A STUDY OF NITROGEN- AND SULFUR-CONTAINING HETEROCYCLES

XI*. SYNTHESIS OF 1-ARYL- AND 5-ALKYL-1-ARYLURACILS

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The reduction of α-cyanoacylurethanes in an aqueous medium in the presence of hydrochlorides of aromatic amines and Raney nickel has given β-arylaminoacryloyl- and α-alkyl-β-arylaminoacryloylurethanes which have been converted by heating with 10 % aqueous caustic alkalis into 1-aryl- and 5-alkyl-1-aryluracils.

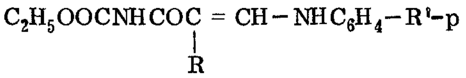
In development of previous work [1, 2] it appeared of interest to study the catalytic reduction of cyanoacylurethanes [3] in order to obtain 1-aryl- and 5-alkyl-1-aryluracils.

The initial cyanoacetylurethane (I) and α-cyanopropionylurethane (II) were obtained by the reaction of urethane with appropriate α-cyanoalkanoic acids in the presence of acetic anhydride.

When I was hydrogenated in water at 45-50°C in the presence of Raney nickel and of hydrochlorides of aromatic amines, β-phenylaminoacryloylurethane [4] (III) and the previously unknown β-arylaminoacryloylurethanes (IV-VII) were obtained. Similarly, II and hydrochlorides of aromatic amines yielded the α-alkyl-β-arylaminoacryloylurethanes (VIII-X) (Table 1).

The formation of compounds III-X probably takes place, as in the case of the β-arylaminoacryloylureas [1], as the result of the reaction of the aromatic amine with the α-formylacylurethane (a). A variation in the nucleophilicity of the amino group in the aromatic amine has a substantial influence on this

TABLE 1.



$$C_2H_5OOCNHCO\underset{\displaystyle R}{\underset{|}{C}}=CH-NHC_6H_4-R'\text{-}p$$

Compound	R	R′	mp, °C (from ethanol)	Empirical formula	Found, %			Calculated, %			IR spectra		UV spectra		Yield, %
					C	H	N	C	H	N	ester C=O	amide C=O	λ_{max}, nm	log ε	
III	H	H	146—148[4]		—	—	—	—	—	—	1733	1654	328	4,53	55
IV	H	CH_3	180—181	$C_{13}H_{16}N_2O_3$	62,9	6,4	11,3	62,8	6,5	11,2	1736	1639	340	4,45	61
V	H	CH_3O	165—166	$C_{13}H_{16}N_2O_4$	58,8	5,8	10,3	59,1	6,1	10,6	1740	1645	340	4,46	42
VI	H	C_2H_5O	173—174	$C_{14}H_{16}N_2O_4$	66,6	5,6	12,9	66,7	5,6	13,0			342	4,44	57
VII	H	HO	147—148	$C_{12}H_{14}N_2O_4$	57,5	5,6	10,7	57,6	5,6	11,2	1730	1640	345	4,05	21
VIII	CH_3	H	157—158	$C_{13}H_{16}N_2O_3$	62,9	6,4	11,3	62,5	6,5	11,5			325	4,53	47
IX	CH_3	C_2H_5O	155—156	$C_{15}H_{18}N_2O_4$	61,9	6,9	9,4	61,6	6,8	9,6			340	4,40	23*
X	CH_3	CH_3O	144—145	$C_{14}H_{16}N_2O_4$	60,4	6,6	10,2	60,4	6,5	10,0	1760	1680	337	4,39	29*

*Yield shown on the α-cyanopropionic acid.

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*For Communication X, see [1].

