Chemistry of Heterocyclic Compounds, Vol. 31, No. 4, 1995

CONDENSED ISOQUINOLINE. 5.* REACTION OF THE 6-METHYL-5-OXOISOQUINO[2,3-a] QUINAZOLINIUM CATION WITH CERTAIN NUCLEOPHILES

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It has been shown that nucleophilic reagents react with the 6-methyl-5-oxoisoquino[2,3-a]quinazolinium cation at the $C_{(2)}$ atom. The structure of the reaction product is determined by the type of reagent. On reaction with sodium borohydride and secondary amines, 12H- and 12-dialkylamino-12H-6-methyl-5-oxo-5,6-dihydro-isoquino[2,3-a]quinazolines are formed. In the case of primary amines the reaction is accompanied by fission of the $C_{(12)}-N_{(13)}$ bond with the formation of 2-[o-(N-alkylformimidoyl)-benzyl]-3-methyl-4-oxoquinazolines.

The synthesis has ben reported in [1] of 6-methyl-5-oxoisoquino[2,3-a]quinazolinium perchlorate (I) by the oxidation of 6-methyl-5-oxo-7,12-dihydroisoquino[2,3-a]quinazolinium perchlorate (II). The cation of salt (I) is of interest as being the first representative of the heteroaromatic 18π-electron isoquino[2,3-a]quinazolinium system. For this reason, and also in view of the prospect of searching for new biologically active compounds among the derivatives of isoquino[2,3-a]quinazoline [2], we have studied the chemical properties of the salt (I).

The reaction of prechlorate (I) with sodium borohydride in alcohol solution leads to 6-methyl-5-oxo-5,6-dihydro-12H-isoquino[2,3-a]quinazoline (III), identical in spectral characteristics and melting point to the substance obtained previously in [1] by the action of base on salt (II). It is known [3] that reduction of salt (II) with sodium borohydride under the same conditions leads to 6-methyl-5-oxo-6,6a,7,12-tetrahydro-5H-isoquino[2,3-a]quinazoline (IV). Consequently we expected that the tetrahydroisoquinoquinazoline (IV) would be formed by the action of an excess of sodium borohydride on salt (I). However, in this case the sole reaction product was the dihydro derivative (III). Furthermore reduction of the salt (I) in the presence of acetic acid leads to the tetrahydro derivative (IV), the same as the reduction under these conditions of base (III), which is not reduced in neutral medium.

The formation of compound (III) on reduction of salt (I) indicates that nucleophilic attack by the borohydride anion is at the $C_{(12)}$ atom of the heterocyclic cation. It must be noted that this position will also be reactive in the interaction of salt (I) with other nucleophiles. In reality 6-methyl-5-oxo-12-dialkylamino-5,6-dihydro-12H-isoquino[2,3-a]quinazolines (V) were obtained by briefly heating (I) in solution in an excess of secondary amine (piperidine, morpholine) with subsequent treatment of the mixture with water. The structure of compound (V) was shown by its spectral characteristics.

Signals were observed in the high field region of the PMR spectra of these compounds as two one-proton singlets at 5.29-5.31 and 6.17-6.18 ppm for the 7-H and 12-H protons respectively. These were in addition to the signals for the amine residues and the methyl group. The assignment was made on the basis of the spectrum of the structurally similar compound (III) in which the signal for the 7-H proton is found at 5.25 ppm [1]. In addition an increase of 31% was noted in the intensity of the singlet for the 7-H proton in the spectrum of the piperidine derivative (Va) on irradiation at the resonance frequency of the methyl group protons under conditions of a nuclear Overhauser effect (nOe). In another experiment on saturation at the resonance frequency of the 12-H methine proton an increase of 13% was observed in the intensity of the multiplet for the protons in positions 2′ and 6′ of the piperidine ring. This indicates the close proximity of the piperidine ring to this proton.

*See [1] for the preceding communication.

