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TRANSFORMATION OF INDOLINE SPIROPYRANS TO BRIDGED 1,3-BENZOXAZEPINO[3,2-*a*]INDOLES *VIA* CARBANIONS STABILIZED BY A CYANO GROUP

A. Šačkus[1], E. Valaitytė[1], V. Amankavičienė[1], U. Berg[2], C. Schicktanz[3], K. Schlothauer[3]

Condensation of 1-cyanomethyl-2,3,3-trimethyl-3H-indolium perchlorate with ortho-hydroxy-substituted aromatic aldehydes afforded 1-cyanomethylindoline spiropyrans. The latter underwent rearrangement to bridged 1,3-benzoxazepino[3,2-a]indoles on treatment with a base. The mechanism of the rearrangement includes generation of a carbanion stabilized by a cyano group.

Keywords: carbanions, 5a,13-methano-1,3-benzoxazepino[3,2-*a*]indoles. spiropyrans, cyclization.

Indoline spiropyrans have attracted considerable attention because of their photochromic properties [1]. However, most studies have focused on their synthesis and reversible transformation to a colored merocyanine form [2–8], while the chemical properties of indoline spiropyrans remain poorly investigated.

We have recently developed a new method for the construction of the pyrrolo[1,2-*a*]indole ring systems based on the base-catalyzed rearrangement of the 1',3'-dihydrospiro[1-benzopyran-2,2'-indole] system to the 5a,13-methano-1,3-benzoxazepino[3,2-*a*]indole system followed by oxazepine ring opening. The proposed mechanism of such transformation included generation of an intermediate azomethine ylide stabilized by the N-substituted amide moiety [9, 10]. 5a,13-Methano-1,3-benzoxazepino[3,2-*a*]indole derivatives found application in the preparation of imprinted polymer stationary phases [11].

We now report further synthetically useful examples where indoline spiropyrans, bearing a substituted methylene group at the nitrogen atom, are transformed to bridged heterocycles. In the present work, the synthesis and base-initiated rearrangement of 1'-cyanomethyl-1',3'-dihydrospiro[1-benzopyran-2,2'-indole] have been explored.

The most common route for the preparation of 1',3'-dihydrospiro[1-benzopyran-2,2'-indole] derivatives is based on the condensation of 1-substituted-2,3,3-trialkyl-3H-indolium salts or the corresponding methylene bases with *ortho*-hydroxy-substituted aromatic aldehydes [1]. The reaction of 1-cyanomethyl-2,3,3-trimethyl-3H-indolium perchlorate (**1**) [12] with 5-nitrosalicylaldehyde in ethanol in the presence of a catalytic amount of piperidine afforded 1'-cyanomethyl-1',3'-dihydrospiro[1-benzopyran-2,2'-indole] (**2a**). Analogously, 1-cyanomethyl-1,3-dihydrospiro[indole-2,2'-naphtho[2,1-*b*]pyran] **2b** was prepared from the perchlorate **1** and 2-hydroxy-1-naphthalenecarbaldehyde (Scheme 1).

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[1]Institute of Synthetic Chemistry, Kaunas University of Technology, Kaunas LT-50254, Lithuania; e-mail: algirdas.sackus@ktu.lt. [2]Organic Chemistry 1, Department of Chemistry, Lund University, 22100 Lund, Sweden; e-mail: ulf.berg@orgkl.lu.se. [3]Faculty of Informatics and Nature Sciences, University of Applied Sciences, 06217 Merseburg, Germany; e-mail: klaus.schlothauer@hs-merseburg.de. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1322-1328, September, 2007. Original article submitted July 5, 2006.

