ACETALS OF LACTAMS AND AMIDES.

60.* N- AND O-ALKYLATION OF 5-OXO-5,6,7,8-TETRAHYDROCARBOSTYRYILS. SYNTHESIS OF ISOXAZOLO[5,4-f]- AND PYRAZOLO[3,4-f]QUINOLINES

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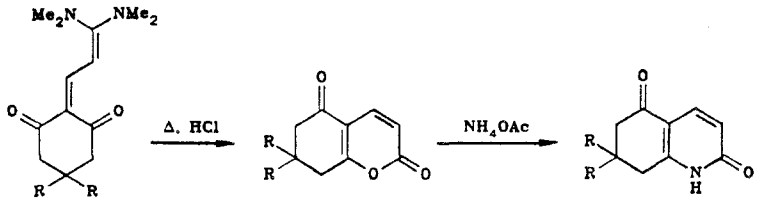
UDC 547.728.2.04

The alkylation of 5-oxo-5,6,7,8-tetrahydrocarbostyrils has been examined by GLC. It has been found that, irrespective of the reaction conditions and the alkylating agent used, both N- and O-alkylation occur. When triethyloxonium fluoroborate and N,N-DMF diethyl acetal are used O-alkylation predominates, and with alkyl halides, N-alkylation. Reaction of N-ethyl-5-oxo-5,6,7,8-tetrahydrocarbostyril and 2-ethoxy-5-oxo-5,6,7,8-tetrahydrotetrahydroquinoline with DMF diethyl acetal gives the 6-dimethylaminomethylene derivatives, treatment of which with hydrazine hydrate or hydroxylamine affording isoxazolo[5,4-f]- or pyrazolo[3,4-f]quinolines.

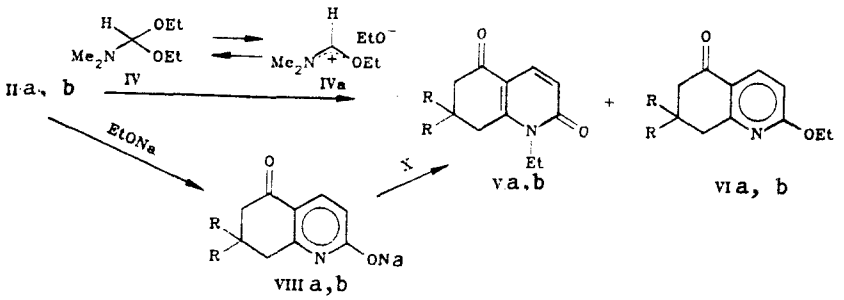
We have previously reported [2, 3] a novel method of preparation of 7,7-dimethyl-5-oxo-5,6,7,8-tetrahydrocoumarin (Ia), followed by its conversion by standard methods [4] into 5-oxo-5,6,7,8-tetrahydrocarbostyril (IIa). Continuing these studies, we have used a similar method with the dienediaminodiketone (IIIb) [2] to obtain the novel coumarin (Ib):



IIIa,b — Ia,b — IIa,b

I–III a R=Me; b R=H

On attempting to obtain novel heterocyclic systems from (IIa, b) and DMF diethyl acetal (IV) (Table 1), instead of the expected condensation products, a mixture of O- and N-alkylated compounds (Va, b) and (VIa, b) were obtained, which were separated preparatively.



VIIIa,b — Va,b — VIa, b

II, V, VI, VIII a R=Me, b R=H; X=EtI, $Et_3O^+BF_4^-$

*For Communication 59, see [1].

S. Ordzhonikidze All-Union Research Institute for Pharmaceutical Chemistry, Moscow 119815. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 1, pp. 86-92, January, 1991. Original article submitted February 14, 1989.

