

A STUDY OF LACTAMS.

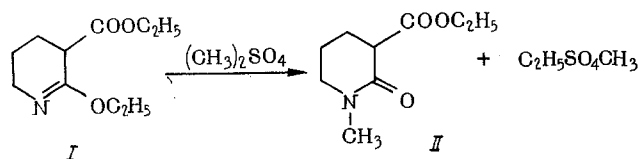
XIII. AN APPROACH TO THE SYNTHESIS OF 8-SUBSTITUTED-4-HYDROXY-5,6,7,8-TETRAHYDROPYRIDO[2,3-d]PYRIMIDINES FROM A LACTIM ETHER OF 3-CARBETHOXY-2-PIPERIDONE

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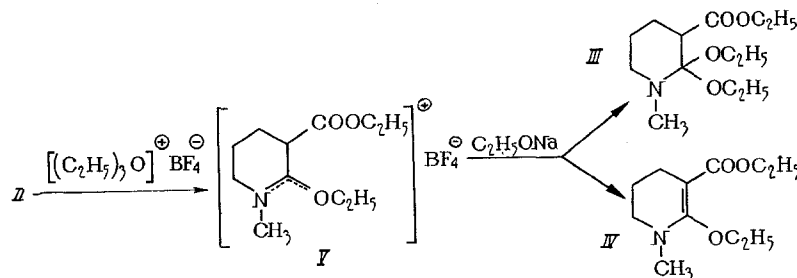
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In a preceding communication we have described the preparation of des-aza analogs of tetrahydropyridines—tetrahydropyrido[2,3-d]pyrimidines—from a lactim ether of 3-carbethoxy-2-piperidone (I) [1]. In the present work we have worked out an approach to the synthesis of 8-alkyl-5,6,7,8-tetrahydropyrido[2,3-d]pyrimidines from I in the case of the synthesis of 2-substituted-8-methyl-4-hydroxy-5,6,7,8-tetrahydropyrido[2,3-d]pyrimidines.

In connection with the fact that selective alkylation of tetrahydropyrido[2,3-d]pyrimidines in the 8-position is made very difficult by the possibility of alkylation in several directions, it was planned to introduce the substituent into the piperidine ring before construction of the pyrimidine part of the pyrido[2,3-d]pyrimidine molecules. We selected N-methyl-3-carbethoxy-2-piperidone (II) [2] as the starting material for this purpose. We have developed a new method of preparing II, based on converting lactim ethers into N-alkyllactams under the influence of catalytic amounts of dialkyl sulfates [3, 4]. However, in distinction from this method, to convert I into II we used not catalytic but equimolecular amounts of dimethyl sulfate, to exclude the possibility of forming a mixture of II and N-ethyl-3-carbethoxy-2-piperidone, which allowed us to accomplish the transformation of I into II smoothly and in high yield:



On the basis of the data of Meerwein [5] and Brederick [6] on the alkylation of N-substituted lactams and amides and on treatment of the intermediate complexes with sodium alkoxides, the O-ethylation of II with triethyloxonium fluoroborate could take place in two ways—with formation of the acetal (III) or the O,N-ketene acetal (IV):



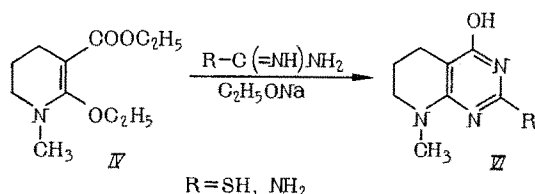
Upon reaction of II with triethyloxonium fluoroborate and treatment of the intermediate complex (V) with sodium ethoxide, a compound was isolated which, judging from elemental analysis, was N-methyl-2-ethoxy-3-carbethoxy-1,4,5,6-tetrahydropyridine (IV). This compound, being a substituted enamine, is rather unstable and is converted into II on storage, according to thin-layer chromatographic data.

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The structure of IV was confirmed by its infrared spectrum, in which there was an absorption band for the C=C bond at 1580 cm^{-1} , but the absorption band for the COOC_2H_5 group was shifted to 1690 cm^{-1} , as takes place in the case of carbethoxy groups at double bonds [7]. An absorption maximum at $293\text{ m}\mu$ was observed in the ultraviolet spectrum of IV. The bathochromic shift of the maximum in the spectrum of IV relative to unsubstituted enamines [8] can also be explained by conjugation of the double bond with the carbethoxy group.

Since both enamine IV and also acetal III can be formed on treatment of complex V with sodium ethoxide, while conversion of III into IV could take place during the process of distilling III, we compared the ultraviolet spectra of IV and of the reaction mixture obtained on treatment (at $0-2^\circ$) of the complex with sodium ethoxide. On the basis of the identity of these spectra, it was shown that formation of IV takes place during the treatment of V with sodium ethoxide.

2-Substituted-8-methyl-4-hydroxy-5,6,7,8-tetrahydropyrido[2,3-d]pyrimidines (VI) were obtained upon condensation of IV with thiourea or guanidine in the presence of sodium ethoxide:



It must be noted that an attempt to effect the condensation of IV with urea failed: according to thin-layer chromatographic data, the reaction product was apparently a mixture of II and IV.

Comparison of the ultraviolet spectra of the type VI compounds with the spectra of the appropriate tetrahydropyrido [2,3-d]pyrimidines unsubstituted in the 8-position shows that introduction of the methyl group into the piperidine ring leads to a shift of the absorption maximum into the longer wavelength part of the spectrum.