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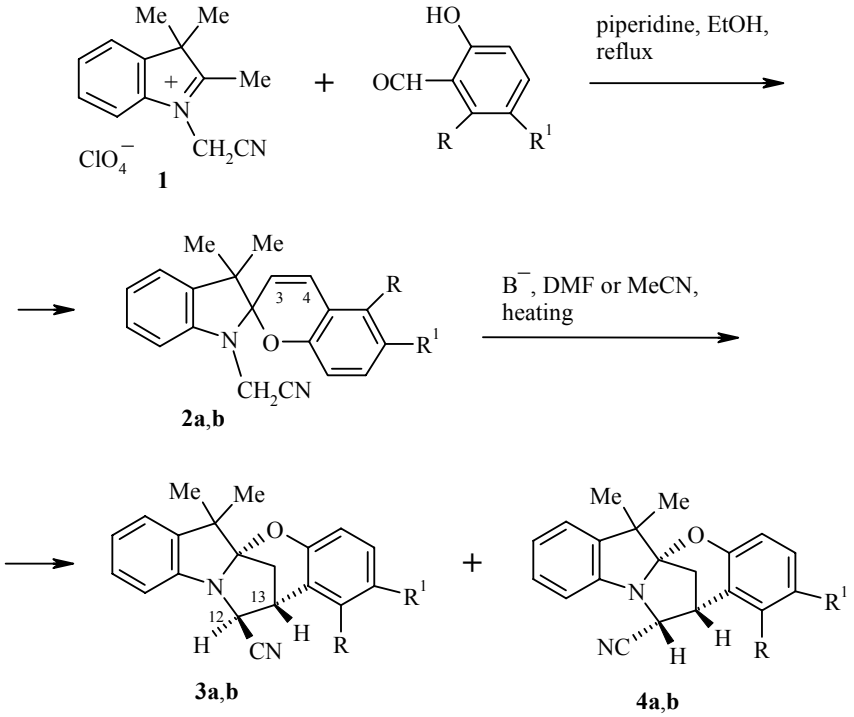
Scheme 1



2–4 a R = H, $R^1 = NO_2$; **b** R + R^1 = CH=CH–CH=CH

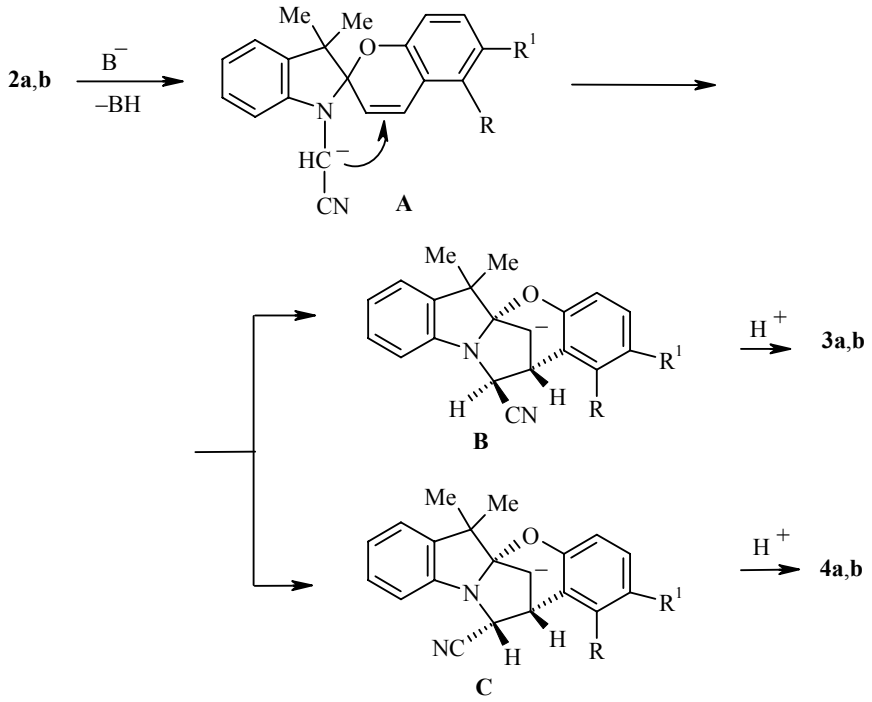
The structures of the synthesized compounds **2a**,**b** were supported by spectral data; in the case of **2a**, the MS exhibited an ion peak at *m*/*z* 348 [M+1], and the IR spectrum revealed the CN absorption at 2244 cm^{-1}. The ^1H NMR spectrum of **2a** contained a doublet of the methine proton at 5.84 ppm with $^3J_{3,4}$ = 10.2 Hz, which indicates *cis*-arrangement of H-3 and H-4 at the vinylic double bond in the molecule [13].

