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CONDENSED ISOQUINOLINES. 16*. ENAMINE PROPERTIES OF BENZO[4,5]IMIDAZO[1,2-*b*]-ISOQUINOLIN-11(5H)-ONE IN TERMS OF ITS ACYLATION REACTIONS

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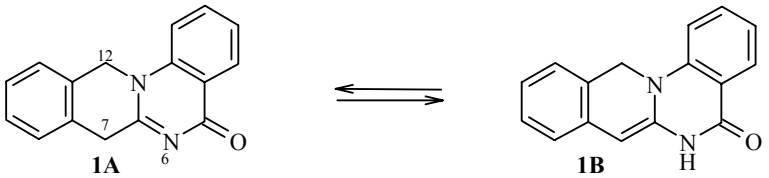
A study has shown that the acylation of benzo[4,5]imidazol[1,2-b]isoquinolin-11(5H)-one occurs at $N_{(5)}$ or at $C_{(6)}$ depending on the nature of the acylating reagent and the reaction conditions. It was found that principally C-acylation takes place in the absence of base. The reaction with α-halo-substituted carboxylic acid chlorides leads to the formation of C-acylated products which are converted to derivatives of the novel heterocyclic system 7H-2a,6b-diazabenzo[b]cyclopenta[l,m]fluorene-1,7(2H)-dione in the presence of base.

Keywords: heterocyclic enamines, enamines with a secondary nitrogen atom, benzo[4,5]imidazo-[1,2-*b*]isoquinolin-11(5H)-one and 7H-2a,6b-diazabenzo[*b*]cyclopenta[*l,m*]fluorene-1,7(2H)-dione derivatives, acylation.

A study of the properties and chemical reactions of heterocyclic enamines is an interesting area of organic chemistry. A synthesis of complex heterocyclic systems on this basis is a vigorously evolving area of organic synthesis [2]. Enamines with a secondary nitrogen atom occupy a special place [3] since, in principle, they may have an enamine or a tautomeric imine structure. The behavior of such heterocyclic enamines is most typified by their acylation and alkylation reactions but others are difficult to predict *a priori* because of the complexity of calculating the nature of the heterocycle, the effect of functional groups, and other factors [4].

An investigation of the properties of the 7,12-dihydro-5H-isoquino[2,3-*a*]quinazolin-5-one (**1**) has shown that it reacts with electrophiles as the enamine **1B** and is alkylated at the $C_{(7)}$ atom [5]. According to the ^{1}H NMR spectroscopic data, compound **1** exists in solution in the imine form **1A**, hence the formation of derivatives substituted at the atom $C_{(7)}$ is interpreted by us as due to the presence of modest amounts of the enamine form **1B** in equilibrium with **1A**.



* For Communication 15 see [1].

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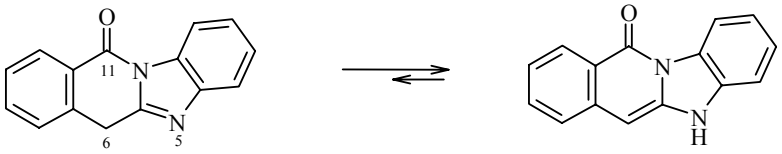
With the aim of widening our knowledge of the chemical behavior of secondary heterocyclic enamines we have turned in this investigation to the benzo[4,5]imidazo[1,2-*b*]isoquinolin-11(5H)-one (**2**). Judging by the ^{1}H NMR spectroscopic data, compound **2** exists in DMSO-d_6 solution in the cross conjugated enamine form **2B** which anticipates the possible involvement of the triad of atoms C=C–NH in novel heterocyclizations.



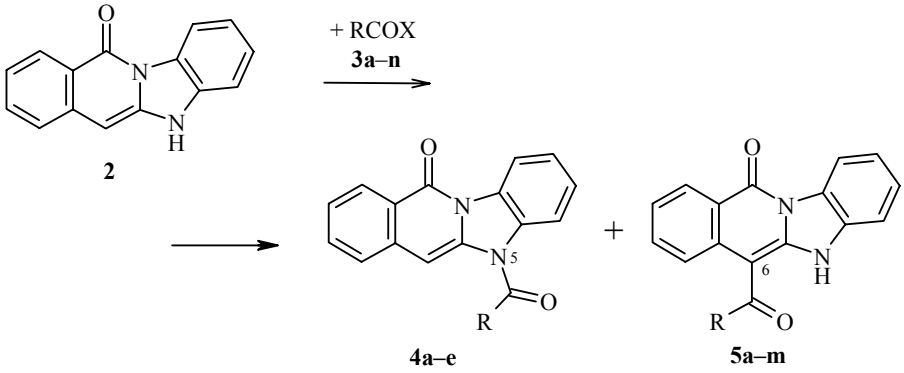
2A
imine

2B
enamine

The reaction of compound **2** with electrophiles has been mentioned in the studies [6-8]. However, the quoted results are incomplete and sometimes contradictory. Hence, although the author of the study [6] obtained exclusively the N-acylated derivatives independently of the conditions, the report [8] indicates the formation of a mixture of the N- and C-acylated compounds in the ratio 1:5. It is also known [3] that, for a compound with a stable enamine structure, typical acylation occurs at the β-position (in our case at the $C_{(6)}$ atom of system **2**).

In this work the conditions in the quoted studies were followed and the scope of the type **3** reagents was broadened for different variants of the most typical reaction of enamines – that of acylation. We have found that the outcome of the acylation depends on the reaction conditions and on the nature of the acylating reagent. For the acylation of compound **2** with acid chlorides, systems containing dioxane (method A), dioxane and AcONa (method B), and pyridine (method C) were investigated.

It was noted that the yield of the N-acylation products when the reaction was carried out in the presence of base increased by an average of 10 (method B) and 15% (method C) in the case of the acylation with the acid chlorides **3a-e**.



