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ENAMINES OF THE 1,2,3,4-TETRAHYDROISOQUINOLINE SERIES IN THE CHICHIBABIN SYNTHESIS OF PYRROLO[2,1-*a*]ISOQUINOLINES AND IN REACTION WITH OXALYL CHLORIDE

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It has been shown that the Chichibabin reaction of enamines of the 1,2,3,4-tetrahydroisoquinoline series and 1,2,3,4-tetrahydrobenzo[f]isoquinoline series with p-bromophenacyl bromide leads to pyrrolo[2,1-a]isoquinoline derivatives. The same heterocyclic system is obtained on interaction of 1-alkyl-3,4-dihydroisoquinolines or their benzo[f]-analogs with oxalyl chloride. The obtained dioxopyrrolines form derivatives of benzo[g]quinoxalino[2,3-b]indolizine on condensation with o-phenylenediamine.

Keywords: 1-alkyl-3,4-dihydroisoquinolines, benzo[*g*]quinoxalino[2,3-*b*]indolizine derivatives, *p*-bromophenacyl bromide, enamines of the 1,2,3,4-isoquinoline series, oxalyl chloride, pyrrolo[2,1-*a*]isoquinolines, 1,2,3,4-tetrahydrobenzo[*f*]isoquinolines, Chichibabin reaction, condensation with *o*-phenylenediamine.

Pyrrolo[2,1-*a*]isoquinolines are used widely in organic synthesis, medicine, and other areas [1]. The classical method of design the pyrrolo[2,1-*a*]isoquinoline system is the interaction of 1-alkylisoquinolines with α-halo ketones (the Chichibabin reaction) [1, 2]. It is known [3] that on cyclization with the formation of condensed systems a determining role is played by the radicals in position 3 of the isoquinoline ring. The aim of the present work is an investigation of the potentialities of this reaction in the presence of two methyl groups in position 3 and also of a different structure for the enamine fragment.

The reaction of enamines of the 1,2,3,4-tetrahydroisoquinoline series with oxalyl chloride has also been widely investigated [1, 4, 5]. In the given examples, both bases, in the molecules of which the structure of the enamine is already fixed, and compounds in the imino form, enter into this reaction. The latter is characteristic for derivatives of 1-alkylisoquinoline [6, 7], the alkyl residue in the structure of which, unlike carbonyl or just withdrawing groups, does not aid stabilization of the enamine form. Consequently our aim is the study of the conditions of carrying out and the structures of the products of the named reaction in the presence of an alkyl residue at position 1 of the isoquinoline ring.

The investigations showed that the reaction of enamines **1a-c** with *p*-bromophenacyl bromide proceeds readily on boiling in alcohol in the presence of Na_2CO_3 and compounds **2a-c** are formed. On using drotaverine (*no-spa*) base as the initial enamine the reaction product is compound **2d**. Enamino amides and enamino esters of the benzo[*f*]isoquinoline series, analogous in structure to compounds **1a-c,** form the corresponding tetracyclic derivatives **3a-c** in this reaction.

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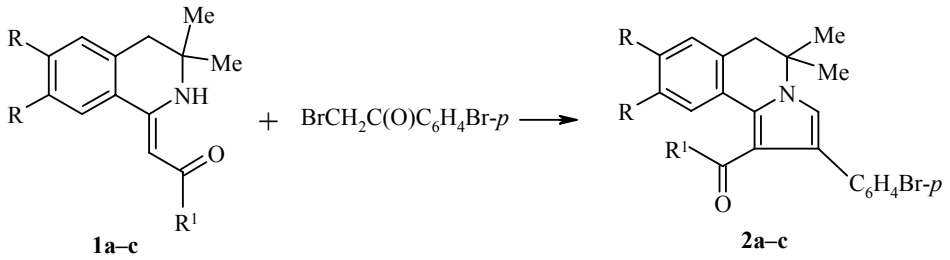
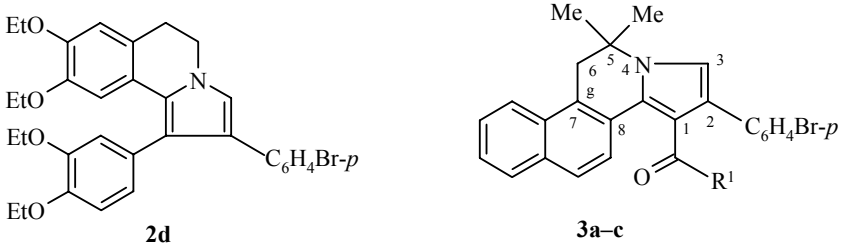


