Chemistry of Heterocyclic Compounds, Vol. 44, No. 12, 2008

HETEROCYCLIZATION OF N-PROPENYL-SUBSTITUTED PHENOTHIAZINES AND PHENOXAZINES USING ELECTROPHILES IN AN ANHYDROUS MEDIUM

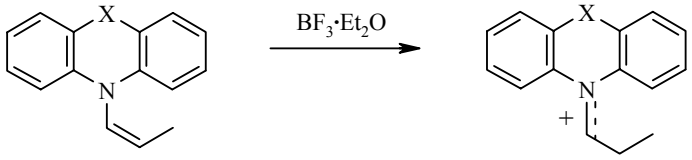
E. E. Sirotkina[1], A. I. Khlebnikov[2], and O. A. Napilkova[2]

10-Propenylphenothiazine reacts with a catalytic amount of $BF_3 \cdot Et_2O$ in dry ethyl acetate via intramolecular heterocyclization of an intermediate dimeric cation to give mainly 1-ethyl-2-methyl-3-(phenothiazin-10-yl)-2,3-dihydro-1H-pyrido[3,2,1-k,l]phenothiazine and a minor product through fission of phenothiazine which is 1-ethyl-2-methyl-1H-pyrido[3,2,1-k,l]phenothiazine. Under similar conditions 10-propenylphenoxazine gave an oligomer (degree of polymerization 4.4) and the minor product 1-ethyl-2-methyl-1H-pyrido[3,2,1-k,l]phenoxazine likely formed similarly to the phenothiazine analog from the corresponding product of intramolecular heterocyclization (the latter not being observed in the reaction mixture).

Keywords: 1H-pyrido[3,2,1-*k,l*]phenoxazines, 1H-pyrido[3,2,1-*k,l*]phenothiazines, propenyl-substituted, phenoxazine, phenothiazine, heterocyclization, electrophilic catalysts.

The high interest in the chemistry of phenothiazine and phenoxazine is due in many ways to the biological activity of their derivatives [1-5]. We have previously reported the prototropic isomerization of N-allyl derivatives of phenothiazine and phenoxazine to give *cis*-10-propenylphenothiazine (**1**) [6] and *cis*-10-propenylphenoxazine (**2**) [7]. In the case of the acid hydrolysis of these compounds it has been shown [8] that they demonstrate an increased activity with relation to electrophilic reagents while the initial position of attack of a proton to form the carbenium-immonium intermediate of type **A** is the α-carbon atom of the substituent (Scheme 1).

Scheme 1



1, 2 **A1, A2**

1, A1 X = S, **2, A2** X = O

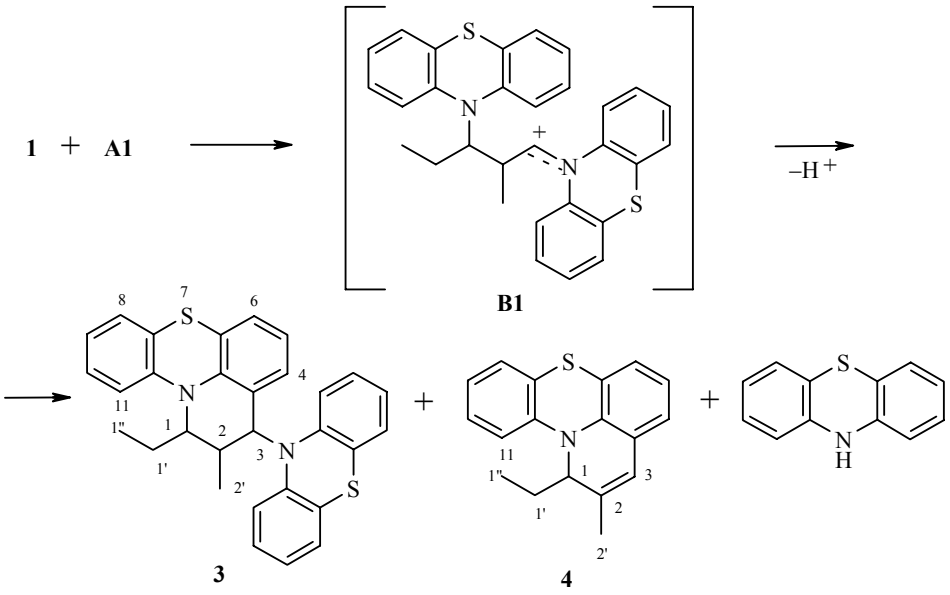
* Dedicated to Academician of the Russian Academy of Sciences B. A. Trofimov on his jubilee.

