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# Benzoxocin, benzoxepin and benzofuran frameworks from 5-glyco-4-nitrocyclohex-1-enes through Nef reaction and intramolecular cyclization

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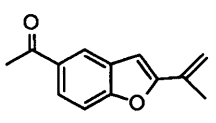
**Abstract**

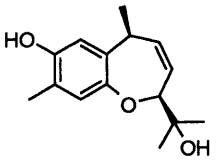
By treatment of sodium nitronate salts of 5-glyco-4-nitrocyclohexenes with hydrochloric acid, five new bicyclic ethers with six-membered rings fused to five-, seven-, or eight-membered rings have been synthesized; also a mechanism for their formation is proposed. Structural elucidation of the new compounds is based on spectroscopic data, as well as on their comparison with those of closely related substances. 

*Keywords:* 1-benzoxepin; benzoxocin; benzofuran; nitronate salts; Nef reaction; intramolecular cyclization.

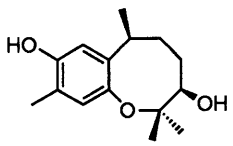
In recent years, the synthesis of benzo-fused five-, six-, seven-, and eight-membered cyclic ether skeletons has received increasing interest,[1] mainly due to their presence in a wide variety of natural products with interesting biological activities. Thus, dehydrotremetone[2] (**1**) and other benzofuran derivatives that were originally isolated from plants, have shown physiological properties, used in the treatment of several human diseases such as angina pectoris, rheumatism, or asthma.[3] The 1-benzoxepin moiety is a common structural feature[4] in heliannuols B (**2**), C, D or artonin S,[5] whereas the benzoxocin framework is present in heliannuol A (**3**).[6] The family of heliannuols, obtained from cultivated sunflowers *Helianthus annuus*, represents a promising group of allelopathic compounds that are considered as natural herbicide models.[1,4] On the other hand, monochlorinated constituents as **4**, with probable antibiotic activity, have been recently isolated[7] from the latex of the fungus *Mycena galopus*.



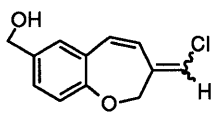

**1**




**2, Heliannuol B**




**3, Heliannuol A**




**4**

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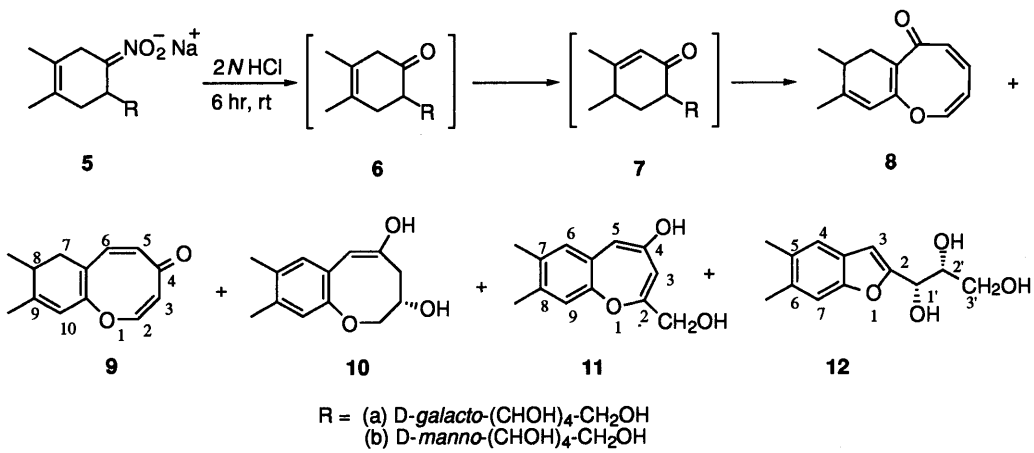
Since the major drawback to obtain the above and other structurally related compounds is the low yield often achieved after tedious or long synthetic or isolation processes, we wish to report here a new procedure that affords the mixture of oxygenated heterocycles (**8**–**12**, see Scheme 1). Although in view of the number of the resulting products, none of our individual yields were good, we think the advantage of our method lies in its simplicity and also because the starting materials can be used in multigram quantities. Thus, stirring of the sodium nitronate salt of 5-glyco-4-nitrocyclohexene (**5a**) with 2N hydrochloric acid in methylene chloride for 6 h at room temperature, followed by washing of the organic layer with aqueous sodium hydrogen carbonate and water led, after drying (magnesium sulfate) and evaporation of the solvent, to an oil that was subjected to column chromatography (silica gel; hexane–ethyl acetate 4:1), affording pure compounds **8** (33%), **9** (17%), **10** (5%), **11** (5%), and **12** (19%) (unoptimized yields). On the other hand, when these same reaction conditions were applied to **5b**, a slightly more complex mixture was formed, and we isolated pure the above cited compounds **8** (28%) and **9** (5%). The starting sodium salts[8a] **5a** and **5b** were quantitatively obtained by treatment of the corresponding nitro compounds[8b] with an excess of sodium methoxide.




Scheme 1.

