OXIDATION OF SOME DERIVATIVES OF TETRAHYDROPYRIMIDINE-5-CARBOXYLIC ACID WITH SELENIUM DIOXIDE

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UDC 547.854.9'855.3'859:542.943

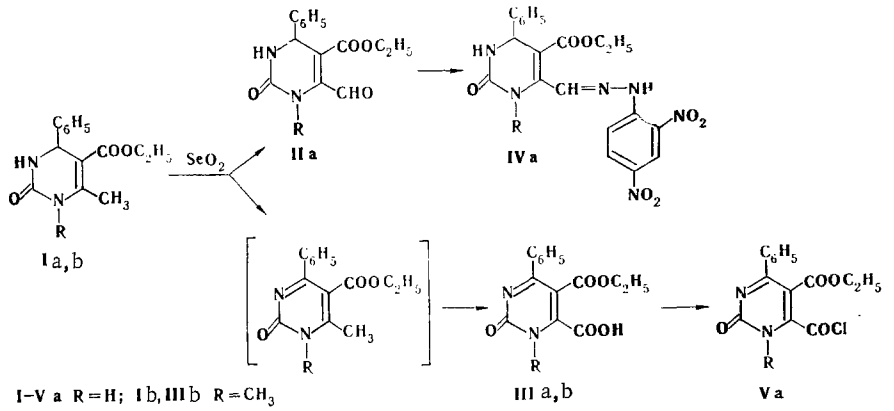
The oxidation of derivatives of 2-oxo-4-phenyl-6-methyl-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid with selenium dioxide was studied. It was observed that the 6-methyl group is oxidized to a hydroxymethyl, formyl, or carboxy group (in the latter case probably after dehydrogenation of the ring). The structure of the final product depends on the degree of substitution of the ring with respect to the nitrogen atom and on the substituent in the 5 position.

Derivatives of 2-oxo-4-phenyl-6-methyl-1,2,3,4-tetrahydropyrimidine-5-carboxylic acids are known as biologically active substances [1].

Interesting reactions of this group of compounds include decarboxylation [2], bromination of the 6-methyl group with subsequent amination [3, 4], and dehydrogenation of the dihydropyrimidine system [5].

Continuing our study of oxidation in this series we carried out the oxidation of some derivatives of the acid indicated above by means of a selective oxidizing agent, viz., selenium dioxide.

The principal product in the oxidation of 2-oxo-4-phenyl-5-ethoxycarbonyl-6-methyl-1,2,3,4-tetrahydropyridimine (Ia) was 2-oxo-4-phenyl-5-ethoxycarbonyl-1,2-dihydropyrimidine-6-carboxylic acid (IIIa); a very small amount of 2-oxo-4-phenyl-5-ethoxycarbonyl-6-formyl-1,2,3,4-tetrahydropyrimidine (IIa) was also formed. The only product in the oxidation of N-1-methyl derivative Ib was the corresponding 1,2-dihydropyrimidine-6-carboxylic acid (IIIb).



As in the case of Ib, in the oxidation of the synthesized 1,6-dimethyl-2-oxo-4-phenyl-5-carbamoyl-1,2,3,4-tetrahydropyrimidine (VI) oxidation of the 6-methyl group evidently proceeds all the way to the acid, and the pyrimidine ring is also dehydrogenated. As a result, we obtained 1-methyl-2-oxo-4-phenyl-5-carbamoyl-1,2-dihydropyrimidine-6-carboxylic acid (VIII), which readily split out water and was converted to the final product, viz., 1-methyl-2,5,7-trioxo-4-phenyl-1,2,5,7-tetrahydropyrrolo[3,4-d]pyrimidine (IX).

Two competitive reactions, viz., oxidation of the methyl group and dehydrogenation of the dihydropyrimidine ring, evidently take place; heteroaromatization of the ring occurs initially and activates the methyl group, which is oxidized more readily to give the acid.

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Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 4, pp. 535-538, April, 1982. Original article submitted February 11, 1981.

