Chemistry of Heterocyclic Compounds, Vol. 36, No. 5, 2000

CONDENSED ISOQUINOLINES. 9.* ALKYLATION OF 7,12-DIHYDRO-5H-ISOQUINO[2,3-*a*]QUINAZOLIN-5-ONES*[2]

V. M. Kisel', L. M. Potikha, and V. A. Kovtunenko

The alkylation of 7,12-dihydro-5H-isoquino[2,3-a]quinazolin-5-one proceeds at $N_{(6)}$ or $C_{(7)}$ depending on the type of alkylating agent and reaction conditions. $C_{(7)}$-Alkylation occurs in the presence of base. The secondary alkylation of the 7-alkyl derivatives occurs at the same position under these conditions. Depending on the conditions, the reaction with o-xylylene dibromide leads to spiro[5H-isoquino-[2,3-a]quinazolin-7(12H),2'-indane]-5-one or 11-oxo-4b,5,10,16-tetrahydro-11H-10a-azonia-15b-azadibenz[a,e]pleiadene bromide, which are derivatives of new heterocyclic systems.

Keywords: condensed isoquinolines, condensed quinazolines, alkylation.

The alkylation of 7,12-dihydro-5H-isoquino[2,3-*a*]quinazolin-5-one (**1**) by methyl tosylate proceeds at $N_{(6)}$ to give quaternary salt **2a** [3]. In a continuation of a study of isoquino[2,3-*a*]quinazolines, we investigated the alkylation of isoquinoquinazolone **1** by various alkylating agents under different conditions and attempted to study secondary alkylation of the monoalkylation products synthesized in the first step.

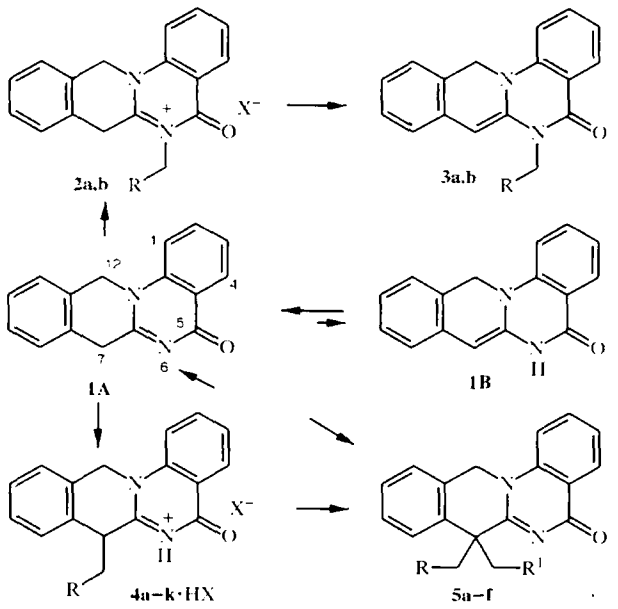
The alkylation of isoquinoquinazolone **1** with excess ethyl iodide in acetonitrile proceeds also as alkylation at $N_{(6)}$ to give 6-ethyl-5-oxo-7,12-dihydro-5H-isoquino[2,3-*a*]quinazolinium iodide (**2a**). The action of triethylamine on salt **2b** gave the corresponding anhydrobase identified as 6-ethyl-6,12-dihydro-5H-isoquino[2,3-*a*]quinazolin-5-one (**3b**). The IR and ^{1}H NMR spectra of **2b** and **3b** are similar to the spectra of N-methyl analogs **2a** and **3a** synthesized in our previous work [3, 4], which confirms their structure. On the other hand, fusion of isoquinoquinazolone **1** with a small excess of benzyl halides at 100-120°C unexpectedly gave hydrohalide salts of 7-benzyl-7,12-dihydro-5H-isoquino[2,3-*a*]quinazolin-5-ones (**4a-4h**·HX). Heating solutions of isoquinoquinazolone **1** with phenacyl bromides in acetonitrile at reflux gives hydrobromide salts of 7-phenacyl-7,12-dihydro-5H-isoquino[2,3-*a*]quinazolin-5-ones (**4i**·HBr and **4j**·HBr). The reaction of isoquinoquinazolone **1** and methyl bromoacetate under the same conditions gave the methyl ester of (5-oxo-7,12-dihydro-5H-isoquino[2,3-*a*]quinazolin-7-yl)acetic acid (**4k**·HBr). These salts are converted by the action of triethylamine into free bases **4a-4k**. These compounds were identified as $C_{(7)}$-alkylation products using their ^{1}H NMR spectra (Tables 1 and 2), in which A_2X and ABX spin systems are found for the protons of the $C_{(7)}\underline{H}$–$C\underline{H}_2$–R fragment. The proton at $C_{(7)}$ in some of the salts such as **4i** and **4j** are readily exchanged by deuterium. Thus, the signal for this proton is lacking in the spectra of their freshly prepared solutions in deuterotrifluoroacetic acid, while the protons of the 7-$C\underline{H}_2$ methylene group are seen as a two-proton doublet with 18 Hz geminal coupling constant. Complete deuterium exchange is observed for the other salts **4** after letting their solutions stand for several days. In all cases, the methylene protons at $C_{(12)}$ give two doublets with 16 Hz geminal coupling constant, which is a consequence of the molecular asymmetry of the $C_{(7)}$-alkylation products.

