NMR Spectra of Dimethyl 1-Acetyl-1,2-dihydro-2-quinolyl-phosphonate and Related Compounds

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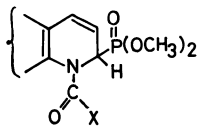
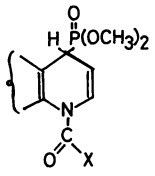
(Received February 20, 1986)

Synopsis. ^{1}H, ^{13}C, and ^{31}P NMR spectra of the products from the Reissert type reactions using acyl halides and trimethyl phosphite were measured and correlated with their structures. ^{31}P Chemical shift of dimethoxyphosphinyl group and ^{13}C chemical shift of the α-carbon atom, as well as $^{1}J_{CP}$ and $^{2}J_{PH}$, can be criteria to differentiate the 1,2- and the 1,4-adducts from each other. Thus, there NMR parameters can be a clue to elucidate the regioselectivity of the reactions.

Pyridine and similar heterocycles containing six-membered azaaromatic ring were shown to react with acyl halides and trimethyl phosphite to give the corresponding 1-acyl-1,2-dihydro-1-azaaromatic phosphonates by Akiba and co-workers.[1] In some instances, the formation of 1,4-adducts was also reported.[2,3] In relation to our recent studies[4] on the Reissert type reactions of some azaheterocycles, some diazanaphthalenes and mono- and diazaphenanthrenes were allowed to react with similar reagents and the structures of the products were elucidated by means of ^{1}H, ^{13}C, and ^{31}P NMR spectroscopy.



1,2-Adduct



1,4-Adduct

Results and Discussion

1-Azaphenanthrene (**1**), 1,5-diazaphenanthrene (**2**), and 1,8-diazanaphthalene (**3**) were allowed to react with trimethyl phosphite in the presence of several acyl and sulfonyl chlorides. The structures of the products were determined by NMR spectroscopy in view of examining the regioselectivity (1,2- vs. 1,4-addition) of the reactions. In order to have unambiguous knowledge on the NMR spectral characteristics of the 1,2- and the 1,4- adducts, the adducts were also prepared from phthalazine (**4**), 9-azaphenanthrene (**5**), and acridine (**6**). The adducts thus obtained were used as the reference compounds of known regioselectivity. Only the 1,2-adducts are expected to be formed in the cases of (**4**) and (**5**). In contrast, acridine (**6**) should give the 1,4-adduct.

The ^{1}H, ^{13}C, and ^{31}P chemical shifts, as well as $^{1}J_{CP}$ and $^{2}J_{PH}$ spin-spin coupling constants, of these *N*-acyl-dihydroazaaromatic phosphonates are given in Table 1. The structural feature of the adducts is reflected in the NMR spectral parameters of the phosphonate parts of the molecules, i.e. ^{31}P chemical shift of dimethoxyphosphinyl group, ^{13}C chemical shift of the carbon atom directly bonded to the phosphorus atom (named α-carbon atom, hereafter), ^{1}H chemical shift of the proton on the α-carbon atom, one bond ^{13}C–^{31}P coupling constant, and two bond ^{1}H–^{31}P coupling constant.

The Chemical Shifts. In the 1,2-adducts which have the *N*-acylated nitrogen atom on the α-carbon atom, ^{31}P and α-^{13}C chemical shifts fall in the ranges of 19 to 21 ppm and 48 to 54 ppm, respectively. The ^{13}C chemical shift differences among the 1,2-adducts are relatively small. The ^{13}C chemical shift is affected far more significantly by the substituent on the nitrogen atom than the skeletal structure of the heterocycle. When the substituent on the nitrogen atom (COX) was changed from acetyl ($COCH_3$) to benzoyl (COC_6H_5), a low field shift of 1 to 1.5 ppm is generally induced.[5] Considerably larger low field shift was observed when the substituent COX was ethoxycarbonyl ($COOC_2H_5$) or diphenylcarbamoyl ($CON(C_6H_5)_2$).

