საქართველოს მეცნიერებათა ეროვნული აკადემიის მოამბე, ტ. 10, №4 2016
BULLETIN OF THE GEORGIAN NATIONAL ACADEMY OF SCIENCES, vol. 10, no. 4, 2016

Organic Chemistry

Synthesis of some Novel Derivatives of Indole and Pyrroloindole

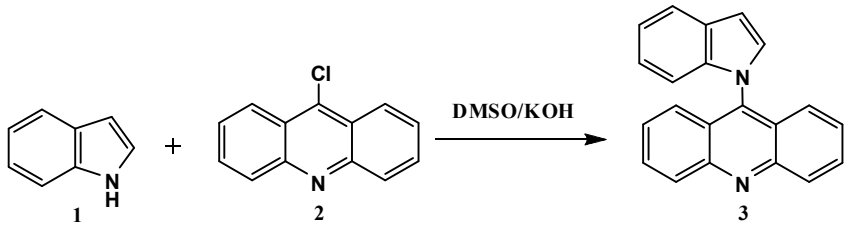
Shota Samsoniya[*], Dali Kajrishvili[**], Nana Targamadze[**], Naira Narimanidze[**], Ioseb Chikvaidze[**]

[*] *Academy Member, Faculty of Exact and Natural Sciences, Ivane Javakhishvili Tbilisi State University, Tbilisi, Georgia*
[**] *Faculty of Exact and Natural Sciences, Ivane Javakhishvili Tbilisi State University, Tbilisi, Georgia*

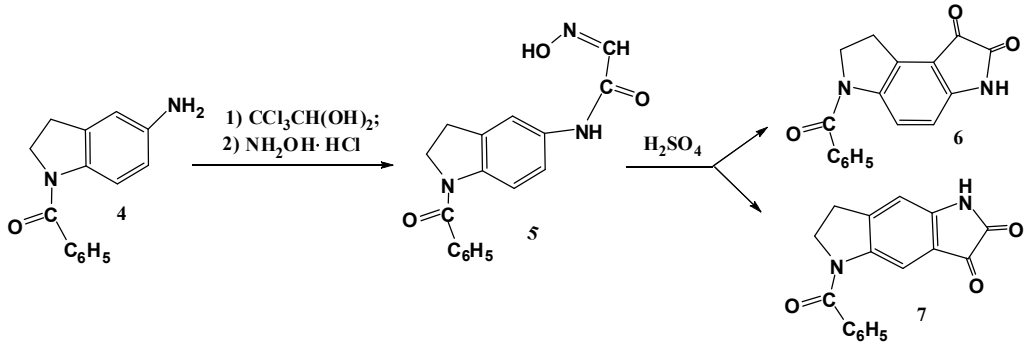
ABSTRACT. One-step synthesis of 9-(1H-indole-1-il)acridine was developed basing on the direct hetarylation of indole with 9-chloracridine in the super basic medium. The yield is almost quantitative. Isomeric pyrroloisatins were synthesized with the aim of modeling structural fragments of highly active antitumor antibiotics of the duocarmycin group. Joining of an isatine fragment to a benzene ring of indoline was conducted under the Sandmeier reaction conditions. A mix of angular and linear products: 6-benzoil-3H,6H-1,2-dioxo-7,8-dihydropyrrolo[3,2-e]indole and 5-benzoil-1H,5H-2,3-dioxo-6,7-dihydropyrrolo[2,3-f]indole with the ratio 1:3.335 was obtained from 5-amino-N-benzoilindoline. From the mixture of products obtained in analogous manner from 6-amino-N-acetylindoline only a linear isomer was isolated. The yield of 7-acetyl-1H,7H-2,3-dioxo-5,6-dihydropyrrolo[3,2-f]indole was 54%. In our view, the formation of angular isomers is limited due to influence of spatial factors. Structures of these synthesized compounds were confirmed by spectral methods. *© 2016 Bull. Georg. Natl. Acad. Sci.*

Key words: Indole, Acridine, Pyrroloisatine, hetarylation

Indole derivatives easily get combined with various biomolecules. More than 50 years they are considered to be privileged structures while creating new potential drugs [1]. An indole ring is connected with another heterocycle in many natural compounds. An indole fragment is a part of many natural compounds, in most of which it is annelated with an aromatic ring or another heterocycle. This fact provides multiplicity of indole alkaloids with wide variety of simple and complex structures [2]. Highly active antitumor antibiotic CC-1065 contains three pyrroloindoline fragments [3]. A single aromatic system of isomeric pyrroloindoles, containing two nitrogen atoms being in different positions and their derivatives, is a subject of longtime interest for researchers. Noncondensed indole compounds, containing fragments of other heterocycles, may also be of great interest for search of novel physiologically active compounds and, among them, preparations having antitumor activity. Isomeric pyrrolophenantridines and indolilphenantridines [4], 9-(1H-indole-1-il)acridine and 9-(1H-indole-5-il)aminoacridine and some derivatives [5-7] are synthesized, which revealed antitumor and antileukemic activity [6,7]. The authors of [5,6] have synthesized 9-(1H-indole-1-il)acridine by