* Communication 8, see ref. [1].

*[2] See also Letter to Editor [2].

Taras Shevchenko Kiev University, 252017 Kiev, Ukraine; e-mail: vkysil@mail.univ.kiev.ua. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 643-652, May, 2000. Original article submitted February 23, 1999.

 0009-3122/00/3605-0560$25.00©2000 KluwerAcademic/Plenum Publishers



2,3	R
a	H
b	Me

2	X^-
a	$TosO^-$
b	I^-

4	R	X^-
a	Ph	Cl^-
b	2-MeC_6H_4	Br^-
c	2,4-$Me_2C_6H_3$	Cl^-
d	4-ClC_6H_4	Cl^-
e	3-$O_2NC_6H_4$	Cl^-
f	2-NC-C_6H_4-	Br^-
g	2-$NCCH_2C_6H_4$	Br^-
h	3-$HOOCC_6H_4$	Br^-
i	PhCO	Br^-
j	4-BrC_6H_4CO	Br^-
k	MeOOC	Br^-

5	R	R^1
a	H	H
b	Me	Me
c	Ph	Ph
d	Ph	H
e	Ph	2-MeC_6H_4
f	Ph	3-$O_2NC_6H_4$

On the basis of a formal examination of the structure of isoquinoquinazolone **1** as a 1,2-dialkyl-1H-quinazolin-4-one, the formation of salts **2** using methyl tosylate or ethyl iodide as the alkylating agents is quite expected [5]. The differences in the direction of alkylation noted for the other cases requires an explanation, especially, since the product yields suggest regioselectivity in this reaction. Since imine form **1A** does not explicitly contain a C-nucleophilic site, isoquinoquinazolone **1**, by analogy to enamines and enamides, probably undergoes C-alkylation only in enamine form **1B** similarly to enamines of structurally related pyrimido[1,2-*b*]isoquinolines [7]. Thus, we attempted to detect the presence of the enamine form in solutions of isoquinoquinazolone **1** by spectral methods. However, independently of the solvents used, the ^1H NMR spectra of this compound show only one set of signals corresponding to imino form **1A**. We also compared the electronic absorption spectra of isoquinoquinazolone **1** and an isoelectronic analog of enamine form **1B**, namely, anhydrobase **3b**, which has a long-wavelength maximum at 345 nm. 7,7-Diethyl-7,12-dihydro-5H-isoquino[2,3-*a*]quinazolin-5-one **5b**, whose synthesis is described below, was used as the model compound for imine form **1A**. Tautomeric transformation to the enamine is impossible for **5b**. Figure 1 shows that form **1B** is absent in solution in amounts detectible by such a sensitive method. Nevertheless, the readiness of deuterium exchange of the protons of the $C_{(7)}$-methylene group established by ^1H NMR spectroscopy suggests the existence of an equilibrium. The signal of the $C_{(7)}$-methylene group protons is somewhat broadened in comparison with the signal for $C_{(12)}H_2$ and disappears in the presence of D_2O or CF_3CO_2D. If we assume that the rate of alkylation of **1** is slower than the rate of the interconversion **1A** ⇌ **1B**, then, in accord with the Curtin–Hammett principle [8],

