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C-Acylation of Electron-Rich Heterocyclic Compounds with Kirsanov Isocyanate

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ABSTRACT: *Pyrroles, indoles, indolizines, and 2-methylfuran are vigorously C-acylated with isocyanatophosphoryl dichloride. The resulting heteroaryl-substituted isocyanatophosphoryl dichlorides provide a convenient access to a variety of products.*© 1999 John Wiley & Sons, Inc. Heteroatom Chem 10: 343–348, 1999

INTRODUCTION

The recently published monograph on phosphorus isocyanates [1] threw light both on advances and on a number of interesting but, as yet, unrealized lines in this realm. In particular, no attention has been paid to the application of the compounds concerned in C-acylation of classic electron-rich heterocycles, namely, pyrrole, indole, and furan.

Certain heterocyclic systems with more complex constitutions and higher reactivity toward electrophiles, namely, 2-methylindolizine and 1,2,4-trimethylpyrrolo[1,2-α]benzimidazole, were efficiently C-acylated with phosphorylisocyanates [2]. Enamines [3], including heterocyclic ones [4], are also known to undergo C-acylation with these reagents. In the studies mentioned, isocyanates with alkyl, alkoxy, and amido substituents at the phosphorus atom were applied as acylating agents. An accessible and more reactive compound, isocyanatophosphoryl dichloride, was not involved.

The present article presents a study on C-acylation of pyrroles, indoles, indolizines, and 2-methylfuran with isocyanatophosphoryl dichloride, the Kirsanov isocyanate [5]. This reagent provides, due to its reactive chlorine atoms, substituents at the phosphorus that can be modified after C-acylation.

RESULTS AND DISCUSSION

Among π-electron-rich heterocycles, pyrrole is the most reactive in electrophilic substitutions. Pyrroles were shown to react vigorously with sulfonylisocyanates at position 2 of the ring [6,7], the normal target of electrophilic attacks in pyrroles [8]. The Kirsanov isocyanate reacts with *N*-methylpyrrole **1a** at room temperature, exothermally, in a matter of minutes. 1-Methylpyrrole-2-carboxamidophosphoryl dichloride **2a** was isolated in a yield of 90% in the pure state. The comparison of NMR spectra for the products and for other 2-substituted pyrroles [7,8] suggests that the substituent in **2a** is also contained at position 2 of the pyrrole ring.

It is known that the electrophilic substitution of *N*-arylpyrroles occurs nonregioselectively to give a mixture of 2- and 3-substituted isomers [8]. In this case, the lowered regioselectivity is likely to arise from the electron-acceptor effect of the phenyl ring. With respect to the reaction of N-arylpyrroles **1b** and **1c** with the Kirsanov isocyanate, the ^{31}P NMR spec-

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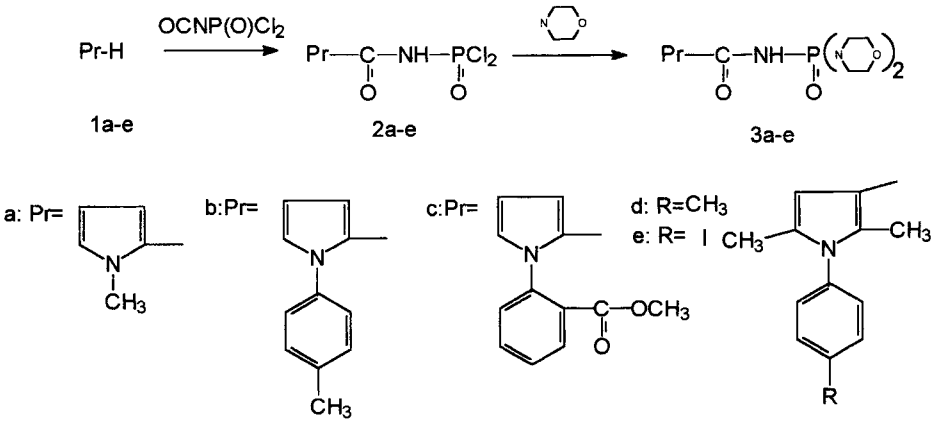