When spiropyran **2a** was heated in DMF containing triethylamine, two diastereomeric 5a,13-methano-1,3-benzoxazepino[3,2-*a*]indole-12-carbonitriles **3a**, **4a** were formed. In the HPLC-MS analysis of the reaction mixture, two peaks were observed after 34.87 and 37.88 min and they both gave prominent peaks at *m*/*z* 348 corresponding to the ion [M+1]. The ~1:2 mixture of **3a** and **4a** was separated by flash chromatography on silica gel. The ^1H NMR spectra of **3a** and **4a** allowed an unambiguous structural assignment based on comparison with the spectra of related compounds [9, 10] and results of MM3* calculations. In the case of *trans*-**3a** the H-12 gave a singlet at 4.74 ppm ($^3J_{12,13}$ = 0 Hz), while the corresponding signal of *cis*-**4a** appeared as a doublet at 4.63 ppm ($^3J_{12,13}$ = 4.5 Hz). Monte Carlo conformational searches using the MM3* force field gave for the optimized structures of *trans*-**3a** and *cis*-**4a** dihedral angle H–$C_{(12)}$–$C_{(13)}$–H values equal to 88.6 and 40.2°, respectively. In this case, vicinal coupling constants ($^3J_{12,13}$) calculated by the Karplus equation [14] are 0.7 Hz for *trans*-**3a** and 5.5 Hz for *cis*-**4a**, which are in good agreement with the experimental values.

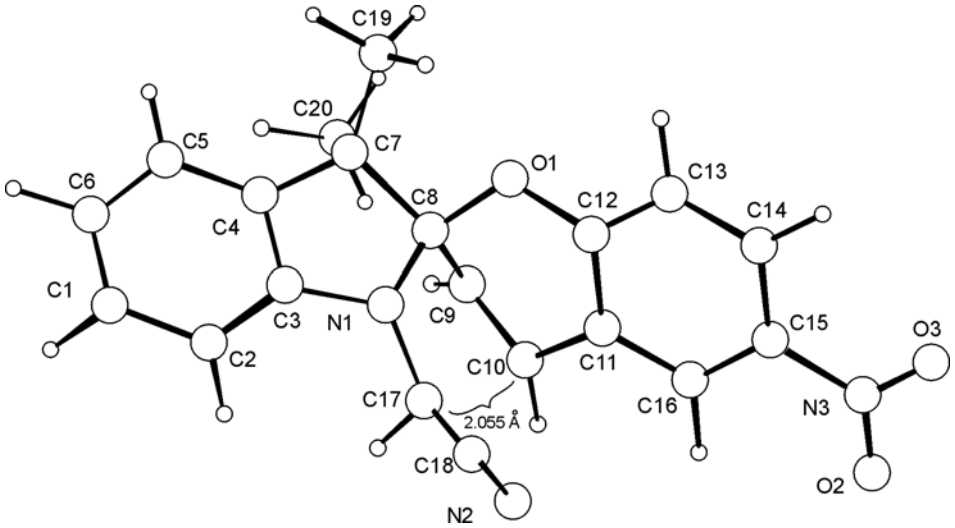
Similarly, two diastereomeric compounds **3b**, **4b** were obtained in a ratio ~3:2 when **2b** was heated in acetonitrile in the presence of potassium hydroxide. Their relative *trans* and *cis* configurations were established by a similar method as described above for **3a**, **4a**. The calculated vicinal coupling constant $^3J_{14,15}$ = 0.7 for *trans*-**3b** and $^3J_{14,15}$ = 6.1 Hz for *cis*-**4b**, and is not far from the experimental values (0 and 4.5 Hz, respectively).

