1,2,4-TRIAZINES IN ORGANIC SYNTHESIS. 9*. SYNTHESIS OF 3-(3-ETHYLINDOL-2-YL)-5,6,7,8-TETRAHYDROISOQUINOLINE USING THE FISCHER REACTION UNDER THE USUAL CONDITIONS AND WITH MICROWAVE IRRADIATION*[2]

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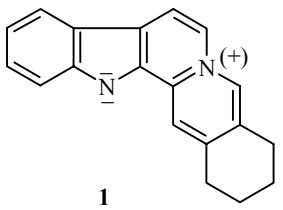
The nucleophilic substitution of hydrogen in 3-methylthio-1,2,4-triazine by the carbanions of nitrobutane and 4-nitrobut-1-ene gave oximes, the selective fission of which using sodium dithionite gave ketones in the case of compounds with a saturated carbon chain. Ketones in Diels-Alder reaction with 1-pyrrolidinocyclohex-1-ene gave 3-acyl-1-methylthio-5,6,7,8-tetrahydroisoquinolines. Phenylhydrazones of the compounds obtained underwent Fischer reaction under usual conditions and also when using microwave irradiation on a solid support. The final 3-(3-ethylindol-2-yl)-5,6,7,8-tetrahydroisoquinoline was obtained via reductive desulfuration using Raney nickel in ethanol.

Keywords: 3-acyl-1-methylthio-5,6,7,8-tetrahydroisoquinoline, 3-(3-ethylindol-2-yl)-5,6,7,8-tetrahydroisoquinoline, 1,2,4-triazines, Diels-Alder reaction, Fischer reaction, microwave irradiation.

The zwitterionic pentacyclic alkaloid sempervirine (**1**) shows antitumor activity [2-4]. It is contained in trace amounts in the plant material *Gelsemium sempervirens*. Since 1949 systematic investigations have been carried out on the complete synthesis of this alkaloid using various strategies for constructing molecule **1** [5].

The synthesis of sempervirine from (3-indol-2-yl)-5,6,7,8-tetrahydroisoquinoline (**2a**) is elaborated in studies [6, 7].



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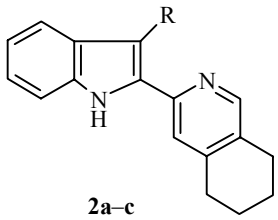


2a–c

2 a R = H, **b** R = Et, **c** R = CH=CH$_2$

* For Communication 8 see [1].

*[2] Respectfully dedicated to Professor L. I. Belen'kii.

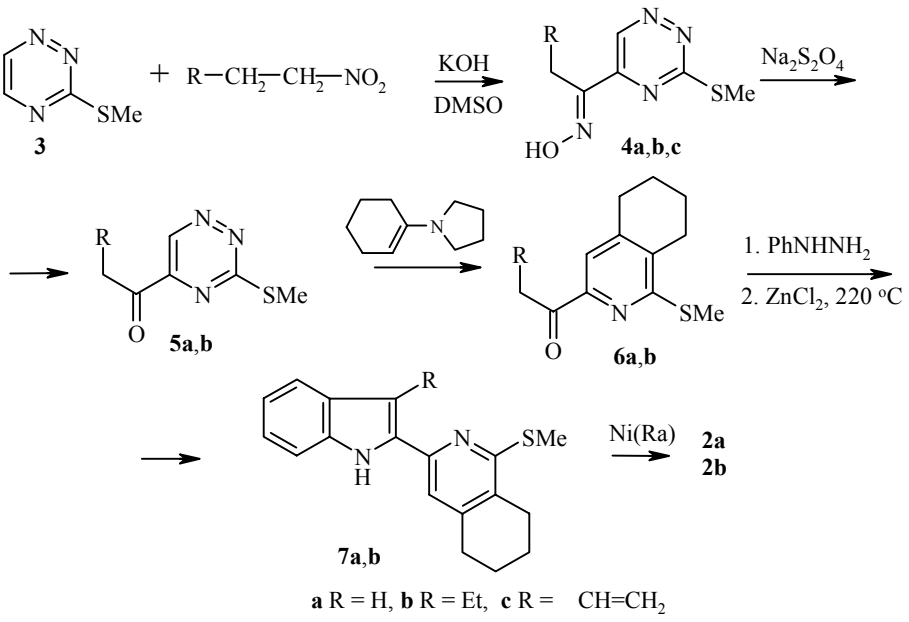
Podlasie University, Siedlce 08-110, Poland; e-mail: tlip@ap.siedlce.pl. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 256-261, February, 2001. Original article submitted October 5, 1999; revision submitted April 30, 2000.

