INVESTIGATION OF NITROGEN- AND SULFUR-CONTAINING HETEROCYCLES

XXVI.* SYNTHESIS OF URACIL DERIVATIVES

V. M. Nesterov, S. K. Elagina, and T. S. Safonova

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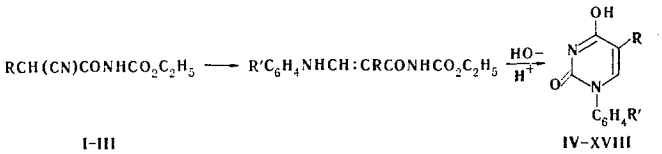
Catalytic hydrogenation of cyanoacetyl-, α-cyanopropionyl-, and cyanobutyrylurethanes in aqueous media in the presence of Raney nickel and the hydrochlorides of o- and p-toluidines, o- and p-alkoxyphenylamines, p-aminoacetophenone, ethyl p-aminobenzoate, and ethyl p-aminophenylacetate, and in the presence of sodium p-aminosalicylate and acetic acid gave the corresponding β-arylaminoacryloyl(or α-alkylacryloyl)urethanes, which were converted, without isolation in the pure state, to 1-aryl- and 1-aryl-5-alkyluracils by heating in dilute alkali solutions.

Hydrogenation of α-cyanoacylurethanes in the presence of the hydrochlorides of aniline, p-toluidine, and p-alkoxyphenylamines gives β-arylaminoacryloyl- and β-alkylacryloylurethanes, which are cyclized to the corresponding 1-aryl- and 1-aryl-5-alkyluracils by the action of alkali. The range of application of this synthesis is ascertained in the present study. The catalytic hydrogenation of cyanoacetylurethane (I) in the presence of o-toluidine and o-anisidine hydrochlorides gives β-arylaminoacryloylurethanes, which are smoothly converted, without isolation in the individual state, to the sodium salts of 1-aryluracils (IV, V) by refluxing with alkali. Similarly, 1-aryl-5-alkyluracils (VI-XI) are obtained from



I-III IV-XVIII

I R=H; II R=CH_3; III R=C_2H_5; IV R=H, R′=o-CH_3; V R=H, R′=o-OCH_3; VI R=C_2H_5, R′=H; VII R=C_2H_5, R′=p-CH_3; VIII R=C_2H_5, R′=o-CH_3; IX R=C_2H_5, R′=o-CH_3; X R=CH_3, R′=o-CH_3; XI R=C_2H_5, R′=p-OCH_3; XII R=C_2H_5, R′=p-OC_2H_5, XIII R=CH_3, R′=p-COOH; XIV R=C_2H_5, R′=p-CH_2COOH; XV R=C_2H_5, R′=p-COOH; XVI R=H, R′=p-COOH; XVII R=H, R′=p-CH_2COOH; XVIII R=H, R′=CH_3CO

α-cyanopropionylurethane (II), α-cyanobutyrylurethane (III), and the hydrochlorides of o- and p-anisidine.

1-Aryl-5-alkyluracils (VI-XV) are more conveniently obtained from the products of acylation of urethane with α-cyanoalkanoic acids. In this case, hydrogenation is carried out in the presence of aromatic amines and sodium acetate, which is used for neutralization of the α-cyanoalkanoic acids.

The proposed method makes it possible to quite easily synthesize 1-aryluracils containing carboxyl and keto groups in the benzene ring. Thus, 5-alkyl-1-uracilyl and 1-uracilylbenzoic acids (XII, XV, and XVI) are obtained by reduction of I-III in the presence of the hydrochloride of ethyl p-aminobenzoate and subsequent refluxing of the reaction product with alkali. When the hydrochloride of ethyl p-aminophenyl-

* See [1] for communication XXV.