[1]Institute of Petroleum Chemistry, Siberian Branch of the Russian Academy of Sciences, Tomsk 634021, Russia; e-mail: see@ipc.tsc.ru. [2]I. I. Polzunov Altai State Technical University, Barnaul 656038, Russia; e-mail: aikhl@chem.org.ru. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 12, pp. 1855-1860, December, 2008. Original article submitted May 23, 2008.

Stabilization of ion **A** is achieved by conjugation of the vacant *p*-orbital with the unshared electron pair of the nitrogen atom, the stabilization being more efficient for ion **A1** than for ion **A2** [9]. The intermediates **A** are readily hydrolyzed in aqueous media to the corresponding heterocycle and propionaldehyde [8]. In this work we have studied the conversion of compounds **1, 2** with the electrophilic catalyst BF3·Et2O in anhydrous ethyl acetate.

Through an initial TLC investigation of the action of an electrophilic catalyst (H_2SO_4, P_2O_5, $BF_3{\cdot}Et_2O$) on compound **1** in various solvents (toluene, ethyl acetate, DMF, methylene chloride) it was found that the process route depended markedly on the amount of the catalyst. High concentrations of catalyst (2×10^{-2} to 0.1 molar) basically gives phenothiazine and tarry products. Direction of the course of the process proved possible by the use of $BF_3{\cdot}Et_2O$ in concentrations around 10^{-3} molar in an anhydrous solvent. The main reaction product of propenylphenothiazine **1** is 1-ethyl-2-methyl-3-(phenothiazin-10-yl)-2,3-dihydro-1H-pyrido-[3,2,1-*k,l*]phenothiazine (**3**), evidently formed through an intramolecular alkylation in the intermediate dimer cation **B1** according to Scheme 2. A similar reaction has been reported before for *cis*-9-propenylcarbazole [1].

Scheme 2



For a targeted synthesis of compound **3** the most convenient solvent is ethyl acetate freshly distilled from P_2O_5. This simplifies the separation of product **3** which is virtually insoluble in ethyl acetate and can be filtered from the reaction mass.

The reaction occurs readily at room temperature leading to a 66-75% yield of product **3** after 2-3 h.

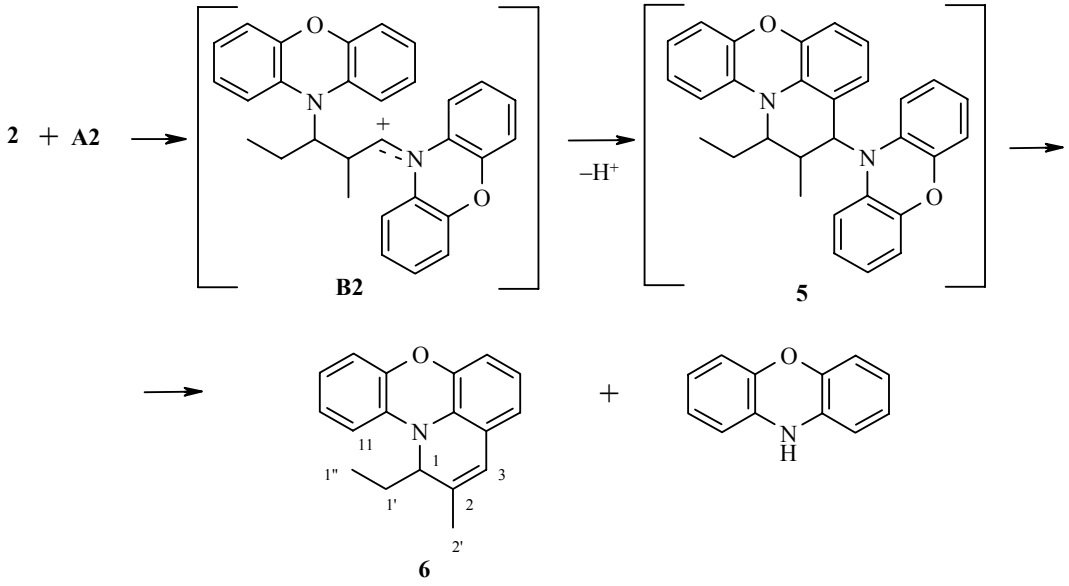
According to TLC data the reaction mixture shows compound **3**, phenothiazine, and tarry products, and also the previously unknown 1-ethyl-2-methyl-1H-pyrido[3,2,1-*k,l*]phenothiazine (**4**) having an R_f close to that of the starting propenylphenothiazine. The oily product **4** was separated by a column chromatographic method. The tetracyclic derivative **4** is evidently formed from **3** *via* fission of phenothiazine. The presence of the latter in the reaction mixture agrees with this proposal.