TABLE 1. Physical Characteristics of Compounds Synthesized

Compound	Empirical formula	Found, % / Calculated, %				mp, °C (solvent)	Yield, %
		C	H	N	Hal		
4a·HCl	$C_{23}H_{18}N_2O$·HCl	73.80 / 73.69	5.21 / 5.11	7.46 / 7.47	9.21 / 9.46	140 (AcOH)	62
4b·HBr	$C_{24}H_{20}N_2O$·HBr	66.53 / 66.52	4.95 / 4.88	6.56 / 6.46	18.31 / 18.44	235 (AcOH)	85
4c·HCl	$C_{25}H_{22}N_2O$·HCl	74.31 / 74.52	5.60 / 5.75	7.09 / 6.95	8.81 / 8.80	164 (AcOH)	73
4d·HCl	$C_{23}H_{17}ClN_2O$·HCl	67.50 / 67.49	4.55 / 4.43	7.12 / 6.84	16.88 / 17.32	161 (AcOH)	68
4e·HCl	$C_{23}H_{17}N_3O_3$·HCl	65.83 / 65.80	4.42 / 4.32	10.03 / 10.01	8.67 / 8.44	193 (AcOH)	47
4f·HBr	$C_{24}H_{17}N_3O$·HBr	64.75 / 64.80	4.01 / 4.08	9.57 / 9.46	18.04 / 17.98	236 (AcOH)	75
4g·HBr	$C_{25}H_{19}N_3O$·HBr	65.42 / 65.51	4.38 / 4.40	9.34 / 9.17	17.66 / 17.43	257 (AcOH)	80
4h·HBr	$C_{24}H_{18}N_2O_3$·HBr	62.18 / 62.22	4.21 / 4.13	6.29 / 6.05	17.46 / 17.25	236 (DMF–*i*-PrOH)	50
4i·HBr	$C_{24}H_{18}N_2O_2$·HBr	64.29 / 64.44	4.21 / 4.28	6.33 / 6.26	18.08 / 17.86	207 (MeOH)	59
4j·HBr	$C_{24}H_{17}BrN_2O_2$·HBr	54.80 / 54.78	3.44 / 3.45	5.16 / 5.32	29.94 / 30.37	178 (MeOH)	67
4k·HBr	$C_{19}H_{16}N_2O_3$·HBr	56.81 / 56.87	4.35 / 4.27	6.79 / 6.98	20.02 / 19.91	202 (MeOH)	25
4a	$C_{23}H_{18}N_2O$	81.57 / 81.63	5.40 / 5.36	8.48 / 8.28		183 (*i*-PrOH)	
4b	$C_{24}H_{20}N_2O$	81.80 / 81.79	5.61 / 5.72	8.00 / 7.95		199 (*i*-PrOH)	
4c	$C_{25}H_{22}N_2O$	82.01 / 81.94	6.00 / 6.05	7.70 / 7.64		171 (MePh)	
4d	$C_{23}H_{17}ClN_2O$	74.18 / 74.09	4.71 / 4.60	7.75 / 7.51	9.63 / 9.51	173 (*i*-PrOH)	
4e	$C_{23}H_{17}N_3O_3$	72.12 / 72.05	4.50 / 4.47	10.54 / 10.96		202 (MeCN)	
4f	$C_{24}H_{17}N_3O$	79.41 / 79.32	4.65 / 4.71	11.74 / 11.56		220 (*i*-PrOH)	
4g	$C_{25}H_{19}N_3O$	79.63 / 79.55	5.15 / 5.07	10.92 / 11.13		170 (*i*-PrOH)	
4h	$C_{24}H_{18}N_2O_3$	75.41 / 75.38	4.62 / 4.74	7.40 / 7.33		259 (DMF–*i*-PrOH)	
4i	$C_{24}H_{18}N_2O_2$	78.70 / 78.67	5.00 / 4.95	7.51 / 7.67		187 (*i*-PrOH)	
4j	$C_{24}H_{17}BrN_2O_2$	64.70 / 64.73	3.96 / 3.85	6.45 / 6.29	17.93 / 17.94	221 (MeOH)	
4k	$C_{19}H_{16}N_2O_3$	71.16 / 71.24	5.01 / 5.03	9.11 / 8.74		205 ($MeNO_2$)	
5a	$C_{18}H_{16}N_2O$	78.31 / 78.24	5.93 / 5.84	10.06 / 10.14		215 (PhH)	48
5b	$C_{20}H_{20}N_2O$	78.89 / 78.92	6.60 / 6.62	9.36 / 9.20		102 (EtOH)	67
5c	$C_{30}H_{24}N_2O$	84.01 / 84.08	5.51 / 5.64	6.79 / 6.54		247 (*i*-PrOH)	87
5d	$C_{24}H_{20}N_2O$	81.86 / 81.79	5.73 / 5.72	9.65 / 9.72		207 (MePh)	55
5e	$C_{31}H_{26}N_2O$	84.01 / 84.13	5.86 / 5.92	6.52 / 6.33		231 (MePh)	68
5f	$C_{30}H_{23}N_3O_3$	75.99 / 76.09	4.73 / 4.89	9.11 / 8.87		228 (MePh)	59

we understand that the observed differences in the direction of the alkylation and its regioselectivity reflect differences in the activation energies of alkylation using agents differing in reactivity. In the case of methyl tosylate and ethyl iodide, the activation energy in the formation of the product of alkylation at $N_{(6)}$ is most favorable and the product of the less reactive isomer (azomethine **1A**) is formed. In the case of benzyl halides and phenacyl bromides, the activation energy for formation of the product of alkylation at $C_{(7)}$ is lower, which leads to