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TABLE 1. Characteristics of the Compounds Obtained

Compound	mp, °C	Empirical formula	Found, %			Calc., %			λ_{max}, nm	lg ε	Yield, %
			C	H	N	C	H	N			
IV	196—198	$C_{11}H_{10}N_2O_2$	65,5	5,2	13,8	65,3	5,0	13,8	270	3,98	40
V	212—214	$C_{11}H_{10}N_2O_3$	60,3	5,1	12,8	60,6	4,6	13,2	268	4,02	41
VI	176—178	$C_{12}H_{12}N_2O_2$	66,8	6,0	12,4	66,6	5,6	12,9	273	4,0	48
VII	170—172	$C_{13}H_{14}N_2O_2$	67,8	6,3	12,3	67,8	6,1	12,2	275	3,91	13
IX	192—193	$C_{13}H_{14}N_2O_3$	63,1	6,1	11,3	63,4	5,7	11,4	272	4,06	12
X	236—237	$C_{12}H_{12}N_2O_2$	66,4	5,1	12,7	62,4	5,2	12,9	274	4,05	15
XI	190—191,5	$C_{13}H_{14}N_2O_3$	63,1	6,0	11,5	63,4	5,7	11,4	272	4,05	35
XII	176	$C_{14}H_{16}N_2O_3$	64,0	6,3	10,7	64,2	6,2	10,8	270	4,08	20
XIII	302—303	$C_{12}H_{10}N_2O_4$	58,5	4,1	11,4	58,6	4,1	11,5	—	—	69
XIV	247—248,5	$C_{14}H_{14}N_2O_4$	60,6	5,3	10,3	61,2	5,2	10,2	275	4,07	7
XV	303—304,5	$C_{13}H_{12}N_2O_4$	60,6	4,6	10,3	60,0	4,7	10,8	275	4,18	15
XVI	353	$C_{11}H_{14}N_2O_3$	56,7	3,6	12,1	56,8	3,4	12,1	268	4,18	57
XVII	292—294	$C_{12}H_{10}N_2O_4$	59,0	4,6	11,6	58,6	4,1	11,5	267	4,05	43
XVIII	295—296	$C_{12}H_{10}N_2O_3$	62,5	4,7	12,4	62,6	4,4	12,6	280	4,14	81
XIX	311—312	$C_{11}H_8N_2O_5$	53,6	3,6	10,9	53,2	3,3	11,2	270	4,20	19
XX	278—279,5	$C_{13}H_{12}N_2O_5$	54,7	4,6	9,7	55,6	4,4	10,2	275	4,12	12

acetate and I and III are used in this reaction, conversion to p-(1-uracilyl)- and p-(5-ethyl-1-uracilyl)-phenylacetic acids (XIV, XVI) is realized. The sodium salts of aromatic amino acids can be used in place of the hydrochlorides of the esters of these acids. Thus, 1-(3-hydroxy-4-carboxyphenyl)uracil and 1-(3-hydroxy-4-carboxyphenyl)-5-ethyluracil (XIX, XX) are obtained by hydrogenation of I and III in the presence of sodium p-aminosalicylate and acetic acid and subsequent cyclization of the reaction product.

We were unable to extend the indicated method to the preparation of 1-alkyl- and 1,5-dialkyluracils, inasmuch as β-alkylaminoacryloylurethanes, which are unstable in aqueous media, are formed in the hydrogenation of I-III in the presence of aliphatic amines.

Heating p-(5-methyl-1-uracilyl)- and p-(1-uracilyl)benzoic acids (XIII and XVI with phosphorus pentachloride in acetyl chloride gave the corresponding benzoyl chlorides, which, without purification, were converted to esters (XXII, XXIV) and amides (XXV, XXVI) by the action of alcohols and amines.

The structures of IV-XX were confirmed by the presence of an absorption maximum in their UV spectra at 261-275 nm, which is characteristic for 1-aryluracils. The latter may be of interest for biological study as antimetabolites.

EXPERIMENTAL

The UV spectra of aqueous solutions (pH 7.5) of the compounds were recorded with an SF-4A spectrophotometer.

