PERIMIDINE IN THE HETARYLATION REACTION

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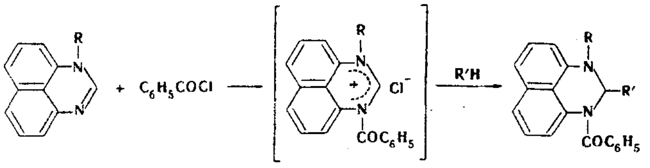
Indoles and pyrroles were hetarylated by perimidines in the presence of benzoyl chloride. N-Acyl derivatives of 2-indolyl(pyrrolyl)-2,3-dihydroperimidine were synthesized.

It has previously been assumed [1] that the hetarylation of CH nucleophiles by nitrogen heterocycles containing a C = N bond in the presence of acylating agents is a general reaction. However, it was recently shown that this is not so. It was found that 1-substituted perimidines undergo opening of the heteroring on reaction with dialkylanilines in the presence of acyl halides in aprotic solvents [2]. It seemed of interest to ascertain whether this transformation is the only one possible for perimidines under these conditions or whether they also might undergo hetarylation in the case of sufficiently strong CH nucleophiles (e.g., indole or pyrrole).

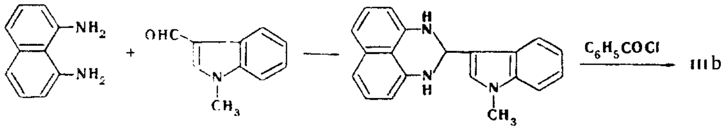
We have found that perimidine (Ia) and 1-methylperimidine (Ib) react readily with indoles and pyrroles in the presence of benzoyl chloride to give N-benzoyl derivatives of 2-indolyl(pyrrolyl)-2,3-dihydroperimidine (III) (Table 1). It may be assumed that the process takes place through a step involving the formation of N-benzoylperimidinium salts of the II type, which attack the π-surplus heterocycles with their electron-deficient meta position:



I a, b   II a, b   III a-e

I a R=H; b R=CH$_3$; II a R=C$_6$H$_5$CO; b R=CH$_3$; III **a** R=CH$_3$, R'=3-indolyl; b R==C$_6$H$_5$CO, R'=1-methyl-3-indolyl; c R=CH$_3$, R'=2-methyl-3-indolyl; d R=CH$_3$, R'=2-pyrrolyl; e R=CH$_3$, R'=2-methyl-5-pyrrole; f R=COC$_6$H$_5$; R'=2-methyl-3-indolyl

The structure of III was verified by the preparation of one of them by an independent method via the scheme



Additional confirmation of the structure of III was obtained from examination of their IR and mass spectra. Thus an absorption band corresponding to an N−H group is absent in the IR spectrum of IIIb; this confirms the cyclic structure of the reaction products. The following groupings have the most characteristic absorption in the IR spectra of III: tertiary amide $\nu_{C=O}$, amide ν_{C-N}, and indole (pyrrole) ν_{N-H} (Table 2). To assign the absorption bands of the C = O and C − N groups we used the ability of these groups to form hydrogen bonds with polar solvents. The IR spectra of III were obtained from CCl$_4$, CHCl$_3$, and n-butyl alcohol solutions. When carbon tetrachloride was replaced by chloroform, the absorption bands of the C = O group were shifted to the low-frequency region by 2-11 cm^{-1}, whereas they were shifted by yet another 15-24 cm^{-1} on passing to n-butyl alcohol. Correspondingly, the ν_{C-N} band was shifted to the high-frequency region by 5-6 cm^{-1} on passing from CCl$_4$ to chloroform. It is apparent from Table 2 that the highest $\nu_{C=O}$ values and the lowest ν_{C-N} values were

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TABLE 1. 1,3-Disubstituted 2-Hetaryl-2,3-dihydroperimidines

