ELSEVIER

Il Farmaco 53 (1998) 680–683

IL FARMACO

One-step synthesis of new 3-oxa- or 3-azabicyclo[3.2.0]hept-5-en-2,7-dione and 5,9-dioxa- or 5,9-diazabicyclo[5.3.0]dec-1-en-3-methyliden-6,8-dione derivatives☆

Leonardo Bonsignore [a],*, Giuseppe Loy [a], Daniela Secci [b], Mario Secci [a], Filippo Cottiglia [a]

[a] *Dipartimento Farmaco Chimico Tecnologico, Università di Cagliari, Via Ospedale 72, I-09124 Cagliari, Italy*
[b] *Dipartimento di Studi di Chimica e Tecnologia delle Sostanze Biologicamente Attive, Università di Roma 'La Sapienza', P.le A. Moro 5, I-00185 Rome, Italy*

Abstract

In this work we describe the synthesis of new compounds of a 3-oxa- or 3-azabicyclo[3.2.0]hept-5-en-2,7-dione (**3a–d**) and 5,9-dioxa- or 5,9-diazabicyclo[5.3.0]dec-1-en-3-methyliden-6,8-dione (**4a–d**) type with potential biological activity, obtained from the reaction of 2-propyn-1-ol or 2-propynylamine derivatives (**1a–d**) with carbon suboxide (**2**) in various molar ratios. © 1998 Elsevier Science S.A. All rights reserved.

Keywords: Carbon suboxide; 3-Oxa- or 3-diazabicyclo[3.2.0]hept-1-en-2,7-dione and 5,9-dioxa- or 5,9-diazabicyclo[5.3.0]dec-1-en-3-methyliden-6,8-dione derivatives

1. Introduction

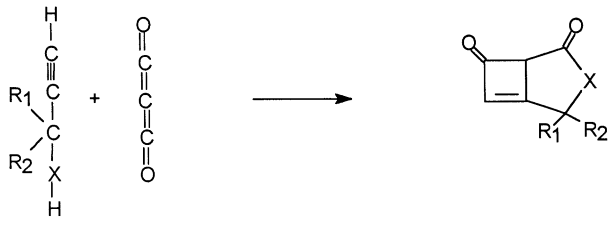
Following our research on the reactivity of carbon suboxide with different substrates [1,2], starting from unsaturated compounds, we have recently synthesized a number of spiroalkandionic derivatives with strong anticoagulant activity [3].

In this work we have extended the study of the reactivity of carbon suboxide with alkin derivatives having a terminal nucleophilic site, in order to synthesize heterocyclic compounds with potential biological activity [4,5].

2. Chemistry

The 3-oxo- or 3-azabicyclo[3.2.0]hept-5-en-2,7-dione derivatives (**3a–d**), that can be structurally correlated with analogous antimicrobial agents [6,7] have been obtained by reacting 0.016 mol of 2-propyn-1-ol or 2-propynylamine derivatives (**1a–d**) with 0.016 mol of carbon suboxide (**2**) in anhydrous chloroform solution. In this ratio, the reaction is carried out in one step but with low yields (Scheme 1).

Considering that the yields of **3a–d** were modest, we repeated the reaction after appropriately changing the molar ratio. By reacting **1a–d** and **2** in a 1:2 molar ratio, we obtained a gummy product, that was probably polymeric or macrocyclic in nature, together with small quantities of **3a–d** [8].



1a-d **2** **3a-d**

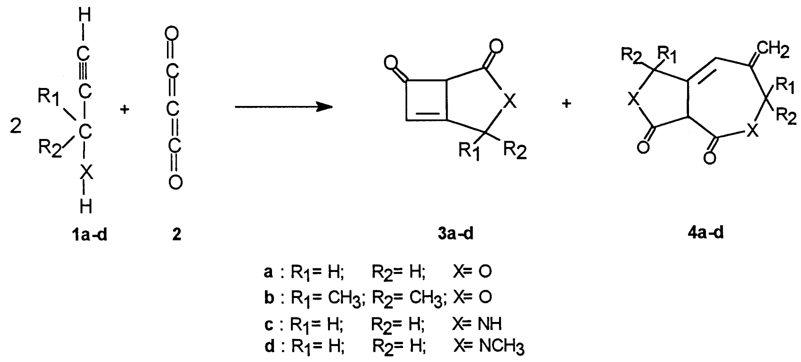
a : R_1= H; R_2= H; X= O
b : R_1= CH_3; R_2= CH_3; X= O
c : R_1= H; R_2= H; X= NH
d : R_1= H; R_2= H; X= NCH_3

Scheme 1.

