RECYCLIZATION REACTIONS OF HETEROCYCLES

XV.* REACTION OF ISOQUINOLINIUM SALTS WITH HYDRAZINES

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The direction of recyclization during hydrazination of isoquinolinium salts is practically independent of the substituent attached to nitrogen and the reaction conditions and leads to compounds with an N-aminoisoquinoline structure.

Recyclization only to the corresponding N-amino derivatives by the action of hydrazines has been described for pyridinium and isoquinolinium salts [2, 3]. According to [3], the recyclization of isoquinolinium salt Ia proceeds through the intermediate formation of addition product II and hydrazone III, which cyclizes under the influence of acids to N-aminoisoquinolinium salt VIII. We have investigated the hydrazination of isoquinolinium salts Ia-f in order to ascertain the possibility of the formation of benzodiazepine system IV.

In a study of the action of hydrazine, hydrazine hydrate, and lithium hydrazide on salts I in aqueous, alcohol, and dioxane media, or in hydrazine itself, and also in the presence of alkali or an organic base under various temperature conditions, we isolated (as a stable product) only a colorless solid with variable physical properties but a constant elementary composition, $(C_9H_8N_2)_n$ (V), which was found to be a mixture of oligomers with $n \geq 2$. In particular, individual oligomers with $n = 2$, 4, and 9 were isolated. The oligomer ratio in the mixtures depends on the hydrazination conditions. The oligomer with $n = 2$ is identical to the dimer of N-iminoisoquinoline – tetrazan VII [3, 4] – both with respect to melting point and other properties and does not depress the melting point of a sample obtained by the method in [3]. On acidification it readily forms salt VIII (R = H), the neutralization of which does not yield monomeric base VI (R = H) – the latter dimerized immediately to tetrazan VII. It should be noted that oligomers V with $n > 2$ are formed along with dimer VII on rapid neutralization with concentrated alkali solution.

The ν_{NH} band is weak in the IR spectrum of VII. The PMR spectrum contains two groups of signals at 5.32 and 6.49 ppm, which are split into a doublet ($J = 7.7$ Hz) and are related to the $-CH=CH-$ protons, a multiplet at 7.14 ppm, which is related to the signals of the benzene ring protons, and a singlet at 5.89 ppm, which corresponds to four protons. When the PMR spectra are recorded at different temperatures, this signal is initially split into two signals as the temperature rises, and at 57-78° one of them is shifted to stronger field. These protons apparently participate in the formation of a hydrogen bond with the solvent [dimethyl sulfoxide (DMSO)], and this makes it possible to assign this signal to the protons of the NH group. Thus the PMR spectral data unambiguously indicate tetrazan structure VII.

The structures of the higher oligomers (V) were not ascertained, although the absence of free terminal hydrazine groups (negative reaction with benzaldehyde and Fehling solution) makes it possible to assume a macrocyclic structure for them.

The formation of only compounds with N-aminoisoquinoline structure (VI-VIII) during the hydrazination of the isoquinolinium salts (in contrast to the pyrylium and thiapyrylium salts [5, 6]) may be associated either with aromatization of the 2,3-benzodiazepine system (IV) or with the possibility of stabilization of

*See [1] for communication XIV.

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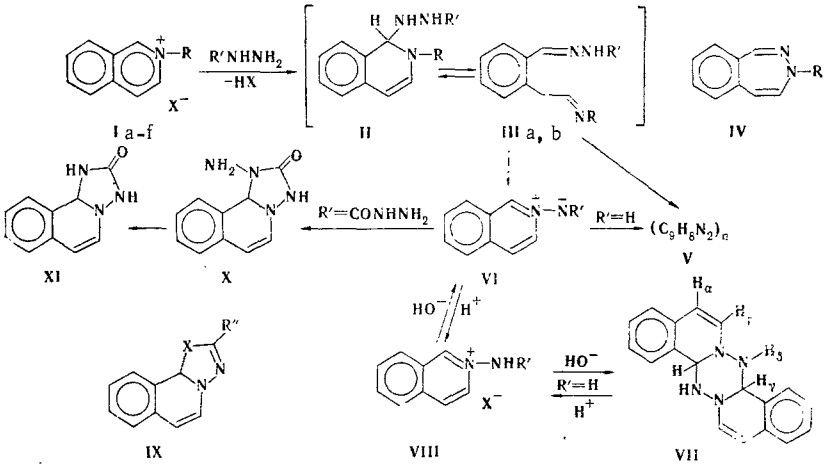
intermediate hydrazone III in the syn configuration (IIIb), as a result of which ring closing to diazepine IV is sterically hindered, while the formation of the N-aminoisoquinoline system VI should not depend markedly on the configuration of intermediate hydrazone III and, in addition, is thermodynamically more favorable.