2

4a–e **5a–m**

3a–l X = Cl, **n**, **m** X = –O–COR; **3–5 a** R = Me, **b** R = Ph, **c** R = 2-MeC_6H_4, **d** R = 2-FC_6H_4, **e** R = 2-Br$CH_2C_6H_4$; **3**, **5 f** R = 4-MeC_6H_4, **g** R = 4-ClC_6H_4, **h** R = 4-C_5H_4N, **i** R = 3-C_5H_4N, **j** R = CH_2Cl, **k** R = CH(Br)Me, **l** R = $CHCl_2$, **m** R = CH_2Me; **3 n** R = Me

When treating compound **2** with acetyl chloride (**3a**, methods B, C), benzoyl chloride (**3B**, method B), and (independently of reaction conditions) with the *ortho*-substituted benzoic acid chlorides (**3c-e**) a mixture of the N- (**4a-e**) and C-acylation products (**5a-e**) was obtained. At the same time, the reaction of compound **2** with acetyl chloride and benzoyl chloride in dioxane and with the acid chlorides **3f-l** independently of the conditions gave exclusively the C-acylated derivatives **5a,b,f-l**[*]. It should be noted that the low overall yield (20%) of

* The spectroscopic parameters and melting points of compounds **5a,b** agreed with those reported [8].

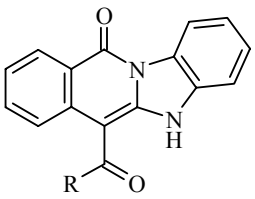
products when treating compound **2** with *o*-bromomethylbenzoyl chloride is accompanied by a significant amount of tarring. Compounds **4c-e** and **5c-e** proved to be extremely close in their solubility and their chromatographic mobility and this, unfortunately, did not allow a complete separation of the mixture. The highest yields (75-89%) of the 6-acetylbenzo[4,5]imidazo[1,2-*b*]isoquinolin-11(5H)-ones **5a,b,f-l** with minimal time consumption (15-20 min) and high product purity was achieved when carrying out the reaction with the corresponding acid chloride **3** in dioxane (method A).

A more significant influence on the direction of the acylation is the structure of the acylating agent. With a decrease in the electron accepting properties of the radical R there is an increase in the N-acyl derivative component **4** in the reaction products. Thus under identical conditions (method B) compound **3a** with R = Me gives a mixture of the C- and N-acyl derivatives while R = CH_2Cl, CH(Br)Me, and $CHCl_2$ give exclusively the C-acylation products. At the same time, the fraction of the N-acyl component in the mixture increases ($0 \rightarrow 16 \rightarrow 67 \rightarrow 75\%$) respectively along the series of aroyl substituents R = 4-Cl-C_6H_4, Ph, 2-F-C_6H_4, 2-Me-C_6H_4) (**3g,b,d,c**, method C).

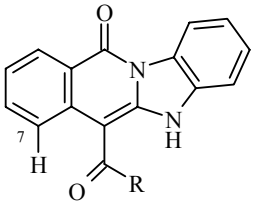
Acylation with propionic and acetic acid anhydrides **3m,n** in the presence of base (AcONa and Na_2CO_3 respectively, method D) gave the C-acyl derivatives **5m,n** in high yield (60 and 70%).

The 6-acyl- (**5**) and 5-acylbenzo[4,5]imidazo[1,2-*b*]isoquinolin-11(5H)-ones (**4**) were identified from their spectroscopic parameters (Table 1). The criteria for assignment as the C-acyl derivatives **5** are the characteristic stretching vibrations for the $N_{(5)}$–H group in the IR spectrum (3120-3300 cm^{-1}) plus the $N_{(5)}$–H singlet at 12.6-13.1 ppm and absence of the absorption for the $C_{(6)}H$ methine proton (seen at 6.33 ppm in the starting compound **2**) in the ^1H NMR spectrum. An assignment of the signal for the $C_{(6)}H$ methine proton in the spectra of the N-acyl derivatives **4a-e** is problematic since it falls in the region of aromatic proton absorption while a one proton doublet (J = 8.0 Hz) is observed at 6.4-6.7 ppm for compounds **4b-e** and this is assigned as the $C_{(4)}H$ signal (which falls in the region of shielding by the benzene ring of the N-aroyl group). The authors of [8] observed a one proton doublet (J = 8.0 Hz) in the spectrum of **4b** at 6.57 ppm and assigned it to the $C_{(6)}H$ resonance. Our assignment is based on the observed one proton $C_{(6)}H$ methine singlet at 7.03 ppm in the recorded ^1H NMR spectrum of the mixture of **4e** and **5e** at 80°C. The integrated intensities of the indicated signals were used by us to determine the composition of the mixtures of compounds **4a,c-e** and **5a,c-e**. There are also differences in the IR spectra of compounds **4** and **5** in the carbonyl stretching band region. The spectra of the 5-acyl derivatives show two $\nu_{C=O}$ bands (1690-1700, 1620-1625 cm^{-1}) but for the 6-acyl derivatives only one broadened band is seen at 1660-1690 cm^{-1}. This result is probably due to the different degree of conjugation in the isoquinoline fragment of the molecule.

We have found that the chemical shift of the aromatic protons in the ^1H NMR spectra of the C-acyl derivatives **5a,b,f-m** change with the structure of the radical R. Whereas in the derivatives with a benzoyl substituent where R = Ar (**5b-i**) the $C_{(7)}H$ signal is found in the same region as in the starting **2** (7.05-7.19 ppm), in compounds with R = alkyl (**5a,j-m**) it is found at a markedly lower field in the region 7.50-8.00 ppm. We associate this with a difference in the population of the synplanar **5***sp* and antiperiplanar **5***ap* conformations of the C-acyl derivatives. For the compound with alkyl substituents the antiperiplanar conformation **5***ap* in which the $C_{(7)}H$ proton falls in the area of deshielding by the carbonyl proves to be the more populated.



5*sp*



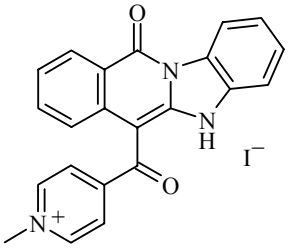
5*ap*

A feature of the spectrum of the α-bromopropionyl substituted compound **5k** is the double set of signals for the methyl group with the absence of any kind of additional signals in the aromatic region. We also associate this with a difference in the population of the conformation of the radical R arising as a result of the steric hindrance to free rotation about the $CH_3CH(Br)–CO$ bond.