The mechanism of the reaction depicted in Scheme 2 involves generation of the carbanion **A** stabilized by the cyano group followed by an intramolecular attack of the negatively charged carbon atom at the vinylic double bond and spontaneous protonation of the formed bicyclic adducts **B** and **C**.

Scheme 2



This mechanism was supported by semiempirical calculations using the AM1 Hamiltonian in the AMPAC v.7.0 program [15]. Transition states were localized by the CHAIN algorithm for the parent molecule stripped from substituents in the gas phase. The proton transfer to a base is an equienergetic process with negligible activation energy in the gas phase, and the ring closure was calculated to proceed with an activation barrier $\Delta E^{\ddagger}$ = 17.8 kcal/mol^{-1}. The transition state geometry for the ring closure step (**A**, R = H, R^1 = NO_2) is shown in the figure.



Transition state geometry for the ring closure step of **2a** calculated using the AM1 Hamiltonian for the gas-phase reaction

In conclusion, we have demonstrated that indoline spiropyrans possessing the cyanomethyl moiety at the nitrogen atom of the indole nucleus can be easily transformed to the bridged 1,3-benzoxazepino[3,2-*a*]indoles *via* generation of an intermediate carbanion.

EXPERIMENTAL

Melting points were determined on a Kleinfeld melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer Spectrum BXII spectrophotometer using KBr pellets. ^{1}H NMR and ^{13}C NMR were recorded (300 and 75 MHz, respectively) on a Varian Gemini 2000 instrument in $CDCl_3$ (compounds **2a**,**b**, **3b**, **4b**) and DMSO-d_6 (compounds **3a**, **4a**), Tetramethylsilane was used as an internal standard. HPLC-MS analysis was performed and mass spectra were recorded on a Waters ZQ 2000 instrument (ion spray). Compounds were separated on an Altima C18 LC-MS column (150×2.1 mm) at a flow rate of 0.2 ml/min using the gradient starting from 45% of the eluent **A** (0.5% acetic acid) and 55% of the eluent **B** (methanol), and in 40 min increasing the content of **B** to 75%, then in 5 min to 100%. For thin layer chromatographic (TLC) analyses, Merck precoated TLC plates (silica gel 60 F254) were used. Separations by flash chromatography were performed on silica gel Merck, 9385, 230-400 mesh.

The molecular mechanics calculations were performed using the MM3* force fields of the Macromodel program version 6.5, using default parameters [16]. The calculations were carried out on a Silicon Graphics O2 workstation. The Polak-Ribiere conjugate gradient algorithm was applied in all minimizations with 300 iterations limit, and a cut-off of 12 Å was used for the non-bonded interactions and energy convergence criterion of 0.05 kJ/mol.

1'-Cyanomethyl-3',3'-dimethyl-6-nitro-1',3'-dihydrospiro[1-benzopyran-2,2'-indole] (**2a**). To a solution of perchlorate **1** (0.30 g, 1.0 mmol) and 5-nitrosalicylaldehyde (0.18 g, 1.1 mmol) in ethanol (5 ml), two drops of piperidine were added, the mixture was refluxed for 2 h and then allowed to reach room temperature. The reaction mixture was kept at 5°C for 24 h, and the precipitated crystals filtered off and recrystallized from ethanol to afford 0.23 g (66%) of **2a**, mp 183–184°C. IR spectrum, ν, cm^{-}: 2244 (CN), 1653, 1611, 1576, 1510, 1458. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.20 (3H, s, CH_3); 1.31 (3H, s, CH_3); 3.98-4.24 (2H, AB-q, *J* = 18.0, NCH_2); 5.84 (1H, d, *J* = 10.2, H-3); 6.72–7.30 (8H, m, ArH and H-4). ^{13}C NMR spectrum, δ, ppm: 19.23, 25.19, 30.83, 52.16, 105.16, 107.40, 115.22, 115.53, 117.38, 119.41, 121.29, 121.67, 122.31, 125.84, 127.54, 129.24, 135.42, 141.0, 143.66, 157.92. Mass spectrum (ES+), *m/z* (I_{rel}, %): 370 [M+Na] (100), 348 [M+1] (28). Found, %: C 69.10; H 5.06; N 12.44. $C_{20}H_{17}N_3O_3$. Calculated, %: C 69.15; H 4.93; N 12.10.