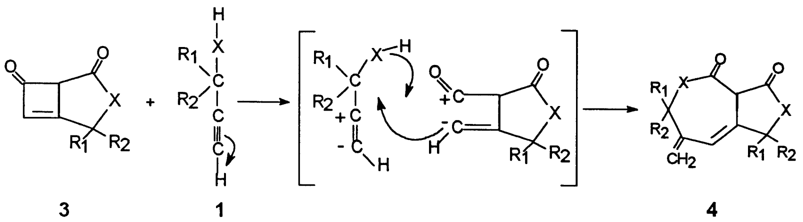
☆ Dedicated to Professor Antonio Maccioni.

* Corresponding author.

0014-827X/98/$ - see front matter © 1998 Elsevier Science S.A. All rights reserved.
PII: S0014-827X(98)00086-X



Scheme 2.



Scheme 3.

On the other hand, by reacting **1a–d** and **2** in a 2:1 molar ratio, we obtained the new 5,9-dioxa- or 5,9-diazabicyclo[5.3.0]dec-1-en-3-methyliden-6,8-dione derivatives (**4a–d**) and small quantities of **3a–d**. In this ratio the reaction is carried out in one step, with satisfactory yields (Scheme 2).

Compounds **4** are probably caused by the rupture of the ring with the greatest binding tension on **3** and consequent attack by **1** (Scheme 3).

On the other hand, as observed in previous papers [9], the structure of **3** is due to the initial attack of **2** to the nucleophilic site of **1** and is confirmed by the disappearance of the hydroxyl band and of the triple bond in the corresponding FT-IR spectra. Moreover, loss of the $[C_3HO_2]^+$ ion, m/z 69, identified as the protonated carbon suboxide, was observed for all compounds following a pathway in agreement with the literature [10]. Consequently, the FT-IR, ^{1}H NMR and mass spectra were in agreement with the assigned structures for compounds **3a–d** and **4a–d**.

3. Experimental

Melting points were determined using a Köfler apparatus and are uncorrected. Boiling points were obtained by distillation at a standard pressure with a boiling point apparatus. The FT-IR spectra were recorded on a Perkin Elmer System 2000 spectrophotometer using KBr mulls. ^{1}H NMR spectra were recorded on a Varian Unit 300 using hexamethyldisiloxane as an internal standard.

Mass spectra were taken by a QMD 1000 instrument (Fisons instrument) at 70 eV using a direct inlet system. The analyses indicated with the symbols of the elements were within ± 0.4% of theoretical values and were carried out on a Carlo Erba Model 1106 elemental analyser.

Reagent-grade commercially available reagents and solvents were used. Carbon suboxide was prepared from the pyrolysis of di-*O*-acetyltartaric anhydride [11]. Silica gel 60 (Carlo Erba) was used for column chromatography. Starting materials were purchased from Aldrich Chemical Co. All the compounds and solvents were rigorously dried before use.

3.1. General procedure for the preparation of compounds *3a–d*

Carbon suboxide (**2**) (16 mmol) was added over 2 h at − 70°C to a stirred solution of **1a**–**d** (16 mmol) in anhydrous chloroform, stabilized with amylenes (300 ml). At completion the mixture was kept at − 5°C for 24 h, then at room temperature for 48 h while stirring continuously. At the end of the reaction, the solvent was evaporated under reduced pressure and the crude residue was flash chromatographed (silica gel, 0.04 mm: 230 mesh, flow 20 ml/min, isopropyl ether:methyl alcohol 5:1 as eluents) to provide **3a** as first eluate, while **3b–d** were isolated by distillation at standard pressure from the reaction mixture.

3.1.1. 3-Oxabicyclo[3.2.0]hept-5-en-2,7-dione (*3a*)

26% yield, b.p. 160–162°C; FT-IR (KBr, cm^{-1}): ν 1760 (C=O), 1740 (C=O); ^{1}H NMR (CDCl$_3$, ppm): 3.36

(s, 1H, CO–CH–CO), 4.20 (s, 2H, CH_2–), 4.69 (s, 1H, CH=); MS (*m*/*z*) 125 (M^+), 100, 96, 69, 56, 55. *Anal.* $C_6H_4O_3$ (C, H).