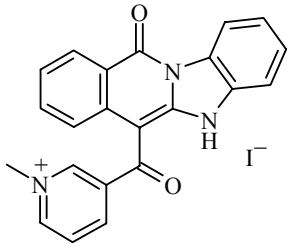
Among the features of the chemical behavior of the acyl derivatives one should note their different stability in acidic medium. While the N-acyl derivatives of the benzo[4,5]imidazo[1,2-*b*]isoquinolin-11(5H)-ones **4** are completely stable the C-substituted **5** are partially deacetylated even upon refluxing in acetic acid for 6-8 h and fully in the presence of perchloric acid after 1 h.

With regard to the increased reactivity of the $N_{(5)}$ atom of compound **2** in the presence of base it was interesting to follow the activity of this position in the 6-acyl derivatives **5**. It was found that compound **5** is stable to the action of acylating and alkylating reagents. Only the 6-isonicotinoyl- and 6-nicotinoylbenzo[4,5]imidazo[1,2-*b*]isoquinolin-11(5H)-ones (**5h,i**) form the N-methylpyridinium salts **6a,b** with methyl iodide, as indicated by the rather large low field shift of the signals for the pyridine ring protons (0.3-0.4 ppm), the presence of the $N_{(5)}$ signal in the 13 ppm region, and the unchanged position of the $C_{(4)}$ signal (Table 1).

The high reactivity of both the 6 and 5 positions of compound **2** suggests a successful cyclization route when using the reagents with two electrophilic centers. With this in mind we investigated oxalyl chloride and α-halo-substituted acid chlorides.



6a



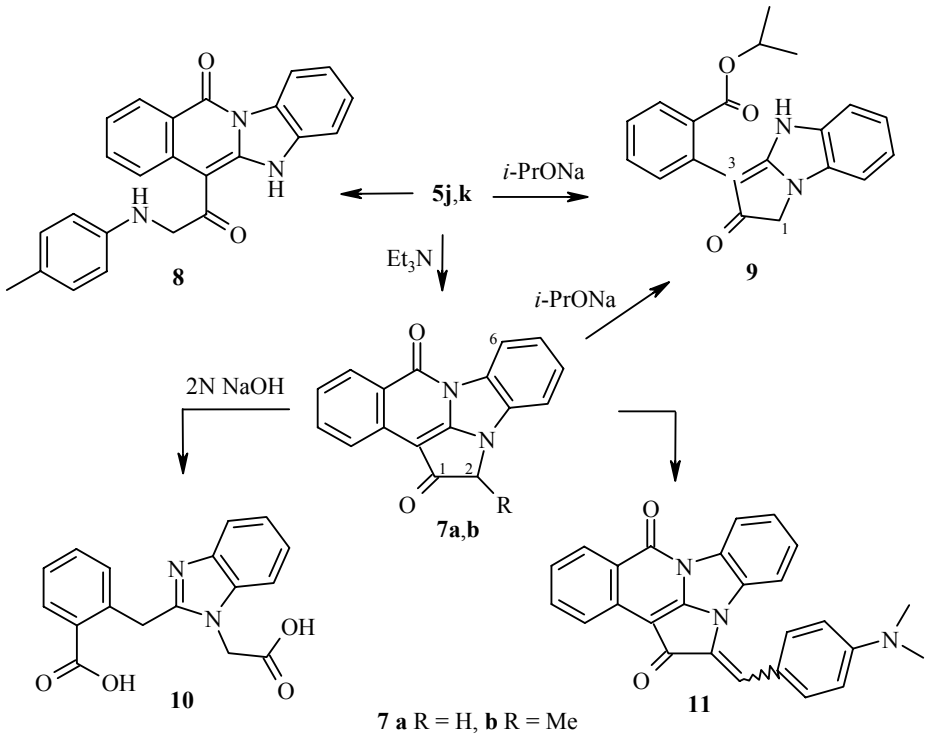
6b

The reaction with oxalyl chloride (**3**, X = Cl, R = Cl–CO–) in dioxane occurs with significant tarring and gives a mixture of unidentified products but chloroacetyl chloride (**3j**), α-bromopropionyl chloride (**3k**), and dichloroacetyl chloride (**3l**) gives the 6-acylbenzo[4,5]imidazo[1,2-*a*]isoquinolin-11(5H)-ones **5j-l**. Upon heating the compounds **5j** and **5k** in DMF in the presence of triethylamine there occurs an intramolecular alkylation at the $N_{(5)}$ atom to give derivatives of the novel heterocyclic system 7H-2a,2b-diazabenzo[*b*]cyclopenta[*l,m*]fluorene-1,7(2H)-dione **7a,b** (Scheme 1).

It should be noted that compound **5k** is readily converted to the cyclic product **7b**, even upon recrystallization from DMF. In the presence of base the dichloroacetyl derivative **5l** undergoes tarring. The structure of the cyclopentafluorenes **7a,b** is confirmed by their spectroscopic properties, *viz*. the absence of a signal for the $N_{(5)}$ group in the ^1H NMR spectra and the high field shift of the $C_{(2)}H$ or CH_2 signals when compared with those in the starting noncyclic products (Table 1). The mass spectroscopic data for compound **7a** also agrees with the structure given.

With the aim of finding optimum conditions for the synthesis of the cyclopentafluorenes we have tried various conditions for the cyclization of 6-chloroacetylbenzo[4,5]imidazol[1,2-*b*]isoquinolin-11(5H)-one (**5j**). In the presence of bases like triethylamine or benzylamine an intramolecular alkylation occurs to give compound **7a** with the greater yield in the former case. Heating compound **5j** with *p*-toluidine leads to the formation of the product of nucleophilic substitution of the halogen **8**. In the presence of a strong base (*i*-PrONa) the intramolecular alkylation of **5j** is accompanied by fission at the $N_{(6b)}–C_{(7)}$ bond to give the isopropyl ester of 2-(2-oxo-2,4-dihydro-1H-benzo[*d*]pyrrolo[1,2-*a*]imidazol-3-yl)benzoic acid (**9**). This is supported by comparison of the IR data (high frequency shift of the $\nu_{C=O}$ band at 1725 cm^{-1}) with the cyclic product **7a** and

