New type of 2-alkyl-substituted 1,8-naphthyridine systems containing a phosphoryl group in the side chain*

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First organophosphorus derivatives of 2-alkyl- and 2,3-alkylene-substituted 1,8-naphthyridines were synthesized by the Friedländer reaction starting from 2-aminonicotinaldehyde and diphenylphosphoryl(cyclo)alkanones, respectively.

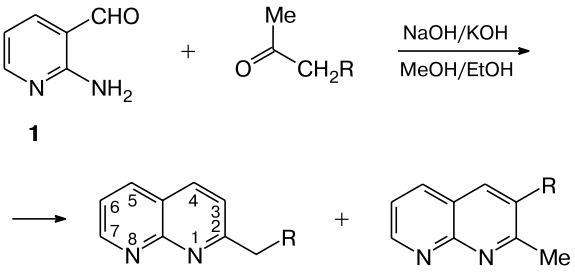
Key words: Friedländer reaction, 2-aminonicotinaldehyde, phosphorylated ketones, annulation, naphthyridines, alkaline catalysis, pyrrolidine.

The chemistry of 1,8-naphthyridines has attracted increasing interest due to the structural features of these compounds. As opposed to five other isomeric naphthyridines, the arrangement of the nitrogen atoms in the heterocyclic system of 1,8-naphthyridines is optimal from the point of view of chelation to metal cations.[1] It should be noted that many functionalized representatives of this class of compounds have a broad range of biological activities.[2]

However, organophosphorus derivatives of 1,8-naphthyridine have attracted attention only in the recent past. A few compounds containing the diphenylphosphine groups at positions 2 and 7 of the naphthyridine moiety were characterized.[3—5] It should also be emphasized that the functionalization of this class of compounds is often complicated by side reactions with the involvement, in particular, of the heterocyclic moiety.[6]

Our research interests in the synthesis of organophosphorus ligands and investigation of their coordination chemistry have generated a need for the development of a convenient procedure for the synthesis of functionalized 2-alkyl-substituted 1,8-naphthyridines containing phosphoryl groups as additional donor centers in the side chain. Earlier, we have synthesized[7] first representatives of this class of compounds, which are potential tridentate heterodifunctional ligands, by the Friedländer reaction starting from phosphorylated derivatives of acetone and cyclopentanone. The main drawback of the Friedländer reaction is that unsymmetrical ketones give both possible regioisomeric naphthyridines in comparable amounts under alkaline catalysis (Scheme 1).

Scheme 1



R = Alk, CH_2Ar, Ar, $P(O)Ph_2$

In the present study, we developed an approach to the solution of the problem of the regioselectivity based on the modification of ketones by replacing one or both hydrogen atoms of the methylene unit, which links the carbonyl group of ketone and the substituent R, with an alkyl group. This approach provides the involvement of only two hydrogen atoms of the methyl group of functionalized unsymmetrical ketones in the reaction, resulting in the formation of the only Friedländer reaction product, *viz.*, the target 2-substituted 1,8-naphthyridine.

Results and Discussion

In the present study, we synthesized various representatives of phosphorylated ketones, which were then introduced into the Friedländer reaction with 2-aminonicotinaldehyde (**1**). The phosphorylation of the starting cycloalkanones with chlorodiphenylphosphine and the synthesis of aldehyde **1** were carried out according to known procedures.[8,9] The Friedländer reaction was catalyzed by either aqueous NaOH or pyrrolidine. In some

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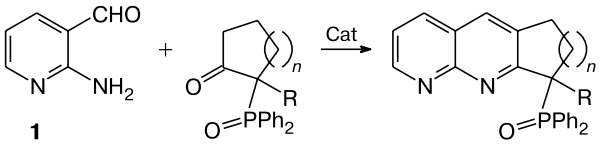
cases, the latter catalyst provides high regioselectivity of the formation of 2-alkyl-substituted products.[10] Ethanol was used as the solvent in the reactions catalyzed by both catalysts. The annulation was monitored by ^{31}P NMR spectroscopy.

Earlier,[7] we have demonstrated (Scheme 2) that the reaction of aldehyde **1** with 2-(diphenylphosphoryl)cyclopentanone (**2a**) catalyzed by pyrrolidine proceeds smoothly to give 8-(diphenylphosphoryl)-7,8-dihydro-6*H*-cyclopenta[*b*][1,8]naphthyridine (**4a**).

