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ACYLATION OF N-PHENYL-2-(INDOL-3-YL)SUCCINIMIDES

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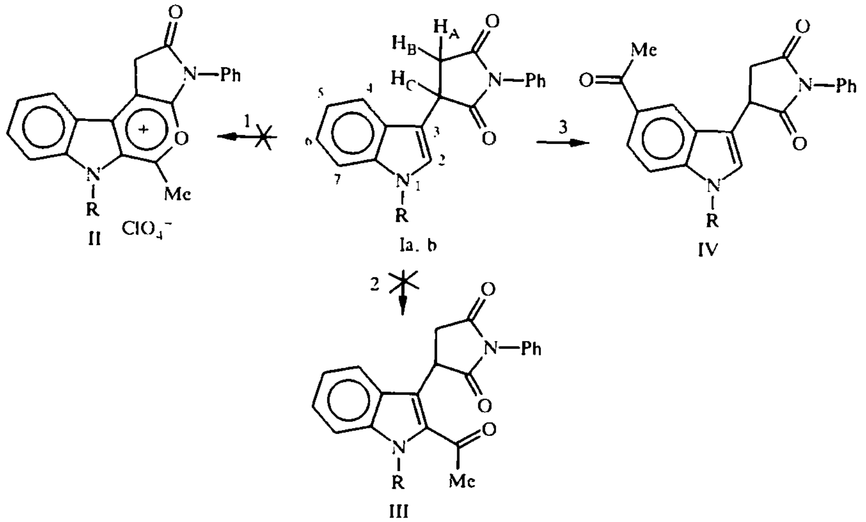
Treatment of N-phenyl-2-(1-R-indol-3-yl)succinimides with acetyl perchlorate leads to acylation of the benzene ring of the indole substituent.

In a previous publication was reported the synthesis and reactions of 2-oxo-5-alkyl-3-phenyl-7,8-dimethoxybenzo[c]-pyrrolo[3,2-e]pyrilium perchlorates which were obtained by acylation of N-phenyl-2-(3,4-dimethoxyphenyl)succinimide with alkanoyl perchlorates [1-3]. It was shown that reaction of the salts obtained with nitrogen containing mono- and binucleophiles gives high yields of functionally substituted hetero- and carbocyclic compounds (isoquinolines, benzo-2,3-diazepin-4(5H)-ones, and 1,3-aminoaphthols). Such a variety in the reactions of the benzo[c]pyrrolo[3,2-e]pyrilium salts and of derived products dictated our quest to prepare pyrrolo[3,2-e]pyrilium derivatives annelated along the c side with heterocyclic rings. In this work we present the results of the acylation of N-phenyl-2-(1-R-indol-3-yl)succinimides.

The starting compounds Ia,b were obtained by alkylation of indole and N-benzylindole by N-phenylmaleimide in nitromethane in the presence of zinc chloride. We expected that reaction of imides Ia,b with acyl perchlorates would give indolo[2,3-c]-pyrrolo[3,2-e]pyrilium derivatives. However, the expected salts were not obtained even though 2-(indol-3-yl)cycloalkanones [4] and 2-(indol-3-yl)-3-hydroxymaleimides [5] are converted to the indolo[2,3-c]pyrilium perchlorates in 50-85% yields under analogous conditions. Reaction of imides Ia,b with acetic anhydride in the presence of perchloric acid occurs with considerable tarring of the reaction mixture, from which compounds without an ionic structure were separated.



a R = H, b R = CH_2Ph

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TABLE 1. PMR Spectra of Compounds Synthesized, δ, ppm, J, Hz

