Synthesis and Nuclear Magnetic Resonance Spectra of 2*H*-Pyrido[1,2-*a*]pyrimidin-2-ones

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Reaction of ethyl phenylpropiolate with several 2-aminopyridines afforded the corresponding 2*H*-pyrido[1,2-*a*]pyrimidin-2-ones in good yields. Analysis of the nmr spectra of these compounds and their hydrobromides were based on comparing their spectra with their 3-deuterated analogues. It was found that in these 2-oxo compounds, the proton at position-7 is shielded and absorbs together with the olefinic proton at position-3 in the region of δ 6.35-6.70 ppm. The latter proton could be used for differentiating these compounds from the corresponding 4-oxo isomers which have already been identified by the deshielded proton at position-6 near δ 9.0 ppm. The ir and nmr spectral data for all these compounds are tabulated and discussed.

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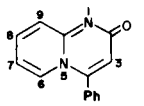
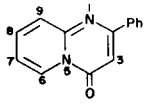
Although a number of methods have been reported for the preparation of 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones (2-7), only limited work has been done regarding the synthesis of 2*H*-pyrido[1,2-*a*]pyrimidin-2-ones. It has been reported that 2*H*-pyrido[1,2-*a*]pyrimidin-2-one was obtained by the reaction of 2-aminopyridine with α-bromoacrylic acid (8). More recently 2*H*-pyrido[1,2-*a*]pyrimidin-2-one and its methyl substituted analogues were obtained together with mono and diadducts formed by the reaction of 2-aminopyridines and ethyl propiolate (9).

Seide (10) claimed that 4-phenyl-2*H*-pyrido[1,2-*a*]pyrimidin-2-one (Ia), m.p. 151°, was isolated from the reaction of 2-aminopyridine with ethyl benzoylacetate. Later, Adams and Pachter (8) have proven on the basis of ultraviolet spectra that the compound obtained by Seide was in fact 2-phenyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (IV). Further evidence for the formation of compound IV was based on the identification of the intermediate β-ketoamide obtained from the above reaction (4). Similarly, the structures of other substituted 2*H*-pyrido[1,2-*a*]-pyrimidin-2-ones, which were prepared from 2-aminopyridines and ketene, and were incorrectly assigned to be the 2-oxo compound (11), were later revised by Yale and coworkers, and identified to be the 4-oxo analogues on the basis of X-ray crystallography and nmr study (5). Analysis of the nmr spectra were carried out using Eu(fod)$_3$ as a shift reagent. The deshielded proton at position-6 of a number fo these 4-oxo compounds which absorbed near δ 9.0 ppm was considered to be a characteristic absorption fo these 4-oxo compounds and was attributed to the anisotropy of the carbonyl group (5,6). On the other hand, no detailed nmr assignments were reported for the 2-oxo compounds except for the work done by Wilson and Bottomely (12) where the protons at position-3 and 4 were assigned.



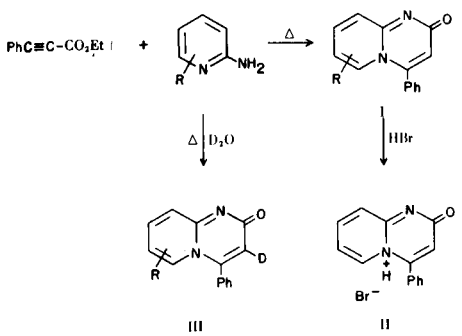
Ia



IV

As an extension of our recent work on the reactivity of acetylenic esters toward compounds having active methylene groups (13), in this paper we report the condensation of ethyl phenylpropiolate with a series of substituted

Scheme I



a, R = H
b, R = 6-CH$_3$
c, R = 7-CH$_3$
d, R = 8-CH$_3$
e, R = 9-CH$_3$
f, R = 6,8-CH$_3$
g, R = 7-Cl
h, R = 7-Br
i, R = 6-NH$_2$
j, R = 7-NO$_2$