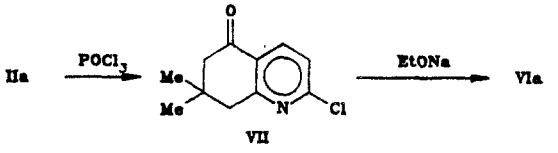
0009-3122/91/2701-0071$12.50

TABLE 1. N- and O-Alkylation Data for (IIa, b) and (VIIIa, b)*

Starting material	Method	Reaction conditions				Ratio		
		solvent	T, °C	reagent	t, h	N—H	N—Et	O—Et
VIIIa	A	Alcohol	60	EtI	10	—	74,4	25,6
	B	Alcohol	20	EtI	10	26,6	60,1	13,3
	C	Toluene	60	EtI	10	93,2	6,8	—
	D	Toluene	60	EtI, TEBAC	10	80,1	17,0	2,9
	E	DMF	60	EtI	10	—	67,0	33,0
IIa	F	Benzene		50% NaOH (H_2O), EtI	10	57,3	41,5	1,2
	G	Toluene	110	Acetal IV	3	24,0	32,0	44,0
	H	Chloroform	20	$Et_3O^+BF_4^+$	18	62,1	4,8	33,1
VIIIa	I	Chloroform	20	Et_3OBF_4	1	10,1	17,1	72,9
VIIIb	J	Alcohol	60	EtI	10	2,1	72,8	25,1
IIb	K	Toluene	110	Acetal IV	3	34,9	26,5	33,6

*Obtained by GLC.

Comparison of the UV spectra of these compounds with those of the starting carbostyrils showed that although the spectrum of one of the products was unchanged [$\lambda_{max}(\varepsilon)$ for carbostyril (IIa) (alcohol) 207 (9720), 285 nm (17,200); for (Va) 213.5 (11,720), 286.5 nm (190,000)], that of the other isomer showed marked differences [for (VIa) 214.3 (11,500), 256.5 (11,400), 288 nm (14,200)]. Similar spectra were obtained for (Vb) and (VIb). This leads to the conclusion that (Va, b) are the N-ethyl, and (VIa, b) ethoxy-derivatives. Final proof of the structures of the compounds was obtained by direct synthesis of the ethoxy-compound (VIa) from the carbostyril (IIa) via the chloro-compound (VII):



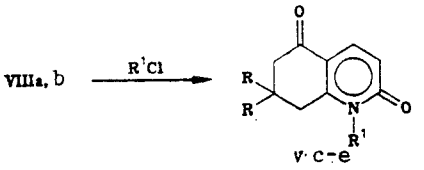
A similar account of the alkylation of condensed pyridones by acetal (IV) has been given recently [5], in which a likely mechanism for these reactions was given. Since the substrate for alkylation is undoubtedly a mesomeric ion, formed by removal of a proton from the NH group of the carbostyrils (II), it was of interest to compare the alkylation of carbostyrils (IIa, b) by acetal (IV) with the alkylation of the sodium salts of these compounds by ethyl iodide and diethyloxonium fluoroborate.

According to GLC (Table 1), (IV) and triethyloxonium fluoroborate gave larger amounts of the ethoxy-derivatives than of the N-ethylated compounds, while in the latter case the selectivity of the reaction (alkylation at oxygen) was much higher, in full accordance with an earlier report [6] of the greater tendency of this reagent to form O-alkyl derivatives. It is noteworthy that the reaction of $Et_3O^+BF_4^-$ with the quinolone (IIa) itself (rather than its salt) also gives mainly the ethoxy-derivative, although in this case substantial amounts of the starting quinolone (IIa) remained. The extent of conversion of (IIa) (used as the sodio-derivative (VIIIa) on reaction with ethyl iodide was highly dependent on the solvent and temperature. For instance, when the alkylation was carried out in alcohol at 20°C 27% of the starting material remained unreacted, whereas at 60°C conversion of (IIa) was 100%. In both instances N-alkylation predominated. Similar behavior is seen when the polar DMF is used. When the reaction was carried out in toluene, only small amounts of the N-alkylated product were obtained, but somewhat smaller amounts of the starting material remained when a phase-transfer catalyst was used under these conditions, thus increasing the solubility of the salt. Even more of the N-ethylated product was obtained when the reaction was carried out in a two-phase system (benzene–aqueous KOH) in the presence of TEBAC. In all cases, however, N-alkylation predominated.

