Novel Reactions of Carbon Suboxide. Synthesis of 1,5-Benzodioxepins, 1,5-Benzoxathiepins and 1,5-Benzoxazepins (1)

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The preparation of 1,5-benzodioxepins, 1,5-benzoxathiepins and 1,5-benzoxazepins derivatives is described here. The structure of the products has been determined by elemental analysis and spectroscopic data.

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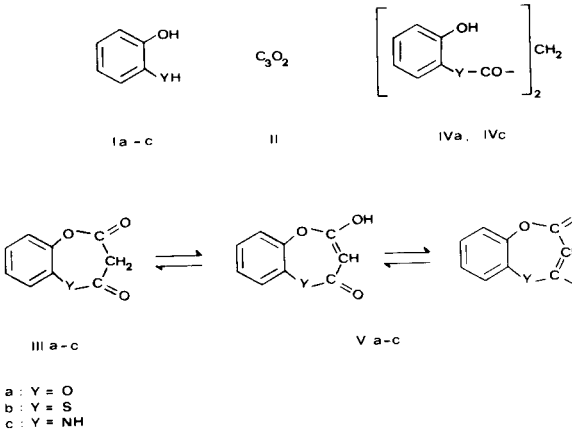
It is well known that oxazepins and dioxepins constitute an important class of biologically active compounds (2). The great interest in these derivatives prompted us to find a new approach to some novel benzo derivatives of seven-membered heterocyclic rings which are likely to show biological activity.

By reacting equimolar amounts of 1,2-benzodiol (Ia), 2-hydroxythiophenol (Ib), 2-hydroxyaniline (Ic) with carbon suboxide (II) in a dilute solution of diethyl ether, the compounds IIIa-c have been obtained, respectively. As by-products of the reactions of II with Ia and Ic we obtained, together with IIIa and IIIc, the esters IVa and IVc, respectively. When the reactions were carried out in a concentrated solution of diethyl ether, the esters IVa and IVc were isolated as the sole product.

The structure of the heterocycles obtained was determined by analytical and spectroscopic methods. Furthermore, ir and nmr spectra showed that IIIa and IIIc existed as a mixture of the two tautomeric forms III-V both in solution and in the solid state. In fact, the ir spectra of IIIa showed the OH band at 3400 cm^{-1} in addition to the characteristic band of C=O group at 1780 and 1730 cm^{-1}; the nmr spectra showed the characteristic signals of both methine and methylene protons at δ 7.23 and δ 3.91 ppm, respectively, in a 1:1 ratio, together with an OH signal at δ 6.95 ppm.



Compound IIIc featured an analogous behaviour; also in this case the two tautomeric forms were present in a 1:1 ratio.

On the contrary, the ir spectrum of IIIb did not show any characteristic OH absorption and the nmr spectrum did not give any signal attributable to a methine proton. In spite of this the uv spectra of IIIb at different *p*H values indicated the existence of a tautomeric mixture. So, while at *p*H 1.0 and *p*H 7.0 a spectrum with maxima at 279, 235 and 215 nm was obtained, at *p*H 12.8 the above said data were shifted at 302, 250 and 220 nm, respectively. An intrinsic instability of the compound IIIb in basic conditions can be ruled out since upon acidification the maxima values became the initially observed values.

Compounds IIIa and IIIc behaved similarly.

EXPERIMENTAL

Literature procedures were followed in the preparation 2-hydroxythiophenol (Ib) (3) and carbon suboxide (II) (4).

Melting points were determined on a Kofler hot stage microscope and are uncorrected. The ir spectra were obtained on a Perkin-Elmer model 157G spectrophotometer using potassium bromide mulls. The nmr spectra were recorded on a Varian FT 80A spectrometer and the chemical shifts were determined using tetramethylsilane as the internal standard. The uv spectra were recorded with a Beckman model 25 spectrophotometer. Solutions for ultraviolet spectral determinations were prepared by diluting an aliquot of an ethanol solution with 0.1*N* hydrochloric acid, or phosphate buffer, or 0.1*N* sodium hydroxide until *p*H 1.0, 7.0 and 12.8 were reached, respectively. Mass spectra were measured with an "Hitachi" Perkin-Elmer RMU-6D spectrometer at 70 eV. Microanalyses for C, H, N and S were carried out on a Carlo Erba model 1106 Elemental Analyzer.

3*H*-1,5-Benzodioxepine-2,4-dione (IIIa).