Scheme 1. Synthesis of 9-chloroacridine (3)



Scheme 2. Synthesis of 6-benzoil-3H,6H-1,2-dioxo-7,8-dihydropyrrolo[3,2-e]indole (6) and 5-benzoil-1H,5H-2,3-dioxo-6,7-dihydropyrrolo[2,3-f]indole (7)

indoline hetarylation with 9-chloracridine in anhydrous pyridine with further dehydrogenation of the obtained 9-(1H-indole-1-il)acridine.

We have developed one-stage method for the synthesis of 9-(1H-indole-1-il)acridine (3) by the direct hetarylation of indole with 9-chloracridine (1) at the room temperature, and in the super basic medium - ÊÎÍ-DMSO suspension by the described method [8]. 9-(1H-indole-1-il) acridine (3) is formed with almost quantitative yield (Scheme 1).

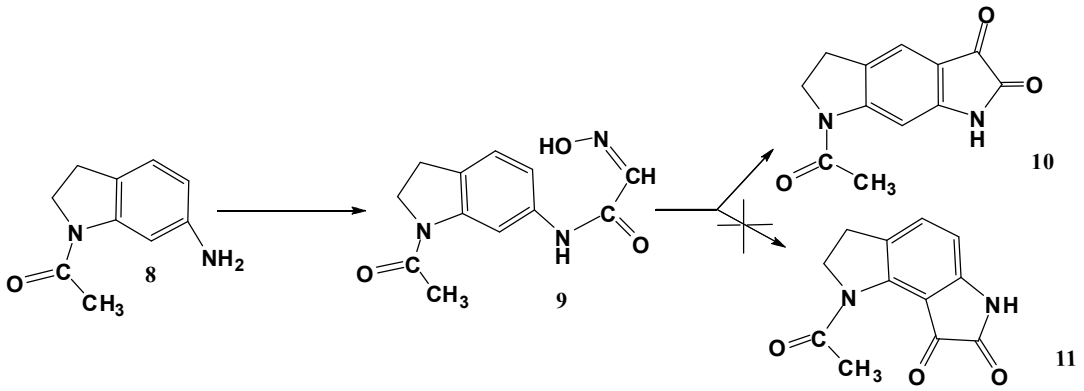
Highly active antitumor antibiotic CC-1065 belongs to the group of duocarmycins [3], in the pyrroloindole fragments of which 3-oxi-indole segments exist, e.g. duocarmycins A.B,C and D. 2,3,5,6-tetraoxo-1H,7H-pyrrolo[3.2-f]indole [9] and isomeric imidazoindoles [10] are synthesized.

We have synthesized isomeric dihydropyrroloisatynes using a scheme including joining of an isatine fragment to a benzene ring of indoline. The synthesis was conducted according to the Sandmeier reaction scheme [11]. 5-amino-N-benzoilindoline (1) was used as initial component (Scheme 2).

A patent has been taken out for synthesis of a linear isomer of a 5-acetylderivative type from 5-amino-N-acetylindoline [12]. But we could not isolate corresponding intermediate isonitrosoacetamide due to intense resinification of the reaction mixture. 5-amino-N-acetylindoline (4) is readily acetylated by a chloralhydrate and hydroxilamine mix at boiling in diluted HCI at the presence of Na_2SO_4 with the 85% yield of the corresponding isonitrosoacetamide (5). By cyclization of this compound in concentrated H_2SO_4 a mix of angular (6) and linear (7) isomers with the ratio 1:3.335 was obtained. Obviously, a direction of the reaction is defined by steric factors. From the complex mix of cyclization products of isonitrosoacetamide (8) obtained from 6-amino-N-acetylindoline (9) we succeeded only in isolation of a linear isomer 10 with the 54% yield (scheme 3). Apparently, angular isomer 11 is not formed because of strong spatial difficulties in comparison with isomer 6.

A structure of the synthesized compounds was verified by spectral methods.