N-Iminoisoquinoline derivatives VI (R' = COR''), which, because of delocalization of the negative charge, are extremely stable also in the base form, are formed in the reaction of isoquinolinium salts with acylhydrazines, in which the amide nitrogen atom usually manifests lower nucleophilic activity [6]. The synthesis of N-acyliminoisoquinolines VI (R' = COR'') from isoquinoline N-sulfotrioxide (If) proved to be a particularly convenient method in a preparative respect as compared with other methods [2]. Isomeric cyclic structure IX (X = O), which does not have separated charges, can be proposed for N-acyliminoisoquinolines VI (R' = COR''). However, the chemical properties, particularly the high solubility in acids to give salts VIII and the IR spectral data – the presence of characteristic frequencies of the $(-N-C-O)^{\oplus}$ grouping at 1550-1600 and 1350 cm^{-1} – constitute evidence in favor of betaine structure VI, even when R = NH_2 or C_6H_5NH (also see the data in [3]). However, in the case of recyclization of isoquinolinium salts under the influence of carbohydrazide (under more severe conditions, of course) X was isolated along with a certain amount of an unidentified product. The structure of X and its difference from open isomer VI (R' = $CONHNH_2$) are confirmed by the spectral and chemical data. The characteristic bands of the $(-N-C-O)^{\oplus}$ group are not observed in the IR spectrum of this substance, but the spectrum does contain an intense broad band at 1680 cm^{-1} (C = O). In contrast to betaines VI, it is not soluble in dilute mineral acids and does not have a free hydrazine group. Benzylidene derivative XII is formed with benzaldehyde, and this constitutes evidence for the presence of a free amino group. Monodeamination to give XI occurs under the influence of nitrous acid.



I a R = 2,4-$(NO_2)_2C_6H_3$, X = Cl; b R = CH_3, X = I; c R = CH_3, X = p-$CH_3C_6H_4SO_3$;
d R = C_2H_5, X = I; e R = $CH_2C_6H_5$, X = Cl; f RX = SO_3

In conclusion, we sincerely thank V. M. Bilobrov for recording the IR spectra.

EXPERIMENTAL

The IR spectra of potassium bromide pellets of the compounds were recorded with a UR-10 spectrometer. The PMR spectra of DMSO solutions were recorded with a YaMR-5535 spectrometer at 40 MHz relative to cyclohexane as the internal standard; the chemical shifts were converted to the tetramethylsilane scale. The molecular weights were determined by the Zigner–Clark isothermal distillation method [8] in chloroform.

The N-alkylisoquinolinium salts were obtained by heating equimolar amounts of freshly distilled alkyl halides or methyl tosylate with isoquinoline in dry dioxane. The melting points of the salts obtained were in good agreement with the handbook values.

Isoquinoline N-sulfotrioxide was obtained by a somewhat modified method [7] by addition of freshly distilled sulfur trioxide to an equimolar amount of isoquinoline in dry alcohol-free chloroform at 0-5°.

