STUDY OF THE LACTAMS. XV. SYNTHESIS OF 2,4,8,10-SUBSTITUTED HYDROPYRIDO (2,3-d) PYRIMIDINES

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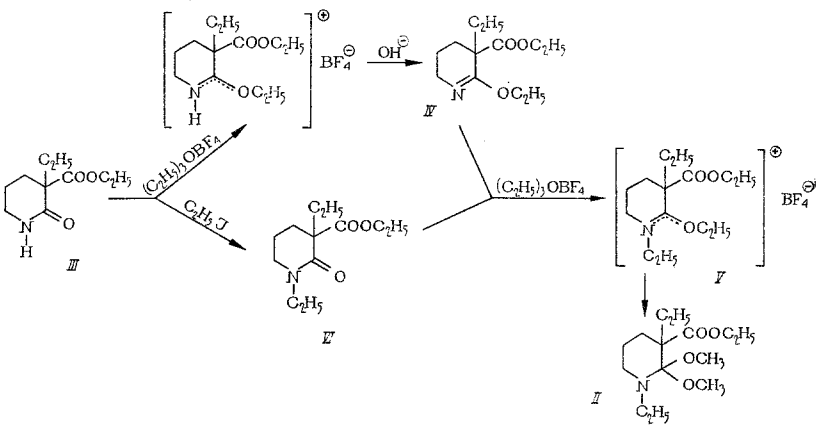
The derivatives of pyrido[2,3-d]pyrimidine may be regarded as the deazo analogs of the pteridines; the introduction of an alkyl group in position 10 causes them to resemble the soporific drugs—the 5,5-disubstituted barbituric acids. Because the synthetic approach to obtaining the different substituted pyrido-[2,3-d]pyrimidines is very limited, in the present work, as a result of the synthesis of 2-imino-4-oxy-8,10-diethyl-2,3,4,5,6,7,8,10-octahydropyrido(2,3-d)pyrimidine (I), it has been shown possible to introduce substitution groups in positions 2 and 4 of the pyrimidine ring, to the nitrogen atom of the piperidine ring, and also to the angular substitution group in position 10, with the result that a more detailed investigation may now be made of pyrido[2,3-d]-pyrimidine.

1,3-Diethyl-2,2-dimethoxy-3-carbethoxyhexahydropyridine (II) required for the production of I may be made from 3-ethyl-3-carbethoxypiperidone-2 (III) in two ways, as follows:



It has been shown that the method of producing II through the intermediate lactim ester IV has important advantages over the method involving alkylation of III into VI, because of the low yield of VI.

Because the synthesis of III by alkylation of 3-carbethoxypiperidone (VII) with C_2H_5I involves considerable difficulty [1], we have used another method corresponding to the preparation of VII from the malonic ester [1], and consisting in the transformation of ethyl malonate (VIII) by Michael's reaction into ethyl-beta-cyanethylmalonic ester (IX) and by reductive cyclization of IX into III:

From III obtained in this way, through IV we synthesized II whose condensation with guanidine produced I:

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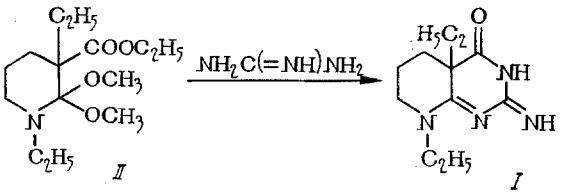
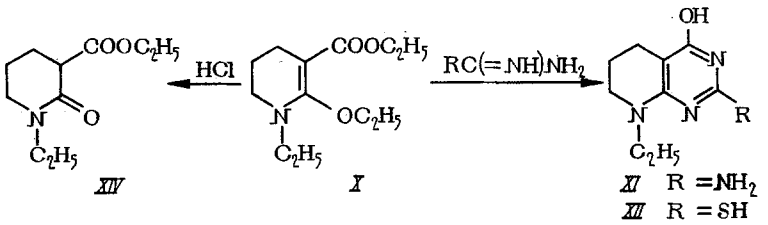