Compound	mp, °C[a]	R_f[b]	Empirical formula	Found, %			Calculated, %			Yield, %
				C	H	N	C	H	N	
IIIa	201—202	0,46	$C_{27}H_{21}N_3O$	80,3	5,8	10,4	80,4	5,2	10,4	60
IIIb	258—259[c]	0,20	$C_{34}H_{25}N_3O_2$	79,9	5,6	8,6	80,1	5,3	8,2	48
IIIc	255—255,5	0,30	$C_{26}H_{23}N_3O$	80,7	5,3	10,0	80,6	5,5	10,0	49
IIId	150—151	0,16	$C_{23}H_{19}N_3O$	78,7	5,4	12,2	78,6	5,3	11,9	33
IIIe	167—168[d]	0,64	$C_{24}H_{21}N_3O$	77,0	5,8	11,4	78,5	5,7	11,4	65
IIIf	175—176	0,13	$C_{34}H_{25}N_3O_2$	80,0	5,3	8,2	80,1	5,5	8,2	42

[a] From butanol.
[b] In a chloroform–benzene–hexane (30 : 6 : 1) system.
[c] From glacial acetic acid.
[d] From diethyl ether.

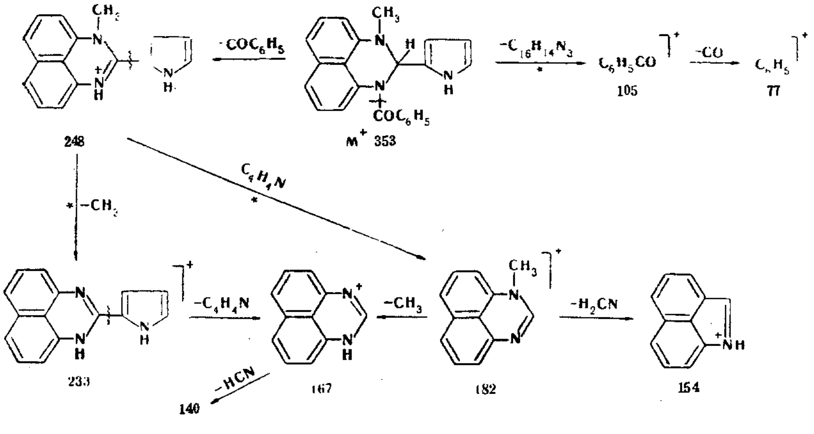
TABLE 2. IR Spectra of 1,3-Disubstituted 2-Hetaryl-2,3-Dihydroperimidines (ν, cm^{-1})

Compound*	Chloroform			Tetrahydrofuran		CCl_4			n-Butanol
	C=O	C–N	N–H	C=O	C–N	C=O	C–N	N–H	C=O
IIIa	1670	1424	3485	1650	1424	1650	1419	3491	1626
IIIb	1656	1424	—	1660	1424	1660	1418	—	1644
IIIc	1656	1424	3479	1660	1424	1658	1419	3496	1643
IIId	1680	1420	3481	1650	1420	1685	1415	3485	1625
IIIe	1685	1420	3490	1659	1420	1691	1413	3487	1625
IIIf	1671	1424	3479	1650	1424	1680	1418	3487	1626

*The concentration of III in all solvents except CCl_4 was 0.25 M ($1 \cdot 10^{-4}$ M in CCl_4).

observed in dilute CCl_4 solutions; this is due to the absence of intermolecular hydrogen bonds and of hydrogen bonds of III with the solvent. The same frequencies of the C = O and C – N groups were observed in concentrated tetrahydrofuran (THF) solutions; this can be explained by the absence of intra- and intermolecular hydrogen bonds for these groups, since the NH group of the indole or pyrrole rings in III is completely tied up by the solvent.