Scheme 1



the presence of the ν_{C-O} at 1240 cm^{-1} in the area typical of esters. The ^1H NMR spectra show signals for the isopropyl group and the CH_2, and $N_{(9)}H$ together with changes in the pattern for the aromatic protons which are characteristic of the benzo[4,5]imidazo[1,2-*b*]isoquinolin-11(5H)-one heterosystem. The signals for the $C_{(1)}H$ and $C_{(10)}H$ protons in the region 8.0-8.8 ppm are also absent supporting the disturbance to the cyclic structure. This result is not unexpected since the instability of the benzimidazo[1,2-*b*]isoquinoline heterosystem towards strong base has been previously reported [9, 10]. In this connection it should be noted that heating compound **7a** in a 2N alcoholic solution of base caused not only fission of the amide $N_{(6b)}$–$C_{(7)}$ bond but also the $C_{(11b)}$–$C_{(1)}$ to give 2-{[1-(carboxymethyl)-1H-benzimidazol-2-yl]methyl}benzoic acid (**10**). It is likely that the acid **10** exist in the dimeric form in view of the low frequency shift of the absorption of the C=O and O–H groups and the presence of a strong, broad band at 1240 cm^{-1} for the deformational vibrations of the O–H bond. In the presence of *i*-PrONa only the isoquinoline ring is broken to yield the ester **9**. The CH_2 methylene group proves active in the Ehrlich reaction. Refluxing a solution of **7a** in acetic anhydride with *p*-dimethylaminobenzaldehyde gives 2-[1-(4-dimethylaminophenyl)methylidene]-1,2-dihydro-7H-2a,2b-diazabenzo[*b*]cyclopenta[*l,m*]fluorene-1,7-dione (**11**).

Refluxing compound **2** with arylisocyanates in dioxane gives the 6-carbamoyl derivatives **12** in good yield (80-85%). The ^1H NMR spectra of these compounds is characterized by the presence of two low field N–H signals at 11.9 and 10.2 ppm (see Table 1). An attempt to carry out the reaction of compound **2** with phenylisothiocyanate gave an unexpected result. The reaction product has a very close spectroscopic resemblance to the starting compound but differs from it by the absence of a $C_{(6)}H$ signal in the ^1H NMR spectrum and a basic difference in the "fingerprint" region of the IR spectrum.

TABLE 1. Spectroscopic Characteristics for the 6-R-Benzimidazo[1,2-*b*]isoquinolin-11(5H)-ones

Compound	IR spectrum, ν, cm^{-1}		^{1}H NMR spectrum, δ, ppm (*J*, Hz)								
	C=O	N–H	H-5, s	H-1, d, *J* = 8.0	H-10, d, *J* = 8.0	H-4, d, *J* = 8.0	H-8, t, *J* = 8.0	H-3, H-9	H-2, t, *J* = 8.0	H-7, d, *J* = 8.0	Substituent signals
1	2	3	4	5	6	7	8	9	10	11	12
5b	1673	3280	12.69	8.65	8.35	7.70	7.55	7.34 (1H, t, *J* = 8.0, H-9); 7.29 (1H, t, *J* = 8.0, H-3)	7.22	7.08	7.60 (2H, d, *J* = 6.8, H-2', H-6'); 7.47-7.43 (3H, m, H-3', H-4', H-5')
5f	1675	3300	12.59	8.66	8.35	7.66	7.45	7.35-7.30 (2H, m)	—*	7.17	7.52 (2H, d, H-2', H-5'); 7.26-7.22 (3H, m, H-3', H-5', H-2); 2.43 (3H, s, C<u>H</u>$_3$)
5g	1675	3270	12.70	8.63	8.36	7.68	7.50	7.44-7.36 (2H, m)	7.28	7.11	7.64 (2H, d, *J* = 8.0, H-2', H-6'); 7.54 (2H, d, *J* = 8.0, H-3', H-5')
5h	1680	3120	13.02	8.66	8.38	7.78	7.49	7.42-7.34 (2H, m)	7.29	7.04	8.84 (2H, d, *J* = 6.2, H-3', H-5'); 7.73 (2H, d, *J* = 6.2, H-2', H-6')

TABLE 1 (continued)

1	2	3	4	5	6	7	8	9	10	11	12
5i	1675	3200	12.86	8.66	8.39	7.73	7.48	7.41-7.36 (2H, m)	7.29	7.19	8.80 (1H, d, J_m = 1.7, H-2'); 8.67 (1H, dd, J_o = 5.2, J_m = 1.7, H-6'); 8.28 (1H, d, J_o = 8.0, H-4'); 7.78 (1H, dd, J_o = 5.2, J_o = 8.0, H-5')
6a	1670	3240	13.16	8.67	8.40	7.81	7.52	7.43 (2H, t, J = 8.0)	7.34	7.08	9.14 (2H, d, J = 6.2, H-3', H-5'); 8.17 (2H, d, J = 6.2, H-2', H-6'); 4.45 (3H, s, C<u>H</u>$_3$)
6b	1650	3240		—*[2]	8.57	9.65	8.02	7.83-7.72 (4H, m)			10.02 (1H, s, H-2'); 9.33 (1H, d, J = 6.8, H-6'); 9.24 (1H, d, J = 6.0, H-4'); 8.93-8.87 (2H, m, H-5', H-1); 4.60 (3H, s, C<u>H</u>$_3$)
5a	1670	3180	12.87	8.62	8.42	8.09	7.74 (2H, m)	7.43	7.38-7.31 (2H, m)		2.73 (3H, s, C<u>H</u>$_3$)
5j	1680	3160	13.06	8.58	8.39	7.93	7.44	7.76-7.71 (2H, m)	7.38-7.32 (2H, m)		4.88 (2H, s, C<u>H</u>$_2$Cl)
5k	1670	3300	13.02	8.59	8.42	8.07	7.84	7.76 7.52	7.47-7.39 (2H, m)		5.55 (1H, m, C<u>H</u>); 1.89 (d, J = 6.8, C<u>H</u>$_3$)*[3], 1.70 (d, J = 6.8, C<u>H</u>$_3$)*[3]

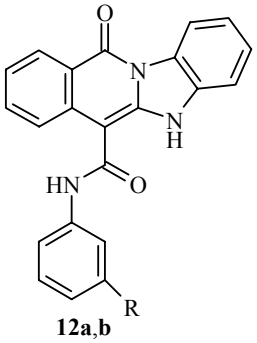
TABLE 1 (continued)