The bicyclic products **8**–**12** were oils, whose structural elucidation was based on their IR, $^1$H (Table 1) and $^{13}$C NMR[9] data, as well as on their high-resolution mass spectra; thus, molecular formulae for **8**–**11** have been established by HRCIMS, showing in all cases fragmentations that suggested losses of carbon monoxide and methyl, and of hydroxyl groups or water in the case of compounds **10** and **11**.

For the non-aromatic compounds **8** and **9**, $^1$H NMR spectra exhibited signals at ca. $\delta$ 1.2, 2, 2.5, and 3, assigned to protons of methyl on aliphatic C-8, protons of methyl on olefinic C-9, methinic H-8, and methylenic H-7,7′, respectively. The resonances for H-10 appeared as broad singlets, at $\delta$ 6.56 in **9** and at $\delta$ 7.38 in **8**, this difference probably being due to the major proximity to the carbonyl group in the last compound; also, the position of H-7,7′ protons (at somewhat lower field in **8**), could be similarly explained. In both cases, the assignment for H-10 was confirmed by the long-range coupling with one of the methylene protons at C-7 ($J_{7,10} \approx 2$ Hz); furthermore, the two spectra showed four additional signals between $\delta$ 5.9 and 7.7 that were attributed, in each case, to the four olefinic protons on the heterocyclic moiety. Concerning

Table 1
$^1$H NMR[a] spectral data ($\delta$ values, $J$ Hz in parentheses) for compounds **8**–**12**

| H | **8** | **9** | **10** | **11** | **12**[b] |
|---|---|---|---|---|---|
| 2 | 7.52, d (1.9) | 7.67, d (3.4) | 3.73, brd (10.6, 1.0) | – | – |
| 2′ | – | – | 3.57, dd (10.6, 6.1) | – | – |
| 3 | 6.48, dd (3.4, 1.9) | 6.45, dd (3.4, 1.6) | 4.12, m | 6.53[c], s | 6.67, s |
| 4 | 6.61, brd (3.4) | – | 2.93, m | – | 7.26, s |
| 5 | 6.01, brs | 5.92, brs | – | 6.48[c], s | – |
| 6 | – | 7.43, d (1.3) | 6.40, brs | 7.26, s | – |
| 7 | 3.27, dd (15.5, 3.9) | 3.02, ddd (14.8, 6.0, 1.8) | 7.24, s | – | 7.30, s |
| 7′ | 3.06, ddd (15.5, 5.5, 2.2) | 2.46, dd (14.8, 4.5) | – | – | – |
| 8 | 2.51, m | 2.50, m | – | – | – |
| 9 | – | – | – | 7.22, s | – |
| 10 | 7.38, brs | 6.56, brs | 7.20, s | – | – |
| $CH_2OH$ | – | – | – | 4.37, brs | – |
| $CH_3$ | 2.01, s | 1.98, s | 2.34, s | 2.35, s | 2.36, s |
| | 1.17, d (7.1) | 1.17, d (6.8) | 2.32, s | 2.31, s | 2.33, s |

[a] At 400 MHz in $CDCl_3$.
[b] Sugar side chain: H-1′, 5.05, d (8.5); H-2′, 4.44, m; H-3′, 3.95, dd (12.3, 2.9); H-3″, 3.69, dd (12.3, 3.6).
[c] These values may be interchanged.

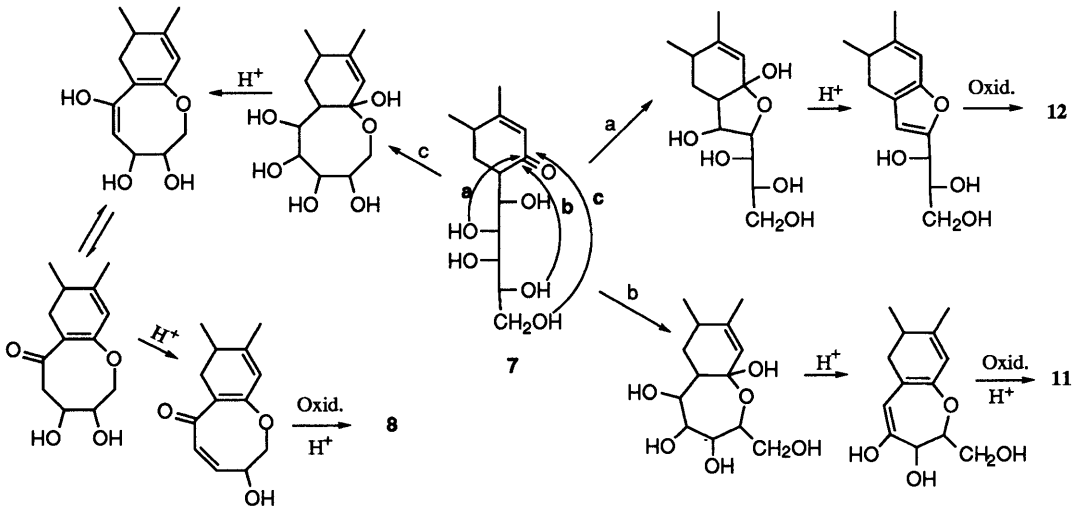
$^{13}$C NMR data, it is noteworthy that chemical shift for C-6a changes from $\delta$ 151.6 in **9** (position $\gamma$ to the carbonyl group) to $\delta$ 129.6 in **8** (position $\alpha$).

