Novel Reactions of Carbon Suboxide. XI. Synthesis of 1,5-Cycloalkadioxepins and 1,5-Cycloalkadiazepines [1]

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Cis-1,2-dihydroxy- and -1,2-diaminocycloalkanes react with carbon suboxide to give cycloalka-derivatives of seven membered heterocyclic rings. In contrast the *trans*-isomers give malonic esters accompanied, in some cases, by macrocycles. A new separation procedure of geometrical isomers has been devised.

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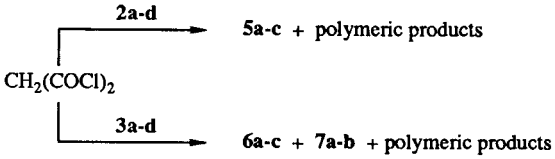
It has been previously shown that carbon suboxide (**1**) reacts with bifunctionalized benzene derivatives to yield benzocondensed heterocyclic compounds with one or two heteroatoms [2]. For instance, 1,2-dihydroxy-, 1-hydroxy-2-mercapto-, and 1-hydroxy-2-amino-substituted benzenes give seven membered heterocyclic derivatives containing respectively oxygen-oxygen, oxygen-sulphur and oxygen-nitrogen atoms [3].

Due to the biological importance of epinic derivatives, we have extended the study of this reaction to cycloaliphatic derivatives bifunctionalized with vicinal *cis* or *trans* hydroxy- and amino-groups in order to obtain cycloalka-derivatives of seven membered heterocyclic rings.

The reactions were run in dilute chloroform solution at room temperature (*ca.* 6.4 x 10^{-2} *M* for both reagents).

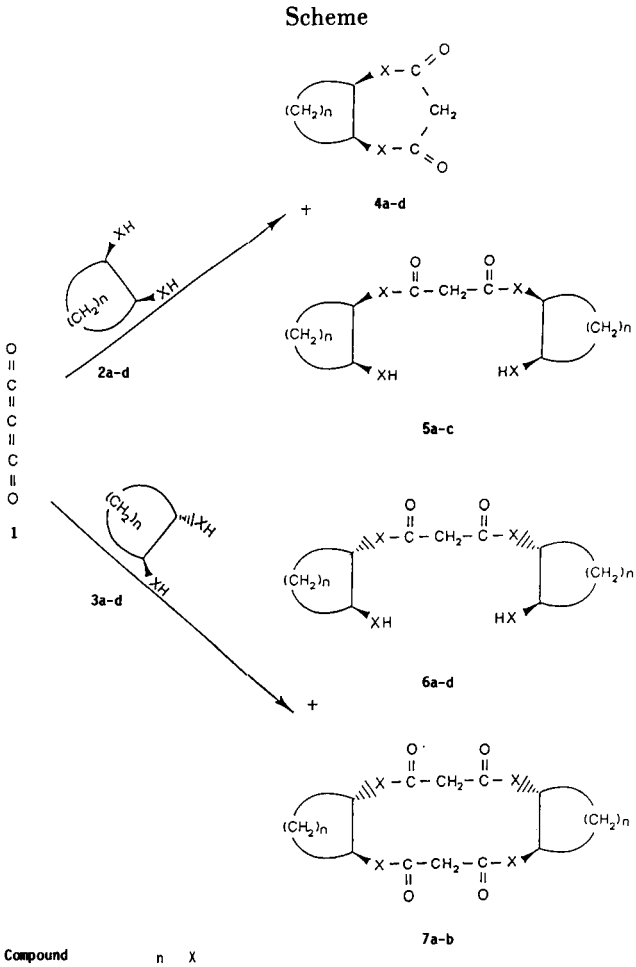
Products analysis has shown that *cis*-diols **2a-c** react with **1** yielding heterocycles **4a-c** along with 7-12% of malonic esters **5a-c**. *Cis*-diamine **2d** yields only the heterocyclic compound **4d**. On the other hand, *trans*-derivatives **3a-d** yield only malonic esters **6a-d** and no traces (less than 3%) of epinic derivatives; **3a** and **3b** give, together with malonic esters **6a** and **6b**, about 30% of macrocycles **7a** and **7b**.