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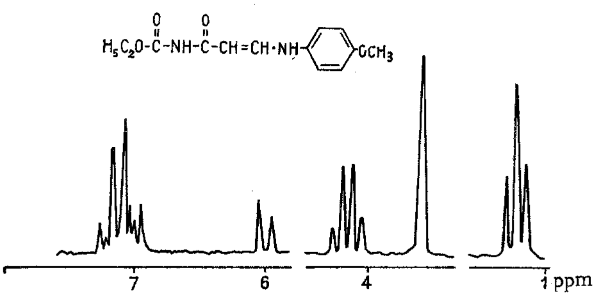
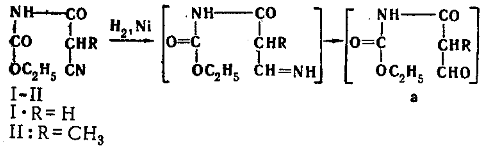
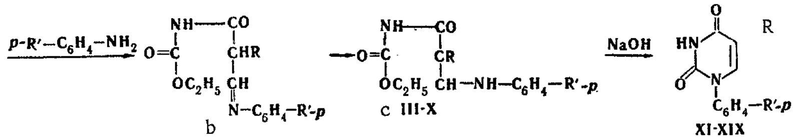


Fig. 1. PMR spectrum of V.

process. Thus, by the hydrogenation of cyanoacetylurethane in the presence of aromatic amines with electron-donating substituents (p-toluidine, p-alkoxyaniline, etc.) IV-VI were isolated with yields of about 60 %. When aromatic amines with electron-accepting groups (for example, p-chloro- and p-nitroanilines, etc.) were used it was impossible to obtain the corresponding β-arylaminoacryloylurethanes.





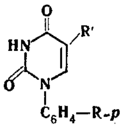
Compounds III-X form colorless crystalline substances withstanding prolonged boiling with water and ethanol. They, like the β-arylaminoacryloylureas, exist predominantly in the form of the derivatives c, and not as the Schiff's bases b. Thus, in the PMR spectrum of V taken in $CDCl_3$ there are no signals of the $\rangle CH_2—CH{=}N$ fragment which is present in structure b but there are signals of olefinic protons; a doublet with a center at 5.97 ppm, the lines of a second doublet being strongly displaced in the downfield region and, apparently, being overlaid by the signals of the protons of the benzene ring (see Fig. 1).

The UV spectra of III-X contain absorption maxima at 330-340 nm. The IR spectra lack the band of a CN group and have the absorption bands of ester and amide C=O groups (1730-1740 cm^{-1} and 1640-1680 cm^{-1}, respectively).

When compounds III-X were heated with 10 % aqueous caustic soda, 1-phenyluracil [4] (XI) and a series of other 1-aryl- and 1-aryl-5-methyluracils (XII-XIX) were obtained with yields of 80-90 % (Table 2).

It has been shown that the passage from the cyanoacylurethanes to the 1-aryluracils can be effected more conveniently without the isolation of the β-arylaminoacryloylurethanes III-X: the reduction product together with a catalyst is heated with 10 % caustic soda solution and the resulting sodium salts of the 1-aryluracils are separated from the catalyst and converted into XI-XIX by treatment with sulfuric acid. This method enables the 1-aryluracils to be obtained practically in one stage with a yield of 60-65 % calculated on the α-cyanoacylurethanes.

TABLE 2



Compound	R	R′	mp, °C (from water)	Empirical formula	Found, %			Calculated, %			UV spectra	
					C	H	N	C	H	N	λ_{max}, nm	log ε
XI	H	H	246—248[4]	—	—	—	—	—	—	—	265	4,09
XII	CH_3	H	234—235	$C_{11}H_{10}N_2O_2$	65,3	4,9	13,8	65,4	4,9	13,9	267	4,07
XIII	CH_3O	H	235—237	$C_{11}H_{10}N_2O_3$	60,4	4,7	12,9	60,5	4,6	12,8	265	4,11
XIV	C_2H_5O	H	252—253	$C_{12}H_{12}N_2O_3$	62,2	5,1	12,1	62,1	5,2	12,1	—	—
XV	HO	H	298	$C_{10}H_8N_2O_3$	59,0	4,0	14,6	58,8	3,9	13,7	265	3,93
XVI	H	CH_3	199—200 (cf. [5])	—	—	—	—	—	—	—	275	4,15
XVII	CH_3	CH_3	217—218	$C_{12}H_{12}N_2O_2$	66,7	5,5	12,7	66,7	5,6	13,0	276	4,08
XVIII	CH_3O	CH_3	214—215,5	$C_{12}H_{12}N_2O_3$	62,2	5,1	12,2	62,1	5,2	12,1	273	4,09
XIX	C_2H_5O	CH_3	190—191	$C_{13}H_{14}N_2O_3$	63,5	5,8	11,7	63,4	5,7	11,4	270	4,05

The structures of XII-XIX were confirmed by their UV spectra. Thus, in the spectra of the 1-aryluracils XI-XV there are absorption maxima at 265 nm coinciding with the absorption maximum of the known 1-phenyluracil [4]. In the spectra of the 1-aryl-5-methyluracils XVI-XIX, this band exhibits a bathochromic shift of 5-10 nm.