1-Cyanomethyl-3,3-dimethyl-1,3-dihydrospiro[indole-2,3'-naphtho[2,1-*b*]pyran] (**2b**). To a solution of perchlorate **1** (0.60 g, 2.0 mmol) and 2-hydroxy-1-naphthalenecarbaldehyde (0.36 g, 2.1 mmol) in ethanol (8 ml), three drops of piperidine were added, and the mixture was refluxed for 5 h and then allowed to reach room temperature. The reaction mixture was poured into 5% sodium acetate (50 ml). The aqueous phase was extracted with ether (3×10 ml), and the combined organic layers washed with water (10 ml), dried over $MgSO_4$, filtered off, and concentrated *in vacuo*. The residue was crystallized from ethanol to afford 0.48 g (68%) of **2b** with mp 210-211°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.25 (3H, s, CH_3); 1.37 (3H, s, CH_3); 3.96-4.24 (2H, AB-q, *J* = 18.0, NCH_2); 5.80 (1H, d, *J* = 10.5, H-3'); 6.73–8.06 (11H, m, ArH and H-4'). ^{13}C NMR spectrum, δ, ppm: 20.10, 25.67, 31.55, 51.86, 104.06, 107.71, 109.95, 116.01, 116.14, 117.43, 120.54, 121.28, 122.13, 123.70, 126.41, 126.97, 127,80, 128.71, 129.08, 129.61, 130.82, 136.62, 144.65, 151.71. Mass spectrum (ES+), *m*/*z* (I_{rel}, %): 375 [M+Na] (100), 353 [M+1] (66). Found, %: C 81.86; H 6.01; N 7.74. $C_{24}H_{20}N_2O$. Calculated, %: C 81.79%; H 5.72; N 7.95.

(5*aR,12*R**,13*S**)-5a,13-Methano-6,6-dimethyl-2-nitro-12,13-dihydro-6H-1,3-benzoxazepino[3,2-*a*]-indole-12-carbonitrile (*trans*-3a) and its (5*aR**,12*S**,13*S**)-isomer (*cis*-4a)**. To a solution of compound **2a** (200 mg, 0.58 mmol) in DMF (3 ml) triethylamine was added (0.3 ml); the mixture was heated at 120°C in a closed vessel for 2 h and then allowed to reach room temperature. The reaction mixture was poured into water (50 ml) and the aqueous phase was extracted with ether (2×10 ml). The combined organic layers were dried over $MgSO_4$, filtered off and concentrated *in vacuo*. The residue (180 mg) was chromatographed on a silica gel column with acetone–hexane, 1:5, as eluent. The *trans*-**3a** isomer was eluted first, followed by the *cis*-**4a** isomer. Subsequent recrystallization from acetone gave **3a** (50 mg, 25%) and **4a** (83 mg, 42%) in the pure state.

trans-**3a**: mp 164-165°C (ethanol). IR spectrum, ν, cm^{-1}: 2231 (CN), 1611, 1605, 1586, 1514, 1482 cm^{-1}. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.41 (3H, s, CH_3); 1.60 (3H, s, CH_3); 2.31 (d, *J* = 12.6, 0.5 CH_2); 2.51 (1H, dd, *J* = 3.9, *J* = 12.6, 0.5 CH_2); 3.87 (1H, d, *J* = 3.9, H-13); 4.74 (1H, s, H-12); 6.58-8.12 (7H, m, ArH). ^{13}C NMR spectrum, δ, ppm: 24.02, 28.43, 31.37, 46.01, 46.21, 58.67, 109.12, 111.46, 116.03, 118.38, 123.03, 123.47, 124.31, 125.84, 126.50, 128.89, 141.51, 141.95, 142.37, 159.38. Mass spectrum (ES+), *m/z* (I_{rel}, %): 370 [M+Na] (29), 348 [M+1] (100). Found, %: C 9.45; H 5.06; N 11.86. $C_{20}H_{17}N_3O_3$. Calculated, %: C 69.15; H 4.93; N 12.10.

