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A REARRANGEMENT DURING ALKYLATION OF 7,12-DIHYDRO-5H-ISOQUINO[2,3-*a*]QUINAZOLIN-5-ONE

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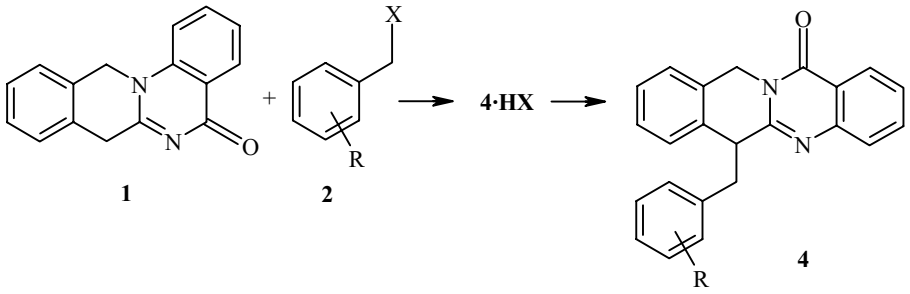
Melting 7,12-dihydro-5H-isoquino[2,3-*a*]quinazolin-5-one (**1**) with benzyl halides **2** at 130°C occurred by alkylation at $C_{(7)}$ to give the corresponding 7-benzyl-7,12-dihydro-5H-isoquino[2,3-*a*]quinazoline-5-one hydrogen halides (**3**·HX) which were characterized in the form of the free bases **3** [1]. When the temperature and the reaction time were increased the intermediate salts **3**·HX underwent rearrangement to the 6-benzyl-6,13-dihydro-13H-isoquino[3,2-*b*]quinazolin-13-one hydrogen halides (**4**·HX).



1 **2** **4**

2a, **4a** R = H; **2b**, **4b** R = 3-NO_2; **2c**, **4c** R = 2-CH_3; **2a,b**, **4a,b** X = Cl; **2c**, **4c** X = Br

Conclusions about rearrangements under these conditions and the structure of the reaction products are based on the results of the analogous high temperature conversion of isoquinoquinazolinone hydrobromide **1**·HBr into 6,13-dihydro-13H-isoquino[3,2-*b*]quinazolin-13-one hydrobromide (**5**·HBr) [2]. Comparison of the physical and spectroscopic properties of the angular isoquinoquinazolinones **3** with those of the linear isomers **4** (as the free bases and as the salts **4**·HX) established that the observed differences in pairs of isomers **3** and **4** are in complete agreement with those observed for isomers **1** and **5**. These differences, taken with the conclusions of previous work [3], provided the basis for the establishment of the structure of compound **5**. The correctness of the linear structure for isomer **5** is found in [4], in which an independent synthesis of this compound by an unambiguous method is described.

It has been established that the linear isoquinoquinazolinone **5** is not alkylated by benzyl halides under the conditions described, but the salts of the benzylated angular isoquinoquinazolinones **3**·HX when boiled in dimethylacetamide solution are converted into the linear isomers **4**·HX. Consequently alkylation precedes rearrangement in the conversion **1** $\rightarrow$ **4**·HX.

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In a standard experiment an equimolar mixture of isoquinoquinazolinone **1** and benzyl halide was kept at 160-190°C until the reaction was completed (1.5-2 h, monitored by TLC on Silufol UV 254 strips with benzene–ethanol, 9:1, in the presence of piperidine as eluent), the cooled melt was triturated with acetone, the crystalline product was filtered off, and washed carefully with acetone. The following compounds were obtained by this method from isoquinoquinazolinone **1** and benzyl and 3-nitrobenzyl chlorides and 2-methylbenzyl bromide.

Compound 4a·HCl: Yield 53%; mp 169-170°C (acetic acid). ^{1}H NMR spectrum (CF_3CO_2D), δ, ppm, *J* (Hz): 8.5-6.7 (13 H, m, H-Ar); 5.7 (1H, d, ^2J = 16, 12-H_A); 5.0 (1H, m, 7-H); 4.0 (1H, d, ^2J =16, 12-H_B); 3.5 (1H, m, 7-CH_2). IR spectrum (KBr), ν, cm^{-1}: 1700 (C=O), 1642 (C=N), 2480 (N-H). Found, %: C 73.59; H 5.01; N 7.46; Cl 9.44. $C_{23}H_{18}N_2O$·HCl. Calculated, %: C 73.69; H 5.11; N 7.47; Cl 9.46.

