIc	$C_{15}H_{17}NO$	80.10 79,29	7.30 7,48	6.00 6,16	Oil	0,38	1680	$[M]^+$ 227(68), $[M - CH_3]^{+\cdot}$ 219(100), 210(16), $[M - COCH_3]^{+\cdot}$ 184(42), $[M-Ph]^+$ 150(21), $M^+/2$ 113, 59(47), 105(53), 77(63), 57(79)	30
Z-IIc	$C_{15}H_{17}NO$	80.05 79,29	7.18 7,48	5.91 6,16	Oil	0,19	1685	M^+ 227	12
IId	$C_{20}H_{19}NO$	83.45 83,04	6.41 6,57	4.49 4,87	112...115	0,6	1679	$[M]^+$ 289(91), $[M - CH_3]^{+\cdot}$ 272(100)	7
IIe	$C_{18}H_{17}NOS$	73.57 73,22	5.57 5,78	4.80 4,74	131...134	0,6	1682	$[M]^+$ 295(100), $[M - CH_3]^{+\cdot}$ 280(71), $[M - CS]^{+\cdot}$ 251(188), $[M - Ph]^{+\cdot}$ 218(19), $[M - C_4H_3S]^{+\cdot}$ 212(19), $[M - O{=}C{-}C_4H_3S)^{+\cdot}$ 184(96), 77(83)	6
IIf	$C_{13}H_{14}N_2O_2$	67.82 67,44	6.07 6,21	12.17 12,09	Oil	0,6†	1352, 1537, 1620, 1640	M^+ 230	40
IIg	$C_{14}H_{16}N_2O_2$	68.78 68,37	6.55 6,94	11.47 11,73	Oil	0,76†	1371, 1556, 1636	M+ 244	16
III	$C_{24}H_{23}NO$	83.99 84,45	6.50 6,74	4.31 4,10	47...49	0,41	1700	M^+ 341	30

*Parameters for E-IIa have been reported in the short communication [3].

†In the system benzene–ether (2:1).

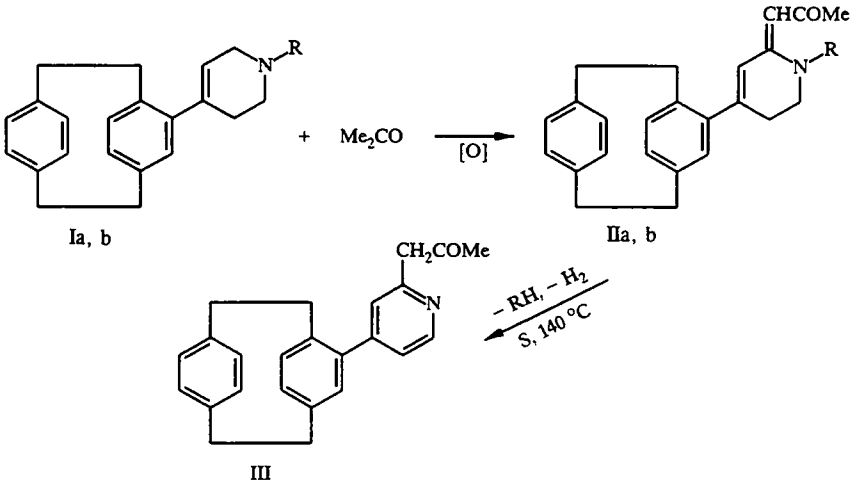
TABLE 2. NMR Spectral Data for Compounds Synthesized

