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SYNTHESIS OF FUNCTIONALLY SUBSTITUTED DERIVATIVES OF THIAZOLO[4,5-f]QUINOLINE, PYRIDAZINO[3,4-f] QUINOLINE AND 5-HYDROXYQUINOLINE BASED ON 3-CYANO-6-BROMO-1,2,5,6,7,8-HEXAHYDROQUINOLINE-2,5-DIONE

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Recently, data has appeared in the literature on the pronounced cardiotonic activity of derivatives of thiazolo[4,5-f] quinoline [1]. During investigations to synthesize derivatives of the 3-cyano-2-pyridone series having cardiotonic activity [2], in the present work we have undertaken the synthesisis of members of the thiazolo[4,5-f]quinoline series, based on the reaction developed in [1] and on the reaction of 3-cyano-6-bromo-1,2,5,6,7,8-hexahydroquinoline-2,5-dione (I) with different thioamides. For the latter we chose thiocyanacetamide (II) and lactam derivatives: 1-thiocarbamoylmethyl-2-pyrrolidone (IIIa), -thio-2-pyrrolidone (IIIb), and -caprolactam (IIIc), obtained either by treating the corresponding N-cyanomethyllactams with NH_4HS [3], or (in the case of IIIb) by reacting piracetam – 1-carbamoyl-2-pyrrolidone – with phosphorus pentasulfide [4]. On attempting to reproduce a known method for obtaining bromoderivative I [1], we encountered significant difficulties: by bromination of 3-cyano-1,2,5,6,7,8- hexahydroquinoline-2,5-dione (V) in acetic acid, it was not possible to obtain the desired product, and quinolinedione (V) was isolated in greater than 70% yield.

The optimal solvent for the bromination was found to be DMFA; the reaction proceeds smoothly in it and compound I was obtained in good yield. Condensation of compound I with thioamides II and IIIa-c, as in [1], was carried out in DMFA. However, in these cases, harsher conditions are required: for IIIa-c, heating for 7 h at 60°C; for II, the reaction does not go under these conditions, and to obtain the desired product (VIa), a mixture of I and II is heated for 7 h at 100°C. As a result, we obtained 5-substituted and 3-cyanothiazolo[4,5-f]-2-pyridones (VIa-d) in satisfactory yields.

Considering that in recent years, a number of active cardiotonic preparations have been found among hydrogenated 3-pyridazines and condensed systems containing a 3-tetrahydropyridazinone fragment [5], in the present work we study the possibility of transforming the bromoderivative of I to systems of this type. For this purpose, bromoketone I was added to a reaction with the sodium salt of malonic ester in benzene with heating in the presence of an interphase catalyst, triethylbenzylammonium chloride (TEBAC). Under these conditions, however, the reaction proceeded mainly in the direction of dehydrobromination and formation of 3-cyano-5-hydroxy-2-quinoline (VII) in 68% yield. The desired product, 3-cyano-6-(diethoxycarbonyl)methyl-1,2,5,6,7,8-hexahydroquinoline-2,5-dione, was isolated in a yield of only 10%. Reaction of this compound with hydrazine hydrate results in the formation of the hydrazide of 3-cyano-1,2,6,7,8,8a,9,10-octahydropyridazino[3,4f]quinoline-2,7-dione-8-carboxylic acid (IX).

An attempt was made to avoid the reaction involving dehydrobromination of I by using its 7,7-dimethyl derivative (X). By bromination of 7,7-dimethyl-3-cyano-1,2,5,6,7,8-hexahydroquinoline-2,5-dione (XI) [6] we sythesized the previously undescribed bromoketone (X), the structure of which followed from its ^{1}H-NMR spectrum (d7-DMFA). Since a molecule of X contains an asymmetric carbon atom (C^6), the methyl groups at C^7 and the protons of the 8-CH_2 group are nonequivalent; the methyl groups are present in the spectrum as two singlets at 1.21 and 1.23 ppm (intensity of 3 proton units (p.u.) each, and the 8-CH_2 group as two doublets (1 p.u.) at 2.94 ppm (^{2}JJ-18 Hz) and 3.10 ppm. The methyl proton at C^6 forms a weakly broadened singet in the spectrum with a chemical shift of 4.72 ppm (remote spin–spin coupling with C^8H). The signal of the aromatic proton C^4H is observed at 8.45 ppm (s, 1H). We believed that the difficulty in dehydrobrominating bromoketone X, caused by the presence of 7,7-dimethyl groups, would permit synthesis of the dimethyl analog (diester) of VIII (XII) in satisfactory yield. It turned out, however, that on reaction with $NaCH(COOEt)_2$ under the above-described conditions, compound