2-aminopyridines (Scheme I) together with the analysis of the nmr spectra of the resulting 2*H*-pyrido[1,2-*a*]pyrimidin-2-ones (I). The ir spectra of compounds I showed a common pattern of absorptions in the solid phase and in the following regions: 1670-1650 (m), 1650-1630 (s-vs), 1620-1600 (s) and 1483-1470 (s) cm^{-1} (Table I). In chloroform solution the ir spectra showed better resolution of the higher frequency band. Generally, the nmr spectra of compounds I showed a sharp singlet between δ 6.48-6.35 ppm attributed to the ethylenic proton at position-3 (Table II). The above signal disappeared in the spectra of the corresponding 3-deuterated compounds (III). Moreover, the nmr spectra of compounds I showed an absorption of another proton in the above region. The pattern of splitting of the latter proton was clearly observed in the spectra of the deuterated compounds (III). Similar observations were found by running the spectra of compounds I in deuteriodimethylsulfoxide instead of deuteriochloroform in which the above proton was deshielded along with a slight shielding to the proton at

Table I

Ir Spectral Data of 2*H*-Pyrido[1,2-*a*]pyrimidin-2-ones and their Hydrobromides

Compound Number	ν max/cm^{-1} (a)					
Ia	1660 (m),	1648 (vs),	1620 (sh),	1610 (s),	1480 (vs),	1380 (m)
Ib	1650 (sh),	1635 (vs),	1617 (vs),	1460 (vs),	1380 (s)	
Ic	1650 (m),	1630 (vs),	1597 (vs),	1540 (vs),	1480 (vs),	1370 (s)
Id	1670 (sh),	1650 (s),	1620 (s),	1470 (vs),	1380 (vs)	
Ie	1660 (m),	1640 (s),	1615 (s),	1575 (s)	1475 (vs)	
If	1670 (m),	1635 (vs),	1580 (m),	1540 (m),	1465 (vs),	1370 (s)
Ig	1649 (vs),	1635 (s),	1610 (vs),	1538 (m),	1475 (vs),	1360 (m)
Ih	1643 (vs),	1635 (vs),	1605 (s),	1530 (m),	1470 (vs),	1357 (m)
IIa	2700 (br),	1710 (vs),	1650 (s),	1515 (s),	1460 (s),	1370 (s)
IIb	2700 (br),	1710 (vs),	1640 (s),	1510 (s),	1460 (s),	1370 (s)
IId	2700 (br),	1695 (vs),	1650 (s),	1450 (s),	1380 (s),	1350 (s)
IIe	2700 (br),	1700 (vs),	1630 (s),	1450 (s),	1370 (s),	1350 (s)
IIf	2700 (br),	1700 (vs),	1640 (s),	1450 (s),	1440 (s),	1375 (s)

(a) Nujol spectrum.

Table II

Nmr Spectral Data δ (PPm) of 2*H*-Pyrido[1,2-*a*]pyrimidin-2-ones (a)

Compound Number	C_3-H (b)	C_7-H	Other Protons
Ia (c)	6.48 (s)	6.7 (dt, J = 2 and 6 Hz)	7.3-7.8 (m, 8H)
Ib (d)	6.4 (s)	6.55 (d, J = 6.5 Hz)	1.87 (s, 3H, C_6-CH_3) 7.17 [(J = 6 Hz), 1H, C_9-H] 7.3-7.8 (m, 6H)
Ic	6.4 (s)		2.18 (s, 3H, C_7-CH_3) 7.3-7.7 (m, 8H)
Id	6.4 (s)	6.5 [dd (J = 2 and 6.5 Hz)]	2.37 (s, 3H, C_8-CH_3) 7.07 (s, 1H, C_9-H) 7.3-7.7 (m, 7H)
Ie (e)	6.43 (s)	6.6 (t, J = 6 Hz)	2.5 (s, 3H, C_9-CH_3) 7.3-7.7 (m, 7H)
If	6.35 (s)	6.36 (s)	1.85 (s, 3H, C_6-CH_3) 2.34 (s, 3H, C_8-CH_3) 7.0 (s, 1H, C_9-H) 7.2-7.6 (m, 5H)
Ig	6.48 (s)		7.35-7.8 (m, 8H)
Ih	6.45 (s)		7.3-7.9 (m, 8H)