Experimental part. IR spectra are recorded with an instrument Thermo Nikolet Avatar-370 in petroleum jelly and KBr tablets. NMR ^{1}H spectra are recorded with a spectrometer Bruker AM-400 in dimethylsulphox-



Scheme 3. Synthesis of 7-acetyl-1H,7H-2,3-dioxo-5,6-dihydropyrrolo[3,2-f]indole (10)

ide-D_6, inner standard TMS. Mass-spectra are obtained with a spectrometer Finigan MAT-95. The data of mass- and NMR spectra are collected in the Department of Organic Chemistry at the Zaarland University (Germany).

9-(1Í-indole-1-il)acridine (3). 2.24 g (0.04 mole) of KOH suspension and 1.17 f (0.01 mole) of indole were mixed in 50 ml of DMCO for 1 h, then 3.2 g (0.015 mole) of 9-chloracridine was added and mixed again for 4 h. The mix was poured into 100 ml water. Precipitated crystals were filtered, air dried and recrystallized from ethanol. The yield was 2.82 g (96%). T_m - 213-215^{0}C, R_f 0.29 (hexan-ester, 3:1) IR spectrum, ν, cm^{-1}: 3085-2854 (CH), 1627.7 (C=C). UV spectrum, λ_{max} nm (lgε): 274 (4.896); 337 (4.870); 368 (3.842); 397 (3.206). NMR spectrum ^{1}H ($CDCl_3$, δ, ppm, J, Hz): 8.332 (2H, d, J=8.27, H-4^1, H-5^1); 7.925 (2H, t, J=8.0, H-3^1, H-6^1 H-3^1, H-6^1); 7.828(1H, d, J=3.0, H-2); 7.817 (1H, d, J=8.9, H-4); 7.826 (1H, d, J=8.9, H-4); 7.592 (2H, t, J=8.0, H-2^1, H-7^1); 7.354 (2H, d, J=9.0, H-1^1, H-8^1); 7.183(1H, t, J=7.5, H-6); 7.058(1H, t, J=7.5, H-5); 6.983 (1H, d, J=3.0, H-3); 6.675 (1H,d,J=8.0, H-7); NMR spectrum ^{13}C ($CDCl_3$) δ, ppm: 149.049; 140.351, 138.047; 131.008; 130.782; 129.502; 127.900; 127.407; 123.351; 122.998; 122.536; 120.921; 120.404; 110.177; 103.805; Found: m/z 294.1188 [M^+]. $C_{21}H_{14}N_2$. Calculated: M=294.

1-benzoil-5-isonitrosoacetamideindoline (5). 10.3 g (0.032 mole) of $Na_2SO_4 \cdot 10H_2O$ was added to the 0.66 g (0.004 mole) chloralhydrate solved in 10 ml water. Then solution of 1g (0.004 mole) 1-benzoil-5-aminoindoline (4) and 0.88g (0.013 mole) hydroxilamine hydrochloride in 50 ml water and 0.5 ml concentrated HCL was added. The mix is stirred and boiled for 1 h. Settled after cooling sediment was filtered, washed with water until neutral reaction and dried. The yield was 1g (85%). The obtained product was purified on the column with silica gel, eluent – benzene-aceton, 1:1. R_f 0.63 (benzene-acetone, 3:1). T_m = 230-231 ^{0}C. IR spectrum (petroleum jelly), ν, cm^{-1}: 3260 (NH), 3190 (=N-OH), 1770 (C=O), 1650 (C=N). NMR spectrum ^{1}H (DMSO- D_6, δ, ppm, J, Hz): 12.1 (1H, c, H-ON); 10.12 (1H, c, H-N); 7.67 (1Í, d, J=7.5,H-7); 7.56 (1H, c, H-4); 7.49 (1H, d, J=7.5, H-6); 7.47-7.43 (5H, m, H-Ph); 3.98 (2H, t, J=8.0, N-CH2); 3.07 (2H, t, J=8.0, CH2-CH2); 2.07 (1Í, c, H-C=N). Found: m/z 309.1085 [M^+]. $C_{17}H_{15}N_3O_4$. Calculated: M=309.

