Chemistry of Heterocyclic Compounds, Vol. 42, No. 1, 2006

3-ACETYL-4-METHYLPYRIDO[2,1-*a*]-ISOQUINOLIN-2-ONES. [2+4] CYCLOCONDENSATION OF 3,4-DIHYDROISOQUINOLINES WITH TRIACETYLMETHANE

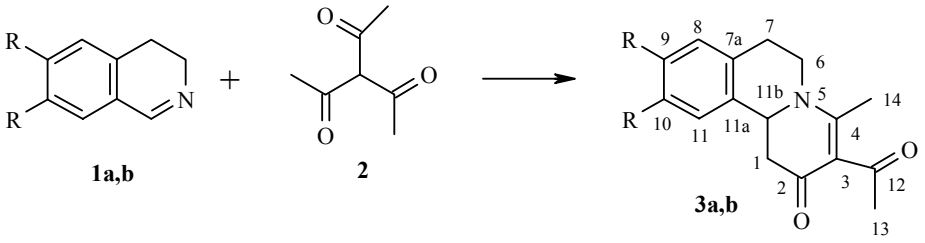
O. V. Gulyakevich[1], P. V. Kurman[2], A. S. Lyakhov[3], and A. L. Mikhal'chuk[1]

Treatment of 3,4-dihydroisoquinolines with triacetylmethane in refluxing alcohol for 2-3 h gave 3-acetyl-4-methylpyrido[2,1-a]isoquinolin-2-ones. Their basic physicochemical properties have been studied.

Keywords: azomethines, benzo[*a*]quinolizines, 3,4-dihydroisoquinolines, Schiff's base, pyrido[2,1-*a*]-isoquinolines, triacetylmethane, annelation, [2+4] cyclocondensation.

We have previously [1-6] studied the reactions of 3,4-dihydroisoquinolines and related cyclic azomethines with different β-dicarbonyl and also with alicyclic and heterocyclic β,β'-tricarbonyl compounds (TCC) which occur *via* a [2+4] cyclocondensation type annelation scheme. This leads to the preparation of various polycyclic heterocycles which are valuable synthons and possess important biological properties [7-9]. However, up to this time such a reaction with the simplest of the aliphatic TCC has not been reported. In this work we have studied the reaction of the 3,4-dihydroisoquinolines **1a,b** with triacetylmethane **2**.

Refluxing equimolar mixtures of the compounds **1a,b** with the triketone **2** in alcohol for 2-3 h (the reaction not occurring at room temperature) gave the pyrido[2,1-*a*]isoquinolines **3a,b** in 30-40% yields (see Scheme 1). The reaction is accompanied by significant tarring and preparative chromatography was used for purification of the final products. It will be recalled that the analogous reactions of cyclic azomethines with alicyclic TCC occurred in higher [10, 11] or, for sterically hindered azomethines, in comparable yields [12].

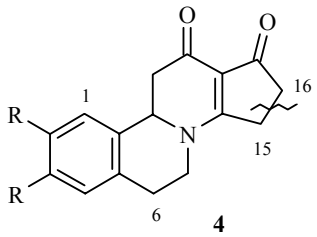


1,3 a R = H, **b** R = OMe

[1] State Science Establishment, Institute of Bioorganic Chemistry, Belarus National Academy of Sciences, Minsk 220141; e-mail: mikhalch@imaph.bas-net.by. [2] RTSC "Ecomir", Belorussian Republic Academy of Sciences, Minsk 220012. [3] F. Skorina Science Research Center, Belorussian State University, Minsk 220050. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 1, pp. 77-85, January, 2006. Original article submitted January 23, 2004.

 0009-3122/06/4201-0070

It should be noted that the pyridoisoquinolines obtained **3a,b** can be regarded as 15,16-*seco* analogs of 8-azagonanes or benzo[*a*]cyclopentano[*f*]quinolizines **4** which show immunodepressant properties [13, 14]. With this in mind it was undoubtedly of interest to study their structure-function and structure-property correlation.



4

The structure of the pyridoisoquinolines **3a,b** was confirmed by combined physicochemical data.