Malonyl chloride does not constitute a valid alternative to carbon suboxide in the preparation of epinic heterocycles. In fact, neither *cis*-diols nor *trans*-diols yield epinic heterocycles. Only malonic esters **5a-c** along with polymeric mixtures are obtained. *Trans*-diols **3a** and **3b** also give macrocycles **7a** and **7b** in 15-20% yield. *Cis*- and *trans*-diamines **2d** and **3d** give only unidentified polymeric mixtures.



It is interesting to note that *cis*-derivatives react with carbon suboxide faster than *trans*-derivatives as quantitatively determined by measuring the disappearance of the reagents by glc. In the reported experimental conditions

Scheme



Compound	n	X
2a,3a,4a,5a,6a,7a	3	O
2b,3b,4b,5b,6b,7b	4	O
2c,3c,4c,5c,6c	5	O
2d,3d,4d,6d	4	NH

cis-diols react in about 16 hours, while the *trans*-diols presence is still significant after 40 hours. *Cis*-1,2-diaminocyclohexane (**2d**) disappears in 1 hour while the *trans*-derivative **3d** needs more than 3 hours.

The above results have suggested a new separation procedure for geometrical isomers whose functional groups can react with **1**. Equimolar mixtures of each of **2a-d** (1 mole) and the corresponding isomers **3a-d** (1 mole) react with **1** (1.25 moles) yielding the epinic derivatives **4a-d** along with unreacted *trans*-isomers **3a-d** and 25% of malonic esters **6a-d**. The *trans*-isomers can be separated easily by simple flash-chromatography from malonic esters and from epinic derivatives. From the latter the *cis*-isomers **2a-d** can be obtained upon saponification or reduction with lithium aluminum hydride.

EXPERIMENTAL

Melting points were determined on a Kofler apparatus and are uncorrected. The ^{1}H-nmr spectra were determined using a Varian FT-80A spectrometer; chemical shifts are relative to tetramethylsilane. Mass spectral data were collected on an Hitachi Perkin-Elmer RMU-6D mass spectrometer at 70 eV, using a direct-inlet system. The ir spectra were taken on a Perkin-Elmer 157G spectrophotometer. The glc analyses were carried out on a Carlo Erba 5300 gas chromatograph using a 25 m x 0.32 mm OV17 capillary column and a flame ionization detector. Flash column chromatography was carried out on Merck silica gel 60 (230-400 mesh). Elemental analyses were carried out on a Carlo Erba 1106 Elemental Analyzer.

Reagent-grade commercially available reagents and solvents were used. The carbon suboxide (**1**) was prepared from pyrolysis of the di-*O*-acetyltartaric anhydride [4]. The derivatives **2d** and **3a-d** were purchased from Fluka A. G. or Aldrich Chemical Co., while the compounds **2a-c** were prepared according to literature procedures [5,6]. All these compounds were purified and dried rigorously.

General Procedure for the Reactions of Compounds **2a-d** and **3a-d** with Carbon Suboxide.

To a stirred solution of each of **2a-d** (40 mmoles) or each of **3a-d** (40 mmoles) in anhydrous chloroform (700 ml), **1** was slowly added at 0°. When the addition was completed, the mixture was kept at room temperature with stirring. The solution was evaporated under reduced pressure and the residue flash chromatographed using 3:1 benzene/ethyl acetate to provide each of **4a-d**, **5a-c**, **6a-d** and **7a-b**.

Cis-2,6-Dioxabicyclo[5.3.0]decan-3,5-dione (**4a**) and Propanedioic Acid *cis*-Bis(2-hydroxycyclopentyl) Ester (**5a**).

Following the general procedure (*vide supra*), **2a** and **1** were combined for 15 hours at which time glc indicated complete disappearance of starting **2a**. Flash chromatography of the residue gave two fractions. The first fraction was **4a** as white crystals, yield 82%, mp 60°; ir (chloroform): 1730 cm^{-1} (C=O); ^{1}H-nmr (deuteriochloroform): δ 3.68-3.50 (m, 2H, CH), 3.29 (s, 2H, CH_2CO), 1.90-1.40 (m, 4H, CH_2), 1.30-1.10 (m, 2H, CH_2); ms: m/z 170 (M$^+$).