This behavior was largely unaffected when the quinolone (IIb) was used as starting material; alkylation of the sodium salt (VIIIb) with ethyl iodide gave predominantly the N-alkyl derivative (Vb), while alkylation with (IV) or $Et_3O^+BF_4^-$ gave the ethoxy-compound (VIb).

Thus, the use of charged alkylating agents [the ambident cation of (IVa) in alkylation with (IV) or the triethyloxonium cation] results mainly in O-alkylation, and use of uncharged reagents (ethyl iodide and some others – see below), in N-alkylation.

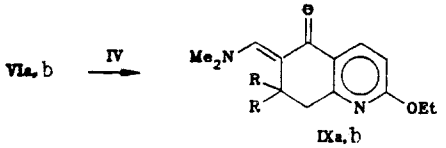
Under the conditions which are optimum for N-alkylation of 2-quinolones (alcohol, 60°C), the use of other alkylating agents (benzyl chloride and dimethylaminoethyl chloride) afforded the N-substituted quinolones (Vc-e). Compounds (Vc, d) were isolated as their hydrochlorides.



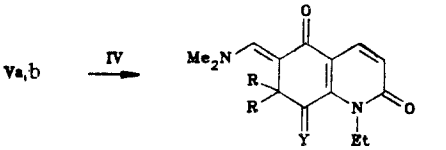
V c R=Me, $R^1=CH_2NMe_2 \cdot HCl$; d R=H, $R^1=CH_2NMe_2 \cdot HCl$; e R=H, $R^1=C_6H_5$

The mass spectra of (VIc-e) showed, in addition to the ion peaks, peaks formed by elimination of the substituent at nitrogen, such as $[M^+-CH_2=CH-NMe_2]^+$ 191(5)* for quinolone (Vb), and $[M^+-CH_2C_6H_5]^+$ 162(5) for (Ve). The strongest peaks correspond to elimination of the fragments $CH_2=CH-NMe_2$ 71(100) and $C_7H_7^+$ 91(100). The UV spectra of the products showed a single absorption band at 230-240 nm [λ_{max} 285 for (Vc), 283 for (Vd), and 284 nm for (Ve)], indicating the formation of N-substituted quinolones.

Attempts to introduce the dimethylaminomethyl grouping into (IIa) or (IIb) using the acetal (IV) were complicated by alkylation, and these complications were therefore avoided by using the N- and O-alkylated derivatives (V) or (VI). Condensation then occurred, although under very severe conditions (toluene, 180-200°C, autoclave):

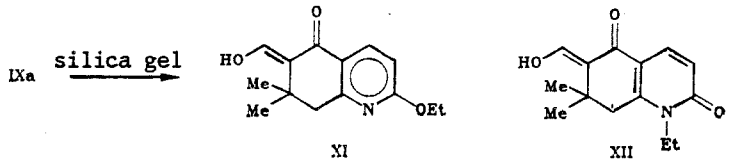


IXa, b



Xa–c Xa, b Y=H_2; c Y=CHNMe_2

It was found that the use of the 7,7-dimethylquinolines (Va) and (VIa) in this reaction resulted in considerable resinification, and column chromatography on silica gel resulted in the recovery of up to 70% of the starting materials (Va) and (VIa). With respect to the expected reaction products (IXa) and (Xa), in the case of the 2-ethoxyquinoline (VIa), a fraction was obtained which was shown by mass spectroscopy to contain both the enamine (IXa) [$M^{+\cdot}$ 247 (38)] and the product of its hydrolysis on silica gel (XI) [$M^{+\cdot}$ 247 (38)]. In the case of the quinolone (Va), hydrolysis of the reaction product (Xa) on silica gel proceeded to completion to give (XII) [$M^{+\cdot}$ 247].



XI XII

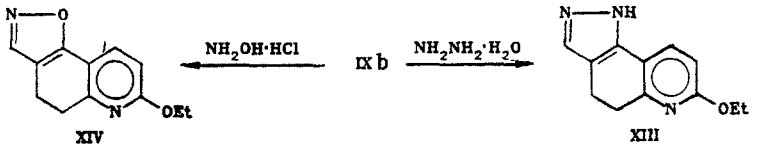
It was not, however, possible to obtain either (IXa) or (Xa) in the pure state.

