SYNTHESIS OF INDOLO- AND PYRROLOQUINAZOLONES

O. N. Chupakhin, T. L. Pilicheva, I. Ya. Postovskii, and N. A. Klyuev

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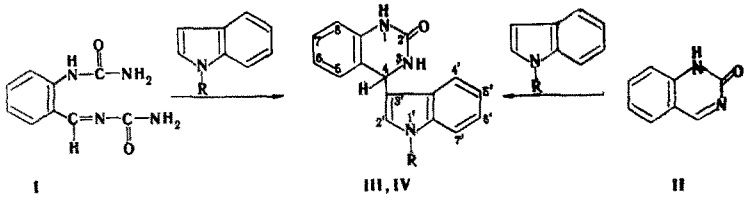
2-Quinazolone reacts with various π-surplus systems (indoles and pyrroles) to give 3,4-dihydro-4-substituted 2-quinazolones. These compounds are capable of oxidation to 4-substituted 2-quinazolones. o-Carbamidobenzylideneurea gives identical products in these reactions.

In a preceding paper [1] we showed that o-carbamidobenzylideneurea (I) in some reactions, for example, with arylamines, undergoes cyclization with splitting out of urea to give the same derivatives that are obtained from 2-quinazolone (II). In the present research we have investigated the reactions of I and II with π-surplus heteroaromatic systems – indoles, pyrroles, and thiophene. The 2-quinazolone derivatives obtained may be of pharmacological interest [2].

The corresponding 3,4-dihydro-4-substituted 2-quinazolones (III, IV) are formed when I or II is refluxed with 1-methylindole or indole, respectively, in dimethylformamide (DMF).

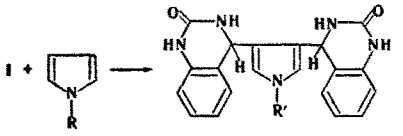


I III, IV II

III R=CH_3; IV R=H

As in the case of arylamines [1], the products obtained as a result of the reaction of I or II with indoles are identical. Thus, both III and IV can be used for the synthesis of III and IV, but the yields are higher when I is used.

Colorless 2,5-bis(3,4-dihydroquinazol-2-on-4-yl)pyrrole (V) is formed in the reaction of I with pyrrole at 20°C:



V, VI

V R'=H; VI R'=CH_3

Refluxing I with 1-methylpyrrole gives 1-methyl-2,5-bis(3,4-dihydroquinazol-2-on-4-yl)pyrrole (VI). Heterocycles with a deficient (as compared with the π system under consideration) system, for example, 1-phenylpyrrole and thiophene, proved to be unreactive in similar transformations: reaction products are not detected even chromatographically.

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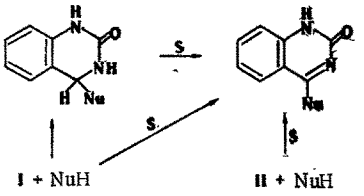
The 3,4-dihydro-2-quinazolones can be rearomatized by oxidation. Thus 4-(1-methyl-3-indolyl)-2-quinazolone and 4-(3-indolyl)-2-quinazolone, respectively, are formed when III and IV are fused with sulfur. These same products are readily obtained by heating I or II with 1-methylindole or indole with sulfur in DMF.

It has been shown [3] that the analogous 3,4-dihydroquinazoline compounds are not dehydrogenated under various conditions.

Thus 3,4-dihydro-2-quinazolones, which can be considered to be intermediate products in the nucleophilic substitution of 4-H in 2-quinazolone, are less stable than compounds of the 3,4-dihydroquinazoline series [3].

Consequently, the tendency for retention of aromatic character is expressed more strongly in the case of 2-quinazolone than in the case of the dihydroquinazolinium cation, which is capable of stabilization through amidine resonance [4].



Nu — indolyl, 1-methylindolyl

The IR spectra of the synthesized compounds show the presence of a carbonyl group (narrow band at 1660-1690 cm^{-1}) and an N–H bond (3230-3450 cm^{-1}).

The loss of aromatic character of the quinazolone portion of the molecule in III and IV is accompanied by the hypsochromic shift of the absorption bands characteristic for 2-quinazolone (λ_{max} 225, 275, and 340 nm) of 20-45 nm. The typical spectrum of 2-quinazolone derivatives is observed in the case of oxidized products VII and VIII.

The PMR spectra of III and IV contain the singlet at 7.20 and 7.38 ppm that is characteristic for the indole 2-H proton [5], which is shifted to weaker field (8.20 ppm) for oxidized compound VII, inasmuch as the resulting aromatic system of the quinazolone portion of the molecule somewhat deshields the indole 2-H proton. On the basis of this, it might be assumed that addition to 2-quinazolone occurs at the 3 position of the indole residue. The 3-H (9.17, 9.31 ppm) and 4-H (5.76, 5.83 ppm) singlets of the quinazolone portion of the molecule in the spectra of III and IV vanish in the spectrum of VII, and this makes it possible to conclude that it has an oxidized structure. The signals of the aromatic protons of the annelated benzo ring in the quinazolones and in indole compounds appear as a multiplet (6.80-7.70 ppm), and the 1-H protons of quinazolones and indoles give singlets at weak field (12 and 11.53 ppm). The spectrum of V attests to diaddition of the quinazolone residues to pyrrole. There is also a pyrrole 3-H and 4-H singlet (5.85 ppm) in the spectrum [5].