Scheme 2



1 **2a,b**, **3a,b** **4a,b**, **5b**

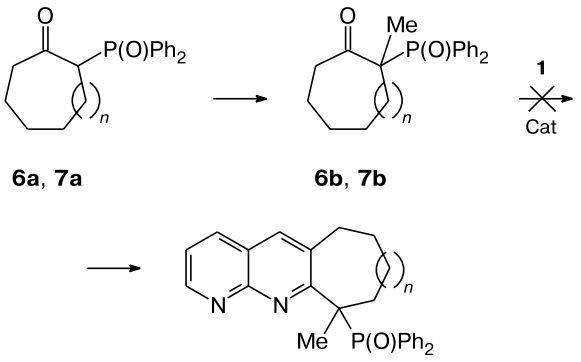
R = H (**a**), Me (**b**); *n* = 1 (**2**, **4**), 2 (**3**, **5**)
Cat is the catalyst

However, 2-(diphenylphosphoryl)cyclohexanone (**3a**) virtually does not react with aldehyde **1** under these conditions even under reflux. The alkaline-catalyzed reaction also does not give the desired result. The ^{31}P NMR spectrum of the reaction mixture shows a signal at δ 19—20 assigned to the diphenylphosphinate anion. The intensity of this signal increases with time, whereas the intensity of the signal in the region expected for target product **5a** is very low. An analogous situation is observed for compound **2a** in the presence of alkaline catalysts. Apparently, the C_{Alk}—P bond cleavage occurs in probable intermediates, *viz.*, enolate anions, which are generated in an alkaline medium *via* the proton abstraction from the tertiary C atom of the aliphatic ring of ketones **2a** and **3a**. Taking into account this experiment, we performed the premethylation of these ketones with iodomethane according to an improved procedure[11] and obtained new ketones **2b** and **3b**, in which the hydrogen atom bound to the tertiary carbon atom is replaced by the methyl group. Ketone **2b** readily reacts with aldehyde **1** regardless of the reaction conditions, whereas ketone **3b** is involved in this reaction only in the presence of alkaline catalysts. In both cases, the corresponding naphthyridines **4b** and **5b** were isolated in good yields as high-melting-point finely crystalline dull-yellow products.

Unfortunately, attempts to perform the Friedländer reaction (Scheme 3) of aldehyde **1** with new methylated ketones **6b** and **7b** synthesized from ketones **6a** and **7a**, respectively, failed.

In the presence of alkaline catalysts, the reaction virtually does not proceed at 20 °C, whereas the refluxing of the reaction mixture leads to the C_{Alk}—P bond cleavage

Scheme 3



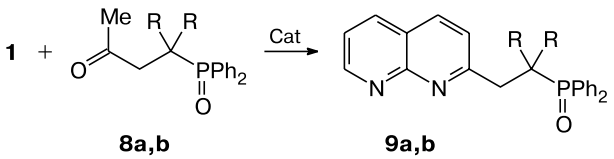
6a, **7a** **6b**, **7b**

n = 1 (**6a,b**), 2 (**7a,b**)

in ketones. Apparently, the conformational features of cyclic α-phosphorylated ketones possessing a seven-membered or larger ring give rise to steric hindrance in the course of annulation with 2-aminonicotinaldehyde (**1**). This, in turn, facilitates the elimination of the bulky diphenylphosphoryl substituent from the molecule.

In addition to cyclic ketones, we performed the Friedländer reaction of aldehyde **1** with acyclic phosphorus-containing ketones **8a,b**, in which the phosphoryl group is in the β position with respect to the carbonyl group (Scheme 4).

Scheme 4



8a,b **9a,b**

R = H (**a**), Me (**b**); Cat is pyrrolidine

We synthesized ketones **8a,b** according to modified procedures by the reaction of Ph_2PCl with methyl vinyl ketone[12] or mesityl oxide,[13] respectively. It should be noted that ketone **8b** was synthesized for the first time. The annulation with aldehyde **1** catalyzed with pyrrolidine at 20 °C proceeds regioselectively to give the target 2-substituted naphthyridines **9a,b** in good yields.

The structure of naphthyridine **9b** was confirmed by X-ray diffraction data (Fig. 1). The bond lengths and bond angles are typical of compounds of the corresponding class[14] (Table 1). The naphthyridine ring N(1)C(1)—C(7)N(2)—C(8) is planar to within 0.01 Å. The Cambridge Structural Database[15] contains, along with the data on unsubstituted 1,8-naphthyridine,[16,17] the structures of one 2-substituted 1,8-naphthyridine, *viz.*, *N*-butyl-*N*′-([1,8]naphthyridin-2-yl)urea,[18] and one phosphorus-substituted naphthyridine, *viz.*, 7-diphenyl-