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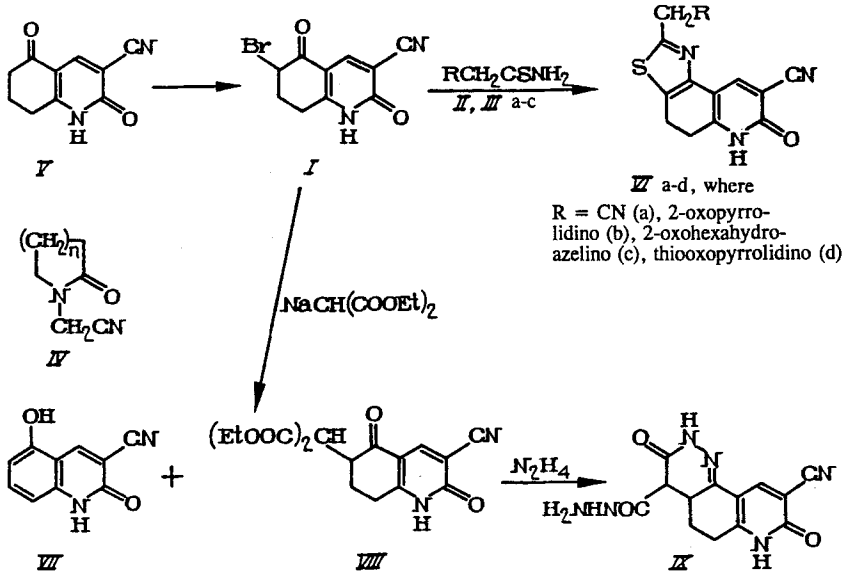
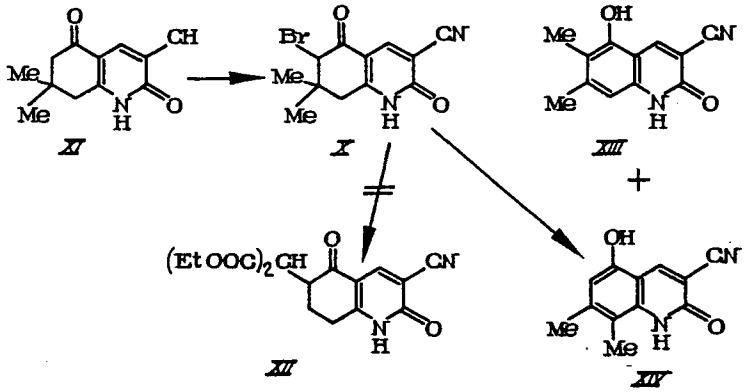


XII is not formed at all (^{1}H-NMR and mass spectral data), and the main direction of the process is dehydrobromination, accompanied by migration of one of the methyl groups. A mixture of isomers (XIII and XIV) is formed with a total yield of 72%, analysis of which was carried out by ^{1}H-NMR spectroscopy.



One feature of the ^{1}H-NMR spectrum of the isolated product (D_2O + NaOD) is the doubling of all signals, caused by the presence of compounds (XIII, XIV) in different relative amounts. Detailed analysis of the multiplicity of signals allows one to reliably assign the observed signals to the appropriate isomers. Thus, in the predominant isomer (content of 85%), the signal of proton C^4H (δ 8.64 ppm) is clearly split into a doublet due to remote spin–spin coupling with C^8H ($SSCC^5JC^4H$, C^8H = 0.7 Hz). The signal of C^8H (δ 6.46) is additionally broadened due to spin–spin coupling with the ortho 7-Me group (δ 2-29 ppm). The second methyl group at position 6 is observed as a narrow singlet at 2.08 ppm. In the spectrum of the minor isomer, proton C^4H is present as a narrow singlet at 8.61 ppm, while the signal of C^6H is weakly broadened because of spin-spin coupling with the ortho methyl 7-Me group (δ 2.26 ppm). The second methyl group 8-Me forms a narrow singlet in the spectrum at 2.24 ppm. Thus, during the reaction, aromatization of the cyclohexane ring occurs, with formation of 6,7 and 7,8-dimethyl derivatives XIII and XIV in a ratio of 85:15. It may be that the preference for aromatization (compared with substitution of the bromine atom by a malonic ester residue) is due to the considerable steric hindrance to attack at position 6 of the molecule, caused by the presence at C^7 of the bulky methyl groups.