The considerable steric hindrance created by the two methyl groups in the 7-position of (Va) and (VIa) led us to attempt the use in this reaction of the 7-unsubstituted quinolines (Vb) and (VIb). In these cases, the reaction proceeded fairly smoothly to give high yields. With (Vb), reaction at 180°C resulted in the formation of the monosubstituted quinolone (Xb) [$M^{+\cdot}$ 246 (100)], while at 200-210°C afforded the disubstituted product (Xc) [$M^{+\cdot}$ 301 (78)].

The PMR spectra ($CDCl_3$) of (IXb) showed some changes. In addition to signals for the protons characteristic of the starting 2-ethoxyquinoline (VIb) (see Experimental), new signals were seen at 3.13 (NMe_2, s, 6H) and 7.65 ppm (α-CH, s, 1H) for the enamine fragment; the signals for one CH_2 group of the cyclohexene ring disappeared, and the signals for the other

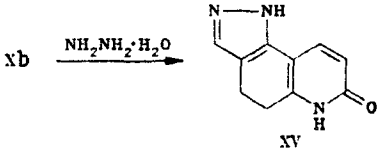
*Here and subsequently, the m/z (I_{rel}, % of maximum ion peak) are given for the ion peaks.

two merged, being seen as a multiplet of intensity 4H at 3.01-2.88 ppm. Hence, the PMR and mass-spectral findings indicate the formation of the monosubstitution product (IXb). However, reaction of (VIb) with the acetal (IV) could occur at either the 6- or the 8-position of the starting quinoline (VIb), and the spectral data do not show at which position substitution has taken place. To resolve this question, (IXb) was condensed with hydrazine hydrate and hydroxylamine hydrochloride, to give the tricyclic pyrazole (XIII) ($M^{+\cdot}$ 215) and isoxazole (XIV) (M^{+} 216), showing conclusively that reaction of the quinolone (VIb) with (IV) resulted in the formation of (IXb):



XIV XIII

Similar behavior is seen in the case of (Vb). The PMR spectrum ($CDCl_3$) of the product of condensation of (Vb) with (IV) showed, in addition to signals for the protons characteristic of (Vb) (see Experimental), signals for the protons of the NMe_2 and α-CH groups at 3.12 (s, 6H) and 7.57 ppm (s, 1H) corresponding to the enamine fragment, while the signals for one of the CH_2 groups of the cyclohexene ring disappeared, and the signals for the protons of the other two groups were seen as a multiplet at 2.88-3.07 ppm (m, 4H). Cyclocondensation with hydrazine hydrate afforded the pyrazoloquinoline (XV) ($M^{+\cdot}$ 215), showing that condensation of (Vb) with (IV) had taken place at the 6-position:



XV

EXPERIMENTAL

PMR spectra were obtained on a Varian XL-200, internal standard TMS. Mass spectra were obtained on a Varian MAT-112 (Phinnigan) with direct insertion of the sample into the ion source. The ionization chamber temperature was 180°C, and the ionizing electron energy 70 eV. Melting points were determined on a Boetius hot plate. The reaction mixtures were analyzed by GLC on a Carlo Erba (Italy) GC 6000 Vega Series 2 chromatograph with a flame ionization detector with a column of length 1 m, 5% OV-17 on Chromaton N-DMCS, T_{evap} 250°C, T_c programming, T_{init} 60°C, heating rate 10°C/min to 110°C, held for 2 min, then heating at 10°C/min to 220°C. The elemental analyses for (Ia), (VII), (Va-e), (IXb), (Xb, c), (XIII), (XIV), and (XV) were in agreement with the calculated values.