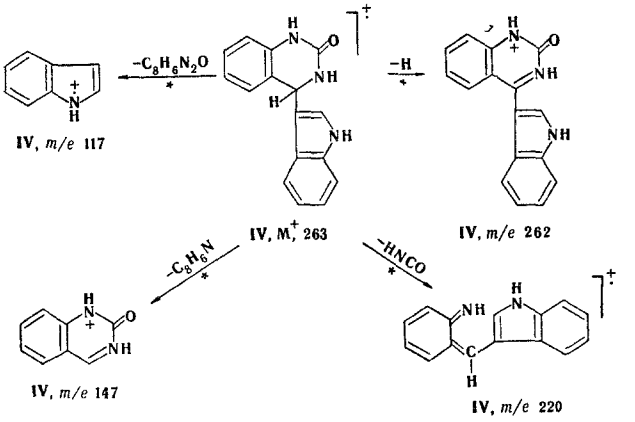
Information proving the structures of the synthesized compounds was obtained by mass spectroscopy [6, 7]. A molecular-ion peak is distinctly recorded in the mass spectra of IV, VI, VII, and VIII.

It is known [6] that if the bond between the rings of a partially hydrogenated bisheterocyclic system is realized through a tetrahedral carbon atom, the disintegration of such compounds under the influence of electron impact is characterized by cleavage of the σ bond between the rings (the fragment ions correspond to the structure of the rings composing the bisheterocyclic system and are always observed in the mass spectrum), an intensive dehydrogenation process leading to aromatization of the molecule as a whole, and low stability (W_M) of the molecular ion with respect to electron impact. In fact (see Table 1), the peak of the cation of the quinazolonim structure with mass 147 and peaks of ions with m/e 117 and 81 with indole and 1-methylpyrrole structures, respectively, are observed in the mass spectra of IV and VI. The formation of peaks of pseudomolecular ions is due to migration of a hydrogen atom (see the fragmentation scheme below). The subsequent fragmentation of these ions has been studied in detail [8], and the interpretation of the resulting fragments does not raise any difficulties: for the indole derivatives (IV) we have ion peaks with m/e 131, 130, 117, 116, 103, 102, 91, 90, and 77; for 2-quinazolone we have, respectively, 147, 146, 118, 76, 65, and 64; for 1-methylpyrrole (VI) we have 82, 81, 80, 54, and 53. In addition to the peaks listed above, the $(M - H)^+$ and $(M - HNCO)^+$ ion peaks have high intensities, and the latter is extremely character-

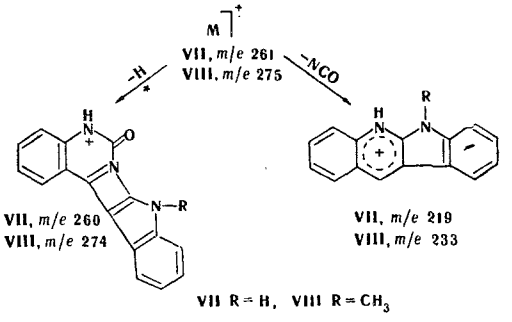
TABLE 1. Characteristic Ion Peaks in the Mass Spectra of IV, VI, VII, and VIII (the peak intensity is given in percent of the total ion current)

Ions	Compounds			
	IV	VI	VII	VIII
M^+	8,4	0,5	14,7	19,7
$(M-H)^+$	8,1	—	4,9	9,6
$(M-NCO)^+$	—	—	14,0	3,4
$(M-HNCO)^+$	1,8	1,4	2,1	—
m/e 147	2,0	2,7	—	—
m/e 117	6,4	—	—	—
m/e 81	—	2.5	—	—

istic for uracils [9] (Table 1). The disintegration of IV is illustrated by the following scheme:



The disintegration of the M^+ ion of VI proceeds similarly [6]. In the first step, instead of the $(M-H)^+$ process, one of the quinazolone rings is detached and the system is stabilized, as attested to by the high intensity of the peak of the fragment ion with m/e 227 (9.8% of the total ion current). For bisheterocyclic completely aromatic systems [6, 7], the bond between the rings (particularly between the quinazolone and pyrrole or indole rings in VI and VII) acquires π-bond character under the condition that the orientation of the rings is close to coplanar. In this case the disintegration of the M^+ ion is sufficiently selective. The excited molecule has considerable stability (W_M) with respect to electron impact. The fragment ions formed during the disintegration of the M^+ ion have, as a rule, the structure of a polycyclic conjugated system, whereas fragments that may be caused by destruction of the bond between the rings are not recorded in the mass spectrum. All of the phenomena noted above are characteristic for the disintegration of the M^+ ions of VII and VIII (see the scheme below and Table 1), and this confirms the structures of the synthesized compounds.