In their IR spectra the pyridoisoquinolines **3a,b**, like their tetracyclic analogs 8-azasteroids [15, 16], have a similar pattern of absorption in the C=O, C=C stretching and C–H deformation vibration regions (1700-1350 cm^{-1}). Certain differences in the C=O vibrations of the pyridoisoquinolines **3a,b** and 8-azasteroids are probably related to the differences in their structures (see [17]). Hence if the 8-azasteroid N(8)–C(14)=C(13)(–C(12)=O))–C(15)=O(15) has a fixed N-*cis*-*s*-*trans* – -*trans*-*s*-*trans* configuration then the most preferred is the N-*cis*-*s*-*trans* – -*trans*-*s*-*cis* configuration for the pyrido[2,1-*a*]isoquinolines **3a,b**. The differences seen in the IR spectra of the 8-azasteroids **4** [10, 14] and the derivatives **3a,b** are related to differences in their steric structure, in particular to the configurations of the carbonyl groups at C(3) in compounds **3** and at C(17) in compounds **4**.

The UV spectra of the pyridoisoquinolines are similar to the UV spectra of the 8-azasteroids which also have an α-acyl-β-aminovinylcarbonyl or enaminodicarbonyl group in their structure [10, 11] and they are characterized by two strong absorption bands in the regions ~270 and ~320 nm. Moreover, the long wavelength absorption band (~320 nm) is bathochromically shifted relative to the analogous absorption bands in the related dibenzo[*a,f*]quinolizines [10] and this is due to the configurational differences at the C(3) and C(17) carbonyl groups in the derivatives **3** and **4** respectively.

The ^{1}H NMR spectra of the obtained pyrido[2,1-*a*]isoquinolines **3a,b** shown characteristic signals which correspond to the proposed structure. Hence in the region 2.30-2.55 ppm there are observed resonance signals for the absorptions of the C(4)-methyl and C(3)-acetyl groups which appear as three-proton singlets. The 2.40-2.80 and 4.65-4.85 ppm regions show signals for the absorptions of the ABX spin system of the C(1)–C(11b) fragment in the pyrido[2,1-*a*]isoquinoline molecules **3a,b**. The ^{1}H NMR spectrum of the derivative **3b** has signals corresponding to the C(9)- and C(10)-methoxy groups. The remaining signals for the other molecular fragments of the pyrido[2,1-*a*]isoquinolines **3a,b** are given in the Experimental.

The ^{13}C NMR spectra of the pyrido[2,1-*a*]isoquinolines **3a,b** showed sets of resonance absorption signals required by the proposed structures, amongst which are the characteristic resonance signals for the C(3), C(4) and C(11b) nuclei at ~115, ~168, and ~56-57 ppm respectively.

The definitive structure for the pyrido[2,1-*a*]isoquinolines **3a,b** was confirmed by an X-ray diffraction experiment on a monocrystal of the derivative **3a** (Figures 1 and 2 and Tables 1-3). This data confirms the structural assignments made on the basis of the spectroscopic data and yields information about the spatial structure of this compound.

Based on the X-ray analytical data, the molecule of derivative **3a** has the following geometrical parameters. Ring **A** is planar, the mean deviation of the atoms from the mean square plane being 0.005(2) Å. The valence angles in the ring are close to 120° (Table 1) and the bond lengths forming this ring of atoms lie in