5-Oxo-5,6,7,8-tetrahydrocoumarin (Ib). A solution of 23.6 g (0.2 mole) of the dienediaminodiketone (IIIb) [2] in 500 ml of 10% aqueous HCl was boiled for 2 h, cooled, extracted with chloroform (3 × 150 ml), the extracts dried over sodium sulfate, and the chloroform evaporated. Mp 50-52°C (from heptane), $M^{+\cdot}$ 164, yield 11.9 g (73%).

5-Oxo-5,6,7,8-tetrahydrocarbostyril (IIb). A mixture of 1.64 g (0.01 mole) of the coumarin (Ib) and 1.93 g (0.025 mole) of ammonium acetate in 5 ml of glacial acetic acid was boiled for 1 h, evaporated, cooled, and the solid filtered off, washed with 10 ml of water, and dried to give 0.89 g (60%) of the carbostyril (IIb). The mother liquors were evaporated, and the residue triturated with 5 ml of water to give a further 0.42 g (26%) of IIb, mp 292-293°C (from DMF) (according to [7], mp 289-291°C (from methanol).

Sodium Salt of 5-Oxo-5,6,7,8-tetrahydrocarbostyril (VIIIa). To a solution of sodium methoxide (from 2.3 g of metallic sodium and 40 ml of methanol) was added 19.1 g (0.1 mole) of the carbostyril (IIa). When the solid had dissolved, 100 ml of dry toluene was added, and the methanol–toluene azeotrope distilled off up to 110°C. The reaction mixture was cooled, and the sodium salt (VIIIa) filtered off. Mp 300°C, yield 21.2 g (100%).

N-Ethyl-5-oxo-7,7-dimethyl-5,6,7,8-tetrahydrocarbostyril (Va), $C_{13}H_{17}NO_2$) and 2-Ethoxy-4-oxo-7,7-dimethyl-5,6,7,8-tetrahydrocarbostyril (VIa). A. A solution of 2.13 g (0.01 mole) of the sodium salt (VIIIa) in 10 ml of absolute ethanol was heated to 60 °C, 6.24 g (0.04 mole) of ethyl iodide added, and the mixture kept at this temperature for 10 h. It was then evaporated, 10 ml of water added, acidified with HCl to pH 4-5, extracted with chloroform (3 × 50 ml), dried, and evaporated. The resulting mixture was separated on a column (silica gel 4/100, benzene). The

first fraction contained 0.55 g (25%) of (VIa), mp 52°C (from heptane), and the second 1.62 g (74%) of (Va), mp 130-132°C (from methanol).

B (for VIa). **2-Chloro-5-oxo-7,7-dimethyl-5,6,7,8-tetrahydroquinoline (VII, $C_{11}H_{12}ClNO$).** In 30 ml of phosphoryl chloride were dissolved 3.82 g (0.02 mole) of the carbostyril (IIa) and 2 g of $Et_3N \cdot HCl$, the mixture boiled for 30 min, the phosphoryl chloride distilled off, neutralized with 40% aqueous NaOH and ice, extracted with chloroform (3 × 50 ml), dried, and the chloroform evaporated to give 3.24 g (77%) of (VII) [$M^{+\cdot}$ 209 (^{35}Cl)], mp 82-83°C (from heptane).

In 20 ml of absolute ethanol was dissolved with heating 2.09 g (0.01 mole) of the 2-chloroquinoline (VII), and 6.8 g (0.1 mole) of sodium ethoxide in 50 ml of ethanol (from 2.3 g of metallic sodium in 50 ml of ethanol) added. The mixture was evaporated, 20 ml of water added, extracted with chloroform (3 × 20 ml), dried, and evaporated to give 2.1 g (96%) of the 2-ethoxyquinoline (VIa).

Sodium Salt of 5-Oxo-5,6,7,8-tetrahydrocarbostyril (VIIIb). Obtained as for (VIIIa), yield 18.4 g (100%), mp 300 °C.

