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Graphical Abstract

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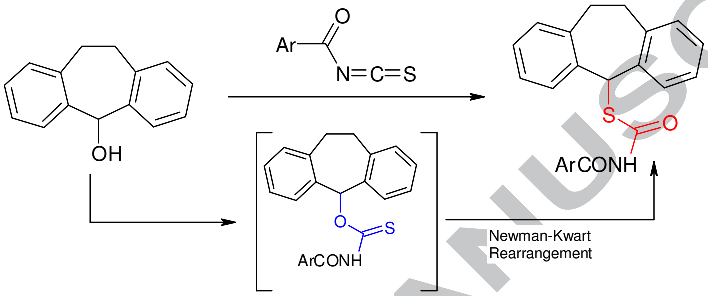

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Synthesis of new 10,11-dihydrodibenzo[*a,d*]cycloheptene *S*-thiocarbamate derivatives *via* a benzylic Newman-Kwart rearrangement

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ABSTRACT

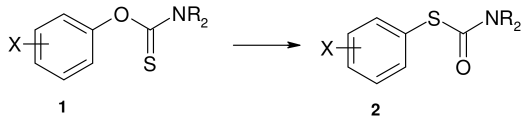
New *S*-thiocarbamates possessing a 10,11-dihydro-5*H*-dibenzo[*a,d*]cycloheptene moiety were obtained unexpectedly in the process of preparing new *O*-thionocarbamates starting from 5-dibenzosuberol (10,11-dihydro-5*H*-dibenzo[*a,d*]cyclohepten-5-ol) and aroyl-isothiocyanates. These compounds were obtained *via* a benzylic Newman-Kwart rearrangement mechanism. The structures of the new thiocarbamates were confirmed by elemental analysis, IR and NMR spectroscopy and by X-ray crystallography.

The 10,11-dihydrodibenzo[*a,d*]cycloheptene scaffold can be considered a privileged structure[1] as it is found in marketed drugs such as triptyline, amitriptyline, nortriptyline, cyproheptadine and cyclobenzaprine, which are included in the class of tricyclic antidepressants (TCAs),[2,3] but possess a wide range of other medicinal applications.[4,5]

In attempts to prepare new bioactive molecules we decided to synthesize some new *O*-thionocarbamate derivatives having a 10,11-dihydro-5*H*-dibenzo[*a,d*]cycloheptene structure.

To our surprise, instead of the expected *O*-aryl thionocarbamates we obtained the corresponding *S*-thiocarbamates, which suggests the formation of these new compounds through a Newman-Kwart type rearrangement.[6] The Newman-Kwart rearrangement and its key features as a synthetic tool for obtaining complex organic molecules has been reviewed.[7,8]

Usually, the Newmann-Kwart rearrangement converts *O*-aryl-thionocarbamates **1** into their *S*-aryl isomers **2** (Scheme 1) at temperatures between 150 and 350 °C.[6-9] The same rearrangement can also be carried out at a lower temperature and using a palladium catalyst,[10] or under microwave irradiation at different temperatures.[11] The Newman-Kwart rearrangement is a thione-thiol rearrangement characteristic of thiocarbamate derivatives with an oxygen atom attached to an aryl radical (the oxygen atom is linked to an sp^2 carbon atom).[8,12]



Scheme 1

Allylic[13] and benzylic[14,15] Newman-Kwart rearrangements are interesting and rarely encountered in the literature.

Herein we present the synthesis and structural characterization of new *S*-thiocarbamate derivatives of 10,11-dihydro-5*H*-dibenzo[*a,d*]cycloheptene by the *in situ* benzylic Newman-Kwart rearrangement of the corresponding *O*-aryl thionocarbamates. This reaction could provide an easily accessible synthetic route to dibenzo[*a,d*]cycloheptadiene derivatives, all the starting materials being commercially available.

