CONDENSED IMIDAZO-1,2,4-AZINES

22.* ALKYLATION OF 5H-IMIDAZO[1,2-b]-1,2,4-TRIAZEPIN-4-ONES

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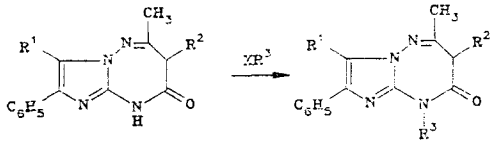
Substituted 5H-imidazo[1,2-b]-1,2,4-triazepin-4-ones react with alkyl (alkenyl) halides, 2-chloroethanol, glycerin dichlorohydrin, haloacetic acids, the methyl ester and amide of monochloroacetic acid in a methanol—sodium methylate system to form $N_{(5)}$-alkylation products, and with hydroxylamino-O-sulfonic acid to form 5-aminoimidazo[1,2-b]-1,2,4-triazepin-4-one.

It has already been shown [2] that for the representatives of the 5H-imidazo[1,2-b]-1,2,4-triazepin-4-one (I, II), the ketoform predominates, irrespective of the aggregate state. Such a structure of compounds I, II indicates alkylation at the $N_{(5)}$ atom. In order to study the reactivity of imidazo[1,2-b]-1,2,4-triazepines [3], and to synthesize new compounds with possible biological activity, we investigated the reaction of bicyclic compounds I, II with alkyl (alkenyl) halides, 2-chloroethanol, glycerin dichlorohydrin, haloacetic acids, methyl ester and amide of monochloroacetic acid, and also with hydroxylamino-O-sulfonic acid (HASA).

Attempts to carry out the reaction in neutral or acidic media and also in aqueous alkali solutions resulted only in obtaining the starting compounds. By varying the solvents, the temperature regime and by changing the alkaline agent, we found that the optimal method for alkylating imidazotriazepines I, II by halogen-substituted reagents is to boil a mixture of these compounds in methanol with a threefold excess of sodium methylate, thus giving a maximum yield of the desired end products IIIa-j (Table 1).



I, II III a-j

I, III a—i $R^1=C_6H_5$, $R^2=H$; a $R^3=CH(CH_3)_2$; b $R^3=(CH_2)_6CH_3$; c $R^3=CH_2CH=CH_2$; d $R^3=(CH_2)_2OH$; e $R^3=CH_2CH(OH)CH_2Cl$; f $R^3=CH_2COOH$; g $R^3=CH_2COOCH_3$; h $R^3=CH_2C(O)NH_2$; i $R^3=NH_2$; II, III j $R^1=H$, $R^2=C_2H_5$; $R^3=CH_3$; X=Cl, Br, SO_4H

Absorption bands are observed in the IR spectra of compounds IIIa-j which correspond to the stretching vibrations of the carbonyl groups and the C=C and C=N bonds (Table 1).

In the PMR spectrum of amide IIIh, the proton signals of the methyl, C- and N-methylene groups appear in the form of singlets at 1.94, 3.55, and 4.58 ppm, respectively, while the signals of the aromatic protons of the phenyl groups form a complex multiplet in the 6.72-7.24 region.

The IR spectrum of the amino-substituted bicyclic compound IIIi differs little from that of the initial compound I [2], but the bands at 1510 and 3310 cm^{-1} may be assigned to the NH bond vibrations in the N,N-disubstituted hydrazino group [4]. In the PMR spectrum of compound IIIi in addition to the proton signals of the methyl (2.77 ppm), methylene (2.65 ppm) and two phenyl groups (7.16-7.62 ppm), a broadened two-proton singlet of the amino group is observed in the 10.14 ppm region. In the mass spectrum of compound IIIi a peak of molecular ion (M^+)

*For Communication 21, see [1].

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TABLE 1. Characteristics of the Synthesized Compounds

Compound	Empirical formula	mp, °C	IR spectrum, ν, cm^{-1}			pK_a	Yield, %
			C=O	C=C	C=N		
IIIa	$C_{22}H_{22}N_4O$	202...204	1680	1605	1630	−0,28	60
IIIb	$C_{29}H_{36}N_4O$	105...106	1680	1605	1630	−0,85	45
IIIc	$C_{22}H_{20}N_4O$	180...182	1680	1605	1625	−0,18	60
IIId	$C_{21}H_{20}N_4O_2$	190...192	1700	1605	1630	−0,74	72
IIIe	$C_{22}H_{21}ClN_4O_2$	182...184	1690	1610	1630	−1,33	40
IIIf	$C_{21}H_{18}N_4O_3$	226...228	1700, 1710 sh.	1605	1625	−0,9	58
IIIg	$C_{23}H_{22}N_4O_3$	170...172	1700, 1760	1603	1640	—	69
IIIh	$C_{21}H_{19}N_5O$	228...230	1670, 1710	1605	1625	−1,35	65
IIIi	$C_{19}H_{19}N_5O$	219...221	1700	1605	1625	3,57	40
IIIj	$C_{16}H_{17}N_4O$	109...110	1690	1608	1625	—	75

*The compounds were recrystallized: IIIa, c, d, g, i – from isopropanol, IIIb, e, j – from methanol, IIIh, f – from aqueous DMFA.