α-Cyanoacylurethanes (II, III). These compounds were obtained by the method [7] used to obtain cyanoacetylurethane. The residue remaining after removal of the acetic acid and other volatile components in vacuo (3-5 mm) at 100° was used for the synthesis.

The 1-Aryl- and 1-aryl-5-alkyluracils (IV-XVI) were obtained under the conditions described in [3]. The yields of VI-XV and XX are based on the α-cyanoalkanoic acid (Table 1).

1-(3-Hydroxy-4-carboxyphenyl)uracil (XIX) and 1-(3-Hydroxy-4-carboxyphenyl)-5-ethyluracil (XX). These compounds were obtained from I and III, sodium salicylate, and sodium acetate under similar conditions (Table 1).

p-(1-Uracilyl)benzoyl Chloride (XXI). A 3.75-g (18 mmole) sample of phosphorus pentachloride was added in two portions to 5 g (22 mmole) of XVI in 50 ml of acetyl chloride, and the mixture was stirred and refluxed for 24 h. The acetyl chloride and phosphorus oxychloride were removed by vacuum distillation, and the residue was washed with 20 ml of anhydrous carbon tetrachloride to give 4.8 g of a product with mp 308-310°

p-(5-Methyl-1-uracilyl)benzoyl Chloride (XXII). A mixture of 3 g (12 mmole) of XII, 3.6 g (12 mmole) of phosphorus pentachloride, and 6 ml of acetyl chloride was refluxed for 4 h, after which the acetyl chloride and phosphorus oxychloride were removed by vacuum distillation, and the residue was washed with 10 ml of anhydrous chloroform to give 2.98 g of a product with mp 294-296°.

Ethyl p-(1-Uracilyl)benzoate (XXIII). A 0.5-g (2 mmole) sample of acid chloride XXI was added to 10 ml of anhydrous ethanol, and the mixture was refluxed for 3 h, after which the alcohol was removed by

distillation to dryness. The residue was washed with 2 ml of 20% sodium carbonate solution and 6 ml of water with stirring for 1 h. The solid was removed by filtration, washed with water, and dried to give 0.35 g (79%) of a product with mp 268-270° (from ethanol). Found, %: C 60.1; H 4.9; N 11.0. $C_{13}H_{12}N_2O_4$. Calculated, %: C 60.0; H 4.6; N 10.8. UV spectrum (in ethanol): λ_{max} 265 nm (log ε 4.48).

Ethyl p-(5-methyl-1-uracilyl)benzoate (XXIV), with mp 239.5-241.5° (from ethanol), was similarly obtained in 85% yield from acid chloride XXII and anhydrous ethanol. Found, %: C 61.3; H 5.2; N 10.3. $C_{14}H_{16}N_2O_4$. Calculated, %: C 61.3; H 5.1; N 10.2. UV spectrum: λ_{max} 275 nm (log ε 4.0) (in ethanol).

p-(1-Uracilyl)benzoic Acid Isobutylamide (XXV). A mixture of 2.4 g (9.5 mmole) of acid chloride XXI and 2 ml of isobutylamine was allowed to stand at room temperature for 1 h, after which the isobutylamine was removed by distillation, and the residue was dissolved in water. The solution was filtered, and the product was precipitated from the filtrate with 15% sulfuric acid at pH 6. The precipitate was removed by filtration and stirred with 10 ml of 20% sodium carbonate solution at 20° for 1 h. The solid was separated from the solution and washed with water to give 2.0 g (92%) of a product with mp 266.5-267° (from water). Found, %: 62.4; H 6.0; N 14.7. $C_{15}H_{17}N_3O_3$. Calculated, %: C 62.7; H 5.9; N 14.6.

p-(1-Uracilyl)benzoic acid morpholylamide (XXVI), with mp 281-283° (from water), was similarly obtained in 83% yield. Found, %: C 60.0; H 5.0; N 13.6. $C_{15}H_{15}N_3O_4$. Calculated, %: C 59.8; H 5.0; N 13.9.

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