6-benzoil-3H,6H-1,2-dioxo-7,8-dihydropyrrolo[3,2-e]indole (6) and 5-benzoil-1H,5H-2,3-dioxo-6,7-dihydropyrrolo[2,3-f]indole (7). 1.1g (0.0036 mole) of 1-benzoil-5-isonitrosoacetamido indoline (5) was added slowly, by small portions to 10 ml concentrated H_2SO_4 heated up to 50^0 C. The mix was heated to 80^0 C, stirred for 30 min, cooled and poured in 100g grinded ice. The sediment was filtered, washed with water until neutral reaction and dried. The yield was 0.9g (87%). The mixture of isomers was divided on the column with silica gel, eluent – benzene-acetone, 4:1. A fraction R_f 0.5 (benzene-acetone, 2:1) contains

0.15g (14.5%) of 6-benzoil-3H,6H-1,2-dioxo-7,8-dihydropyrrolo[2,3-e]indole (6). T_m = 243-2440C. IR-spectrum (KBr), ν, cm^{-1}: 3456 (NH), 1743.42 (C=O -Bz), 1738 (C=O -amide), 1635.42 (C=O -ketone). NMR spectrum ^1H (DMSO- D_6, δ, ppm, J, Hz): 11.04 (1H, c, H-N); 7.50 (1H, d, J=7.3, H-4); 6.72 (1H, d, J=7.3, H-5); 7.57-7.35 (5H, m, H-Ph); 4.03 (2H, t, J=8.2, N- CH_2); 3.20 (2H, t, J=8.2, CH_2-CH_2). Found: m/z 292.0843 [M^+]. $C_{17}H_{12}N_2O_3$. Calculated: M=292.

Fraction R_f 0.3 (benzene-acetone, 2:1) contains 0.5g (48.36%) of 5-benzoil-1H,5H-2,3-dioxo-6,7-dihydropyrrolo[3,2-e]indole (7). T_m = 273-274^{0}C. IR-spectrum (KBr), ν, cm^{-1}: 3471.41 (NH), 1743.42 (C=O -Bz), 1740 (C=O -amide), 1627.71 (C=O -ketone). NMR spectrum ^1H (DMSO-D_6, δ, ppm, J, Hz): 10.96 (1H, c, H-N); 7.49 (1H, c, H-4); 7.57-7.49 (5H, m, H-Ph); 6.84 (1H, c, H-8); 3.98 (2H, t, J=7.3, N- CH_2); 3.11 (2H, t, J=7.3, CH_2-CH_2). Found: m/z 292.0806 [M^+]. $C_{17}H_{12}N_2O_3$. Calculated: M=292.

1-acetyl-6-isonitrosoacetamidoindoline (9) was obtained in analogous manner as compound 2 from 1g (0.0057 mole) 1-acetyl-6-aminoimdolime (8), 1.04 g (0.0057 mole) chloralhydrate, 14.8g $Na_2SO_4 \cdot 10H_2O$ and 1.25g (0.021 mole) hydrochloride hydroxylamine. The yield 0.52 g (36.9%). It was purified on the column with silica gel, eluent – benzene-acetone, 1:1. R_f - 0.63 (benzene-acetone, 3:2). T_m = 233-235 ^{0}C. IR spectrum (vaseline oil), ν, cm^{-1}: 3300 (NH), 3210 (=N-OH), 1680 (C=O), 1640 (>C=N). NMR spectrum ^1H (DMSO-D_6, δ, ppm, J, Hz): 12.08 (1H, c, H-ON); 10.15(1H, c, H-N); 8.26 (1H, c, H-7); 7.46 (1H, d, J=8.2, H-4); 7.14 (1H, d, J=8.2, H-5); 4.08 (2H, t, J=8.35, N-CH_2); 3.06 (2H, t, J=8.35, CH_2-CH_2); 2.14(3H, c, CH_3); 2.07 (1Í, c, H-C=N). Found: m/z 347.0927 [M^+]. $C_{12}H_{13}N_3O_3$. Calculated: M=247.

7-acetyl-1H,7H-2,3-dioxo-5,6-dihydropyrrolo[3,2-f]indole (10) was obtained analogously of compound 4 from 0.5 g (0.002 mole) of 1-acetyl-6-isonitrozoacetamidoindoline (6). It was purified on the column with silica gel, eluent – benzene-acetone 3:1. R_f - 0.63 (benzene-acetone, 3:2). R_f 0.39 (benzene-acetone, 3:2). T_m. 261^{0}C (decomposes). IR spectrum (petroleum jelly), ½, cm^{-1}: 3220 (NH), 1725(C=O -Ac), 1718 (C=O- amide), 1620 (C=O -ketone). NMR spectrum ^1H (DMSO-D_6, δ, ppm, *J*, Hz): 10.38 (1H, c, H-N); 7.76 (1H, c, H-8); 7.02 (1H, c, H-4); 3.64 (2H, t, *J*=8.2, N-CH_2); 2.87 (2H, t, *J*=8.2, CH_2-CH_2); 2.10(3H, c, CH_3). Found: m/z 230.0668 [M^+]. $C_{17}H_{12}N_2O_3$. Calculated : M=230.