331* is observed. The high resolution mass spectrum (HRMS) obtained gives the empirical formula of the molecule of IIIi (determined: 331.3831; calculated: 331.3812 for the formula $C_{19}H_{17}N_5O$). The splitting off of the NH particle observed at the first stage of the dissociation of M^+ (316; determined 316.1291; calculated: 316.1324 for the formula $C_{19}H_{16}N_4O$) is characteristic for α,α-disubstituted hydrazines [5, 6], which confirms the presence of the amino group at the $N_{(5)}$ atom in the bicyclic compound IIIi. The direct splitting off of the NH particle from M^+ was confirmed by the mass spectra of the meta stable ions (the DADI technique). The subsequent course of the fragmentation of the $[M-NH]^+$ ion is accompanied by the elimination of the CH_3CN particle and the formation of the $[(M-NH)-CH_3CN]^+$ ion (275; determined: 275.1069; calculated: 275.1059 for the formula $C_{17}H_{13}N_3O$). This fragmentation is accompanied by the contraction of the triazepin ring to the imidazoline ring with further decomposition of the ion formed in three directions, due to the elimination of the CO (247), HCO (246), and NHCO (234) particles. The fragmentation pattern of the $M[M-NH]^+$ ion coincides completely with that previously described for imidazo[1,2-b]-1,2,4-triazepin-4-one I [2], which further confirms the correctness of the proposed structure of compound IIIi.

To evaluate the influence of substituents at the $N_{(5)}$ atom on the basicity of the imidazo[1,2-b]-1,2,4-triazepin-4-one, the acid-base properties of compounds I, IIIa-f, i, h were examined spectrophotometrically. The analysis of absorption spectra of these compounds, obtained in aqueous solutions of various acidities (from 4M HCl to 4M KOH) in the wavelength range from 200-350 nm showed that the changes in the spectra with change in the pH are reversible, while the dependence of the optical density on pH in an acid medium has a clearly pronounced sigmoid character, which we related to the protonation of compounds I, IIIa-f, h. The presence of isobestic points made it possible to determine the pK_a values for the protonated bicyclic compounds IIIa-f, h and to study the influence of the substituents at the $N_{(5)}$ atom on their basicity (Table 1). In all the cases under consideration, an increase in the basicity of the imidazotriazine system is observed, as compared with the starting compound I (pK_a −2.15), in which there is no substituent at the $N_{(5)}$ atom. The increase in the pK_α value is directly dependent on the value of the inductive effect of the substituent, whereby the bulky substituents (compounds IIIb, d-f, h) have a lesser influence on the increase in the basicity of the heterocyclic system than the compact substituents (bicyclic compounds IIIa, c). The latter fact can be explained by steric factors in accordance with the analysis of the Stuart-Briegleb models of compounds IIIa, b, e, h, which shows that in the case of bulky substituents a screening of the $N_{(1)}$ and $N_{(5)}$ atoms is observed, whereas the compact substituents screen only the $N_{(1)}$ atom.

EXPERIMENTAL

The IR spectra were run on an IKS-22 spectrophotometer in KBr tablets and in $CHCl_3$ and the UV spectra on an SF-26 spectrophotometer. The PMR spectra of the compounds were recorded on a Bruker WH-90 spectrometer in acetone-D_6, using TMS as internal standard. The mass spectra were run on a MAT-311A spectrometer with direct introduction of the sample into the ionic

*The numbers characterizing the ion, determine the m/z value.

source under standard conditions of exposure [8]. The high resolution mass spectra were obtained under the same conditions at M/ΔM 10,000, using perfluorokerosene as a standard.

The data of the elemental analysis of the compounds obtained for C, H, N correspond to the calculated values.

3-R^2-5-R^3-8-R^1-Imidazo[1,2-b]-1,2,4-triazepin-4-ones (IIIa-h, j). Imidazotriazepinone I or II (3.16 g, 10 mmoles) was added in small portions at 50°C to a solution of 0.69 g (3 mmoles) of sodium in 30 ml of methanol, and then 30 mmoles of the corresponding halogen derivative was added. The reaction mixture was boiled for 4 h in the case of compounds IIIa, c-h, j, and for 8 h in the case of compound IIIb. After cooling, the precipitate that separated out was filtered off, washed with a warm water, and dried. Compounds IIIa-h, j were obtained (Table 1).

5-Amino-2-methyl-7,8-diphenylimidazo[1,2-b]-1,2,4-triazepin-4-one (IIIi). A 3.16 g portion (10 mmoles) of triazepinone I was added with stirring to a solution of 0.69 g (30 mmoles) of sodium in 30 ml of methanol. The mixture was cooled to 15°C and 3.9 g (30 mmoles) of hydroxylamine-O-sulfonic acid neutralized by an $NaHCO_3$ solution was added in small portions. The reaction mixture was then heated to 30°C and stirred for 2 h. After cooling, the precipitate was filtered off, washed with cold methanol and water, and dried. Mass spectrum, m/z (%): 332 (19), 331 (M^+, 82), 317 (11), 316 (84), 276 (15), 275 (77), 248 (13), 247 (64), 246 (87), 234 (34), 219 (20), 218 (20), 194 (13), 193 (63), 192 (10), 178 (94), 165 (39), 104 (40), 103 (100), 91 (12), 77 (48).

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