A STUDY OF NITROGEN- AND SULFUR-CONTAINING HETEROCYCLES

X*. THE REDUCTIVE CYCLIZATION OF CYANOACETYLUREA TO FORM URACIL AND ITS 1-ALKYL DERIVATIVES

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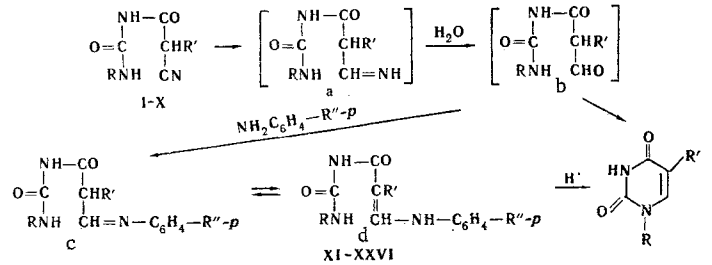
The catalytic hydrogenation of N-α-cyanoacylureas and 1-alkyl-3-α-cyanoacylureas in the presence of hydrochlorides of aromatic amines has given N-β-arylaminoacryloyl-, 1-alkyl-3-β-arylaminoacryloyl-, N-α-alkyl-β-arylaminoacryloyl-, and 1-alkyl-3-α-alkyl-β-arylaminoacryloylureas. The action of N-β-phenylaminoacryloyl- and 1-methyl-3-β-phenylaminoacryloylureas of ethanolic hydrogen chloride has given uracil and 1-methyluracil.

It has been reported previously [2, 3] that the reductive cyclization of cyanoacetylureas in the presence of acetic acid has given uracil and 1-alkyl- and 1,5-dialkyluracils. In continuation of an investigation [3] having the aim of determining the sequence of the reactions leading to uracils, we have studied the reduction of the cyanoacetylureas I-X in the presence of hydrochlorides of aromatic amines [4].

It has been shown that the hydrogenation of the cyanoacetylurea (I) and of 1-methyl-, 1-ethyl-, and 1-isobutyl-3-cyanoacetylureas (II-IV) in water in the presence of aniline hydrochloride and Raney nickel at 40-50°C forms β-phenylaminoacryloylurea (IX) and 1-alkyl-β-phenylaminoacryloylureas (XII-XIV) (see Table 1).



The reduction of I-IV and of 1-isopropyl- and 1-β-ethoxyethyl-3-cyanoacetylureas (V, VI) in the presence of toluidine hydrochloride has given the β-toluidinoacryloylureas XV-XX. Similarly, the hydrogenation of α-cyanopropionyl- and α-cyanovaleroylureas (VII and VIII) and of 1-methyl- and 1-ethyl-3-cyanopropionylureas (IX and X) in the presence of the hydrochlorides of aniline, toluidine, and ethyl p-aminobenzoate has given the arylaminoacryloylureas XXI-XXVI. The production of XI-XXVI is facilitated by the fact that, because of their low solubility in water, they separate out as precipitates as they are formed.

*For Communication IX, see [1].

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TABLE 1

R—NH—CO—NH—CO—CR′=CH—NH—C_6H_4—R″-*p*

Compound	R	R′	R″	Mp, °C (from ethanol)	Empirical formula	Found, %			Calculated, %			UV spectrum		Yield, %
						C	H	N	C	H	N	λmax, nm	log ε	
XI	H	H	H	208—209	$C_{10}H_{11}N_3O_2$	58,5	5,3	20,5	58,5	5,3	20,0	330	4,56	55
XII	CH_3	H	H	178—179 (from methanol)	$C_{11}H_{13}N_3O_2$	60,0	6,1	19,0	60,2	5,9	19,2	334	4,55	59
XIII	C_2H_5	H	H	153—154	$C_{12}H_{15}N_3O_2$	61,5	6,4	18,1	61,8	6,4	18,0			53
XIV	*i*-C_4H_9	H	H	165—166	$C_{14}H_{19}N_3O_2$	64,1	7,5	16,2	64,4	7,3	16,1	332	4,55	51
XV	H	H	CH_3	199	$C_{11}H_{13}N_3O_2$	60,0	6,0	19,0	60,2	5,9	19,2			17
XVI	CH_3	H	CH_3	197—200	$C_{12}H_{15}N_3O_2$	61,8	6,5	18,0	61,8	6,4	18,0			60
XVII	C_2H_5	H	CH_3	189—190	$C_{13}H_{17}N_3O_2$	63,1	6,7	17,0	63,1	6,8	17,0			34
XVIII	*i*-C_3H_7	H	CH_3	188—189 (from acetone)	$C_{14}H_{19}N_3O_2$	64,0	7,2	15,8	64,4	7,3	16,1	335	4,51	54
XIX	*i*-C_4H_9	H	CH_3	124	$C_{15}H_{21}N_3O_2$	65,8	8,0	15,5	65,4	7,6	15,3	330	4,55	22
XX	β-$C_2H_4OC_2H_5$	H	CH_3	137—138	$C_{15}H_{21}N_3O_3$	62,0	7,5	14,6	61,8	7,2	14,4	335	4,54	50
XXI	H	CH_3	H	156—157	$C_{11}H_{13}N_3O_2$	59,7	5,5	18,8	60,2	5,9	19,2			21
XXII	H	CH_3	CH_3	140—141	$C_{12}H_{15}N_3O_2$	61,6	6,6	17,8	61,8	6,4	18,0	335	4,45	52
XXIII	H	CH_3	$COOC_2H_5$	189—191	$C_{14}H_{17}N_3O_4$	57,7	6,0	14,4	57,7	5,8	14,4	345	4,66	58
XXIV	H	*n*-C_3H_7	CH_3	160—161	$C_{14}H_{19}N_3O_2$	64,5	7,0	16,1	64,4	7,3	16,1			55
XXV	CH_3	CH_3	CH_3	170—171	$C_{13}H_{17}N_3O_2$	62,9	6,8	16,9	63,1	6,8	17,0			27
XXVI	C_2H_5	CH_3	CH_3	149—150	$C_{14}H_{19}N_3O_2$	64,6	7,1	16,0	64,4	7,3	16,1	335	4,57	27