EXPERIMENTAL

Cyanoethylurethane (I) was obtained by the method of Conrad and Schulze [6].

α-Cyanopropionylurethane (II). A mixture of 14 g (0.142 mole) of α-cyanopropionic acid, 12.6 g (0.142) mole) of urethane, and 35 ml of acetic acid was heated in the boiling water bath for 3 hr. The acetic acid and the excess of acetic anhydride were evaporated off to dryness, and the residue was distilled in vacuum the fraction with bp 73°C (3 mm) being collected. The oily substance was triturated with ethanol until crystallization began and was left for 10-12 hr. The crystals that had deposited were filtered off, giving 3.1 g (24 %) of a substance with mp 86-87°C. Colorless crystals with mp 89°C (from petroleum ether) soluble in water, ethanol and acetone. Found, %: C 49.4; H 6.0; N 16.8. Calculated for $C_7H_{10}N_2O_3$, %: C 49.4; H 5.9; N 16.5.

General Method for the Preparation of the β-Arylaminoacryloylurethanes (III-X). A mixture of 0.03 mole of an α-cyanoacylurethane, 0.03 mole of the hydrochloride of an aromatic amine, and 8 g of a moist paste of Raney nickel in 100-125 ml of water was hydrogenated at 45-50°C for 2-3 hr. The reaction mixture was cooled to 15-20°C and the precipitate was filtered off together with the catalyst and extracted with ethanol and then with acetone. The ethanolic and acetonic extracts were combined, evaporated to 1/3 of their original volume and cooled to 5-10°C, and the β-arylaminoacryloylurethane that deposited was filtered off and recrystallized. Evaporation of the mother solution and treatment of the residue with water gave an additional amount of β-arylaminoacryloylurethanes. In the synthesis of IX and X technical II was used without purification by vacuum distillation and recrystallization.

General Method for Obtaining the 1-Aryluracils XI-XX. A. At 90°C, 0.03-0.04 mole of a β-arylaminoacryloylurethane was added to 10-15 ml of a 10 % aqueous solution of caustic soda, and the mixture was stirred at this temperature until the substance had dissolved completely. The solution was acidified to pH 3 and cooled to 10-15°C and the precipitate of 1-aryluracil that had deposited was filtered off, washed with water, dried, and recrystallized. Yield 80-90 %.

B. Hydrogenation was carried out as described above with 0.03 mole of an α-cyanoacylurethane, 0.03 mole of the hydrochloride of an aromatic amine, and 8 g of nickel catalyst in 100-125 ml of water. The β-arylaminoacryloylurethane that separated out was filtered off together with the catalyst and transferred into 20-25 ml of a 10 % aqueous solution of caustic soda (or caustic potash) heated to 90-95°C. After the mixture had been stirred at this temperature for 3-5 min, the solution was acidified to pH 3 and treated as described for method A. The yield of 1-aryluracil was 60-65 % calculated on the α-cyanoacylurethane.

Substances XI and XIV were chromatographed on paper (ascending chromatography) in systems 1-3. System 1: $n\text{-}C_4H_9OH-CH_3COOH-H_2O$ (4 : 1 : 5); system 2: $n\text{-}C_4H_9OH-CH_3COOH-H_2O$ (4 : 1 : 1); system 3: $i\text{-}C_3H_7OH-NH_3-H_2O$ (10 : 1 : 1). They had the following R_f values in the given systems: XI – 0.80 (1); 0.71 (2); 0.73 (3); XIV – 0.87 (1); 0.82 (2); 0.90 (3).

The IR spectra were taken on a UR-10 instrument in paraffin oil and the UV spectra on an SF-4 instrument. The PMR spectrum was taken on a JNM-4N-100 instrument with TMS as internal standard in $CDCl_3$.

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