Novel Heterocycles. 9. Synthesis of the Benzofuro[2,3-*c*][1,2]thiazine Ring System

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The treatment of 2-coumaranone with the Vilsmeier reagent affords three products: 2-chloro-3-benzofurancarboxaldehyde (**3**), 3-dimethylaminomethylene-2-(3*H*)benzofuranone (**4**), and 3-dimethylaminomethylene-2,3-dihydro-2-oxo-6-benzofurancarboxaldehyde (**5**). Both **4** and **5** are isolated as a mixture of *E* and *Z* isomers. The reaction of **3** with the anion of *N*-methylmethanesulfonamide affords the title compound 1-methyl-1*H*-benzofuro[2,3-*c*][1,2]-thiazine 2,2-dioxide (**6**). Spectral data is also discussed.

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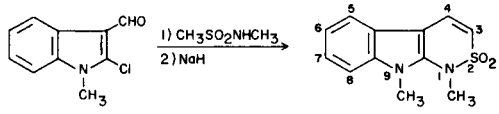
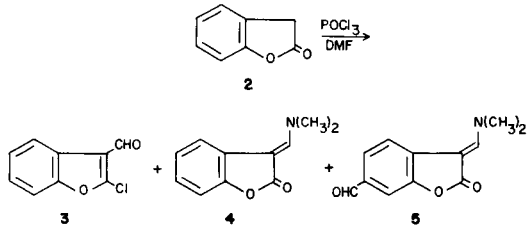
The synthesis of the 1,9-dihydrothiazino[3,4-*b*]indole ring system (**1**), by the reaction of 2-chloroindole-3- carboxaldehydes with *N*-methylmethanesulfonamide followed by treatment with sodium hydride, has been described by us in a recent report (1).



1

It became of interest to synthesize the corresponding compound in which the nitrogen (N-CH_3) in the 9-position is replaced with oxygen. It was rationalized that a similar reaction with 2-chloro-3-benzofurancarboxaldehyde and *N*-methylmethanesulfonamide should produce the desired product.

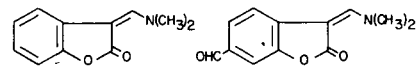
Since 2-chloro-3-benzofurancarboxyaldehyde (**3**) is not known, its synthesis was accomplished by the reaction of 2-coumaranone (**2**) with the Vilsmeier reagent (dimethylformamide-phosphorus oxychloride). Unlike the corresponding reaction with oxindoles, this reaction affords three products.



2 **3** **4** **5**

The major product, **3**, was isolated in 46% yield while the yields of **4** and **5** were 10% and 24%, respectively.

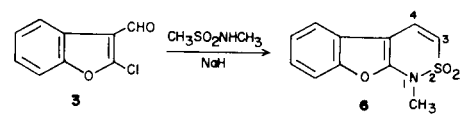
The ir spectrum of **3** exhibits the aldehyde absorption at 1685 cm^{-1}. The second product **4** produces two absorptions in the carbonyl region at 1740 and 1725 cm^{-1} and an additional two at 1625 and 1605 cm^{-1}. The latter two are probably due to the O=C-C=C-N moiety. The presence of the dimethylaminomethylene function is also supported in the nmr spectrum by the observed signals at δ 7.45 (singlet, 1 proton, C=CHN), 3.4 (multiplet) and 3.3 (singlet, both peaks represent a total of 6 protons, $N(CH_3)_2$). The multiplicity of the methyl peaks may be explained by the presence of both *E* and *Z* isomers. In the E isomer (as drawn in structure **4**), rotation about the double bond is rapid, therefore the N-CH_3 signal is seen as a sharp singlet (δ 3.3). In the *Z* isomer (**4a**), rotation about the double bond is slow on the nmr time scale which causes the methyl groups to be magnetically nonequivalent and appear as a multiplet (δ 3.4). The two isomers also explains the dual absorption in the ir spectrum. It was determined by nmr that the isomer E:Z ratio is 70:30.



