NOVEL REACTIONS OF CARBON SUBOXIDE. VII. SYNTHESIS OF HETEROCYCLIC RINGS BY REACTION WITH BIFUNCTIONAL ALIPHATIC COMPOUNDS

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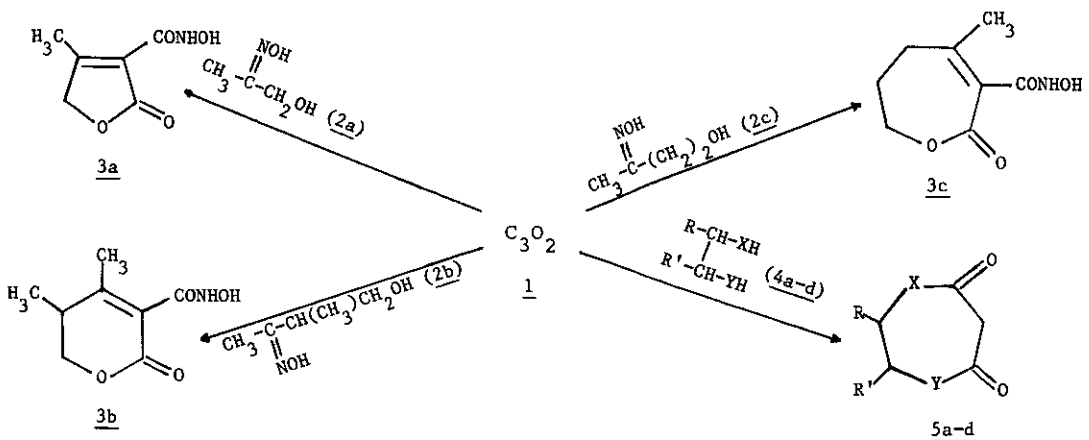
Abstract - Carbon suboxide reacts with various bifunctional aliphatic compounds yielding derivatives of furan, pyran, oxepin, diazepine, oxazepine and dioxepin. A description of the synthesis is given. The structure of the reaction products was determined by elemental analysis and spectroscopic methods.

In recent years we started an investigation with the aim of developing new synthetic methods for the preparation of five-, six- and seven-membered heterocyclic compounds which might possess biological activity. We used as a starting material carbon suboxide (1) whose versatility and reactivity are well known.[1]

Scheme 1



4a, 5a: X=Y=NH, R=R'=H; 4b, 5b: X=O, Y=NH, R=R'=H;
4c, 5c: X=Y=O, R=C_6H_5, R'=H; 4d, 5d: X=Y=O, R=R'=CH_3

The results so far obtained have shown that (1) combines with bifunctional benzene compounds to yield benzocondensed six- and seven-membered heterocyclic rings.[2-5]

In order to obtain heterocyclic rings which are not condensed with the benzene ring we extended similar methods to bifunctional aliphatic compounds. We thus expected to find alternative sinthe-ses of substituted butenolides, which are interesting precursors of cephalosporin C,[4] and of pyran-2-one derivatives which also have pharmacological applications.[6,7]

The reaction of oximes (2a-c) with carbon suboxide gave the corresponding hydroxamic acids of the furan (3a), pyran (3b) and oxepin (3c) in satisfactory yields (Scheme 1).

Table 1. Yields, mp, IR and ^{1}H NMR Spectral Data of 3 and 5

Compd. No	Yield (%)	mp (°C) [bp/mmHg]	IR (nujol) νmax (cm^{-1})	^{1}H NMR (solvent) δ
3a	63	74-75	3400, 3200 (NH and OH) 1730, 1660 (C=O)	($CDCl_3$): 7.25 (1H, s, NH, D_2O exchanged), 4.66 (2H, s, OCH_2), 3.45 (1H, s, OH, D_2O exchanged), 1.88 (3H, s, CH_3)
3b	81	198-200	3500, 3300 (NH and OH) 1770, 1750, 1650 (C=O)	($CDCl_3$): 7.20 (1H, s, NH, D_2O exchanged), 4.42 (1H, m, CH_3-CH), 3.39 (2H, d, OCH_2), 2.10 (1H, s, OH, D_2O exchanged), 1.85 (3H, s, CH_3-C=), 1.10 (3H, d, CH_3-CH)
3c	58	83-84	3500, 3300 (NH and OH) 1760, 1730, 1650 (C=O)	($CDCl_3$): 7.28 (1H, s, NH, D_2O exchanged), 4.10 (2H, t, OCH_2), 3.47 (2H, t, CH_2-C=), 2.53 (1H, s, OH, D_2O exchanged), 2.20 (2H, m, $CH_2CH_2CH_2$), 1.83 (3H, s, CH_3)
5a	92	289-290	3270 (NH and OH), 1640, 1630 (C=O)	Insoluble in common nmr solvents
5b	44	109-110	3280 (NH and OH), 1740 1640 (C=O)	[$(CD_3)_2CO$]: 6.83 (1H, s, CH=), 6.58 (1H, t, NH, D_2O exchanged), 3.48 (2H, m, CH_2-NH), 3.23 (2H, t, OCH_2), 3.06 (2H, s, CH_2-CO), 2.75 (1H, s, OH, D_2O exchanged)
5c	70	54-55	3390 (OH), 1750, 1730 (C=O)	($CDCl_3$): 7.30-7.26 (5H, m, Ar-H), 7.10 (1H, s, CH=), 4.70 (1H, t, CH_2-CH), 3.57 (2H, d, CH_2-CH), 2.40 (1H, s, D_2O exchanged), 2.13 (2H, s, CH_2-CO)
5d	60	[133-134 /760]	3420 (OH), 1730 (C=O)	($CDCl_3$): 4.83 (2H, m, CH_3-CH), 3.35 (2H, s, CH_2-CO), 1.13 (6H, d, CH_3-CH)

