Spirans. 16. 3,3′-Spirobi[3,4-dihydro-2*H*-[1,3]oxazino[3,2-*a*]benzimidazole] and Its Thia Analogue†

Stefan Smoliński* and Agnieszka Czarny

Stereochemical Laboratory, Institute of Chemistry, Jagellonian University, 30-060 Kraków, Krupnicza 41, Poland

(Received November 10, 1977)

In order to obtain spiran the sodium derivative of *o*-phenylenediamine was subjected to reaction with 1,3-dibromo-2,2-bis(bromomethyl)propane in *N,N*-dimethylformamide. The compound was also synthesized by the reaction of the sodium derivative of 2,3-dihydro-1*H*-benzimidazol-2-one with 1,3-dibromo-2,2-bis(bromomethyl)propane. By this procedure the thia analogue of the spiran was obtained. In both cases the condensation route was unexpected. This is due to the fact that the solvent (DMF) takes part in the reaction and a stereo-electronic situation occurs, which is similar to that covered by Bredt's exclusion rule.

In order to obtain suitable tetraazaspirans the condensation of two moles of the sodium derivative of *o*-phenylenediamine, obtained by treating *o*-phenylenediamine in the presence of sodium hydride in dry dioxane with 1,3-dibromo-2,2-bis(bromomethyl)-propane in *N,N*-dimethylformamide was carried out. After heating for 100 h under reflux a product melting at 385—390 °C (with decomposition) was obtained. From elemental analysis and the molecular weight estimated from mass spectra it was found necessary to ascribe the structure of the required spiran enriched with two CO groupings to the product. Under the above conditions, it can be assumed that *N,N*-dimethylformamide reacts most likely with *o*-phenylenediamine yielding its monoformyl derivative, which gives with the other molecule of *N,N*-dimethylformamide 2,3-dihydro-1*H*-benzimidazol-2-one. Consequently it was established that spiran is formed in the condensation of the sodium derivative of 2,3-dihydro-1*H*-benzimidazol-2-one with 1,3-dibromo-2,2-bis(bromomethyl)propane in cellosolve. We have also found that 2,3-dihydro-1*H*-benzimidazol-2-one is obtained when *o*-phenylenediamine is heated with sodium hydride in dioxane with *N,N*-dimethylformamide. We have proposed two structures for the spiran compound obtained:

(**1**) a structure containing the urea grouping that has the CO group bridging in a 7-membered ring,

(**2**) a constitutionally symmetrical spiro compound of six rings containing the dihydrooxazine-benzimidazole arrangement.

In order to determine which structure is correct, the IR, UV, mass and NMR spectra were obtained. In the IR spectra the band at 1625 cm^{-1} indicates

