1,2,3,4-TETRAHYDROPYRIMIDINES AND SOME OTHER COMPOUNDS BASED ON PROPIOLIC ACID DERIVATIVES

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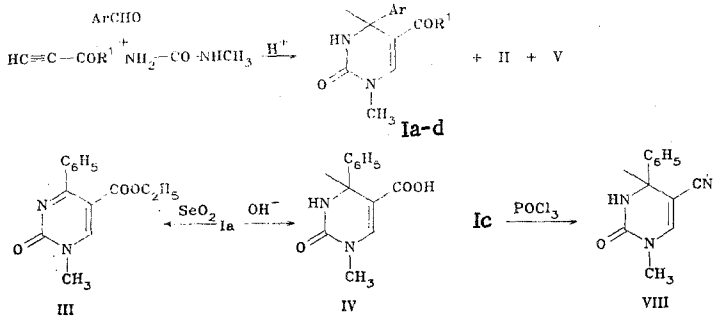
The reactions of ethyl propiolate and propiolamide with methylene and benzaldehyde and anisaldehyde in an acidic medium, in which the corresponding 2-oxo-1,2,3,4-tetrahydropyrimidines and 1,4-dihydropyridines or a 3,4-dihydropyrimidine derivative are formed, were studied.

The goal of the present research was to extend the limits of application of the Biginelli condensation by using, instead of the classical β-dicarbonyl component [1], compounds with an activated triple bond, viz., ethyl propiolate and propiolamide, for the synthesis of 2-oxo-1,2,3,4-tetrahydropyrimidines that do not have a substituent in the 6 position. The reaction of propiolic acid itself with urea in an acidic medium is known [2]; it is assumed that the mechanism of the formation of 2-oxo-4-methyl-5-ureido-1,2,3,4-tetrahydropyrimidine is similar to the mechanism of the Biginelli condensation.

The chief products in the condensation of ethyl propiolate with methylurea and benzaldehyde, as well as with p-methoxybenzaldehyde, are 1-methyl-2-oxo-4-aryl-5-ethoxycarbonyl-1,2,3,4-tetrahydropyrimidines (Ia, b).* However, we were also able to isolate known [4] 1-methyl-4-aryl-3,5-diethoxycarbonyl-1,4-dihydropyridines (IIa, b) from the reaction mixture in 6-8% yields.



I a $R^1=OC_2H_5$, $Ar=C_6H_5$; b $R^1=OC_2H_5$, $Ar=C_6H_4OCH_3$-*p*; c $R^1=NH_2$, $Ar=C_6H_5$; d $R^1=NH_2$, $Ar=C_6H_4OCH_3$-*p*

The chemical properties of the synthesized tetrahydropyrimidines were studied in the case of Ia. Oxidation of Ia gave the corresponding 1,2-dihydropyrimidine III, and alkaline hydrolysis gave 1-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid (IV).

The reaction of methylurea and benzaldehyde with propiolamide also proceeds ambiguously — a mixture of 1-methyl-2-oxo-4-phenyl-5-carbamoyl-1,2,3,4-tetrahydropyrimidine (Ic) and product V with a molecular-ion peak at m/z 262 in approximately equal amounts is formed. According to the spectral data, the 2-phenyl-4-oxo-5-benzyl-3,4-dihydropyrimidine structure seems more likely for product V. One might assume that a homolog of V, viz., 2-phenyl-4-oxo-5-benzyl-6-methyl-3,4-dihydropyrimidine, was isolated as a side product in the reaction of β-aminocrotonamide with benzaldehyde [5]. The formation of both side products II and V is then readily explained by assuming that methylurea is partially hydrolyzed under the reaction conditions [6], and β-aminoacrylic acid derivatives (VI) are formed.

*Compound Ia was previously described in [3].

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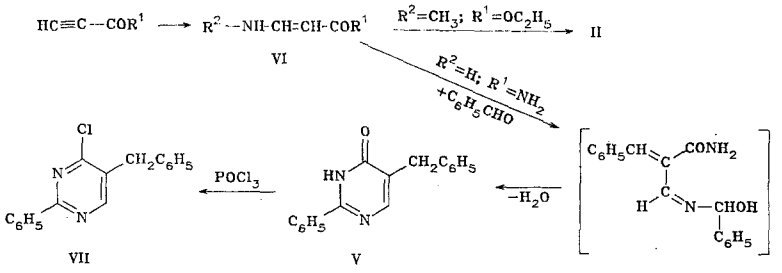

The VI → II transformations are a modification of the Hantzsch synthesis [4], and the VI → V reaction is completely explained by the chemical mechanism proposed for the 6-methyl homolog of V in [5].