tra of the reaction mixtures each showed two signals, presumably corresponding to the acylated positions 2 and 3. For *N*-tolylpyrrole **1b**, the peaks at δ −4.26 and 4.58 with the intensity ratio 3:1 were observed, whereas *N*-(2-carbomethoxyphenyl)pyrrole **1c** exhibited a 10:1 ratio of resonances at δ 6.60 and −3.79. An increase in selectivity for **1c** compared to **1b** is attributable to the weakened acceptor effect of the phenyl ring due to the break of the system planarity. We succeeded in isolating in the individual state amides **3b,c**, the main products of 2-C-acylation of pyrroles **1b,c**.

2,5-Dimethyl-*N*-arylpyrroles **2** react with isocyanatophosphoryl dichloride to afford the products with a 3-acylated pyrrole ring. In general, *N*-arylpyrroles are less active than *N*-methylpyrrole in this reaction. As an example, the acylation of 2,5-dimethyl-1-tolylpyrrole **1d** is complete within 30 minutes, while it requires 2 hours for 2,5-dimethyl-1-(4-iodophenyl)pyrrole **1e**.

Amidophosphoryl dichlorides **2d,e** were isolated in the pure states. Like compounds **2a**, they represent colorless crystalline substances stable for a long time in the absence of atmospheric moisture. All amidophosphoryl dichlorides **2a–e** were converted into the corresponding amides **3a–e**.

Electrophilic reagents are known to react with indoles at position 3 of the heterocycle [7,9]. We demonstrated the C-acylation of indoles **4a–c** with the Kirsanov isocyanate to proceed at the same position.

The resulting amidophosphoryl dichlorides **5a–c** are rather stable colorless crystalline substances. The substituent position in indole **5a** is unambiguously proved by the NMR and IR resonances originating from the N-H group and by the absence of signals that could be assigned to the proton at position 3 of the indole nucleus. Compounds **5a–c** were reacted with morpholine to yield amides **6a–c**.

A mention of the C-acylation of 2-methylindolizine with phenylisocyanate can be found in the literature [10]. Just as in the reaction with isocyanato substituted derivatives of phosphorus acids [2], the products of 3-acylation of 2-methylindolizine formed. Analogous reactions of 2-phenylindolizine are as yet unknown. We therefore investigated the reaction of 2-methyl and 2-phenylindolizines **7a,b** with the Kirsanov isocyanate.

Compounds **7a,b** react with $OCNP(O)Cl_2$, 2-phenylindolizine being much slower in this reaction. By NMR spectroscopy and analysis of literature data [11], we have shown that the electrophilic attack on indolizines **7a,b** by the Kirsanov isocyanate occurs at position 3 of the heterocycle, as is the case with carbonyl chlorides [12] and haloid derivatives of P(III) acids [11].

In 2,3-disubstituted indolizines, C-acylation with the Kirsanov isocyanate proceeds at position 1, with the reaction rate being much lower as compared to 2-methylindolizine, since the electronic density on the C-1 atom is reduced due to the electron-withdrawing effect of the acyl substituent at C-3. Thus, acyl-substituted indolizine **10** requires 48 hours to react with the Kirsanov isocyanate completely.

We failed to introduce two acyl residues into the molecules of N-methylpyrrole **1a** and 2-methylindolizine **7a**. Compounds **1a** and **7a** form no diacylated products even on long standing with a significant excess of $OCNP(O)Cl_2$.

As reported in Ref. [7], 2-methylfuran does not react with *o*-chlorophenylsulfonyisocyanate even if heated in chlorobenzene for hours. In contrast, the reaction with isocyanatophosphoryl dichloride occurs at room temperature in the course of 12 hours to give resinous products. Dichloride **13** was not isolated; for characterization, it was converted into diamide **14**.

