Chemistry of Heterocyclic Compounds, Vol. 37, No. 8, 2001

4a-ALKYL DERIVATIVES OF 5-OXO-4H-4a,5-DIHYDRO-INDENO[1,2-*b*]PYRIDINE

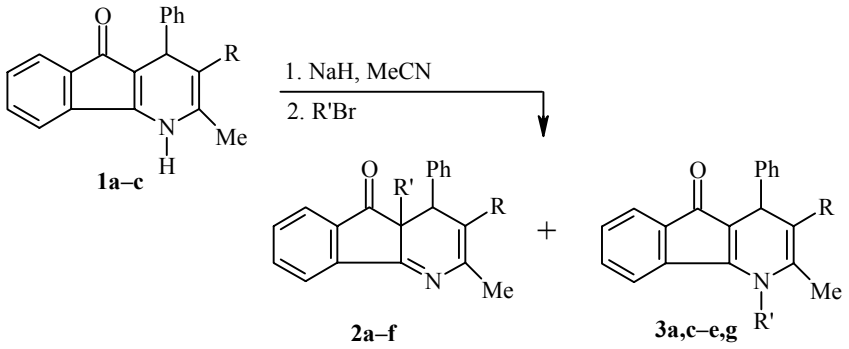
D. Muceniece, S. Stupnikova, and V. Lusis

High selectivity has been discovered for the C-alkylation of ambident anions of 5-oxo-1H-4,5-dihydroindeno[1,2-b]pyridines with ethyl bromoacetate, allyl, propargyl, and phenacyl bromides, which leads to the formation of the corresponding 4a-substituted 5-oxo-4H-4a,5-dihydroindeno[1,2-b]-pyridines in high yield.

Keywords: dihydroindeno[1,2-*b*]pyridines, alkylation.

The methylation of 5-oxo-1H-4,5-dihydroindeno[1,2-*b*]pyridines in alkaline medium leads to the formation of a mixture of the corresponding N- and $C_{(4a)}$-methyl derivatives [1]. The latter are used for the synthesis of angular substituted 1H-fluoren-9-ones [2].

In the present work a method is considered for preparatively obtaining 4a-substituted 5-oxoindeno-[1,2-*b*]pyridines containing an unsaturated or modified carbonyl function in the alkyl chain at $C_{(4a)}$. A variant of the alkylation method developed for the synthesis of $C_{(4a)}$-methyl derivatives proved to be unsuitable since the alkyl bromides used (allyl and propargyl bromides, ethyl bromoacetate, and phenacyl bromide) were hydrolyzed more rapidly by the excess of alkali than interact with the dihydroindenopyridine anion. Due to the comparatively slow course of the alkylation secondary oxidation of the anionic form of the dihydroindenopyridine also occurs by air, which makes it necessary to carry out the reaction in an inert atmosphere.



1a, **2a**, **3a** R = H; **1b**, **2b** R = COMe; **1c**, **2c–2f**, **3c–e**, **g** R = COOEt;
2a–c, **3a**,**c** R' = $CH_2CH{=}CH_2$; **2d**, **3d** R' = $CH_2C{\equiv}CH$; **2e**, **3e** R' = CH_2COOEt;
2f R' = CH_2COPh; **3g** R' = $CH{=}C{=}CH_2$

Latvian Institute of Organic Synthesis, Riga LV-1006; e-mail: lusis@osi.lv. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 8, pp. 1071-1075, August, 2001. Original article submitted August 25, 2000.

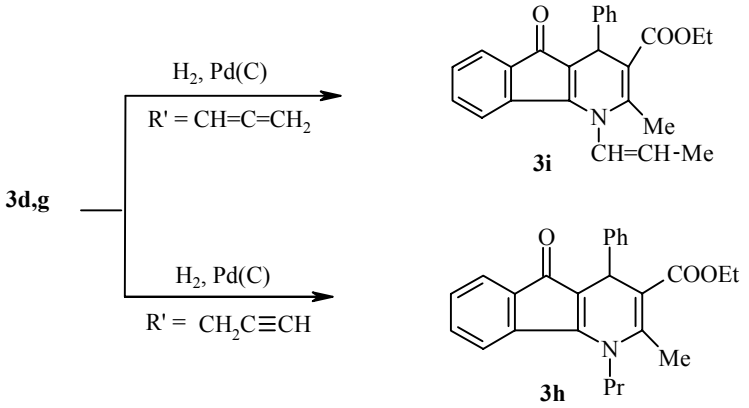
 0009-3122/01/3708-0982$25.00

The alkylation of dihydroindeno[1,2-*b*]pyridines in aprotic solvents leads to a mixture of N- and $C_{(4a)}$-alkyl derivatives. On using methyl iodide and KOH (to generate dihydroindenopyridine cation) the highest yield of 4a-methyl derivative was achieved in acetonitrile and the ratio of N- and C-alkylation products was 1 : 3.1 [1].