Anal. Calcd. for $C_8H_{10}O_4$: C, 56.46; H, 5.92. Found: C, 56.56; H, 6.00.

The second fraction was **5a** as a yellow oil, yield 8%; ir (neat): 3320 (OH), 1720 cm^{-1} (C=O); ^{1}H-nmr (deuteriochloroform): δ 4.40 (s, 2H, OH), 3.85-3.60 (m, 4H, CH), 3.35 (s, 2H, CH_2CO), 2.05-1.65 (m, 8H, CH_2), 1.45-1.10 (m, 4H, CH_2); ms: m/z 272 (M$^+$).

Anal. Calcd. for $C_{13}H_{20}O_6$: C, 57.34; H, 7.40. Found: C, 57.17; H, 7.29.

Propanedioic Acid *trans*-Bis(2-hydroxycyclopentyl) Ester (**6a**) and *trans*-Dicyclopento[*b,i*]-1,4,8,11-tetraoxacyclotetradecane-5,7,12,14-tetraone (**7a**).

Following the general procedure (*vide supra*), **3a** and **1** were combined for 40 hours. Flash chromatography of the residue gave two fractions. The first fraction was **6a** as a yellow oil, yield 70%; ir (neat): 3330 (OH), 1730 cm^{-1} (C=O); ^{1}H-nmr (deuteriochloroform): δ 4.30 (s, 2H, OH), 3.75-3.50 (m, 4H, CH), 3.30 (s, 2H, CH_2CO), 1.90-1.50 (m, 8H, CH_2), 1.40-1.00 (m, 4H, CH_2); ms: m/z 272 (M$^+$).

Anal. Calcd. for $C_{13}H_{20}O_6$: C, 57.34; H, 7.40. Found: C, 57.20; H, 7.33.

The second fraction was **7a** as white crystals, yield 27%, mp 56°; ir (nujol): 1730 cm^{-1} (C=O); ^{1}H-nmr (deuteriochloroform): δ 4.30-3.90 (m, 4H, CH), 3.20 (s, 4H, CH_2CO), 1.85-1.40 (m, 8H, CH_2), 1.15-0.90 (m, 4H, CH_2); ms: m/z 340 (M$^+$).

Anal. Calcd. for $C_{16}H_{20}O_8$: C, 56.46; H, 5.92. Found: C, 56.60; H, 6.01.

2,6-Dioxa-*cis*-bicyclo[5.4.0]undecen-3,5-dione (**4b**) and Propanedioic Acid *cis*-Bis(2-hydroxycyclohexyl) Ester (**5b**).

Following the general procedure (*vide supra*), **2b** and **1** were combined for 16 hours at which time glc indicated complete disappearance of starting **2b**. Flash chromatography of the residue gave two fractions. The first fraction was **4b** as white crystals, yield 75%, mp 118-120°; ir (nujol): 1740 cm^{-1} (C=O); ^{1}H-nmr (DMSO-d_6): δ 3.65-3.45 (m, 2H, CH), 3.35 (s, 2H, CH_2CO), 1.70-1.30 (m, 8H, CH_2); ms: m/z 184 (M$^+$).

Anal. Calcd. for $C_9H_{12}O_4$: C, 58.68; H, 6.56. Found: C, 58.90; H, 6.82.

The second fraction was **5b** as white crystals, yield 12%, mp 177-178°; ir (nujol): 3350 (OH), 1730 cm^{-1} (C=O); ^{1}H-nmr (DMSO-d_6): δ 4.15 (s, 2H, OH), 3.75-3.50 (m, 4H, CH), 3.35 (s, 2H, CH_2CO), 1.70-1.40 (m, 16H, CH_2); ms: m/z 300 (M$^+$).

Anal. Calcd. for $C_{15}H_{24}O_6$: C, 59.98; H, 8.05. Found: C, 59.81; H, 7.97.