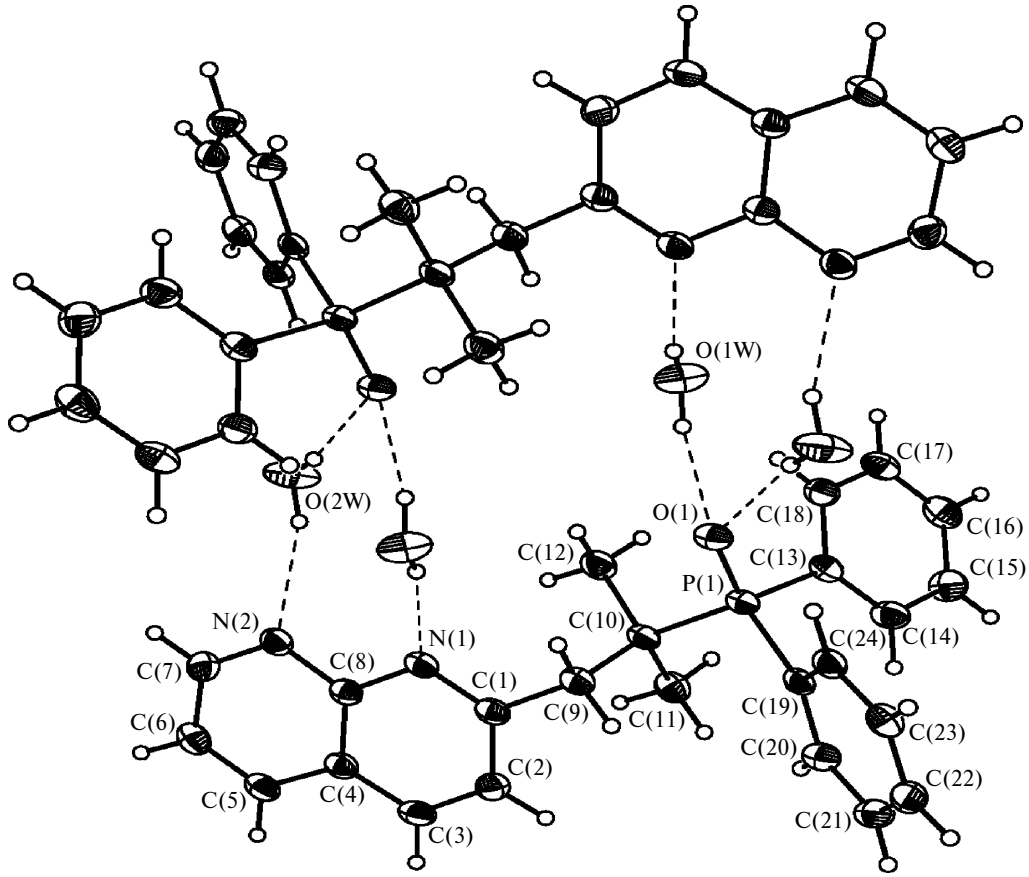


Fig. 1. Structure of tetrahydrate of dimer **9b** with displacement ellipsoids at the 50% probability level. The atomic numbering scheme is given only for the asymmetric unit cell; the second molecule is generated by the symmetry operation $-x + 1, -y + 1, -z$. The hydrogen bonds are indicated by dashed lines.

Table 1. Selected bond lengths (d) and bond angles (ω) in molecule **9b**

Bond	d/Å	Angle	ω/deg	Angle	ω/deg
P(1)—O(1)	1.4951(17)	O(1)—P(1)—C(19)	109.23(10)	C(3)—C(4)—C(8)	117.9(2)
P(1)—C(19)	1.810(2)	O(1)—P(1)—C(13)	111.47(10)	C(6)—C(5)—C(4)	119.5(2)
P(1)—C(13)	1.814(2)	C(19)—P(1)—C(13)	106.55(11)	C(5)—C(6)—C(7)	118.8(2)
P(1)—C(10)	1.851(2)	O(1)—P(1)—C(10)	110.57(10)	N(2)—C(7)—C(6)	124.1(2)
N(1)—C(1)	1.321(3)	C(19)—P(1)—C(10)	111.89(11)	N(2)—C(8)—N(1)	114.9(2)
N(1)—C(8)	1.371(3)	C(13)—P(1)—C(10)	107.07(11)	N(2)—C(8)—C(4)	122.6(2)
N(2)—C(7)	1.327(3)	C(1)—N(1)—C(8)	117.9(2)	N(1)—C(8)—C(4)	122.5(2)
N(2)—C(8)	1.361(3)	C(7)—N(2)—C(8)	117.0(2)	C(1)—C(9)—C(10)	114.18(19)
C(1)—C(2)	1.415(3)	N(1)—C(1)—C(2)	123.2(2)	C(11)—C(10)—C(12)	109.1(2)
C(1)—C(9)	1.513(3)	N(1)—C(1)—C(9)	117.0(2)	C(11)—C(10)—C(9)	111.56(19)
C(2)—C(3)	1.366(4)	C(2)—C(1)—C(9)	119.8(2)	C(12)—C(10)—C(9)	110.8(2)
C(3)—C(4)	1.412(4)	C(3)—C(2)—C(1)	119.5(2)	C(11)—C(10)—P(1)	113.19(17)
C(4)—C(5)	1.408(3)	C(2)—C(3)—C(4)	119.0(2)	C(12)—C(10)—P(1)	105.47(16)
C(4)—C(8)	1.413(3)	C(5)—C(4)—C(3)	124.1(2)	C(9)—C(10)—P(1)	106.51(16)
C(5)—C(6)	1.354(4)	C(5)—C(4)—C(8)	118.0(2)		
C(6)—C(7)	1.412(3)				
C(9)—C(10)	1.556(3)				
C(10)—C(11)	1.534(3)				
C(10)—C(12)	1.543(3)				

