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ACID CATALYSED CONDENSATION OF UREIDO-OXY COMPOUNDS WITH ACETYLACETONE

SYNTHESIS AND PROPERTIES OF N-ALKOXY AND N-HYDROXY DERIVATIVES OF 1,2-DIHYDRO-4,6-DIMETHYL-2-OXOPYRIMIDINE

G. ZVILICHOVSKY

Department of Organic Chemistry, The Hebrew University of Jerusalem, Jerusalem, Israel

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Abstract—The condensation of ethyl ureido-oxyacetate, O-methyl and O-benzylhydroxyurea with acetylacetone in ethanolic hydrogen chloride was found to be a facile reaction which led to 1-carbethoxymethoxy, 1-methoxy and 1-benzyloxy-1,2-dihydro-4,6-dimethyl-2-oxopyrimidine respectively. The N-methoxy (Ib) and N-benzyloxy (Ic) derivatives could be transformed with 27% HBr in acetic acid to 1,2-dihydro-4,6-dimethyl-1-hydroxy-2-oxopyrimidine (III). Hydroxyurea gave with acetylacetone only a small yield of the N-oxide (III). Dissociation constants, IR and UV spectra in various hydrogen ion concentrations were used to elucidate the tautomeric structure of these pyrimidine-N-oxide derivatives.

PYRIMIDINE-N-OXIDES are generally prepared by oxidation of pyrimidines by hydrogen peroxide[1] or by peracids.[2] Klötzer[3] used O-methyl and O-benzylhydroxyurea in the preparation of N-alkoxy derivatives of uracil, aminouracil, barbituric acid, cytosine and thymine by basic catalysis of sodium ethoxide.

In the present work N-alkoxy derivatives of 1,2-dihydro-4,6-dimethyl-2-oxopyrimidine were prepared by a smooth acid catalysed[4] condensation. The condensation products are obtained as their hydrochlorides (I) in about 80–90% yield, from acetylacetone and hydroxyurea derivatives in 6–10% ethanolic hydrogen chloride. Ring closure takes place within a few minutes, since complete crystallization of the products could be obtained after 20 minutes.

When ureido-oxyacetic acid[5] was used, esterification occurred prior to condensation resulting in the ester Ia which is obtained from ethyl ureido-oxyacetate. In the absence of acetylacetone, ureido-oxyacetic acid underwent, under the same conditions, in a few minutes complete esterification.

The fact that these oxopyrimidine derivatives give stable hydrochlorides is consistent with other 2-oxopyrimidines.[6] The hydrochlorides melt with decomposition accompanied by dark colouration; the simple alkoxy derivatives Ib and Ic become dark violet, and the carbethoxymethoxy derivative Ia gets a deep red colour in the range of the melting temperature. By neutralization with sodium bicarbonate the free 1-alkoxy-1,2-dihydro-4,6-dimethyl-2-oxopyrimidines (II) could be obtained.

