REACTIONS OF 1-METHYL-DERIVATIVES OF 2-OXO-1,2,3,4-TETRAHYDROPYRIMIDINE WITH PHOSPHORUS PENTACHLORIDE AND PHOSPHORUS OXYCHLORIDE

E. L. Khanina, É. É. Liepin'sh, D. Kh. Mutsenietse, and G. Ya. Dubur

UDC 547.854.3:542.944.4:543.422.25

In the reaction of 4-phenyl- and 4,6-diphenyl-1-methyl-2-oxo-5-ethoxycarbonyl-1,2,3,4-tetrahydropyrimidines with phosphorus pentachloride, oxidation and dealkylation takes place in addition to chlorination and as a result one obtained 4-phenyl- and 4,6-diphenyl-1-methyl-5-ethoxycarbonyl-2-pyrimidones and also 4-phenyl-, (4,6-diphenyl)-5-ethoxycarbonyl-2-chloropyrimidines. 1,6-Dimethyl-2-oxo-4-phenyl-5-ethoxycarbonyl-1,2,3,4-tetrahydropyrimidine in the same reaction gives 1-methyl-2-oxo-4-phenyl-5-ethoxycarbonyl 6-dichloromethyl-1,2,3,4-tetrahydropyrimidine, together with 6-chloromethylene- and 6-dichloromethylene-1-methyl-2-oxo-4-phenyl-5-chloro-5-ethoxycarbonylhexahydropyrimidines.

It is known that the reaction of 1H-derivatives of 2-oxo-3,4-dihydropyrimidines with phosphorus oxychloride proceeds with replacement of an oxo- or tautomeric hydroxy group by chlorine [1]. In the reaction of 1-substituted 2-pyrimidones with a mixture of $POCl_3$ and PCl_5 [2] dealkylation at N_1 first occurs and only then the formation of the 2-chloropyrimidine, the presence of PCl_5 in the chlorinating mixture giving a considerable increase in the yield of the chloro-product.

We have studied the reaction of derivatives of 1-methyl-2-oxo-1,2,3,4-tetrahydropyrimidines Ia-c, differing in the substituent on the $C_{(6)}$ atom, with PCl_5 and $POCl_3$. Reaction takes place under fairly rigorous conditions – on melting with PCl_5 or on boiling in a solution of PCl_5 in phosphorus oxychloride. Under these conditions 1-methyl-2-oxo-4-phenyl-5-ethoxycarbonyl-1,2,3,4-tetrahydro pyrimidine (Ia) and 1-methyl-2-oxo-4,6-diphenyl-5-ethoxycarbonyl-1,2,3,4-tetrahydropyrimidine (Ib) are oxidized and dealkylated, evidence of which is the separation of the oxidation products IIa, b and the 2-chloro-derivatives of pyrimidine IIIa, b. For the example of the 4,6-diphenylpyrimidine Ib it was established that increase in reaction time results in the formation of the 2-chloropyrimidine IIIb exclusively. It was shown also that the presence of the 1-methyl group in the starting material facilitates the formation of the chloro-product. Thus, the yield of 2-chloro-4,6-diphenyl-5-ethoxycarbonylpyrimidine (IIIb) prepared under identical conditions by reaction of phosphorus pentachloride with 1-unsubstituted 2-oxo-4,6-diphenyl-5-ethoxycarbonyl-1,2,3,4-tetrahydropyrimidine or with its 1-methyl derivative amounted to 47 and 70% respectively.

In the reaction of 1,6-dimethyl-2-oxo-4-phenyl-5-ethoxycarbonyl-1,2,3,4-tetrahydropyrimidine (Ic) with PCl_5 in phosphorus oxychloride solution replacement of the 2-oxogroup by chlorine did not occur and the products were 1-methyl-2-oxo-4-phenyl-5-ethoxycarbonyl-6-dichloromethyl-1,2,3,4-tetrahydropyrimidine (V), 1-methyl-2-oxo-4-phenyl-5-chloro-5-ethoxycarbonyl-6-chloromethylenehexahydropyrimidine (VI), and 1-methyl-2-oxo-4-phenyl-5-chloro-5-ethoxycarbonyl-6-dichloromethylenehexahydropyrimidine (VII). It is known [3] that a methyl group at the 6-position of the pyrimidine ring is readily halogenated and the appearance of the 6-dichloroderivative among the products of the reaction is in conformity with this. The formation of the pyrimidine derivatives VI and VII with exocyclic double bonds can be assumed to result from addition of chlorine to the $C_{(5)}=C_{(6)}$ bond of the tetrahydropyrimidine ring of Ic. It follows from the results of [4] that the action of chlorine proceeds as a cis-addition and the halogen at $C_{(6)}$ has a pronounced tendency to split off. It can be supposed that the same spatial addition occurs in the case of compound Ic and as a result the 5,6-dichloro-derivative of the corresponding hexahydropyrimidine is formed; as a result of the absence of hydrogen on the $C_{(5)}$ atom chlorine is split off from the $C_{(6)}$ atom in the