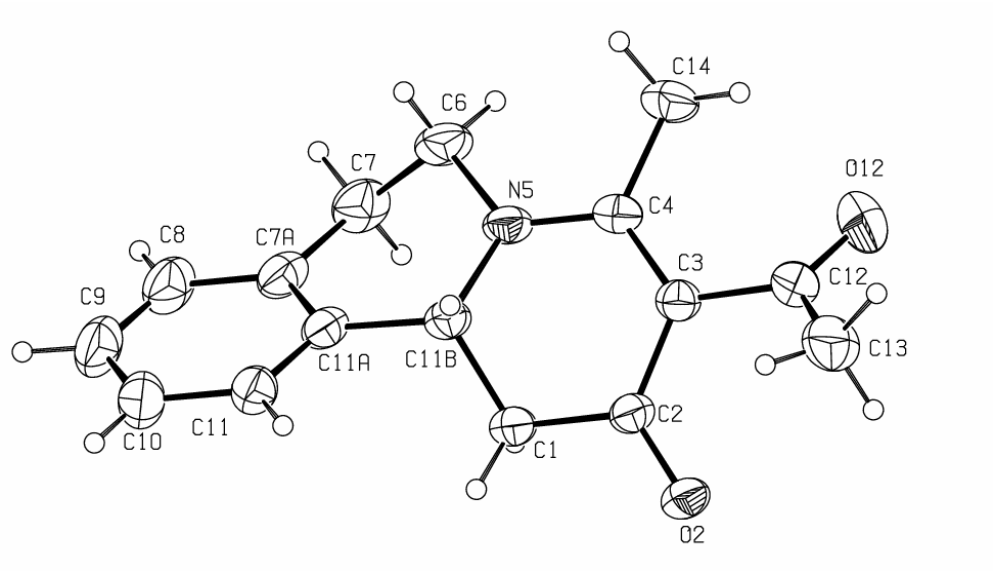


Fig. 1. Structure of the pyrido[2,1-*a*]isoquinoline molecule **3a**.

the range 1.373(3)-1.395(2) Å thus confirming its aromatic character. Ring **B** has a *boat* conformation as clearly seen in Fig. 1. The partially hydrogenated γ-pyridone ring **C** has a *half-chair* conformation with the C(1) and C(11B) atoms lying to different sides of the plane formed by the C(2), C(3), C(4), and N(5) atoms (Table 2).

From the X-ray data the α-acyl-β-aminovinyldicarbonyl (AADC) fragment N(5)–C(4)=C(3)(–C(2)=O))–C(12)=O(12) in compound **3a** has a configuration close to N-*cis*-*s*-*trans* – N-*trans*-*s*-*cis* in the crystal (Fig. 1). Because, according to AM1 quantum-chemical calculations such a configuration is most energetically preferred it might be expected that it would also be the most populated in solutions of derivative **3a**. Analysis of the geometric and electronic parameters for the AADC fragment establishes that the *p*-π electronic system is

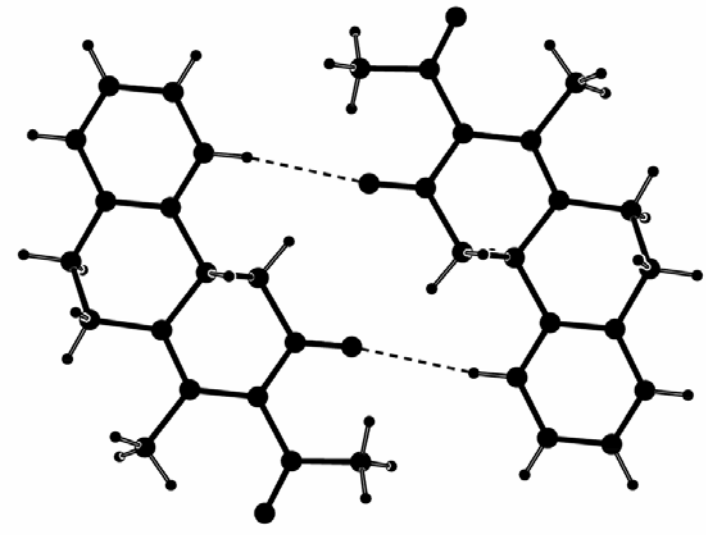


Fig. 2. Dimeric aggregates in the crystal structure of the pyrido[2,1-*a*]isoquinoline **3a**.
Dashed lines show the C–H···O hydrogen bonds.

TABLE 1. Bond Lengths (*d*) in the Pyrido[2,1-*a*]isoquinoline Molecule **3a**

Bond	*d*, Å	Bond	*d*, Å
C(1)–C(11B)	1.502(2)	C(7)–C(7A)	1.489(3)
C(1)–C(2)	1.515(2)	C(7A)–C(8)	1.387(3)
C(2)–O(2)	1.2287(18)	C(7A)–C(11A)	1.395(2)
C(2)–C(3)	1.445(2)	C(8)–C(9)	1.373(3)
C(3)–C(4)	1.398(2)	C(9)–C(10)	1.374(3)
C(3)–C(12)	1.477(2)	C(10)–C(11)	1.381(3)
C(4)–N(5)	1.338(2)	C(11)–C(11A)	1.379(3)
C(4)–C(14)	1.507(2)	C(11A)–C(11B)	1.509(2)
N(5)–C(6)	1.471(2)	C(12)–O(12)	1.221(2)
N(5)–C(11B)	1.480(2)	C(12)–C(13)	1.501(3)
C(6)–C(7)	1.504(3)		