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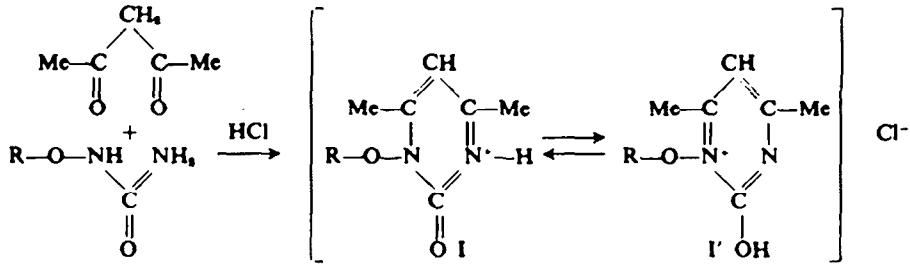
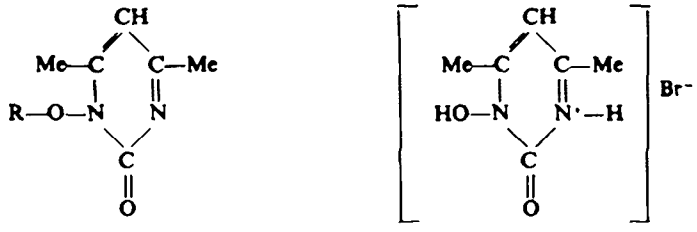
[2] E. Ochiai and H. Yamanakana, *Pharm. Bull., Tokyo* **3**, 175 (1955).
[3] W. Klötzer, *Monatsh. Chem.* **95**, 265 (1964); *Ibid.* **95**, 1729 (1964); *Ibid.* **96**, 169 (1965); W. Klötzer and M. Herberg, *Ibid.* **96**, 1721 (1965).
[4] P. N. Evance, *J. Prakt. Chem.* **48**, 493 (1893).
[5] G. Zvilichovsky, *Tetrahedron* **22**, 1445 (1966).
[6] D. J. Brown, *Nature, Lond.* **165**, 1010 (1950).

Hydrogenation of 1-carbethoxymethoxy-1,2-dihydro-4,6-dimethyl-2-oxopyrimidine hydrochloride (Ia) for a short period in the presence of Pd–C, resulted in reduction to 4,6-dimethyl-2-hydroxypyrimidine hydrochloride; longer periods caused further reduction of the ring system.





II III

a, R = CH_2CO_2Et; b, R = Me; c, R = CH_2Ph

N-Methoxy and N-benzyloxy pyrimidine derivatives Ib and Ic could be transformed to 1,2-dihydro-4,6-dimethyl-1-hydroxy-2-oxopyrimidine hydrobromide (III) upon heating with 27% HBr in acetic acid.[3] This product which may be regarded as either a pyrimidine-N-oxide derivative or as a cyclic hydroxamic acid, gives pink colour with $FeCl_3$. The N-carbethoxymethoxy pyrimidine derivative Ia yielded with 27% HBr in acetic acid under the same conditions 1-carboxymethoxy-1,2-dihydro-4,6-dimethyl-2-oxopyrimidine hydrobromide (IV). The hydrobromide (IV) was prepared alternatively by the condensation of ureidooxyacetic acid with acetylacetone in 13% HBr in acetic acid, but in a poor yield, The N-methoxy group in IIb could be estimated quantitatively by Zeisel method.

Hydroxyurea gave with acetylacetone in ethanolic hydrogen chloride only about 15% yield of 1,2-dihydro-4,6-dimethyl-1-hydroxy-2-oxopyrimidine hydrochloride. The greater part of the hydroxyurea decomposed, the reaction proceeded with gas effervescence and the second product which was isolated was urethane.

Disubstituted hydroxyurea e.g. ethyl ε-phenylureido-oxyacetate[5] did not condense with acetylacetone in ethanolic hydrogen chloride, and the starting material was recovered unchanged.

The oxopyrimidine derivatives (I–IV) which had been prepared here were titrated potentiometrically, and the mol. wts and dissociation constants were consistent with the postulated structures (Table). From the pK_a values it can be seen that these oxopyrimidines are somewhat stronger bases than 2-hydroxypyrimidine ($pK_a = 2{\cdot}24$)[6] and somewhat weaker than 4,6-dimethyl-2-hydroxypyrimidine. The UV spectra of the N-alkoxy derivatives II are the same in neutral and in basic aqueous solutions (λ_{max}

298 mμ, ε = 7500–8000) and different in pH = 1 (λ_{max} 308 mμ, ε = 10,700–11,700) which is 2 units below the pK_a value, thus ensuring the presence of over 99% of the solute in the ionized condition. These spectral data indicate that the amide form predominates, as they resemble those of 1,2-dihydro-1-methyl-2-oxopyrimidine rather than those obtained for 2-methoxypyrimidine.[7]