Chemical shifts of the hydrogen atom on the α-carbon atom (named α-hydrogen atom, hereafter) are renging between 5.6 and 6.5 ppm in the series of the 1,2-adducts. Small but definite deviation dependent on the structure of the parent heterocyle was observed among them. Thus the ^{1}H chemical shifts of the 1,2-adducts of 1,8-diazanaphthalene (**3**) appear at a little higher fields, while those of 9-azaphenanthrene (**5**) at lower fields, than the average. As a whole, the chemical shift of α-hydrogen is more sensitive to the skeletal structure of the heterocycle than that of α-carbon. When the substituent COX was changed from acetyl to benzoyl, the ^{1}H chemical shift generally moves towards a high field in contrast to the low field shift of the ^{13}C signal of α-carbon caused by the same structural modification.[5]

The corresponding ^{31}P ^{13}C, and ^{1}H chemical shifts of the 1,4-adducts fall in the range of 23—24 ppm, 34—45 ppm, and 4.4—4.9 ppm, respectively. The ranges of the chemical shifts overlap to each other in neither cases. Therefore, the chemical shift values can be good criteria to differentiate the 1,2- and the 1,4-adducts.

The Spin-Spin Coupling Constant. The ^{1}H-decoupled spectrum of α-carbon atom is split into a doublet by the coupling with the phosphorus nucleus from which $^{1}J_{CP}$ was determined. The $^{1}J_{CP}$ values of the 1,2-adducts fall within a relatively narrow range between 149 and 154 Hz, again the difference among the 1,2-adducts not being large.

Table 1. NMR Spectra of Fused Dimethyl 1-Acyl-1,2-dihydro-2-pyridylphosphonates and -1,4-Dihydro-4-pyridylphosphonates
(solvent: $CDCl_3$, concentration ca. 0.3 mol/l)