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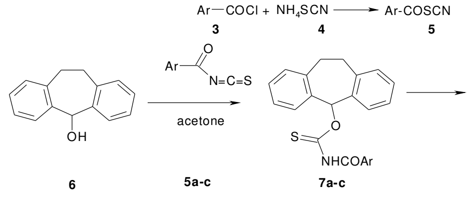
The new 10,11-dihydrodibenzo[*a,d*]cycloheptene *S*-thiocarbamate derivatives **8** were synthesized using a condensation reaction between alcohol **6** (5-dibenzosuberol), and the corresponding aroylisothiocyanates **5**, in anhydrous acetone. The aroylisothiocyanates **5** were generated in anhydrous acetone by the reaction between the corresponding aromatic acid chlorides **3** and ammonium thiocyanate **4** (Scheme 2), and were used further without isolation. Three new thiocarbamate derivatives were obtained in yields of 72-76%. The new light yellow crystalline compounds were crystallized from isopropanol.



a: Ar=C_6H_5; b: Ar=2-BrC_6H_4; c: Ar=4-BrC_6H_4

Scheme 2

The structures of the new compounds **8a-c** and their key NMR features are presented in Table 1.

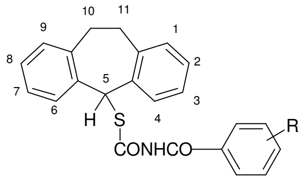


Table 1: Characteristic spectral NMR data of **8a-c**

Product	R	NMR-solvent	N-H δ (ppm)	H-5 δ (ppm)	C-5 δ (ppm)	C=O δ (ppm)	
8a	H	DMSO-d_6	11.79	6.08	51.11	168.31	166.45
		$CDCl_3$	9.00	6.19	53.33	169.76	165.15
8b	2-Br	DMSO-d_6	11.92	6.03	52.07	167.23	166.76
		$CDCl_3$	8.86	6.13	53.48	168.80	165.29
8c	4-Br	DMSO-d_6	11.85	6.07	52.04	168.24	165.65
		$CDCl_3$	9.27	6.17	53.72	170.19	164.89

The structures of compounds **8a-c** were deduced on the basis of elemental analysis, NMR spectroscopy,[16] and confirmed for a representative compound (**8a**) by X-ray analysis.

The characteristic features in the ^{1}H-NMR spectra of compounds **8a-c** are the presence of NH protons which appear in the range 8.86-9.27 ppm in $CDCl_3$ and 11.79-11.92 ppm in DMSO-d_6. The chemical shifts of the benzylic protons are in the range 6.13-6.19 ppm. It is noteworthy that in all cases the four methylenic protons at positions 10 and 11 appear as A_2B_2 systems.

The most specific characteristic of the ^{13}C-NMR spectra is the value of the chemical shift of the benzylic carbon (C-5), which is strongly shielded (ca. 53 ppm) in comparison with 5-dibenzosuberol (ca. 72 ppm). This is strong evidence that the C-5 atom is attached to a sulfur atom rather than an oxygen atom. The two carbon atoms in the carbonyl groups are the most deshielded atoms. Their chemical shift values are in the range 164.9-170.2 ppm, which indicated the presence of a carbonyl group instead of a C=S group.[15] All the other carbon atoms appeared in the expected ranges.

The IR spectra show evidence of a C-S single bond.[17] This bond is highlighted by the medium intensity stretching band at ~900 cm^{-1}. The stretching bands of the two carbonyl groups are in the range 1619-1630 cm^{-1} and 1696-1706 cm^{-1}.

The Newman-Kwart rearrangement is a type of reaction in which the aryl group of *O*-aryl thionocarbamates migrates from the oxygen atom to the sulfur atom, forming *S*-aryl thiocarbamates.[6-8] The three new *S*-thiocarbamate compounds with a 10,11-dihydro-5*H*-dibenzo[*a,d*]cycloheptene structure were obtained unexpectedly *via* a benzylic Newman-Kwart rearrangement from the *O*-isomer (-O-CS-NH-CO-Ar) to the *S*-isomer (-S-CO-NH-CO-Ar), under the reaction conditions. The difference between the usual Newman-Kwart rearrangement and the rearrangement described herein is that the oxygen or sulfur atom are linked to an sp^3 hybridized carbon atom (the carbon atom located at position 5 of the dibenzo[*a,d*]cycloheptane ring) and the nitrogen atom is linked to an acyl radical (-CO-Ar).