The formation of product **4** was confirmed by us by independent experiments studying the thermal and catalytic ($BF_3{\cdot}Et_2O$) decomposition of compound **3**. According to TLC data the reaction mixtures have the same composition as in the condensation of the propenylphenothiazine **1**. The composition and structure of compounds **3** and **4** are confirmed by the results of elemental analysis, IR spectroscopic data (for compound **3**), and also from their ^1H and ^{13}C NMR spectra (see Experimental section).

It is obviously that compounds **3** and **4** are convenient intermediate products for the preparation of various pyridophenothiazines. Promising use has been shown for the pyridophenothiazines **3, 4** in increasing the thermooxidative stability of lubricating oils and as polyolefine stabilizers [11].

By contrast with compound **1** the product **5** (analog of compound **3**) is not found in the action of $BF_3 \cdot Et_2O$ in dry ethyl acetate on the propenylphenoxazine **2** but there occurs a rather ready oligomerization of monomer **2** at the double bond. A thermostable oligomer with a softening temperature of 180-200ºC was obtained in 23% yield at 0ºC after 18 min. Increasing the temperature up to 60ºC and continuing the process for 80 h did not significantly affect the yield of the oligomer product. The molecular weight of the oligomer was determined by the Rast method (in camphor) as 980 g/mol which corresponds to a mean degree of polymerisation of 4.4. The IR spectrum of the oligomer shows the absence of absorption bands for C=C and N–H bonds and the presence of bands at 1610 and 740 cm^{-1} assigned respectively to stretching vibrations of the aromatic rings and to deformation of the 1,2-disubstituted benzene ring. On this basis it can be confirmed that oligomerization of the 10-propenylphenoxazine **2** is not complicated by rearrangement of the cation arising as happens in the case of 9-isobutenylcarbazole or 9-styrylcarbazole [12]. The oligomer obtained forms films which have good adhesion to glass and metals and can be used in electrophotography since it is known that polyalkenyl-phenoxazines are organic photosemiconductors [13, 14].

Scheme 3



The oligomer was separated *via* precipitation from the reaction mixture with ethyl alcohol and subsequent filtration. Column chromatography of the filtrate on silica gel also gave a 13.5% yield of the 1-ethyl-2-methyl-1H-pyrido[3,2,1-*k,l*]phenoxazine (**6**). It is likely that, along with the oligomerization of monomer **2** similarly to compound **1**, there occurs an intramolecular alkylation of the dimer cation **B2** arising to give the intermediate 1-ethyl-2-methyl-3-(phenoxazin-10-yl)-2,3-dihydro-1H-pyrido[3,2,1-*k,l*]phenoxazine (**5**). Separation of phenoxazine under the reaction conditions gives compound **6** (Scheme 3). The presence of unsubstituted phenoxazine in the reaction mixture is shown by TLC. The relative ease of formation of product **6** is a feature of the oligomerization of the alkenylphenoxazine **2** since, in the series of carbazole [10] and phenothiazine dimers, similar to compound **5**, are stable, high-melting materials.

The composition and structure of compound **6** are confirmed by the results of elemental analysis and also by their IR, ^1H and ^{13}C NMR spectra, similarly to that of compound **4**.