1	2	3	4	5	6	7		8	9	10	
5l	1690	3120	13.21	8.60	8.43	7.87 (2H, m)		7.79	7.55	7.50-7.43 (3H, m, H-2, H-9, C<u>H</u>Cl$_2$)	
5m	1663	3200	12.93	8.59	8.39	8.12	7.74 (2H, m)		7.49	7.39-7.34 (2H, m)	3.07 (2H, q *J* = 7.0, C<u>H</u>$_2$); 1.22 (3H, t, *J* = 7.0, C<u>H</u>$_3$)
8	1660	3260	—*[2]	8.62	8.44	8.08	7.78	7.75	7.44	7.37 (1H, t, *J* = 8.0, H-9); 7.33 (1H, t, *J* = 8.0, H-2)	10.0 (br., H-5, N<u>H</u>CH$_2$); 6.86 (2H, d, *J* = 8.0, H-2', H-6'); 6.54 (2H, d, *J* = 8.0, H-3', H-5'); 4.55 (2H, s, C<u>H</u>$_2$); 2.17 (3H, s, C<u>H</u>$_3$)
12a	1660	3260, 3360	11.92	8.64	8.39	8.05	7.63	7.49	7.38	7.28 (1H, t, *J* = 8.0, H-9); 7.23 (1H, t, *J* = 8.0, H-2)	10.19 (1H, s, N<u>H</u>); 7.80 (2H, d, *J* = 8.0, H-2', H-6'); 7.33 (2H, t, *J* = 8.0, H-3', H-5'); 7.06 (1H, t, *J* = 8.0, H-4')
12b	1665	3280, 3360	11.98	8.64	8.40	8.04	—*[2]	7.50	7.39	7.24 (1H, t, *J* = 8.0, H-2, H-9*[2])	10.38 (1H, s, N<u>H</u>); 8.01 (1H, s, H-2'); 7.68-7.63 (2H, m, H-6', H-8); 7.31 (2H, t, *J* = 8.0, H-5', H-9); 7.06 (1H, d, *J* = 8.0, H-4')

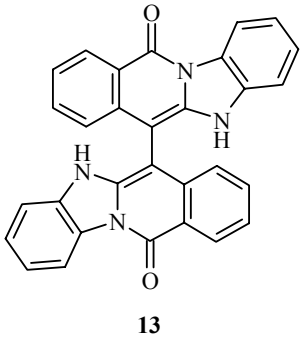
* All of the compounds were recrystallized from DMF.

*[2] For assignment of the proton signals of the benzimidazo[1,2-*b*]isoquinoline ring and the signals of the 6-substituent see the "substituent signals" column.

*[3] Overall intensity 3H.



12a,**b**



13

12 a R = H, **b** R = Cl

The ^{13}C spectrum showed a signal for a quaternary carbon at 82.77 ppm in the region which is characteristic of aliphatic carbon atoms. On the basis of this and mass spectroscopic data which shows the presence of a molecular ion corresponding to double the molecular weight of the starting benzimidazoisoquinoline we deduce that this unknown product is the dimer 6-(11-oxo-5,11-dihydrobenzimidazo[1,2-*b*]isoquinolin-6-yl)benzimidazo[1,2-*b*]isoquinolin-11(5H)-one (**13**). It should be noted that the stability of the molecular ion is very low (I = 4%). The basic directions for fragmentation (fission of the $C_{(6)}$–$C_{(6')}$ bond and loss of the C=O group) agree fully with data obtained previously for the starting

TABLE 2. Physicochemical Parameters for the Compounds Synthesized

Compound	Empirical formula	Found, % / Calculated, %				mp, °C*	Yield, %
		C	H	N	Hal		
5b	$C_{22}H_{14}N_2O_2$	78.12 / 78.09	4.26 / 4.17	8.09 / 8.28		299	84
5f	$C_{23}H_{16}N_2O_2$	78.39 / 78.20	4.58 / 4.43	7.59 / 8.03		312	80
5g	$C_{22}H_{13}ClN_2O_2$	70.88 / 70.69	3.51 / 3.43	7.51 / 7.65	9.51 / 9.50	289	86
5h	$C_{21}H_{13}N_3O_2$	74.33 / 74.13	3.86 / 3.73	12.38 / 12.51		288	70
5i	$C_{21}H_{13}N_3O_2$	74.33 / 74.19	3.86 / 3.71	12.38 / 12.45		240 (dec.)	71
6a	$C_{22}H_{15}IN_3O_2$	54.90 / 54.79	3.14 / 3.05	8.73 / 8.91		287	67
6b	$C_{22}H_{15}IN_3O_2$	54.90 / 54.78	3.14 / 3.10	8.73 / 8.85		300 (dec.)	65
5a	$C_{17}H_{12}N_2O_2$	74.05 / 73.90	4.50 / 4.38	9.95 / 10.14		295	75
5j	$C_{17}H_{11}ClN_2O_2$	65.71 / 65.64	3.57 / 3.49	9.02 / 9.14	11.41 / 11.48	213	89
5k	$C_{18}H_{13}BrN_2O_2$	58.56 / 58.40	3.55 / 3.46	7.59 / 7.68	21.64 / 21.60	222	83
5l	$C_{17}H_{10}Cl_2N_2O_2$	59.15 / 59.08	2.92 / 2.89	8.12 / 8.19	20.54 / 20.59	260	75
5m	$C_{18}H_{14}N_2O_2$	74.45 / 74.47	4.90 / 4.86	9.70 / 9.65		191	70
8	$C_{24}H_{19}N_3O_2$	75.57 / 75.50	5.02 / 4.93	11.02 / 11.19		201	58
12a	$C_{22}H_{15}N_3O_2$	74.78 / 74.65	4.28 / 4.15	11.89 / 11.95		337	79
12b	$C_{22}H_{14}ClN_3O_2$	68.13 / 68.01	3.64 / 3.53	10.84 / 10.96	9.14 / 9.21	285	81

* All of the compounds were recrystallized from DMF.

benzimidazoisoquinoline **2** [8] and 10-alkylimidazo[1,2-*b*]isoquinolin-5-one [8] – a structural analog of compound **2**. It appears that compound **2** is extremely prone to dimerization in the presence of different oxidants including sulfur compounds (phenylisothiocyanate, chlorosulfonic acid, *p*-toluenesulfonyl chloride, DMSO), nitrobenzene, aromatic aldehydes, and ketones. The highest yield of the dimerization product **13** (90%) was obtained by reaction in dioxane dibromide.