0009-3122/01/3702-0231$25.00

The multistage methods for the synthesis of synthon **2a** and its conversion to sempervirine, are difficult to realize and occur in low yield and this stimulates a novel investigation in this respect. We have reported [8] a new method for the synthesis of compound **2a** from 3-methylthio-1,2,4-triazine (**3**). In recent times a modification of the key step (the Fischer synthesis) has been carried out, the basis of which is the use of microwave irradiation [9]. In our work starting with the synthesis of some new potential synthons of sempervirine (substituted analogs of compound **2a** having ethyl (**2b**) or vinyl (**2c**) group in position 3 of the indole fragment) the results of our investigations are presented which broaden the use of the methods developed already. The R = Et and $CH=CH_2$ substituents referred to can then form the missing central unit of the alkaloid **1** molecule.

The reaction scheme involving the original methods of synthesis of compounds **2a**, **2b**, and **2c** is given in Scheme 1.

Scheme 1

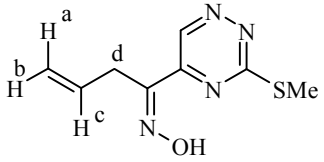


a R = H, **b** R = Et, **c** R = $CH=CH_2$

The first step is the nucleophilic substitution of hydrogen in the 5 position of 3-methylthio-1,2,4-triazine **3** by the nitroalkane carbanion and the formation of oximes **4a-c** [10]. The process can be considered as a specific acylation of the 1,2,4-triazine system in those examples where the obtained oximes can selectively undergo fission to ketones. The indole derivative **2a** unsubstituted in the 3 position was obtained using nitroethane [8].

Compound **2b** is formed via the reaction of compound **3** with nitrobutane (R = Et). It was identified [11] as the reduction product of sempervirine using Raney nickel and also discovered as one of the dehydration products of yohimbine when using selenium [12].

In order to prepare 3-(3-vinylindol-2-yl)-5,6,7,8-tetrahydroisoquinoline (**2c**) as a further suitable synthon in the synthesis of sempervirine, 4-nitrobut-1-ene was used in the first step of the reaction. By comparing the reactions of 3-methylthio-1,2,4-triazine with three different nitro compounds it can be seen that oximes with a saturated carbon atom chain **4a** and **4b** are obtained in good yield (70-75 %). Oxime of the allyl derivative **4c** was prepared in 35-40% yield.



4c

The transfer from oximes **4a-c** to ketones **5a-c** was brought about under hydrolysis conditions at room temperature using an aqueous-dioxane solution of $Na_2S_2O_4$ [10]. The 1,2,4-triazine system was sensitive to other methods of oxime fission, especially acidic. Hence use of the conditions that we have developed for the synthesis provided the desired reaction. Propyl 3-(methylthio)-1,2,4-triazin-5-yl ketone (**5b**) was obtained in 51% yield [13], which is only a little less than the yield of the methyl-substituted compound **5a** (64%) [8]. However, under the same conditions, ketone with the unsaturated carbon chain (**5c**) was not obtained. Under the reaction conditions, oxime **4c** undergoes complete degradation to low-molecular compounds which were not identified and further investigations were carried out only with compounds **5a** and **5b**.