phosphino-2,4-dimethyl[1,8]naphthyridine.[19] In all these compounds, including **9b**, the bond lengths and bond angles in the planar naphthyridine ring are virtually equal.

According to the X-ray diffraction study, single crystals of naphthyridine **9b** contain water solvent molecules, which are involved in strong intermolecular hydrogen bonds linking two naphthyridine molecules (see Fig. 1). The phosphoryl oxygen atom is involved in a bifurcated hydrogen bond. For the O(1W)—H(1W)...N(1), O(1W)—H(2W)...O(1), O(2W)—H(3W)...O(1), and O(2W)—H(4W)...N(2) contacts, the distances between the nonhydrogen atoms are 2.850(3), 2.775(3), 2.873(3), and 2.953(3) Å and the angles are 155.3, 167.6, 161.4, and 156.8°, respectively. Molecules **9b** are linked by hydrogen bonds to form dimers with the composition $2C_{24}H_{23}N_2OP \cdot 4H_2O$. In the crystal structure, the dimers are located one above another along the crystallograghic *b* axis (Fig. 2).

The conditions of the Friedländer reaction, yields, melting points, and elemental analysis data for the reaction products are given in Tables 2 and 3. The spectroscopic characteristics are presented in Tables 4 and 5.

The experimental data obtained in the present study provide estimates of the prospects of using the above-considered compounds as catalysts for the Friedländer reaction as applied to ketones containing the diphenylphosphoryl substituent from the viewpoint of regioselectivity of annulation. Alkaline catalysts are convenient only in the case of compounds containing no hydrogen atoms at the α-carbon atom of the ketone moiety adjacent to the P=O group. Less active pyrrolidine is passive with respect to derivatives of cyclic ketones (except for very reactive cyclopentanones) but it provides the regioselective formation of 2-substituted naphthyridines in the case of acyclic unsymmetrical methyl ketones (except for diphenylphosphorylacetone).[7]

In the ^{1}H NMR spectra of all naphthyridines synthesized in the present study (see Table 4), the signals for the

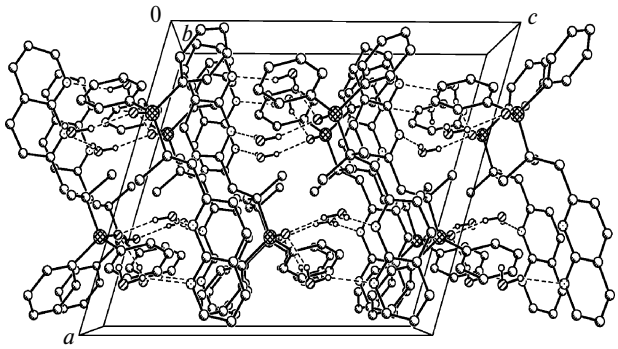


Fig. 2. Crystal packing of dimer **9b** projected along the crystallographic *b* axis. The hydrogen atoms, which are not involved in hydrogen bonding, are omitted. The hydrogen bonds are indicated by dashed lines.

Table 2. Yields, melting points, and elemental analysis data for ketones **2b**, **3b**, and **6a,b**—**8a,b**

Compound	Yield (%)	M.p. /°C	Found / Calculated (%) C	H	P	Molecular formula
2b	76	97—98	72.50 72.47	6.38 6.42	10.27 10.38	$C_{18}H_{19}O_2P$
3b	64	116—117	73.10 73.06	6.72 6.78	9.92 9.91	$C_{19}H_{21}O_2P$
6a	70	135—136	73.12 73.06	6.69 6.78	9.86 9.91	$C_{19}H_{21}O_2P$
6b	72	144—145	73.60 73.54	7.19 7.10	9.59 9.50	$C_{20}H_{23}O_2P$
7a	69	150—151	73.47 73.60	7.14 7.10	9.44 9.50	$C_{20}H_{23}O_2P$
7b	74	171—172	74.07 74.10	7.29 7.40	9.14 9.10	$C_{21}H_{25}O_2P$
8a	91	105—106	70.49 70.58	6.22 6.30	11.34 11.37	$C_{16}H_{17}O_2P$
8b	59	83—84	71.85 71.97	6.95 7.05	10.31 10.31	$C_{18}H_{21}O_2P$

