LACTAM STUDIES

XVII. LACTIM ETHERS OF SUBSTITUTED DIHYDROCARBOSTYRILS IN THE SYNTHESIS OF HYDROGENATED PYRIMIDO[4,5-b]QUINOLINES

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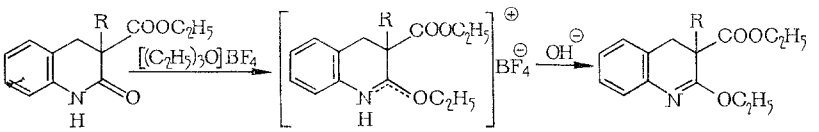
UDC 547.85'831:542.9

We have previously [1, 2] shown the possibility in principle of synthesizing condensed heterocyclic compounds which have pyrimidine and piperidine nuclei in their make up from lactim ether, in the case of preparing derivatives of piperido[2,3-d]pyrimidine from 3-carbethoxy-2-piperidone.

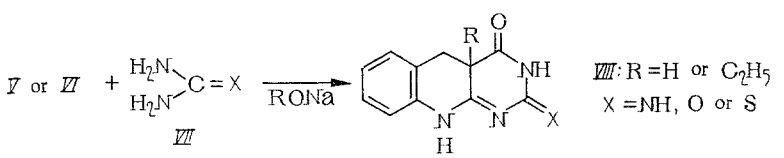
In the present work we have used this scheme to synthesize hydrogenated pyrimido[4,5-b]quinolines which have a structural similarity (as desaza analogs) with pyrimido[4,5-b]quinoxalines, which enter into the composition of flavins [3].

Most of the pyrimido[4,5-b]quinolines have been synthesized by two routes: from substituted pyrimidines [4-6] or from 2-aminoquinoline derivatives [7,8]. However, only aromatized pyrimido[4,5-b quinolines] have been prepared by such methods, and their hydrogenated analogs have remained essentially unavailable up until now. In 1960 an attempt was made to condense derivatives of 3-carbomethoxydihydrocarbostyril with various compounds of the amidine type, but only in one case – when guanidine was used in this reaction – was it possible to isolate a derivative of dihydropyrimido[4,5-b]quinoline [9]. The difficulties which arose in carrying out this condensation with such compounds as urea and thiourea were caused first of all by the low reactivity of the amide function in dihydrocarbostyril toward nucleophilic reagents. In this connection, to perform such a type of condensation successfully, we employed preliminary activation of the amide function by converting 3-carbethoxy- and 3-ethyl-3-carbethoxy-3,4-dihydrocarbostyril (I and II) into the lactim ethers V and VI:



I: R=H; II: R=C_2H_5 III: R=H; IV: R=C_2H_5 V: R=H; VI: R=C_2H_5

By condensation of V or VI with amidine compounds of the general formula VII, we synthesized the 2-substituted 4-oxo-2,3,4,4a,5,10-hexahydropyrimido[4,5-b]quinolines (VIII) (see Table 1):



VII: X=NH, O or S

VIII: R=H or C_2H_5; X=NH, O or S

The reaction of V with VII took place smoothly and with good yields. We also succeeded in preparing VIII (R = C_2H_5, X = NH or O) from VI, although here the presence of the angular ethyl group disrupted the aromatization of the pyrimidine. In the condensation of V with VII, 3,4-dihydrocarbostyril was isolated

S. Ordzhonikidze All-Union Pharmaceutical Chemistry Scientific-Research Institute, Moscow. Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 4, No. 6, pp. 21-25, June, 1970. Original article submitted September 10, 1969.

TABLE 1. Pyrimido[4,5-b]quinolines

Compound	R	X	Mp, °C*	Yield, %	3,4-Dihydrocarbostyril obtained, %	Recovered VI, %	Found, %				Empirical formula	Calculated, %				λ_{max} (in m μ) and log ε
							C	H	N	S		C	H	N	S	
VIII	H	S	>300	78	20	—	57,02	4,09	18,57	13,85	$C_{11}H_9N_3OS$	57,14	3,90	18,18	13,85	278(4,51), 400(3,00)‡
	H	NH	>300	75	20	—	61,38	4,36	26,35	—	$C_{11}H_{10}N_4O$	61,68	4,68	26,18	—	258(4,71), плечо 312‡ (3,68) 319(3,73), 387(3,88)‡
	H	O	>300	65	34	—	61,30	4,35	19,72	—	$C_{11}H_9N_3O_2$	61,39	4,19	19,48	—	241(4,28), 259(4,27), 314(4,0)[8]
	C_2H_5	NH	>300	80	—	16	64,12	5,66	22,85	—	$C_{13}H_{14}N_4O$	64,46	5,78	23,14	—	280(3,78), 325(4,19)**
	C_2H_5	O	284	20	—	56	64,26	5,57	17,12	—	$C_{13}H_{13}N_3O_2$	64,20	5,35	17,28	—	228(4,32), 303(4,01)‡
XII		SH	>300	40†	—	—	60,16	4,67	16,11	12,21	$C_{13}H_{13}N_3OS$	60,23	5,02	16,22	12,36	227(4,64), 296(4,52), плечо 335(3,94), 363(4,09), 436(438)
		NH_2	272	31	—	—	64,83	5,49	22,91	—	$C_{13}H_{14}N_4O$	64,46	5,78	23,14		220(4,45), 253(4,36), 280(4,5) 332(4,02), 387(4,08)
		OH	~300	10	—	—	63,99	5,32	17,00	—	$C_{13}H_{13}N_3O_2$	64,20	5,35	17,28		263(4,21), 320(4,02), 396(3,83)