At the same time from N,O-diethyl-3-carbethoxypiperidine fluoroborate, described in our previous communication [2], we produced 1-ethyl-2-ethoxy-3-carbethoxy-1,4,5,6-tetrahydropyridine (X), from which by condensation with guanidine and thiourea we synthesized XI and XII—2-amino- and 2-mercapto-4-oxy-8-ethyl-5,6,7,8-tetrahydropyrido[23-d]pyrimidines:



The object of the present work has been to compare the reactivities of II, X, and the lactim ester of 3-carbethoxypiperidone-2 (XIII).

It is known that XIII, and particularly II, are very unstable compounds which are hydrolyzed in water to the corresponding lactams.

A study of the hydrolysis of X showed that this compound, unlike II and XIII, is more resistant to hydrolysis, and only when heated with concentrated hydrochloric acid does it become transformed into N-ethyl-3-carbethoxypiperidone-2 (XIV). A similar situation concerning the relative reactivities was found by condensation of II, X, and XIII with guanidine. As judged by the yield of substituted pyrido[2,3-d]pyrimidines, II is the most reactive, then comes XIII, and the least reactive is X.

EXPERIMENTAL

1,3-Diethyl-3-carbethoxypiperidone-2 (IV). Into 20 ml of boiling absolute toluene was added 0.8 g Na, bit by bit. The temperature was lowered to 70°, and 6 g of 3-ethyl-3-carbethoxypiperidone-2 (III) was added; the mixture was cooled to 55°, and 4.8 g of ethyliodide was added. After being heated for $1^{1/2}$ hours at 90-100°, the reaction mixture was cooled, the NaI was filtered, the toluene was distilled off, and the residue distilled in vacuum. We obtained 2.2 g (32%) of IV, having a boiling point of 118-127° at 3-4 mm. For analysis the substance was redistilled, boiling point 127-128° at 4-5 mm, $n_D^{24} = 1.4738$. Found, %: C 63.65; H 9.54; N 6.16. Formula $C_{12}H_{21}NO_3$; calculated, %: C 63.44; H 9.25; N 6.17. $\nu_{COOC_2H_5} = 1734\ cm^{-1}$, $\nu_{CO\text{-amide}} = 1650\ cm^{-1}$.

3-Ethyl-3-carbethoxypiperidone-2 (III). In 376 g of ethyl malonate (VIII) we dissolved 4 g of Na at 60°, maintaining this temperature for 1 hour. We added 160 g of acrylonitrile, raised the temperature to 80°, and maintained it there for 2 hours. Heating then ceased, and the mixture was stirred for 1 hour, cooled, neutralized with glacial acetic acid; 300 ml of dichlorethane were added, and 200 ml of water. The layer of dichlorethane was separated, washed in water, dried over anhydrous Na_2SO_4; the solvent was distilled off, and the residue distilled in vacuum. We obtained 445 g (91%) of ethyl-β-cyanethylmalonate (IX), bp 155-160° at 6 mm. On standing IX crystallized out, mp 46° [3].

To a solution of 220 g of IX in 1 liter of alcohol we added 50 g of Raney nickel the mixture was hydrogenated for 2 hours at 50° and at a hydrogen pressure of 90 atms; the mixture was cooled, filtered, the alcohol evaporated off, and the residue was distilled in vacuum. We obtained 144 g (80%) of III bp 162-168° at 4 mm. On standing III crystallized out; mp 46° [1].