4a **5a**

The structure of the third product **5** was determined based on the following spectral evidence. The ir spectrum exhibits two carbonyl absorptions at 1735 (O-C=O) and 1685 (-CHO) cm^{-1}. In the nmr spectrum the aldehyde signal is observed as a singlet at δ 9.8. The appearance of three protons plus one vinyl proton in the aromatic region suggests the aldehyde function resides in the aromatic ring, the position of which is determined by analysis of carbon-13 spectral data.

Compound **5** also exists as an isomeric mixture and the effect on the N-CH_3 groups in the nmr is even more pronounced than that of compound **4**. The *E* isomer affords a singlet at δ 3.5 while in the *Z* isomer **5a** the methyls appear as two distinct singlets at δ 3.45 and 3.7. Spectrally, the isomer *E:Z* ratio was determined to be approximately 50:50.



3 **6**

0022-152X/81/040845-02$02.25

When 2-chloro-3-benzofurancarboxaldehyde (**3**) was treated with *N*-methylmethanesulfonamide in the presence of sodium hydride, tricycle **6** was formed in 24% yield. Unlike the indole series (1), where similar treatment resulted in a 50:50 mixture of cyclic and acyclic material, in this reaction only the cyclic compound was isolated.

The ir spectrum of **6** exhibits two intense absorptions at 1335 and 1150 cm^{-1} which are attributable to the sulfonamide S=O stretching vibrations. In the nmr, the proton at the 3-position is seen as a doublet at δ 6.3 (J = 10 Hz) while the proton in position 4 is obscured by the aromatic signals. The N-CH_3 peak is represented by a singlet at δ 3.6.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover Unimelt apparatus and are uncorrected. The ir spectra were recorded on Perkin-Elmer Model 257 and 457 spectrophotometers. Absorption frequencies are quoted in reciprocal centimeters. The proton nmr spectra were recorded on Varian T-60 and EM-360 spectrometers using tetramethylsilane as an internal reference. Chemical shifts are quoted in parts per million (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet). The mass spectra were determined on an LKB 9000 spectrometer.

The carbon-13 magnetic resonance spectra were obtained in the Fourier transform mode on a Varian XL-100-12 spectrometer system equipped with a Varian 620/L computer with 16K memory. The spectra were obtained at an observing frequency of 25.159 MHz. Sample concentrations were *ca.* 0.5 molar in deuteriochloroform in 10 mm (od) sample tubes. General nmr spectral and instrumental parameters employed were: Internal deuterium lock to the solvent; spectral width of 5120 Hz; a pulse width of 25 μs corresponding to a 43° pulse angle; and a pulse repetition time of 1.8 seconds. For all spectra, 8K time-domain points were used. All shifts reported are referenced to internal TMS and are estimated to be accurate to $\pm$0.05 ppm.

Unless otherwise stated, all solutions of organic compounds were washed with brine and dried over sodium sulfate. No attempt has been made to optimize the yields of the described reactions.

2-Chloro-3-benzofurancarboxaldehyde (**3**).

To a solution of 20.0 g. of dimethylformamide in 100 ml. of chloroform was added dropwise 31.0 g. of phosphorus oxychloride (the temperature of the reaction mixture was kept below 10° by ice cooling). After stirring at 0-5° for 5 minutes, a solution of 10.7 g. of 2-coumaranone in 75 ml. of chloroform was added dropwise under ice cooling and then refluxed for 18 hours. The chloroform was removed under reduced pressure and water was added to the residue. Solid potassium acetate was added until *p*H 5, then 2*N* sodium hydroxide was added until *p*H 7 was reached. The mixture was extracted with methylene chloride, dried over sodium sulfate, and the solvent removed under reduced pressure. The residue was chromatographed on a column of silica gel using chloroform to elute the product, 6.6 g. (46%) of **3**. An analytical sample was sublimed at 60°, m.p. 83-86°, ir (chloroform): 1685 cm^{-1}; nmr (deuteriochloroform): δ 10.1 (s, 1, -CHO), 8.1 (m, 1), 7.4 (m, 3).

Anal. Calcd. for $C_9H_5ClO_2$: C, 59.9; H, 2.8; Cl, 19.6. Found: C, 60.2; H, 3.0; Cl, 19.5.