*VIII and XII were crystallized from aqueous or dry dimethylformamide; they melt with decomposition.

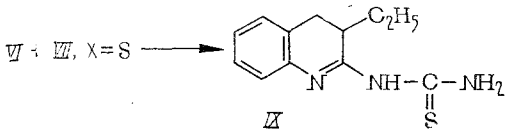
†From XI the yield was 21%.

‡In 0.1 N sodium hydroxide solution.

**In 0.1 N hydrocholoric acid solution.

from the mother liquors, apparently due to hydrolysis of V which had not entered into reaction and decarboxylation of the 3,4-dihydrocarbostyril-3-carboxylic acid. Judging from the yields, the reaction which forms VIII took place considerably easier than the analogous reaction in the synthesis of piperido[2,3-d]-pyrimidines [2]. The increased reactivity in benzo analogs of the lactim ethers of 3-carbethoxy-2-piperidone in condensation with VII can be explained by the electron-acceptor effect of the benzene nucleus, which facilitates nucleophilic substitution at the lactim carbon atom.

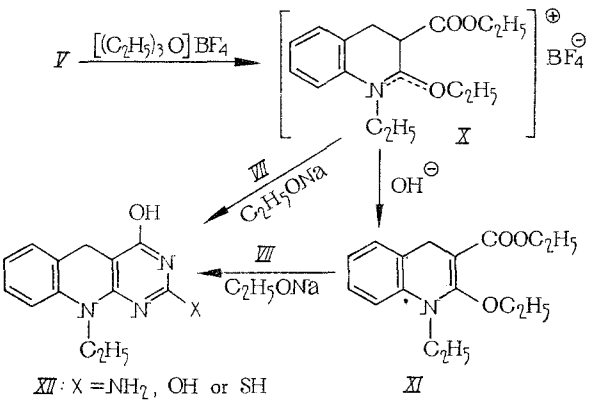
Similarly to the reaction of the lactim ether of 3-ethyl-3-carbethoxy-2-piperidone with VII (X = S) [2], upon reaction of VI with thiourea (VII, X = S), 2-(N-thioureido)-3-ethyl-3,4-dihydroquinoline (IX) was obtained:



In connection with the high biological activity of trinuclear heterocycles of the type of phenothiazine, isalloxazine, etc., the introduction of substitutents into the 10 position of pyrimido[4,5-b]-quinolines presents special interest. Since direct N_{10}-alkylation of the latter is hampered because of the presence of two nitrogens in them, we decided to introduce the substituents before constructing the pyrimidine part of the molecule. Here N-alkylation of metal salts of I is excluded because of the more readily proceeding alkylation in the 3-position. On the other hand, introduction of a carbethoxy group in the 3-position of N-alkyl-3,4-dihydrocarbostyrils is hindered [9].

For these reasons, we employed N-alkylation of V with triethyloxonium fluoborate. This method had been successfully used earlier to prepare derivatives of an N-alkyl-2-piperidone [10].

As a result of alkylation of V with triethyloxonium fluoborate, a complex X was obtained, upon treatment of which with a 50% potassium carbonate solution 1-ethyl-2-ethoxy-3-carbethoxy-1,4-dihydroquinoline (XI) was obtained:



Conclusions about the structure of XI were made on the basis of its elemental analysis and spectral data. Comparison of its UV spectrum with the UV spectra of V and VI shows that, along with the absorption maximum at 250 mμ which is present in the spectra of V and VI, a maximum at 327 mμ appears in the spectrum of XI, which is characteristic of cyclic α-alkoxyenamines [11].

It has been shown earlier that enamines of this type react with amidine compounds to form condensed pyrimidines [10]. 2-Substituted 4-hydroxy-10-ethyl-5,10-dihydropyrimido[4,5-b]quinolines (XII, where X = NH_2, OH or SH) (see Table 1) were obtained by condensation of XI with VII. When this method was worked through, it was established that it is preparatively more convenient to introduce into the reaction not XI but its fluoborate complex (X).