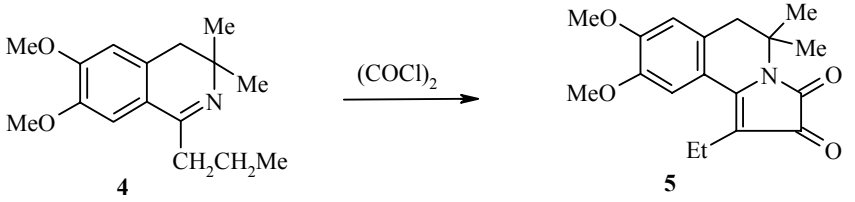
1a–c **2a–c**



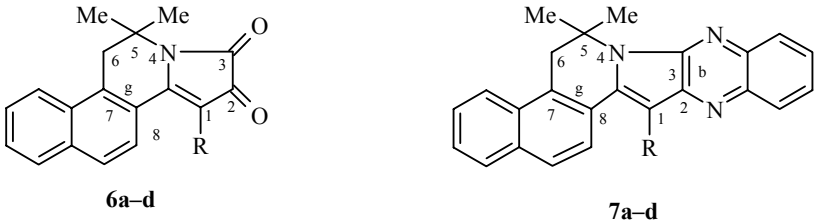
2d **3a–c**

1, **2 a** R = OMe, **b**, **c** R = H; **1–3 a** R^1 = N-pyrrolidinyl, **b** R^1 = N-morpholinyl, **c** R^1 = OEt

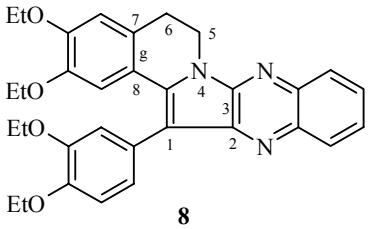
1-Alkyl-substituted isoquinolines, such as compound **4**, react with oxalyl chloride with the formation of condensed pyrroledione **5**. 4-Alkyl-2,2-dimethyl-1,2-dihydrobenzo[*f*]isoquinolines react analogously, forming substances **6a-d**. The investigations showed that a temperature of -10 to 0°C is optimal for carrying out the reaction. The character of residue R has no influence on the yield. The reaction occurs analogously to the already known when R = H [8] (compound **6a**).



4 **5**



6a–d **7a–d**



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6, **7 a** R = H, **b** R = Me, **c** R = Et, **d** R = Pr

TABLE 1. Characteristics of the Compounds Synthesized

Compound	Empirical formula	Found, % / Calculated, %				mp, °C	Yield, %
		C	H	Br	N		
2a	$C_{27}H_{29}BrN_2O_3$	63.6 / 63.7	5.6 / 5.7	15.5 / 15.7	5.6 / 5.5	268-269	57
2b	$C_{25}H_{25}BrN_2O_2$	64.4 / 64.5	5.3 / 5.4	17.0 / 17.2	6.0 / 6.0	264-266	67
2c	$C_{23}H_{22}BrNO_2$	65.0 / 65.1	5.1 / 5.2	18.7 / 18.8	3.4 / 3.3	215 (dec.)	62
2d	$C_{32}H_{34}BrNO_4$	66.5 / 66.7	5.7 / 5.9	13.8 / 13.9	2.5 / 2.4	146-148	68
3a	$C_{29}H_{27}BrN_2O$	69.6 / 69.7	5.4 / 5.5	15.8 / 16.0	5.7 / 5.6	256-258	70
3b	$C_{29}H_{27}BrN_2O_2$	67.4 / 67.6	5.2 / 5.3	15.4 / 15.5	5.3 / 5.4	281-282	78
3c	$C_{27}H_{24}BrNO_2$	68.2 / 68.4	5.0 / 5.1	16.7 / 16.8	3.1 / 3.0	239-241	67
5	$C_{18}H_{21}NO_4$	68.4 / 68.6	6.6 / 6.7	—	4.5 / 4.4	145-147	58
6b	$C_{19}H_{17}NO_2$	78.2 / 78.3	5.7 / 5.9	—	4.9 / 4.8	210-212	54
6c	$C_{20}H_{19}NO_2$	78.5 / 78.7	6.2 / 6.3	—	4.6 / 4.6	205-207	61
6d	$C_{21}H_{21}NO_2$	78.8 / 79.0	6.5 / 6.6	—	4.5 / 4.4	204-206	63
7a	$C_{24}H_{19}N_3$	82.3 / 82.5	5.3 / 5.5	—	12.1 / 12.0	203-205	64
7b	$C_{25}H_{21}N_3$	82.5 / 82.6	5.7 / 5.8	—	11.6 / 11.6	212-214	62
7c	$C_{26}H_{23}N_3$	81.2 / 81.4	6.0 / 6.1	—	11.2 / 11.0	223-225	59
7d	$C_{27}H_{25}N_3$	82.7 / 82.8	6.3 / 6.4	—	10.8 / 10.7	204-205	56
8	$C_{32}H_{33}N_3O_4$	73.3 / 73.4	6.3 / 6.4	—	8.1 / 8.0	155-157	61