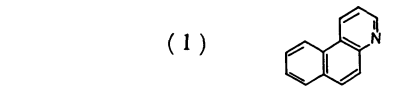
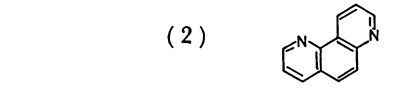
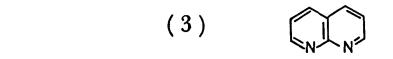
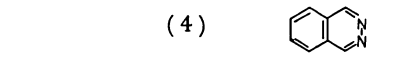
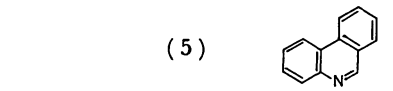
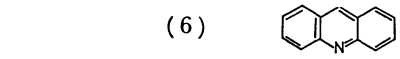
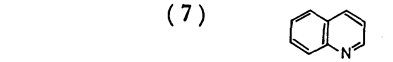
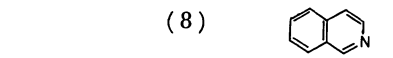
Starting compound		Acyl	Orientation of addition	Chemical shift/ppm						Coupling constant/Hz		
				^{31}P	$^{13}C(\alpha)$	$^{13}C(OCH)$	$^{13}C(C=O)$	$^{1}H(\alpha)$	$^{1}H(OCH)$	$^{1}J_{CP}$	$^{2}J_{HP}$	$^{3}J_{POCH}$
(1)		CH_3CO	1,2	20.43	48.46	53.34	170.30	6.3	3.49	153.8	—	10.7
		C_2H_5CO	1,2	20.63	48.71	53.34	174.17	6.3	3.48	153.8	—	10.7
		C_6H_5CO	1,2	20.63	50.14	53.42	169.83	6.01	3.53	151.4	20.7	10.8
		C_2H_5OCO	1,2	20.39	50.98	53.47	154.10	5.75	3.48	152.6	22.0	13.2
		CH_3CO	1,4	23.79	35.31	53.57	168.37	4.74	3.57	146.6	24.2	10.7
		C_2H_5CO	1,4	23.73	35.33	53.70	171.82	4.76	3.57	144.0	24.2	10.7
		C_6H_5CO	1,4	24.23	35.77	53.81	168.04	4.83	3.68	146.5	24.4	10.7
(2)		CH_3CO	1,2	20.16	48.93	53.21	169.95	6.35	3.53	148.9	19.8	10.7
		C_6H_5CO	1,2	20.33	50.68	53.69	169.46	6.03	3.58	151.4	21.0	10.6
		C_6H_5CO	1,4	25.41	33.80	53.65	168.26	5.59	3.75	141.6	21.5	10.7
(3)		CH_3CO	1,2	19.76	49.08	53.42	170.54	6.06	3.69	151.4	17.3	10.8
		C_6H_5CO	1,2	19.45	51.09	53.69	168.37	5.91	3.64	148.9	20.5	10.7
		CH_3SO_2	1,2	19.42	52.50	53.82	—	5.73	3.64	153.8	19.0	10.6
(4)		CH_3CO	1,2	19.59	48.16	53.53	171.52	6.35	3.65	153.8	16.1	10.7
		C_6H_5CO	1,2	19.65	49.19	53.66	169.78	6.52	3.69	151.4	16.3	10.8
		$(Ph)_2NCO$	1,2	20.39	50.71	53.12	156.46	6.19	3.69	151.4	15.3	10.8
		CH_3SO_2	1,2	19.08	51.41	53.63	—	5.85	3.67	153.8	12.4	10.6
		$C_6H_5SO_2$	1,2	18.04	51.74	53.79	—	5.98	3.65	158.7	15.6	10.7
(5)		CH_3CO	1,2	21.24	51.03	52.75	168.92	6.57	3.43	151.4	20.3	10.4
		C_6H_5CO	1,2	21.14	52.82	52.82	167.94	6.47	3.46	148.9	19.7	10.7
		C_2H_5OCO	1,2	21.20	53.58	52.50	153.10	6.12	3.37	153.8	20.3	10.7
(6)		CH_3CO	1,4	23.36	45.13	53.74	169.57	4.41	3.56	139.2	25.9	10.7
(7)		CH_3CO	1,2	20.36	48.43	53.26	169.89	6.13	3.56	151.4	—	10.6
		C_6H_5CO	1,2	20.43	50.44	53.42	169.35	5.94	3.61	148.9	20.3	10.7
(8)		CH_3CO	1,2	21.27	50.93	53.39	168.16	6.29	3.60	151.4	17.6	10.6
		C_6H_5CO	1,2	21.44	51.97	53.22	168.28	6.39	3.63	148.9	20.7	10.4
		$(Ph)_2NCO$	1,2	21.88	54.55	53.74	156.56	5.89	3.59	148.9	16.4	9.0

Table 2. Summary of the Characteristic Differences in NMR Spectra of 1,2- and 1,4-Adducts

NMR	1,2-Adduct	1,4-Adduct
^{31}P	19—21 ppm	23—24 ppm
$^{13}C(\alpha)$	48—54 ppm	35—45 ppm
$^{1}H(\alpha)$	5.9—6.5 ppm	4.4—4.9 ppm
$^{1}J_{CP}$	148—154 Hz	139—146 Hz
$^{2}J_{HP}$	16—21 Hz	21—26 Hz

$^{1}J_{CP}$ becomes 2—3 Hz smaller when *N*-acyl substituent is changed from acetyl to benzoyl. The $^{2}J_{PH}$ of the 1,2-adducts are ranging from 15 to 21 Hz and are considerably smaller than those of the 1,4-adducts. Those of phthalazine (**4**) adducts is around 16 Hz, being considerably smaller than the average. The $^{1}J_{CP}$'s and $^{2}J_{PH}$'s of the 1,4-adducts are 139—146 Hz and 21—26 Hz, respectively. These ranges do not overlap with the corresponding ranges for the 1,2-adducts. Therefore, the coupling constants will provide an additional clue to characterize the isomeric 1,2- and the 1,4-adducts by NMR spectroscopy.