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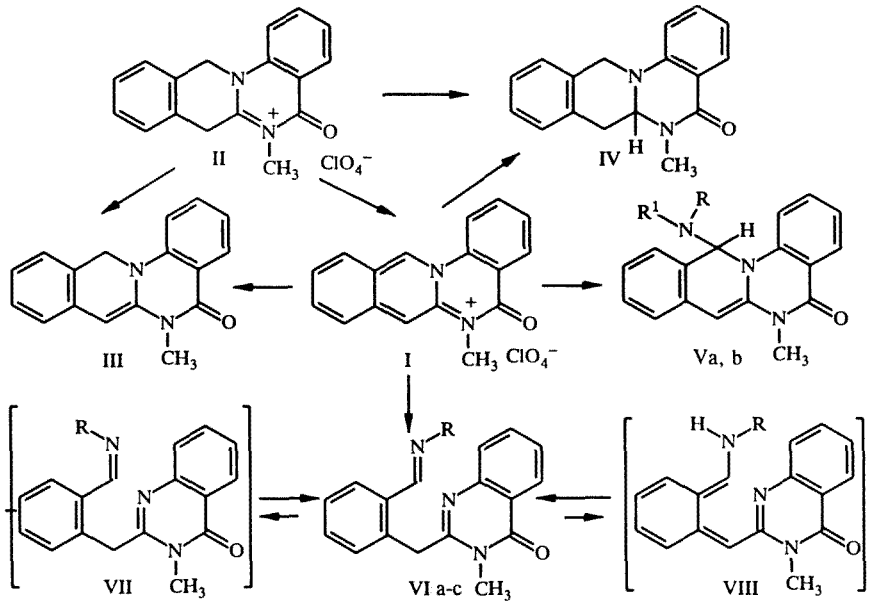
0009-3122/95/3104-0457$12.50 ©1995 Plenum Publishing Corporation



V a RR^1 = -$(CH_2)_5$, b RR^1 = -$(CH_2)_2O(CH_2)_2$-; VI a R = -$CH_2C_6H_5$, b R = -$CH(CH_3)_2$, c R = -$(CH_2)_4CH_3$

Comparison of the ^{13}C NMR spectrum of the piperidine derivative (Va) with the spectrum of model compound (III) also confirms the presumed structure of substance (V). The differences between the were limited solely to the appearance of signals of the piperidine ring and the regular low field displacement of the $C_{(12)}$ signal from 48.98 [in (III)] to 74.45 ppm [in (Va)] with the simultaneous increase of the $C_{(12)}-H$ coupling constant by 9 Hz caused by the effect of the nitrogen atom of the piperidine substituent. In the spectrum of compound (Va) the $C_{(7)}$ carbon atom gives a doublet at 84.14 ppm with J_{CH} = 166 Hz, characteristic of an sp^2-hybridized carbon atom [5].

The reaction of salt (I) with primary amines (benzyl-, isopropyl-, and amylamines) under the same conditions leads to a type of substance fundamentally different in structure and correspondingly in spectral characteristics, viz. 2-[o-(N-alkylformimidoyl)benzyl]-3-methyl-4-oxoquinazoline (VI). Signals were observed in their PMR spectra for the protons of the substituent R, the methyl group, and the aromatic protons. In addition a one-proton low-field singlet was observed for the aldimine proton at 8.48-8.59 and a two-proton singlet for the methylene group at 4.72 ppm [in the spectrum of compound (VIa) the position of the latter coincides with the position of the singlet of the methylene group of the benzyl residue]. The presence of an N-alkylaldimine fragment was confirmed by the results of a nOe experiment. An increase of 19% in the intensity of the multiplet of the methine proton of the isopropyl group was observed in the spectrum of compound (VIb) on saturating at the resonance frequency of the methine proton at 8.48 ppm. This also indicates an anti structure for this aldimine. Evidence of disturbance of the rigid tetracyclic structure in the reaction products is the absence of significant nOe values for the methyl group signal on irradiation at the resonance frequency of the methylene group at 4.72 ppm, since an internuclear spatial interaction between the protons of the 6-CH_3 group and the protons at $C_{(7)}$ is always observed for all 6-methyl substituted isoquino[2,3-a]quinazolines (see, for example, above and in [1, 3]). In the C^{13} NMR spectrum of compound (VIb) there was an intense doublet at low field for the carbon of the aldimine group and a triplet was observed at high field for the methylene group together with the signals of the methyl and isopropyl groups.