Using the bromoalkyl derivatives mentioned above as alkylating agents and carrying out the alkylation of 5-oxo-1H-4,5-dihydroindeno[1,2-*b*]pyridines **1** in an aprotic medium (acetonitrile, hexamethylphosphoramide) in the presence of NaH we unexpectedly observed a very high selectivity for C-alkylation. In acetonitrile the corresponding N-alkyl derivatives **3** are formed in insignificant yield (≤5%), which enables 4a-alkyldihydroindenopyridines **2** to be obtained in the pure state in yields of 70-80% by simple crystallization of the reaction products. Hexamethylphosphoramide, as might have been expected, increases the yield of N-alkyl derivatives, however the selectivity of C-alkylation remains high. The ratio of C- and N-alkylation products was within the range 4 : 1 to 10 : 1.

The alkylation of the anionic form of dihydroindenopyridines is in good agreement with the principle that soft alkylating agents interact preferentially with the softest center, i.e. with the $C_{(4a)}$ atom of the ambident anion. The alkylating agents used contain readily polarizable double bonds at the reaction center and may be assigned to the soft reagents. The hardness/softness of an alkylating agent is characterized by the hardness of both the alkyl residue and by the leaving group. In the cases being considered Br (harder than I) is such a group, consequently so sharp an increase in the selectivity of C-alkylation by the alkyl bromides compared with MeI, a typical soft alkylating agent, is unexpected. An additional contribution to the increase in selectivity is probably caused by replacement of the counterion (we used Na derivatives of the dihydroindenopyridines; previously potassium salts were used in the investigation of methylation). It is known that freely dissociated ambident ions and the ion pairs formed by them are capable of alkylation. Change of K to Na as counterion usually increases the fraction of ion pairs and Na is bonded in turn with the harder center of the ion pair. In the examples being considered the nitrogen atom is preferred which leads to screening of the latter.

On alkylating dihydroindenopyridine **1c** with propargyl bromide in hexamethylphosphoramide two products of N-substitution were isolated in addition to the predominant 4a-propargyl derivative **2c**. One of them was characterized as the N-propargyl derivative **3d** and the structure of N-allenyldihydroindenopyridine **3g** was established for the other. The formation of the latter indicates that in hexamethylphosphoramide the alkylation reaction is displaced into the S_N1/S_N2 boundary region. The formation of the N-allenyl derivative is the result of the rearrangement of propargyl cation into allenyl cation. As a result of catalytic hydrogenation (10% Pd/C, 2 atm H_2) the propargyl derivative **3d** was reduced to N-propyldihydroindenopyridine **3h** but the allenyl derivative **3g** only to the N-(1-propenyl)dihydroindenopyridine **3i**.



Reduction of the double bond of the N-propenyl substituent did not occur even on increasing the pressure to 5 atm. According to the ^{1}H NMR spectrum, the C=C bond of the N-propenyl fragment of compound **3i** has the *Z*-configuration. In the ^{1}H NMR spectra of all the 4a-substituted 5-oxo-4H-4,5-dihydroindeno[1,2-*b*]-pyridines **2** investigated, an allylic coupling was observed between the 4-H proton and the 2-CH_3 group. The similar interaction was absent in the spectra of the N-substituted isomers **3**.

EXPERIMENTAL

The ^{1}H NMR spectra were taken on a Bruker WH-90/DS (90 Mhz) spectrometer for solutions in $CDCl_3$ (internal standard was TMS), the IR spectra on a Perkin-Elmer 580B spectrometer in nujol, and the mass spectra on an AEI MS-50 instrument. A check on the course of reactions was effected by TLC (Silufol UV 254, EtOAc–hexane, 3 : 8).