TABLE 2. Spectral Characteristics of 7,12-Dihydro-5H-isoquino[2,3-*a*]quinazolin-5-one Derivatives

Compound	IR spectra, ν, cm^{-1}				^{1}H NMR spectra (CF_3CO_2D), δ, ppm					
	C=O	C=N	N–H	other bands	ArH, m	12-H_A, d, ^2J = 16 Hz	12-H_B, d, ^2J = 16 Hz	7-H, t, ^3J = 6 Hz	7-CH_2, d, ^3J = 6 Hz	other signals
1	2	3	4	5	6	7	8	9	10	11
4a·HCl	1713	1625	2600		8.73-6.63 (13H)	5.53	4.14	4.96, m	3.59 m	
4b·HBr	1721	1616	2740		8.71-6.59 (12H)	5.73	4.63	4.86	3.61	1.92 (s, CH_3)
4c·HCl	1720	1619	2600		8.73-6.48 (11H)	5.74	4.72	4.85	3.57	2.29 (s, 2'-CH_3) 1.90 (s, 4'-CH_3)
4d·HCl	1700	1630	2600		8.73-7.00 (12H)	5.66	4.53	4.96	3.55	
4e·HCl	1717	1618	2540	1348, 1523 (NO_2)	8.75-7.00 (12H)	5.92	5.14	4.93, m	3.62, m	
4f·HBr	1715	1618	2600	2230 (CN)	8.70-6.83 (12H)	6.07	5.48	5.05, m	3.77 m	
4g·HBr	1720	1625	2750	2250 (CN)	8.75-7.00 (12H)	5.86	5.02	4.92, m	3.62 m	3.37; 3.17 (d, 2'-CH_2)*
4h·HBr	1720	1618	2500	2900 (OH)	8.72-7.15 (12H)	5.79	4.76	5.11	3.65	
4i·HBr	1715	1620	2670		8.67-7.49 (13H)	6.07	5.82		4.36; 4.09*[2]	
4j·HBr	1720	1626	2700		8.68-7.57 (12H)	6.09	5.86		5.07; 5.36*[2]	
4k·HBr	1730	1605	2800		8.65-7.57 (8H)	6.05	5.76	5.22	3.49	3.80 (s, CH_3)
4a	1637	1600			8.16-6.66 (13H)	5.42	4.29	4.38	3.22	
4b	1635	1592			8.18-6.57 (12H)	5.54	4.65	4.29	3.19	1.75 (s, CH_3)
4c	1640	1600			8.18-6.46 (11H)	5.57	4.70	4.26	3.14	2.16 (s, 2'-CH_3) 1.77 (s, 4'-CH_3)
4d	1625	1605			8.23-6.82 (12H)	5.59	4.77	4.41	3.20	
4e	1630	1595		1345, 1520 (NO_2)	8.18-7.10 (12H)	5.55	4.90	4.44	3.30	

TABLE 2 (continued)

1	2	3	4	5	6	7	8	9	10	11
4f	1632	1595		2220 (CN)	8.17-6.95 (12H)	5.72	5.03	4.40	3.37	
4g	1630	1595		2230 (CN)	8.18-6.81 (12H)	5.60	4.98	4.36	3.64	3.24 (m, 2'-CH_2)
4h	1650	1580		2900 (OH)	8.19-6.95 (12H)	5.43	4.54	4.40	3.30	
4i	1675 1630	1600			8.16-7.29 (13H)	5.67	5.45	4.70	3.99	
4j	1675 1625	1590			8.15-7.30 (12H)	5.67	5.42	4.69	3.97	
4k	1735 1640	1605			8.20-7.40 (8H)	5.61	5.28		3.32; 3.04*[3]	3.32 (s, CH_3)
5a	1633	1595			8.36-7.25 (8H)	5.27 (2H, s)			1.75 (6H, s)	
5b	1635	1605			8.50-7.25 (8H)	5.29 (2H, s)			2.67 m; 2.02 m	0.55 (6H, t, CH_3)*[4]
5c	1635	1598			8.55-6.50 (18H)	4.13 (2H, s)			4.23; 3.43*[5]	
5d	1635	1600			8.50-6.31 (13H)	4.86	3.50		3.49 (4H); 2.98 (4H)*[5]	2.14 (s, CH_3)
5e	1635	1600			8.50-6.25 (17H)	4.15 (2H, s)			4.31; 3.46*[5] 4.22; 3.51*[5]	2.02 (s, CH_3)
5f	1630	1595		1340, 1515 (NO_2)	8.50-6.45 (17H)	4.51	3.82		4.56; 3.65*[5] 4.03; 3.36*[5]	