Institute of Organic Synthesis, Academy of Sciences of the Latvian SSR, Riga 226006.
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 668-671, May, 1987. Original article submitted November 18, 1986.

 0009-3122/87/2305-0554$12.50

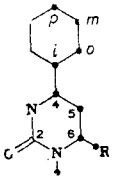
TABLE 1. Characteristics of Pyrimidine Derivatives II, III, and V-VII

Compound	mp, °C	IR spectrum, cm^{-1}	Found, %			Empirical formula	Calculated, %		
			C	H	N		C	H	N
IIb	133—134	1680, 1715	71,4	5,3	8,2	$C_{20}H_{18}N_2O_3$	71,8	5,4	8,4
IIIa	67—68	1715	59,8	5,1	11,2	$C_{13}H_{11}ClN_2O_2$	59,4	4,2	10,7
IIIb	112—113	1730, 1740	66,9	4,6	7,9	$C_{19}H_{15}ClN_2O_2$	67,4	4,5	8,3
V	187—189	1690, 1710, 3220	51,9	4,3	8,6	$C_{15}H_{16}Cl_2N_2O_3$	52,5	4,7	8,2
VI	133—134	1690, 1745, 3205	52,1	4,3	8,6	$C_{15}H_{16}Cl_2N_2O_3$	52,5	4,7	8,2
VII	153—154	1720 mp, 1730, 3400	46,9	4,2	7,6	$C_{15}H_{15}Cl_3N_2O_3$	47,7	4,0	7,4

TABLE 2. Proton NMR Spectra of Compounds IIb, IIIa, b, and V-VII (in DMSO-D_6)

Compound	1-CH_3 (3H, s)	3-NH (1H, d)	4-H (1H, d)	4-C_6H_5 (arom.)	5-$COOC_2H_5$		6-R (s)	$^3J_{3,4}$, Hz
					(2H, q)	(3H, t)		
IIb	3,16	—	—	7,49 s	3,67	0,64	7,49 (arom.)	—
IIIa	—	—	—	7,40 s	4,16	1,08	8,98 (1H)	—
IIIb	—	—	—	7,56 s	4,04	0,91	7,56 (arom.)	—
V	3,42	8,22	5,20	7,18 m	4,11	1,15	8,33 (1H)	4,5
VI	2,93	7,96	4,69	7,16 s	3,67	0,8	6,00 (1H)	4,2
VII	3,18	7,73	4,96	7,24 s	3,82	0,96	—	4,1

TABLE 3. Chemical Shifts in Carbon-13 NMR Spectra of Pyrimidines I, and V-VII



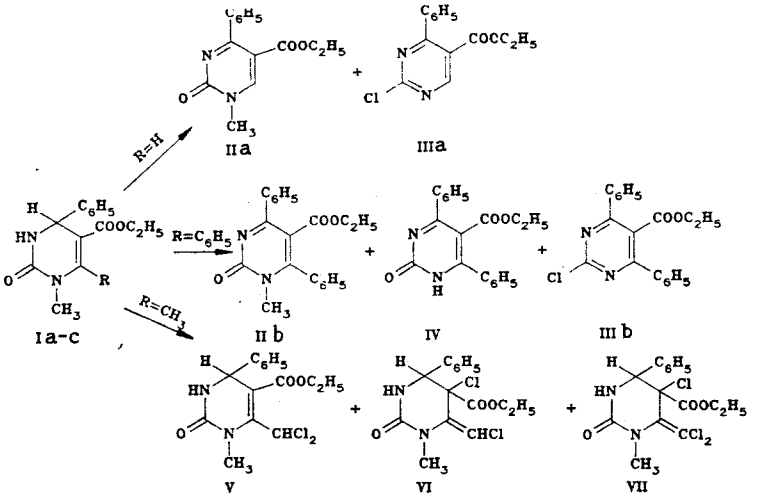
Compound	$C_{(2)}$	$C_{(4)}$	$C_{(5)}$	$C_{(6)}$	6-R	N—CH_2	$C_{C_6H_5}$				$COOC_2H_5$		
							i-	*o*-	*m*-	*p*-	CO	CH_2	CH_3
Ic	153,09	52,46	102,57	150,46	16,04	29,72	144,10	127,28	128,42	126,05	165,61	59,49	14,05
V	153,30	62,66	106,14	142,02	52,20	31,25	144,62	127,98	128,86	125,87	164,29	61,37	13,70
VI	152,45	62,25	66,85	135,98	108,29	36,46	137,36	128,24	128,80	127,96	164,31	63,07	13,43
VII	158,31	64,59	76,02	133,12	112,42	36,85	138,00	129,03	128,49	127,97	164,32	62,65	13,37