Our particular case implies that, for the first time, acyl-isothiocyanates can be used for obtaining *S*-thiocarbamates *via* a benzylic Newman-Kwart rearrangement.

The structure of the new compounds was unequivocally elucidated by X-ray diffraction analysis of the representative compound **8a** (Figure 1).[18] The bond lengths and angles are summarized in Table 2 (and Table 1S in the Supporting Information).

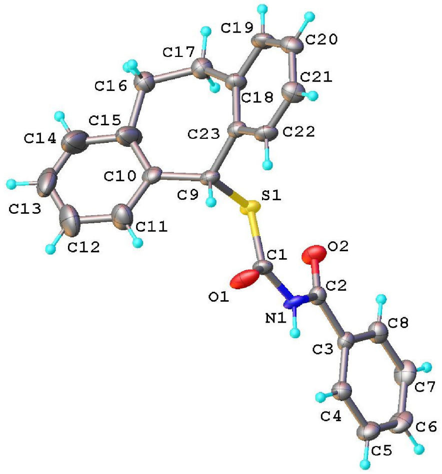


Figure 1. X-ray molecular structure of compound **8a** with thermal ellipsoids at 40% probability level. Only the major component of the disordered cycloheptane is shown.

Table 2: Selected bond lengths (Å) for **8a**

S1-C1	1.759(4)	C3-C8	1.388(5)
S1-C9	1.857(4)	C18-C19	1.382(5)
O2-C2	1.209(4)	C18-C17	1.519(1)
O1-C1	1.228(4)	C20-C19	1.383(6)
N1-C2	1.385(5)	C20-C21	1.373(5)
N1-C1	1.377(5)	C22-C21	1.374(5)
C2-C3	1.485(5)	C8-C7	1.385(6)

C4-C3	1.382(5)	C6-C5	1.378(6)
C4-C5	1.374(5)	C6-C7	1.361(6)
C10-C9	1.530(5)	C11-C12	1.378(6)
C10-C11	1.373(6)	C15-C14	1.405(7)
C10-C15	1.369(5)	C15-C16	1.5195(9)
C23-C18	1.392(5)	C17-C16	1.5194(9)
C23-C9	1.512(5)	C13-C14	1.331(8)
C23-C22	1.385(5)	C13-C12	1.348(7)

In the crystal packing, two centrosymmetrically related molecules are associated into a dimer via H-bonds where N1 acts as a donor and O1 as an acceptor (Figure 2).

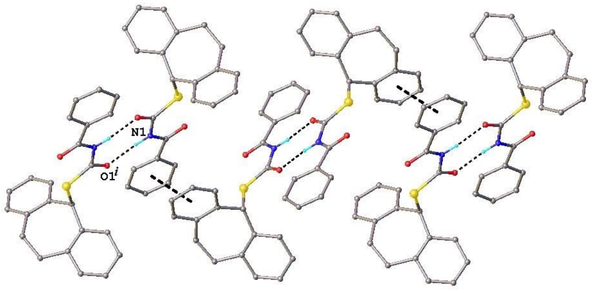


Figure 2. Hydrogen bonding and π-π stacking interactions in the crystal structure. Symmetry code; (i) 0.5 – x, 0.5 – y. 1- z. H-bond parameters: N1–H···O1 [N1–H 0.91 Å, H···O1(0.5 - x, 0.5 - y, 1 - z) 2.03 Å, N1···O1 2.918(4) Å, N1–H···O1 165.3°].

Apart from the H-bonding, significant π-π stacking interactions are observed in the crystal packing. They occur between adjacent C3-C8 and C18-C23 aromatic rings with a centroid-to-centroid distance of 3.915 Å and shift of 1.742 Å. Thus, each associated H-bond is involved in the stacking interaction along four directions, such that the crystal structure can be characterized as a three-dimensional supramolecular network.