Because of this, XI-XXVI escape from the reaction sphere and are not hydrogenated further. The aromatic amines were used in this reaction in the form of the hydrochlorides for the same purpose as acetic acid [3] – to bind the ammonia liberated in the hydrolysis of the intermediate imines *a* to the *α*-formylacetylureas b and, consequently, to prevent the cyclization of the cyanoacetylureas I-X into 6-aminouracil derivatives [3]. The formation of the *α*-formylacetylurea derivatives XI-XXVI shows that the reductive cyclization of the cyanoacetylureas may take place via the stage of the formation of the *α*-formylacetylureas b (see scheme).

In order to find conditions for passing from the *β*-arylaminoacryloylureas to uracil and its N-alkyl derivatives, we studied the behavior of these substances to acidic agents. Thus, it was shown that the action of an ethanolic solution of hydrogen chloride on *β*-phenylaminoacryloylurea (XI) and 1-methyl-3-*β*-phenylacryloylurea (XII) forms uracil and 1-methyluracil, respectively.

The structure of the *β*-arylaminoacryloylureas XI-XXVI was confirmed by their UV and PMR spectra. Thus, in the PMR spectrum of XXIV taken in $CDCl_3$ there are the lines of the signals of olefinic protons: a doublet with a chemical shift of 5.03 ppm with a coupling constant of 8 Hz; the lines of a second doublet are shifted strongly in the downfield direction and are overlaid by the signals of the protons of the benzene ring. Furthermore, the spectrum contains the signals of the protons of an isobutyl group: a triplet corresponding to the signals of the protons of the $>CH_2$, interacting with the protons of the >CH and –NH groups; the multiplet relating to the >CH proton, and the signals of the protons of two methyl groups. The absence of the signals of the protons of the $-CH_2-CH=N-$ fragment indicates that compounds XI-XXVI exist predominantly in the form d and not as the Schiff's bases c.

The UV spectra of compounds XI-XXVI show strong absorption in the 330-335-nm region, probably due to the presence of a system of conjugated bonds in the molecule, which is the case to a greater extent in structure d than in c.

EXPERIMENTAL

The synthesis of the initial compounds I-X has been described previously [3].

General Method of Preparing Compounds XI-XXVI. To a suspension of 0.04 mole of a cyanoacetylalkylurea and 0.044 mole of an arylamine hydrochloride in 200-250 ml of water was added 5-15 g of a moist paste of Raney nickel, and the mixture was hydrogenated at 40-50°C and atmospheric pressure until 0.04 mole of hydrogen had been absorbed. The reaction mixture was cooled to room temperature, and the precipitate of *β*-arylaminoacryloylurea, together with the catalyst, was filtered off, washed with water, and extracted with ethanol or acetone. The ethanolic (or acetonic) extract was evaporated to small volume, and the *β*-arylaminoacryloylurea that had separated out was filtered off and recrystallized from the appropriate solvent. Evaporation of the mother solution gave an additional amount of *β*-arylaminoacryloylurea. Compounds XI-XXVI are colorless crystalline substances.

Uracil. A mixture of 0.9 g (0.0044 mole) of XI and 2.5 ml of an 8.5% solution of hydrogen chloride in anhydrous ethanol was left at 0-4°C for 3-4 days. The precipitate that had formed was filtered off, washed with 0.5 ml of ethanol, and treated with 20 ml of 15% ammonia solution. The insoluble residue was filtered off and washed with 15% ammonia (2 × 1 ml), and the combined filtrates were acidified with 60% sulfuric acid to pH 3. The mixture was cooled to 5°C and the precipitate was filtered off, washed with 3 ml of water, and dried. This gave 0.26 g of product with mp 315-319°C. Evaporation of the mother solution gave an additional 0.12 g with mp 309-315°C. After recrystallization from water, mp 331-333°C. According to the literature [5], mp 335°C. Total yield 0.38 g (77.3%). A mixture with an authentic sample of uracil gave no depression of the melting point.

1-Methyluracil. This was obtained in a similar manner to uracil from 2.5 g (0.0114 mole) of XII and 5.9 ml of an 8.5% solution of hydrogen chloride in ethanol. Yield 1.48 g (80%), mp 231-232°C (from water). According to the literature [6], mp 232°C. A mixture with an authentic sample of 1-methyluracil gave no depression of the melting point.

The PMR spectrum was taken on a JNM-4H-100 instrument in $CDCl_3$, with TMS as internal standard. The UV spectra were taken on an SF-4 spectrophotometer in ethanol.

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