cis-**4a**: mp 203-204°C (ethanol). IR spectrum, ν, cm^{-1}: 2249 (CN), 1618, 1605, 1586, 1509, 1480. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.43 (3H, s, CH_3); 1.44 (3H, s, CH_3); 2.23 (1H, dd, *J* = 1.2, *J* = 12.3, 0.5 CH_2); 2.29 (1H, dd, *J* = 3.6, *J* = 12.3, 0.5 CH_2); 4.03-4.05 (1H, m, H-13); 4.63 (1H, d, *J* = 4.5, H-12); 6.68–8.33 (m, 7H, ArH). ^{13}C NMR spectrum, δ, ppm: 23.52, 25.75, 30.70, 41.36, 44.58, 62.86, 109.80, 110.15, 117.10, 118.38, 122.07, 122.65, 124.48, 125.58, 126.12, 128.31, 138.45, 140.55, 147.02, 158.15. Mass spectrum (ES+), *m*/*z* (I_{rel}, %): 370 [M+Na] (53), 348 [M+1] (100). Found, %: C 68.92; H 4.71; N 11.95. $C_{20}H_{17}N_3O_3$. Calculated, %: C 69.15; H 4.93; N 12.10.

(7*aR,14*R**,15*S**)-7a,15-Methano-8,8-dimethyl-14,15-dihydro-8H-naphth[1',2':6,7][1,3]oxazepino-[3,2-*a*]indole-14-carbonitrile (*trans*-3b) and its (7*aR**,14*S**,15*S**)-isomer (*cis*-4b)**. To a solution of compound **2b** (200 mg, 0.57 mmol) in acetonitrile (5 ml) of potassium hydroxide (30 mg) was added and the mixture was refluxed for 1.5 h. The reaction mixture was poured into water (30 ml) and the aqueous phase was extracted with ether (2×10 ml). The combined organic layers were dried over $MgSO_4$, filtered off and concentrated *in vacuo*. The residue (190 mg) was chromatographed on a silica gel column with acetone–hexane, 1:4, as an eluent. The *trans*-**3b** isomer was eluted first, followed by the *cis*-**4b** isomer. Subsequent recrystallisation from ethanol gave **3b** (80 mg, 40%) and **4b** (52 mg, 26%) in the pure state.

trans-**3b**: mp 184-185°C (ethanol); IR spectrum, ν, cm^{-1}: 2230 (CN), 1621, 1594, 1484, 1458. ^{1}H NMR spectrum, δ, ppm: 1.48 (3H, s, CH_3); 1.64 (3H, s, CH_3); 2.41 (1H, d, *J* = 12.0, 0.5 CH_2); 2.64 (1H, dd, *J* = 3.9, *J* = 12.0, 0.5 CH_2); 4.45 (1H, d, *J* = 3.9, H-15); 4.81 (1H, s, H-14); 6.54–7.90 (10H, m, ArH). ^{13}C NMR spectrum, δ, ppm: 23.89, 27.29, 30.65, 40.83, 44.98, 58.13, 107.37, 110.74, 116.18, 116.33, 118.61, 120.52, 121.73, 122.68, 123.67, 127.21, 127.91, 128.95, 129.03, 129.93, 130.64, 140.88, 142.73, 150.77. Mass spectrum (ES+), *m*/*z* (I_{rel}, %): 375 [M+Na] (78), 353 [M+1] (100). Found, %: C 81.70; H 5.98. $C_{24}H_{20}N_2O$. Calculated, %: C 81.79; H 5.72.