TABLE 2. Valence angles (ω) in the Molecule of Compound **3a**

Angle	ω, deg.	Angle	ω, deg.
C(11B) –C(1)–C(2)	109.84(13)	C(8)–C(7A)–C(7)	122.96(18)
O(2)–C(2)–C(3)	124.56(15)	C(11A)–C(7A)–C(7)	118.31(16)
O(2)–C(2)–C(1)	119.03(14)	C(9)–C(8)–C(7A)	121.0(2)
C(3)–C(2)–C(1)	116.06(13)	C(8)–C(9)–C(10)	119.98(19)
C(4)–C(3)–C(2)	119.64(14)	C(9)–C(10)–C(11)	120.0(2)
C(4)–C(3)–C(12)	122.07(15)	C(11A)–C(11)–C(10)	120.37(19)
C(2)–C(3)–C(12)	117.88(15)	C(11)–C(11A)–C(7A)	120.00(17)
N(5)–C(4)–C(3)	121.10(14)	C(11)–C(11A)–C(11B)	118.09(15)
N(5)–C(4)–C(14)	116.30(15)	C(7A)–C(11A)–C(11B)	121.91(16)
C(3)–C(4)–C(14)	122.55(16)	N(5)–C(11B)–C(1)	108.25(14)
C(4)–N(5)–C(6)	123.29(14)	N(5)–C(11B)–C(11A)	113.65(13)
C(4)–N(5)–C(11B)	117.34(13)	C(1)–C(11B)–C(11A)	113.62(14)
C(6)–N(5)–C(11B)	119.23(14)	O(12)–C(12)–C(3)	122.86(19)
N(5)–C(6)–C(7)	110.41(15)	O(12)–C(12)–C(13)	118.76(19)
C(7A)–C(7)–C(6)	110.54(17)	C(3)–C(12)–C(13)	118.35(17)
C(8)–C(7A)–C(11A)	118.7(2)		

most efficiently brought about for the N-*cis*-*s*-*trans* path fragment while the N-*trans*-*s*-*cis* path is less conjugated (as indicated by the C(2)=O(2), C(12)=O(12), C(2)–C(3), and C(3)–C(4) bond lengths (Table 1). This puts under doubt the previously suggested claim for a preferred N-*trans*-*s*-*trans* conjugation when compared with an N-*cis*-*s*-*trans* conjugation in AADC fragments [18].

It should be noted that the N(5) atom has a virtually planar trigonal configuration the sum of its valence angles being 359.86° and its deviation from the plane of the three connected atoms C(4), C(6), and C(11B) being 0.03(3) Å. Attention is also drawn to the rather marked deformation of the valence angles for the nitrogen atom (Table 2), probably as a result of *p*-π interactions with the enedione fragment.

In the crystal, the structure **3a** undergoes weak interactions with C(11)–H(11)···O(2) (*d* C(11)···O(2) = 3.427(2) Å and ω C(11)–H(11)···O(2) = 162.2°) combining the molecules as dimers (Fig. 2). They determine the molecular packing in the crystalline structure along with the van der Waal interactions.

No other shortening of intermolecular contacts which might be associated with the above geometric deformation in the molecular structure were observed. Hence these deformations were due exclusively to the intramolecular interactions. Other specific features of the structure of the newly prepared pyrido[2,1-*a*]-isoquinolines are given in Tables 1-3.