* ^2J = 18 Hz.
*[2] dd, ^2J = 18 Hz.
*[3] d, ^2J = 15 Hz.
*[4] ^3J = 7 Hz.
*[5] d, ^2J = 13 Hz.

the product from the more reactive isomer (enamine **1B**) although energy is required for the tautomeric transformation of the intermediate to the less favorable tautomer **1A** → **1B**.

The direction of the alkylation of the enolate generated from isoquinoquinazolone **1** by the action of strong bases is independent of the alkylating agent but it proved impossible to stop the reaction at the monoalkylation stage. Thus, carrying out the reaction of isoquinoquinazolone **1** in the presence of sodium isopropylate in 2-propanol with a slight excess of alkylating agent leads to a mixture containing unreacted starting compound as indicated by thin layer chromatography. The formation of a single reaction product is observed when using a two-fold excess of sodium isopropylate and alkylating agents such as methyl iodide, ethyl iodide, and benzyl chloride. In this case, products are formed by alkylation at $C_{(7)}$, namely, 7,7-dialkyl-7,12-dihydro-5H-isoquino[2,3-*a*]quinazolin-5-ones **5a-c**. Dimethylation product **5a** is indicated by the magnetic equivalence of the methyl groups protons, which give an upfield six-proton singlet. The protons of the methylene groups at $C_{(7)}$ in the ^{1}H NMR spectra of **5b** and **5c** are not equivalent, probably due to steric hindrance to rotation about the $C_{(7)}$–CH_2–R bonds. These protons give complex multiplets in the spectrum of **5b**, while two doublets with geminal coupling constant 13 Hz are found in the spectrum of **5c**. In all cases, the $C_{(12)}\underline{H}_2$ protons are equivalent and the position of their singlet in the spectra of **5a** and **5b** hardly differs from the position of this signal in the spectrum of starting **1** (5.22 ppm) [9]. We should note the significant upfield shift of the signal of these protons in dibenzyl derivative **5c**, which we attribute to conformational rigidity of the benzyl substituents, symmetrically oriented above and below the plane of the isoquinoquinazoline fragment such that the $C_{(12)}\underline{H}_2$ protons are subject to magnetic shielding of both benzene rings. This explanation is in good accord with the observed significant upfield shift of the doublet of one of these protons in the spectra of monobenzyl derivatives **4a-h**.

The formation of dialkyl derivatives **5** indicates that the enolates generated both from isoquinoquinazolone **1** and the intermediates of its monoalkylation **4** undergo alkylation at $C_{(7)}$. This hypothesis was confirmed by synthesis of **5c** through the reaction of benzylisoquinoquinazoline **4a** with benzyl chloride in the presence of base. Alkylation of isoquinoquinazoline **4a** under these conditions by other alkylating agents leads to asymmetrically substituted 7,7-dialkylisoquinoquinazolines **5d-f**.

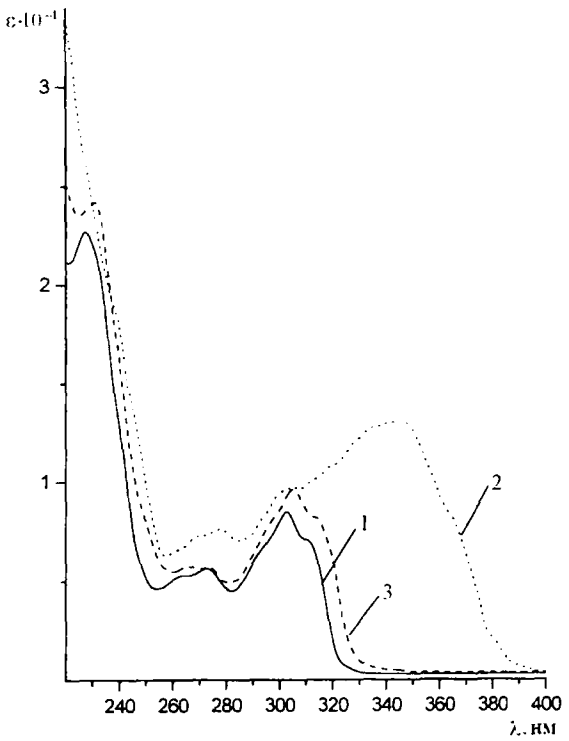
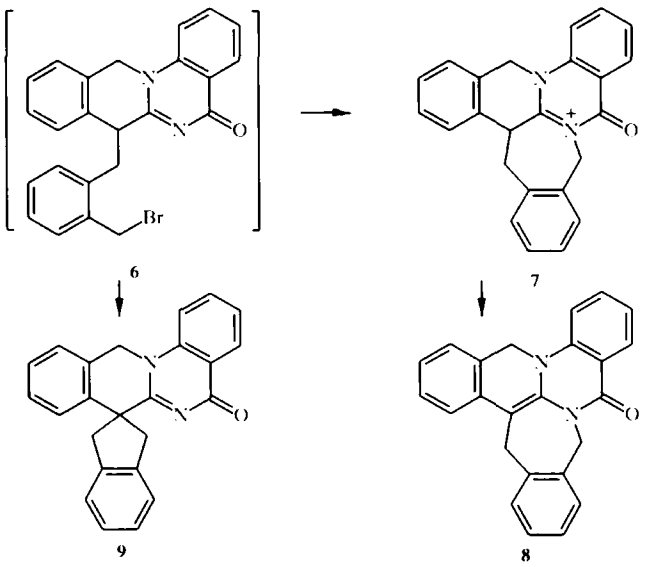