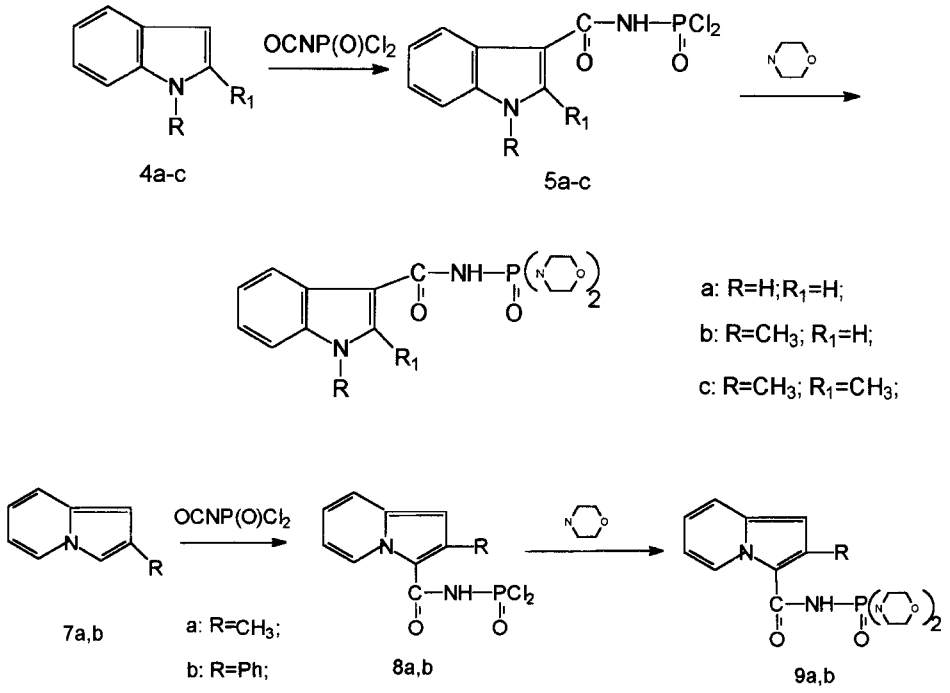


TABLE 1 Yield, Melting Point, and ^{31}P Spectra of Compounds **2–14**

N	*Formula*	*m.p.* (°*C*)	*NMR*^{31}*P* (*δ*, *m.d.*)	*Yield* (*%*)
2a	$C_5H_7Cl_2N_2O_2P$	130–132	2.41 (CH_2Cl_2)	90
2d	$C_{14}H_{15}Cl_2N_2O_2P$	165–166	−2.63 (CH_2Cl_2)	91
2e	$C_{13}H_{12}Cl_2IN_2O_2P$	129–130	0.24 (CH_2Cl_2)	88
3a	$C_{13}H_{23}N_4O_4P$	214–215	10.38 (CH_2Cl_2)	82
3b	$C_{20}H_{27}N_4O_4P$	235–236	10.23 (CH_2Cl_2)	73
3c	$C_{21}H_{27}N_4O_6P$	194–195	11.188 (CH_2Cl_2)	76
3d	$C_{22}H_{31}N_4O_4P$	219–220	11.48 (CH_2Cl_2)	87
3e	$C_{21}H_{28}IN_4O_4P$	217–218	11.30 (CH_2Cl_2)	85
5a	$C_9H_7Cl_2N_2O_2P$	150–155	−2.55 (DMSO)	89
5b	$C_{10}H_9Cl_2N_2O_2P$	180–183	−2.58 (DMSO)	91
5c	$C_{11}H_{11}Cl_2N_2O_2P$	—	3.64 (C_6H_6)	85
6a	$C_{17}H_{23}N_4O_4P$	180–183	11.17 (CH_2Cl_2)	87
6b	$C_{18}H_{25}N_4O_4P$	210–212	12.46 (CH_2Cl_2)	84
6c	$C_{19}H_{27}N_4O_4P$	206–207	10.18 (CH_2Cl_2)	82
9a	$C_{17}H_{23}N_4O_4P$	203–205	9.83 (CH_2Cl_2)	75
9b	$C_{23}H_{18}N_4O_4P$	165–166	9.61 (CH_2Cl_2)	45
11	$C_{25}H_{28}N_5O_7P$	200–202	9.82 (CH_2Cl_2)	53
14	$C_{14}H_{22}N_2O_5P$	180–181	9.90 (CH_2Cl_2)	30

The structures of the substances synthesized were supported by elemental analysis, ^{31}P and ^{1}H NMR, and IR spectra.