3.1.2. 3-Oxabicyclo[3.2.0]hept-5-en-4-dimethyl-2,7-dione (3b)

29% yield, b.p. 141–143°C; FT-IR (KBr, cm^{-1}): *v* 1760 (C=O), 1740 (C=O); ^1H NMR ($CDCl_3$, ppm): 1.51 (s, 6H, $2CH_3$), 3.35 (s, 1H, CO–CH–CO), 4.45 (s, 1H, CH=); MS (*m*/*z*) 152 (M^+), 127, 125, 109, 83, 69. *Anal.* $C_8H_8O_3$ (C, H).

3.1.3. 3-Azabicyclo[3.2.0]hept-5-en-2,7-dione (3c)

25% yield, m.p. 41°C; FT-IR (KBr, cm^{-1}): *v* 3250 (NH), 1730 (C=O), 1650 (C=O); ^1H NMR ($CDCl_3$, ppm): 3.08 (s, 1H, CO–CH–CO), 3.28 (s, 1H, CH=), 3.84 (s, 2H, CH_2–), 8.47 (s, 1H, NH, D_2O exch); MS (*m*/*z*) 123 (M^+), 98, 95, 80, 69, 54. *Anal.* $C_6H_5NO_2$ (C, H, N).

3.1.4. 3(N-Methyl)-azabicyclo[3.2.0]hept-5-en-2,7-dione (3d)

30% yield, b.p. 130–132°C; FT-IR (KBr, cm^{-1}): *v* 1740 (C=O), 1650 (C=O); ^1H NMR ($CDCl_3$, ppm): 2.98 (s, 3H, CH_3), 3.30 (s, 1H, CO–CH–CO), 3.38 (s, 2H, CH_2–), 3.47 (s, 1H, CH=); MS (*m*/*z*) 137 (M^+), 113, 110, 81, 69, 68. *Anal.* $C_7H_7NO_2$ (C, H, N).

3.2. General procedure for the preparation of compounds **4a–d**

Carbon suboxide (**2**) (16 mmol) was added over 2 h at −70°C to a stirred solution of **1a**–**d** (32 mmol) in anhydrous chloroform, stabilized with amylenes (300 ml). At completion the mixture was kept at −5°C for 24 h, then at room temperature for 72 h while stirring continuously. At the end of the reaction, the solvent was evaporated under reduced pressure and the crude residue was crystallized with isopropyl ether to provide **4a–d**.

3.2.1. 5,9-Dioxabicyclo[5.3.0]dec-1-en-3-methyliden-6,8-dione (4a)

48% yield, m.p. 68–70°C; FT-IR (KBr, cm^{-1}): *v* 1770 (2C=O); ^1H NMR ($CDCl_3$, ppm): 3.36 (s, 1H, CO–CH–CO), 3.37 (s, 1H, CH=), 4.12 (s, 4H, $2CH_2$–), 4.69 (s, 2H, CH_2=); MS (*m*/*z*) 180 (M^+), 149, 137, 125, 123, 111, 95, 79, 69. *Anal.* $C_9H_8O_4$ (C, H).

3.2.2. 5,9-Dioxabicyclo[5.3.0]dec-1-en-3-methyliden-4,10-dimethyl-6,8-dione (4b)

40% yield, m.p. 60–62°C; FT-IR (KBr, cm^{-1}): *v* 1760 (2C=O); ^1H NMR ($CDCl_3$, ppm): 1.45 (s, 12H, $4CH_3$), 3.30 (s, 1H, CO–CH–CO), 3.35 (s, 1H, CH=), 3.37 (s, 2H, CH_2=); MS (*m*/*z*) 236 (M^+), 205, 196, 149, 125, 105, 83, 69. *Anal.* $C_{13}H_{16}O_4$ (C, H).

3.2.3. 5,9-Diazabicyclo[5.3.0]dec-1-en-3-methyliden-6,8-dione (4c)

60% yield, m.p. 133–135°C; FT-IR (KBr, cm^{-1}): *v* 3240 (2NH), 1655 (C=O), 1640 (C=O); ^1H NMR ($CDCl_3$, ppm): 3.05 (s, 1H, CO–CH–CO), 3.27 (s, 1H, CH=), 3.80 (s, 2H, CH_2=), 4.10 (s, 4H, $2CH_2$–), 8.36 (s, 2H, 2NH, D_2O exch); MS (*m*/*z*) 178 (M^+), 151, 123, 95, 82, 69. *Anal.* $C_9H_{10}N_2O_2$ (C, H, N).