cis-**4b**: mp 201–202°C (ethanol). IR spectrum, ν, cm^{-1}: 2242 (CN), 1622, 1596, 1486, 1460. ^{1}H NMR spectrum, δ, ppm: 1.52 (3H, s, CH_3); 1.55 (3H, s, CH_3); 2.15 (1H, dd, *J* = 3.9, *J* = 11.7, 0.5 CH_2); 2.29 (1H, dd, *J* = 0.9, *J* = 11.7, 0.5 CH_2); 4.27 (1H, d, *J* = 4.5, H-14); 4.34–4.36 (1H, m, H-15); 6.75–7.94 (10H, m, ArH). ^{13}C NMR spectrum, δ, ppm: 23.32, 26.35, 31.72, 37.52, 44.92, 64.75, 108.81, 110.65, 115.93, 118.06, 118.09, 121.22, 122.32, 122.50, 123.75, 127.07, 128.49, 128.83, 129.12, 130.24, 131.39, 138.52, 148.59, 150.63. Mass spectrum (ES+), *m*/*z* (I_{rel}, %): 375 [M+Na] (100), 353 [M+1] (72). Found, %: C 82.03; H 5.52. $C_{24}H_{20}N_2O$. Calculated, %: C 81.79; H 5.72.

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REFERENCES

1. R. C. Bertelson, *Spiropyrans*, in *Organic Photochromic and Thermochromic Compounds*, J. C. Crano, R. J. Guglielmetti (Eds.), Plenum Press, New York, London, 1999, vol. 1, p. 11.
2. H. Choi, B.-S. Ku, S.-R. Keum, S.O. Kang, J. Ko, *Tetrahedron*, **61**, 3719 (2005).
3. V. Amankavičienė, S. J. Asadauskas, J. Girnienė, A. Šačkus, *J. Chem. Res*., 508 (2005).
4. J. Sworakowski, S. Nešpurek, P. Toman, G. Wang, W. Bartowiak, *Synth. Met.*, **147**, 241 (2004).
5. J. H. Kim, Y. S. Ban, S. Kaihua, D.H. Choi, *Dyes Pigments*, **58**, 105 (2003).
6. M. Querol, B. Bozic, N. Salluce, P. Belser, *Polyhedron*, **22**, 655 (2003).
7. Y. Abe, H. Ebara, S. Okada, R. Akaki, T. Horii, R. Nakao, *Dyes Pigments*, **52**, 23 (2002).
8. G. Berkovic, V. Krongauz, V. Weiss, *Chem. Rev*., **100**, 1741 (2000).
9. N. Kleizienė, V. Martynaitis, U. Berg, A. Šačkus, *XTC*, 561 (2001). [*Chem. Heterocycl. Comp.*, **37**, 517 (2001)].
10. V. Martynaitis, A. Šačkus, U. Berg, *J. Heterocycl. Chem*., **39**, 1123 (2002).
11. E. Machtejevas, B. Sellergren, V. Martynaitis, P. K. Owens, A. Maruška, *J. Sep. Sci*., **27**, 547 (2004).
12. A. Šačkus, V. Martynaitis, *XTC*, 279 (2001). [*Chem. Heterocycl. Comp*., **37**, 256 (2001)].
13. S.-R Keum, K.-B. Lee, P. M. Kazmaier, R. A. Manderville, E. Buncel, *Magn. Res. Chem*., **30**, 1128 (1992).
14. A. A. Bothner-By, *Adv. Magn. Res*., **1**, 195 (1965).
15. The AMPAC Program Is Available from: Semichem, P. O. Box 1649, 7128 Summit, Shawnee, KS 66216, USA.
16. F. Mohamadi, N. G. J. Richards, W. C. Guida, R. Liskamp, M. Lipton, C. Caufield, G. Chang, T. Hendrickson, W. C. Still, *J. Comput. Chem*., **11**, 440 (1990).