Thus, isocyanatophosphoric acid chlorides are the most active C-acylating agents among isocyanates of phosphoric acids, and they could be used for acylation of both nitrogen- and oxygen-containing heterocycles. An additional advantage of the isocyanates is an availability of the dichlorophosphoryl group, which can be further derivatized.

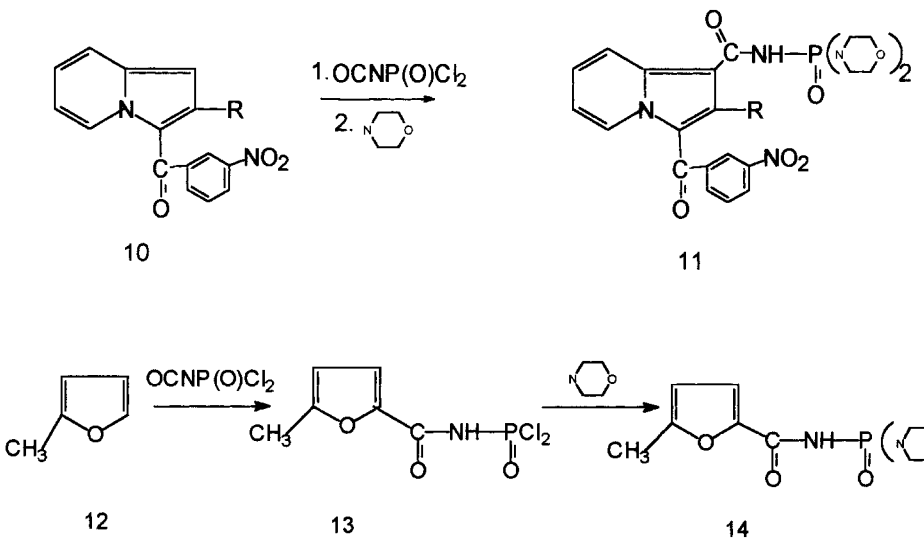
EXPERIMENTAL

IR spectra were recorded on a UR-20 spectrophotometer in KBr tablets. The ^{1}H and ^{31}P resonances were registered with a Varian Gemini-200 instrument using TMS as an internal standard for ^{1}H signals, and 85% H_3PO_4 as an external standard for ^{31}P signals.

N, P, and Cl contents derived from elemental analytical data correspond to those calculated for the compounds under study.

IR spectra exhibit characteristic absorption bands of the C=O (1670–1680 cm^{-1}) and P=O (1200–1210 cm^{-1}) groups.

1-Methylpyrrole-2-carboxamidophosphoryl Dichloride (**2a**). To a stirred and water-cooled solution of 0.71 g of N-methylpyrrole (0.1 mol) in octane (10 mL), a solution of 1.6 g of isocyanatophosphoryl dichloride (0.1 mol) in octane (5 mL) was added. After 15 minutes, the resulting precipitate was filtered off by the dry method, washed with octane, and held under vacuum at room temperature. ^{1}H-NMR (DMSO-D6) *δ*: 3.90 (s, 3H, N-CH_3); 6.20 (m, 1H, H_4-Het); 7.22 (m, 1H, H_3-Het); 7.50 (m, 1H, H_5-Het); 9.42 (m, 1H, NH).



2,5-Dimethyl-1-(4-methylphenyl)pyrrole-3-carboxamidophosphoryl Dichloride (**2d**). This compound was prepared similarly to compound (**2a**). The reaction was run at room temperature. The precipitate of the product was filtered off after 1 hour. ^{1}H-NMR ($CDCl_3$) δ: 1.97 (s 3H, 5-CH_3); 2.14 (s, 3H, 2-CH_3); 2.44 (s, 3H, Ar-CH_3); 6.12 (s, 1H, H-Het); 7.16 (d, J_{HH} = 7.5 Hz, 2H, m-H-Ar); 7.31 (d, J_{HH} = 7.5 Hz, 2H, o-H-Ar); 10.65 (d, J_{HH} = 7.5 Hz, 1H, NH).