For benzoxocin **10**, its $^1$H NMR spectrum presented a multiplet for H-3 at $\delta$ 4.12, in a region that is characteristic[10] for resonances of protons on hydroxylic carbon atoms. Irradiation on this signal collapses both the AB system centered at $\delta$ 3.65 and the $A_2$ system at $\delta$ 2.93, hence assigned to methylenic protons on C-2 and C-4, respectively. In a similar way, decoupling of the broad singlet at $\delta$ 6.40 (H-6) removed the small splitting of the resonance at $\delta$ 7.20, thus being assigned to H-10. The $^{13}$C NMR spectrum showed two signals at $\delta$ 153.8 and 154.1 (C-5 and C-10a) that disappeared in a DEPT experiment; also disappearing were the three aromatic carbons (C-8, C-9, C-6a), whereas four signals remained unchanged (C-10, C-7, C-6, C-3), and those at $\delta$ 65.9 and 32.7 were inverted (C-2 and C-4, respectively). The absolute configuration at C-3 has been proposed as the same that it had in the D-*galacto* sugar side-chain of the starting 5-glyco-4-nitrocyclohex-1-ene.

For 1-benzoxepin **11**, a broad $^1$H NMR singlet at $\delta$ 4.37 was assigned to allylic methylene protons on the primary hydroxyl group, whereas four sharp singlets between $\delta$ 6.48 and 7.26 corresponded to the four olefinic protons. Its $^{13}$C NMR data supported the presence of six quaternary carbons (DEPT), two of them clearly at a lower field because of their junction to oxygen ($\delta$ 153.5, C-4 and C-9a).

Finally, the structure of compound **12** was established by spectral comparison (IR, $^1$H and $^{13}$C NMR) with 2-[(1′*R*,2′*R*)-1′,2′,3′-trihydroxypropyl]benzofuran,[11] previously obtained by our group. The long-range coupling between H-3 and H-7 supported[12] that the sugar side-chain is on C-2 of the benzofuran nucleus.

The formation of these novel bicyclic-fused heterocycles could be explained through a sequential cascade mechanism (Scheme 2), involving: (1) a Nef reaction followed by an acid-catalyzed isomerization[13] to $\alpha,\beta$-unsaturated ketone (**7**); (2) cyclization to hemiketals



Scheme 2.

corresponding to intramolecular nucleophilic attacks *a*, *b*, or *c*; (3) dehydration processes, promoted by the acid medium, with generation of conjugated double bonds with the cyclohexene or cyclohexadiene rings; (4) keto–enol tautomerism of the enols, where appropriate; and (5) oxidation of the highly conjugated intermediates to aromatic rings. Concerning step (2), it is noteworthy that cyclization occurred mainly from the more distant primary hydroxyl group.

In conclusion, we have shown an easy method in which starting from available sodium nitronate salts of 5-glyco-4-nitrocyclohexenes, bicyclic ethers can be obtained. These structures are closely related to natural or synthetic compounds with important biological activities.

## Acknowledgements

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9. $^{13}C$ NMR (100 MHz, $CDCl_3$), **8**: 187.9 (C-6), 166.3 (C-10a), 143.8 (C-2), 129.6 (C-6a), 126.5 (C-5), 122.1, 115.7, 111.9 (C-3, C-4, C-5, C-10), 34.9 (C-8), 34.0 (C-7), 22.9 (Me-9), 19.5 (Me-8); **9**: 188.7 (C-4), 165.1 (C-10a), 151.6 (C-6a), 143.3 (C-2), 129.1 (C-9), 128.1, 124.3, 115.1, 112.5 (C-3, C-5, C-6, C-10), 42.7 (C-7), 36.5 (C-8), 22.6 (Me-9), 18.2 (Me-8); **10**: 154.1, 153.8 (C-5, C-10a), 132.6, 131.2, 126.3 (C-8, C-9, C-6a), 120.6 (C-7), 111.4 (C-10), 103.8 (C-6), 70.6 (C-3), 65.9 (C-2), 32.7 (C-4), 20.4, 19.9 (Me-8, Me-9); **11**: 153.5 (C-4, C-9a), 133.7, 132.0, 126.7, 104.4 (C-2, C-7, C-8, C-5a), 129.6, 120.9, 119.2, 111.4 (C-3, C-5, C-6, C-9), 63.2 ($CH_2OH$), 20.5, 19.9 (Me-7, Me-8); **12**: 155.5 (C-7a), 150.6 (C-2), 128.3 (C-3a), 121.8 (C-6), 119.5 (C-5), 117.1 (C-4), 110.7 (C-7), 104.7 (C-3), 72.3 (C-1′), 64.3 (C-2′), 62.1 (C-3′).
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