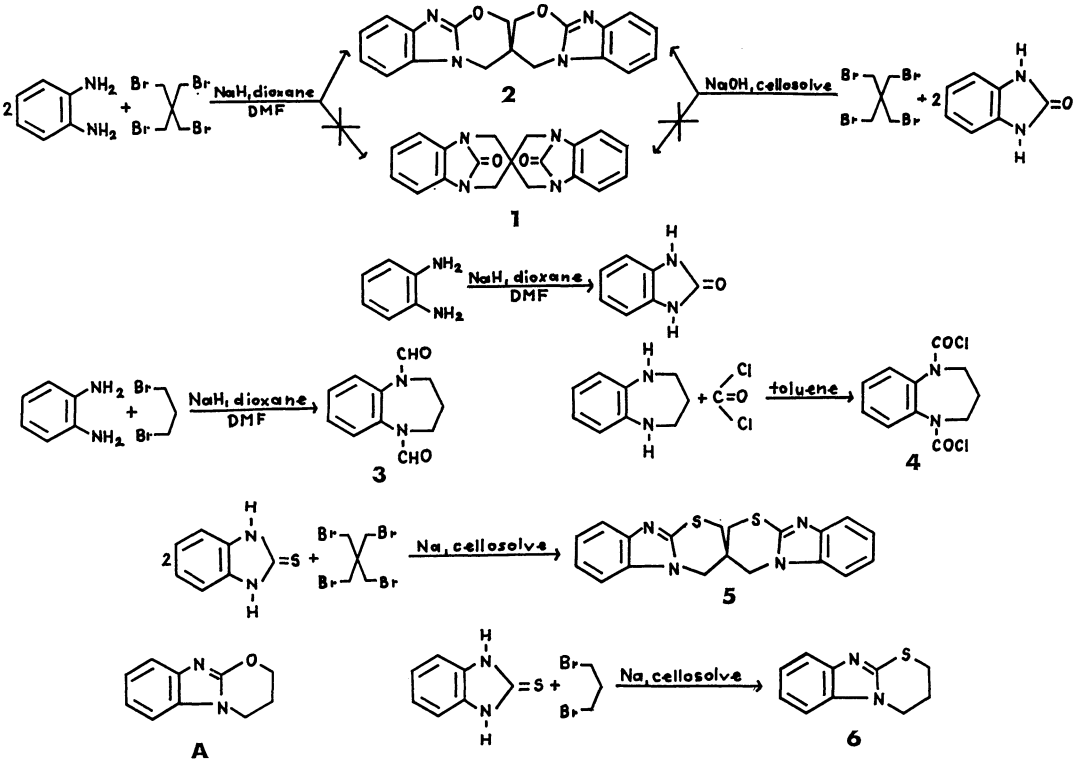

Fig. 1.

† Presented at the 26th IUPAC Congress, Tokyo (September 1977).

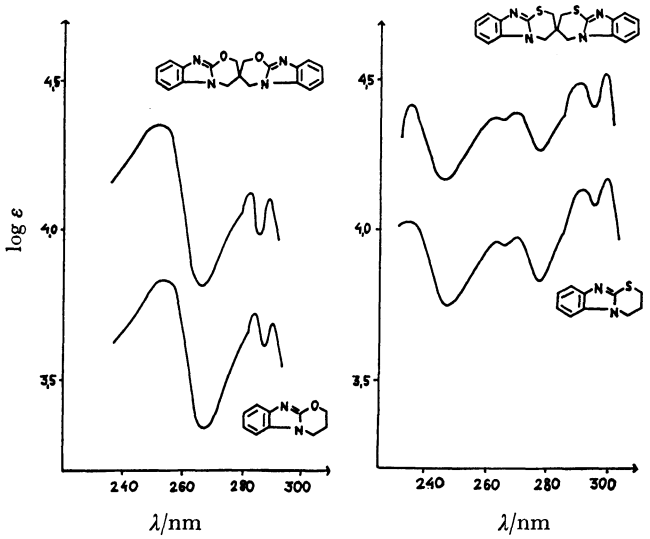

Fig. 2. UV-absorption spectra of compounds **2**—A and **5**—**6** in CH_2Cl_2.

the presence of the C=N group but not C=O; absorption bands indicate the presence of amine, methylene and aromatic groups. The NMR spectrum also suggests that structure (**2**) is correct. It was thus decided that the reported method of comparison[1-5] could be used and that the "half-compound" of the spiran obtained should be synthesized. The UV curves of the spiran and the "half-compound" could then be measured and compared. We expect them to have an analogous shape, the λ_{max} having different value in the extinction coefficient of λ_{max}. In spite of attempts, no "half-compound" of structure (**1**) could be obtained. Only compound **3** was obtained by treating 1,3-dibromopropane with *o*-phenylenediamine in the presence of sodium hydride in dioxane and *N*,*N*-dimethylformamide. 2,3,4,5-Tetrahydro-1*H*-1,5-benzodiazepine was treated with phosgene in toluene. Only product **4** was obtained. The structures of compounds **3** and **4** were confirmed by IR, NMR, and mass spectra.

2,3,4,5-Tetrahydro-1*H*-1,5-benzodiazepine was heated with *N*,*N*-dimethylformamide, but it remained unchanged. We followed the method of Htay and Meth-Cohn[6] to get the "half-compound" of the spiran **2** (structure A) by condensing the sodium derivative of 2,3-dihydro-1*H*-benzimidazol-2-one with 1,3-dibromopropane. By measuring the UV-absorption spectra of spiran **2** and compound A, low hyperchromism was found (at λ_{max}=250 nm the ratio of extinction coefficients was 1:3.25; at λ_{max}=282 nm 1:2.57; 288 nm 1:2.64) indicating that the dominant conformation of spiran **2** is as shown in Fig. 3a.

