Chemistry of chelocardin. V.[1] Condensation with amino reagents

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Received August 22, 1980

DANIEL T. W. CHU, STUART N. HUCKIN, EDITH BERNSTEIN, DAVID L. GARMAISE, RICHARD S. EGAN, and RUTH S. STANASZEK. Can. J. Chem. **59**, 763 (1981).

The nature of the products obtained from the reaction of chelocardin (**1**) and the model compound 2-acetyldimedone (**5**) with a variety of amines was investigated. It was observed that amines react with β-triketones having an exocyclic carbonyl side-chain to give exclusively β,β′-diketoenamines with substitution at the side-chain carbonyl.

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On a étudié la nature des produits provenant de la réaction de la chélocardine (**1**) et du composé type l'acétyl-2 dimédone (**5**) avec différentes amines. On a observé que les amines réagissent avec les β tricétones ayant sur la chaîne latérale un groupe carbonyle exocyclique pour conduire exclusivement aux β,β′-dicétoénamines portant le substituant au niveau du carbonyle de la chaîne latérale.

[Traduit par le journal]

Chelocardin, a broad spectrum antibiotic that was first described in 1962 (1) and subsequently shown to be **1** (2), possesses a β-triketone system in ring A. During the course of our chemical investigation on the modifications of chelocardin, it was found that the ring A β-triketone is the most reactive center in the molecule and is highly susceptible to chemical modification.

We have reported that chelocardin hydrochloride (**1**) reacted with a variety of amino compounds (amines, hydrazines, hydrazides, and aromatic amines) to yield 2a-substituted derivatives (**2**)[6] having antibacterial spectra similar to the parent antibiotic (3) as illustrated in Scheme 1.

The same reaction course was observed with *N*-carbobenzoxychelocardin (**3**) (4). Condensation of **3** with amino compounds also yielded 2a-substituted derivatives **4**. This exclusive substitution reaction represents a preferential attack of the side chain carbonyl to provide a novel β,β′-diketoenamine structure. An analogous condensation of the exocyclic carbonyl in the β-tricarbonyl system of usnic acid has recently been reported (5). However, the spectroscopic data were not sufficient to establish the substitution at the exocyclic carbonyl instead of the other two carbonyl groups. The correctness of the structural assignments was only established by X-ray analysis.

This article presents our results on further chemical studies with model β-triketones designed to provide spectroscopic evidence to firmly establish the position of amino substitution.

The nmr spectra of chelocardin and its derivatives (other than a few 4-*N*-acyl derivatives) are poorly resolved. Hence, their nmr spectra offer little clue as to which carbonyl in ring A has undergone substitution. However, the ^{13}C nmr spectrum shows one resonance for each carbon in the molecule, and the structural assignments of these derivatives were based on extensive analyses of the ^{13}C nmr data.

The three carbonyl carbons of the A-ring β-triketone system and the C(12) carbonyl make up the four most downfield resonances of chelocardin hydrochloride and its derivatives in the ^{13}C nmr spectra. These resonances are all generally found between 170 ppm and 210 ppm. Comparison of the chemical shifts of 2-acetyldimedone (**5**) with ring A resonances of chelocardin hydrochloride (1) and *N*-carbobenzoxychelocardin (**3**) permits assignments of the corresponding carbons (Table 1).

[1]For Part IV of this series, see ref. 8.

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[6]In this paper structures are given as tautomer (I) for simplicity but an equilibrium with other tautomeric forms II and III and the geometric isomer IV is not excluded.

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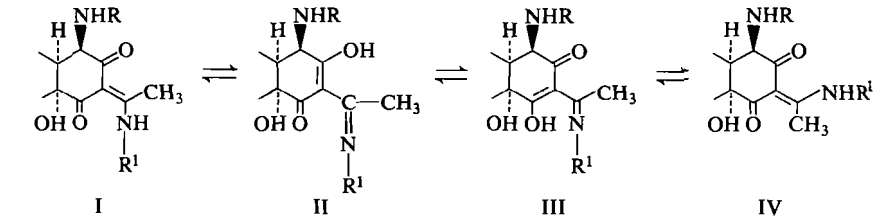
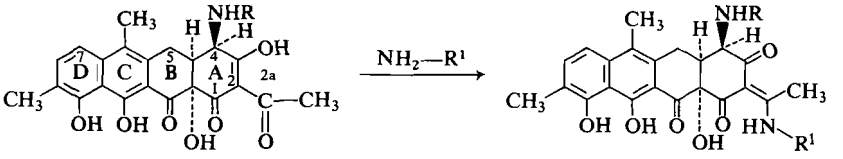
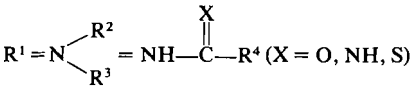