The dihydroindenopyridines **1a,b** and **1c** were obtained by the known procedures of [3] and [4] respectively.

Alkylation of Derivatives of 4,5-Dihydro-1H-indeno[1,2-*b*]pyridines 1. General Procedure. A. A 60% suspension of NaH (0.16 g, 4.2 mmol) in toluene was added in an argon atmosphere with stirring and heating (50-60°C) to a solution of indenopyridine **1** (1.2 g, 3.5 mmol) in acetonitrile (150 ml). After evolution of hydrogen had ceased (15-30 min) the alkylating agent (7.0 mmol) was added to the dark blue solution and stirring was continued until disappearance of the blue color (0.5-1.0 h). The solution was filtered, the filtrate evaporated, and the residue rubbed with ethanol (3-5 ml). The yellow solid C-alkylation product **2** was isolated, and was recrystallized from ethanol (for yields see below).

B. Alkylation of indenopyridine (3.5 mmol) in hexamethylphosphoramide (6 ml) was carried out analogously. At the end of the reaction (about 1 h) ethanol (1-2 ml) and water (50 ml) were added sequentially to the reaction mixture. The precipitated solid, a mixture of the products of C- and N-alkylation **2** and **3**, was crystallized from ethanol and product **2** was isolated. The filtrate was evaporated and the N-substituted products **3** (for yields see below) were isolated by column chromatography (silica gel L 0.037-0.07 mm, EtOAc–hexane, 3 : 8). An additional quantity of the corresponding C-alkylated derivatives was also isolated (total yield of **2c** 78%, of **2d** 55%, and of **2e** 63%). On alkylating with propargyl bromide N-allenylindenopyridine **3g** was isolated in addition to the N- and C-propargyl derivatives **2d** and **3d**.

4a-Allyl-2-methyl-5-oxo-4-phenyl-4H-4a,5-dihydroindeno[1,2-*b*]pyridine (2a). Yield 78%; mp 95-96°C. IR spectrum, ν, cm^{-1}: 1720 (5-C=O). ^{1}H NMR spectrum, δ, ppm, *J* (Hz): 2.28 (3H, t, *J* = 1.0, 2-CH_3); 2.60 (2H, d, *J* = 7.4, 4a-CH_2); 3.69 (1H, m, ^3J = 6.6, ^5J = 1.0, 4-H); 4.94 (1H, m, =CH_2); 5.04 (1H, m, =CH_2); 5.48 (1H, m, ^3J = 6.6, ^4J = 1.0, 3-H); 5.33-5.89 (1H, m, -CH=); 7.02 (5H, s, 4-Ph); 7.37-7.87 (3H, m, 7-, 8-, and 9-H); 7.98-8.19 (1H, m, 6-H). Found, %: C 84.16; H 6.12; N 4.43. $C_{22}H_{19}NO$. Calculated, %: C 84.31; H 6.11; N 4.47.

3-Acetyl-4a-allyl-2-methyl-5-oxo-4-phenyl-4H-4a,5-dihydroindeno[1,2-*b*]pyridine (2b). Yield 77%; mp 113-114°C. IR spectrum, ν, cm^{-1}: 1723 (5-C=O); 1670 (3-C=O). ^{1}H NMR spectrum, δ, ppm, *J* (Hz): 2.18 (3H, s, $COCH_3$); 2.54 (2H, d, *J* = 6.8, 4a-CH_2); 2.65 (3H, d, *J* = 1.0, 2-CH_3); 4.23 (1H, q, *J* = 1.0, 4-H); 4.98 (1H, m, =CH_2); 5.09 (1H, m, =CH_2); 5.32-5.87 (1H, m, –CH=); 6.98 (5H, s, 4-Ph); 7.38-7.79 (3H, m, 7-, 8-, and 9-H); 7.94-8.16 (1H, m, 6-H). Found, %: C 80.97; H 5.96; N 3.89. $C_{24}H_{21}NO_2$. Calculated, %: C 81.10; H 5.96; N 3.94.