Compound	PMR spectrum, chemical shift, δ, ppm, spin-spin coupling (J, Hz)						
	heterocycle			substituent			
	3-(1H)	5-H	6-H	-CH(c)	COR[1]	N-R	$C_{(4)}$-Ar
E*-IIa	5,13 (s)	2,45 (1H, m), 2,79 (1H, m)	3,40 (2H,m)	8,21	2,21 (3H, s)	2,91 (3H, s)	6,46...6,54 (4H, m); 6,57 (1H), 6,68 (1H) and 6,83 (1H) (three d.d J = 7,9 and 1,8)
IIb*	5,26 (s)	2,60...2,90 (2H, m)	3,32 (2H, m)	8,26	2,25 (3H, s)	1,26 (3H, t, CH_3); 3,4 (2H,q, CH_2)	6,36...6,95 (7H, m)
E-IIc	5,08 (s)	2,68 (2H, t, J = 7,0)	3,35 (t, J = 7,0)	8,38	2,12 (3H, s)	2,91 (3H, s)	7,33 (3H, m); 7,55 (2H, d, J = 8,2)
Z-IIc	5,09 (s)	3,35...3,60 (4H, br. m)		8,33	2,15 (3H, s)	3,0 (3H, s)	7,33 (3H, m), 7,6 (2H, m)
IId	5,78 (s)	2,77 (2H, t, J = 7,0)	3,47 (t, J = 7,0)	8,54	7,40...7,90 (5H, m)	3,07 (3H, s)	7,25...7,7 (5H, m)
IIe	5,08 (s)	2,68 (2H, t)	3,35 (t, J = 7,0)	8,55	7,0...7,40 (3H, m)	3,07 (3H, s)	7,3...7,6 (5H, m)
IIf	6,78 (s)	2,83 (2H, t, J = 9,0)	3,55 (t, J = 9,0)	8,28		3,03 (3H, s)	7,3...7,65 (5H, m)
IIg	6,67 (s)	2,72 (2H, t)	3,60 (t, J = 9,0)	8,35		1,30...3,55 (5H, m)	7,2...7,6 (5H, m)
III*	7,26 (d, J = 1,8)	7,24 (1H, d.d, J = 5,0 and 1,8)	8,60 (1H, d, J = 5,0)		2,7 (3H, s)		6,45...6,75 (7H, m)

Compound	^{13}C NMR spectrum, chemical shift, δ, ppm									
	heterocycle					substituent				
	$C_{(2)}$	$C_{(3)}$	$C_{(4)}$	$C_{(5)}$	$C_{(6)}$	-CH	C=O	N—CH3	C—CH_3	Ar
E-IIa	140,4	94,4	137,0	29,1	49,4	121,5	194,4	39,1	31,6	129,5...135,8 (CH); 138,8...154,3 (C_{quat})
E-IIc	142,8	95,0	138,3	26,1	49,2	118,4	194,7	39,2	31,7	125,5...128,5 (CH); 154,5 (C_{quat})
Z-IIc	143,5	94,9	137,1	50,3	60,4	119,7	195,3	38,7	31,7	126,2...129,1 (CH); 154,4(C_{quat})
IIf	146,9	112,4	137,8	26,1	49,9	115,9		40,1		126,1...129,9 (CH); 153 (C_{quat})

*Proton signals for the four paracyclophane methylene groups of IIa, b and III occur at 2.8-3.3 ppm as complex multiplets which, for III, cover the signals of the two methylene protons in the CH_2COCH_3 group at the pyridine C_2.

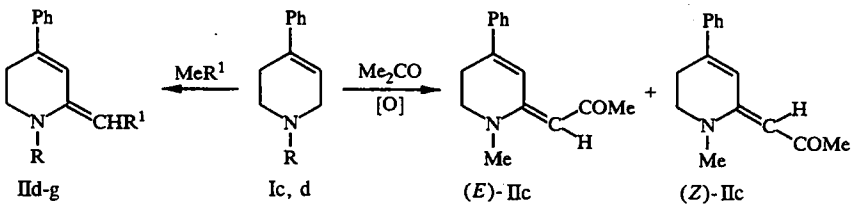
the substitution at atoms C_4 and C_2. The signal at 2.7 ppm (3H, s) confirms the presence of the CH_3 group in the acetyl fragment in III. X-ray structural data for the acylmethylene derivative IIa* [6] show the heterocycle to have a distorted half chair conformation. The geometry of the substituent relative to the exocyclic double bond indicates a largely E configuration for the stable molecule (compound E-IIa, obtained in 75% yield). The paracyclophane system is turned through 29.5° relative to the piperidine plane.



Ia, IIa R = Me; Ib, IIb R = Et

Bearing in mind the x-ray data, the discussed PMR results for IIa, b allow one to make certain assignments for the two singlet signals at 5.13-5.26 and 8.21-8.26 ppm. The first of these corresponds to the expected region for a vinyl proton resonance as found at the heterocycle C_3 atom. Compared with the corresponding proton signal in the starting piperidines Ia, b [1], it has undergone a high field shift of $\Delta\delta$ = 0.69-0.49 ppm thanks to the magnetic anisotropic effect of the acetyl group oxygen atom. The second signal is found at a record-breaking low field position for vinyl protons and is assigned to the exocyclic methine proton. Such a marked shift must be related to the effect of two electronegative heteroatoms, occurring in the acyldienamine system. The two singlets indicated can be used as reference signals for confirming the structures of other analogous derivatives. In fact, condensation of 4-phenyl-Δ^3-piperidine (Ic) with acetone, acetophenone, and 2-acetylthiophene gives the 2-acylmethylene derivatives (IIc-e) whose PMR spectra also show these "characteristic" pairs of signals at 5.08-5.78 (3-H) and 8.33-8.54 ppm (CH=CO).