TABLE 1. LIGHT ABSORPTION AND pK_a VALUES

1,2-Dihydro-2-oxopyrimidine	pK_a	UV spectra pH	UV spectra λ_{max} mμ	UV spectra $\varepsilon_{max} \cdot 10^{-3}$ cm^2 . mol^{-1}	IR spectra in nujol cm^{-1} salt	IR spectra in nujol cm^{-1} free
1-N-Carbethoxy-methoxy-4,6-dimethyl-	2·85	1	308	10·7	1890 m; 1750 s 1610 s	1750 s; 1700 s 1610 s
		5–13	298; 214	7·5; 5·7		
4,6-Dimethyl-1-N-methoxy-	3·1	1	308	10·7	1890 m; 1750 s 1610 s	1700 s 1610 s
		5–13	298; 214	7·5; 7·0		
1-N-Benzyloxy-4,6-dimethyl-	3·1	1	308	11·7	1890 m; 1750 s 1610 s	1750 w; 1700 s 1610 s
		5–13	298	7·5		
4,6-Dimethyl-1-N-hydroxy-	2·85	1	308	8·5	1750 s; 1610 s	—
	6·1	4·8	334; 222	8·0; 14·7		
		13	318; 218	8·2; 20·0		
1-N-Carboxy-methoxy-4,6-dimethyl-	2·4	0	307	9·0	1750 s; 1700 s 1610 s	—
	3·0	13	298	6·5		
4,6-Dimethyl-(4,6-Dimethyl-2-hydroxy-pyrimidine)-	3·75	1	302	9·0	1750 s; 1610 s	—
	9·9	6	295; 215	7·0; 9·4		
		13	289; 221	6·0; 9·3		

The light absorption of the cationic form of the N-hydroxy-2-oxo derivative III at 308 mμ resembles that of the N-alkoxy derivatives (Ia–Ic), whereas in the basic range there is a bathochromic shift to 318 mμ, resulting from the formation of the enolate ion, instead of a hypsochromic shift that exists in the latter substances. In a solution of a pH which is numerically between the two pK_a values this compound III has a still greater bathochromic shift to 334 mμ; owing to the neutral form which is probably zwitterionic. This form has also a maximum absorption at 222 mμ, similar to that of the anionic form of 4,6-dimethyl-2-hydroxypyrimidine (Table).

From the IR light absorption data, which are given in the Table, we could get further evidence for the ketonic form, both in the neutral and cationic forms of the 1-alkoxy-2-oxo-pyrimidine derivatives (I, II). A characteristic band of the hydrochlorides at 1890 cm^{-1} disappears in the free substance; this band seems to be typical for the alkyl aminoxide structure I′ as it does not appear in the hydrochlorides of 4,6-dimethyl-2-oxopyrimidine and its 1-hydroxy derivative III.

The condensation of other dicarbonyl derivatives, e.g. malonaldehyde, other β-diketones and dialdehydes are under investigation.

EXPERIMENTAL

General procedure for preparation of 1-alkoxy-1,2-dihydro-4,6-dimethyl-2-oxopyrimidine hydrochlorides

0-Alkylhydroxyurea (0·01 mole) and acetylacetone (0·012 mole) were boiled for 2 min in 6%

[7] D. J. Brown, E. Hoerger and S. F. Mason, *J. Chem. Soc.* 211 (1955).

ethanolic HCl (10 ml), while the reactants dissolved and the product began to precipitate. By boiling for longer periods (20 min) crystallization occurred rapidly but with some loss of yield. After cooling overnight the oxopyrimidine hydrochloride was collected and washed with EtOH and dry ether. The hydrochlorides could be recrystallized from 90% EtOH. By keeping the reaction for 2 days at room temp without heating, the yields could be increased by 10%. By increase of HCl concentration to 10%, the time of the reaction at room temp was shortened, and crystallization occurred within 20 min. A further small amount was obtained by addition of ether (10 ml) to the filtrate. The melting of the hydrochlorides is accompanied by a deep violet or red colouration.