Fig. 1. Electronic absorption spectra of isoquinoquinazolone **1** (curve *1*), **3b** (*2*), and **5b** (*3*).

A study of the direction of the secondary alkylation of bases of monobenzylisoquinoquinazolines **4a** and **4b** in the absence of additional base showed that the alkylation of isoquinoquinazolone **1** hardly proceeds at relatively low temperatures, while the reaction above 120°C leads to a complex mixture of unidentified products. The observed inertness of the bases corresponding to salts **4a** and **4b** relative to alkylation is attributed to steric hindrance of the potential reaction sites at $C_{(7)}$ and $N_{(6)}$ by the bulky substituents at $C_{(7)}$ and their reduced reactivity in comparison with the generated enolates.

This question was studied for an intramolecular variant of this reaction. The alkylation of isoquinoquinazolone **1** was carried out with *o*-xylylene dibromide, which proceeds initially to give $C_{(7)}$-alkylation intermediate **6**·HBr. Under these conditions (fusion at 110-120°C), the reaction is accompanied by deprotonation of this salt and repeated intramolecular $N_{(5)}$-alkylation to give 11-oxo-4*b*,5,10,16-tetrahydro-11H-10*a*-azonia-15*b*-azadibenz[*a*,*e*]pleiadene (**7**). This structure was indicated by elemental analysis since neither the IR or ^{1}H NMR spectrum permitted an unequivocal assignment. Thus, the ^{1}H NMR spectrum of this compound has two AB and one ABX spin systems for aliphatic protons. However, such a pattern may correspond both to salts **6**·HBr and **7** since both these structures contain an element of molecular asymmetry. Thus, in order to establish the structure of the reaction product, salt **7**, obtained by the action of triethylamine, was converted into the free base identified as 5,10-dihydro-11H,16H-10*a*,15*b*-diazadibenz[*a*,*e*]pleiaden-11-one (**8**). Only three two-proton aliphatic proton singlets are noted in its ^{1}H NMR spectrum, which is possible only for proposed structure **8**. Treatment of **8** with hydrobromic acid gave a salt identical to **7** obtained directly from isoquinoquinazolone **1** and *o*-xylylene dibromide.



As expected, repeated intramolecular alkylation at $C_{(7)}$ occurs in monoalkylation intermediate **6** in basic media as indicated by formation of a compound with a fundamentally different structure obtained in the reaction of isoquinoquinazolone **1** and *o*-xylylene dibromide in the presence of excess sodium isopropylate. The finding of a single two-proton singlet and two-proton doublets with 16.5 Hz geminal coupling constant in the upfield portion of the ^{1}H NMR spectrum of this compound leads to its unequivocal identification as spiro[5H-isoquino-[2,3-*a*]quinazolin-$7_{(12)}$,2'-indan]-5-one (**9**). The downfield doublet is assigned to the signals of those methylene protons at $C_{(1')}$ and $C_{(3')}$ of the indane system, which are located in the magnetic deshielding zone of the isoquinoline benzene ring. The yields of heterospiran **9** and salt **7** are 80 and 75%, respectively, which indicates high regioselectivity also in the secondary alkylation reaction (at least, in its intramolecular variant). We especially note that we were unable to find any information in the literature on heterocyclic systems whose derivatives **7-9** were obtained in this work.

