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NITRATION OF 3,5-DICARBONYL DERIVATIVES OF 4-PHENYL-1,4-DIHYDROPYRIDINE

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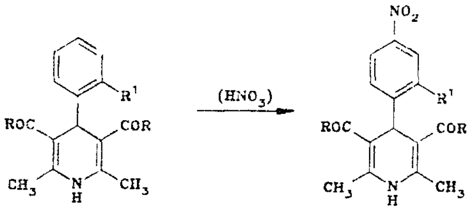
The nitration of the phenyl ring of 4-phenyl-1,4-dihydropyridines with retention of the 1,4-dihydropyridine structure was accomplished.

In connection with the ever increasing interest in 1,4-dihydropyridine (1,4-DHP) derivatives as physiologically active compounds, it has become necessary to study their reactivities. Up until now, the most characteristic reaction of 1,4-DHP was assumed to be oxidation; it has now been shown that these compounds also undergo other reactions, but little study has been devoted to their nitration — treatment with nitric acid usually leads to oxidation of pyridine [1]. Only 4,4-dialkyl-3,5-dicyano-1,4-DHP derivatives, which are extremely resistant to oxidation, are nitrated at the 2- and 6-methyl groups [2, 3].

In the present research we have shown that 3,5-dicarbonyl derivatives of 4-phenyl-1,4-DHP are nitrated relatively easily in a solution of sulfuric acid at low temperatures by nitric acid *in status nascendi* with the formation of the corresponding 4-(p-nitrophenyl)-1,4-DHP.



I II

I, II a $R=CH_3$, b, d $R=OCH_3$, c $R=OC_2H_5$; a–c $R^1=H$, d $R^1=OCHF_2$

With respect to their melting points (Table 1) and UV spectra (Table 2), the IIa-c obtained by this method correspond to the previously described compounds obtained by the Hantzsch method. The structures of IIa-c were also confirmed by the PMR, IR, and mass spectra (Table 2). Compound IId was synthesized for the first time. It is interesting to note that only the p-nitro compounds are obtained in all cases, i.e., the dihydropyridine ring acts as a p-orienting substituent. An attempt to nitrate the pivalyl derivative of I [$R = C(CH_3)_3$] was unsuccessful, since splitting out of tert-butyl alcohol and destruction of the molecule occur under the conditions used.

EXPERIMENTAL

The UV spectra were obtained with a Hitachi UV-vis 557 spectrophotometer. The IR spectra of mineral oil suspensions of the compounds were recorded with a Perkin-Elmer IR-580B

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TABLE 1. Characteristics of II

Compound	mp, °C	R_f*	Found, %			Empirical formula	Calculated, %		
			C	H	N		C	H	N
IIa	197—200; 202 [4]	0,30	64,9	6,1	8,5	$C_{17}H_{18}N_2O_4$	65,0	5,8	8,9
IIb	192—194; 196 [5]	0,14	58,5	5,2	7,8	$C_{17}H_{18}N_2O_6$	59.0	5,2	8,1
IIc	129—131; 128—129 [4]	0,80	59,6	6,0	7,0	$C_{19}H_{22}N_2O_6$	61,0	5,9	7,2
IId	172—174	0,40	51,8	4,4	6,8	$C_{18}H_{18}F_2N_2O_7$	52,4	4,4	6,8

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*In chloroform—ethyl acetate—hexane (1:1:1) for IIa, and in chloroform—ethyl acetate—hexane (1:1:3) for IIb-d.

TABLE 2. Spectral Characteristics of IIa-d

Compound	UV spectrum, λ_{max}, nm (log ε)	IR spectrum, cm^{-1}	PMR spectrum, δ, ppm	Mass spectrum, m/z (rel. intensity, %)
IIa	210 (4,18), 253 (4,32), 382 (3,73)	3325 (NH), 1603 (C=C), 1515 (NO_2)	2,25 (6H, s, CH_3), 2,37 (6H, s, $COCH_3$), 5,30 (1H, s, 4-H), 5,96 (1H, s, NH), 7,25—7,50 (2H, d, *o*-H), 7,90—8,15 (2H, d, *m*-H)	314 (5) (M^-), 283 (3) (M^+-NO,H), 271 (9) (M^+-COCH_3), 267 (6) (M^+-NO_2,H), 192 (100) ($M^+-C_6H_4NO_2$)
IIb	205 (4,36), 236 (4.39), 284 (4,10), 361 (3,70)	3343 (NH), 1700 (CO), 1650 (C=C), 1525 (NO_2)	2,37 (6H, s, CH_3), 3,63 (6H, s, $COOCH_3$), 5,13 (1H, s, 4-H), 6,03 (1H, s, NH), 7,18—7,55 (2H, d, *o*-H), 7,94—8,20 (2H, d, *m*-H)	346 (1) (M^+), 331 (2) (M^+-CH_3), 315 (3) (M^+-OCH_3), 299 (1) (M^+-NO_2,H), 287 (4) ($M^+-COOCH_3$), 224 (100) ($M^+-C_6H_4NO_2$)
IIc	210 (4,30), 233 (4.23), 279 (4,03), 360 (3,64)	3308 (NH), 1703 (CO), 1648 (C=C), 1520 (NO_2)	1,20 (6H, t, CH_2CH_3), 2,44 (6H, s, CH_3), 4,08 (4H, q, CH_2CH_3), 5,08 (1H, s, 4-H), 5,96 (1H, s, NH), 7,20—7,50 (2H, d, *o*-H), 7,90—8,10 (2H, d, *m*-H)	374 (13) (M^+), 372 (11) (M^+-2H), 345 (5) ($M^+-C_2H_5$), 329 (5) ($M^+-OC_2H_5$), 328 (29) (M^+-NO_2), 301 (6) ($M^+-COOC_2H_5$), 252 (100) ($M^+-C_6H_4NO_2$)
IId	211 (4.23), 238 (4,35), 277 (sh: 3,88), 365 (3,73)	3400 (NH), 1708 (CO), 1660 (C=C), 1530 (NO_2)	2,54 (6H, s, CH_3), 3.58 (6H, s, $COOCH_3$), 5,36 (1H, s, 4-H), 5,88 (1H, t, NH), 6,63 (1H, t, $OCHF_2$, $J=73{,}0$ Hz), 7,05—7,50 (1H, m *o*-H), 7,90—8,30 (2H, m, *m*-H)	412 (1) (M^+), 397 (3) (M^+-CH_3), 381 (3) (M^+-OCH_3), 353 (6) ($M^+-COOCH_3$), 224 (100) ($M^+-C_6H_3OCHF_2NO_2$)

spectrometer. The PMR spectra were obtained with a Bruker WH-90/DS spectrometer. The mass spectra were recorded with an MS-50 spectrometer.

A 16-mmole sample of dihydropyridine I was added with vigorous stirring in the course of 20-25 min to 75 ml of cooled (to 0°C) concentrated H_2SO_4, after which stirring was continued for another 15 min while simultaneously lowering the temperature to —8°C. A 24-mmole sample of sodium nitrate was then added in the course of 20 min, and the mixture was stirred for another 10 min. It was then poured into 750 ml of cold water. The precipitate was recrystallized from ethanol to give nitro compounds II in 56-72% yields.

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