In this way the following compounds were prepared:

1-*Carbethoxymethoxy*-1,2-*dihydro*-4,6-*dimethyl*-2-*oxopyrimidine hydrochloride* (Ia), 85% yield, m.p. 169°. (Found: C, 45·78; H, 5·73; N, 10·63; Cl, 13·52; OEt, 18·00. $C_{10}H_{13}N_2O_4Cl$ requires: C, 45·72; H, 5·75; N, 10·66; Cl, 13·49; OEt, 17·15%); The same product was obtained from ureido-oxyacetic acid in 63% yield. (Found: C, 45·83; H, 5·66; N, 10·56; Cl, 13·51; OEt, 17·20%); 1,2-*dihydro*-4,6-*dimethyl*-1-*methoxy*-2-*oxopyrimidine hydrochloride* (Ib) (75% yield); m.p. 182°. (Found: C, 44·16; H, 6·10; N, 14·60; Cl, 18·30; OMe, 16·70. $C_7H_{11}N_2O_3Cl$ requires: C, 44·09; H, 5·81; N, 14·69; Cl, 18·59; OMe, 16·27%); 1-*benzyloxy*-1,2-*dihydro*-4,6-*dimethyl*-2-*oxopyrimidine hydrochloride* (Ic) (87% yield); m.p. 188°. (Found: C, 58·31; H, 5·62; N, 10·70; Cl, 12·90. $C_{13}H_{15}N_2O_3Cl$ requires: C, 58·53; H, 5·66; N, 10·50; Cl, 13·29%.)

1-*Carbethoxymethoxy*-1,2-*dihydro*-4,6-*dimethyl*-2-*oxopyrimidine* (IIa). The hydrochloride Ia (1·25 g) was dissolved in water (7 ml) and $NaHCO_3$ (0·42 g) was added. The free base was extracted with 12 portions of ether (20 ml each). The combined organic extracts were dried with Na_2SO_4 and evaporated to dryness *in vacuo* at 0°; while the product deposited in a pure crystalline form (0·66 g, 60% yield); m.p. 98°. (Found: C, 53·17; H, 6·41; N, 12·85; OEt, 19·80. $C_{10}H_{14}N_2O_4$ requires: C, 53·09; H, 6·23; N, 12·38; OEt, 19·91%.)

1,2-*Dihydro*-4,6-*dimethyl*-1-*methoxy*-2-*oxopyrimidine* (IIb). The hydrochloride Ib was treated as the hydrochloride in the procedure above. The free product which was thus obtained (40% yield) was liquid at room temp, m.p. ca. - 5°. (Found: N, 18·00. $C_7H_{10}N_2O_3$ requires: N, 18·17%.)

1-*Benzyloxy*-1,2-*dihydro*-4,6-*dimethyl*-2-*oxopyrimidine* (IIc). The hydrochloride Ic (0·13 g) was dissolved in water (5 ml) and sat $NaHCO_3$aq (1 ml) was added. After shaking the soln the free oxopyrimidine derivative precipitated (0·09 g, 80% yield) m.p. 132°. (Found: C, 67·38; H, 6·11; N, 12·51. $C_{13}H_{14}N_2O_3$ requires: C, 67·80; H, 6·12; N, 12·17%.)

1,2-*Dihydro*-4,6-*dimethyl*-1-*hydroxy*-2-*oxopyrimidine hydrobromide* (III). Compound Ic (0·5 g) was heated by gentle reflux in 27% HBr in AcOH (10 ml) for 15 min, while the soln became clear and new crystals deposited. After keeping for a few hr at room temp, III was collected (0·32 g) and washed with AcOH and ether; a further crop (0·08 g) was obtained by addition of ether (20 ml), overall yield was 95%, m.p. 235–240° (dec); III gives a pink colour with $FeCl_3$. (Found: C, 32·61; H, 4·13; N, 12·70; Br, 35·70. $C_6H_9N_2O_2Br$ requires: C, 32·60; H, 4·10; N, 12·67; Br, 36·15%.)