4a-Allyl-3-ethoxycarbonyl-2-methyl-5-oxo-4-phenyl-4H-4a,5-dihydroindeno[1,2-*b*]pyridine (2c). Yield 77%; mp 149-150°C. IR spectrum, ν, cm^{-1}: 1720 (5-C=O); 1694 (3-C=O). ^{1}H NMR spectrum, δ, ppm, *J* (Hz): 1.16 (3H, t, *J* = 6.9, $CH_2\underline{CH_3}$); 2.47 (2H, d, *J* = 6.8, 4a-CH_2); 2.63 (3H, d, *J* = 1.0, 2-CH_3); 4.05 (2H, q, *J* = 6.9, OCH_2); 4.16 (1H, q, *J* = 1.0, 4-H); 4.91 (1H, m, =CH_2); 5.07 (1H, m, =CH_2); 5.23-5.76 (1H, m, –CH=); 6.97 (5H, s, 4-Ph); 7.32-7.78 (3H, m, 7-, 8-, and 9-H); 8.03 (1H, m, 6-H). Found, %: C 77.89; H 6.04; N 3.59. $C_{25}H_{23}NO_3$. Calculated, %: C 77.90; H 6.01; N 3.63.

3-Ethoxycarbonyl-2-methyl-5-oxo-4-phenyl-4a-propargyl-4H-4a,5-dihydroindeno[1,2-*b*]pyridine (2d). Yield 70%; mp 195-197°C. IR spectrum, ν, cm^{-1}: 3258 (≡CH); 1720 (5-C=O); 1690 (3-C=O). ^{1}H NMR spectrum, δ, ppm, *J* (Hz): 1.15 (3H, t, *J* = 6.9, $CH_2\underline{CH_3}$); 1.75 (1H, t, *J* = 2.8, ≡CH); 2.67 (3H, d, ^5J = 1.0, 2-CH_3); 2.70 (2H, d, *J* = 2.8, 4a-CH_2); 4.11 (2H, q, *J* = 6.9, OCH_2); 4.33 (1H, q, *J* = 1.0, 4-H); 6.98 (5H, s, 4-Ph); 7.40-7.83 (3H, m, 7-, 8-, and 9-H); 7.98-8.15 (1H, m, 6-H). Found, %: C 78.29; H 5.52; N 3.60. $C_{25}H_{21}NO_3$. Calculated, %: C 78,31; H 5.52; N 3.65.

3-Ethoxycarbonyl-4a-ethoxycarbonylmethyl-2-methyl-5-oxo-4-phenyl-4H-4a,5-dihydroindeno-[1,2-*b*]pyridine (2e). Yield 77%; mp 134-135°C. IR spectrum, ν, cm^{-1}: 1732 (CH_2C=O); 1720 (5-C=O); 1698 (3-C=O). ^{1}H NMR spectrum, δ, ppm, *J* (Hz): 0.93 (3H, t, *J* = 7.0, CH_3 in R'); 1.18 (3H, t, *J* = 6.9, CH_3 in R); 2.69 (3H, d, *J* = 1.0, 2-CH_3); 3.00 (2H, s, 4a-CH_2); 3.84 (2H, q, *J* = 7.0, CH_2 in R'); 4.13 (2H, q, *J* = 6.9, CH_2 in R); 4.38 (1H, br. s, 4-H); 6.78-7.16 (5H, m, 4-Ph); 7.42-7.84 (3H, m, 7-, 8-, and 9-H); 8.00-8.22 (1H, m, 6-H). Found, %: C 72.34; H 5.89; N 3.16. $C_{26}H_{25}NO_5$. Calculated, %: C 72.37; H 5.84; N 3.25.

3-Ethoxycarbonyl-2-methyl-5-oxo-4a-phenacyl-4-phenyl-4H-4a,5-dihydroindeno[1,2-*b*]pyridine (2f). Yield 35%; mp 172-173°C. IR spectrum, ν, cm^{-1}: 1720 (5-C=O); 1690 (3-C=O); 1682 (COPh). ^{1}H NMR spectrum, δ, ppm, *J* (Hz): 1.20 (3H, t, *J* = 7.0, $CH_2\underline{CH_3}$); 2.63 (3H, d, *J* = 0.8, 2-CH_3); 3.77 (2H, s, CH_2CO); 4.11 (2H, q, *J* = 7.0, OCH_2); 4.39 (1H, br. s, 4-H); 6.64-7.14 (5H, m, 4-Ph); 7.31-7.89 (8H, m, 7-, 8-, 9-H, and COPh); 7.94-8.17 (1H, m, 6-H). Found, %: C 77.67; H 5.42; N 2.99. $C_{30}H_{25}NO_4$. Calculated, %: C 77.73; H 5.44; N 3.02.

