HYDROXY- AND AMINOMETHYLATION OF 1-METHYL-2-AMINO-4-IMIDAZOLINONE

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The corresponding imidazolo[3,2-a]-1,3,5-triazines are formed as a result of the aminomethylation of 1-methyl-2-amino-4-imidazolinone (creatinine) and its 5-benzylidene derivative with paraformaldehyde and primary aliphatic amines. Hydroxymethylation is directed to the $C_{(5)}$ position of the creatinine heteroring.

1-Methyl-2-amino-4-imidazolinone (Ia, creatinine) is one of the end metabolites of protein metabolism, while its hydrate creatine is involved in the regulatory mechanisms of higher organisms [1]. Creatinine (Ia) has diverse pharmacological activity [2], is used in biochemical and functional studies [1, 3], and is the object of analytical determination in various biological materials [2]. However, its chemical properties have not been adequately studied, and some data have not been reproduced for almost a century, in view of which there is some doubt regarding their reliability [2]. In particular, the aminomethylation of creatinine (Ia) has not been studied, while the only research on hydroxymethylation [4] requires revision of the data on the structure of the product that are reported in it.

We were unable to select conditions for aminomethylation with primary aromatic amines; in all of the investigated cases the degree of occurrence of the reaction, according to TLC data, was very small, and Mannich bases were not isolated. Attempts to isolate products of aminomethylation of creatinine (Ia) with secondary amines — diethylamine and dipropylamine — were also unsuccessful, although, according to TLC data, new compounds that differ from the starting compound were present in the reaction mixtures when the reaction was carried out with formalin in methanol or with paraformaldehyde in benzene. Viscous oils that were not separated into individual components were formed after removal of the solvent by distillation.

The aminomethylation of creatinine (Ia) with primary aliphatic amines was accomplished in preparative yields by using paraformaldehyde as the methylene component and methanol as the solvent.

As in the case of the 1-thia analog — pseudothiohydantoin [5] — a triazine ring that is annelated with the starting imidazoline ring is formed as a result of the aminomethylation of creatinine (Ia), and the compounds obtained have imidazolo[3,2-*a*]-1,3,5-triazine structures IIa-h with one or two hydroxymethyl groups in the 7 position (see Table 1).

Aminomethylation with methylamine could be carried out only under heterophase conditions using aqueous solutions of the amine and formaldehyde with benzene as the solvent. A product (IIi) of crotonic condensation of the corresponding imidazolotriazine with formaldehyde was isolated from the reaction mixture.

The optimum creatinine (Ia):formaldehyde:amine ratio for which the yields of aminomethylation products are maximal is 1:4:2. If two or fewer equivalents of formaldehyde with respect to creatinine (Ia) are used, IIa-h are not formed at all according to TLC data. This constitutes evidence for competitive (with respect to N-aminomethylation) C-hydroxymethylation in the 5 position. In fact, by treating creatinine (Ia) with formalin in ethanol we obtained 5,5-bis(hydroxymethyl) derivative III, to which the 2′,3-bis(hydroxymethyl)creatinine structure was erroneously assigned in [4]. Compound III forms hydrobromide IV on attempts to convert it to a bromomethyl derivative.

Excess amounts of aminomethylating agents promote an increase in the yields of imidazolotriazines II, evidently once again because of the intermediate formation of 2′,3-substituted derivatives and as a consequence of the reversibility of the N-hydroxy- and N-aminomethylation reactions [6], which precede the formation of the triazine ring.

Compounds IIa-i are solvolytically unstable and undergo complete decomposition to starting Ia when they are refluxed in ethanol for 10 min. At the spectrophotometric concentrations the decomposition is virtually complete, so that the UV spectra of IIa-i and creatinine (Ia) do not differ.

The signals of the $C_{(2)}H_2$ and $C_{(4)}H_2$ protons of the triazine ring in the PMR spectra of IIa-i are found at almost the same fields as the signals of the analogous thiazolo[3,2-*a*]-1,3,5-triazines [5, 7]. Spin-spin coupling (SSC) of the

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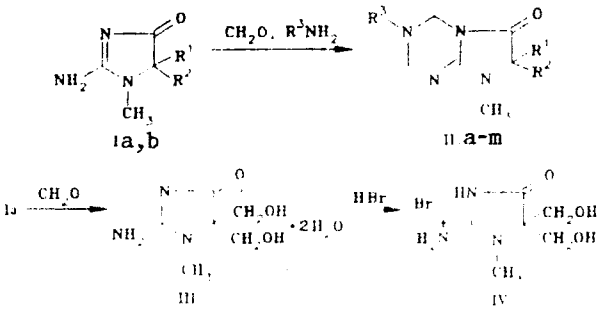
TABLE 1. Characteristics of II-IV