Similarly, diazepine (5a), oxazepine (5b) and dioxepin (5c-d) compounds have been obtained in good yield starting from 1,2-ethanediamine (4a), 2-aminoethanol (4b) and glycols (4c-d). The results are shown in Tables 1 and 2. Attempts to obtain (3a-c) by treating (2a-c) with malonic esters or malonyl chloride gave unsatisfactory results. An alternative synthesis of (5a-d) by the reaction of (4a-d) with malonic esters or malonyl chloride resulted in the formation of the desired products in very low yield (10%) together with a large amount of possibly polymeric products. Consequently, the isolation of the products was quite difficult and required repeated column chromatography. It must be noticed that similar reactions of malonyl derivatives with bifunctional benzene compounds, amidoxime ethers, hydrazines and anilides, give good yields of the heterocyclic compounds.[8-11]

Table 2. Mass Spectral and Analytical Data of 3 and 5

Compd. No.	Formula	Ms m/e	Microanalyses (Calcd.) C (%)	H (%)	N (%)
3a	$C_6H_7NO_4$	157 (M^+), 125, 97	45.45 (45.86)	4.51 (4.49)	8.80 (8.91)
3b	$C_8H_{11}NO_4$	185 (M^+), 153, 125	51.68 (51.88)	6.05 (5.98)	7.48 (7.56)
3c	$C_8H_{11}NO_4$	185 (M^+), 153, 125	51.79 (51.88)	6.07 (5.98)	7.51 (7.56)
5a	$C_5H_8N_2O_2$	128 (M^+), 100, 86	46.72 (46.86)	6.23 (6.29)	21.72 (21.86)
5b	$C_5H_7NO_3$	129 (M^+), 101, 87	46.39 (46.50)	5.38 (5.47)	10.77 (10.85)
5c	$C_{11}H_{10}O_4$	206 (M^+), 178, 164	64.15 (64.07)	4.81 (4.89)	
5d	$C_7H_{10}O_4$	158 (M^+), 130, 116	53.28 (53.16)	6.32 (6.37)	

The synthesized compounds have good elemental analytical results and spectral characteristics in accord with the reported structures. Compounds (3a-c) display ir bands between 3500 and 3200 cm^{-1} (NH and OH), bands between 1770 and 1650 cm^{-1} indicating the presence of lactonic C=O and exonuclear amidic C=O.[12,13] ^1H Nmr spectra display a NH amidic signal at about δ 7.2. Finally, mass spectra, besides the molecular ion, have the base peak at (M^+-NHOH) and the peak at (M^+-CONHOH).

The structure of compounds (5a-d) is also consistent with elemental analytical results and spectral data. Ir and ^1H nmr spectra of (5b) and (5c) show that they exist in a mixture of tautomeric species both in solution and in the solid state. In fact, the ir spectra besides the C=O bands show also OH bands; ^1H nmr spectra display signals which are characteristic of both methine and methylene protons and OH signals from which a 3:7 ratio of tautomeric products can be calculated. Ir spectra of (5a) and (5d) also show a characteristic OH band indicating the presence of the enolic tautomer. However, the ratio could not be determined by ^1H nmr spectroscopy since (5a) is insoluble in the common organic solvents and (5d) has a concentration of the enolic tautomer too small to be detected.

EXPERIMENTAL

Melting points were obtained on a Kofler hot stage microscope and are uncorrected. Ir spectra were run using NaCl plates on a Perkin-Elmer 157G grating spectrophotometer. ^{1}H Nmr spectra were recorded on a Varian FT 80A spectrometer using Me_4Si as the internal standard. Mass spectra were obtained with an "Hitachi" Perkin-Elmer RMU-6D spectrometer at 70 eV, using direct-inlet system. Literature procedures were followed in the preparation of (1)[14] and oximes (2a-c),[15-17] while the compounds (4a-d) were commercial products.

General Procedure for the Preparation of 3 and 5

To a stirred solution of (2) or (4) (16 mM) in dry ether (for 2a, 2b, 4c, 4d) or dry chloroform (for 2c) or dry benzene (for 4a, 4b) (250 ml) (1) (17 mM) was added during 1 h at -70°C. When the addition was complete, the mixture was stirred at 0° for 5 h and then kept at room temperature for 48 h with stirring. The reaction mixture was evaporated and the residue chromatographed on silica gel column using n-hexane-EtOAc (3:1, v/v) as eluent to give (3) or (5).

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