The obtained dioxopyrrolines **6a-d** on boiling with *o*-phenylenediamine in glacial acetic acid readily form condensed quinoxalines **7a-d**. The course of the reaction is easily followed by the change in color of the reaction mixture. The initial dioxopyrrolines have a bright-red color, the reaction products are bright-yellow. A derivative of drotaverine **8** was obtained analogously. A previously obtained dicarbonyl compound [9] was taken as starting material in this case. Solutions of compounds **7a-d, 8** have a marked luminescence. The electronic absorption and luminescence spectra of analogs of compounds **7a-d**, having no benzoannelated ring in their structure, were studied previously [10]. Benzoannelation (compounds **7a-d**) and the introduction of auxochromic ethoxy groups (compound **8**) must lead to a strengthening of properties useful in practice, such as light absorption and luminescence.

Bases **2**, **3** are light-yellow substances, dioxopyrrolines bright-red, and quinoxalines **7**, **8** bright-yellow. On dissolving compounds **7**, **8** in conc. H_2SO_4 halochromism is displayed, the solutions become dark-blue, and on dilution with water the color changes to red (Table 1).

In the ^{1}H NMR spectra of pyrrolo[2,1-*a*]isoquinolines **2** and **3** (Table 2), in contrast to the spectra of the initial enamines, singlets for the protons of the ring NH group and the CH of the enamine fragment were not present, but a singlet was present for the CH group of the pyrrole fragment (5.8-6.5 ppm). In the spectrum of compound **5** a triplet (1.1) and a quadruplet (2.6 ppm) characteristic of the ethyl group were present, and there were also signals for the corresponding alkyl groups in the spectra of compounds **6b-d** and **7b-d**. In the spectrum of quinoxaline **8** there was no singlet for the methylene group of the benzyl fragment characteristic of drotaverine base.