EXPERIMENTAL

3-Carbethoxy-3,4-dihydrocarbostyril (I). To a solution of 200 g of diethyl o-nitrobenzalmalonate [12] in 1.5 liters of methanol was added 70 g of Raney nickel and the mixture was hydrogenated for 3 h at

30° and a pressure of 90 atm; then another 80 g of Raney nickel was added and the hydrogenation was continued for another 3 h under the same condtions. The nickel was filtered off, the methanol was stripped under vacuum, and the residue was crystallized from aqueous alcohol. Yield, 110 g (73%), mp 137-138° [13].

3-Ethyl-3-carbethoxy-3,4-dihydrocarbostyril (II). To a solution of sodium ethoxide (from 2.3 g of metallic sodium and 90 ml of absolute alcohol) was added 21.9 g of I, the mixture was stirred until a thick homogeneous mass was formed, 9 ml of ethyl iodide was added, and the mixture was boiled for 1.5 h. After 30 min a solution was formed, from which a precipitate fell once again. The alcohol was distilled off and 100 ml of water was added to the residue; the precipitate was filtered off, washed with water, and dried. yield, 23.4 g (95%), mp 113-114° [14].

2-Ethoxy-3-carbethoxy-3,4-dihydroquinolinium fluoborate (III). To a suspension of 21.9 g of I in 50 ml of dry choloroform was added 20 g of triethyloxonium fluoborate, the mixture was stirred for 6 h, and it was allowed to stand overnight. The chloroform was distilled off almost to dryness, the solid was filtered off, and it was washed with absolute ether. The yield was quantitative, mp 119-119.5° (from a mixture of chloroform and carbon tetrachloride). Found %: C 50.30; H 5.65; N 4.35. $C_{14}H_{17}NO_3HBF_4$. Calculated %: C 50.15; H 5.39; N 4.18. ν_{NH} 3210 cm^{-1}, $\nu_{C=0}$ 1760 cm^{-1}, $\nu_{C=N}$ 1665 cm^{-1}; $\nu_{BF_4^{\ominus}}$ –1000-1100 cm^{-1}, λ_{max} (in alcohol), 251 mμ, (log ε = 4.02).

2-Ethoxy-3-ethyl-3-carbethoxy-3,4-dihydroquinolinium fluoborate (IV). This was prepared from 23 g of II and 22 g of triethyloxonium fluoborate under the same conditions as III. The yield was quantitative, mp 122-123° (from a chloroform-carbon tetrachloride mixture). Found %: C 53.13; H 6.25; N 4.11. $C_{16}H_{21}NO_3 \cdot HBF_4$. Calculated %: C 52.89; H 6.06; N 3.84. ν_{NH} 3200 cm^{-1}, $\nu_{C=0}$ 1750 cm^{-1}, $\nu_{C=N}$ 1660 cm^{-1}, $\nu_{BF_4^{\ominus}}$ 1010-1100 cm^{-1}, λ_{max} (in alcohol), 225 mμ, (log ε 3.99).

2-Ethoxy-3-carbethoxy-3,4-dihydroquinoline (V). A 50% potassium carbonate solution (14 ml) was added dropwise to a suspension of 24 g of III in carbon tetrachloride at 2°, and the mixture was stirred for 15 min. A precipitate of potassium fluoborate fell. The carbon tetrachloride layer was separated. The precipitate and aqueous layer were additionally extracted with carbon tetrachloride. The combined extract was dried with sodium sulfate and was evaporated. The residue was distilled. Yield, 14.7 g (83%), bp 128° (1 mm), n_D^{20} 1.5381. Found %: C 67.70; H 6.74; N 5.41. $C_{14}H_{17}NO_3$. Calculated %: C 68.02; H 6.88; N 5.67. $\nu_{C=0}$ 1750, cm^{-1}, $\nu_{C=N}$ 1650 cm^{-1}, λ_{max} (in alcohol), 258 mμ, (log ε 3.97).

2-Ethoxy-3-ethyl-3-carbethoxy-3,4-dihydroquinoline (VI). This was prepared from 11.4 g of IV by the action of 8 ml of 50% potassium carbonate solution under the same conditions as V. The yield of 7.45 g (90%), bp 116-117° (1 mm), n_D^{20} 1.529. Found %: C 69.57; H 7.55; N 5.06. $C_{16}H_{21}NO_3$. Calculated %: C 69.85; H 7.64; N 5.09. $\nu_{C=0}$ 1743 cm^{-1}, $\nu_{C=N}$ 1640 cm^{-1}, λ_{max} (in alcohol), 260 mμ, (log ε 3.96).