Other NMR Parameters. The chemical shifts and the spin-spin coupling constants of other ^{1}H and ^{13}C nuclei are rather insensitive to the mode of addition. The ^{1}H and ^{13}C chemical shifts of dimethoxyphosphinyl group are almost unaffected by the change of *N*-acyl group and by the modification of ring structure, ranging 3.3 to 3.8 ppm (two lines) and 52.8 to 53.8 ppm (two lines usually), respectively. The $^{3}J_{POCH}$ values are rather insensitive to the structure of the adducts and not versatile to the discrimination of the two isomeric adducts. As expected, the carbonyl chemical shifts of the acyl groups are determined by the nature of acyl groups, i.e. 168 to 171 ppm for acetyl, 168 to 170 for benzoyl, around 157 ppm for diphenylcarbamoyl, and around 153 ppm for ethoxycarbonyl.

Experimental

Preparation of Materials. Fused 1-acyl-1,2-dihydro-2-pyridylphosphonates from **1—5** were newly prepared by the present authors by the following procedures: To an ice-cooled solution of the azaaromatic compound (9.6 mmol) dissolved in 40 ml of acetonitrile, slightly excess (10.6 mmol) of acyl chloride was added dropwise under stirring, and the whole was kept stirring for 20 min after the completion of addition. Then trimetyl phosphite (10.6 mmol) and sodium iodide (14 mmol) were added successively. The mixture was warmed to 50 °C and left standing for additional 30 min. The solvent was distilled off, and 30 ml of 5% aqueous Na_2CO_3 solution was added to the residue. The crude *N*-acyldihydroazaaromatic phosphonate(s) obtained by extracting the aqueous solution with dichloromethane. In cases when isomeric (1,2- and 1,4-) adducts were formed, they were separated by column chromatography on silica gel.

Measurement of NMR Spectra. All NMR spectra were measured on a JEOL JNM FX-90Q spectrometer in chloroform-*d* solutions at room temperature (26 °C in the probe) unless otherwise remarked. ^{1}H and ^{13}C chemical shifts were determined in reference to the signal of TMS added in the solution, and ^{31}P chemical shifts in reference to the external phosphoric acid standard.

References

1) K. Akiba, Y. Negishi, and N. Inamoto, *Synthesis*, **1979**, 55.

2) K. Akiba, H. Matsuoka, and M. Wada, *Tetrahedron Lett.*, **22**, 4093 (1981).

3) K. Akiba, T. Kasai, and M. Wada, *Tetrahedron Lett.*, **23**, 1709 (1982).

4) a) I. Takeuchi, Y. Shibata, and Y. Hamada, *Yakugaku Zasshi*, **104**, 1133 (1984); b) I. Takeuchi, Y. Shibata, and Y. Hamada, 9th International Congress on Heterocyclic Chemistry, Tokyo, August 1983, Abstr., p. 101.

5) In the case of the 1,2-adducts derived from isoquinoline, both the ^{1}H and the ^{13}C chemical shifts of α-carbon and the hydrogen attached on it tend to move towards low fields by the change from acetyl to benzoyl in *N*-acyl group. Thus, the quinoline- and isoquinoline-derived adducts were shown to behave apparently different from each other towards the same structural modification, and their behaviors could be explained by the difference in preferred conformation between these two series of adducts. The *N*-benzoyl-1,2-dihydroquinoline-2-phosphonateds are expected to take a favorable conformation in which the aromatic ring of the benzoyl group orient itself towards the α-carbon atom (antiperiplanar about the C(carbonyl)–N bond) to avoid the steric hindrance between the phenyl and the peri-hydrogen atom. On the contrary, a synperiplanar conformation might be favorable in the adducts of isoquinoline-like heterocycles. The fact that the C(3) and C(4) chemical shifts of the latter adducts shift towards high fields by the same change in the *N*-acyl substituent supports the preference of synperiplanar conformation.