TABLE 3. Dihedral Angles (φ) in the Molecule of Compound **3a**

Angle	φ, deg.	Angle	φ, deg.
C(11B)–C(1)–C(2)–O(2)	155.51(15)	C(8)–C(9)–C(10)–C(11)	1.5(3)
C(11B)–C(1)–C(2)–C(3)	-31.0(2)	C(9)–C(10)–C(11)–C(11A)	-0.8(3)
O(2)–C(2)–C(3)–C(4)	166.86(16)	C(10)–C(11)–C(11A)–C(7A)	-0.2(3)
C(1)–C(2)–C(3)–C(4)	-6.2(2)	C(10)–C(11)–C(11A)–C(11B)	179.78(17)
O(2)–C(2)–C(3)–C(12)	-5.9(3)	C(8)–C(7A)–C(11A)–C(11)	0.6(3)
C(1)–C(2)–C(3)–C(12)	-178.97(14)	C(7)–C(7A)–C(11A)–C(11)	178.18(17)
C(2)–C(3)–C(4)–N(5)	16.6(2)	C(8)–C(7A)–C(11A)–C(11B)	-179.41(17)
C(12)–C(3)–C(4)–N(5)	-170.95(15)	C(7)–C(7A)–C(11A)–C(11B)	-1.8(3)
C(2)–C(3)–C(4)–C(14)	-166.24(15)	C(4)–N(5)–C(11B)–C(1)	-50.98(19)
C(12)–C(3)–C(4)–C(14)	6.2(2)	C(6)–N(5)–C(11B)–C(1)	133.21(16)
C(3)–C(4)–N(5)–C(6)	-170.83(16)	C(4)–N(5)–C(11B)–C(11A)	-178.20(14)
C(14)–C(4)–N(5)–C(6)	11.9(2)	C(6)–N(5)–C(11B)–C(11A)	6.0(2)
C(3)–C(4)–N(5)–C(11B)	13.6(2)	C(2)–C(1)–C(11B)–N(5)	57.38(18)
C(14)–C(4)–N(5)–C(11B)	-163.75(14)	C(2)–C(1)–C(11B)–C(11A)	-175.38(14)
C(4)–N(5)–C(6)–C(7)	140.93(18)	C(11)–C(11A)–C(11B)–N(5)	-161.86(15)
C(11B)–N(5)–C(6)–C(7)	-43.5(2)	C(7A)–C(11A)–C(11B)–N(5)	18.2(2)
N(5)–C(6)–C(7)–C(7A)	58.0(2)	C(11)–C(11A)–C(11B)–C(1)	73.8(2)
C(6)–C(7)–C(7A)–C(8)	140.8(2)	C(7A)–C(11A)–C(11B)–C(1)	-106.22(19)
C(6)–C(7)–C(7A)–C(11A)	-36.7(3)	C(4)–C(3)–C(12)–O(12)	-33.2(3)
C(11A)–C(7A)–C(8)–C(9)	0.1(3)	C(2)–C(3)–C(12)–O(12)	139.33(19)
C(7)–C(7A)–C(8)–C(9)	-177.4(2)	C(4)–C(3)–C(12)–C(13)	144.67(19)
C(7A)–C(8)–C(9)–C(10)	-1.1(4)	C(2)–C(3)–C(12)–C(13)	-42.8(2)

Hence the results given point to the main possibility of annelation of 3,4-dihydroisoquinolines by triacetylmethane leading to novel functional derivatives of pyrido[2,1-*a*]isoquinoline which are important for medico-biological and physicochemical study. The products are of interest for the synthesis of alkaloids and related heterocyclic compounds. The data presented points to further, promising studies of the annelation of Schiff bases or azomethines by polycarbonyl compounds. The sum of the quantum-chemical, structural, and spectroscopic parameters we obtained complement data from previous work [15-17] and point to a promising extension of the study of the interaction between structure and properties in the series of condensed quinolizine derivatives.

EXPERIMENTAL

UV spectra were taken on a Specord M-400 spectrophotometer using ethanol and IR spectra on a UR-20 instrument for KBr tablets. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AC-200 radiofrequency spectrometer (200 and 50 MHz respectively) using $CDCl_3$ and with TMS as internal standard. The 3,4-dihydroisoquinolines **1a,b** were prepared by the cyclodehydration of the corresponding phenethylformamides by the Bischler-Napieralski method [19]. Monitoring of the course of the reaction was carried out using TLC on Silufol UV-254 plates with chloroform–methanol (9:1) as eluent. Mass spectra were measured on an HP 5890/5972 GC/MS chromato-mass spectrometer (quartz capillary column HP 5MS, 30 m × 0.25 mm × 0.25 microns, gas carrier helium 0.7-1.0 μl/min, vaporizer temperature 250°C, temperature program 40-300°C at 6°C/min). Melting points were taken on a Boetius heating block.