In conclusion, we have synthesized three new *S*-thiocarbamates with a 10,11-dihydro-5*H*-dibenzo[*a,d*]cycloheptene moiety. These new compounds were obtained following the condensation reaction between 5-hydroxy-10,11-dihydro-5*H*-dibenzo[*a,d*]cycloheptene and the corresponding aroylisothiocyanates. The new *S*-thiocarbamates are derived *via* a benzylic Newman-Kwart rearrangement from the *O*-isomer into the *S*-isomer. The structures of these new derivatives were confirmed by elemental analysis, spectrometric methods (IR, ^{1}H-NMR, ^{13}C-NMR) and X-ray crystallography.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found in the online version at DOI:

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16. ***S*-(10,11-dihydro-5*H*-dibenzo[*a,d*]cyclohepten-5-yl)-*N*-benzoylcarbamothioate** (**8a**). To an acetone solution of aroylisothiocyanate **5a** (obtained in a previous step) was added 5 mmol of an anhydrous acetone solution of 5-dibenzosuberol. The reaction mixture was heated under reflux for 3 h and then evaporated to dryness under vacuum. The final compound **8a** was crystallized from isopropanol (see Supporting Information for **8a-c**). Yield=72%; mp=165-166 °C; Anal. Calcd. for $C_{23}H_{19}NO_2S$: C 73.97%, H 5.13%, N 3.75%, S 8.58%; Found: C 74.12%, H 4.99%, N 3.89%, S 8.33%. **FT-IR** (solid in ATR, ν cm^{-1}): 3263m; 3058w; 3023w; 2973w; 2914w; 2829w; 1695m; 1620vs; 1456m; 1441m; 1425m; 1251s; 1187s; 1156m; 1102m; 906m; 870w; 848w; 767w; 698m; 671m; 617m. **^{1}H-NMR** ($CDCl_3$, 300 MHz δ ppm, T=298 K): 9.00 (br s, 1H, NH-CS, deuterable); 7.82 (dd, *J* = 1.4, 7.9 Hz, 2H, Ph); 7.58 (tt, *J* = 1.4, 7.7 Hz, 1H, Ph); 7.48 (dd, *J* = 7.9, 7.7 Hz, 2H, Ph); 7.42 (d, *J* = 7.2 Hz, 2H, H-1, H-10); 7.22-7.09 (m, 6H, H-1, H-2, H-3 and H-7, H-8, H-9); 6.19 (s, 1H, H-5); 3.60 (m, 2H, H-10, H-11, syst. A_2B_2); 2.98 (m, 2H, H-10, H-11, syst. A_2B_2). **^{13}C-NMR** ($CDCl_3$, 75 MHz, δ ppm, T=298 K): 169.76 (CONH); 165.15 (COPh); 140.32 (C-4a, C-5a); 137.75 (C9a, C-11a); 133.37 (Ph); 131.92 (Ph); 130.75 (C-4, C-6); 130.35 (CH); 129.03 (CH); 128.06 (CH); 127.57 (CH); 126.36 (CH); 53.33(C-5); 33.14 (C-10, C-11).
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18. Crystal data: $C_{23}H_{19}NO_2S$, Mr = 373.45 g mol^{-1}, size 0.5 × 0.1 × 0.05 mm^3, monoclinic, space group $C2/c$, a = 27.401(4) Å, b = 8.0970(7) Å, c = 17.799(3) Å, β = 108.865(16)°, V = 3736.8(8) Å^3, Z = 8, ρ_{calcd} = 1.328 g cm^{-3}, μ(Mo$K\alpha$) = 0.191 mm^{-1}, F(000) = 1568, 7287 reflections in h(-33/24), k(-6/9), l(-21/21), measured in the range 3.14 ≤ Θ ≤ 52°, T = 173 K, completeness Θ_{max}=99.98%, 3666 independent reflections, R_{int} = 0.0489, 246 parameters, 19 restraints, R_{1obs}=0.0776, wR_{2obs} = 0.1623, R_{1all} = 0.1332, wR_{2all} = 0.1881, GoF = 1.035, largest difference peak and hole: 0.92/-0.58 e A^{-3}. CCDC-991426 contains the supplementary crystallographic data and can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.