EXPERIMENTAL

N-Methyl-3-carbethoxy-2-piperidone (II). A mixture of 10 g (0.05 mole) of 2-ethoxy-3-carbethoxy-3,4,5,6-tetrahydropyridine [9] and 6.3 g (0.05 mole) of dimethyl sulfate was heated to about 70° , the heating was stopped, and the temperature spontaneously rose to about $95-100^\circ$; the mixture was kept at this temperature for 1 h. By distillation there was obtained 6.1 g (87%) of ethyl methyl sulfate, bp $60-64^\circ$ (4-5 mm), $n_D^{22} 1.3985$ (lit. [10], bp 85° [15 mm, $n_D^{16.5} 1.399$) and 8 g (86%) of II, bp $150-150.5^\circ$ [6-7 mm, $n_D^{21} 1.4782$, COOC_2H_5 absorption frequency 1740 cm^{-1} , amide carbonyl absorption frequency, 1650 cm^{-1} . Found, %: C 58.05; H 7.94; N 7.60. $\text{C}_9\text{H}_{15}\text{NO}_3$. Calculated, %: C 58.38; H 8.11; N 7.57. According to the literature [2], the bp of II is 82° (0.05 mm), COOC_2H_5 absorption frequency, 1740 cm^{-1} , amide carbonyl absorption frequency, 1640 cm^{-1} .

N-Methyl-2-ethoxy-3-carbethoxy-1,4,5,6-tetrahydropyridine (IV). To 7.85 g (0.042 mole) of II was added, in small portions, 8.7 g (0.045 mole) of triethyloxonium fluoroborate, at 20° . After 15 min stirring, the temperature was raised to 28° and two layers were formed. Stirring was continued for 1 h at room temperature; after this the mixture was washed three times with 15 ml portions of dry ether and the residues from the ether were concentrated in vacuum at room temperature; 12.5 g of O-ethyl-N-methyl-3-carbethoxypiperidonium fluoroborate (V) was obtained, which was used for the preparation of IV without additional treatment.

Compound V (12.5 g) was added over a 15 min period to a solution of sodium ethoxide (from 1.2 g of Na and 25 ml of absolute alcohol) at $0-2^\circ$; the mixture was kept at this temperature for 20 min, the precipitated NaBF_4 was filtered off, and it was washed with chilled alcohol; the alcohol was stripped off, and by distillation of the residue there was obtained 6.1 g (67%) of IV, bp $129-131^\circ$ [4-5 mm, $n_D^{23} 1.5101$, λ_{max} (from alcohol) $293\text{ m}\mu$ ($\log \epsilon = 3.93$), carbethoxy-group absorption frequency, 1690 cm^{-1} , C=C absorption frequency 1580 cm^{-1} . Found, %: C 62.65; H 9.31; N 6.58. $\text{C}_{11}\text{H}_{19}\text{NO}_3$. Calculated, %: C 61.97; H 8.92; N 6.57.

2-Mercapto-4-hydroxy-8-methyl-5,6,7,8-tetrahydropyrido[2,3-d]pyrimidine (VI). To a solution of sodium ethoxide (from 0.35 g of Na) in 25 ml of absolute alcohol was added 0.76 g (0.01 mole) of thiourea and 2.13 g (0.01 mole) of IV, the mixture was boiled for 3 h, the alcohol was evaporated under vacuum, the residue was dissolved in 10 ml of water, it was cooled to about 5°, and the solution was neutralized with a 2N HCl solution. There was obtained 1.65 g of VI, R=SH (84%). For analysis it was crystallized from water (1:50); the yellow crystals had mp 290-291° (dec.), λ_{\max} (from 0.1 N NaOH solution) 258 m μ (log ϵ = 4.51) and 296 m μ (log ϵ = 4.08); λ_{\max} (from alcohol) 259 m μ (log ϵ = 4.23) and 294 m μ (log ϵ = 4.26). Found, %: C 48.78; H 5.57; N 20.85; S 16.57. C₈H₁₁N₃OS. Calculated %: C 48.73; H 5.58; N 2.22; S 16.24.

Compound VI, R=NH₂, 25% yield, was prepared similarly, mp > 300° (from DMF), λ_{\max} (from 0.1 N NaOH solution), 281 m μ (log ϵ = 4.13); λ_{\max} (from 0.1 N HCl solution) 288 m μ (log ϵ = 4.34); λ_{\max} (from alcohol) 228 m μ (log ϵ = 4.42) and 287 m μ (log ϵ = 4.39). Found, %: C 53.26; H 6.85; N 30.68. C₈H₁₂N₄O. Calculated, %: C 53.33; H 6.67; N 31.11.

CONCLUSION

N-Methyl-2-ethoxy-3-carbethoxy-1,4,5,6-tetrahydropyridine has been prepared by reaction of N-methyl-3-carbethoxy-2-piperidone with triethyloxonium fluoroborate with subsequent treatment of the intermediate complex with sodium ethoxide. In the case of condensation of the first compound mentioned above with compounds of the general formula R-C(=NH)NH₂, which takes place with formation of 2-substituted-8-methyl-4-hydroxy-5,6,7,8-tetrahydropyrido[2,3-d]pyrimidines, a method has been developed for introducing a substituent into the 8-position of tetrahydropyrido[2,3-d]pyrimidines.

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