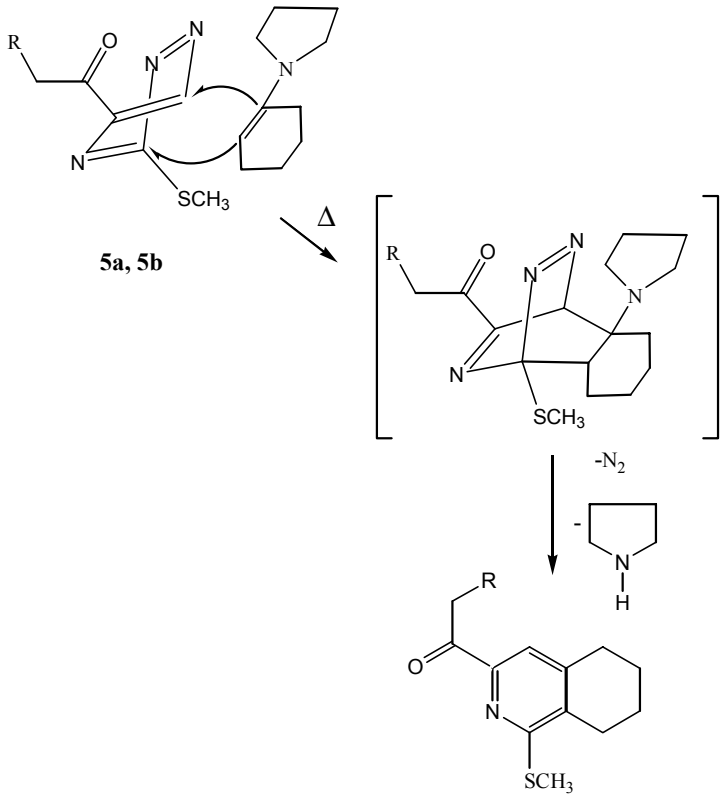
The next step in the synthesis is the Diels-Alder reaction between the heterocyclic azadienes **5a,b** and 1-pyrrolidinocyclohex-1-ene [13]. Under the reaction conditions (refluxing in dioxane) the process does not stop at the stage of formation of the cycloadduct but proceeds further with liberation of nitrogen and pyrrolidine to give the aromatic derivatives **6a,b**. As a result of the reaction the 1,2,4-triazine ring is converted to 5,6,7,8-tetrahydroisoquinoline derivative with retention of the functional groups in the heterocycle. The ease of formation of the transition complex and then the adduct is well rationalized in terms of the theory of compensation of the electric field in the molecule [14, 15].

Acylpyridines **6a,b** are converted to the corresponding phenylhydrazones and are introduced into the Fischer reaction with the aim of preparing the indole-substituted tetrahydroisoquinolines **7a** [8, 9] and **7b**. Literature data [6] pointing to the need to carry out the Fischer reaction under drastic temperature conditions were fully confirmed. Under classical conditions, heating a mixture of phenylhydrazone with excess solid anhydrous zinc chloride at a temperature above 200°C in methylnaphthalene [8] gave compounds **7a,b** but the yield did not exceed 25-35%. The reason for the modest yield is the decomposition of the reagents and reaction products due to the continuous heating at high temperature.

The subject of our investigation [9] was the modification of the Fischer reaction conditions which lead to the pyridyl-substituted indole systems. Microwave irradiation of phenylhydrazone, coated on K10 montmorillonite modified by zinc chloride, led to the conversion to the indole derivative during a three minute exposure to microwaves at 200-220°C. The yield of indoles was 50-65%. A longer irradiation at high temperature led to lowering of the yield due to decomposition processes and, with a shorter irradiation, the starting compounds did not fully undergo the reaction.

Compounds **7a** and **7b** possess a methylthio group which is absent in the natural sempervirine. Fission and removal of this group was brought about [8] using the system $NiCl_2$ + $NaBH_4$ in aqueous ethanol solution. In subsequent investigations it was found that it is more convenient to use excess Raney nickel in ethanol at room temperature. The yield from desulfuration using this method is 60-65%. 3-(Indol-2-yl)-5,6,7,8-tetrahydroisoquinoline **2a** prepared following the developed method was identical to compounds obtained by other methods [6, 7]. 3-(Ethylindol-2-yl)-5,6,7,8-tetrahydroisoquinoline (**2b**) has been obtained by us for the first time using the reported reaction. For this compound, designated tetrahydroisoyobirine, which has been found previously amongst the products of partial decomposition of sempervirine [11] and yohimbine [12], little analytical data have been published. The spectroscopic investigation of compound **2b** obtained by us fully confirmed its structure.