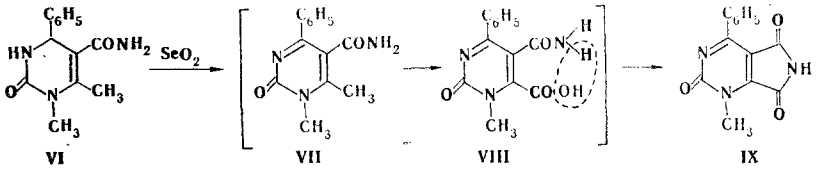
 0009-3122/82/1804- 0412$07.50

TABLE 1. Products of the Oxidation of 2-Oxo-4-phenyl-6-methyl-1,2,3,4-tetrahydropyrimidines

Compound	mp.* °C	UV spectrum, λmax, nm (log ε)	IR spec., cm⁻¹ νCO	IR spec., cm⁻¹ νNH, OH	Found, % C	Found, % H	Found, % N	Empirical formula	Calc. % C	Calc. % H	Calc. % N	Yield, %
IIa	193—195 †	205 (4,4); 218 sh (4,2); 285 (4,1)	1685, 1710	3110‡ 3230	61,8	4,7	10,1	$C_{14}H_{14}N_2O_2$	61,5	4,8	10,3	10
IIIa	121—123	205 (4,6); 222 (4,5); 282 (4,4); 330 (3,3)	1690, 1715, 1730	3230, 3360	57,9	4,9	9,3	$C_{14}H_{12}N_2O_5$	58,3	4,2	9,7	50
IIIb	172—174	205 (4,5); 248 (4,5); 285 (4,2); 330 (3,4)	1700, 1715, 1730	3350	60,2	5,2	9,8	$C_{15}H_{14}N_2O_5$	59,6	4,7	9,3	54
Va	198—200		1720, 1770		54,7	3,7	8,7	$C_{14}H_{11}ClN_2O_4$	54,8	3,6	9,1	35
VI	252—254	205 (4,3); 215 sh (4,3); 270 (3,7)	1665, 1700	3185, 3370	63,6	6,0	16,7	$C_{13}H_{15}N_3O_2$	63,6	6,2	17,1	85
IX	202—203	208 (4,5); 252 (4,2); 298 (4,0)	1660, 1700, 1790	3270	60,6	3,7	16,1	$C_{13}H_9N_3O_3$	61,2	3,6	16,5	36
X	99	205 (4,7); 285 (4,4)	1692, 1712		64,5	6,4	8,9	$C_{17}H_{20}N_2O_4$	64,5	6,7	8,9	50
XIII	144—147	208 (4,5); 285 (4,3)	1690, 1710, 1755		62,4	5,1	9,7	$C_{15}H_{14}N_2O_4$	62,4	4,9	9,8	30

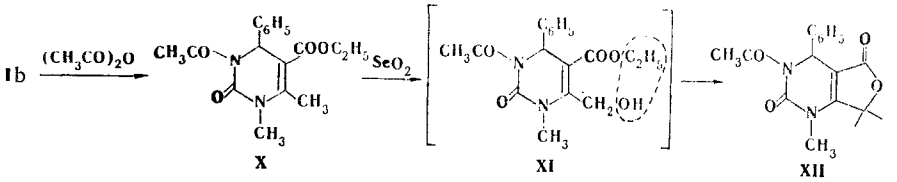
*The compounds were crystallized: IIa, Va, IX, and X from ethanol, IIIa, b from benzene, and VI from isobutyl alcohol.
†The 2,4-dinitrophenylhydrazone (IVa) had mp 311-313°C.
‡IR spectrum of IVa: 1690, 1710, 3220, 3360, and 3410 cm^{-1}.

If heteroaromatization of the ring does not occur for some reason, oxidation proceeds up to the aldehyde (in the case of IIa) or the alcohol.



VI VII VIII IX

This assumption is confirmed in the case of N_3-acylated X. The acetyl group hinders dehydrogenation of the ring, and oxidation yields 1-methyl-2,5-dioxo-3-acetyl-4-phenyl-1,2,3,4,5,7-hexahydrofuro[3,4-d]pyrimidine (XII), the product of cyclization of probable intermediate XI.



X XI XII

The structures of the compounds obtained were proved by chemical and physicochemical methods. Aldehyde IIa gives a qualitative reaction with 2,4-dinitrophenylhydrazine, thereby forming the corresponding hydrazone IVa, while acid IIIa forms stable acid chloride Va.

EXPERIMENTAL

The IR spectra of mineral oil suspensions of the compounds were recorded with an IK-20 spectrometer. The UV spectra of solutions of the compounds in ethanol (c $5 \cdot 10^{-5}$ M) were recorded with a Specord UV-vis spectrophotometer. The PMR spectra of solutions of the compounds in d_6-DMSO were recorded with a Bruker WH 90/DS spectrometer with tetramethylsilane as the internal standard. The course of the reaction and the purity of the products were monitored by means of thin-layer chromatography (TLC) on Silufol UV-254 plates.

