CYCLIZATION OF N-(2-R-1-ANTHRAQUINONYL)UREAS TO ANTHRAPYRIMIDINE DERIVATIVES

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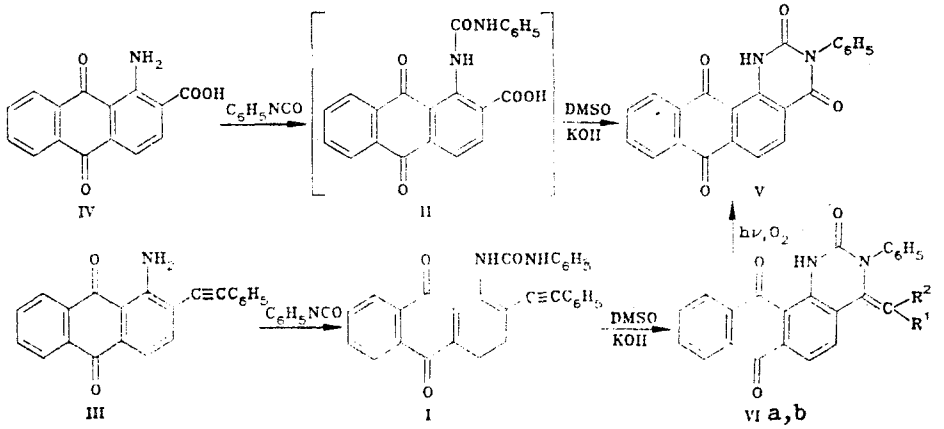
3-Phenyl-1H-naphtho[2,3-h]quinazoline-2,4,7,12-tetrone, 3-phenyl-4-benzylidene-1H-naphtho[2,3-h]quinazoline-2,7,12-trione were synthesized by intramolecular cyclization in the KOH—DMSO system of anthraquinonylureas with a phenylethynyl or carboxy group in the 2 position of the anthraquinone ring.

In DMSO in the presence of bases N-(1-anthraquinonyl)-N′-arylureas form anions that undergo cyclization to anthra[1,2-d]imidazole derivatives [1]. To obtain angular heterocyclic anthraquinone derivatives with a larger heteroring size it seemed expedient to extend this reaction to anthraquinonyl-substituted ureas with a substituent in the 2 position that is capable of reacting with the anionic center of the urea fragment such as, for example, a substituent containing a multiple bond [2-4]. In the present research we studied the transformations of N-(2-phenylethynyl-1-anthraquinonyl)-N′-phenylurea (I) and N-(2-carboxy-1-anthraquinonyl)-N′-phenylurea (II) in the KOH—DMSO system.

Anthraquinonylureas are synthesized by heating aminoanthraquinones and isocyanates in pyridine [5]. We found that urea I is formed in ~60% yield from 1-amino-2-phenylethynylanthraquinone (III) and phenyl isocyanate under these conditions. In conformity with the data in [4], the analogous reaction in the case of 1-aminoanthraquinone-2-carboxylic acid (IV) proceeds less selectively, which hinders the isolation of the desired product — urea II — from the reaction mixture. In this connection we investigated the possibility of the cyclization of anthraquinonylurea II without isolating it in pure form; in this case we obtained a product of cyclization of urea II, viz., 3-phenyl-1H-naphtho[2,3-h]quinazoline-2,4,7,12-tetrone (V), the structure of which was confirmed by analytical and spectral data.



VI a $R^1=H$, $R^2=C_6H_5$; b $R^1=C_6H_5$, $R^2=H$

On the basis of the data in [2, 6] it might be assumed that intramolecular addition of the anionic fragment to both carbon atoms of the ethynyl group to give anthrapyrimidine VI or an anthradiazepine is possible in the case of urea I. We established that treatment of urea I with an aqueous solution of KOH in DMSO at room temperature leads to the formation of two red compounds, which on melting undergo interconversion, whereas in the case of photolysis on the surface of a Silufol chromatographic plate or in solutions they are converted to anthrapyrimidine V.

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The conversion of the products of cyclization of anthraquinonylurea I to anthrapyrimidine V constitutes evidence that a mixture of Z and E isomers of anthrapyrimidine VI is formed in the cyclization. The conversion of VI to anthrapyrimidine V is an oxidative process and probably proceeds with the participation of air oxygen. A similar transformation was described by Riezebos and Havinga [7] in the oxidation of a substituted benzylideneimidazolidine with potassium permanganate to an imidazolidinone.