Scheme 2



Hence the reported method can be regarded as general method for the synthesis of indole derivatives which are linked to a pyridine system and which have an alkyl chain at position 3.

EXPERIMENTAL

Melting points were measured on a Büchi apparatus and are not corrected. IR spectra were taken on a Nicolet FTIR 670 instrument and mass spectra – on an AMD-604 spectrometer. ^{1}H NMR spectra were recorded on a Varian Gemini spectrometer (200 MHz) with TMS as internal standard and $CDCl_3$ as solvent. The Fischer reaction under microwave irradiation conditions was carried out in a Prolabo Synthewave 402 reactor (300 W) with computer control of the programming and measurement of the temperature during the reaction (IR detector). For the column chromatography Kieselgel 40 (0.063-0.200 mm) was used activated by heating in vacuo at 1.3-2.0 kPa at 150°C for 2 h. Monitoring of the course of the reaction and the column chromatography was carried out on Kieselgel 60F-254 plates and visualized using UV light. Montmorillonite K10, modified with zinc chloride, was prepared according to the previously reported method [9]. The starting 3-methylthio-1,2,4-triazine (**3**) was obtained from hydrogen iodide, S-methylthiosemicarbazide, and glyoxal according to the method reported in the literature [16]. The synthesis of compounds **2a, 4a-7a** has been described in a more recent publication [8]. 1-Nitrobutene was a commercial reagent from Aldrich. Compounds **4b-6b** were obtained by the method described by us [13]. 4-Nitrobut-1-ene was prepared from 4-bromobut-1-ene (Aldrich) by the method reported in [17].

Allyl 3-(methylthio)-1,2,4-triazin-5-yl ketoxime (4c). 3-Methylthio-1,2,4-triazine **3** (0.26 g, 2 mmol) and 4-nitrobut-1-ene (0.41g, 4 mmol) in dry DMSO (1.5 ml) were added to suspension of potassium hydroxide (0.8 g) in dry DMSO (1 ml). After the reaction had finished (monitored by TLC) the mixture was poured into ice water (30 ml) and neutralized with acetic acid. The formed yellow precipitate was filtered off, washed with cold water, dried in air, and then in a vacuum desiccator to give chromatographically pure compound **4c** (0.17 g, 40%) with mp 118-120°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm, *J* (Hz): 2.69 (3H, s, SCH_3); 3.67 (2H, dt, d-H, J_{cd} = 6.4, J_{ad} = J_{cd} = 1.5); 5.09 (1H, dq, b-H, J_{bc} = 10.1, J_{ab} = J_{bd} = 1.5); 5.16 (1H, dq, a-H, J_{ab} = J_{ad} = 1.5); 5.91 (1H, ddt, c-H, J_{ac} = 17.3, J_{bc} = 10.1, J_{cd} = 1.5); 8.75 (1H, s, OH); 9.44 (1H, s, 6-H). Found: M^+ 210.05753. $C_8H_{10}N_4OS$. Calculated: M 210.05896.

3-Butyryl-1-methylthio-5,6,7,8-tetrahydroisoquinoline Phenylhydrazone. Phenylhydrazine (0.37 g, 3.5 mmol) and 5 drops (about 0.06 g) of glacial acetic acid were added to ketone **6b** (0.8 g, 3.2 mmol) in anhydrous ethanol (10 ml). The mixture was heated to reflux for 15 min. After cooling to -5°C the precipitate was filtered off, washed with cold ethanol, and dried to give a compound (1.05 g, 96%) with mp 125-126°C. This was used without additional purification for the Fischer indolization process.