It is evident that the quinazolines (VI) are formed as a result of a series of conversions which begin with nucleophilic attack by the primary amine at $C_{(12)}$ atom of the salt (I) cation with the formation of adducts of type (V) (R^1 = H) as occurs with secondary amines. These adducts then undergo breakage of the $C_{(12)}-N_{(13)}$ bond. The products of this decomposition are capable of existing in three tautomeric forms (VI)-(VIII) of which only form (VI) exists, since it retains a high degree of conjugation in both the benzene and quinazoline fragments. To confirm the scheme proposed we recorded the spectrum of a freshly prepared solution of salt (I) in a mixture of deuterochloroform and amylamine. In addition to the signals of compound (VIc) and the excess of amylamine, two singlets of equal intensity were observed at 5.39 and 6.32 ppm which were assigned, on the basis of data of the spectra of model compounds (V), to the resonance of proton at 7-H and 12-H respectively in the intermediate adduct of structure (V) (R = C_5H_{11}, R^1 = H). The intensity of these signals fell with time, accompanied by an

increase in the intensity of the signals for compound (VIc), and after 30 min had disappeared completely. We carried out a separate experiment to confirm that the formation of compound (VI) is accompanied by a tautomeric prototropic transfer. On treating a solution of salt (I) in acetonitrile with a mixture of the isopropylamine and an excess of D_2O, compound (VIb) was isolated monodeuterated at the benzyl position, in the PMR spectrum of which the integrated intensity of the methylene group signal at 4.72 ppm was one proton unit but the signal itself has the shape of a doublet with J_{HD} = 2.5 Hz. It must be noted that no deuterium labeling occurs on treating a prepared solution of salt (I) in isopropylamine with an excess of D_2O. The noted observations also indicate the intramolecular nature of the prototropic transfer occurring on fission of the isoquinoline ring, in which the reagent (amine) and solvent (water) may participate. The most probable mechanism for the conversion of (V) into (VI) assumes, in our opinion, the sequential protonation by the alkylammonium ion (formed in the first stage) or hydroxonium ion (when carrying out the reaction in water) of the adduct (V) at the $C_{(7)}$ carbon atom, fission of the $C_{(12)}-N_{(13)}$ bond, and subsequent deprotonation of the intermediate immonium salt by the excess of amine, completing the formation of the aldimines (VI).

Both the formation of the adduct (V) and the decomposition of the isoquinoline ring with the formation of compound (VI) are reversible processes. It turned out that the initial salt (I) is readily formed in high yield on treating acetic acid solutions of both compounds with perchloric acid.

EXPERIMENTAL

The IR spectra of compounds were recorded in KBr disks on a Pye-Unicam SP3 300 instrument. The NMR spectra of compounds were obtained on a Bruker WP 100 SY instrument in $CDCl_3$, internal standard was TMS. A description of the signals of the nuclei of the aromatic carbon atoms is given with spectra obtained under conditions of complete decoupling from protons.

The data of elemental analysis corresponded with calculated values.