3-Dimethylaminomethylene-2-(3*H*)benzofuranone (**4**).

The second most polar fraction from the column chromatography described above was eluted with 1% methanol/chloroform to yield 1.5 g. (10%) of **4**. An analytical sample was crystallized from methylene chloride/ether, m.p. 123-125°; ir (chloroform): 1740, 1725, 1625, 1605 cm^{-1}; nmr (deuteriochloroform): δ 7.45 (s, 1), 7.4-6.9 (m, 4), 3.4 (m), 3.3 (s, the sum of both peaks is 6 protons); ^{13}C-nmr (deuteriochloroform): δ 172.5 (O-C=O), 151.2 (=CHN), 124.4 (C, 6-position) arom, 122.8* (C, 5-position) arom, 120.1* (C, 4-position) arom, 110.3 (C, 7-position) arom, 90.2 (C=C-N), 44.3 (N-CH_3); ms (70 ev): m/e 189 (M^+).

Anal. Calcd. for $C_{11}H_{11}NO_2$: C, 69.8; H, 5.9; N, 7.4. Found: C, 69.4; H, 5.7; N, 7.1.

3-Dimethylaminomethylene-2,3-dihydro-2-oxo-6-benzofurancarboxaldehyde (**5**).

The most polar fraction from the column chromatography described above was eluted with 2% methanol/chloroform to yield 4.2 g. (24%) of **5**. An analytical sample was crystallized from methylene chloride/ether, m.p. 143-145°; ir (chloroform): 1735, 1685, 1630, 1595 cm^{-1} ; nmr (deuteriochloroform): δ 9.8 (s, 1, -CHO), 7.65-7.1 (m, 4), 3.7 (s), 3.5 (s), 3.45 (s, the sum of the three peaks is 6 protons, $N(CH_3)_2$); ^{13}C-nmr (deuteriochloroform): δ 191.13, 191.02 (-CHO), 153.29, 151.03 (=CHN), 150.66, 149.29 (C-O) arom, 126.41, 126.13 (C, 5-position) arom, 119.49, 114.12 (C, 4-position) arom, 109.54, 109.05 (C, 7-position) arom, 89.72, 88.16 (C=C-N), 48.11, 43.04 (N-CH_3). Two values are given for each assignment because of the 50:50 *E/Z* isomer mixture and at this time it is not known which values correspond to which isomer; ms (70 ev): m/e 217 (M^+).

Anal. Calcd. for $C_{12}H_{11}NO_3$: C, 66.3; H, 5.1; N, 6.4. Found: C, 66.0; H, 4.9; N, 6.2.

1-Methyl-1*H*-benzofuro[2,3-*c*][1,2]thiazine 2,2-Dioxide (**6**).

To a solution of *N*-methylmethanesulfonamide (2) in 100 ml. of dimethylacetamide was added 1.7 g. of sodium hydride (50% in mineral oil, pentane washed) in portions (hydrogen evolution occurs). After stirring at room temperature for 30 minutes, 6.0 g. of **3** was added then the mixture was stirred at 95° for 3 days. The solvent was removed under reduced pressure and water was added to the residue. The organic material was extracted into methylene chloride and was dried over sodium sulfate. The solvent was removed under reduced pressure and the residue was chromatographed on a column of silica gel using chloroform to elute the product, 1.9 g. (24%) of **6**. An analytical sample was crystallized from methylene chloride/ether, m.p. 165-168°; ir (chloroform): 1610, 1335, 1150 cm^{-1}; nmr (deuteriochloroform): δ 7.6-7.1 (m, 5), 6.3 (d, 1, J = 10 Hz), 3.6 (s, 3).

Anal. Calcd. for $C_{11}H_9NO_3S$: C, 56.2; H, 3.9; N, 6.0; S, 13.6. Found: C, 56.3; H, 4.1; N, 6.0; S, 13.4.

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REFERENCES AND NOTES

(1) G. M. Coppola and G. E. Hardtmann, *J. Heterocyclic Chem.*, **14**, 1117 (1977).

(2) B. Helferich and H. Grünert, *Chem. Ber.*, **73**, 1131 (1940).