EXPERIMENTAL

Melting points for the compounds synthesized were determined on a Boetius type heating block and were not corrected. IR spectra (KBr tablets) were recorded on a Pye-Unicam SP3-300 instrument. ^{1}H NMR spectra for compounds **4e,d, 5e,d**, **13** were obtained on a Bruker WP-100 SY (100 MHz) instrument and compounds **2, 4c, 5c,f-m, 6-12** on a Varian Mercury 400 (400 MHz) in DMSO-d_6. ^{13}C NMR spectra were taken on the Varian Mercury 400 (100 MHz) in DMSO-d_6. For all of these, TMS was used as internal standard. Mass spectra were taken on a Waters Integrity System instrument with a Thermabeam detector (mobile phase CH_3CN). Monitoring of the course of the reaction and the purity of the compounds prepared was carried out using TLC on Silufol UV-254 plates.

5,11-Dihydrobenzo[4,5]imidazo[1,2-*b*]isoquinolin-11-one (2) was prepared by method [6]. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 11.61 (1H, s, NH); 8.62 (1H, d, *J* = 8.0, $C_{(1)}$H); 8.28 (1H, d, *J* = 8.0, $C_{(10)}$H); 7.51 (2H, m, $C_{(3)}$H + $C_{(8)}$H); 7.32 (1H, t, *J* = 8.0, $C_{(9)}$H); 7.27 (1H, d, *J* = 8.0, $C_{(7)}$H); 7.19-7.12 (2H, m, $C_{(2)}$H + $C_{(4)}$H); 6.25 (1H, s, $C_{(6)}$H).

The starting **acid chlorides 3** were prepared by treating the corresponding acids with an excess of $SOCl_2$. The physical parameters corresponded with those reported [11, 12].

Acylation of 5,11-dihydrobenzo[4,5]imidazo[1,2-*b*]isoquinolin-11-one (2). A. The corresponding carboxylic acid chloride **3** (12 mmol) was added to a refluxing suspension of benzimidazoisoquinoline **2** (2.34 g, 10 mmol) in dry dioxane (10 ml) and refluxed for 20 min. After cooling, the precipitate formed was filtered and thoroughly washed with water and alcohol. Recrystallization from DMF gave the 6-acyl substituted 5,11-dihydrobenzo[4,5]imidazo[1,2-*b*]isoquinoline-11-ones **5a,b,f-l**.

The reaction with the *o*-substituted benzoic acid chlorides was carried out similarly. Recrystallization from DMF gave a mixture of compounds **4c-e** and **5c-e** in the ratio 3:1, 2.5:1, and 3:1.5 respectively. The overall yield of the mixture was 75 (**4c** + **5c**), 80 (**4d** + **5d**), and 20% (**4e** + **5e**).

Mixture of 5-(2'-Methylbenzoyl)- and 6-(2'-Methylbenzoyl)-5,11-dihydrobenzo[4,5]imidazo[1,2-*b*]-isoquinolin-11-ones (4c, 5c). IR spectrum, ν, cm^{-1}: 1670, 1620 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 13.18 (s, NH, **5c**); 8.76 (d, *J* = 8.0, $C_{(1)}$H); 8.35 (d, *J* = 8.0, $C_{(10)}$H); 7.19-7.80 (m, Ar); 6.41 (d, *J* = 8.0, $C_{(4)}$H, **4c**); 2.33 (s, 2'-CH_3, **5c**); 2.30 (s, 2'-CH_3, **4c**).

Mixture of 5-(2-Fluorobenzoyl)- and 6-(2-Fluorobenzoyl)-5,11-dihydrobenzo[4,5]imidazo[1,2-*b*]-isoquinolin-11-ones (4d, 5d). IR spectrum, ν, cm^{-1}: 1670, 1625 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 12.96 (s, NH, **5d**); 8.78 (d, *J* = 8.0, $C_{(1)}$H); 8.38 (d, *J* = 8.0, $C_{(10)}$H); 7.09-7.98 (m, Ar); 6.76 (d, *J* = 8.0, $C_{(4)}$H, **4d**).

Mixture of 5-(2'-Bromomethylbenzoyl)- and 6-(2'-Bromomethylbenzoyl)-5,11-dihydrobenzo[4,5]-imidazo[1,2-*b*]isoquinolin-11-ones (4e, 5e). IR spectrum, ν, cm^{-1}: 1670, 1625 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 13.00 (s, NH, **5e**), 8.79 (d, *J* = 8.0, $C_{(1)}$H); 8.35 (d, *J* = 8.0, $C_{(10)}$H); 7.12-8.18 (m, Ar); 6.55 (d, *J* = 8.0, $C_{(4)}$H, **4e**); 4.84 (s, 2'-CH_2, **5e**); 4.91 (s, 2'-CH_2, **4e**).

B. The corresponding carboxylic acid chloride **3** (12 mmol) was added to a refluxing suspension of benzimidazoisoquinoline **2** (2.34 g, 10 mmol) and NaOAc (1.23 g, 15 mmol) in dry dioxane and refluxed for 20 min. After cooling, the precipitate formed was filtered and thoroughly washed with water and alcohol. Recrystallization from DMF gave the 6-acyl substituted 5,11-dihydrobenzo[4,5]imidazo[1,2-*b*]isoquinolin-11-ones **5b,f-l**.

The reaction with the acid chloride and chlorides of the *o*-substituted benzoic acids was carried out similarly. Recrystallization from DMF gave a mixture of the compounds **4a,c-e** and **5a,c-e** in the ratios 1:4.5, 4.5:1, 3:1, and 3:1 respectively. The overall yield of the mixture was 63 (**4a** + **5a**), 75 (**4c** + **5c**), 80 (**4d** + **5d**), and 20% (**4e** + **5e**).