Monocrystals of compound **3a** were prepared by crystallization from a mixture of alcohol and ether (4:6). A crystal of size 0.38 × 0.28 × 0.24 mm was selected. A three dimensional set of diffraction data was collected on an automatic, four circle Nicolet R3m diffractometer (MoKα irradiation, graphite monochromator

θ/2θ scanning to $2\theta_{max}$ = 60°), The overall number of collected reflections was 4209, 3953 of which were independent (R_{int} = 0.0155). The compound crystallized in the monoclinic crystal system with space group *c*2/*c*. The unit cell parameters are: *a* = 18.310(4), *b* = 7.644(2), *c* = 19.639(5) Å; β = 101.29(2)°; *V* = 2695.5(11) Å^3; *Z* = 8; d_{xray} = 1.258 g/cm^3; μ = 0.83 cm^{-1}. The compound structure was solved by a direct method (SIR97 [20]). The positions of the hydrogen atoms were calculated geometrically. The refinement (SHELXL-97 [21]) was carried using full-matrix least-squares analysis based on anisotropic thermal parameters for the non-hydrogen atoms. The hydrogen atoms were refined using the "riding" model. The final difference factors were *R*1 = 0.0536, *wR*2 = 0.1514 ($I > 2\sigma(I)$; *R*1 = 0.0919, *wR*2 = 0.1852 (all data); goodness of fit Goof 1.067.

***rac*-3-Acetyl-4-methyl-1,6,7,11b-tetrahydro-2H-pyrido[2,1-*a*]isoquinolin-2-one (3a).** A solution of isoquinoline **1a** (0.328 g, 2.5 mmol) and triacetylmethane **2** (0.355 g, 2.5 mmol) in ethanol (5 ml) was left for 24 h at 12°C and then refluxed using a reflux condenser for 2 h. The mixture obtained was evaporated to dryness and the residue was dissolved in chloroform and chromatographed on 5/40 μ silica gel (13 g) to give colorless crystals (0.19 g, 30%); mp 129-130°C. UV spectrum, λ_{max}, nm (log ε): 269.3 (4.11), 320.0 (4.30). IR spectrum, ν, cm^{-1}: 3100-2830, 1665, 1640 sh, 1624, 1550-1520, 1508. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.46 (3H, s, 4-CH_3); 2.54 (3H, s, 3-$COCH_3$); 2.59 (1H, t, $J_{1,2}$ = 15.0, H_a-1); 2.76 (1H, dd, J_1 = 15.0, J_2 = 4.0, H_e-1), 2.84 (1H, tt, J_1 = 13.0, $J_{2,3}$ = 3.5, H_e-7); 3.07 (1H, ddd, $J_{1,2}$ = 130, J_3 = 3.5, H_a-7); 3.38 (1H, ddd, $J_{1,2}$ = 13.0, J_3 = 3.5, H_a-6); 4.24 (1H, tt, J_1 = 13.0, $J_{2,3}$ = 3.5, H_e-6); 4.83 (1H, dd, J_1 = 15.0, J_2 = 4.0, H_a-11b); 7.14-7.37 (4H, m, H-8,9,10,11). ^{13}C NMR spectrum, δ, ppm: 19.17 (4-CH_3), 29.84 (C(7)), 32.69 (3-CO<u>C</u>H$_3$), 44.69 (C(1)), 45.29 (C(6)), 57.04 (C(11b)), 115.7 (C(3)), 125.94 (C(11)), 127.37 (C(9)), 127.47 (C(10)), 128.382 (C(8)), 133.48 (C(11a)), 134.24 (C(7a)), 168.24 (C(4)), 189.37 (C(12)), 200.81 (C(2)). Mass spectrum*, *m/z* (I_{rel}, %): 255 [M]$^{+\cdot}$ (64); 240 (100); 212 (49); 198 (5); 184 (12); 132 (40); 131 (10); 130 (30); 129 (12); 128 (14); 117 (24); 116 (15); 115 (27); 103 (13); 101 (11); 100 (21); 96 (11); 91 (13); 77 (14); 67 (36); 43 (28). Found, %: C 75.16, 75.12; H 6.65; N 5.38. $C_{16}H_{17}NO_2$. Calculated, %: C 75.27; H 6.71; N 5.49. M 255.32.