A molecular ion peak (M^+) is clearly seen in the mass spectra of III. The positive charge in M^+ is localized primarily on the heteroatom, and this determines the entire trend of the fragmentation of M^+. The mass spectrum can be interpreted in the case of 1-methyl-2-(2-pyrrolyl)-3-benzoyl-2,3-dihydroperimidine (IIId*). A similar fragmentation pathway is also observed for other compounds of the III type:



It is apparent from the fragmentation scheme presented above that the substituted 2,3-dihydroperimidine fragment of the molecule shows up well in this spectrum, whereas the peaks of ions with mass numbers 67 and 66, which correspond to the pyrrole structure, have low intensities. The process m/e 248 – C_4H_4N → m/e 182 (the apparent mass of the metastable transition is 133.2) offers indirect proof of the existence of this sort of molecular fragment. The appearance of a rather intense ion with a mass number of 130 (IIIb, c) attests to the

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*The numbers under the formulas correspond to the mass numbers of the corresponding ions, and the asterisks denote that the process is confirmed by the corresponding metastable transition.

presence of an indole fragment in the spectra of IIIa-c. It is known [3] that the ion with m/e 130 corresponds to a methyl-substituted indole structure.

Thus, alternative synthesis and the IR and mass spectra of synthesized III unambiguously confirm their structures.

EXPERIMENTAL

The IR spectra of the compounds were recorded with a UR-20 spectrometer. The mass spectra were obtained by direct introduction of the samples into the ion source of a Varian MAT-311 spectrometer (accelerating voltage 30 kV, cathode emission current 1.0 mA, and ionizing voltage 70 eV). The apparent masses of the metastable transitions were recorded with a partially unadjusted MKh-1303 apparatus. Chromatography was accomplished in a loose thin layer of activity II (Brockmann classification) aluminum oxide. The chromatograms were developed with iodine vapors and in UV light.

1-Methyl-3-benzoyl-2-(2-pyrrolyl)-2,3-dihydroperimidine (IIId). A mixture of 1.82 g (10 mmole) of 1-methylperimidine, 0.34 g (5 mmole) of pyrrole, and 0.58 ml (5 mmole) of benzoyl chloride in 25 ml of dry benzene was refluxed for 7 h, after which it was steam distilled, and the residue in the distillation flask was separated, dried, washed with diethyl ether, and recrystallized from butanol to give 0.6 g (33%) of a product with mp 150-151° and R_f 0.16 [in a chloroform–benzene–hexane system (30 : 6 : 1)]. Mass spectrum: m/e 51 (15.0); 52 (5.2); 77 (75.0); 78 (14.2); 80 (22.5); 105 (83.3); 100 (14.2); 115 (5.1); 118 (6.8); 127 (7.4); 128 (7.3); 140 (14.2); 154 (10.8); 167 (16.7); 168 (13.3); 169 (10.8); 181 (9.2); 182 (28.3); 183 (11.7); 232 (26.7); 233 (35.8); 234 (7.8); 246 (5.5); 247 (12.5); 248 (55.8); 249 (13.3); 257 (12.5); 258 (6.2); 352 (7.5); 353 (100.0); 354 (20.3). Found: C 78.7; H 5.4; N 12.2%; M 353 (mass spectrometrically). $C_{23}H_{19}N_3O$. Calculated: C 78.6; H 5.3; N 11.9%; M 353. The other III (Table 1) were also obtained by a similar method.

1,3-Dibenzoyl-2-(1-methyl-3-indolyl)-2,3-dihydroperimidine (IIIb).* A solution of 2.8 g (2.4 ml) of benzoyl chloride in 10 ml of benzene was added dropwise with stirring to a cooled (to 10°) mixture of 3 g of 2-(1-methyl-3-indolyl)-2,3-dihydroperimidine, 2.5 g of sodium carbonate, and 100 ml of benzene. After 45 min, another 2.5 g of sodium carbonate was added, and the mixture was stirred at room temperature for 1 h and at the boiling point of the mixture for 4 h. It was then cooled, the resulting precipitate was removed by filtration, and the reaction product was extracted from it with chloroform (while heating). Workup gave 3.6 g (70%) of colorless crystals of IIIb with mp 258-259° (from acetic acid or from chloroform–alcohol) and R_f 0.20 [in a chloroform–benzene–hexane–methanol system (30 : 6 : 1 : 1)]. The results of analysis, the spectral and chromatographic properties, and the melting point of the compound were identical to those of a sample obtained by hetarylation of 1-methylindole with perimidine in the presence of benzoyl chloride.

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*The synthesis was accomplished by N. I. Starshikov.