The spatial configurations of geometrical isomers VIa, b were determined on the basis of spectral data. Thus a comparison of the PMR spectra of VIa and VIb revealed that the location of the singlet of the proton of the $-CH=C_6H_5-$ fragment differs by 0.8 ppm. In the case of Z isomer VIa this signal should probably be located at weaker field as a consequence of the deshielding effect of the benzenoid ring of anthraquinone. In analogy with stilbene derivatives [8], the UV spectrum of Z-(trans)-isomer VIa differs from the spectrum of E-(cis)-isomer VIb by a 15 nm shift of the absorption band of the aromatic ring to the long-wave region and higher absorption intensity. In addition, VIa had a higher melting point and was much less soluble than its isomer VIb, which is also in agreement with the physical properties of cis- and trans-stilbenes.

Thus previously unknown anthrapyrimidine derivatives were synthesized by the intramolecular cyclization of N-(1-anthraquinonyl)-N′-phenylureas with a phenylethynyl or carboxy group in the 2 position of the anthraquinone ring. It should be expected that the use of other 2-R-1-anthraquinonyl-substituted ureas in this reaction will make it possible to obtain new heterocyclic derivatives of anthraquinone.

EXPERIMENTAL

The IR spectra of KBr pellets of the compounds were recorded with a UR-20 spectrometer. The UV spectra of solutions in chloroform were obtained with a Specord UV-vis spectrophotometer. The PMR spectra of solutions in $CDCl_3$ were recorded with a Bruker AM-400 spectrometer with $CHCl_3$ as the internal standard (δ 7.24 ppm). The mass spectra were obtained with a Finnigan MAT 8200 spectrometer. The course of the reactions and the purity of the synthesized compounds were monitored by TLC on Silufol UV-254 plates in chloroform.

The results of elementary analysis of the synthesized compounds for C, H, and N were in agreement with the calculated values.

N-(2-Phenylethynyl-1-anthraquinonyl)-N′-phenylurea (I, $C_{29}H_{18}N_2O_3$). A mixture of 0.88 g (2.7 mmole) of amine III, 1.5 ml (13.9 mmole) of phenyl isocyanate, and 3 ml of pyridine was heated for 1.5 h at 90°C, after which it was cooled, and the precipitate was separated and recrystallized from dioxane—methanol (3:1) to give a product with mp 237-239°C. IR spectrum: 1670 (CO), 2205 (C≡C), 3280 cm^{-1} (NH). UV spectrum, λ_{max}, nm ($\log\varepsilon$): 249 (4.62), 280 (4.66), 450 (3.94). The yield was 0.71 g (59%).

3-Phenyl-1H-naphtho[2,3-h]quinazoline-2,4,7,12-tetrone (V, $C_{22}H_{12}N_2O_4$). A 2-ml (18.5 mmole) sample of phenyl isocyanate was added at 90°C to a solution of 0.82 g (3.1 mmole) of amine IV in 8 ml of pyridine, and the mixture was maintained at 90°C for 2.5 h. It was then cooled, and the precipitate (0.78 g) was separated and dissolved in 50 ml of DMSO. The solution was treated with 3 ml (2.8 mmole) of 5% aqueous KOH solution, and the mixture was maintained at room temperature without stirring for 7 days. It was then poured into 250 ml of water, and the precipitate was separated and chromatographed with a column packed with silica gel (elution with benzene) to give a product with mp 325-328°C (dioxane). IR spectrum: 1650, 1675, 1725 (CO); 3255 cm^{-1} (NH). UV spectrum, λ_{max}, nm ($\log\varepsilon$): 252 (4.53), 281 sh (4.27) 342 (3.62), 415 (3.90). PMR spectrum: 7.48 (5H, m, C_6H_5), 8.00 (2H, m, 9-H and 10-H), 8.06 (1H, d, J = 8 Hz, 5-H), 8.26 (2H, m, 8-H and 11-H), 8.49 (1H, d, J = 8 Hz, 6-H), 11.89 ppm (1H, s, N—H). Mass spectrum: $[M]^+$ 368.0975; M_{calc} 368. The yield was 0.3 g (27%).

3-Phenyl-4-benzylidene-1H-naphtho[2,3-h]quinazoline-2,7,12-trione (VI, $C_{29}H_{18}N_2O_3$). A mixture of 0.55 g (1.2 mmole) of urea I, 2.5 ml (2.3 mmole) of 5% aqueous KOH solution, and 150 ml of DMSO was stirred at room temperature for 3 h, after which it was poured into 600 ml of water. The precipitate was separated and chromatographed with a column packed with silica gel (elution with chloroform) to give 0.45 g of a mixture of Z and E isomers, which was separated by chromatography on Silufol plates (elution with chloroform).