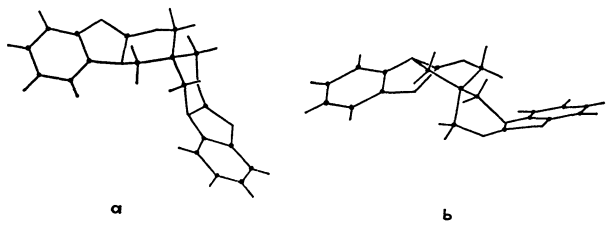

Fig. 3. The possible conformations of spiran **2**.

In conformation 3a the benzimidazole components are placed nearly orthogonally whereas the dihydrooxazine rings possess a chair conformation. Conformation 3b can be represented by two nearly parallel planes of the benzimidazole components annulated with dihydrooxazine rings in the biplanar conformation. Such geometry would have caused a higher hyperchromism.[5] Thus it is assumed that, in the reaction to obtain spiran **2**, 2,3-dihydro-1*H*-benzimidazol-2-one undergoes reaction in the tautomeric form, which in the presence of 1,3-dibromo-2,2-bis(bromomethyl)propane, forms the *O*-derivative from which spiran **2** resulted. Some analogy can be found with the experiments and results obtained by Htay and Meth-Cohn.[6]

In order to confirm the assumption we obtained the sulfur analogue of spiran **2**. 2,3-Dihydro-1*H*-benzimidazol-2-thione was heated with 1,3-dibromo-2,2-bis(bromomethyl)propane in the presence of metallic sodium in cellosolve; spiran **5**, mp 365—370 °C (with decomposition) and its dipicrate were obtained. Its "half-compound" (**6**) was synthesized in a similar way.[6] The measurement of UV-absortpion of spiran **5** and "half-compound" **6** revealed a hyperchromism of nearly the same magnitude as in the former case (at λ_{max}=235 nm the ratio of extinction coefficients was 1 : 1, 99; at λ_{max}=264 nm 1 : 2.6; 271 nm 1 : 2.6; 291 nm 1 : 2.25; 299 nm 1 : 2.2).

Considering the reactions, the following conclusion has been reached: Formation of structure (**2**) neglecting structure (**1**), is a result of the stereo-electronic effect. Structure (**1**) is inherently improbable, being of high energy due to steric inhibition of resonance the N lone pair and CO π-orbitals become necessarily orthogonal. The geometrical aspect is responsible for the case discussed being analogous with the arrangements covered by Bredt's rule concerning monocarbocyclic bridged ring system. The case is therefore considered to be included in Bredt's rule (whose nature is of stereo-electronic character), since there is no steric hindrance involved in the formation of spiran **1**.

It seems that failure[7,8] in obtaining 2-quinuclidinone and its 2-thione analogue (system [2.2.2]) which differs from the system considered here [3.2.1] but in which a similar stereo-electronic effect can be expected, confirms the assumption.

Experimental

IR spectra were measured with a Zeiss UR-10 spectrometer, UV-absorption spectra with a Unicam SP-1800, NMR spectra with a Tesla BS 487 at 80 MHz using TMS as a standard, and mass spectra with a LKB 9000 S apparatus at 70 eV.

*3,3'-Spirobi[3,4-dihydro-2*H*-[1,3]oxazino[3,2-a]benzimidazole] (2) from o-Phenylenediamine.* In a three necked flask 9.6 g of sodium hydride (0.2 m) in a 50% oil suspension were washed with dry benzene. 10.8 g (0.1 m) of *o*-phenylenediamine in 150 ml of dry dioxane was then added. The mixture was heated with stirring under reflux until no further hydrogen was evolved (3—4 h). A solution of 19.4 g (0.05 m) of 1,3-dibromo-2,2-bis(bromomethyl)propane in 150 ml of DMF was then added dropwise and the mixture refluxed for 100 h. The NaBr precipitate was separated and the

solvents removed by evaporation. The residue was treated with dilute hydrochloric acid (2:1). After filtering off the unreacted 1,3-dibromo-2,2-bis(bromomethyl)propane (10%) and resinous substances the spiran was precipitated from the acidic filtrate by addition of concentrated sodium hydroxide solution. The crude product was purified by sublimation at 320 °C in a high vacuum (0.1 mmHg); 510 mg (3%) of a colourless, crystalline product, mp 385—390 °C with decomposition.