Table 3. Reaction times (*t*), yields, melting points, and elemental analysis data for naphthyridines **4a,b**, **5b**, and **9a,b**

Compound	*t* /h	Yield (%)	M.p. /°C	Found / Calculated (%) C	H	N	P	Molecular formula
4a	36	48	210—211	74.68 74.58	5.22 5.17	7.55 7.56	8.15 8.36	$C_{23}H_{19}N_2OP$
4b	6	70	190—191	75.05 74.99	5.44 5.51	7.32 7.29	7.95 8.06	$C_{24}H_{21}N_2OP$
5b	6	75	205—206	75.29 75.36	5.86 5.82	7.11 7.03	7.71 7.77	$C_{25}H_{23}N_2OP$
9a	12	77	166—167	73.64 73.73	5.36 5.34	7.79 7.81	8.52 8.64	$C_{22}H_{19}N_2OP$
9b	12	68	202—203	74.54 74.60	5.97 6.00	7.23 7.25	7.98 8.02	$C_{24}H_{23}N_2OP$

H(5), H(6), and H(7) protons of the heterocyclic moiety are observed as doublets of doublets. The chemical shifts of these signals differ only slightly from each other. The signal for the H(4) proton of the naphthyridine moiety in the spectra of **4b** and **5b** is observed as a singlet at δ ~7.75. In the spectrum of naphthyridine **9a**, the signal for this proton appears as a pronounced doublet at δ 8.03; in the spectrum of naphthyridine **9b**, the region of this signal coincides with the region of the *o*-Ph protons of the diphenylphosphoryl group. In the spectra of compounds **9a,b**, the signal for the H(3) proton of the naphthyridine moiety is observed as a doublet at δ 7.35—7.38. An analysis of the ^{1}H NMR spectra of compounds **4b** and **5b** allows conclusions about the steric hindrance in these

Table 4. IR spectroscopic data and $^{31}P\{^1H\}$ and ^1H NMR spectroscopic data for naphthyridines **4b**, **5b**, and **9a,b**

Compound	IR, ν/cm^{-1}		NMR ($CDCl_3$), δ (*J*/Hz)	
	ν(P=O)	ν_{cycl}*	^{31}P	^1H
4b	1180	1620, 1600, 1560	33.1	1.89 (d, 3 H, Me, $J_{H,P}$ = 15.2); 2.15—2.24, 2.51—2.60, 2.85—2.91, 3.37—3.46 (all m, 1 H each, CH_2); 7.02—7.07 (m, 2 H, *m*-H_{Ph}); 7.20—7.23 (m, 1 H, *p*-H_{Ph}); 7.35—7.42 (m, 3 H, 2 *m*-H_{Ph} + 1 H(6)); 7.51—7.54 (m, 3 H, 2 *o*-H_{Ph} + 1 *p*-H_{Ph}); 7.76 (s, 1 H, H(4)); 8.07 (dd, 1 H, H(5), $^1J_{H,H}$ = 1.9, $^2J_{H,H}$ = 8.0); 8.50—8.54 (m, 2 H, *o*-H_{Ph}); 9.06 (dd, 1 H, H(7), $^1J_{H,H}$ = 1.9, $^2J_{H,H}$ = 4.1)
5b	1169, 1182 sh	1616, 1601, 1554	37.4	1.74—1.80 (m, 1 H, CH_2); 1.84 (d, 3 H, Me, $J_{H,P}$ = 16.1); 1.98—2.10, 2.64—2.76 (both m, 2 H each, CH_2); 2.85—2.91 (m, 1 H, CH_2); 7.03—7.08 (m, 2 H, *m*-H_{Ph}); 7.20—7.24 (m, 1 H, *p*-H_{Ph}); 7.31—7.35 (m, 2 H, *m*-H_{Ph}); 7.44 (dd, 1 H, H(6), $^1J_{H,H}$ = 4.2, $^2J_{H,H}$ = 8.0); 7.52—7.54 (m, 3 H, 2 *o*-H_{Ph} + 1 *p*-H_{Ph}); 7.74 (s, 1 H, H(4)); 8.07 (dd, 1 H, H(5), $^1J_{H,H}$ = 1.9, $^2J_{H,H}$ = 8.0); 8.40—8.45 (m, 2 H, *o*-H_{Ph}); 9.06 (dd, 1 H, H(7), $^1J_{H,H}$ = 1.9, $^2J_{H,H}$ = 4.2)
9a	1183	1610, 1549	32.6	3.01—3.08 (m, 2 H, CH_2P); 3.34—3.41 (m, 2 H, CH_2C); 7.35 (d, 1 H, H(3), $^1J_{H,H}$ = 8.2); 7.40—7.49 (m, 7 H, 4 *m*-H_{Ph} + 2 *p*-H_{Ph} + 1 H(6)); 7.77—7.82 (m, 4 H, *o*-H_{Ph}); 8.03 (d, 1 H, H(4), $^1J_{H,H}$ = 8.2); 8.13 (dd, 1 H, H(5), $^1J_{H,H}$ = 1.8, $^2J_{H,H}$ = 8.1); 9.06 (dd, 1 H, H(7), $^1J_{H,H}$ = 1.8, $^2J_{H,H}$ = 8.1)
9b	1169	1607, 1553	38.2	1.32 (d, 6 H, Me, $J_{H,P}$ = 15.8); 3.35 (d, 2 H, CH_2, $J_{H,P}$ = 7.8); 7.38 (d, 1 H, H(3), $J_{H,H}$ = 8.4); 7.43 (dd, 1 H, H(6), $^1J_{H,H}$ = 8.2, $^2J_{H,H}$ = 4.2); 7.45—7.51 (m, 6 H, *m*-H_{Ph} + *p*-H_{Ph}); 8.00—8.05 (m, 5 H, 4 *o*-H_{Ph} + 1 H(4)); 8.13 (dd, 1 H, H(5), $^1J_{H,H}$ = 8.2, $^2J_{H,H}$ = 2.0); 9.05 (dd, 1 H, H(7), $^1J_{H,H}$ = 4.2, $^2J_{H,H}$ = 2.0)