Compound	A-H	B-H	C-H	2-H	4-H	5-H	6-H	7-H	H_{arom}	H_{alk}	NH
Ia	3,02 dd , J_{AB} = 17,2, J_{AC} = 5,0	3,38 dd , J_{AB} = 17,2, J_{BC} = 10,0	4,56 dd , J_{AC} = 5,0, J_{BC} = 10,0	7,49 s		7,03 m, J_{56} = 7,0, J_{54} = 7,0, J_{57} = 0,8	7,12m, J_{65} = 7,0, J_{67} = 7,0, J_{64} = 0,8		7,31...7,60m, 7H		11,20
Ib	3,00 dd , J_{AB} = 17,5, J_{AC} = 5,0	3,35 dd , J_{AB} = 17,2, J_{BC} = 10,0	4,58 dd , J_{AC} = 5,0, J_{BC} = 10,0						7,18...7,62m, 15H	5,51 s 2H, CH_2	
IVa	2,85 dd , J_{AB} = 17,4, J_{AC} = 5,5	3,25 dd , J_{AB} = 17,4, J_{BC} = 10,0	4,55 dd , J_{AC} = 5,5, J_{BC} = 10,0	7,78 s	8,36 d, J_{46} = 2,0		7,89 dd , J_{67} = 8,2, J_{64} = 2,0	7,71 d, J_{76} = 8,2	7,30...7,51m, 5H	2,71 s 3H, CH_3	10,35
IVb	3,09 dd , J_{AB} = 17,9, J_{AC} = 5,4	3,43 dd , J_{AB} = 17,9, J_{BC} = 9,5	4,69 dd , J_{AC} = 5,4, J_{BC} = 9,5	7,74 s	8,32 d, J_{46} = 1,5		7,79 d, J_{67} = 8,5, J_{64} = 1,5	7,62 d, J_{76} = 8,5	7,2...7,55m, 10H	2,58 s 3H, CH_3; 5,45 s 2H, CH_2	

TABLE 2. Physicochemical Parameters in the IR Spectra of the Compounds Synthesized

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	IR spectrum, ν, cm^{-1}	Yield, %
		C	H	N			
Ia	$C_{18}H_{14}N_2O_2$	74,23 74,46	4,80 4,86	9,77 9,65	160...162	3380 (NH), 1730 (CO)	69
Ib	$C_{25}H_{20}N_2O_2$	78,66 78,92	5,20 5,30	7,40 7,37	115...117	1725 (CO)	75
IVa	$C_{20}H_{16}N_2O_3$	72,05 72,26	4,70 4,86	8,75 8,43	219...221	1715, 1675 (CO), 3340 (NH)	17
IVb	$C_{27}H_{22}N_2O_3$	76,15 76,75	5,10 5,25	6,75 6,63	181...182	1715, 1670 (CO)	40

The IR spectra of the obtained products show a C=O group absorption band for the succinimide ring as well as a new absorption band in the range 1670-1680 cm^{-1}, pointing to the presence of an acetyl substituent in the reaction products. The absorption band for the ClO_4 anion at 1100 cm^{-1} is absent and elemental analytical data also confirm the absence of halogen. On the basis of a number of features of the PMR spectra of the starting compound and the reaction products, we propose that the course of the reaction involves products of indole ring acylation with structure III or IV.

In the spectrum of imide Ia (R = H), the following identifying features stand out. Double doublets at 3.02, 3.38, and 4.56 ppm, each with one proton integrated intensity, are typical of the ABC proton spin system for a five-membered imide rings (as seen by us before in the spectrum of N-phenyl-2-(3,4-dimethoxyphenyl)succinimide [1]). The low field part of the spectrum shows two multiplets at 7.03 and 7.12 ppm assigned to the indole 5-H and 6-H protons and a multiplet (including the 2-H proton singlet at 7.49 ppm) for the remaining aromatic protons. The NH group proton appears as a singlet at 11.2 ppm. The PMR spectrum of imide Ib (Table 1) has the same character but is more complex due to overlap of the phenyl group signals of the benzyl substituent. Obviously, the course of reactions 1 and 2 is associated with retention of the characteristic indole benzene ring ABCD spin system in the spectrum. Occurrence of reaction routes 2 and 3 is associated with preservation of the five-membered ring ABC multiplet to high field. In the third route, the indole ring 2-H proton remains. All of the reactions described lead to the appearance in the spectrum of an acetyl methyl group signal.

The spectra of the acylation products show a singlet methyl group confirming the presence of the acetyl substituent together with retention of the imide ABC ring spin system having almost unchanged parameters. In addition, there are clearly seen in both cases a singlet 2-H indole proton which is shifted to low field by 0.2-0.3 ppm when compared with the starting material. The low field part of the spectrum shows a well resolved 1,24-substituted phenyl ring ABM type spin system consisting of doublets for 4-H and 7-H and double doublet for 6-H of the indole fragment. The assignments were also confirmed by double resonance experiments.