Compound	Empirical formula	mp, °C	IR spectrum,* cm^{-1}		UV spectrum,** λ_{max}, nm (log ε)	PMR spectrum, δ, pp		Yield, %
			C=O	C=N		2-H	4-H	
IIa	$C_{14}H_{26}N_4O_3$	147...149	1750	1665	235 (3,67)	4,12	4,38	40
IIb	$C_{11}H_{18}N_4O_3$	187...189	1740	1660	235 (3,54)	4,10	4,40	45
IIc	$C_{11}H_{20}N_4O_3$	166...168	1725	1665	235 (3,85)	4,10	4,40	41
IId	$C_{12}H_{22}N_4O_3$	168...170	1740	1670	235 (3,78)	4,20	4,44	15
IIe	$C_{10}H_{18}N_4O_2$	134...136	1730	1685	235 (3,85)	4,10	4,40	18
IIf	$C_{13}H_{24}N_4O_2$	80...82	1750	1675	235 (3,70)	4,08	4,34	18
IIg	$C_{10}H_{16}N_4O_2$	99...101	1745	1655	235 (3,54)	4,08	4,34	20
IIh	$C_{11}H_{20}N_4O_2$	136...138	1740	1670	235 (3,68)	4,12	4,48	20
IIi	$C_8H_{12}N_4O$	105...107	1730	1680	245 (3,06), 295 (3,35)	4,32	4,60	4
IIj	$C_{17}H_{22}N_4O$	146...148	1710	1680	236 (4,10), 352 (4,32)	4,34	4,64	17
IIk	$C_{16}H_{20}N_4O$	112...114	1725	1680	236 (3,93), 352 (4,30)	4,36	4,64	42
III	$C_{20}H_{20}N_4O$	86...88	1700	1670	230 (4,07), 350 (4,25)	4,32	4,52	39
IIm	$C_{19}H_{24}N_4O$	154...156	1715	1670	236 (3,98)	4,34	4,60	43
III	$C_6H_{11}N_3O_3 \cdot H_2O$	>260 (~250 [4])	1740	1680	235 (4,42)			72
IV	$C_6H_{11}N_3O_3 \cdot HBr$	175...177	1795	1695	235 (4,64)			60

*The IR spectra of IIa-m were recorded in mineral oil, while the spectra of III and IV were recorded in KBr.

**The UV spectra of IIa-m were recorded in ethanol, while the spectra of III and IV were recorded in water.



I a $R^1=R^2=H$, b $R^1+R^2=CHC_6H_5$; II a–d $R^1=CH_2OH$, e–h $R^1=H$, i $R^1+R^2=CH_2$, j–m $R^1+R^2=CHC_6H_5$; a–h $R^2=CH_2OH$; a, f $R^3=C_6H_{13}$, b, g $R^3=$allyl, c, e, k $R^3=i$-Pr; d, h, j $R^3=t$-Bu, i $R^3=CH_3$, l $R^3=CH_2C_6H_5$, m $R^3=C_6H_{11}$

vicinal protons in the $C_{(7)}CH_2OH$ fragments with J_{vic} = 5 Hz is observed in the spectra of bis(hydroxymethyl) derivatives IIa-d. After D_2O is added, the splitting of the signal of the $C_{(7)}CH_2$ protons (3.38-3.42 ppm) and the signal of the hydroxy protons (4.82-4.92 ppm) vanish. In the PMR spectra of mono(hydroxymethyl) derivatives IIe-h the multiplet absorption of the protons of the $C_{(7)}HCH_2OH$ structural element is an ABCX spin system (ABC is the part at 3.62-3.66 ppm, and X is the part at 4.82-4.92 ppm).

1-Methyl-2-amino-5-benzylidene-4-imidazolinone (Ib) also undergoes aminomethylation under the same conditions as those used for creatinine (Ia) to give the corresponding imidazolo[3,2-*a*]-1,3,5-triazines IIj-m. In contrast to IIa-i, these compounds do not decompose after brief refluxing in ethanol. Their UV spectra in this solvent are reproducible 2 h after preparation of the solutions and differ from the UV spectrum of the starting 5-benzylidenecreatinine (Ib).

EXPERIMENTAL

The PMR spectra of solutions of the compounds in d_6-DMSO were recorded with a Tesla BS-497C spectrometer (100 MHz) with hexamethyldisiloxane (HMDS) as the internal standard. The IR spectra of suspensions in mineral oil were recorded with an IKS-29 spectrometer. The UV spectra of solutions in ethanol were recorded with an SF-26 spectrophotometer. The molecular mass of IIi was determined with an MKh-1303 spectrometer with a system for direct

introduction of the samples at an ionizing voltage of 70 eV and an input-system temperature of 75°C. Thin-layer chromatography was carried out on Silufol UV-254 plates with ethyl acetate—ethanol—water—ammonia (60:30:40:1) (for IIa-h), ethanol—chloroform (1:4) (for IIj-m), and ethanol—chloroform (1:10) (for IIi) as the eluents.