(a) In deuteriochloroform. (b) The assignment of C_3-H was based on running the nmr spectra of all the corresponding 3-deuterated compounds (III). (c) In deuteriodimethylsulfoxide the nmr values are: 6.3 (s, 1H, C_3-H), 7.33 [dd (J = 2 and 8 Hz), 1H, C_6-H], 6.92 [dt (J = 2 and 6 Hz), 1H, C_7-H], 7.88 [dd (J = 2 and 6 Hz), 1H, C_9-H] and 7.5-7.7 (m, 6H, C_6H_5 and C_8-H). (d) In deuteriodimethylsulfoxide the nmr values are: 6.28 (s, 1H, C_3-H), 1.8 (s, C_6-CH_3), 6.7 [d (J = 6 Hz), 1H, C_7-H], 7.12 [d (J = 8 Hz), 1H, C_9-H], 7.5-7.8 (m, 6H, C_6H_5 and C_8-H). (e) The position of C_6-H in the 4-oxo compound is 9.0 ppm (6).

position-3 (see footnotes c,d, Table II). The above absorption was assigned to the proton at position-7 based on the analysis of different 7-substituted 2*H*-pyrido[1,2-*a*]pyrimidin-2-ones mentioned below. The nmr spectra of the 7-methyl (Ic), chloro (Ig), and bromo (Ih) compounds showed only a sharp signal between δ 6.48-6.4 ppm due to the proton at position-3. Furthermore, while the proton at position-9 absorbed as a sharp singlet at δ 7.07 and 7.0 ppm in the 8-methyl (Id) and 6,8-dimethyl (If) compounds, respectively, it absorbed as a doublet at δ 7.17 ppm in the 6-methyl compound (Ib). The absorption of the proton at position-8 and the aromatic protons

Table III

Nmr Spectral Data δ (ppm) of the Hydrobromides of 2*H*-Pyrido[1,2-*a*]pyrimidin-2-ones (a)

Compound Number	C_3-H	C_6-H	C_7-H	C_8-H	C_9-H	C_6H_5
IIa	6.96 (s)	7.83	7.5 (dt, J = 2 and 7 Hz)	8.4 (dt, J = 2 and 7 Hz)	8.24 (d, J = 7 Hz)	7.65 (s)
IIb	6.96 (s)	1.97 (s, 3H, C_6-CH_3)	7.43 (d, J = 6 Hz)	8.4 (dd, J = 7 Hz)	7.72 (dd, J = 2 and 8 Hz)	7.6 (s)
IId	6.83 (s)	8.09 (d, J = 6.4 Hz)	7.38 (dd, J = 2 and 7 Hz)	2.6 (s, 3H, C_8-CH_3)	7.6 (s)	7.65 (s)
IIe	7.05 (s)	8.2 (b)	7.4 (t, J = 7 Hz)	8.2 (b)	2.6 (s, 3H, C_9-CH_3)	7.7 (s)
IIf	6.9 (s)	1.94 (s, 3H, C_6-CH_3)	7.4 (s)	2.56 (s, 3H, C_8-CH_3)	7.5 (s)	7.6 (s)

(a) In deuteriodimethylsulfoxide. (b) C_6-H and C_8-H are overlaped and appear as multiplets.