***rac*-3-Acetyl-9,10-dimethoxy-4-methyl-1,6,7,11b-tetrahydro-2H-pyrido[2,1-*a*]isoquinolin-2-one (3b).** A mixture of the isoquinoline **1b** (0.478 g, 2.5 mmol) and triacetylmethane **2** (0.366 g, 2.5 mmol) in ethanol (5 ml) was refluxed with a reflux condenser in a stream of argon for 3 h. The reaction mixture was then evaporated to dryness and the residue was dissolved in chloroform and chromatographed on 5/40μ silica gel (9 g) using a mixture of chloroform and methanol (29:1) to give the product **3b** (0.29 g, 36.8%) as colourless crystals; mp 178-179°C. UV spectrum, λ_{max}, nm (log ε): 202.7 (5.02), 231.2 (4.32), 272.3 (4.43), 319.6 (4.58); λ_{min}, nm (log ε): 221.9 (4.28), 247.3 (3.98), 288.1 (4.35). IR spectrum, ν, cm^{-1}: 3100-2830, 1680, 1633, 1540 sh. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.35 (3H, s, 4-CH_3); 2.44 (3H, s, 3-$COCH_3$); 2.47 (1H, t, $J_{1,2}$ =15.5, H_a-1); 2.63 (1H, dd, J_1 = 15.5, J_2 = 4.0, H_e-1); 2.75 (1H, tt, J_1 = 15.0, $J_{2,3}$ = 3.5, H_a-7); 2.92 (1H, dtd, J_1 = 15.0, J_2 = 13.0, J_3 = 3.5, H_e-7); 3.23 (1H, dtd, J_1 = 15.0, J_2 = 13.0, J_3 = 3.5, H_e-6) ; 3.78 (3H, s, OCH_3); 3.81 (3H, s, OCH_3); 4.16 (1H, tt, J_1 = 13.0, $J_{2,2}$ = 3.5, H_a-6); 4.66 (1H, dd, J_1 = 15.5, J_2 = 4.0, H_a-11b); 6.54 (1H, s, H-8); 6.60 (1H, s, H-11). ^{13}C NMR spectrum, δ, ppm: 19.12 (4-CH_3), 29.34 (C(7)), 32.72 (3-CO<u>C</u>H$_3$), 44.76 (C(1)), 45.73 (C(6)), 56.00 (C(11b)), 56.06 (10-OCH_3), 56.86 (9-OCH_3), 108.53 (C(11)), 110.94 (C(8)), 115.13 (C(3)), 125.52 (C(7a)), 126.05 (C(11a)), 148.25 (C(10)), 148.52 (C(9)), 168.21 (C(4)), 189.58 (C(2)), 200.89 (C(12)). Mass spectrum, *m/z* (I_{rel}, %): 315 [M]$^+$ (49), 300 (58); 272 (100); 256 (15); 192 (22); 191 (10); 190 (29); 189 (12); 177 (32); 176 (26); 150 (17); 146 (19); 133 (10); 131 (14); 117 (10); 115 (17); 103 (14); 95 (15); 91 (18); 77 (19); 67 (49); 65 (10); 44 (15); 43 (49). Found, %: C 68 44; H 6.62; N 4.34. $C_{18}H_{21}NO_4$. Calculated, %: C 68.55; H 6.71; N 4.44. M 315.37.

The authors express thanks to Academician A. A. Akhrem of the Belarus National Academy of Sciences for interest to our investigation and for useful discussion of the results.

* The M and ion peaks with intensity greater than 10% are quoted. Isotopic ion peaks are not given.