Propanedioic Acid *trans*-Bis(2-hydroxycyclohexyl) Ester (**6b**) and *trans*-Dicyclohexo[*b,i*]-1,4,8,11-tetraoxacyclotetradecane-5,7,12,14-tetraone (**7b**).

Following the general procedure (*vide supra*), **3b** and **1** were combined for 42 hours. Flash chromatography of the residue gave two fractions. The first fraction was **6b** as white crystals, yield 51%; mp 180-185°; ir (nujol): 3300 (OH), 1720 cm^{-1} (C=O); ^{1}H-nmr (DMSO-d_6): δ 4.10 (s, 2H, OH), 3.60-3.40 (m, 4H, CH), 3.35 (s, 2H, CH_2CO), 1.55-1.30 (m, 16H, CH_2); ms: m/z 300 (M$^+$).

Anal. Calcd. for $C_{15}H_{24}O_6$: C, 59.98; H, 8.05. Found: C, 59.87; H, 7.95.

The second fraction was **7b** as white crystals, yield 32%, mp 233-234° [lit (7), mp 233-235°). Spectral data (ir, ^{1}H-nmr and ms) were identical to those previously reported [7].

2,6-Dioxa-*cis*-bicyclo[5.5.0]dodecan-3,5-dione (**4c**) and Propanedioic Acid *cis*-Bis(2-hydroxycycloheptyl) Ester (**5c**).

Following the general procedure (*vide supra*), **2c** and **1** were combined for 17 hours at which time glc indicated complete disappearance of **2c**. Flash chromatography of the residue gave two fractions. The first fraction was **4c** as white crystals, yield 77%, mp 46-48°; ir (nujol): 1750 cm^{-1} (C=O); ^{1}H-nmr (deuteriochloroform): δ 3.80-3.60 (m, 2H, CH), 3.35 (s, 2H, CH_2CO), 1.60-1.40 (m, 10H, CH_2); ms, m/z 198 (M^+).

Anal. Calcd. for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.60; H, 7.30.

The second fraction was **5c** as a yellow oil, yield 7%; ir (neat): 3430 (OH), 1730 cm^{-1} (C=O); ^{1}H-nmr (deuteriochloroform): δ 4.00-3.70 (m, 4H, CH), 3.35 (s, 2H, CH_2CO), 2.85 (s, 2H, OH), 1.85-1.40 (m, 20H, CH_2); ms: m/z 328 (M^+).

Anal. Calcd. for $C_{17}H_{28}O_6$: C, 62.17; H, 8.59. Found: C, 62.10; H, 8.48.

Propanedioic Acid *trans*-Bis(2-hydroxycycloheptyl) Ester (**6c**).

Following the general procedure (*vide supra*), **3c** and **1** were combined for 45 hours. Flash chromatography of the residue gave **6c** as a yellow oil, yield 65%; ir (neat): 3460 (OH), 1720 cm^{-1} (C=O); ^{1}H-nmr (deuteriochloroform): δ 3.90-3.50 (m, 4H, CH), 3.40 (s, 2H, CH_2CO), 2.80 (s, 2H, OH), 1.70-1.30 (m, 20H, CH_2); ms: m/z 328 (M^+).

Anal. Calcd. for $C_{17}H_{28}O_6$: C, 62.17; H, 8.59. Found: C, 62.31; H, 8.63.

2,6-Diaza-*cis*-bicyclo[5.4.0]undecan-3,5-dione (**4d**).

Following the general procedure (*vide supra*), **2d** and **1** were combined for 1 hour at which time glc indicated complete disappearance of starting **2d**. Flash chromatography of the residue gave **4d** as yellow crystals, yield 95%, mp 156-158°; ir (nujol): 3300 (NH), 1670 cm^{-1} (C=O); ^{1}H-nmr (DMSO-d_6): δ 4.20 (s, 2H, NH), 3.40 (s, 2H, CH_2CO), 3.35-3.00 (m, 2H, CH), 1.65-1.25 (m, 8H, CH_2); ms: m/z 182 (M^+).