N-Ethyl-5-oxo-5,6,7,8-tetrahydrocarbostyril (Vb, $C_{11}H_{13}NO_2$) and 2-Ethoxy-5-oxo-5,6,7,8-tetrahydrocarbostyril (VIb) were obtained as for (Va) and (VIa) (method A). Carbostyril (VIb): mp 57-58°C (from heptane); according to [7], mp 53-55°C (from DMF-water). PMR spectrum ($CDCl_3$): 6.48 (1H, d, 3-H), 7.97 (1H, d, 4-H, $^3J_{3,4}$ = 9.5 Hz) (cis), 3.00 (2H, t, 6-H), 2.54 (2H, t, 8-H), 2.27-2.14 (2H, m, 7-H), 1.4 (3H, t, CH_3CH_2), 4.14 ppm (2H, q, CH_3CH_2). Yield 0.48 g (25%). Compound (Vb): mp 147-150°C. PMR spectrum ($CDCl_3$): 6.68 and 7.95 (1H each, d, 3-H and 4-H, $^3H_{HH}$ = 9.5) (cis), 3.01 and 2.54 (2H each, to, 6-H and 8-H), 2.17-2.27 (2H, m, 7-H), 1.34 (3H, t, CH_3CH_2), 4.63 ppm (2H, q, CH_3CH_2).

N-(β-Dimethylaminoethyl)-5-oxo-7,7-dimethyl-5,6,7,8-tetrahydrocarbostyril Hydrochloride (Vc, $C_{15}H_{22}N_2O_2 \cdot HCl$). To a suspension of 2.13 g (0.01 mole) of the sodium salt (VIIIa) in 10 ml of absolute ethanol at 80°C was added 3.23 g (0.03 mole) of β-dimethylaminoethyl chloride. The mixture was kept at this temperature for 5 h, evaporated, 50 ml of water added, extracted with chloroform (3 × 50 ml), dried, and evaporated. The oil was dissolved in 10 ml of 2-propanol, and a solution of HCl in 2-propanol added dropwise until no more solid separated to give 2.15 g (72%) of the hydrochloride (Vc), mp 193-195°C (from 2-propanol), $M^{+\cdot}$ 263.

N-(β-Dimethylaminoethyl)-5-oxo-5,6,7,8-tetrahydrocarbostyril Hydrochloride (Vd, $C_{13}H_{18}N_2O_2 \cdot HCl$). This was obtained as for the hydrochloride (Vc), from the sodium salt (VIIIb). Mp 216-219°C, $M^{+\cdot}$ 235. Yield 1.16 g (43%).

N-Benzyl-5-oxo-5,6,7,8-tetrahydrocarbostyril (Ve, $C_{16}H_{15}NO_2$). To a solution of 1.85 g (0.01 mole) of the sodium salt (VIIIb) in 20 ml of absolute ethanol at the boil was added 1.52 g (0.012 mole) of benzyl chloride. The mixture was boiled for 2 h, cooled to 20°C, and filtered. The filtrate was evaporated, triturated with 2 ml of 2-propanol, and the quinoline (Ve) (1.75 g, 60%) filtered off, mp 118-122°C, $M^{+\cdot}$ 253.

Alkylation of 5-Oxo-7,7-dimethyl-5,6,7,8-tetrahydrocarbostyril (IIa) and Its Sodium Salt (VIIIa) with Ethyl Iodide Under Various Conditions, and with Triethyloxonium Fluoroborate and DMF Dimethyl Acetal (IV). These reactions were carried out as described for (Va) and (VIa), method **A**. In case **D**, 0.22 g (10% by weight of TEBAC was added. In case **I**, the mixture was treated with 60 ml of 25% aqueous potassium carbonate solution.

The ratios of N- to O-alkylation products were measured by GLC of the chloroform solutions after workup of the reaction mixtures (Table 1).

The alkylation of (IIb) and (VIIIb) was carried out as described for the alkylation of carbostyril (IIa) and its sodium salt (VIIIa).

2-Ethoxy-5-oxo-6-dimethylaminomethylene-5,6,7,8-tetrahydroquinoline (IXb, $C_{14}H_{18}N_2O_2$). A solution of 1.91 g (0.01 mole) of the quinoline (VIb) and 14.7 g (0.1 mole) of DMF dimethyl acetal (IV) in 20 ml of dry toluene was kept at 200°C in an autoclave for 6.5 h. The reaction mixture was evaporated, and the residue washed with petroleum ether to give 2.05 g of (IXb), $M^{+\cdot}$ 246.