* Skeletal vibrations of the naphthyridine rings.

Table 5. IR spectroscopic data and $^{31}P\{^1H\}$ and ^1H NMR spectroscopic data for ketones **2b**, **3b**, and **6a,b**—**8a,b**

Compound	IR, ν/cm^{-1}		NMR ($CDCl_3$), δ (*J*/Hz)	
	P=O	C=O	^{31}P	^1H
2b	1175	1732	31.5	1.37 (d, 3 H, Me, $J_{P,H}$ = 15.8); 1.73—1.82 (m, 2 H, CH_2); 1.89—1.97, 2.03—2.11, 2.23—2.30, 2.70—2.81 (all m, 1 H each, CH_2); 7.40—7.44 (m, 2 H, *p*-H_{Ph}); 7.49—7.59 (m, 4 H, *m*-H_{Ph}); 7.78—7.86, 8.09—8.15 (both m, 2 H each, *o*-H_{Ph})
3b	1190	1710	36.2	1.31 (d, 3 H, Me, $J_{P,H}$ = 15.2); 1.59—1.78 (m, 4 H, 2 CH_2); 2.20—2.28 (m, 2 H, CH_2); 2.44—2.50, 2.82—2.90 (both m, 1 H each, $CH_2C(O)$); 7.38—7.43 (m, 2 H, *p*-H_{Ph}); 7.44—7.53 (m, 4 H, *m*-H_{Ph}); 7.76—7.80, 7.93—7.98 (both m, 2 H each, *o*-H_{Ph})
6a	1190	1700	30.0	1.14—1.46, 1.84—2.07 (both m, 4 H each, 4 CH_2); 2.30—2.34, 2.79—2.85 (both m, 1 H each, $CH_2C(O)$); 3.53—3.60 (m, 1 H, CHP); 7.41—7.52 (m, 6 H, *m*-H_{Ph} + *p*-H_{Ph}); 7.72—7.79 (m, 4 H, *o*-H_{Ph})
6b	1180	1690	31.9	1.11—1.28 (m, 2 H, CH_2); 1.30—1.39 (m, 1 H, CH_2); 1.34 (d, 3 H, Me, $J_{H,P}$ = 16.0); 1.75—1.85 (m, 4 H, CH_2); 2.22—2.27, 2.44—2.53, 2.66—2.72 (all m, 1 H each, CH_2); 7.40—7.55 (m, 6 H, *m*-H_{Ph} + *p*-H_{Ph}); 7.76—7.81, 7.89—7.94 (both m, 2 H each, *o*-H_{Ph})
7a	1180	1695	30.1	1.08—1.19, 1.28—1.37, 1.41—1.50 (all m, 1 H each, CH_2); 1.55—1.74 (m, 4 H, CH_2); 1.80—1.87, 1.90—1.98, 2.04—2.09, 2.37—2.52, 2.82—2.89 (all m, 1 H each, CH_2); 3.46—3.55 (m, 1 H, CHP); 7.40—7.55 (m, 6 H, *m*-H_{Ph} + *p*-H_{Ph}); 7.72—7.80 (m, 4 H *o*-H_{Ph})
7b	1180, 1190	1690	32.2	0.74—0.84, 1.20—1.29 (both m, 1 H each, CH_2); 1.30 (d, 3 H, Me, $J_{H,P}$ = 16.0); 1.44—1.81 (m, 6 H, CH_2); 1.92—2.01, 2.94—3.09 (both m, 2 H each, CH_2); 7.39—7.55 (m, 6 H, *m*-H_{Ph} + *p*-H_{Ph}); 7.78—7.87 (m, 4 H, *o*-H_{Ph})
8a	1180	1720	32.5	2.09 (s, 3 H, Me); 2.48—2.55 (m, 2 H, $CH_2C(O)$); 2.71—2.77 (m, 2 H, CH_2P); 7.42—7.53 (m, 6 H, *m*-H_{Ph} + *p*-H_{Ph}); 7.67—7.74 (m, 4 H *o*-H_{Ph})
8b	1173, 1185 sh	1723	37.2	1.39 (d, 6 H, CMe_2, $J_{H,P}$ = 16.2); 2.08 (s, 3 H, C(O)Me); 2.70 (d, 2 H, CH_2, $J_{H,P}$ = 7.7); 7.45—7.53 (m, 6 H, *m*-H_{Ph} + *p*-H_{Ph}); 7.93—7.98 (m, 4 H, *o*-H_{Ph})