2,5-Dimethyl-1-(4-iodophenyl)pyrrole-3-carboxamidophosphoryl Dichloride (**2e**). This was prepared similarly to compound (**2a**). The reaction was carried out at room temperature. The precipitate of the product was filtered off after 2.5 hours. ^{1}H-NMR (DMSO-D6) δ: 1.92 (s, 3H, 5-CH_3); 2.25 (s, 3H, 2-CH_3); 7.16 (d, J_{HH} = 7.8 Hz, 2H, m-H-Ar); 7.36 (s, 1H, H-Het); 7.92 (d, J_{HH} = 7.8 Hz, 2H, o-H-Ar); 8.23 (d, J_{HH} = 9.4 Hz, 1H, NH).

1-Methylpyrrol-2-carboxamidophosphoric Dimorpholide (**3a**). To a stirred and water-cooled suspension of 2.31 g of compound (**2a**) (0.1 mol) in benzene (50 mL), a solution of 3.48 g of morpholine (0.4 mol) in benzene (10 mL) was added. After 1 hour, the resulting precipitate was filtered off and dissolved in water (10 mL). The product was extracted with methylene chloride (3 × 10 mL), and the solvent was evaporated to dryness. ^{1}H-NMR (DMSO-D6) δ: 3.07 (m, 8H, N-CH_2); 3.52 (m, 8H, O-CH_2); 3.80 (s, 3H, N-CH_3); 6.02 (t, J_{HH} = 3.5 Hz, 1H, H_4-Het); 7.01 (s, 1H, H_3-Het); 7.15 (d, J_{HH} = 3.5 Hz, 1H, H_5-Het); 8.80 (d, J_{HH} = 3.5 Hz, 1H, NH).

1-(4-Methylphenyl)pyrrol-2-carboxamidophosphoric Dimorpholide (**3b**). To a stirred solution of 1.57 g of N-(4-methylphenyl)pyrrole (0.1 mol) in octane (10 mL), a solution of 1.6 g of isocyanatophosphoryl dichloride (0.1 mol) in octane (5 mL) was added. After 1.5 hours, a solution of 3.48 g of morpholine (0.4 mol) in octane (2 mL) was added to the stirred and water-cooled reaction mixture; 30 minutes later, the product was isolated as with (**3a**). On removal of methylene chloride, the residue was washed with acetonitrile (1 mL), filtered off, and dried. ^{1}H-NMR (DMSO-D6) δ: 2.31 (s, 3H, Ar-CH_3); 3.03 (m, 8H, N-CH_2); 3.30 (m, 8H, O-CH_2); 6.24 (s, 1H, H_4-Het); 7.22 (s, 1H, H_3-Het); 7.26 (s, 1H, H_5-Het); 7.30 (d, J_{HH} = 8.5 Hz, 2H, m-H-Ar); 7.44 (d, J_{HH} = 8.5 Hz, 2H, o-H-Ar).

1-(2-Carbomethoxyphenyl)pyrrol-2-carboxamidophosphoric Dimorpholide (**3c**). This compound was synthesized in a similar way to compound (**3b**) in benzene. ^{1}H-NMR (DMSO-D6) δ: 2.99 (m, 8H, N-CH_2); 3.48 (m, 8H, O-CH_2); 3.59 (s, 3H, O-CH_3); 6.26 (s, 1H, H_4-Het); 7.02 (s, 1H, H_3-Het); 7.35 (m, 3H, H_5-Het, o-H-Ar, NH); 7.53 (t, J_{HH} = 6.2 Hz, 1H, m-H-Ar); 7.69 (t, J_{HH} = 6.2 Hz, 1H, p-H-Ar). 7.90 (d, J_{HH} = 6.2 Hz, 1H, o-Ar-C=O).