The presence of an endocyclic carbonyl group in the 4 position in pyrimidone V was proved by the synthesis of 2-phenyl-4-chloro-5-benzylpyrimidine (VII) by the action of phosphorus oxychloride on V. 1-Methyl-2-oxo-4-phenyl-5-cyano-1,2,3,4-tetrahydropyrimidine (VIII) was obtained under the same conditions from Ic.

EXPERIMENTAL*

The IR spectra of mineral oil suspensions of the compounds were recorded with a Perkin-Elmer 580B spectrometer. The UV spectra of ethanol solutions of the compounds ($5 \cdot 10^{-5}$ mole/liter) were obtained with a Specord UV-vis spectrophotometer. The PMR spectra of solutions of the compounds in d_6-DMSO ($CDCl_3$ in the case of Ib) were recorded with a Brucker WH-90 spectrometer with tetramethylsilane as the internal standard. The course of the reactions and the purity of the products obtained were monitored on Silufol UV-254 plates in a chloroform–hexane–acetone system (9:7:1).

1-Methyl-2-oxo-4-aryl-5-ethoxycarbonyl-1,2,3,4-tetrahydropyrimidines (Ia, b). These compounds were synthesized by the method in [3]. Repeated crystallization from alcohol gave pure Ia and Ib. Evaporation of the mother liquors and crystallization of the residues from benzene gave substances corresponding to IIa and IIb with respect to their physicochemical characteristics [4]. PMR spectrum of Ib: 3.15 (3H, s, NCH_3), 7.28 (1H, d, NH), 5.26 (1H, d, 4-CH), 6.75-7.15 (4H, m, C_6H_4–OCH_3), 3.73 (3H, s, C_6H_4–OCH_3), 4.06 (2H, q, OC_2H_5), 1.1 (3H, t, OC_2H_5), and 7.26 ppm (1H, s, 6-CH).

1-Methyl-2-oxo-4-phenyl-5-ethoxycarbonyl-1,2-dihydropyrimidine (III). A 0.7-g (2.5 mmole) sample of Ia and 0.4 g of SeO_2 were refluxed in 20 ml of dioxane for 3 h, after which the mixture was cooled, diluted with water, and extracted with chloroform (five 25-ml portions). The solvent was removed by evaporation, and the resulting colorless precipitate was crystallized from alcohol. PMR spectrum: 3.5 (3H, s, NCH_3), 7.40 (5H, s, 4-C_6H_5), 4.02 (2H, q, OC_2H_5), 0.97 (3H, t, OC_2H_5), and 8.8 ppm (1H, s, CH).

1-Methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylic Acid (IV). A 0.26-g (1 mmole) sample of Ia and 0.1 g (2 mmole) of KOH were refluxed in 30 ml of 50% alcohol for 1 h, after which the alcohol was evaporated, the residue was acidified with dilute HCl, and the colorless precipitate was crystallized from alcohol. PMR spectrum: 3.12 (3H, s, NCH_3), 7.70 (H, d, NH), 5.26 (1H, d, 4-CH), 7.24 (5H, s, C_6H_5), 11.8 (1H, broad s, COOH), and 7.43 ppm (1H, s, 6-CH).

1-Methyl-2-oxo-4-aryl-5-carbamoyl-1,2,3,4-tetrahydropyrimidines (Ic, d) and 2-Phenyl-5-benzyl-4-oxo-3,4-dihydropyrimidine (V). A mixture of 6.9 g (0.1 mole) of propiolamide, 7.4 g (0.1 mole) of methylurea, and 0.1 mole of the aromatic aldehyde in acetic acid was refluxed for 8 h. A certain amount of a polymeric product, the structure of which was not established, was liberated during the reaction. The reaction mixture was filtered, and the filtrate was diluted with water. The colorless precipitate was removed by filtration and refluxed repeatedly in alcohol. The undissolved part of the precipitate was crystallized from acetone. Cooling of the alcohol solution precipitated Ic or Id. PMR spectrum of Ic: 3.0 (3H, s, NCH_3), 7.69 (1H, d, NH), 5.25 (1H, d, 4-CH), 7.25 (5H, s, C_6H_5), 6.9 (2H, broad s, NH_2), and 7.27 ppm (1H, s, 6-CH). PMR spectrum of Id: 3.47 (3H, s, NCH_3), 7.8 (1H, d, NH), 7.40 (2H, d, C_6H_4–OCH_3), 7.07 (2H, d, C_6H_4–OCH_3), 3.97 (3H, s, C_6H_4–OCH_3), 5.4 (1H, d, CH), 7.13 (2H, s, NH_2), and 7.49 ppm (1H,

*We thank V. D. Shat-ts for carrying out the high-performance liquid chromatography for the determination of the yield of II.