In one example it was possible to separate chromatographically the two configurational isomers at the exocyclic olefinic bond to give E-IIc and Z-IIc in 30 and 12% yield respectively. The problem of assignment of IIc to the E or Z series was resolved by comparison of the ^1H and ^{13}C NMR spectra with those of the reference IIa whose E structure had been established using the x-ray method.



Ic, IId R = Me, R^1 = COPh; IIe R = Me, R^1 = CO-(thienyl); IIf R = Me, R^1 = NO_2;

It initially seemed that the methine protons of the C_4=C_3H−C_2=C_1H−Ac should be sensitive to the differences in chemical environment for the E and Z isomer. However, as is seen in the PMR spectra of IIa, c (see Table 2), the chemical shift values for the indicated protons do not differ significantly for both isomers ($\Delta\delta$ = 0.01-0.05 ppm). However, the geome-

*As in Russian original. No footnote found−Translator.

trical isomerism is reflected in the spectral parameters for the C_5 and C_6 methylene protons, i.e., in that part of the piperidine molecule markedly removed from the place of structural change. For one of the isomers of IIc, the chemical shifts of these protons occur at 2.68 and 3.35 ppm, almost coinciding with similar protons of reference compound IIa ($\Delta\delta$ = 0.03-0.07 ppm), hence it is given the E configuration. In the other isomer of IIc with the Z configuration, the analogous protons occur at much lower field (3.35-3.60 ppm) as broadened, partly obscured multiplets. Similar effects are seen in the ^{13}C NMR spectra of these three materials: 1) insignificant chemical shift differences ($\Delta\delta$ = 0.1-3.1 ppm) for all of the carbon atoms in the acetylmethylenepiperidine fragments of E-IIa and E-IIc; 2) virtual coincidence of the chemical shifts of thirteen (of 15) carbons ($\Delta\delta$ = 0.0-1.3 ppm) in E- and Z-IIc with a marked low field shift only for C_5 and C_6 of the Z isomer of IIc ($\Delta\delta$ = 23.9 and 11.2 ppm respectively). This noted effect for Z, E isomers based on the NMR spectral parameters for the 5-CH_2 and 6-CH_2 groups may prove diagnostic for similar 2-methylene-piperidines.

In contrast to acetone, aromatic ketones like acetophenone and 2-acetylthiophene react conjugatively with piperidine Ic only with difficulty to give 2-acylmethylene derivatives IId, g in low yield. The PMR spectra of these compounds show them to exist as the E isomers.

In addition to methyl ketones as compounds containing an activated methyl group taking part in oxidative conjugation, acetonitrile and nitromethane were also studied. The first of these did not react conjugatively, favoring mainly an oxidative hydroxylation [1, 2]. Nitromethane reacted conjugatively with piperidines Ic, d to give the 2-nitromethylenetetrahydropyridines IIf, g in 40 and 16% yield respectively. The PMR spectrum of product IIf also showed the characteristic pair of singlet signals for the two methine proton of the diene fragment. The proton of the nitromethylene part of the molecule occurred in the usual region for an acylmethylene group (8.28 ppm) while, in contrast to IIa-e, the signal for the C_3 proton is found not at higher but at lower field than in the spectrum of the starting Ic ($\Delta\delta \sim 0.8$ ppm). A similar effect is noted for the C_3 ^{13}C NMR signal in the nitro product IIf, which is also found at lower field (at 112.4 ppm, $\Delta\delta$ = 17 ppm) than seen for the corresponding signals in the acetyl derivatives IIa, c. These observations can be rationalized in terms of the following two considerations. First, the separated product IIf has the E configuration from comparison of the parts of the NMR spectrum assigned to the 5 and 6 methylene groups in the E-IIa/IIf pair (see their ^1H and ^{13}C NMR data in Table 2). Second, the nitro group is evidently not fully coplanar with the diene fragment plane. This is confirmed by the ^1H and ^{13}C NMR signals for the signals of the proton and carbon of the nitromethylene group which is shifted to higher field when compared with the analogous signals of the less electron accepting acylmethylene group in E-IIc. It therefore follows that the heterocyclic C_3=H group in the E isomer of IIf must experience a magnetic anisotropic effect of the nitro group.