N-Ethyl-5-oxo-6-dimethylaminomethylene-5,6,7,8-tetrahydrocarbostyril (Xb, $C_{14}H_{18}N_2O_2$) and N-Ethyl-5-oxo-6,8-dimethylaminomethylene-5,6,7,8-tetrahydrocarbostyril (Xc, $C_{17}H_{23}N_3O_2$). A. Compound (Xb) was obtained as described for (IXb) at 180°C. The yield of (Xb) was 1.55 g (63%), $M^{+\cdot}$ 246.

B [for the preparation of a mixture of (Xb) and (Xc)]. The reaction was carried out as described for method **A**, but at 200°C. The oil following evaporation was triturated with 10 ml of ethyl acetate, the solid filtered off to give 0.5 g of (Xb), and the filtrate evaporated and triturated with 5 ml of ethyl acetate to give 0.5 g (17%) of the quinolone (Xc).

7-Ethoxy-5,6-dihydropyrazolo[3,4-f]quinoline (XIII, $C_{12}H_{12}N_2O_2$). A solution of 2.46 g (0.01 mole) of the enamine (IXb) and 1.04 g (0.015 mole) of hydrazine hydrate in 20 ml of absolute ethanol was stirred for 1 h, evaporated, the oil triturated with 2-propanol, and 1.2 g (56%) of the pyrazoloquinoline (XIII) filtered off. Mp 144.5-145.5°C, $M^{+\cdot}$ 215.

7-Ethoxy-5,6-dihydrooxazolo[5,4-f]quinoline (XIV, $C_{12}H_{12}N_2O_2$). A solution of 2.46 g (0.01 mole) of the enamine (IXb) and 1.04 g of hydroxylamine hydrochloride in 10 ml of glacial acetic acid was boiled for 3.5 h with the addition of 1-2 drops of concentrated sulfuric acid, evaporated, and passed through a column (silica gel 40/100, ethyl acetate). The first fraction contained 0.82 g (38%) of the isoxazolinone (XIV), mp 93.5-94°C, $M^{+\cdot}$ 216.

5-Ethyl-6-oxo-4,5,7,8-tetrahydropyrazolo[3,4-f]quinoline (XV, $C_{12}H_{13}N_3O$) was obtained as described for (XIII) from the enamine (Xb), but the reaction mixture was kept for 3 days, evaporated, the oil rubbed with 2 ml of ethyl acetate, and the pyrazoloquinoline (XV) filtered off (1.81 g, 84%), mp 248-253°C, M^+ 215.

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PMR SPECTROSCOPIC STUDY OF THE KINETICS OF H/D EXCHANGE IN METHYL GROUPS IN A SERIES OF HETEROCYCLIC AZINES

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UDC 543.422.25:541.124'-127:547.823'854.04

The rate of H/D exchange among methyl group protons in a series of substituted 3-hydroxypyridines, 5-hydroxypyrimidines, and their N-oxides has been shown to increase with increasing acidity of the medium. The most reactive form of these molecules is the cationic form at pH < 2. The rate of H/D exchange of CH_3 group protons in 3-hydroxypyridine derivatives has also been found to be several orders of magnitude lower than the rates of exchange for methyl-substituted 5-hydroxypyrimidine and its N-oxide. Effective rate constants for methyl group proton exchange have been estimated. In the case of methyl-substituted 5-hydroxypyrimidine N-oxide derivatives it has been established that the rate of proton exchange is greater for an ortho-methyl group than for a methyl group in the para-position relative to the N-oxide site.

Nitrogen heterocycles (such as β-hydroxypyridine and pyrimidine derivatives, for instance) serve as the basis for the synthesis of many pharmaceutical agents. Studies of the characteristic reactivity of side chain protons in series of substituted

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Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 1, pp. 93-96, January, 1991. Original article submitted June 13, 1989.

0009-3122/91/2701-0076$12.50