N-Ethyl-3-carbethoxypiperidone-2 (XIV). To 2.3 g of N-ethyl-O-ethyl-3-carbethoxy-1,4,5,6-tetrahydropyridine (X) [2] was added 1.5 ml of concentrated hydrochloric acid; the mixture was heated and kept at 60° for 5 minutes; it was evaporated in a vacuum, and the residue distilled. We obtained 1.2 g (60%) of XIV,

bp 135° at 4 mm; $n_D^{19}=1.476$. Found, %: C 60.25; H 8.44; N 7.06. Formula $C_{10}H_{17}O_3$; calculated, %: C 60.30; H 8.54; N 7.06 $\nu_{COOC_2H_5}=1740$ cm^{-1}, $\nu_{CO\text{-amide}}=1650$ cm^{-1}.

2-Mercapto-8-ethyl-4-oxy-5,6,7-tetrahydropyrido[2,3-d]pyrimidine (XII). To a solution of sodium ethoxide (obtained from 0.35 g Na and 25 ml of absolute alcohol) we added 0.76 g of thiourea and 2.3 g of X; the mixture was boiled for 3 hours, the alcohol evaporated off in vacuum, and the residue taken up in 10 ml of water, cooled to 5°, and neutralized with 2 N HCl. We obtained 1.4 g (66%) of XII (R=SH). For analysis we recrystallized from an aqueous solution (1:25), and yellow prismatic crystals separated out; mp 236-237°. Ultraviolet spectrum (in alcohol): $\lambda_{max}=260$; 301 nm. Log ε 4.44; 4.14. UV spectrum (in 0.1 N NaOH); $\lambda_{max}=258$; 295 nm. Log ε 4.52; 4.12. Found, %: C 50.60; H 6.16; N 20.17; S 15.31. Formula $C_9H_9N_3OS$; calculated, %: C 51.18; H 6.16; N 19.95; S 15.16.

Similarly we obtained IX (R=NH_2), yield 12%, mp 286-288° (from water). UV spectrum (in alcohol); λ_{max} 228, 288 nm. Log ε 4.41; 4.23. UV spectrum (in 0.1 N HCl); λ_{max} 290 nm. Log ε 4.28. Found %: C 55.40; H 7.38; N 28.65. Formula $C_9H_{14}N_4O$; calculated, %: C 55.67; H 7.22; N 28.87.

2-Imino-4-oxo-8,10-diethyl-2,3,4,5,6,7,8,10-octahydropyrido[2,3-d]pyrimidine (I). Complex (V) made from 7.1 g IV and 6.6 g triethyloxonium fluoroborate [2] was added to a solution of sodium methoxide (0.95 g Na in 30 ml absolute methanol) at −10°; the mixture was agitated for 15 minutes, the $NaBF_4$ was filtered off, washed with methanol, and without further treatment the methanolic solution of II was used for condensation with guanidine hydrochloride.

To a solution of sodium methoxide (1.85 g Na in 40 ml of absolute methanol) were added 3.15 g guanidine hydrochloride and a solution of II in methanol. The mixture was boiled for 4 hours, the alcohol evaporated off, and the residue distilled in 15 ml water; the residue was filtered off. The aqueous mother liquor was neutralized with 2 N HCl to pH 8.0, evaporated until crystallization started, cooled to 0°, and compound I was filtered off. Altogether we obtained 4.35 g of I, a yield representing 63.5% of the lactim (IV). For analysis the product was recrystallized from dimethylformamide (1:13), mp 247-248°. UV spectrum (in alcohol): λ_{max} 244; 291 nm. Log ε 4.26; 4.02. UV spectrum (in 0.1 N HCl); λ_{max} 217; 298 nm. Log ε 4.14; 4.23. Found, %: C 59.55; H 8.50; N 25.14. Formula $C_{11}H_{18}N_4O$; calculated, %: C 59.46; H 8.11; N 25.23.

We have synthesized 2-imino-4-oxy-8,10-diethyl-2,3,4,5,6,7,8,10-octahydropyrido[2,3-d]pyrimidine from 1-ethyl-3-carbethoxypiperidone-2; this example indicates that it is possible to obtain various 2,4,8,10-substituted hydrogenated pyrido[2,3-d]pyrimidines.

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