The most probable route for oxidation of I → II evidently includes a stage of radical conjugation and hydroxylation, this being confirmed by the following facts: addition of base does not affect the final product yield (which might have been expected in the case of a nucleophilic type condensation); the conjugation reaction is significantly inhibited by the presence of sulfur; and finally, in previous work it was shown that the same piperidines under analogous conditions but without methyl ketones form 2-piperidone radical oxidation products. Thus a novel condensation reaction of methyl ketones and nitromethane with 4-aryltetrahydropyridines has been found. This oxidative reaction occurs regioselectively (at the methylene group of the heterocycle allylamine fragment) and stereoselectively with predominant formation of E isomers of 2-acyl or nitromethylene-tetrahydropyridines.

EXPERIMENTAL

IR spectra were taken on a UR-20 instrument for KBr tablets. Mass spectra were obtained on an MX-1303 instrument. NMR spectra were measured on a Bruker W-80 instrument with a working frequency of 80 MHz for IIb, e and WM-400 (400 MHz) for the remaining compounds as solutions in $CDCl_3$. The internal standard was TMS. The reaction course and compound purity were monitored by TLC on Silufol UV-254 plates with ether eluent. Separation and purification were performed using column chromatography on L-60 (40/100) grade silica gel. Parameters and spectral data for the synthesized compounds are given in Tables 1 and 2.

Oxidative Conjugation of Tetrahydropyridines Ia-c with Methyl Ketones. A solution of $KMnO_4$ (1.16 mmole) in water (10 ml) was added to a solution of the tetrahydropyridine Ia-d (1.7 mmole) in acetone (30 ml) at room temperature over 40 min with vigorous stirring. The mixture was stirred for a further 30 min and the MnO_2 precipitate was separated and washed with acetone (50 ml). The acetone filtrates were combined, solvent evaporated *in vacuo*, and the residue was extracted with

chloroform. Column chromatography of the extract (eluent ether) gave 2-acetylmethylene-1,2,5,6-tetrahydro-1-methyl-4-([2.2]-paracyclophan-4-yl)pyridine (IIa), 2-acetylmethylene-1,2,5,6-tetrahydro-1-ethyl-4-([2.2]paracyclophan-4-yl)pyridine (IIb) or the E and Z isomers of 2-acetylmethylene-1,2,5,6-tetrahydro-1-methyl-4-phenylpyridine (IIc) respectively.

Similarly, tetrahydropyridine Ic (3.2 mmole) in ethanol (30 ml) and acetophenone or 2-acetylthiophene (3.2 mmole) with solid, finely ground $KMnO_4$ (4.8 mmole) and stirring of the reaction mass for 1.5 h gave 2-benzoylmethylene-1,2,5,6-tetrahydro-1-phenyl-4-phenylpyridine (IId) or 2-(2-thienylcarbonyl)methylene-1,2,5,6-tetrahydro-4-phenylpyridine (IIe) respectively. Chromatography initially gave unreacted starting material (63-71% based on the amount taken) and then the product IId or IIe.

The 2-methylene derivatives IIa, d were obtained as yellow crystals, IIe as a yellow-brown powder, and IIb, c as yellow, viscous oils.

Conjugation of Piperidines Ic, d with Nitromethane. Finely ground $KMnO_4$ (16 g, 0.104 mole) was added in small portions over 0.5 h at room temperature to a solution of the piperidine Ic (4.5 g, 26 mmole) in a mixture of chloroform (20 ml) and nitromethane (6.3 g, 0.1 mole). The mixture was stirred for 2 h (until the TLC spot for the starting Ic had disappeared) and then treated as described for IIa-e to give 1,2,5,6-tetrahydro-1-methyl-2-nitromethylene-4-phenylpyridine (IIf, 2.36 g) as a viscous yellow oil. Similarly, 4-phenyl-1-ethyltetrahydropyridine (Id, 2.5 g, 10 mmole) gave 2-nitromethylene-4-phenyl-2-ethyltetrahydropyridine (IIg, 0.36 g) as a yellow oil.

Aromatization of IIa. A mixture of 2-acetylmethylenetetrahydropyridine (Ia, 150 mg, 0.45 mmole) and sulfur (33 mg, 2.5 g·atom) was held at 140°C for 0.5 h and then cooled and extracted with ether. The extract was purified on a silica column, eluting with ether to give 2-acetylmethyl-4-([2.2]paracyclophan-4-yl)pyridine (III, 42.9 mg) as yellow crystals.

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