To a stirred solution of Ia (45 mmoles) in dry diethyl ether (300 ml), cooled at -5°, II (45 mmoles) was added during two hours. When the addition was complete, the mixture was strongly stirred at -5° for 24 hours and at room temperature for 54 hours. The white substance which precipitated from the reaction mixture was collected and after crystallization from chloroform was shown to be IVa by direct comparison of its ir and nmr spectra with the spectra of an authentic sample, yield 10%, mp 145° [lit (5) mp 140°].

The ether solution was evaporated under reduced pressure and the residue was crystallized from diethyl ether to give IIIa in 38% yield, mp 170°; ir: 3400 (OH), 1780 and 1730 cm^{-1} (C=O); uv: λ max 280 (ϵ, 2,800), 220 (ϵ, 6,500) and 210 nm (ϵ, 11,000) at *p*H 1.0 and at *p*H 7.0; 291 (ϵ,

5,000), 245 (ε, 5,900) and 210 nm (ε, 6,500) at *p*H 12.8; nmr (deuteriochloroform): δ 3.91 (s, 2 H, -C*H*$_2$-), 6.96 (s, 1 H, OH, deuterium oxide exchanged), 7.09 (m, 4 H arom) and 7.23 ppm (s, 1 H, -C*H*=); ms: molecular ion, m/e 178 (Calcd. 178).

Anal. Calcd. for $C_9H_6O_4$: C, 60.68; H, 3.39. Found: C, 60.59; H, 3.37.

Only IVa was obtained in 55% yield by performing the reaction in 50 ml of diethyl ether.

3*H*-1,5-benzoxathiepine-2,4-dione (IIIb).

A solution of Ib (45 mmoles) in dry diethyl ether (300 ml) was treated at 0° with II (45 mmoles) and worked up in the same manner described above. Partial evaporation of the solvent furnished a white precipitate which was filtered off, crystallized from chloroform in the presence of charcoal and identified as IIIb, yield 41%, mp 130°; ir: 1720 cm^{-1} (C=O); uv: λ max 279 (ε, 1,250), 235 (ε, 5,300) and 215 nm (ε, 7,200) at *p*H 1.0 and at *p*H 7.0; 302 (ε, 6,900), 250 (ε, 7,700) and 220 nm (ε, 8,200) at *p*H 12.8; nmr (deuteriochloroform): δ 3.76 (s, 2 H, -C*H*$_2$-) and 7.18 ppm (m, 4 H arom); ms: molecular ion, m/e 194 (Calcd. 194).

Anal. Calcd. for $C_9H_6O_3S$: C, 55.66; H, 3.11; S, 16.50. Found: C, 55.66; H, 3.19; S, 16.58.

The diethyl ether solution was then completely evaporated to give a viscous yellow oil, which was identified as 2,2'-dithiobisphenol, yield 11%, bp 151-152° (0.5 mm) [lit (3), bp 160-170° (2 mm)].

3*H*,5*H*-1,5-Benzoxazepine-2,4-dione (IIIc).

A solution of Ic (90 mmoles) in dry diethyl ether (600 ml) was treated with II (90 mmoles) and worked up in the same manner described above. After solvent evaporation, the residue was triturated with hot ethanol. The soluble fraction, after cooling, gave a white product which was identified as IVc by direct comparison of its ir and nmr spectra with the spectra of an authentic sample, yield 16%, p 223° [lit (6) mp 225°].

The insoluble fraction was crystallized from *N,N*-dimethylformamide to give IIIc in 50% yield, mp 232°; ir: 3390 (NH), 3150 (OH), 1730 cm^{-1} (C=O); uv: λ max 281 (ε, 6,350), 245 (ε, 10,500) and 210 nm (ε, 19,500) at *p*H 1.0 and *p*H 7.0; 315 (ε, 9,500), 260 (ε, 13,000) and 220 nm (ε, 26,300) at *p*H 12.8; nmr (DMSO-d$_6$): δ 3.30 (s, 1 H, OH, deuterium oxide exchanged), 3.70 (s, 2 H, -C*H*$_2$-), 6.80 (m, 4 H arom), 7.83 (d, 1 H, -C*H*=) and 9.69 ppm (d, 1 H, -N*H*-, deuterium oxide exchanged); ms: molecular ion, m/e 177 (Calcd. 177).

Anal. Calcd. for $C_9H_7NO_3$: C, 61.01; H, 3.98; N, 7.91. Found: C, 61.07; H, 4.05; N, 8.00.

Only IVc was obtained in 58% yield when the reaction was performed in 70 ml of diethyl ether.

REFERENCES AND NOTES

(1) This work was supported in part by the National Research Council (CNR), Rome, Italy.

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