EXPERIMENTAL

IR spectra were recorded on an IRS-29 spectrophotometer. ^{1}H NMR spectra were taken on a Bruker AV300 (300 MHz) instrument and ^{13}C NMR spectra on a WP-200 (50 MHz) under conditions of complete suppression of ^{1}H–^{13}C spin-spin interactions with HMDS (δ 0.05 ppm) as internal standard. TLC was carried out using Silufol UV-254 plates with eluent hexane-ether (12:1) for the phenothiazine compounds or hexane–benzene (5:3) for the phenoxazine compounds.

1-Ethyl-2-methyl-3-(phenothiazin-10-yl)-2,3-dihydro-1H-pyrido[3,2,1-*k,l*]phenothiazine (3). A solution (0.5 ml) of $BF_3 \cdot Et_2O$ (0.15 mmol in ethyl acetate) was added to a solution of compound **1** (12 g, 30 mmol) in anhydrous ethyl acetate (50 ml). The reaction mixture was held for 2 h 18 min at room temperature. The precipitate formed was filtered off and washed successively with ethyl acetate (10 ml) and ethanol (50 ml) to give compound **3** (8.4 g, 70%) as white crystals with mp 210-212ºC. Compound **3** is readily soluble in chloroform and benzene and poorly in ethyl acetate, acetone, and hexane. IR spectrum (KBr), ν, cm^{-1}: 760 (1,2-disubstituted benzene ring), and 790 and 740 (1,2,3-trisubstituted benzene ring). NH group absorption bands were absent. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.08 (3H, t, *J* = 8, $C\underline{H}_3CH_2$); 1.28 (3H, d, *J* = 7, CH_3); 1.60 (2H, m, $CH_3C\underline{H}_2$); 2.70 (1H, m, H-2); 4.10 (1H, m, H-1); 4.96 (1H, d, *J* = 5, H-3); 6.60-6.70 (15H, m, H_{arom}). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 11.53 (C-1"); 15.95 (C-2'); 20.80 (C-1'); 29.77 (C-2); 61.33 (C-1); 63.64 (C-3); 114.19 (C-11); 126.29 (C-3'). The signals for the remaining C atoms of the phenothiazine fragments occurred in the region 122-147 ppm. Found, %: C 75.65; H 5.69; N 5.51; S 13.01. $C_{30}H_{26}N_2S_2$. Calculated, %: C 75.28; H 5.47; N 5.85; S 13.40.

1-Ethyl-2-methyl-1H-pyrido[3,2,1-*k,l*]phenothiazine (4). After distillation of the solvent from the filtrate from the synthesis of compound **3** the residue was loaded onto an L 100/160 silica gel column (70×2 cm) and eluted with a mixture of hexane and ether (2:1) to give compound **4** (0.63 g, 9%) with mp 69-70ºC (hexane). ^{1}H NMR spectrum (acetone-d_6), δ, ppm (*J*, Hz): 0.96 (3H, t, *J* = 8, $C\underline{H}_3CH_2$); 1.60 (2H, m, $CH_3C\underline{H}_2$); 2.04 (3H, s, CH_3); 4.54 (1H, dd, *J* = 5, *J* = 3, H-1); 6.20 (1H, s, H-3); 6.60-6.70 (7H, m, H_{arom}). ^{13}C NMR spectrum (acetone-d_6), δ, ppm: 10.06 (C-1"); 21.12 (C-1'); 26.76 (C-2'); 60.39 (C-1); 114.33 (C-11); 120.25 (C-3); 125.25 (C-3'); 136.17 (C-2). The signals for the remaining carbon atoms of the phenothiazine fragments were found in the range 122-147 ppm. Found, %: C 77.54; H 6.29; N 5.22. $C_{18}H_{17}NS$. Calculated, %: C 77.38; H 6.13; N 5.01.