3-*tert*-Butyl-6-oxo-7,7-bis(hydroxymethyl)-8-methyl-2,3,4,5,6,7-hexahydroimidazolo[3,2-*a*]-1,3,5-triazine (IId). A solution of 1.46 g (20 mmole) of *tert*-butylamine in 10 ml of methanol was added dropwise with stirring at 65°C to a suspension of 1.13 g (10 mmole) of creatinine (Ia) and 1.20 g (40 mmole) of paraformaldehyde in 30 ml of methanol, and the mixture was stirred at the indicated temperature for 5 h. The solvent was then removed by distillation to dryness, and the residue was washed with benzene and crystallized from ethyl acetate.

3-Isopropyl-6-oxo-7-hydroxymethyl-8-methyl-2,3,4,5,6,7-hexahydroimidazolo[3,2-*a*]-1,3,5-triazine(IIe). The reaction was carried out as indicated above, after which the solvent was removed by distillation to ≈1/5 of the original volume, and the residue was treated with warm (40°C) benzene (2 × 30 ml). The benzene extract was dried with $MgSO_4$, the benzene was removed by distillation to 1/5 of the original volume, and IIe was precipitated with hexane.

Compounds IIf-h were similarly obtained.

3,8-Dimethyl-6-oxo-7-methylene-2,3,4,5,6,7-hexahydroimidazolo[3,2-*a*]-1,3,5-triazine (IIi). A mixture of 1.13 g (10 mmole) of creatinine (Ia), 2.5 ml (20 mmole) of 25% aqueous methylamine, and 2.4 ml (30 mmole) of formalin was stirred at 70°C in 30 ml of benzene for 6 h, after which the benzene layer was separated and dried with Na_2SO_4. The benzene was removed by vacuum distillation, the oily residue was triturated in hexane, and the resulting precipitate was crystallized from heptane. Found: M 180. Calculated: M 180.3.

3-Isopropyl-6-oxo-7-benzylidene-8-methyl-2,3,4,5,6,7-hexahydroimidazolo[3,2-*a*]-1,3,5-triazine (IIk). A solution of 2.34 g (20 mmole) of isopropylamine in 5 ml of methanol was added to a refluxing mixture of 2.01 g (10 mmole) of imidazolinone Ib and 1.20 g (40 mmole) of paraformaldehyde in 50 ml of methanol, and the mixture was refluxed for 1 h. The undissolved material was removed by filtration of the hot mixture, the filtrate was cooled, and the precipitate was crystallized from hexane—benzene (1:4).

Compound IIm was similarly obtained.

3-*tert*-Butyl-6-oxo-7-benzylidene-8-methyl-2,3,4,5,6,7-hexahydroimidazolo[3,2-*a*]-1,3,5-triazine (IIj). The methanol was removed by distillation to 1/5 of the original volume from the filtrate obtained after filtration of the hot reaction mass (see above), and the resulting precipitate was crystallized from hexane—benzene (1:4).

3-Benzyl-6-oxo-7-benzylidene-8-methyl-2,3,4,5,6,7-hexahydroimidazolo[3,2-*a*]-1,3,5-triazine (IIl). The oil that remained after removal of the methanol by distillation (see above) was treated with warm (40°C) benzene (3 × 20 ml), and the benzene extract was dried with $MgSO_4$. The benzene was removed by distillation to 1/5 of the original volume, the residue was treated with heptane, and the resulting precipitate was crystallized from hexane—benzene (1:4).

5,5-Bis(hydroxymethyl)-2-amino-1-methyl-4-imidazolinone Dihydrate (III). A mixture of 4.52 g (40 mmole) of creatinine (Ia) and 16 ml (200 mmole) of formalin in 30 ml of ethanol was stirred at 70°C for 30 min (until Ia had dissolved completely), after which the solution was cooled, and the precipitate was washed with ethanol and crystallized from 70% ethanol to give 5.0 g of III. PMR spectrum (in d_6-DMSO): 7.24 (2H, NH), 4.56 (2H, OH), 3.32 (4H, 5′-CH_2), 2.82 ppm (3H, 1-NCH_3).

5,5-Bis(hydroxymethyl)-2-amino-1-methyl-4-imidazolinone Hydrobromide (IV). A mixture of 1.0 g (6 mmole) of III with 20 ml of acetic acid was heated to the boiling point, 5 ml of a 32% solution of HBr in acetic acid was added, and the resulting mixture was refluxed for 20 min. It was then cooled to room temperature, and 0.9 g of IV was precipitated with 300 ml of ether. PMR spectrum (in d_6-DMSO): 9.21 (NH), 3.50 (4H, 5′-CH_2), 2.96 ppm (3H, 1-NCH_3).

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