The product III was obtained also from Ib (80% yield) by the same procedure.

1-*Carboxymethoxy*-1,2-*dihydro*-4,6-*dimethyl*-2-*oxopyrimidine hydrobromide* (IV). The hydrochloride Ia (0·26 g) was treated with 27% HBr in AcOH as Ic was treated resulting in (0·27 g, 98% yield) m.p. 170° (dec and red colouration). (Found: C, 33·90; H, 4·05; N, 9·98; Br, 28·08. $C_8H_{11}N_2O_4Br$ requires: C, 34·42; H, 3·97; N, 10·04; Br, 28·63%.)

The same product was obtained in a low yield (10%) by condensation of ureido-oxyacetic acid and acetylacetone in 10% HBr in AcOH at room temp. The product was isolated by precipitation with dry ether; mixed m.p. UV and IR spectra proved this product to be identical with IV described above.

Hydrogenation of 1-N-*alkoxy derivatives.* Compound Ia (0·2 g) was shaken with H (3 atm) on 10% Pd–C (0·05 g) in 60% aqueous EtOH (1 ml) for 25 min. The catalysts was filtered off and the soln evaporated *in vacuo* to dryness. The residue was triturated in EtOH, filtered and washed with ether (0·06 g, 50% yield). The product was found identical with 4,6-dimethyl-2-hydroxypyrimidine hydrochloride which was prepared by Evance's procedure.[4] (Found: C, 45·05; H, 5·80; N, 17·45; Cl, 22·00. Calc. for $C_6H_9N_2OCl$: C, 44·86; H, 5·65; N, 17·44; Cl, 22·07%.)

In a more prolonged hydrogenation a further consumption of hydrogen occurred which caused a decrease in the yield of the above mentioned hydrogenation product.

Reaction of hydroxyurea with acetylacetone. Hydroxyurea (0·76 g) was dissolved in 15% ethanolic HCl (6 ml) and a soln of acetylacetone (1·2 ml) in EtOH (4 ml) was added with cooling. After

keeping the reaction mixture overnight at room temp *1,2-dihydro-4,6-dimethyl-1-hydroxy-2-oxopyrimidine hydrochloride* (0·16 g) was collected and washed with ether. The soln was evaporated *in vacuo* to dryness, ether was added and an additional crop (0·12 g) was collected by filtration, overall yield 15%; m.p. 225–230°. (Found: C, 40·20; H, 5·05; N, 15·7; Cl, 20·10. $C_6H_9N_2O_2Cl$ requires: C, 40·80; H, 5·13; N, 15·86; Cl, 20·76%.) The product gave pink colour reaction with $FeCl_3$ and by recrystallization from 5% HBr in AcOH it was transformed to the hydrobromide which was identical with III.

On evaporation of the ether and crystallization of the residue from pet. ether (40–60°) urethane (0·45 g) was obtained.

It seems as if the great part of the hydroxyurea decomposed and was transformed to a volatile product; such a decomposition did not take place in ethanolic HCl in the absence of acetylacetone. By using more conc. ethanolic HCl and without cooling, the reaction became exothermic and was accompanied by development of gas, with a nauseating smell.

Determination of pK_a values of pyrimidines (listed in the Table). A "Radiometer Copenhagen" titrator with glass and calomel electrodes was used. To 0·06 m·mole of the oxopyrimidine hydrochloride in water (3 ml) 2M NaCl (0·5 ml) and water (6·5 ml) were added. Titrations were carried out with 0·2N NaOH by means of an automatic "Agla" beurette syringe at 30°. The curves were corrected by solvent titration with both 0·2N NaOH and 0·2N HCl; and the pK_a values were taken from the midpoints of the corrected neutralization curves.

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