3-Ethyl-2-(1-methylthio-5,6,7,8-tetrahydroisoquinolin-3-yl)indole (7b). Fischer Reaction Under Conventional Conditions. 1-Methylnaphthalene (3 ml) was added to a mixture of the obtained in previous stage phenylhydrazone (0.34 g, 1 mmol) and freshly calcined zinc chloride (2.7 g, 20 mmol) and then heated in stream of argon to 200-210°C for 3 h. After cooling the solvent was decanted. The mass remaining was treated with 10% solution of sodium bicarbonate (10 ml) and toluene (20 ml), heated to reflux with vigorous stirring for 1 h, cooled, the toluene layer separated, and the aqueous layer extracted with toluene (4 × 20 ml). The toluene extracts were combined, concentrated in vacuo, and purified on chromatography column (300 × 19 mm) using chloroform-petroleum ether (1: 2) as eluent to give indole **7b** (0.1 g, 32%); mp 36°C. IR spectrum: 3460 cm^{-1} (NH). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm, *J* (Hz): 1.35 (3H, t, *J* = 7.5, $CH_2\underline{CH_3}$); 1.72-1.97 (4H, m, 6-H, 7-H isoquinoline); 2.61 (2H, t, *J* = 6.0, 5-H isoquinoline); 2.86 (3H, s, SCH_3); 2.80 (2H, t, *J* = 5.7, 8-H isoquinoline); 3.10 (2H, q, *J* = 7.5, $\underline{CH_2}CH_3$); 7.06-7.25 (3H, m, 4-H isoquinoline, 5-H, 6-H indole); 7.35-7.46 (1H, m, 7-H indole); 7.60-7.69 (1H, m, 4-H indole); 9.16 (1H, s, NH). Mass spectrum, *m/z* (*I*, %): 322 (97.7) M^+, 307 (100). Found: M^+ 322.15036. $C_{20}H_{22}N_2S$. Calculated: M 322.15125.

3-Ethyl-2-(1-methylthio-5,6,7,8-tetrahydroisoquinolin-3-yl)indole (7b). Fischer Reaction Under Microwave Irradiation Conditions. Montmorillonite K10 (0.25 g) modified with zinc chloride (0.012 g, 0.09 mmol) prepared as in the report [9] was added to 3-butyryl-1-methylthio-5,6,7,8-tetrahydroisoquinoline phenylhydrazone (0.23 g, 0.7 mmol) dissolved in anhydrous chloroform (5 ml), vigorously stirred, and chloroform distilled off in vacuo. The residue was transferred to a flat-bottomed flask (3 ml, Pyrex glass) and placed in a reactor for microwave irradiation. A 10 minute irradiation was programmed with a maximum temperature of 210°C, optimizing the temperature control by varying the power of the irradiation set to 100%. Increase of the temperature to 200°C at 300 W power occurs over 4-5 min and irradiation was continued at this temperature for 3 min before the process was stopped. The mixture was extracted with ether (5 × 15 ml). The solvent was distilled off and the residue was purified on a chromatography column under conditions similar to those in the previous experiment. Compound **7b** was obtained (0.14 g, 65%). The spectroscopic data coincided with those for the compound **7b** prepared previously.

3-(3-Ethylindol-2-yl)-5,6,7,8-tetrahydroisoquinoline (2b). Raney nickel (W-2, ~0.75 g) in anhydrous ethanol was added with stirring to solution of compound **7b** (0.1 g, 0.3 mmol) in anhydrous ethanol (10 ml) at room temperature. After 10 min stirring the reaction mixture was filtered and the solvent distilled off in vacuo to give 0.05 g (63%) of residue; mp 160-163°C. After crystallization from ethanol the mp was 168-169°C (lit. [11]: 165.5-167.5). IR spectrum: 3420 cm^{-1} (NH). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm, *J* (Hz): 1.36 (3H, t, *J* = 7.5, $CH_2\underline{CH_3}$); 1.72-1.92 (4H, m, 6-H, 7-H isoquinoline); 2.60 (2H, t, *J* = 6.0, 5-H isoquinoline); 2.75 (2H, t, *J* = 5.8, 8-H isoquinoline); 3.09 (2H, q, *J* = 7.5, $\underline{CH_2}CH_3$); 7.02-7.65 (5H, m, 3-H isoquinoline, 4-H, 5-H, 6-H, 7-H indole); 8.30 (1H, s, 1-H isoquinoline); 9.96 (1H, s, NH). Found, %: C 82.40; H 7.38; N 9.95. $C_{19}H_{20}N_2$. Calculated, %: C 82.56; H 7.30; N 10.14.

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