Table IV

2*H*-Pyrido[1,2-*a*]pyrimidin-2-ones

Compound Number	Reaction Time (hours)	Solvent	Yield % (a)	M.p. °C	Formula		Analysis % C	H	N
Ia	15	Ethanol	92.2 (b)	226-227 (d,f)	$C_{14}H_{10}N_2O$	Calcd.	75.67	4.5	12.6
						Found	75.60	4.57	12.57
Ib	1.5		87.8	199-200 (d)	$C_{15}H_{12}N_2O$	Calcd.	76.27	5.08	11.86
						Found	76.22	5.13	11.53
Ic	3	Water	92.3	211-213 (d)	$C_{15}H_{12}N_2O$	Calcd.	76.27	5.08	11.86
						Found	76.76	5.22	11.67
Id	2		76.5	205-206 (e)	$C_{15}H_{12}N_2O$	Calcd.	76.27	5.08	11.86
						Found	76.37	5.16	11.87
Ie	3		88.0 (c)	225-226 (d, g)	$C_{15}H_{12}N_2O$	Calcd.	76.27	5.08	11.86
						Found	76.20	5.21	11.87
If	1.5		83.8	256-258 (e)	$C_{16}H_{14}N_2O$	Calcd.	76.80	5.08	11.20
						Found	76.94	5.69	11.17
Ig	34	Ethanol	75.3	228-230 (d,h)	$C_{14}H_9CLN_2O$	Calcd.	65.50	3.52	10.91
						Found	65.76	3.61	10.92
Ih	42	Ethanol	81.4	264-266 (d)	$C_{14}H_9BrN_2O$	Calcd.	55.81	2.99	9.30
						Found	56.03	3.29	9.17
Ii	30	Butanol	78.9	187-189 (i)	$C_{14}H_{11}N_3O$	Calcd.	70.88	4.64	17.71
						Found	70.87	4.44	17.55
Ij	50	Ethanol	No Reaction						

(a) Based on the crude solid products. (b) The compound was obtained in 24.8% yield by leaving the reactants overnight at room temperature and in the absence of solvent. (c) The compound was obtained in 73.3% yield by refluxing the reactants in ethanol for 20 hours and in 70.4% yield by refluxing in butanol for 15 hours. (d) Recrystallized from acetone. (e) Recrystallized from benzene. (f) The melting point of the 4-oxo isomer (IV) is 151° (10). (g) The melting point of the 4-oxo isomer is 180-182° (6). (h) The melting point of the 4-oxo isomer is 170-171° (15). (i) Recrystallized from ethanol.

appeared as multiplets (Table II). The shielding effect observed for the proton at position-7 is most likely due to the ring current of the phenyl group at position-4. In fact no such shielding effect was reported for the same compound when the phenyl group was replaced by a hydrogen (12) or a methyl group (7).

The hydrobromide salts (II) of the above 2*H*-pyrido-[1,2-*a*]pyrimidin-2-ones (I) were prepared and their ir spectra in the solid phase showed remarkably more intense and higher carbonyl stretching frequency between 1710-

Table V

3-Deuterated 2*H*-Pyrido[1,2-a]pyrimidin-2-ones (III)

Compound Number	Reaction Time (hours)	Yield % (a)	M.p. °C
IIIa	3	86.20	227-228
IIIb	2.5	77.39	200-202
IIIc	3	92.3	212-214
IIId	2	65.42	206-208
IIIe	3	70.83	225-227
IIIf	1.5	82.64	259-261

(a) The unlabelled compounds (I) were obtained in similar yield when water was used as a solvent.

1700 cm^{-1}, beside a medium band at 1650-1630 cm^{-1}, than compounds I (Table I). Such an increase in the carbonyl frequency compared with compounds I confirms that protonation has in fact occured at the N-atom rather than the O-atom which results in an increase of the double bond character of the carbonyl bond (14). The nmr spectra of the hydrobromides (II) (Table III) have the following features as compared with the parent compounds (I): firts, the protons are better separated and therefore more easily assigned; secondly, generally all the protons are deshielded, but the deshielding of the proton at position-7 is greater than the deshielding at position-3, and therefore they no longer overlap; and third, the assignment of the protons, at position-8 and -9 are possible. When the nmr spectra of compounds I were done in deuteriodimethylsulfoxide with a few drops of deuterated hydrogen chloride added, the deuteriochloride salt of I was formed which absorbed similar to the hydrobromide salts (II).

It can be generalized that the 2*H*-pyrido[1,2-*a*]pyrimidin-2-ones prepared above can be distinguished from their corresponding 4-oxo compounds on the basis of nmr spectra, because the proton at position-7 in the 2-oxo compounds (I) is shielded and absorbs together with the proton at position-3 around δ 6.5 ppm, while the proton at position-6 and in the 4-oxo compounds is deshielded and absorbs near δ 9.0 ppm. Furthermore, the 2-oxo compounds (I) have higher melting points than the corresponding 4-oxo compounds. This observation is based on a comparison of the melting points of a number of 2- and 4-oxo compounds reported in the literature as well as a comparison of our 2-oxo compounds with their corresponding 4-oxo analogues reported elsewhere in the literature (4,5,7,9,15) (see footnotes f-h, Table IV).