1-Allyl-2-methyl-5-oxo-4-phenyl-1H-4,5-dihydroindeno[1,2-*b*]pyridine (3a). Yield 6%; mp 152-154°C. IR spectrum, ν, cm^{-1}: 1654 (br, C=O and C=C). ^{1}H NMR spectrum, δ, ppm, *J* (Hz): 2.01 (3H, t, *J* = 0.6, 2-CH_3); 4.55 (3H, m, 3-H and CH_2); 5.02 (1H, m, ^3J = 4.8, ^5J = 0.6, 4-H); 5.20-5.37 (1H, m, =CH_2); 5.43 (1H, m, =CH_2); 5.79-6.32 (1H, m, -CH=); 6.90-7.54 (9H, m, 6-, 7-, 8-, 9-H, and 4-Ph). Found, %: C 83.66; H 6.12; N 4.43. $C_{22}H_{19}NO$. Calculated, %: C 84.31; H 6.11; N 4.47.

1-Allyl-3-ethoxycarbonyl-2-methyl-5-oxo-4-phenyl-1H-4,5-dihydroindeno[1,2-*b*]pyridine (3c). Yield 8%; mp 134-135°C. IR spectrum, ν, cm^{-1}: 1705 and 1680 (C=O). ^{1}H NMR spectrum, δ, ppm, *J* (Hz): 1.10 (3H, t, *J* = 6.9, $CH_2\underline{CH_3}$); 2.53 (3H, s, 2-CH_3); 4.02 (2H, q, *J* = 6.9, OCH_2); 4.57 (2H, br. s, CH_2); 5.01 (1H, s, 4-H); 5.09-5.55 (2H, m, =CH_2); 5.78-6.29 (1H, m, –CH=); 6.93-7.40 (9H, m, 6-, 7-, 8-, 9-H, and 4-Ph). Found, %: C 77.82; H 6.21; N 3.37. $C_{25}H_{23}NO_3$. Calculated, %: C 77.90; H 6.01; N 3.63.

3-Ethoxycarbonyl-2-methyl-5-oxo-4-phenyl-1-propargyl-1H-4,5-dihydroindeno[1,2-*b*]pyridine (3d). Yield 8%; mp 156-158°C. IR spectrum, ν, cm^{-1}: 3278 (≡CH); 2118 (C≡C); 1680 (C=O). ^{1}H NMR spectrum, δ, ppm, *J* (Hz): 1.13 (3H, t, *J* = 6.9, $CH_2\underline{CH_3}$); 2.58 (1H, t, *J* = 2.0, ≡CH); 2.67 (3H, s, 2-CH_3); 4.04 (2H, q, *J* = 6.9, OCH_2); 4.67 (2H, t, *J* = 2.0, CH_2); 5.00 (1H, s, 4-H); 7.00-7.56 (9H, m, 6-, 7-, 8-, 9-H, and 4-Ph). Found, %: C 78.12; H 5.53; N 3.56. $C_{25}H_{21}NO_3$. Calculated, %: C 78.31; H 5.52; N 3.65.

3-Ethoxycarbonyl-1-ethoxycarbonylmethyl-2-methyl-5-oxo-4-phenyl-1H-4,5-dihydroindeno-[1,2-*b*]pyridine (3e). Yield 11%; mp 136-138°C. IR spectrum, ν, cm^{-1}: 1760 (CH_2C=O); 1680 and 1693 (C=O). ^{1}H NMR spectrum, δ, ppm, *J* (Hz): 1.08 (3H, t, *J* = 6.8, CH_3 in R'); 1.23 (3H, t, *J* = 6.9, CH_3 in R); 2.47 (3H, d, *J* = 0.8, 2-CH_3); 4.04 (2H, q, *J* = 6.9, CH_2 in R); 4.29 (2H, q, *J* = 6.8, CH_2 in R'); 4.69 (2H, s, CH_2); 4.96 (1H, br. s, 4-H); 6.83-7.43 (9H, m, 6-, 7-, 8-, 9-H, and 4-Ph). Found, %: C 72.33; H 5.84; N 3.23. $C_{26}H_{25}NO_5$. Calculated, %: C 72.37; H 5.84; N 3.25.