TABLE 2. ^{1}H NMR Spectra of the Compounds Synthesized

Compound	Chemical shifts, δ,ppm (*J*, Hz)				
	$(CH_3)_2$, s	$CH_2C(CH_3)_2$, s	aromatic protons	HC=, s	other protons
2a	1.2	2.8	6.6 (s, H-7); 7.1 (s, H-10); 7.2 (2H, d, *J* = 8.4); 7.4 (2H, d, *J* = 8.4)	6.0	3.7 (3H, s, CH_3O); 3.8 (3H, s, CH_3O); 1.7-1.8 (2H, m, $2CH_2$–C); 3.2-3.6 (4H, m, $2CH_2$–N)
2b	1.2	2.8	7.1-7.5 (8H, m)	6.0	3.4-3.8 (8H, m, $N(CH_2)_2O$)
2c	1.2	2.8	7.1-7.6 (8H, m)	6.5	1.3 (3H, t, *J* = 7.4, CH_3CH_2O); 4.2 (2H, q, *J* = 7.4, CH_3CH_2O)
2d	—	—	6.6-7.1 (9H, m)	5.8	1.1-1.7 (12H, 4t, *J* = 6.4, CH_3CH_2O); 3.8-4.0 (8H, 4q, *J* = 6.4, CH_3CH_2O); 3.1 (2H, m, CH_2C); 3.5 (2H, m, CH_2N)
3a	1.3 s	3.2s	7.2-7.8 (10H, m)	6.1	1.7-1.9 (4H, m, $2CH_2$–C); 3.1-3.7 (4H, m, $2CH_2N$)
3b	1.3 s	3.2 s	7.2-7.9 (10H, m)	6.1	3.4-3.8 (8H, m, $N(CH_2)_2O$)
3c	1.3 s	3.3 s	7.2-8.1 (10H, m)	6.5	1.3 (3H, t, *J* = 6.5, CH_3CH_2O); 4.3 (2H, q, *J* = 6.5, CH_3CH_2O)
5	1.5	2.8	6.7 (7H, s); 7.3 (10H, s)	—	1.3 (3H, t, *J* = 7.5, CH_3CH_2); 2.6 (2H, q, *J* = 7.5, CH_3CH_2); 3.8 (3H, s, CH_3O); 3.9 (3H, s, CH_3O)
6b	1.6	3.3	7.5-8.0 (6H, m)	—	2.1 (3H, s, 1-CH_3)
6c	1.6	3.3	7.6-8.0 (6H, m)	—	1.2 (3H, t, *J* = 7.4, CH_3CH_2); 2.6 (2H, q, *J* = 7.4, CH_3CH_2)
6d	1.6	3.3	7.6-8.1 (6H, m)	—	1.0 (3H, t, *J* = 7.2, CH_3CH_2); 1.6 (2H, m, CH_3CH_2); 2.5 (2H, m, CH_2-C=)
7a	1.8	3.4	7.5-8.2 (10H, m)	6.7	—
7b	1.9	3.4	7.4-8.0 (10H, m)	—	2.8 (s, CH_3-C=)
7c	1.9	3.4	7.6-8.1 (10H, m)	—	1.4 (3H, t, *J* = 7.5, CH_3CH_2); 3.3 (2H, q, *J* = 7.5, CH_3CH_2)
7d	1.9	3.4	7.5-8.0 (10H, m)	—	1.1 (3H, t, *J* = 7.7, CH_3CH_2); 1.9 (2H, m, CH_3CH_2); 3.3 (2H, m, CH_2–C=)
8	—	—	7.0-7.3 (5H, m, drotaverine); 7.6-8.0 (4H, m, quinoxaline)	—	1.1-1.4 (12H, 4t, *J* = 6.7, CH_3CH_2O); 4.0-4.3 (8H, 4q, *J* = 6.7, CH_3CH_2O); 3.7 (2H, m, CH_2C); 4.5 (2H, m, CH_2N)

The IR spectra of amides **2a,b** and **3a,b** contain characteristic absorption bands for carbonyl groups at 1630-1640, in the spectra of compounds **2c** and **3c** the ester carbonyl absorbs near 1740 cm^{-1}. The spectra of dioxopyrrolines **5** and **6a-d** contain absorption bands for lactam (1705) and ketone (1735 cm^{-1}) carbonyls.

The mass spectra of compounds **2, 3** have peaks* of low intensity (5-25%) for the molecular ions. For amides **2, 3** there are significant peaks corresponding to the removal initially of the tertiary amino group and then carbonyl, for example, for morpholide **2b** they are 100 (378) and 20% (350) respectively. The mass spectrum of ester **3c** contains a peak for the molecular ion (80%, M^+ 474), and also peaks corresponding to removal of carbethoxy (45%, 400) and later methyl (50%, 387) groups. In the spectra of drotaverine derivatives **2d, 8** there are peaks for the molecular ions at M^+ 577 and M^+ 523 respectively, both of 100%.