C. (method from study [7]). Recrystallization from DMF of the products of acylation using the acid chlorides **3a-d,f-i** gave the 6-acyl-substituted 5,11-dihydrobenzo[4,5]imidazo[1,2-*b*]isoquinolin-11-ones **5f-i** and a mixture of compounds **4a-d** and **5a-d** in the ratio 1:4 (**4a** + **5a**, overall yield of the mixture 43%), 1:5 (**4b** + **5b**, 60%), 5:1 (**4c** + **5c**, 72%), 4:1 (**4d** + **5d**, 71%).

D. (method from study [5]). Recrystallization from DMF of the products of acylation using the acetic (**3n**) and propionic (**3m**) acid anhydrides gave the 6-acyl-substituted 5,11-dihydrobenzo[4,5]imidazo[1,2-*b*]-isoquinolin-11-ones **5n,m**.

1-Methyl-4-(11-oxo-5,11-dihydrobenzimidazo[1,2-*b*]isoquinolin-6-ylcarbonyl)pyridinium Iodide (6a). A mixture of 6-isonicotinoylbenzimidazo[1,2-*b*]isoquinoline (**5h**, 0.34 g, 1 mmol) and methyl iodide (0.19 ml, 3 mmol) in DMF (5 ml) was heated on a water bath at 40-45°C for 2 h until the complete solution of the starting **5h**. The solvent and excess methyl iodide were evaporated off under reduced pressure and alcohol (3 ml) was added to the residual oil. The precipitate formed was filtered off and washed with alcohol. It was recrystallized from DMF.

1-Methyl-3-(11-oxo-5,11-dihydrobenzimidazo[1,2-*b*]isoquinolin-6-ylcarbonyl)pyridinium iodide (6b) was prepared similarly using 6-nicotinoylbenzimidazo[1,2-b]isoquinoline **5i**.

7H-2a,6b-Diazabenzo[*b*]cyclopenta[*l,m*]fluorene-1,7-dione (7a). A mixture of 6-chloroacetyl-benzimidazo[1,2-*b*]isoquinoline **5j** (3.1 g, 10 mmol) and triethylamine (0.5 ml) in DMF (5 ml) was refluxed for 1 h. The precipitated solid was filtered off and washed with alcohol. Recrystallization from DMF gave 2.19 g (80%); mp 271-273°C (DMF). IR spectrum, ν, cm^{-1}: 1650 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.34 (2H, t, *J* = 8.0, $C_{(6)}H$, $C_{(8)}H$); 8.05 (1H, d, *J* = 8.0, $C_{(11)}H$); 7.80 (1H, t, *J* = 8.0, $C_{(10)}H$); 7.61 (1H, d, *J* = 8.0, $C_{(3)}H$); 7.54 (1H, t, *J* = 8.0, $C_{(4)}H$); 7.43-7.37 (2H, m, $C_{(5)}H$, $C_{(9)}H$); 4.75 (2H, s, CH_2). Mass spectrum, *m/z*, (*I*, %): 274 $[M]^+$ (100), 246 (29), 190 (6). Found, %: C 74.29; H 3.58; N 10.35. $C_{17}H_{10}N_2O_2$. Calculated, %: C 74.44; H 3.67; N 10.21.

2-Methyl-7H-2a,6b-diazabenzo[*b*]cyclopenta[*l,m*]fluorene-1,7(2H)-dione (7b) was prepared similarly using the derivative **5k** (3.7 g, 10 mmol). Yield 2.50 g (87%); mp 274-277°C (DMF). IR spectrum, ν, cm^{-1}: 1670 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.35 (2H, d, *J* = 8.0, $C_{(6)}H$, $C_{(8)}H$); 8.08 (1H, d, *J* = 8.0, $C_{(11)}H$); 7.75 (1H, t, *J* = 8.0, $C_{(10)}H$); 7.63 (1H, d, *J* = 8.0, $C_{(3)}H$); 7.49 (1H, t, *J* = 8.0, $C_{(4)}H$); 7.10-7.34 (2H, m, $C_{(5)}H$, $C_{(9)}H$); 4.81 (1H, q, *J* = 6.8, $C_{(2)}H$); 1.71 (3H, d, *J* = 6.8, CH_3). Found, %: C 74.80; H 4.18; N 9.90. $C_{18}H_{12}N_2O_2$. Calculated, %: C 74.99; H 4.20; N 9.72.

6-[2-(4-Toluidino)acetyl]benzimidazo[1,2-*b*]isoquinolin-11(5H)-one (8). A mixture of compound **5j** (0.31 g, 1 mmol) and *p*-toluidine (0.16 g, 1.5 mmol) in DMF (3 ml) was refluxed for 4 h. The solid precipitated after cooling was filtered off, washed with alcohol, and recrystallized from DMF.

Isopropyl Ester of 2-(2-Oxo-2,4-dihydro-1H-benzo[*d*]pyrrolo[1,2-*a*]imidazo-3-yl)benzoic Acid (9). A. A mixture of compound **5j** (0.31 g, 1 mmol) and *i*-PrONa (0.12 g, 1.5 mmol) in *i*-PrOH (5 ml) was refluxed for 30 min. The solid precipitated after cooling was washed with alcohol and recrystallized from DMF to give 0.22 g (67%).

B. The reaction was carried out similarly to method A using **7a** (1 mmol). Yield 0.13 g (40%); mp 202-207°C (DMF). IR spectrum, ν, cm^{-1}: 1240 (C–O), 1725 (C=O), 3100 (N–H). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 12.21 (1H, s, $C_{(4)}H$); 7.70 (1H, d, *J* = 8.0, $C_{(3')}H$); 7.50-7.46 (2H, m, $C_{(5')}H$, $C_{(6')}H$); 7.24-7.21 (2H, m, $C_{(4')}H$, $C_{(8)}H$); 7.18 (1H, d, *J* = 8.0, $C_{(5)}H$); 7.10 (1H, t, *J* = 8.0, $C_{(6)}H$); 7.03 (1H, t, *J* = 8.0, $C_{(7)}H$); 5.02 (1H, q, *J* = 6.0, $C\underline{H}(CH_3)_2$); 4.19 (2H, s, $C_{(2)}H$); 1.40 (6H, d, *J* = 6.0, CH_3). Found, %: C 71.69; H 5.31; N 8.45. $C_{20}H_{18}N_2O_3$. Calculated, %: C 71.84, H 5.43; N 8.38.