Compound 4b·HCl: Yield 46%; mp 200-201°C (acetic acid). ^{1}H NMR spectrum (CF_3CO_2D), δ, ppm, *J* (Hz): 8.5-6.9 (12H, m, H-Ar); 6.0 (1H, d, ^2J = 16, 12-H_A); 5.0 (1H, m, 7-H); 4.8 (1H, d, ^2J = 16, 12-H_B); 3.6 (1H, m, 7-CH_2). IR spectrum (KBr), ν, cm^{-1}: 1700 (C=O), 1657 (C=N), 2540 (N-H), 1523 (NO_2), 1348. Found, %: C 65.85; H 4.22; N 10.36; Cl 8.54. $C_{23}H_{17}N_3O_3$·HCl. Calculated, %: C 65.80; H 4.32; N 10.00; Cl 8.44.

Compound 4c·HBr: Yield 45%; mp 254-255°C (acetic acid). ^{1}H NMR spectrum (CF_3CO_2D), δ, ppm, *J* (Hz): 8.6-6.8 (12H, m, H-Ar); 5.7 (1H, d, ^2J = 16, 12-H_A); 5.3 (1H, t, ^3J = 6, 7-H); 4.1 (1H, d, ^2J = 16, 12-H_B); 3.6 (1H, d, ^3J = 6, 7-CH_2); 1.8 (3H, s, CH_3). IR spectrum (KBr), ν, cm^{-1}: 1720 (C=O), 1636 (C=N), 2480 (N-H). Found, %: C 66.60; H 4.75; N 6.99; Br 18.80. $C_{24}H_{20}N_2O$·HBr. Calculated, %: C 66.52; H 4.88; N 6.46; Br 18.44.

The free bases **4** were obtained by heating salts **4**·HX for a short time with an excess of piperidine or morpholine with subsequent treatment with water.

Compound 4a: Yield 89%; mp 147-148°C (*i*-PrOH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm, *J* (Hz): 8.2-6.8 (13H, m, H-Ar); 5.5 (1H, ^2J = 16, 12-H_A); 4.5 (1H, t, ^3J = 6, 7-H); 4.4 (1H, d, ^2J = 16, 12-H_B); 3.3 (1H, m, 7-CH_2). IR spectrum (KBr), ν, cm^{-1}: 1670 (C=O), 1595 (C=N). Found, %: C 81.55; H 5.30; N 8.17. $C_{23}H_{18}N_2O$. Calculated, %: C 81.63; H 5.36; N 8.28.

Compound 4b: Yield 91%; mp 206-207°C (*i*-PrOH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm, *J* (Hz): 8.2-7.1 (12H, m, H-Ar); 5.6 (1H, ^2J = 16, 12-H_A); 5.0 (1H, d, ^2J = 16, 12-H_B); 4.5 (1H, t, ^3J = 6, 7-H); 3.3 (1H, m, 7-CH_2). IR spectrum (KBr), ν, cm^{-1}: 1660 (C=O), 1595 (C=N), 1520, 1345 (NO_2). Found, %: C 71.99; H 4.49; N 11.26. $C_{23}H_{17}N_3O_3$. Calculated, %: C 72.05; H 4.47; N 10.96.

Compound 4c: Yield 85%; mp 170-171°C (*i*-PrOH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm, *J* (Hz): 8.2-6.7 (12H, m, H-Ar); 5.6 (1H, d, ^2J = 16, 12-H_A); 4.6 (1H, d, ^2J = 16, 12-H_B); 4.4 (1H, t, ^3J = 6, 7-H); 3.2 (1H, d, ^3J = 6, 7-CH_2). IR spectrum (KBr), ν, cm^{-1}: 1670 (C=O), 1592 (C=N). Found, %: C 81.65; H 5.68; N 8.20. $C_{24}H_{20}N_2O$. Calculated, %: C 81.79; H 5.72; N 7.95.

REFERENCES

1. V. M. Kisel', L. M. Potikha, and V. A. Kovtunenko, *Khim. Geterotsikl. Soedin.,* 423 (1995).
2. V. M. Kisel', V. A. Kovtunenko, O. V. Turov, A. K. Tyltin, and F. S. Babichev, *Dokl. Akad. Nauk,* **306**, 628 (1989).
3. V. A. Kovtunenko, V. I. Ishchenko, A. K. Tyltin, and F. S. Babichev, *Dokl. Akad. Nauk,* **294**, 375 (1987).
4. W. Wendelin, H. Keimelmayr, and M. Huber, *Sci. Pharm.,* **56**, No. 3, 195 (1988).