EXPERIMENTAL

The IR spectra were obtained for KBr pellets on a Pye Unicam SP3-300 spectrometer and the UV spectra of solutions of **1**, **3b**, and **5b** in methanol were taken on a Shimadzu UV-3100 spectrophotometer. The ^{1}H NMR spectra of salts **4a-k**·HX in CF_3CO_2D, **4a-k** in DMSO-d_6, and **5a-f** in $CDCl_3$ were obtained on a Bruker WP-100 SY spectrometer with TMS as the internal standard.

6-Ethyl-5-oxo-7,12-dihydro-5H-isoquino[2,3-*a*]quinazolinium Iodide (2b). A sample of ethyl iodide (0.88 ml, 11 mmol) was added to a suspension of isoquinoquinazolone **1** (1.24 g, 5 mmol) in acetonitrile (25 ml) and heated at reflux for 3 h. During this period, starting **1** entered the solution. The solvent was evaporated and the residue was dissolved with heating in 2-propanol (15 ml). The yellow precipitate obtained upon cooling was filtered off, washed with 2-propanol, and recrystallized from acetic acid to give 0.4 g (40%) of compound **2b**; mp >300°C (dec.). ^{1}H NMR spectrum (CF_3CO_2D): 9.0-7.5 (8H, m, H arom); 5.87 (2H, s, 12-C$\underline{H}_2$); 4.93 (2H, s, 7-C$\underline{H}_2$); 4.74 (2H, q, ^3J = 7 Hz, 5-C$\underline{H}_2$CH$_3$); 1.66 ppm (3H, t, ^3J = 7 Hz, 5-CH$_2$C$\underline{H}_3$). IR spectrum: 1705 (C=O); 1615 cm^{-1} (C=N$^+$). Found, %: C 53.29; H 4.16; N 7.12. $C_{18}H_{17}IN_2O$. Calculated, %: C 53.48; H 4.24; N 6.93.

6-Ethyl-6,12-dihydro-5H-isoquino[2,3-*a*]quinazolin-5-one (3b) was obtained by treating salt **2b** with excess triethylamine. The free base was precipitated by adding water and recrystallized from ethanol, mp >118°C. ^{1}H NMR spectrum ($CDCl_3$): 8.1-6.9 (8H, m, H arom); 5.03 (2H, s, 12-C$\underline{H}_2$); 5.15 (1H, s, 7-C$\underline{H}$); 4.04 (2H, q, ^3J = 7 Hz, 5-C$\underline{H}_2$CH$_3$); 1.35 ppm (3H, t, ^3J = 7 Hz, 5-CH$_2$C$\underline{H}_3$). IR spectrum: 1650 (C=O); 1600 cm^{-1} (C=N). Found, %: C 78.02; H 5.76; N 10.23. $C_{18}H_{16}N_2O$. Calculated, %: C 78.24; H 5.84; N 10.14.

Alkylation of Isoquinoquinazolone 1 by Benzyl Halides. A mixture of isoquinoquinazolone **1** (1.24 g, 5 mmol) and corresponding benzyl halide (6 mmol) was heated for 3 h on an oil bath at 110-120°C. The cooled melt was triturated with acetone. The solid was filtered off, washed with acetone, and recrystallized from a suitable solvent to give salts **4a-h**·HX.

Alkylation of Isoquinoquinazolone 1 by Phenacyl Bromide and Methyl Bromoacetate. A sample of corresponding α-bromocarbonyl compound (6 mmol) was added to a suspension of compound **1** (1.24 g, 5 mmol) in acetonitrile (25 ml) and heated at reflux for 0.5 h. Then, acetone (20 ml) was added to the cooled mixture and left for 24 h. The precipitate formed was filtered off, washed with acetone, and recrystallized from methanol to give hydrobromides **4i-k**.

Free bases of isoquinoquinazolines **4a-k** were obtained when hydrohalides **4**·HX were dissolved with heating in excess piperidine, cooled, and diluted with a five-fold volume of water. The precipitate formed was filtered off and washed with water and ethanol. In the isolation of base **4h**, the aqueous solution was brought to pH 7 by adding dilute hydrochloric acid.

Alkylation of Isoquinoquinazolone 1 in the Presence of Base. A sample of isoquinoquinazolone **1** (1.24 g, 5 mmol) was added with vigorous stirring to a solution of sodium (0.28 g, 12 mmol) in anhydrous 2-propanol (20 ml). The solution turned bright red. Then, a solution of alkylating agent (11 mmol) in anhydrous 2-propanol (10 ml) was added dropwise and heated for 4 h with stirring. The reaction mixture turned almost colorless. The solvent was distilled off at reduced pressure and the residue was treated with water. The solid was filtered off, washed with water and ethanol, and recrystallized from a suitable solvent to give compound **4a** in 31% yield, **5b** in 35% yield, and **5c** in 86% yield.