naphthyridines. Most likely, the steric hindrance is associated with the fact that the diphenylphosphoryl group in the compounds under consideration is in close proximity to the naphthyridine moiety. This is reflected both on the character of the signals for the phenyl protons of this group and the character of the signals for the protons of the aliphatic moiety of compounds **4b** and **5b**.

The $^{31}P\{H\}$ NMR spectra of all compounds containing the diphenylphosphoryl group, which were synthesized in the present study, show a singlet in the region characteristic of phosphine oxides (δ 28—40).

In the IR spectra of phosphoryl-substituted 1,8-naphthyridines (see Table 4), the absorption band of the phosphoryl group, ν(P=O), is either observed at 1180 cm^{-1} (compounds **4b** and **9a**), which is close the vibrational frequencies of this bond in the corresponding ketones (see Table 5), or is shifted to 1169 cm^{-1} due to hydrogen bonding with water molecules (compound **9b**). In the spectrum of compound **5b**, the ν(P=O) band is split into the same components. The skeletal frequencies of the naphthyridine rings are consistent with the published data.[20,21] The absorption band of the phenyl rings is observed at 1590 cm^{-1}, but the intensity of this band is low. At lower frequencies, the absorption of the phenyl rings does not allow the reliable identification of the vibrations of the naphthyridine fragment. In the spectrum of a crystalline sample of **9b**, the stretching vibrations of the water molecules involved in hydrogen bonding with the nitrogen atoms of the naphthyridine rings and the phosphoryl oxygen atoms appear as complex intense bands with maxima at 3500 and 3425 cm^{-1} (shoulders at 3570 and 3390 cm^{-1}); the bending vibrations of water molecules are observed at 1630 cm^{-1}.

The IR spectra of all phosphorylated cycloalkanones (see Table 5) show the absorption of the P=O group (ν(P=O)) at 1180—1190 cm^{-1}. The ν(C=O) frequency depends on the ring size and is 1732 cm^{-1} for compound **2b** containing the most strained ring, 1710 cm^{-1} for compound **3b**, and 1690—1700 cm^{-1} for ketones containing larger rings.

In conclusion, let us note that the Friedländer synthesis performed in the present study provides an efficient and easy route to new, previously unknown, 1,8-naphthyridines containing the P=O group at the α- or β-carbon atom of the alkylene fragment in position 2 of the heterocyclic moiety. The compounds synthesized in the present study are potential tridentate heterodifunctional ligands. Investigations of the coordination properties of these ligands are presently underway.

Experimental

The NMR spectra were recorded on a Bruker Avance-400 instrument (400.13 MHz for ^{1}H and 161.98 MHz for ^{31}P) at 298 K in $CDCl_3$ using the signals of the protons of the deuterated solvent as the internal standard (^{1}H) and 85% H_3PO_4 as the external standard (^{31}P); the concentration of the solutions was 0.02 mol L^{-1}. The IR spectra were measured in KBr pellets on a Magna-IR750 Fourier-transform spectrometer (Nicolet); the resolution was 2 cm^{-1}, the number of scans was 128.

All operations were carried out under argon. The solvents were saturated with argon, purified, and dried according to known procedures.[22]

The synthesis of α-phosphorylated cycloalkanones **2a**, **3a**, **6a**, and **7a** was carried out according to a procedure described earlier.[8] The yields and physicochemical constants of the ketones are consistent with those published in the literature.

α-Methylation of ketones 2a, 3a, 6a, and 7a (general procedure). Sodium hydride (a 60% suspension in a mineral oil, 5.5 mmol) was added with stirring to a solution of the corresponding ketone (5 mmol) in anhydrous THF (10 mL) at ~20 °C. After the cessation of hydrogen evolution, a solution of MeI (7.5 mmol) in THF (5 mL) was added dropwise to the reaction mixture. After stirring for 2 h, the reaction mixture was refluxed for 1 h, cooled, and filtered. The solvent was removed using a water jet vacuum pump, and the residue was recrystallized from *n*-heptane. The yields and physicochemical constants of the ketones are consistent with those published in the literature.[7,11] The data for previously unknown methylated ketones **6b** and **7b** are given in Tables 2 and 5.