ორგანული ქიმია

ინდოლისა და პიროლოინდოლის ზოგიერთი ახალი ნაწარმის სინთეზი

შ. სამსონია*, დ. ყავჯრიშვილი, ნ. თარგამაძე, ნ. ნარიმანიძე**, ი. ჩიკვაიძე****

** აკადემიის წევრი, ზუსტ და საბუნებისმეტყველო მეცნიერებათა ფაკულტეტი, ივანე ჯავახიშვილის სახ. თბილისის სახელმწიფო უნივერსიტეტი, თბილისი, საქართველო*
*** ზუსტ და საბუნებისმეტყველო მეცნიერებათა ფაკულტეტი, ივანე ჯავახიშვილის სახ. თბილისის სახელმწიფო უნივერსიტეტი, თბილისი, საქართველო*

შემუშავებულია 9-(1H-ინდოლ-1-ილ)აკრიდინის ერთსაფეხურიანი სინთეზი, რომელიც დაფუძნებულია ინდოლის პირდაპირი ჰეტარილირების რეაქციაზე 9-ქლორაკრიდინით სუპერფუძე არეში. გამოსავლიანობა თითქმის რაოდენობრივია. მაღალაქტიური ანტიკანცეროგენული დოუკარმიცინის ჯგუფის ანტიბიოტიკების სტრუქტურული ფრაგმენტების მოდელირების მიზნით სინთეზირებულია იზომერული პიროლოიზატინები. ინდოლინის ბენზოლის ბირთვზე იზატინური ფრაგმენტის მიშენება მოვახდინეთ ზანდმეიერის რეაქციის პირობებში. 5-ამინო-N-ბენზოილინდოლინიდან მიიღება ანგულარული და ხაზოვანი პროდუქტების - 6-ბენზოილ-3H,6H-1,2-დიოქსო-7,8-დიჰიდროპიროლო[3,2-e]ინდოლის და 5-ბენზოილ-1H,5H-2,3-დიოქსო-6,7-დიჰიდროპიროლო[2,3-f]ინდოლის ნარევი 1:3.335 თანაფარდობით. ხოლო 6-ამინო-N-აცეტილინდოლინიდან ანალოგიური გზით მიღებული პროდუქტების ნარევიდან მოვახერხეთ მხოლოდ ხაზოვანი იზომერის გამოყოფა. 7-აცეტილ-1H,7H-2,3-დიოქსო-5,6-დიჰიდრო-პიროლო[3,2-f]ინდოლის გამოსავლიანობა 54% შეადგენს. ჩვენი აზრით, ანგულარული იზომერების წარმოქმნა შეზღუდულია სივრცითი ფაქტორების გავლენის გამო. ყველა სინთეზირებული ნაერთის აღნაგობა დადასტურებულია სპექტრული მეთოდებით.

REFERENCES:

1. *Karchava A.V., Melkonyan F.C., Yurovskaya V.A*. (2012) Khimiya Geterotsiklicheskikh Soedinenii. 3: 415-433 (in Russian).
2. *Barton D., Ollis U.D*. (Editors) (1985) Obshchaia organicheskaia khimia, **8**, 752 p. (in Russian).
3. *Yasuzawa T., Iida T., et all*. (1988) Chem.-Pharm. Bull. (Japan) **36**(9): 3728-31.
4. *Baberkina E.P., Buyanov V.N., Zhukova M.E. et al*. (2001) Khimiia Geterotsiklicheskikh Soedinenii, **10** (412): 1350-1353 (in Russian).
5. *Chaganava N.T*. (1991) Bull. Georg. Acad.Sci. **143**, 1: 153 (in Russian).
6. *Chaganava N.T., Buyanov V.N. et al.* (1991) Khimiko-farmatseticheskii zhurnal. 8: 41-43 (in Russian).
7. *Chaganava N.T. Buyanov V.N. et al*. (1991) Khimiko-farmatseticheskii zhurnal. 12: 27 (in Russian).
8. *Heaney H., Ley S.V.* (1973) J. Chem. Soc. Perkin Trans. 1: 499-500.
9. Toyo Rayon Kabushiki Kaisha (27.10.1971) GB 1251082 [Toray Industries Inc. (JP)].
10. *Chetverikov V.P., Ostapovich Yu.I., Maksimov N.Ya*. (1975) Materiali 4-go mezhdunarodnogo kollokviuma po khimii i farmakologii proizvodnykh indola, Kishinev, Moldova, 54 (in Russian).
11. *Sandmeyer T*. (1919).Helv.Chim.Acta, **2**, 1: 234-242.
12. *Lee D.A*. (1998) US Patent Appl. 5736534.

Received August, 2016