2-Imino-4-oxo-4a-ethyl-2,3,4,4a,5,10-hexahydropyrimido[4,5-b]quinoline (VIII, R = C_2H_5, X = NH). To a solution of sodium ethoxide (from 0.58 g of metallic sodium and 30 ml of absolute alcohol) was added 1 g of guanidine hydrochloride (VII · HCl, X = NH) plus 2.75 g of VI. The mixtures was boiled for 4 h, the alcohol was distilled off, and 10 ml of water plus 15 ml of ether was added to the residue. The aqueous layer was separated and was neutralized with a 2 N hydrochloric acid to a pH of approximately 7.0; the precipitate was filtered off, washed with water, and dried. Compound VIII was obtained. Starting VI was isolated from the ether solution after drying it and evaporating. Compound VIII, where R = C_2H_5 and X = 0, was prepared similarly. By the method described above we also prepared compound VIII, where R = H, and X = 0, NH, or S. 3,4-Dihydrocarbostyril (see Table 1) was extracted with chloroform from the aqueous mother liquors (after evaporation to one-half of the initial volume).

2-(N-Thioureido)-3-ethyl-3,4-dihydroquinoline (IX). This was prepared from 2.75 g of VI and 0.76 g of thiourea (VII, X = S) under the action of sodium ethoxide (from 0.46 g of metallic sodium and 20 ml of absolute alcohol) under the same conditions as VIII. The yield was 0.7 g (30%), mp 156-157°. Found %: C 62.02; H 6.36; N 17.59; S 13.89. $C_{12}H_{15}N_3S$. Calculated %: C 61.80; H 6.44; N 18.03; S 13.73 λ_{max} (in alcohol), 227 mμ, (log ε 4.07), λ_{max} 306 mμ, (log ε 4.41).

From the ether extract there was isolated 0.25 g (9%) of VI, bp 109° (0.5 mm), n_D^{20} 1.5278.

1-Ethyl-2-ethoxy-3-carbethoxy-3,4-dehydroquinolinium fluoborate (X). To a solution of 12.4 g of V in 10 ml of dry methylene chloride was added 10.5 g of triethyloxonium fluoborate (two layers were formed), and the mixture was stirred for 6 h and allowed to stand overnight. The solvent was distilled off, the

precipitate was filtered, and it was thoroughly washed with absolute ethyl acetate. Yield, 10 g (55%), mp 145-147° (from chloroform). Found %: C 53.18; H 6.20; N 4.14. $C_{16}H_{22}NO_3BF_4$. Calculated %: C 52.89; H 6.06; N 3.86. $\nu_{C=O}$ 1760 cm^{-1}, $\nu_{BF_4^-}$ 1040-1090 cm^{-1}, λ_{max} (in alcohol), 248 mμ, (log ε 3.86), 297 mμ, (log ε 3.23).

1-Ethyl-2-ethoxy-3-carbethoxy-1,4-dihydroquinoline (XI). This was prepared from 13.6 g of X in 15 ml of carbon tetrachloride by the action of 10 ml of 50% potassium carbonate solution under the same conditions as V. The yield was 6.9 g (72%), bp 155-157° (1 mm), n_D^{20} 1.5579. Found %: C 69.69; H 7.22; N 5.26. $C_{16}H_{21}NO_3$. Calculated %: C 69.85; H 7.64; N 5.09. $\nu_{C=O}$ 1750 cm^{-1}, $\nu_{C=C}$ 1685 cm^{-1}, λ_{max} (in alcohol), 252 mμ, (long ε 4.01); 327 mμ, (log ε 3.40).

2-Mercapto-4-hydroxy-10-ethyl-5,10-dihydropyrimido[4,5-b]quinoline (XII, X = SH). A. To a solution of sodium ethoxide (from 0.12 g of metallic sodium and 5 ml of absolute alcohol) was added, portionwise over 15 min, 1.5 g of X, at −10°, and the mixture was stirred for 10 min; then a second portion of sodium ethoxide solution (from 0.15 g of metallic sodium and 10 ml of absolute alcohol) was poured in, plus 0.32 g of thiourea, and the mixture was boiled for 4 h. The alcohol was distilled off, 10 ml of water was added, and the mixture was neutralized with 2 N hydrochloric acid solution to pH ~ 7.0. The yield was 0.43 g (40%) of XII (X = SH). Compounds XII (where X = OH or NH_2, see Table 1) were prepared similarly.

B. From 1 g of XI, 0.28 g thiourea, and 0.125 g of metallic sodium in 15 ml of absolute alcohol, analogously to VIII, was prepared 0.2 g (21%) of XII (X = SH).

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