*Ic R = CH_3, V R = $CHCl_2$, VI R = CHCl; VII R = CCl_2.

TABLE 4. Long-Range ^1H-^{13}C Spin Coupling Constants (SSCC) in Tetrahydropyrimidine (VI)

Type of SSCC	^3J, Hz	Type of SSCC	^3J, Hz	Type of SSCC	^3J, Hz
$H_{(4)}$—$C_{(4)}$	61	H_{NCH_3}—$C_{(2)}$	2,8	$H_{(4)}$—$C_{(2)}$	3,5
$H_{(6\text{-}R)}$—$C_{(6\text{-}R)}$	135	H_{NCH_3}—$C_{(6)}$	2,4	$H_{(4)}$—5-CO	2,9
$H_{(6\text{-}R)}$—$C_{(6)}$	8,8	$H_{(3)}$—$C_{(5)}$	4,7	$H_{(6\text{-}R)}$—$C_{(5)}$	2,0
$H_{(4)}$—$C_{(5)}$	6,8	$H_{(4)}$—$C_{(6)}$	4,2		

form of HCl with the participation of hydrogen from the 6-CH_2Cl or $CHCl_2$ group which leads to the formation of the exocyclic double bond of compounds VI and VII.



The structure of compounds V-VII was established on the basis of elemental analysis (Table 1), proton NMR spectra (Table 2), and carbon-13 NMR spectra (Table 3), taking into account the long-range ^1H-^{13}C coupling constants. The considerable upfield shift (~40 ppm) of the signal of the $C_{(5)}$ atom in the carbon-13 spectrum of compounds VI and VII points to sp^3-hybridization of this carbon atom and the appearance of a band at 1740 cm^{-1} in the IR spectrum indicates an isolated CO group. The arrangement of hydrogen and chlorine at the double bond in compound VI was established on the basis of the ^1H-^{13}C long-range spin-spin coupling constants (Table 4). For this purpose, the vicinal coupling constant $^3J^{13}C_{(5)}$-$^1H_{(6\text{-CHCl})}$ = 2.0 Hz was measured. So small a value for this constant would seem to indicate a cis-arrangement of $H_{(6\text{-CHCl})}$ and $C_{(5)}$ [5]. We have not determined the stereochemistry of the addition of chlorine at position 5 of the hexahydropyrimidine ring relative to the 4-Ph and 5-COOEt substituents in compounds VI and VII.

EXPERIMENTAL

Infrared spectra were run on a Perkin Elmer 580B instrument in the form of mulls in mineral oil. A WH-90 NMR spectrometer was used for the proton spectra and a WH-360 for the carbon-13 spectra (TMS internal standard). Monitoring of the progress of the reactions was effected by TLC on Silufol UV-254 plates using 9:7:1 chloroform-hexane-acetone.

Reaction of 1-Methyl-2-oxo-4,6-diphenyl-5-ethxoycarbonyl-1,2,3,4-tetrahydropyrimidine (Ib) with Phosphorus Pentachloride. A. A mixture of 3.36 g (10 mmole) pyrimidine Ib, 4 g (20 mmole) PCl_5, and 60 ml $POCl_3$ was heated at bp for 5 h. The solution was cooled and the pyrimidine IIb filtered off, washed with ether and recrystallized from methanol. Yield 1 g (30%). The acidic filtrate was diluted with 300 ml water and extracted with 150 ml chloroform. After drying over anhydrous sodium sulfate and evaporating the solvent, an oil was obtained which while still warm was rubbed with 20 ml hexane until solid matter was formed. This solid was recrystallized from methanol to yield 0.7 g (20%) of the chloroderivative IIIb. On cooling the hexane, 0.5 g (15%) of the pyrimidine IV was obtained; in terms of mp, and IR and NMR spectra this was identical with the known compound [6].