From 2,3-Dihydro-1H-benzimidazol-2-one. In a thick glass tube a suspension of 4.5 g (0.025 m) of the sodium salt 2,3-dihydro-1*H*-benzimidazol-2-one in 100 ml cellosolve was prepared and 9.7 g (0.025 m, excess) of 1,3-dibromo-2,2-bis(bromomethyl)propane was added. The glass tube was sealed and heated at 120 °C for 100 h. The cellosolve was then distilled off and the spiran was purified as above; 680 mg (16%). IR(KBr): 1010, 1050 (C–O–C); 2940 (C–H aliph.); 770, 3060 (C–H arom.); 1625 cm^{-1} (C=N); UV (CH_2Cl_2): λ (logε)=250 (4.45), 282 (4.22), 288 nm (4.21); NMR(CF_3COOH): δ 4.75 (s, 4H, $-CH_2-N$), 5.2 (s, 4H, $-CH_2-O$), 7.5—7.7 (m, 8H, arom.); mass spectrum: *m/e*= 332. Found: C, 68.65; H, 4.96; N, 16.61%. Calcd for $C_{19}H_{16}N_4O_2$: C, 68.66; H, 4.85; N, 16.86%.

Dipicrate of Spiran **2**: 40 mg of the spiran **2** was treated with 10 ml of saturated picric acid solution in ethanol and refluxed for 1 h. A yellow, crystalline product (cellosolve) with a mp 235—237 °C was obtained. Found: N, 17.60%. Calcd for $C_{31}H_{22}N_{10}O_{16}$: N, 17.71%.

*3,3'-Spirobi[3,4-dihydro-2H-[1,3]thiazino[3,2-a]benzimidazole] (**5**).* 0.46 g (0.02-g atom) of metallic sodium was introduced into a thick glass tube containing 50 ml of cellosolve and then 1.5 g (0.01 m) of 2,3-dihydro-1*H*-benzimidazol-2-thione and 3.9 g (0.01 m, excess) of 1,3-dibromo-2,2-bis(bromomethyl)propane were added. The tube was sealed and heated at 120 °C for 50 h. The cellosolve was then distilled off and the spiran separated and purified as above. 880 mg (48%) of a colourless, crystalline product, mp 365—370 °C (with decomposition) were obtained. IR (KBr): 2935 (C–H aliph.); 770, 3055 (C–H arom.); 1610 cm^{-1} (C=N); UV(CH_2Cl_2): λ(log ε)=235 (4.41), 264 (4.37), 271 (4.38), 291 (4.48), 299 nm (4.50); NMR (CF_3COOH): δ 3.9 (s, 4H, $-CH_2-S$), 4.8 (s, 4H, $-CH_2-N$), 7.5—7.85 (m, 8H, arom.); mass spectrum *m/e*=364. Found: C, 62.45; H, 4.39; N, 15.13%. Calcd for $C_{19}H_{16}N_4S_2$: C, 62.61; H, 4.43; N, 15.37%.

Dipicrate of Spiran **5**: This was prepared according to the procedure for the previously described dipicrate. A yellow, crystalline product (cellosolve), mp 215—217 °C was obtained. Found: N, 16.84%. Calcd for $C_{31}H_{22}N_{10}O_{14}S_2$: N, 17.02%.