Hydrazinolysis of N-Alkylisoquinolinium Salts I. In a typical experiment, a 1.5-fold amount of hydrazine hydrate was added to an aqueous solution of the appropriate I salt, and the mixture was allowed to

TABLE 1. N-Acyliminoisoquinolines VI (R' = COR'')

R''	mp, °C	Empirical formula	Found, %				Calculated, %				IR spectrum, cm^{-1}	Yield, %
			C	H	N	Hal	C	H	N	Hal		
C_6H_5	186—187*	$C_{16}H_{12}N_2O$	77,2	4,8	11,3	—	77,4	4,9	11,3	—	1345, 1560 1600	97
p-ClC_6H_4	183—185	$C_{16}H_{11}ClN_2O$	67,8	4,0	10,1	12,3	68,0	3,9	9,9	12,55	1350, 1565 1605	84
p-BrC_6H_4	186—190 (dec.)	$C_{16}H_{11}BrN_2O$	58,5	3,5	8,4	24,2	58,7	3,4	8,6	24,4	—	82
m-$NO_2C_6H_4$	227—229 (dec.)	$C_{16}H_{11}N_3O_3$	—	—	14,2	—	—	—	14,3	—	1345, 1560 1600	79
p-$(CH_3)_2NC_6H_4$	216—219 (dec.)	$C_{18}H_{17}N_3O$	—	—	14,2	—	—	—	14,4	—	1340, 1560 1610	81
β-$C_{10}H_7$	>270 (dec.)	$C_{20}H_{14}N_2O$	80,8	4,6	9,4	—	80,5	4,7	9.6	—	—	85

*According to [3], this compound has mp 188°.

stand overnight. Slight warming was sometimes necessary. The precipitate was separated, washed with water, and vacuum dried over phosphorus pentoxide without heating. The yields ranged from 80 to 90%. The preparation obtained by this method from N-methylisoquinolinium iodide was an almost colorless powder that began to decompose at ~130°. Found: C 74.8; H 5.3; N 19.7%. $C_9H_8N_2$. Calculated: C 75.0; H 5.6; N 19.4%. Substances of the same composition were obtained as follows: by reaction of isoquinolinium salts I with lithium hydrazide in dioxane at room temperature or by refluxing a suspension of the reactants, by reaction with absolute hydrazine in absolute alcohol at −15° and at room temperature, and by refluxing the reactants, and by reaction with prior alkalization and subsequent addition of hydrazine.

The samples obtained (and the fractions subsequently isolated from them) were found to have molecular weights of 130 to 180 by the Rast method in camphor; however, these results cannot be considered to be correct because of appreciable decomposition of the samples during homogenization of the camphor melt. An effective molecular weight of 500 was obtained by isothermal distillation in chloroform; this value corresponds to an average degree of polymerization of 3.5. In order to accomplish separation of the mixture of oligomers into narrow fractions, the mixture was subjected to fractional precipitation from dioxane solution (the fractions precipitated in the order of decreasing molecular weight) or was fractionated on aluminum oxide (the fractions were eluted in the order of increasing molecular weight). The narrow fractions of the oligomers were crystallized until the products had acceptably constant melting points. The characteristics of two of the samples obtained are presented below.

Nonamer V (n = 9). This compound was obtained as a colorless substance with mp 200-203° (dec., from dioxane). Found: C 74.8; H 5.5; N 19.7%; M 1305. $(C_9H_8N_2)_9$. Calculated: C 75.0; H 5.6; N 19.4%; M 1296.

Dimer V (n = 2). This compound was obtained as colorless crystals with mp 157-160° (from benzene). Found: C 75.1; H 5.7; N 19.4%; M 286. $(C_9H_8N_2)_2$. Calculated: C 75.0; H 5.6; N 19.4%; M 288.

Bis-(1,2-dihydroisoquinolino[2,1-b:2,1-e])-1,2,4,5-tetrazan (VII). A 1.5-fold amount of 3-5% sodium hydroxide solution was added in the cold to an aqueous solution of N-aminoisoquinolinium iodide, and the mixture was allowed to stand for a short time. The resulting precipitate was separated, washed repeatedly with water, and vacuum dried without heating to give a product in 70% yield. Crystallization from benzene in the presence of aluminum oxide gave colorless crystals with mp 158-160° that did not depress the melting point of a sample of dimer V (n = 2). A melting point of 147-150° for VII is presented in [4]; this melting point may be associated with the fact that the observed melting point of VII depends markedly on the heating rate. It is also possible that Huisgen and co-workers [4] were dealing with a sample containing higher oligomers. We observed the formation of oligomeric impurities in the dimer when concentrated solutions of aminoisoquinolinium salt VIII and sodium hydroxide were mixed rapidly.