2-Oxo-4-phenyl-5-ethoxycarbonyl-6-formyl-1,2,3,4-tetrahydropyrimidine (IIa) and 2-Oxo-4-phenyl-5-ethoxycarbonyl-1,2-dihydropyrimidine-6-carboxylic Acid (IIIa). A 1.1-g (0.01 mole) sample of selenium dioxide was added to a solution of 1.3 g (5 mmole) of Ia in 50 ml of dioxane, and the mixture was refluxed for 5 h. It was then diluted with water, cooled, and filtered. The precipitate was refluxed in benzene, during which the admixed red selenium was

TABLE 2. PMR Spectra (ppm)

Compound	1NH	1NHCH$_3$	3NH	3CH$_3$CO	4H	4C$_6$H$_5$	5-OCH$_2$	5-OCH$_2$—CH$_3$	Other signals
IIa	8,84s	—	7,82d	—	5,21d	7,22s	4,08 q	1,08t	10,15s (6-CHO)
IIIa	8,56s	—	—	—	—	7,43s	4,00 q	0,99t	12,5 s (6-COOH)
IIIb	—	3,17s	—	—	—	7,43s	3,89 q	0,86t	11,6 s (6-COOH)
VI	—	3,00s	7,30d	—	5,11d	7,10s	—	—	6,82 s (5-NH$_2$); 2,19 s (6-CH$_3$)
IX	—	3,69s	—	—	—	7,4—8,0m	—	—	11,69 s (6-NH)
X	—	3,07s	—	2,36s	6,44s	7,16 m	4,07 q	1,12t	2,36 s (6-CH$_3$)
XII	—	3,56s	—	2,44s	6,07s	7,27s	—	—	5,04 d (7-CH$_2$)

converted to black selenium. The benzene-insoluble part of the precipitate was removed by filtration and crystallized from alcohol to give IIa. Compound IIIa precipitated from the benzene. Compound IIIb was similarly obtained.

2-Oxo-4-phenyl-5-ethoxycarbonyl-1,2-dihydropyrimidine-6-carboxylic Acid Chloride (Va). A solution of 0.29 g of IIIa in 20 ml of thionyl chloride was refluxed for 5 min, after which it was evaporated, and Va precipitated.

1,6-Dimethyl-2-oxo-4-phenyl-5-carbamoyl-1,2,3,4-tetrahydropyrimidine (VI). A mixture of 7.4 g (0.01 mole) of methylurea, 8.7 g (0.01 mole) of acetoacetamide, and 10.5 g (0.01 mole) of benzaldehyde was refluxed in 200 ml of absolute ethanol to which 15 drops of HCl had been added for 5 h. It was then cooled, and the precipitate was removed by filtration and crystallized from isobutyl alcohol.

1,6-Dimethyl-2-oxo-3-acetyl-4-phenyl-5-ethoxycarbonyl-1,2,3,4-tetrahydropyrimidine (X). A 2.7-g (0.01 mole) sample of Ib was refluxed in acetic anhydride for 4 h, after which the mixture was evaporated, and the resulting oil was treated with hexane until a solid precipitate formed, during which some of the precipitate dissolved in hexane. The remainder was refluxed in ethanol. Compound X precipitated when the hexane and ethanol solutions were cooled. The precipitates were combined and crystallized from ethanol.

1-Methyl-2,5-dioxo-4-phenyl-1,2,3,4,5,7-hexahydrofuro[3,4-d]pyrimidine (XII). A 0.22-g (2 mmole) sample of selenium dioxide was added to a solution of 0.32 g (1 mmole) of X in dioxane, and the mixture was refluxed for 8 h. The precipitate that formed during the reaction was removed by filtration and crystallized from ethanol.

1-Methyl-2,5,7-trioxo-4-phenyl-1,2,3,7-tetrahydropyrrolo[3,4-d]pyrimidine (IX). A 0.22-g (2 mmole) sample of selenium dioxide was added to a solution of 0.24 g (1 mmole) of VI in dioxane, and the mixture was refluxed for 8 h. The precipitate that formed during the reaction was removed by filtration and crystallized from ethanol.

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