1-Allenyl-3-ethoxycarbonyl-2-methyl-5-oxo-4-phenyl-1H-4,5-dihydroindeno[1,2-*b*]pyridine (3g). Yield 10%; mp 115-116°C. IR spectrum, ν, cm^{-1}: 1700 and 1676 (C=O). ^{1}H NMR spectrum, δ, ppm, *J* (Hz): 1.13 (3H, t, *J* = 6.9, $CH_2\underline{CH_3}$); 2.56 (3H, s, 2-CH_3); 4.04 (2H, q, *J* = 6.9, OCH_2); 4.98 (1H, s, 4-H); 5.22 (1H, m, =CH_2); 5.29 (1H, m, =CH_2); 6.71 (1H, t, *J* = 6.0, -CH=); 7.02-7.47 (9H, m, 6-, 7-, 8-, 9-H, and 4-Ph). Found, %: C 78.29; H 5.52; N 3.60. $C_{25}H_{21}NO_3$. Calculated, %: C 78.31; H 5.52; N 3.65.

3-Ethoxycarbonyl-2-methyl-5-oxo-4-phenyl-1-propyl-1H-4,5-dihydroindeno[1,2-*b*]pyridine (3h) was obtained by the reduction of N-propargylindenopyridine **3d** in methanol in the presence of 10% Pd/C (hydrogen pressure 2.5 atm) for 2 h. Yield quantitative; mp 136-138°C. IR spectrum, ν, cm^{-1}: 1698 and 1675 (C=O). ^{1}H NMR spectrum, δ, ppm, *J* (Hz): 1.01 (3H, t, *J* = 7.1, CH_3 in Pr); 1.12 (3H, t, *J* = 6.9, CH_3 in Et); 1.81

(2H, sext., J = 7.1, CH_2 in Pr); 2.56 (3H, s, 2-CH_3); 3.97 (2H, t, J = 7.1, N-CH_2); 4.02 (2H, q, J = 6.9, CH_2 in Et); 5.01 (1H, s, 4-H); 6.91-7.47 (9H, m, 6-, 7-, 8-, 9-H and 4-Ph). Found, %: C 76.90; H 6.49; N 3.51. $C_{25}H_{25}NO_3$. Calculated, %: C 77.49; H 6.50; N 3.61. Mass spectrum, *m/z* (%): M^+ 387 (25), $[M-CH_3]^+$ 372 (100).

3-Ethoxycarbonyl-2-methyl-5-oxo-4-phenyl-1-(1-propenyl)-1H-4,5-dihydroindeno[1,2-*b*]pyridine (3i) was obtained analogously; mp 153-155°C. IR spectrum, ν, cm^{-1}: 1700 and 1678 (C=O). ^{1}H NMR spectrum, δ, ppm, J (Hz): 1.10 (3H, t, J = 6.9, $OCH_2\underline{CH_3}$); 1.67 (3H, dd, ^3J = 6.8, ^4J = 1.6, =CH–$\underline{CH_3}$); 2.44 (3H, s, 2-CH_3); 4.04 (2H, q, J = 6.9, OCH_2); 5.04 (1H, s, 4-H); 5.98 (1H, quint., J = 6.8, =$\underline{CH}$–CH_3); 6.56 (1H, dq, ^3J = 6.8, ^4J = 1.6, N–CH); 7.00-7.53 (9H, m, 6-, 7-, 8-, 9-H, and 4-Ph). Found, %: C 77.72; H 6.23; N 3.35. $C_{25}H_{23}NO_3$. Calculated, %: C 77.90; H 6.01; N 3.63. Mass spectrum, *m/z* (%): M^+ 385 (40), $[M-CH_3]^+$ 370 (100).

REFERENCES

1. V. K. Lusis, D. Kh. Mutsenietse, A. Z. Zandersons, I. B. Mazheika, and G. Ya. Dubur, *Khim. Geterotsikl. Soedin.*, 393 (1984).
2. V. Lusis, D. Muceniece, and G. Duburs, *Tetrahedron*, **42**, 1548 (1986).
3. I. Petrov, I. Saper, and B. Sturgeon, *J. Chem. Soc.*, 2134 (1949).
4. E. Ya. Ozola and G. Ya. Vanag, *Khim. Geterotsikl. Soedin.*, 103 (1969).