N-Acyliminoisoquinolines (VI). A 2.1-g (10 mmole) sample of thoroughly pulverized isoquinoline N-sulfotrioxide was added with vigorous stirring to a cooled (to −5-0°) solution of 2.4 g of sodium hydroxide in 10 ml of water, 1-2 min, after which 10 mmole of the approximate acylhydrazine was added. Stirring was continued, and the substrate was allowed to warm up to room temperature and was held at room temperature until the initially formed color of the suspension almost disappeared. A solution of 10 ml of acetic acid in 20 ml of water was then added to the mixture, and the mixture was boiled for 1-2 min. It was then

cooled and diluted with a three- to fourfold amount of water, and the precipitate was separated, washed with water, vacuum dried and crystallized from an appropriate solvent. Colorless crystals that were only slightly soluble in most organic solvents were obtained. An intense νCO band at ~1700 cm^{-1} appeared in the IR spectra during salt formation, while the $(-N-C-O)^{\oplus}$ absorption band disappeared. The physical constants and yields of the synthesized compounds are presented in Table 1.

1-Amino-2-oxo-2,3,3a,1a-tetrahydrotriazolo-1,2,4-[3,2-a]isoquinoline (X). A mixture of 3.15 g (10 mmole) of N-methylisoquinolinium tosylate and 0.9 g (10 mmole) of carbohydrazide in 15 ml of dimethylformamide was held at 140° for 3-4 h. The mixture was then cooled and diluted with water, and the precipitate was separated and washed with 3% hydrochloric acid and several times with water. Vacuum drying gave ~0.7 g (35%) of colorless crystals with mp 315-320° (dec., from glacial acetic acid). Found: C 59.0; H 5.1; N 27.4%. $C_{10}H_{10}N_4O$. Calculated: C 59.4; H 5.0; N 27.7%. IR spectrum: 1635, 1680, 3150, 3260, and 3350 cm^{-1}.

1-Benzylideneamino-2-oxo-2,3,3a,1a-tetrahydrotriazolo-1,2,4-[3,2-a]isoquinoline (XII). A mixture of 0.2 g (1 mmole) of X and 0.1 g (1 mmole) of benzaldehyde in 10 ml of glacial acetic acid was refluxed for 10 min in the presence of 0.05 g of sodium acetate. The mixture was then cooled and diluted with water, and the precipitate was separated, washed with water, alcohol, and ether, and dried to give 0.25 g (86%) of colorless crystals with mp 255-257° (dec., from dilute acetic acid). Found: C 70.0; H 4.9; N 19.4%. $C_{17}H_{14}N_4O$. Calculated: C 70.3; H 4.8; N 19.3%. IR spectrum: 1630, 1680 cm^{-1}.

2-Oxo-2,3,3a,1a-tetrahydrotriazolo-1,2,4-[3,2-a]isoquinoline (XI). A 0.1-g sample of X was dissolved in 10 ml of acetic acid, 0.05 g of finely ground sodium nitrate was added, and the mixture was stirred and allowed to stand for 1 h. It was then diluted with water, and the resulting precipitate was separated, washed with water, and treated with dilute sodium hydroxide solution. The mixture was filtered, and the filtrate was neutralized with dilute hydrochloric acid. The white precipitate was separated, washed with water, and vacuum dried to give 0.05 g (55%) of a product with mp 285-290° (dec., in a sealed capillary; from dimethylformamide–water) that sublimed above 250°. Found: C 63.9; H 4.7; N 22.2%. $C_{10}H_9N_3O$. Calculated: C 64.2; H 4.8; N 22.5%.

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