Pharmacologic study of derivatives VIa-d and IX did not demonstrate appreciable cardiotonic activity.

EXPERIMENTAL

Mass spectra were obtained on a Varian MAT-112 mass spectrometer, with direct introduction of samples into the ion source. Temperature of the ionization chamber was 180°C. ^{1}H-NMR spectra were recorded in d_6-DMSO on an XL-200 instru-

TABLE 1. Characteristics of Newly Synthesized Compounds

Compound	mp, °C	Yield, %	Empirical formula
IIIc	113—5 (i-PrOH)	60	$C_8H_{14}N_2SO$
VIa	>353	75	$C_{13}H_8N_4SO \cdot H_2O$
VIb	332—3	67	$C_{16}H_{14}SN_4O_2$
VIc	297—8	52	$C_{18}H_{18}N_4SO_2$
VId	>300	53	$C_{16}H_{14}N_4S_2O$
VII	176—7	68	$C_{10}H_6N_2O_2 \cdot 0{,}5H_2O$
VIII	170—3	10	$C_{17}H_{18}N_2O_6$
IX	>300 (aqueous alcohol)	58	$C_{13}N_6H_{12}O_3 \cdot 1{,}1H_2O$
X	267—9 (DMFA)	70	$C_{12}H_{11}BrN_2O_2$

ment (Varian), with TMS as internal standard. Characteristics of compounds synthesized are given in Table 1. Data from elemental analysis corresponded with calculated values.

3-Cyano-6-bromo-1,2,5,6,7,8-hexahydroquinolinedione (I) was prepared according to [1], using DMFA as the solvent.

3-Cyano-6-bromo-7,7-dimethyl-1,2,5,6,7,8-hexahydroquinolinedione (X) was analogously prepared from XI.**8,9-Dihydro-2-oxo-3-cyano-6-cyano-methylthiazolo[4,5-f]quinoline (VIa), 2-Oxo-3-cyano-6-(2′-oxopyrrolidinomethyl)8,9-dihydrothiazolo[4,5-f]quinoline (VIb), 8,9-Dihydro-2-oxo-3-cyano-6-(2′-oxohexahydroazepinomethyl)thiazolo[4,5-f] quinoline (VIc), 2-Oxo-3-cyano-6(2′-thiooxopyrrolidomethyl)-8,3-dihydrothiazolo[4,5-f]quinoline (VId).** A solution of 5.0 mmoles of I and 6.0 mmoles of II and IIIa-c in 10 ml DMFA was heated at 60°C (in the case of II at 100°C) for 7 h, cooled, and the residue was filtered and washed with DMFA and then *i*-PrOH, yielding VIa-d.

3-Cyano-5-hydroxy-2-quinoline (VII), 3-Cyano-6(diethoxycarbonyl)methyl-1,2,5,6,7,8-hexahydroquinoline-2,5-dione (VIII). To a solution of EtONa, obtained from 0.3 g Na and 4 ml EtOH in 50 ml of benzene, was added 1.0 g of I, 0.1 g TEBAC, and 100 ml of benzene. The mixture was refluxed for 10 h, all benzene distilled, the residue cooled, and 80 ml water and 100 ml ether added to it. The suspension was mixed for 1 h and filtered, yielding 0.04 g of I (10%). The aqueous layer was separated and acidified with concentrated HCl to pH 6 and the precipitate filtered, washed with water, and dried, yielding 0.47 g of VII. The ether layer was evaporated and the residue treated with *n*-hexane and filtered, yielding 0.13 g VIII.

A mixture of 85% of 6,7-(XIII) and 15% 7,8-(XIV)dimethyl-3-cyano-5-hydroxy-2-quinolines was obtained in 72% yield as the sole product with analogous reaction of X.

Hydrazyl 3-cyano-1,2,6,7,8,8a,9,10-octahydropyridazino[3,4-f]-quinoline-2,7-dione-8-carboxylic acid (IX). A solution of 0.41 g VIII and 1 ml of hydrazine hydrate in 30 ml of EtOH was refluxed 3 h, cooled, and 0.2 g IX was filtered off.

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