Z-Isomer VIa. This isomer had mp 265-267°C [acetonitrile—dioxane (2:1)]. IR spectrum: 1645, 1670, 1700 (CO); 3260 cm^{-1} (NH). UV spectrum, λ_{max}, nm ($\log\varepsilon$): 270 (4.66), 483 (3.96). PMR spectrum (d_6-DMSO): 6.87* (1H, s, =CH—C_6H_5), 6.90-7.31 (10H, m, $2C_6H_5$), 7.98 (3H, m, 5-H, 9-H, and 10-H), 8.25 (2H, m, 8-H and 11-H), 8.44 (1H, d, J = 8 Hz, 6-H), 11.25 ppm (1H, s, NH). Mass spectrum: $[M]^+$ 442.1336. The yield was 0.08 g (14.5%).

E-Isomer VIb. This isomer had mp 241-243°C [acetonitrile—dioxane (2:1)]. IR spectrum: 1645, 1670, 1690 (CO); 3240 cm^{-1} (NH). UV spectrum, λ_{max}, nm ($\log\varepsilon$): 255 (4.57, 490 (3.78). PMR spectrum: 5.80 (1H, s, =CH—C_6H_5), 7.14 (1H, d, J = 8 Hz, 5-H), 7.26-7.60 (10H, m, $2C_6H_5$), 7.65 (1H, d, J = 8 Hz, 6-H), 7.85 (2H, m, 9-H and 10-H), 8.35

*In $CDCl_3$ δ 6.62 ppm.

(2H, m, 8-H and 11-H), 11.56 ppm (1H, s, NH). Mass spectrum: [M]+ 442.1314; M_{calc} 442. The yield was 0.28 g (51%).

Photolysis of 3-Phenyl-4-benzylidene-1H-naphtho[2,3-h]quinazoline-2,7,12-trione (VI). A 0.13-g (0.7 mmole) sample of a 1:1 mixture of Z- and E-isomers VIa, b was applied to 15 Silufol plates (150 × 150 mm), and the plates were maintained in light until the color changed from red brown to yellow. The photolysis products were extracted with chloroform, chromatographed with a column packed with silica gel (elution with chloroform), and recrystallized from dioxane to give 0.07 g (65%) of anthrapyrimidine V with mp 325-328°C. The IR spectrum was identical to the spectrum of a sample obtained from amine IV.

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SYNTHESIS OF 5-HYDROXY-6-METHYLURACIL 3-β-D-RIBOFURANOSIDE

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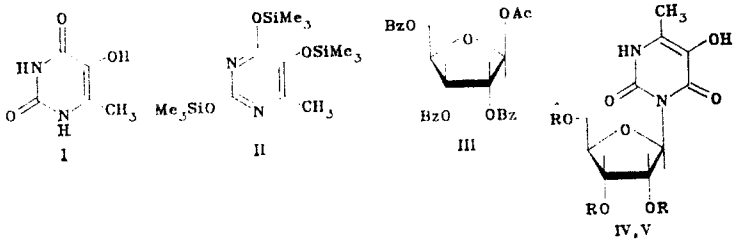
3-(β-D-Ribofuranosyl)-5-hydroxy-6-methyluracil was synthesized by the silyl method in the presence of $SnCl_4$ using 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose as the carbohydrate component. The structures of the glycosides were confirmed by spectral methods.

5-Hydroxy-6-methyluracil (I, hydroxymethacil) is of interest as an immunomodulator and cardiostimulator [1-3]. To obtain the transport form of this compound we began research on the synthesis of nucleosides that are analogs of 6-methylpyrimidine nucleosides [4, 5]. The present communication is devoted to the synthesis of 3-(β-D-ribofuranosyl)-5-hydroxy-6-methyluracil by the silyl method [6].

5-Hydroxy-6-methyluracil (I) was obtained by the method in [7] and was silylated with excess hexamethyldisilazane in the presence of trimethylchlorosilane in dry dioxane as in [8]. The yield of 2,4,5-tris(trimethylsilyloxy)-6-methyluracil (II) was 59%. 1-O-Acetyl-β-D-ribofuranose tribenzoate (III) was obtained by our modification of the method in [9]



IV R=Bz; V R=H; Bz=C_6H_5CO

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