B. The reaction mixture of A was heated at bp for 15 h. It was cooled, decomposed in 200 ml water and the oily deposit recrystallized from methanol. Yield 2.1 g (70%) pyrimidine IVb.

Reaction of 4,6-Diphenyl-2-oxo-5-ethoxycarbonyl-1,2,3,4-tetrahydropyrimidine with PCl_5. A mixture of 1.1 g (~3 mmole) of the tetrahydropyrimidine and 2 g (10 mmole) PCl_5 was heated at bp for 15 h. The reaction mixture was cooled, decomposed in 200 ml ice-cold water and the oily solid filtered off and crystallized from methanol to yield 0.5 g (47%) chloropyrimidine IIIb. The aqueous portion was extracted with 150 ml chloroform, the extract dried and the solvent removed. Crystallization of the residue yielded 0.1 g (10%) pyrimidine IV.

Reaction of 1-Methyl-2-oxo-4-phenyl-5-ethoxycarbonyl-1,2,3,4-tetrahydropyrimidine (Ia) with PCl_5. A mxiture of 2.6 g (10 mmole) pyrimidine Ia and 4 g (20 mmole) PCl_5 was melted at 130°C for 1 h. The reaction mixture was cooled and treated with 30-ml portions of ice water until the washings were neutral. The remaining oil was crystallized from methanol to yield 0.72 g (35%) pyrimidone IIa (obtained previously by another route), mp 121-123°C. The aqueous portions was extracted with chloroform (4 × 50 ml), the extract dried and the solvent removed. The residue was crystallized from hexane to yield 0.27 g (11%) chloro-derivative IIIa.

Reaction of 1,6-Dimethyl-2-oxo-4-phenyl-5-ethoxycarbonyl-1,2,3,4-tetrahydropyrimidine (Ic) with PCl_5. A mixture of 5.58 g (20 mmole) compound Ic, 8 g (40 mmole) PCl_5, and 60 ml $POCl_3$ was heated at bp for 5 h. The reaction mixture was cooled and decomposed in 300 ml water, the water decanted and the oil washed with water until the washings were neutral. It was then crystallized from methanol to yield 1.7 g (25%) pyrimidone V. The combined aqueous solutions were extracted with 4 × 50 ml chloroform, and the extract dried and evaporated along with the filtrate from the crystallization of compound V. The residue was dissolved in 30 ml chloroform and chromatographed in three stages on a preparative plate with silica gel (plate 25 × 25 mm, 40/100 silica gel layer 2-3 mm thickness). The eluent was 5:4:1 chloroform-hexane-ethanol. Two bands absorbing in the UV were collected. From the first band (counting from the front) pyrimidone VI was eluted with acetone and, after evaporating the acetone, recrystallized from benzene to yield 1.5 g (20%). The second band was treated in a similar way and recrystallization from methanol yielded 1.1 g (19%) compound VII.

LITERATURE CITED

1. D. J. Brown, The Pyrimidines, Intersciences, New York (1962), p. 10.
2. G. M. Coppola, G. E. Hardtmann, and B. S. Huegi, J. Heterocycl. Chem., 17, 1479 (1980).
3. G. Zigeuner, H. Hamberger, H. Blaschke, and H. Sterk, Monatsh. Chem., 97, 1408 (1966).
4. G. Zigeuner, H. W. Schramm, A. Fuchsgruter, and A. Wendelin, Monatsh. Chem., 106, 407 (1975).
5. I. L. Marshall, Carbon-Carbon and Carbon-Proton NMR Couplings: Applications to Organic Stereochemistry and Conformational Analysis, Verlag Chemie International, Deerfield Beach, Florida (1983), p. 33.
6. J. P. Freeman, E. J. Duthie, M. J. O'Hare, and J. F. Hansen, J. Org. Chem., 37, 2756 (1972).
7. E. L. Khanina, D. Kh. Mutsenietse, and G. Ya. Dubur, Khim. Geterotsikl. Soedin., No. 4, 529 (1984).