2,5-Dimethyl-1-(4-methylphenyl)pyrrole-3-carboxamidophosphoric Dimorpholide (**3d**). This compound was prepared similarly to compound (**3a**). Within 1 hour after addition of morpholine, the precipitate was filtered off, washed with water (twice) and with ethanol (5 mL), and dried. ^{1}H-NMR ($CDCl_3$) δ: 1.98 (s, 3H, 5-CH_3); 2.28 (s, 3H, 2-CH_3); 2.44 (s, 3H, Ar-CH_3); 3.32 (m, 8H, N-CH_2); 3.69 (m, 8H, O-CH_2); 6.18 (s, 1H, H-Het); 6.81 (d, J_{HP} = 9.6 Hz, 1H, NH); 7.08 (d, J_{HH} = 7.6 Hz, 2H, m-H-Ar); 7.32 (d, J_{HH} = 7.6 Hz, 2H, o-H-Ar).

2,5-Dimethyl-1-(4-iodophenyl)pyrrole-3-carboxamidophosphoric Dimorpholide (**3e**). This was prepared similarly to compound (**3d**). ^{1}H-NMR ($CDCl_3$) δ: 1.95 (s, 3H, 5-CH_3); 2.30 (s, 3H, 2-CH_3); 3.33 (m, 8H, N-CH_2); 3.69 (m, 8H, O-CH_2); 6.22 (s, 1H, H-Het); 6.84 (d, J_{HP} = 9.6 Hz, 1H, NH); 7.10 (d, J_{HP} = 7.6 Hz, 2H, m-H-Ar); 7.36M.A. (d, J_{HP} = 7.6 Hz, 2H, o-H-Ar).

Indole-3-carboxamidophosphoryl Dichloride (**5a**). This compound was obtained analogously to compound (**2a**). ^{1}H-NMR ($CDCl_3$) δ: 7.36 (m, 3H, $H_{5,6,7}$-Het); 7.50 (m, 1H, H_4-Het); 8.15 (s, 1H, H_2-Het); 9.05 (s, 1H, CO-NH); 11.80 (s, 1H, NH-Het).

1-Methylindole-3-carboxamidophosphoryl Dichloride (**5b**). **5b** was obtained analogously to compound (**2a**). ^{1}H-NMR (DMSO-D6) δ: 2.57 (s, 3H, N-CH_3); 7.20 (m, 3H, $H_{5,6,7}$-Het); 7.49 (m, 1H, H_4-Het); 8.20 (s, 1H, H_2-Het); 9.00 (s, 1H, CO-NH).

1,2-Dimethylindole-3-carboxamidophosphoryl Dichloride (**5c**). **5c** was obtained analogously to compound (**2a**). ^{1}H-NMR (DMSO-D6) δ: 2.49 (s, 3H, C-CH_3); 3.63 (s, 3H, N-CH_3); 7.25 (m, 3H, $H_{5,6,7}$-Het); 7.60 (m, 1H, H_4-Het); 12.14 (s, 1H, CO-NH).

Indole-3-carboxamidophosphoric Dimorpholide (**6a**). Compound **6a** was prepared similarly to compound (**3d**). ^{1}H-NMR (DMSO-D6) δ: 3.13 (m, 8H, N-CH_2); 3.55 (m, 8H, O-CH_2); 6.97 (m, 3H, $H_{5,6,7}$-Het); 7.47 (m, 1H, H_4-Het); 8.16 (s, 1H, H_2-Het); 10.75 (s, 1H, CO-NH); 11.82 (s, 1H, NH-Het).

1-Methylindole-3-carboxamidophosphoric Dimorpholide (**6b**). Compound **6b** was prepared similarly to compound (**3d**). ^{1}H-NMR (DMSO-D6) δ: 3.13 (m, 8H, N-CH_2); 3.55 (m, 8H, O-CH_2); 3.83 (s, 3H, N-CH_3); 7.25 (m, 2H, $H_{5,6}$-Het); 7.58 (m, 1H, H_7-Het); 8.16 (m, 1H, H_4-Het); 8.45 (s, 1H, H_2-Het); 8.92 (m, 1H, NH).