4-(Diphenylphosphoryl)butan-2-one (8a).[12] A solution of freshly distilled AcOH (0.66 g, 11 mmol) in benzene (10 mL) was added with stirring to a solution of freshly distilled Ph_2PCl (2.20 g, 10 mmol) and methyl vinyl ketone (0.77 g, 11 mmol) in benzene (10 mL). The reaction mixture was kept at 20 °C in the dark for 42 h. Then the solvent was removed using a water jet vacuum pump, and the residue was recrystallized from ethyl acetate. The product was obtained as a crystalline compound (*cf.* lit. data[12]: oil).

4-Methyl-4-(diphenylphosphoryl)pentan-2-one (8b). The experiment was carried out according to a procedure described for the analogous reaction of Et_2PCl.[13] Mesityl oxide (1.53 g, 15.6 mmol) was added to Ph_2PCl (3.40 g, 15.4 mmol) at 20 °C. The reaction mixture was kept at 20 °C for 24 h. The solidified substance was decomposed with methanol (4 mL). The solvent was removed using a water jet vacuum pump, and the residue was extracted with boiling hexane. The cooling of the extract afforded a colorless oil that crystallized upon storage. The recrystallization from hexane did not lead to an increase in the melting point.

8-Diphenylphosphoryl-8-methyl-7,8-dihydro-6*H*-cyclopenta[*b*][1,8]naphthyridine (4b)[7] and **9-diphenylphosphoryl-9-methyl-6,7,8,9-tetrahydrobenzo[*b*][1,8]naphthyridine (5b) (general procedure).** A solution of the corresponding ketone (**2b** or **3b**, 5 mmol) and aldehyde **1** (5 mmol) in ethanol (5 mL) was stirred at 20 °C for 6 h in the presence of 50% aqueous NaOH (1.2 equiv.). The solvent was removed, and the residue was dissolved in chloroform (20 mL), washed with water (2×15 mL), and dried over K_2CO_3. Chloroform was distilled off, and the residue was triturated to a powder with diethyl ether and recrystallized from ethyl acetate.

2-[2-(Diphenylphosphoryl)ethyl]-1,8-naphthyridine (9a) and **2-[2-(diphenylphosphoryl)-2-methylpropyl]-1,8-naphthyridine (9b) (general procedure).** A solution of the corresponding ketone (**8a** or **8b**, 5 mmol), aldehyde **1** (5 mmol), pyrrolidine (0.45 mL, 5.6 mmol), and concentrated H_2SO_4 (one drop) in ethanol

(5 mL) was kept at 20 °C for 12 h. The solvent was removed using a water jet vacuum pump, and the residue was recrystallized from ethyl acetate.

X-ray diffraction study. Transparent crystals of tetrahydrate of naphthyridine dimer **9b** suitable for X-ray diffraction were grown by isothermal evaporation of a solution of compound **9b** in a 1 : 1 AcOEt—Bu^{t}OMe mixture at room temperature. Colorless plate-like crystals of **9b** are monoclinic, $C_{24}H_{27}N_2O_3P$ (M = 422.45), at 120(2) K: a = 13.5206(14) Å, b = 10.4963(11) Å, c = 16.0308(16) Å, β = 107.689(2)°, V = 2167.5(4) Å^3, space group $P2_1/c$, Z = 4, d_{calc} = 1.295 g cm^{-3}. A total of 18611 reflections were collected on a Bruker Smart 1000 diffractometer at 120 K (Mo-Kα radiation, $2\theta_{max}$ = 52.00°) from a single crystal of dimensions 0.18×0.12×0.04 mm. After merging of equivalent reflections, 4259 independent reflections were obtained (R_{int} = 0.1164), and these reflections were used for the structure solution and refinement. The structure was solved by direct methods. All nonhydrogen atoms were located in difference electron density maps and refined anisotropically based on F^2_{hkl}. All hydrogen atoms were found in difference electron density maps and refined isotropically using a riding model. All calculations were carried out with the use of the SHELXTL ver. 5.10 program package.[23] The final R factors were as follows: R_1 = 0.0459 (based on F_{hkl} for 2681 reflections with $I > 2\sigma(I)$), wR_2 = 0.1150 (based on F^2_{hkl} for all 4259 reflections), GOOF 1.007. The completeness of the data set was 99.9%, the number of parameters in the refinement was 271, and the maximum and minimum residual peaks were 0.409 and −0.346 e Å^{-3}, respectively.

The complete tables of the atomic coordinates, bond lengths, and bond angles were deposited with the Cambridge Structural Database.

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