6-Methyl-5-oxo-5,5-dihydro-12H-isoquino[2,3-a]quinazoline (III). Sodium borohydride (0.15 g, 4 mmole) was added to a suspension of the salt (I) (0.72 g, 2 mmole) in ethanol (20 ml). The mixture was boiled for 1 h, the solvent was distilled off on a rotary evaporator, the residue treated with 10% NaOH, the solid filtered off, washed with a little alcohol, and recrystallized from 2-propanol. The substance obtained proved to be identical in mp, giving no depression of mp in a mixed sample, and in spectral characteristics with the compound obtained previously in [4]. ^{13}C NMR spectrum: 29.47 (q, J = 141 Hz, $N-CH_3$); 48.98 (t, J = 138 Hz, $C_{(12)}$); 82.45 (d, J = 164 Hz, $C_{(7)}$); 110.66, 114.99, 120.18, 122.87, 123.1, 123.74, 124.62, 127.84, 128.48, 132.86, 134.43, 140.00 (aromatic carbon atoms); 141.50 (s, $C_{(13a)}$); 159.38 ppm (s, $C_{(5)}$).

6-Methyl-5-oxo-6,6a,7,12-tetrahydro-5H-isoquino[2,3-a]quinazoline (IV). A mixture of acetic acid (3 ml) and ethanol (7 ml) was added dropwise to a suspension of salt (I) (0.72 g, 2 mmole) and sodium borohydride (0.23 g, 6 mmole) in ethanol (20 ml). The mixture was boiled for 1 h and then treated as in the previous procedure. Compound (IV) was obtained, identical to that obtained previously [4].

Reaction of Salt (I) with Amines. The salt (I) (0.36 g, 1 mmole) was dissolved in the amine (3 ml) by heating. The solution obtained was treated with water (30 ml), the solid which precipitated was filtered off, washed with water, carefully dried, and recrystallized from hexane.

To obtain compound (VIb) monodeuterated at the benzyl position, salt (I) was dissolved on heating in the minimum amount of acetonitrile, the solution obtained was treated with a solution of isopropylamine (3 ml) in D_2O (30 ml), dried, and recrystallized from hexane.

6-Methyl-5-oxo-12-(piperidino)-5,6-dihydro-12H-isoquino[2,3-a]quinazoline (Va) $C_{22}H_{23}N_3O$. mp 186-187°C. IR spectrum: 1658 (C=O) s, 1609 cm^{-1} (C=C) m. PMR spectrum: 1.33 (6H, m) and 2.46 (4H, m, piperidine ring protons); 3.44 (3H, s, $N-CH_3$); 5.29 (1H, s, 7-H); 6.17 (1H, s, 12-H); 6.9-7.6 (7H, m, 1- to 3- and 8- to 11-H); 8.12 ppm (1H, d.d, J_o = 7.5 Hz, J_m = 1.5 Hz, 4-H). ^{13}C NMR spectrum: 23.8 (t, J = 130.9 Hz, $C_{(4)}$); 25.61 (t, J = 128.0 Hz, $C_{(3')}$ and $C_{(5')}$); 29.31 (q, J = 139.7 Hz, $N-CH_3$); 48.10 (t, J = 132.4 Hz, $C_{(2')}$ and $C_{(3')}$); 74.45 (d, J = 147.1 Hz, $C_{(12)}$); 84.14 (d, J = 166.2 Hz, $C_{(7)}$); 112.06, 115.57, 120.30, 122.23, 122.52, 123.16, 126.72, 127.95, 128.36, 133.03, 133.62, 139.99 (aromatic carbon atoms); 142.44 (s, $C_{(13')}$); 159.61 ppm (s, $C_{(5)}$).

6-Methyl-12-(morpholino)-5-oxo-5,6-dihydro-12H-isoquino[2,3-a]quinazoline (Vb) $C_{21}H_{21}N_3O_2$. mp 149-151°C. IR spectrum: 1645 (C=O) s; 1611 cm^{-1} (C=C) m. PMR spectrum: 2.51 (2H, m) and 3.52 (2H, m, morpholine ring protons); 3.44 (3H, s, $N-CH_3$); 5.31 (1H, s, 7-H); 6.18 (1H, s, 12-H); 6.9-7.6 (7H, m, 1- to 3- and 8- to 11-H); 8.12 ppm (1H, d.d, J_0 = 7.5 Hz, J_m = 1.5 Hz, 4-H).