TABLE 1. Characteristics of the Compounds Obtained

Compound	mp, °C	UV spectrum, λ_{max}, nm (log ε)	IR spectrum, cm^{-1}	Found, %			Empirical formula	Calc., %			Yield, %
				C	H	N		C	H	N	
Ia		205 (4,15), 228 sh (3,84), 296 (3,97)	1660, 3230, 1690								80
Ib	178—180	205 (3,6), 222 sh. (3,52), 300 (3,36)	1660, 1705, 1690, 3230	62,0	6,2	9,2	$C_{15}H_{18}N_2O_4$	62,1	6,3	9,6	68
Ic	229—230	207 (4,32), 221 sh. (3,95), 290 (3,98)	1650, 3175, 1690, 3362, 1705	61,9	5,8	17,8	$C_{12}H_{13}N_3O_2$	62,3	5,7	18,2	32
Id	233—235	206 (3,72), 225 sh. (3,68), 298 (3,41)	1650, 3175, 1690, 3485, 1700	59,4	5,3	16,4	$C_{13}H_{15}N_3O_2$	59,8	5,8	16,1	40
III	121—123	205 (3,7), 218 sh, (3,58), 290 (3,17)	1670, 1720, 1690	65,1	5,5	11,0	$C_{14}H_{14}N_2O_3$	65,1	5,1	10,8	36
IV	230—231	208 (3,72), 225 sh, (3,65), 298 (3,41)	1690, 3200, 1710, 3280	61,8	5,0	11,7	$C_{12}H_{12}N_2O_3$	62,1	5,2	12,1	78
V	237—239	207 (4,43), 244 (4,12), 300 (4,18)	1600, 3160, 1650	78,9	5,4	10,7	$C_{17}H_{14}N_2O$	78,7	5,5	10,7	30
VII*	68—70	205 (4,16), 268 (4,18)	1510, 1560, 1610	72,1	4,7	10,0	$C_{17}H_{13}ClN_2$	72,7	4,7	10,0	56
VIII	172—174	205 (3,4), 220 sh, (3,28), 286 (3,73)	1680, 3080, 2220, 3220	67,7	4,3	9,3	$C_{12}H_{11}N_3O$	67,9	4,8	10,1	64

*Found: Cl 12.0%. Calculated: Cl 12.6%.

s, CH). Compound V precipitated from the acetone solution. PMR spectrum: 12.7 (1H, broad s, NH), 7.27 (5H, s, C_6H_5), 7.59-8.08 (5H, m, C_6H_5), 3.65 (2H, s, CH_2), and 7.33 ppm (1H, s, CH). ^{13}C NMR spectrum: 164.05 (C=O); 157.1 (2-C); 152.4 (6-C); 140.61 (C_1—$2C_6H_5$); 133.6 (C_1—$5C_6H_5$); 128.7, 129.4, 129.7 (C_{o+m}—2,5-C_6H_5); 127.2, 132.5 (C_p—2,5-C_6H_5); 33.67 (CH_2).

2-Phenyl-4-chloro-5-benzylpyrimidine (VII). A 0.2-g sample of V was refluxed in 10 ml of $POCl_3$ for 30 min, after which the mixture was evaporated, the residue was treated with hexane, and the colorless precipitate was crystallized from benzene. PMR spectrum: 7.24 (5H, s, C_6H_5), 7.45-8.23 (5H, m, C_6H_5), 8.77 (1H, s, CH), and 4.0 ppm (2H, s, CH_2).

1-Methyl-2-oxo-4-phenyl-5-cyano-1,2,3,4-tetrahydropyrimidine (VIII). This compound was obtained from Ic and $POCl_3$ by the method indicated above and crystallized from alcohol. PMR spectrum: 3.04 (3H, s, NCH_3), 7.90 (1H, d, NH), 5.09 (1H, d, 4-CH), 7.36 (5H, s, C_6H_5), and 7.43 ppm (1H, s, 6-CH).

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