EXPERIMENTAL

Ir spectra were measured with a Beckman IR 10 instrument and H-nmr spectra were determined with a Varian T-60A instrument (tetramethylsilane as the internal standard). Microanalytical samples were analysed using a 185B HP CHN analyser. Melting points were determined on a Kofler block and are uncorrected. The purity of the reaction products were checked by tlc.

Condensation of Ethyl Phenylpropiolate and 2-Aminopyridines.

General Procedure.

Ethyl phenylpropiolate (0.045 mole) and 2-aminopyridines (0.05 mole) were heated at 130-140° in an oil bath for a certain time and in the absence or presence of an appropriate solvent (20 ml.) (Table IV). The solvent was evaporated *in vacuo* and the residue was triturated with ether, filtered off and the yellow solids obtained were recrystallized from the appropriate solvents to give the 2*H*-pyrido[1,2-*a*]pyrimidin-2-ones (I). Generally it was noticed that purer products with better yields were obtained when the reaction was carried out in the presence of a solvent but at the same time more reaction time was required (Table IV). The recrystallization of the products were followed by tlc on glass plates coated with silica gel using chloroform/ethanol (20/1) as an eluent.

Preparation of 3-Deuterated 2*H*-Pyrido[1,2-*a*]pyrimidin-2-ones (III).

Table VI

Hydrobromides of 2*H*-Pyrido[1,2-*a*]pyrimidin-2-ones (II)

Compound Number	Yield %	M.p. °C	Formula		Analysis % C	H	N
IIa	95	295 dec.	$C_{14}H_{11}BrN_2O$	Calcd.	55.46	3.63	9.24
				Found	55.24	3.45	9.08
IIb (a)	82.08	>350	$C_{15}H_{13}ErN_2O$	Calcd.	56.78	4.10	8.83
				Found	56.68	3.90	8.80
IId	97.01	>350	$C_{15}H_{13}BrN_2O$	Calcd.	56.78	4.10	8.83
				Found	56.60	4.39	8.72
IIe	74.63	>350	$C_{15}H_{13}BrN_2O$	Calcd.	56.78	4.10	8.83
				Found	56.51	3.93	8.69
IIf	75.76	>350	$C_{16}H_{15}BrN_2O$	Calcd.	58.01	4.53	8.46
				Found	57.98	4.43	8.39

(a) The *p*-toluenesulfonic acid salt of IIb was prepared according to the literature (6) in 90% yield, m.p. 193-194°. *Anal.* Calcd. for $C_{22}H_{20}N_2O_3S$: C, 64.71; H, 4.90; N, 6.86. Found: C, 64.25; H, 5.12; N, 6.88.

General Procedure.

Ethyl phenylpropiolate (0.01 mole) and 2-aminopyridines (0.01 mole) with deuterium oxide (2 ml., 99.95% D) as a solvent were heated in an oil bath at 130-140° for a specified time indicated in Table V. Distillation of the water and excess deuterium oxide *in vacuo* followed by recrystallization of the residue from the appropriate solvents afforded pure samples of the 3-deuterated compounds (III) listed in Table V.

Preparation of 2*H*-Pyrido[1,2-*a*]pyrimidin-2-one Hydrobromides (II).

General Procedure.

Dry hydrogen bromide was passed through a chloroform solution of compounds I until no further white solid products were formed. Filtration of the solid material followed by recrystallization from ethanol afforded pure samples of the hydrobromides (II) (Table VI).

The above hydrobromides were similarly obtained as follows: Bromine (0.2 ml.) in chloroform (10 ml.) was added dropwise with stirring to a solution of compounds I (0.2 g.) in chloroform (10 ml.). The solids obtained were filtered and purified as above to give the hydrobromide salts II (Table VI).

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