Alkylation of Isoquinoquinazoline 4a in the Presence of Base was carried out analogously using sodium (0.14 g, 6 mmol), alkylating agent (6 mmol), and starting compound **3a** (1.69 g, 5 mmol) to give compound **5d** in 45% yield, **5e** in 86% yield, and **5f** in 75% yield.

11-Oxo-4*a*,5,10,16-tetrahydro-11H-10*b*-azonia-15*b*-azadibenz[*a*,*e*]pleiadene Bromide (7) was obtained analogously to salts **4a-h** from isoquinoquinazolone **1** and *o*-xylylene dibromide in 75% yield; mp 238°C (acetic acid). ^{1}H NMR spectrum (CF_3CO_2D): 8.70-7.10 (12H, m, H arom); 6.5-5.5 ppm (5H, m, 4b-H, 10-H, 16-H). IR spectrum: 1710 (C=O); 1628 cm^{-1} (C=N$^+$). Found, %: C 66.99; H 4.52; N 6.47; Br 18.73. $C_{24}H_{19}BrN_2O$. Calculated, %: C 66.83; H 4.44; N 6.49; Br 18.73.

5,10,11,16-Tetrahydro-10*a*,15*b*-diazadibenz[*a*,*e*]pleiaden-11-one (8) was obtained from salt **7** by the action of piperidine with subsequent precipitation by adding water; mp 157°C (2-propanol). ^{1}H NMR spectrum ($CDCl_3$): 8.0-6.8 (12H, m, H arom); 5.30 (2H, s, 10(16?)-H); 4.67 (2H, s, 16(10?)-H); 4.14 ppm (2H, s, 5-H).

IR spectrum: 1650 cm^{-1} (C=O). Found, %: C 82.01; H 5.10; N 8.09. Calculated, % $C_{24}H_{18}N_2O$: C 82.26; H 5.18; N 7.99.

Spiro[5H-isoquino[2,3-*a*]quinazolin-7(12H),2'-indan]-5-one (9) was obtained analogously to products **5** using *o*-xylylene dibromide (1.58 g, 6 mmol), sodium (0.28 g, 12 mmol), and isoquinoquinazolone **1** (1.24 g, 5 mmol). Yield of **9** 1.4 g (80%); mp 283-285°C (acetic acid). ^{1}H NMR spectrum ($CDCl_3$): 8.45-7.20 (12H, m, H arom); 5.34 (2H, d, ^2J = 16.5 Hz, 1'-H, 3'-H); 3.33 ppm (2H, d, ^2J = 16.5 Hz, 1'-H, 3'-H). IR spectrum: 1635 (C=O); 1590 cm^{-1} (C=N). Found, %: C 82.08; H 5.21; N 7.90. $C_{24}H_{18}N_2O$. Calculated, %: C 82.26; H 5.18; N 7.99.

The authors express their gratitude to Docent Z. V. Voitenko for participating in a discussion of this work.

REFERENCES

1. V. M. Kisel', K. M. Kondratyuk, and V. A. Kovtunenko, *Khim. Geterotsikl. Soedin.*, No. 11, 1576 (1999).
2. V. M. Kisel', L. M. Potikha, and V. A. Kovtunenko, *Khim. Geterotsikl. Soedin.*, No. 3, 423 (1995).
3. V. M. 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', V. A. Kovtunenko, L. M. Potikha, A. K. Tyltin, V. S. Nikitchenko, and F. S. Babichev, *Ukr. Khim. Zh.*, **58**, 790 (1992).
5. T. Williamson, in: R. Elderfield (editor), *Heterocyclic Compounds* [Russian translation], Vol. **6**, Inos. Lit., Moscow (1966), p. 293.
6. K. Blaha and O. Cervinka, *Advances in Heterocyclic Chemistry*, Vol. **6** (1966), p. 147.
7. K. Nagarajan, V. R. Rao, R. K. Shah, S. J. Shenoy, H. Fritz, W. J. Richter, and D. Muller, *Helv. Chim. Acta*, **71**, 77 (1988).
8. F. Carey and R. Sandberg, *Advanced Organic Chemistry. Book 1. Structure and Mechanisms* [Russian translation], Khimiya, Moscow (1981), p. 155.
9. V. M. Kisel', V. A. Kovtunenko, A. V. Turov, A. K. Tyltin, and F. S. Babichev, *Dokl. Akad. Nauk SSSR*, **306**, 628 (1989).