Dimerization and Oligomerization of *cis*-10-Propenylphenoxazine (2). A mixture of compound **2** (3 g, 13.5 mmol) and anhydrous ethyl acetate (23 ml) was heated to 60ºC after which 4 ml of a 0.0894 M solution of $BF_3.Et_2O$ in ethyl acetate was added to it. After 1 h 40 min the initiator was neutralized with a solution of sodium propionate in propyl alcohol. The reaction mixture was poured into ethanol (120 ml), held for 24 h, and filtered. The precipitate was washed with cold ethanol and dried at 50ºC at a pressure of 25-40 hPa to give an oligomer (0.64 g, 21%) as a light-brown, amorphous powder with a softening temperature of 180-200ºC. The filtrate was evaporated to dryness and the residue was transferred to an L 100/160 silica gel column (70×2 cm). It was eluted with a mixture of hexane and benzene (5:3) to give compound **6** (0.29 g, 13.5%) with mp 121-122ºC (hexane). IR spectrum (KBr), ν, cm^{-1}: 1660 (C=C), 750 (1,2-disubstituted benzene ring), and 730 and 780 cm^{-1} (1,2,3-trisubstituted benzene ring). Absorption bands for NH groups were absent. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.92 (3H, t, *J* = 7.5, $C\underline{H}_3CH_2$); 1.68 (2H, m, $CH_3C\underline{H}_2$); 1.75 (3H, s, CH_3); 4.45 (1H, t, *J* = 4, H-1); 6.01 (1H, s, H-3); 6.20-6.80 (7H, m, $H_{arom.}$). Found, %: C 81.92; H 6.38; N 5.14. $C_{18}H_{17}NO$. Calculated, %: C 82.10; H 6.51; N 5.32.

REFERENCES

1. V. I. Ivanskii, *Chemistry of Heterocyclic Compounds* [in Russian], Visshaya shkola, Moscow (1978).
2. B. Keshavan and H. Ramalingaiah, *Synth. React. Inorg. Metal-Org. Chem.*, **28**, 1 (1998).

3. T. Yamamura, K. Suzuki, T. Yamaguchi, and T. Nishiyama, *Bull. Chem. Soc. Jpn.*, **70**, 413 (1997).
4. N. Motohashi, M. Kawase, K. Satoh, and H. Sakagami, *Current Drug Targets*, **7,** 1055 (2006).
5. A. Bolognese, G. Correale, M. Manfra, A. Lavecchia, O. Mazzoni, E. Novellino, V. Barone, A. Pani, E. Tramontano, P. La Colla, C. Murgioni, I. Serra, G. Setzu, and R. Loddo, *J. Med. Chem.*, **45**, 5205 (2002).
6. V. A. Anfinogenov, O. A. Napilkova, E. E. Sirotkina, V. D. Filimonov, and V. D. Ogorodnikov, *Khim. Geterotsikl. Soedin.*, 121 (1986), [*Chem. Heterocycl. Comp.*, **22**, 100 (1986)].
7. V. A. Anfinogenov, A. I. Khlebnikov, V. D. Filimonov, and V. D. Ogorodnikov, *Khim. Geterotsikl. Soedin.*, 1674 (1988). [*Chem. Heterocycl. Comp.*, **24**, 1384 (1988)].
8. A. I. Khlebnikov, V. A. Anfinogenov, V. D. Filimonov, and I. V. Sokolova, *Zh. Org. Khim.*, **25**, 1547 (1989).
9. V. A. Anfinogenov, A. I. Khlebnikov, V. D. Filimonov, and V. D. Ogorodnikov, *Zh. Org. Khim.*, **35**, 481 (1999).
10. S. G. Gorbachev, V. D. Filimonov, and E. E. Sirotkina, *Vysokomolekul. Soed.*, **21B**, 125 (1979).
11. S. P. Zhuravkov, *Authors Abstracts. Dissertations of Candidates in Chemical Sciences*, Tomsk (1997).
12. V. D. Filimonov, S. P. Shvedov, Yu. K. Maksyutin, and N. Ya. Idlova, *Vysokomolekul. Soed.*, **25B**, 173 (1983).
13. E. E. Sirotkina, V. D. Filimonov, L. S. Sizova, and N. A. Tsekhanovskaya, US Patent 3987011 (1976)*; Chem. Abstr.*, **86**, 30298 (1977).
14. E. E. Sirotkina, V. P. Lopatinsky, V. D. Filimonov, R. M. Kogan, V. D. Pirogov, S. I. Kudinova, L. S. Sizova, S. S. Reznikova, and G. N. Ivanov, US Patent 4038468 (1977)*; Chem. Abstr.*, **87**, 109426 (1977).