EXPERIMENTAL METHOD

The IR spectra of mineral oil and perfluorohydrocarbon suspensions of the compounds were recorded with a UR-20 spectrometer. The UV spectra of alcohol solutions ($2 \cdot 10^{-4}$ mole/liter) were recorded with a Perkin–Elmer 420 spectrophotometer. The PMR spectra of dimethyl sulfoxide (DMSO) solutions were measured with a Chart-60 spectrometer (60 MHz) with hexamethyldisiloxane as the internal standard. The mass spectra were recorded with a Varian Mat CH-6 spectrometer with a system for direct introduction of the samples into the ion source. The spectra were recorded at an ionizing electron energy of 70 eV, an emission current of 1.5 mA, and an ionization chamber temperature of 180°.

3,4-Dihydro-4-(1-methyl-3-indolyl)-2-quinazolone (III). A solution of 0.5 g (24 mmole) of I and 0.32 g (24 mmole) of 1-methylindole in 5 ml of DMF was refluxed for 1 h, after which the precipitated product was removed by filtration, washed with ether, and dried to give 0.62 g (65%) of a product with mp 270-272° (from aqueous DMF). Found: C 73.6; H 5.4; N 15.2%. $C_{17}H_{15}N_3O$. Calculated: C 74.0; H 5.2; N 15.5%. UV spectrum: 215, 250, and 288 nm (log ε 1.61, 0.5, and 0.35). IR spectrum: 1691 (C=O) and 3442 cm^{-1}(N-H). PMR spectrum: 9.17 (3-H), 5.76 (4-H), and 7.36 (2'-H) ppm.

3,4-Dihydro-4-(3-indolyl)-2-quinazolone (IV). This compound [0.61 g (64%)] was similarly obtained

and had mp 155-156° (from aqueous DMF). Found: N 16%; M 263. $C_{16}H_{13}N_3O$. Calculated: N 16%; M 263. UV spectrum: 210, 246, 284, and 370 nm (log ε 1.4, 0.4, 0.2, and 0.3). IR spectrum: 1674 (C=O) and 3230 cm^{-1} (N−H). PMR spectrum: 9.31 (3-H), 5.83 (4-H), and 7.20 (2'-H) ppm.

2,5-Bis(3,4-dihydroquinazol-2-on-4-yl)pyrrole (V). Compound V precipitated from a solution of 0.8 g (39 mmole) of I and 0.13 g (20 mmole) of pyrrole in 25 ml of glacial acetic acid after 5-6 h at room temperature. It was removed by filtration, washed with water, and dried to give 1.04 g (72%) of a product with mp 320° (after reprecipitation from DMSO by the addition of water and drying over P_2O_5 at 160°). Found: C 63.4; H 5.3; N 18.6%. $C_{20}H_{18}N_5O_2 \cdot H_2O$. Calculated: C 63.5; H 5.3; N 18.5%.

1-Methyl-2,5-bis(3,4-dihydroquinazol-2-on-4-yl)pyrrole (VI). A solution of 0.8 g (39 mmole) of I and 0.16 g (20 mmole) of 1-methylpyrrole in 25 ml of glacial acetic acid was refluxed for 3 h, after which the solution was cooled and diluted with water. The resulting precipitate was removed by filtration, washed with water, and dried to give 0.45 g (34%) of a product with mp 188-190° (from aqueous ethanol). Found: C 67.3; H 5.3; N 18.7%; M 373. $C_{21}H_{19}N_5O_2$. Calculated: C 67.4; H 5.4; N 18.7%; M 373.

4-Indolyl-2-quinazolone (VII). A solution of 0.5 g (24 mmole) of I, 0.28 g (24 mmole) of indole, and 0.08 g (24 mmole) of sulfur in 5 ml of DMF was refluxed for 1 h, and the resulting precipitate was removed by filtration, washed with benzene and ether, and dried to give 0.5 g (77%) of a product with mp 318-320° (from DMF). Found: C 73.6; H 4.4; N 16.1%. $C_{16}H_{11}N_3O$. Calculated: C 73.2; H 4.3; N 16.1%. PMR spectrum: 12.00 (1-H), 11.53 (1'-H), and 8.20 (2'-H) ppm.

4-(1-Methylindolyl)-2-quinazolone (VIII). This compound [0.6 g (67%)], with mp 302-304° (from DMF), was obtained by the method used to prepare VII. Found: C 74.3; H 4.8; N 15.8%; M 261. $C_{17}H_{13}N_3O$. Calculated: C 74.2; H 4.8; N 15.3%; M 261.

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