1,2-Dimethylindole-3-carboxamidophosphoric Dimorpholide (**6c**). Compound **6c** was prepared similarly to compound (**3d**). ^{1}H-NMR (DMSO-D6) δ: 2.61 (s, 3H, C-CH_3); 3.13 (m, 8H, N-CH_2); 3.56 (m, 8H, O-CH_2); 3.69 (s, 3H, N-CH_3); 7.17 (m, 3H, $H_{5,6,7}$-Het); 7.40 (m, 1H, H_4-Het); 7.75 (m, 1H, NH).

2-Methylindolizine-3-carboxamidophosphoric Dimorpholide (**9a**). **9a** was prepared similarly to compound (**3d**). After having been washed with acetonitrile (3 mL), the product was dried. ^{1}H-NMR (DMSO-D6) δ: 2.54 (s, 3H, CH_3); 3.14 (m, 8H, N-CH_2); 3.57 (m, 8H, O-CH_2); 6.39 (s, 1H, H_1-Het); 6.79 (t, J_{HH} = 7.2 Hz, 1H, H_6-Het); 7.02 (t, J_{HH} = 7.2 Hz, 1H, H_7-Het); 7.81 (d, J_{HH} = 9.0 Hz, 1H, H_8-Het); 9.07 (d, J_{HH} = 7.0 Hz, 1H, H_5-Het).

2-Phenylindolizine-3-carboxamidophosphoric Dimorpholide (**9b**). **9b** was prepared similarly to compound (**3b**) in benzene. Within 3 hours after addition of morpholine, the precipitate formed was filtered off and thrice washed with water. ^{1}H-NMR ($CDCl_3$) δ: 3.07 (m, 8H, N-CH_2); 3.60 (m, 8H, O-CH_2); 6.21 (d, J_{PH} = 9.6 Hz, 1H, NH); 6.47 (s, 1H, H_1-Het); 6.85 (t, J_{HH} = 7.2 Hz, 1H, H_6-Het); 7.11 (t, J_{HH} = 7.2 Hz, 1H, H_7-Het); 7.51 (m, 6H, H_8-Het, Ph); 9.74 (d, 1H, J_{HH} = 7.0 Hz, H_5-Het).

2-Methyl-3-(3′-nitro)benzoyl-1-carboxamidophosphoric Dimorpholide (**11**). Compound **11** was prepared analogously to compound (**3b**) in benzene. A solution of 3.48 g morpholine (0.4 mol) was added within 48 hours after the reaction had been started, and the reaction mixture was stirred at room temperature for 2 hours. The resulting precipitate was filtered off, dried in the air, and dissolved in water (10 mL). An insoluble remainder was filtered off and crystallized from acetone. ^{1}H-NMR ($CDCl_3$) δ: 2.19 (s, 3H, CH_3); 3.34 (m, 8H, N-CH_2); 3.71 (m, 8H, O-CH_2); 7.30 (t, J_{HH} = 8.1 Hz, 1H, H_6-Het); 7.47 (t, J_{HH} = 8.7 Hz, 1H, H_7-Het); 7.74 (t, J_{HH} = 8.1 Hz, 1H, m-H-Ph); 8.02 (d, J_{HH} = 6.6 Hz, 1H, H_8-Het); 8.19 (d, J_{HH} = 8.7 Hz, 1H, o-H-Ph); 8.46 (d, J_{HH} = 7.5 Hz, 1H, p-H-Ph); 8.53 (s, 1H, o-H-Ph); 9.61 (d, J_{HH} = 6.9 Hz, 1H, H_5-Het).

2-Methylfuran-5-carboxamidophosphoric Dimorpholide (**14**). This compound was prepared in a similar way to compound (**3a**). The solvent was evaporated to dryness. The product was crystallized from diethyl ether twice. ^{1}H-NMR (DMSO-D6) δ: 2.34 (s, 3H, CH_3); 3.07 (m, 8H, N-CH_2); 3.52 (m, 8H, O-CH_2); 5.80 (m, 1H, NH); 6.20 (s, 1H, H_4-Het); 7.46 (s, 1H, H_3-Het).

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