Analysis of the spectral parameters for the starting materials and the acylation products confirms that the compounds we obtained are the N-phenyl-2-(1-R-acetylindol-3-yl)succinimides IVa,b. This was confirmed by the strong low field shift of the 4-H, 7-H, and 6-H indole proton signals in the acylation products due to the presence of the electron acceptor $COCH_3$ group in the benzene ring. Unfortunately, we were not able unambiguously to determine whether the acetyl group was in indole position 5 or 6 by spectral methods. Nonetheless, one need only consider that the pyrrole ring nitrogen atom is ortho-para directing in indole electrophilic substitution [6]. In the case of steric hindrance to electrophilic attack at the indole ring C_2 atom (associated with the presence of the succinimide substituent) it is most likely that acylation will occur at the alternative position 5. One should also note the dependence of the acylation product yield on the size of the substituent on the indole nitrogen atom (18 and 40% for the acetylimides IVa (R = H) and IVb (R = CH_2Ph) respectively).

EXPERIMENTAL

IR spectra were measured in Vaseline oil using a UR-20 spectrometer and ^1H NMR spectra on a Gemini-200 spectrometer with TMS internal standard. The spectra of Ia,b and IVb were measured in DMSO-D_6 and IVa in DMF-D_7. Analytical parameters, melting points, and spectral data for the synthesized compounds are given in Tables 1 and 2. Standard Gemini-200 spectral conditions were used to study the spectral parameters for imides Ia,b and acetylimides IVa,b.

N-Phenyl-2-(indol-3-yl)succinimide (Ia). A solution of N-phenylmaleimide (17.3 g, 0.1 mole) and indole (11.7 g, 0.1 mole) in nitromethane (100 ml) was added to a mixture of anhydrous zinc chloride (13.6 g, 0.1 mole) in nitromethane (100 ml). The reaction product was stirred for 5 h at 70-80°C, cooled, and poured into a mixture of water (100 ml), ice (300 g), and concentrated HCl (30 ml). The aqueous layer was extracted with dichloroethane. The combined extract was washed with 5% hydrochloric acid solution and water to pH 7 and dried with anhydrous sodium sulfate. The solvent was evaporated *in vacuo* and the residue recrystallized from benzene to give imide Ia.

N-Phenyl-2-(1-benzylindol-3-yl)succinimide (Ib) was obtained by the same method from N-phenylmaleimide and N-benzylindole.

Acylation of Imides Ia,b. A mixture of acetic anhydride (20 mmole) and 70% $HClO_4$ (2.2 mole) was added to a suspension of the starting imide I (2 mmole) in glacial acetic acid (5 ml). The reaction mixture was stirred for 3-4 h at 20-25°C, the precipitated acetylimide IV was filtered off, washed with acetic acid and then water, and recrystallized from 2-propanol.

REFERENCES

1. S. L. Bogza, A. A. Malienko, S. Yu. Suikov, M. Yu. Zubritskii, K. I. Kobrakov, and V. I. Dulenko, Zh. Org. Khim., **32** (1966), in press.
2. S. L. Bogza, A. A. Malienko, M. Yu. Zubritskii, K. I. Kobrakov, and V. I. Dulenko, Khim. Geterotsikl. Soedin., No. 12, 1690 (1995).
3. S. L. Bogza, A. A. Malienko, M. Yu. Zubritskii, K. I. Kobrakov, and V. I. Dulenko, Khim. Geterotsikl. Soedin., No. 12, 1692 (1995).
4. V. I. Dulenko, A. A. Luk'yanenko, A. V. Kibal'nyi, A. A. Malienko, and Yu. A. Nikolyukin, Khim. Geterotsikl. Soedin., No. 3, 363 (1985).
5. S. L. Bogza, Yu. A. Nikolyukin, M. Yu. Zubritskii, and V. I. Dulenko, Zh. Org. Khim., **25**, 1480 (1993).
6. G. I. Zhungietu, V. A. Budylin, and A. N. Kost, Preparative Chemistry of Indoles [in Russian], Shtiintsa: Kishinev (1975), p. 75; Chem. Abstr., **85**, 177238q (1976).