3.2.4. 5,9(N,N′-Methyl)-diazabicyclo[5.3.0]dec-1-en-3-methyliden-6,8-dione (4d)

58% yield, m.p. 85–87°C; FT-IR (KBr, cm^{-1}): *v* 1690 (C=O), 1680 (C=O); ^1H NMR ($CDCl_3$, ppm): 3.01 (s, 3H, CH_3), 3.13 (s, 3H, CH_3), 3.45 (s, 1H, CO–CH–CO), 3.59 (s, 1H, CH=), 4.15 (s, 2H, CH_2=), 4.20 (s, 4H, $2CH_2$–); MS (*m*/*z*) 206 (M^+), 163, 149, 135, 120, 110, 96, 80, 69. *Anal.* $C_{11}H_{14}N_2O_2$ (C, H, N).

Acknowledgements

This work was partly supported by the Ministero dell'Università e della Ricerca Scientifica, MURST (Rome).

References

[1] L. Bonsignore, A. De Logu, G. Loy, S.M. Lavagna, D. Secci, Synthesis and antimicrobial activity of coumarin and benzodioxazepine-diazazepine- and benzoxazepine-substituted penicillins, Eur. J. Med. Chem. 29 (1994) 479–485.

[2] L. Bonsignore, F. Cottiglia, H. Elkhaili, F. Jehl, S.M. Lavagna, G. Loy, F. Manna, H. Monteil, D. Pompei, D. Secci, Synthesis and antimicrobial activity of coumarin 7-substituted cephalosporins and sulfones, Farmaco 53 (1998) 425–430.

[3] L. Bonsignore, G. Loy, F. Cottiglia, A. Calignano, One-step synthesis and pharmacological activity of new (N-substituted)amino-spiroalkan-dione derivatives, Farmaco 52 (1997) 663–666.

[4] G. Steiner, R. Munschauer, T. Hoeger, L. Unger, H.J. Teschendorf, Preparation of 6-aryl-3-(arylaminoalkyl)-3-azabicyclo-[3.2.0]heptanes and analogs as psychotropics, Ger. Offen. DE 4,427,647 (1996); [Chem. Abstr. 124 (1996) 289257a].

[5] N. Buehler, M. Baumann, D. Bellus, E. Sturm, Cyclobutanedicarboximides and their use as fungicides: intermediate products, Eur. Pat. Appl. 17,994 (1980); [Chem. Abstr. 94 (1981) 103157b].

[6] M. Sakamoto, K. Chiba, Y. Tominaga, A. Minami, Preparation of 1,8-naphthyridine- and benzopyridonecarboxilic acid derivatives substituted by bicyclic amines as intermediate thereof, PCT Int. Appl. WO 95 21,163 (1995); [Chem. Abstr. 124 (1996) 55933r].

[7] S. Nakagawa, N. Otake, H. Kiyonaga, K. Yamada, H. Jona, S. Okada, M. Ogawa, H. Imamura, R. Ushijima, M. Nakano, Preparation of novel carbapenem derivatives as antibacterials, PCT Int. Appl. WO 96 08,491 (1996); [Chem. Abstr. 125 (1996) 58197k].

[8] L. Bonsignore, G. Loy, Synthesis of new 2H,4H-benzopyrano[3,4-*b*]pyridine-1,3,5-trione derivatives via carbon suboxide, J. Heterocyclic Chem. 35 (1998) 117–119.

[9] L. Bonsignore, G. Loy, M. Secci, S. Cabiddu, G. Gelli, Novel reactions of carbon suboxide. Part 8. Kinetic study of the reaction with substituted 2-hydroxybenzaldehyde oximes, J. Chem. Soc., Perkin Trans. II (1988) 1247–1250.

[10] A. Selva, A. Citterio, L. Merlini, Mass spectrometry of heterocyclic compounds. VIII. Electron-impact-induced fragmentation of 1,2-diphenylpyrazolidine-3,5-dione and 4-substituted derivatives, Org. Mass Spectrom. 10 (1975) 606–616.

[11] L. Crombie, P.A. Gilbert, R.P. Houghton, A ^{14}C, ^{18}O, and mass spectral study of the pyrolytic formation of carbon suboxide from diacetyltartaric anhydride and acetoxymaleic anhydride, J. Chem. Soc. C (1968) 130–141.