REFERENCES

1. A. A. Akhrem, O. V. Gulyakevich, and A. L. Mikhal'chuk, in: *Enamines in Organic Synthesis* [in Russian], Ural Section, Russian Academy of Sciences, Yekaterinburg (2001), p. 47.
2. A. A. Akhrem, O. V. Gulyakevich, and A. L. Mikhal'chuk, in: V. G. Kartsev and G. A. Tolstikov (editors), *Nitrogen Heterocycles and Alkaloids* [in Russian], Vol. 1, Iridium Press, Moscow (2001), p. 31.
3. D. B. Rubinov, M. V. Budnikova, T. A. Zheldakova, and A. L. Mikhal'chuk, in: V. G. Kartsev and G. A. Tolstikov (editors), *Nitrogen Heterocycles and Alkaloids* [in Russian], Vol. 1, Iridium Press, Moscow (2001), p. 503.
4. A. L. Mikhal'chuk, O. V. Gulyakevich, V. P. Peresada, A. M. Likhosherstov, and A. A. Akhrem, *Dokl. Russ. Acad. Sci*, **356**, 769 (1997).
5. O. V. Gulyakevich, A. L. Mikhal'chuk, and A. A. Akhrem, *Izv. Akad. Nauk, Ser. Khim.*, 1358 (1997).
6. A. L. Mikhal'chuk, O. V. Gulyakevich, and A. A. Akhrem, *Zh. Prikl. Khim.*, **71**, 645 (1998).
7. J. R. Huff, P. S. Anderson, J. J. Baldwin, B. V. Clineschmitt, J. P. Guare, V. J. Lotti, D. J. Pettibone, W. C. Randale, and J. P. Vacca, *J. Med. Chem.*, **28**, 1756 (1985).
8. E. S. Viri, I. Toth, G. T. Somogyi, L. Szabo, L. G. Harsing, Jr., and Cs. Szantay, *J. Med. Chem.*, **30**, 1355 (1987).
9. T. Kametani, S. A. Surgenor, and K. Fukumoto, *Heterocycles*, **14**, 303 (1980).
10. O. V. Gulyakevich, A. L. Mikhal'chuk, A. I. Verenich, D. B. Rubinov, A. A. Zenyuk, and A. A. Akhrem, in: *Enamines in Organic Synthesis* [in Russian], Ural Section, Russian Academy of Sciences, Yekaterinburg (1996), p. 111.
11. A. L. Mikhal'chuk, O. V. Gulyakevich, and A. A. Akhrem, *Khim. Geterotsikl. Soedin.*, 1239 (1993).
12. A. L. Mikhal'chuk, O. V. Gulyakevich, A. A. Zenyuk, Yu. V. Shklyaev, V. S. Shklyaev, and A. A. Akhrem, *Zh. Obshch. Khim.*, **63**, 1891 (1993).
13. A. A. Akhrem, B. B. Kuz'mitskii, F. A. Lakhvich, V. A. Khripach, and Yu. L. Zhuravkov, in: *The Chemistry and Biology of Immunoregulators* [in Russian], Zinatne, Riga (1985), p. 265.
14. A. A. Akhrem, F. A. Lakhvich, V. N. Pshenichnyi, O. V. Gulyakevich, I. I. Petrusevich, B. B. Kuz'mitskii, N. K. Kevra, G. I. Reutskaya, and I. A. Gorbacheva, Russian Patent 974800; *Buyl. Izobr.*, No. 39-40, 200 (1993).
15. A. A. Akhrem, O. V. Gulyakevich, G. N. Lysenko, A. L. Mikhal'chuk, and G. B. Tolstorozhev, *Zh. Prikl. Spektrosk.*, **68**, 427 (2001).
16. A. A. Akhrem, O. V. Gulyakevich, G. N. Lysenko, A. L. Mikhal'chuk, and G. B. Tolstorozhev, *Zh. Prikl. Spektrosk.*, **68**, 551 (2001).
17. N. A. Borisevich, O. V. Gulyakevich, A. L. Mikhal'chuk, and I. V. Skornyakov, *Zh. Prikl. Spektrosk.*, **70**, 28 (2003).
18. V. Z. Kurbako, *Dokl. Akad. Nauk Beloruss. SSR,* **34**, 716 (1990).
19. V. M. Uelli and T. R. Govindachari, *Organic Reactions* [Russian translation], Inostr. Lit., Vol. 6, Moscow (1953), p. 98.
20. A. Altomare, M. C. Burla, M. Camalli, G. Cascarano, C. Giacovazzo, A. Guagliardi, A. G. G. Moliterni, G. Polidori, and R. Spagna, *J. Appl. Crystallogr.*, **32**, 115 (1999).
21. G. M. Sheldrick, *Program for Crystal Structure Refinement*, Göttingen University, Göttingen, Germany (1997).