2-{[1-(Carboxymethyl)-1-benzimidazol-2-yl]methyl}benzoic Acid (10). The cyclopentafluorene **7a** (0.27 g, 1 mmol) was refluxed in 2N NaOH in methanol (4 ml) for 1 h. The solvent was evaporated in vacuo. The remaining oil was dissolved in water (5 ml) and a dilute solution of hydrochloric acid added to pH 5. After 2 h the precipitated solid was filtered off, washed with alcohol, and recrystallized from methanol. Yield 0.20 g (63.5%); mp 235-238°C (methanol). IR spectrum, ν, cm^{-1}: δ_{O-H} 1240, $\nu_{C=O}$ 1685, ν_{O-H} 2600 cm^{-1}. ^1H NMR spectrum, δ, ppm (*J*, Hz): 13.01 (2H, br. s, OH); 7.89 (1H, d, *J* = 8.0, $C_{(3')}H$); 7.50-7.46 (3H, m, $C_{(4)}H$, $C_{(7)}H$, $C_{(5')}H$); 7.37 (1H, t, *J* = 8.0, $C_{(4)}H$); 7.29 (1H, d, *J* = 8.0, $C_{(6')}H$); 7.18-7.10 (2H, m, $C_{(5)}H$, $C_{(6)}H$); 5.09 (2H, s, 1-CH_2); 4.55 (2H, s, 2-CH_2). Found, %: C 65.70; H 4.39; N 9.19. $C_{17}H_{14}N_2O_4$. Calculated, %: C 65.80; H 4.55; N 9.03.

2-{[4-(Dimethylamino)phenyl]methylidene}-7H-2a,6b-diazabenzo[*b*]cyclopenta[*l,m*]fluorene-1,7-(2H)-dione (11). A mixture of the cyclopentafluorene **7a** (0.27 g, 1 mmol) and *p*-dimethylaminobenzaldehyde (0.22 g, 1.5 mmol) in Ac_2O (4 ml) was refluxed for 30 min. The solvent was evaporated and the remaining oil treated with 2-propanol (3 ml). The precipitated solid was filtered off, washed with *i*-PrOH, and recrystallized from DMF. Yield 0.27 g (68%); mp 264-266°C (DMF). IR spectrum, ν, cm^{-1}: 1645 (C=O). ^1H NMR spectrum, δ, ppm (*J*, Hz): 8.45-8.30 (3H, m, $C_{(6)}H$, $C_{(8)}H$, =CH); 8.16 (2H, d, *J* = 8.0, $C_{(3)}H$, $C_{(11)}H$); 7.78 (1H, t, *J* = 8.0, $C_{(10)}H$); 7.58 (1H, t, *J* = 8.0, $C_{(4)}H$); 7.50-7.32 (4H, m, $C_{(5)}H$, $C_{(9)}H$, $C_{(2')}H$, $C_{(5')}H$); 6.73 (2H, d, *J* = 8.0, $C_{(3')}H$, $C_{(4')}H$); 3.05 (6H, s, CH_3). Found, %: C 76.89; H 4.61; N 10.44. $C_{26}H_{19}N_3O_2$. Calculated, %: C 77.02; H 4.72; N 10.36.

11-Oxo-N-aryl-5,11-dihydrobenzimidazo[1,2-*b*]isoquinoline-6-carboxamides (12a,b). The corresponding aryl isocyanate (12 mmol) was added to a refluxing suspension of the benzimidazoisoquinoline **2** (2.34 g, 10 mmol) in dry dioxane (10 ml) and refluxed for 2 h. After cooling, the solid formed was filtered off, throughly washed with water and alcohol, and recrystallized from DMF.

6-(11-Oxo-5,11-dihydrobenzimidazo[1,2-*b*]isoquinolin-6-yl)-5,11-dihydrobenzimidazo[1,2-*b*]-isoquinolin-11(5H)-one (13). A solution of bromine (0.5 ml, 10 mmol) in dioxane (5 ml) was added dropwise with stirring to a suspension of the benzimidazoisoquinoline **2** (2.34 g, 10 mmol) in dry dioxane (10 ml) which was heated on a water bath. It was heated with stirring for a further 15 min and cooled. The precipitate formed was filtered off and throughly washed with alcohol. Yield 2.1 g (90%); mp > 360°C (DMF). IR spectrum, ν, cm^{-1}: 1645 (C=O), 3140 (N–H). ^1H NMR spectrum, δ, ppm (*J*, Hz): 11.34 (2H, s, $C_{(5,5')}H$); 8.72 (2H, d, *J* = 2.0, $C_{(1,1')}H$); 8.47 (2H, d, *J* = 2.0, $C_{(10,10')}H$); 7.49 (2H, t, *J* = 2.0, $C_{(8,8')}H$); 7.37 (2H, t, *J* = 2.0, $C_{(3,3')}H$); 7.29 (2H, t, *J* = 2.0, $C_{(9,9')}H$); 7.24 (2H, t, *J* = 2.0, $C_{(2,2')}H$); 7.14 (4H, d, *J* = 2.0, $C_{(7'7')}H$, $C_{(4,4')}H$). ^{13}C NMR spectrum: 160.00 (C-11,11'); 142.04 (C-5a,5a'); 139.51 (C-11b,11b'); 134.04 (C-4a,4a'); 132.78 (C-10,10'); 129.23 (C-10a,10a'); 128.10, 126.64, 123.10, 122.15, 120.82 (C-2,2', C-3,3', C-7 to 9,7' to 9'); 119.13 (C-6a,6a'); 116.52 (C-4,4'); 109.86 (C-1,1'); 82.77 (C-6,6'). Mass spectrum, *m/z* (*I*, %): 466 $[M]^+$, 234 (33), 222(12), 205 (11), 149 (49), 125 (35), 98 (100). Found, %: C 77.09; H 4.05; N 12.20. $C_{30}H_{18}N_4O_2$. Calculated, %: C 77.24; H 3.89; N 12.01.

Parameters for the compounds **5, 6, 8** and **12** are given in Tables 1 and 2.

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