2-[o-(N-Benzylformimidoyl)benzyl]-3-methyl-4-oxoquinazoline (VIa) $C_{24}H_{21}N_3O$. mp 104-105°C. IR spectrum: 1665 (C=O) s; 1630 cm^{-1} (C=N) m. PMR spectrum: 3.42 (3H, s, $N-CH_3$); 4.72, 4.73 (4H, s, overlap of signals of methylene group protons); 7.0-8.8 (7H, m, aromatic protons); 8.24 (1H, d.d, J_0 = 7.5 Hz, J_m = 1.5 Hz, 4-H); 8.59 ppm (1H s, CH=N).

2-[o-(N-Isopropylformimidoyl)benzyl]-3-methyl-4-oxo-quinazoline (VIb) $C_{20}H_{21}N_3O$. mp 107-108°C. IR spectrum: 1665 (C=O) s; 1630 cm^{-1} (C=N) m. PMR spectrum: 1.11 [6H, d, J = 7 Hz, $CH(\underline{CH_3})_2$]; 3.39 [1H, m, $\underline{CH}(CH_3)_2$]; 3.55 (3H, s, $N-CH_3$); 4.72 (2H, s, CH_2); 7.0-8.8 (7H, m, aromatic protons); 8.26 (1H, d.d, J_0 = 7.5 Hz, J_m = 1.5 Hz, 4-H); 8.48 ppm (1, s, CH=N). ^{13}C NMR spectrum: 23.86 [q, J = 123.5 Hz, $C(\underline{CH_3})_2$]; 30.17 (q, J = 141.2 Hz, $N-CH_3$); 39.92 (t, J = 129.0 Hz, CH_2); 62.06 (d, J = 135 Hz, CH); 119.77, 125.85, 126.00, 126.20, 126.84, 129.53, 129.78, 131.22, 133.33, 134.61, 146.88 (aromatic carbon atoms); 156.0 (s, $C_{(2)}$); 158.2 (d, CH=N); 162.18 ppm (s, $C_{(4)}$).

2-[o-(N-Amylformimidoyl)benzyl]-3-methyl-4-oxoquinazoline (VIc) $C_{22}H_{25}N_3O$. mp 92.5-94°C. IR spectrum: 1655 (C=O) s; 1640 cm^{-1} (C=N) m. PMR spectrum: 0.80 (3H, d, J = 7 Hz, $CH_2\underline{CH_3}$); 1.19 (4H, m, $\underline{CH_2CH_2}CH_3$); 1.56 (2H, m, $N-CH_2\underline{CH_2}$); 3.54 (5H, s and t, $N-CH_3$ and $N-\underline{CH_2}-CH_2$); 4.72 (2H, s, CH_2); 7.0-8.8 (7H, s, aromatic protons); 8.26 (1H, d.d, J_0 = 1.5 Hz, J_m = 1.5 Hz, 4-H); 8.47 ppm (1H, s, CH=N).

REFERENCES

1. V. M. Kisel', V. A. Kovtunenko, L. M. Potikha, A. K. Tyltin, V. S. Nikitchenko, and F. S. Babichev, Ukr. Khim. Zh., **58**, 790 (1992).
2. F. S. Babichev, L. A. Gromov, V. A. Kovtunenko, V. V. Ishchenko, and V. M. Kisel', Synthesis, Pharmacology and Clinical Aspects of New Psychotropic and Cardiovascular Substances: Abstracts, Volgograd (1989).
3. V. I. Kisel', V. A. Kovtunenko, A. V. Turov, A. K. Tyltin, and F. S. Babichev, Khim. Geterotsikl. Soedin., No. 3, 389 (1991).
4. V. M. Kisel' and F. S. Babichev, Dokl. Akad. Nauk. SSSR, **306**, 628 (1989).
5. G. C. Levy and G. L. Nelson, Carbon-13 Nuclear Magnetic Resonance for Organic Chemists, Wiley–Interscience, New York (1972).