The phenomenon of halochromism in the condensed quinoxaline series is seen visually in the example of drotaverine derivative **8** containing four auxochromic groups in the side chain. The absorption spectrum of this compound was recorded in ethanol beginning from 200 nm. The aromatic fragment is displayed by the presence of a β-band of the π→π* transition in the region of 230 nm (log ε 3.72) [11]. A K-band for general π-π conjugation in the molecule is observed at 390 nm (log ε 4.18) [12]. The broad band at 440 nm (log ε 3.64) has a lower intensity linked with the presence of the ethoxy groups (R-band of substituent). The dark-blue solution of quinoxaline **8** in conc. H_2SO_4 changes color on dilution with water. Dilution of 1 : 1 (by volume) causes a green coloration, on further dilution to threefold the solution acquires a raspberry color. In conc. H_2SO_4, in comparison with the spectrum in alcohol, the main changes are observed in the visible region. In comparison with the unionized form a strong bathochromic shift occurs (λ_{max} 627 nm, log ε 4.18). In solution diluted 1 : 1, as usual the most intense band remains at 627 nm (log ε 4.23), however a new peak appears at 415 nm (log ε 3.86), corresponding probably to the presence of an unionized or less ionized form. After further dilution the band at 627 nm disappears (destruction of the solvate shell occurs) and two bands of approximately equal intensity are displayed at 435 (log ε 4.34) and 505 nm (log ε 4.38). Analogous halochromism phenomena were detected previously for compounds close in structure to substance **8** [10].

EXPERIMENTAL

The ^1H NMR spectra of compounds **2d, 8** were recorded on a Bruker DRX 500 (500 MHz) instrument, the spectra of the remaining substances were recorded on a Tesla BS 567 (100 MHz) instrument in $CDCl_3$, internal standard was HMDS (δ 0.05 ppm). The IR spectra were recorded on a Specord 80 spectrometer in nujol. Mass spectra were described on a MAT 311 instrument (70 eV, EI), and UV spectra on a SF-46 instrument.

Checking for purity of the obtained substances was effected by TLC on Silufol UV-254 plates in acetone–ethanol–chloroform, 1 : 3 : 6, visualization in UV light and with iodine vapor.

All compounds were recrystallized from isopropyl alcohol.

The starting materials for the synthesis of compounds **2**, **3** are described in [6, 13, 14], and of substances **5**, **6** in [15]. Drotaverine base was isolated from tablets with a suitable expiry date, mp 58-60°C, its purity was checked by TLC.

2-(*p*-Bromophenyl)-1-(R^2-carbonyl)-5,5-dimethyl-6,7-(R^1)$_2$-5,6-dihydropyrrolo[2,1-*a*]isoquinolines 2a-c, 1-(3',4'-Diethoxyphenyl)-8,9-diethoxy-5,6-dihydropyrrolo[2,1-*a*]isoquinoline (2d), and 2-(*p*-Bromophenyl)-1-(R^2-carbonyl)-5,5-dimethyl-5,6-dihydronaphtho[1,2-*g*]indolizines 3a-c (General Method). The appropriate enamine (10 mmol) in 2-propanol (50 ml) was boiled for 1-2 h with *p*-bromophenacyl bromide (2.0 g, 10 mmol) in the presence of Na_2CO_3 (1.5 g) (check by TLC). The solution was cooled to 20°C, diluted with water (100 ml), the precipitated solid was filtered off, dried, and recrystallized.

* Here and subsequently values of *m/z* are given for ion peaks.

1-Ethyl-8,9-dimethoxy-5,5-dimethyl-2,3-dioxo-2,3,5,6-tetrahydropyrrolo[2,1-*a*]isoquinoline (5) and 1-R^3-5,5-Dimethyl-2,3,5,6-tetrahydronaphtho[1,2-*g*]indolizine-2,3-diones 6a-d (General Method). A mixture of the appropriate enamine and triethylamine (2.80 g, 20 mmol) in ether (150 ml) was added during 15 min to oxalyl chloride (0.86 ml, 10 mmol) in absolute ether (50 ml) at -10 to 0°C. The reaction mixture was brought to 20°C and left at this temperature for a further 30 min. The precipitated solid was filtered off, dried, and recrystallized.

1-R^3-5,5-Dimethyl-2,3,5,6-tetrahydronaphtho[1,2-*g*]quinoxalino[2,3-*b*]indolizines 7a-d and 1-(3',4'-Diethoxyphenyl)-2,3,5,6-tetrahydro(3",4"-diethoxybenzo)[*g*]quinoxalino[2,3-*b*]indolizine (8) (General Method). *o*-Phenylenediamine (1.08 g, 10 mmol) was added to a solution of the initial dioxopyrroline (10 mmol) in glacial acetic acid (25 ml). The mixture was boiled for 1 h, cooled, diluted with 25% ammonia solution (100 ml), the precipitated solid was filtered off, washed with water, dried, and recrystallized.

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