*1,5-Diformyl Derivative of 2,3,4,5-Tetrahydro-1H-1,5-benzodiazepine (**3**).* In a three necked flask, 9.6 g (0.2 m) of sodium hydride in a 50% oil suspention were washed with dry benzene, 10.8 g (0.1 m) of *o*-phenylenediamine in 150 ml of dry dioxane was then added. The mixture was heated with stirring under reflux until no further hydrogen was evolved (3—4 h). A solution 20.2 g (0.1 m) of 1,3-dibromopropane in 150 ml of DMF was then added dropwise and the mixture refluxed for 50 h. The NaBr precipitate was separated and the solvents removed by evaporation. The residue was treated with dilute hydrochloric acid (2:1). After filtration, the filtrate was treated with concentrated sodium hydroxide solution and decanted off, leaving oily impurities, and extracted with butanol. From the extract, 150 mg (0.7%) of a colourless, crystalline product (1-butanol) were recovered, mp 170—172 °C. IR(KBr): 1670 (C=O), 790, 3040 (C–H arom.), 2950 cm^{-1} (C–H aliph.); NMR ($CDCl_3$): δ 2.0 (q, 2H, $-CH_2-$), 3.8 (t, 4H, $-CH_2-N$), 7.1—7.5 (m, 4H, arom.), 8.25 (s, 2H, H–C=O); mass spectrum: *m/e*=204. Found: C, 64.58; H, 6.13; N, 13.56%. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.72; H, 5.93; N, 13.74%.

*1,5-Bis(chloroformyl) Derivative of 2,3,4,5-Tetrahydro-1H-1,5-benzodiazepine (**4**).* A solution of 0.75 g (0.005 m) of 2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine in 120 ml of dry toluene was prepared in a three necked flask fitted with a reflux condenser and stirrer. While being mixed 4.2 g of a 12% solution of phosgene in toluene (0.005 m) was added and the reaction mixture stirred for 3 h. After amine hydrochloride had been removed and toluene distilled off, the solid residue was purified chromatographically on an Alox column in benzene. 120 mg (8.8%) of a colourless, crystalline product, mp 165—166 °C were obtained. IR(KBr): 2965 (C–H aliph.), 785, 3050 (C–H arom.), 675 (C–Cl), 1725 cm^{-1} (C=O); mass spectrum: *m/e*=272. Found: C, 48.46; H, 3.75; N, 10.27%. Calcd for $C_{11}H_{10}N_2O_2Cl_2$: C, 48.37; H, 3.69; N, 10.29%.

*3,4-Dihydro-2H-[1,3]thiazino[3,2-a]benzimidazole (**6**).* 0.92 g (0.04 g-atom) of metallic sodium was introduced into 50 ml of cellosolve in a three necked flask equipped with reflux condenser and stirrer and then 1.5 g (0.02 m) of 2,3-dihydro-1*H*-benzimidazol-2-thione and 4 g (0.02 m) of 1,3-dibromopropane were added. The mixture was refluxed for 3 h. The cellosolve was distilled off and the product was purified chromatographically on an Alox column in benzene. 120 mg (6.3%) of a colourless, crystalline (benzene) product, mp 133—135 °C were obtained. IR (KBr): 2935 (C–H aliph.), 775, 3040 (C–H arom.), 1610 cm^{-1} (C=N); UV (CH_2Cl_2): λ(log ε)=235 (4.12), 264 (3.95), 270 (3.97), 292 (4.13), 300 nm (4.16); NMR ($CDCl_3$): δ 2.2—2.5 (m, 2H, $-CH_2-$), 3.1 (t, 2H, $-CH_2-S$), 4.0 (t, 2H, $-CH_2-N$), 7.0—7.7 (m, 4H, arom.); mass spectrum: *m/e*=190. Found: C, 62.97; H, 5.22; N, 14.66%. Calcd for $C_{10}H_{10}N_2S$: C, 63.12; H, 5.29; N, 14.73%.

References

1) S. Smoliński, *Tetrahedron*, **22**, 199 (1966).
2) S. Smoliński and G. Kinyua, *Tetrahedron*, **27**, 265 (1971).
3) S. Smoliński and J. Jamrozik, *Tetrahedron*, **27**, 4977 (1971).
4) S. Smoliński, I. Deja, and J. Nowicka, *Tetrahedron*, **31**, 1527 (1975).
5) S. Smoliński, J. Nowicka, J. Mokrosz, M. Jamrozik, M. Jaworski, and E. Wiekiera, *Tetrahedron*, **33**, 1219 (1977).
6) M. M. Htay and O. Meth-Cohn, *Tetrahedron Lett.*, **1976**, 79.
7) L. N. Yakhontov and M. V. Rubtsov, *Zh. Obshch. Khim.*, **27**, 72 (1957).
8) H. Pracejus, M. Kehlen, H. Kehlen, and H. Matschiner, *Tetrahedron*, **21**, 2257 (1965).