Anal. Calcd. for $C_9H_{14}N_2O_2$: C, 59.32; H, 7.74; N, 15.37. Found: C, 59.52; H, 7.61; N, 15.18.

trans-N,N'-Bis(2-aminocyclohexyl)propanediamide (**6d**).

Following the general procedure (*vide supra*), **3d** and **1** were combined for 4 hours. Flash chromatography of the residue gave **6d** as yellow crystals, yield 90%, mp 223-225°; ir (nujol): 3260, 3220 (NH), 1660 cm^{-1} (C=O); ^{1}H-nmr (DMSO-d_6): δ 3.60 (s, 2H, NH), 3.45 (s, 2H, CH_2CO), 3.35-3.25 (m, 4H, CH), 2.95 (s, 4H, NH_2), 1.80-1.40 (m, 16H, CH_2); ms: m/z 296 (M^+).

Anal. Calcd. for $C_{15}H_{28}N_4O_2$: C, 60.78; H, 9.52; N, 18.90. Found: C, 60.51; H, 9.73; N, 18.78.

Reaction of **2a-d** and **3a-d** with Malonyl Chloride.

To a stirred solution of each of **2a-d** or each of **3a-d** (40 mmoles), anhydrous ether (500 ml) and triethylamine (80 mmoles) malonyl chloride (40 mmoles) in anhydrous ether (100 ml) was added at 0°. When the addition was completed, the mixture was kept at room temperature with stirring. The reaction was followed by glc for the disappearance of the starting diol. At completion of the reaction (observed by glc), the solution was filtered from unidentified polymeric products, evaporated under reduced pressure and the residue flash chromatographed using 3:1 benzene/ethyl acetate. In this manner, **5a** in 30% yield was obtained starting from **2a**; **5b** in 33% yield was obtained from **2b**; **5c** in 20% yield was obtained from **2c**; **6a** in 40% yield and **7a** in 15% yield were obtained from **3a**; **6b** in 42% yield and **7b** in 20% yield were obtained from **3b**; **6c** in 37% yield was obtained from **3c**; only unidentified polymeric products were obtained from **2d** and from **3d**.

Reaction of a Mixture of **2a-d** and **3a-d** with **1**.

To a stirred solution of each of **2a-d** (20 mmoles) and each of **3a-d** (20 mmoles) in anhydrous chloroform (700 ml), **1** (25 mmoles) was slowly added at 0°. When the addition was completed, the mixture was kept at room temperature with stirring. Disappearance of **2a-d** was observed by glc. The solution was then evaporated under reduced pressure and the residue flash chromatographed using 3:1 benzene/ethyl acetate to provide three fractions. The first fraction was each of **4a-d** in nearly 90% yield. These compounds were identical with those of the above products in all respects.

The second fraction was each of the unreacted **3a-d**.

The third fraction was each of **6a-d** in nearly 25% yield.

Each of the compounds **4a-d** were reconverted into **2a-d** in almost quantitative yields after hydrolysis with ethanolic potassium hydroxide or after treatment with lithium aluminum hydride in ether.

REFERENCES AND NOTES

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

[2] L. Bonsignore, G. Loy, M. Secci, S. Cabiddu and G. Gelli, *J. Chem. Soc., Perkin Trans. 2*, 1247 (1988).

[3] L. Bonsignore, S. Cabiddu, G. Loy and M. Secci, *J. Heterocyclic Chem.*, **19**, 1241 (1982).

[4] L. Crombie, P. A. Gilbert and R. P. Houghton, *J. Chem. Soc. C*, 130 (1968).

[5] W. Reischl and E. Zbiral, *Tetrahedron*, **35**, 1109 (1979).

[6] V. VanRheenen, D. Y. Cha and W. M. Hartley, in Organic Syntheses, Coll Vol **6**, John Wiley and Sons, New York, NY, 1988, p 342.

[7] C. Anchisi, L. Corda, A. M. Fadda, A. Maccioni and G. Podda, *J. Heterocyclic Chem.*, **22**, 577 (1984).