I II III IV



1 R = H·HCl
3 R = $COOCH_2C_6H_5$

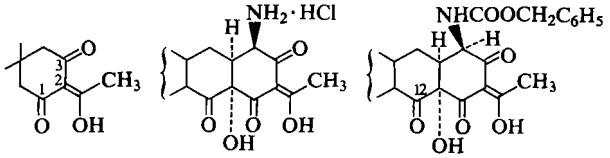
2 R = H·HCl
4 R = $COOCH_2C_6H_5$



R^2, R^3, R^4 = alkyl or aromatic or H

SCHEME 1

TABLE 1. Comparative ring A ^{13}C nmr chemical shift data[a] of chelocardin (**1**), *N*-carbobenzoxychelocardin (**3**), and 2-acetyldimedone (**5**)



5 1 3

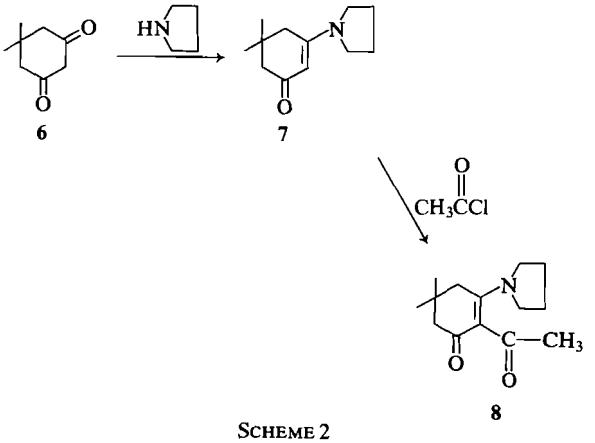
Assignments	5	1	3
C(1)	196.3	190.6	190.6
C(3)	196.3	191.1	196.0
C(2)	112.0	110.7	111.2
C(2a)	201.6	200.0	200.5
C(2a)CH_3	28	26.5	26.3
C(12)	—	199.6	200.8

[a]Chemical shift data are given in ppm downfield from internal Me_4Si and spectra taken in Me_2SO.

The specific C(1) and C(3) assignments were made on the basis of relative insensitivity of C(1) to changes in the substituent at C(4). Differentiation between C(2a) and C(12) in *N*-carbobenzoxychelocardin (**3**) was made on the basis of long range couplings visible in coupled spectra; the 200.5 ppm resonance is clearly split into a quartet as a consequence of coupling with the methyl protons. Excellent agreement for C(2), C(2a), and C(2a)-methyl resonances was also observed. Hence a positive correlation with known derivatives of 2-acetyldimedone with respect to their ^{13}C nmr chemical shifts would firmly establish the position of substitution by the amino reagents.

2-Acetyl-5,5-dimethyl-3-*N*-pyrrolidylcyclohex-2-en-1-one (**8**) was prepared according to the method of Alt and Speziale (6) as shown in Scheme 2. Its structure was shown by nmr analysis to have no vinyl proton, and to possess two sets of nonequivalent methylene protons at δ 2.07 and δ 2.56 ppm.

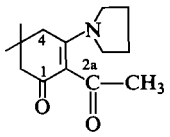
Reaction of acetyldimedone (**5**) with pyrrolidine under similar experimental conditions as those for the preparation of aminochelocardin derivatives gave the pyrrolidylacetyldimedone (**9**). This compound is different from compound **8**, having a different R_f value in the thin-layer chromatographic analysis. Its nmr spectrum shows the presence of a singlet at δ 2.12 corresponding to four methylene protons. On the basis of symmetry considerations, the presence of the pyrrolidyl group at the side chain was fully established. This represents the first time a complete structure proof for the product of condensation of amines with a β-triketone sys-

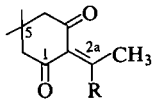


6 7 8

SCHEME 2

TABLE 2. Comparative ^{13}C nmr chemical shift data[a] of 2-acetyldimedone (**5**) and substituted 2-acetyldimedones





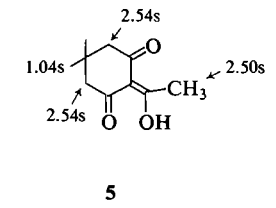
Assignments	**8**	**5** (R = OH)	**9** R = 	**10** (R = NH_2)
C(1)	192.8	196.3	189.7	196.5
C(3)	164.8	196.3	189.7	196.5
(C2)	112.3	112.0	110.3	106.5
C(2a)[b]	198.1	201.6	176.0	173.2
C(2a)CH_3[b]	32.2	28	23.5	24
C(4)	43.1	48.8	51.6	52.3
C(6)	51.0	48.8	51.6	52.3
2C(5)CH_3	27.7	27.5	28.1	27.8

[a]See corresponding footnote to Table 1.
[b]Substantial changes occurred with substitution.

tem having an exocyclic carbonyl side chain was obtained by spectroscopic methods.

Aminoacetyldimedone (**10**) prepared by treatment of acetyldimedone (**5**) and hexamethyldisilazane or ammonium acetate (7) shows the presence of a singlet at δ 2.54 ppm corresponding to four methylene protons in its nmr spectrum. Its structure was established based on symmetry and off-resonance single frequency decoupling (ORSFD) considerations.

The nmr chemical shift data of 2-acetyldimedone (**5**) as well as the amino substituted 2-acetyldimedone derivatives **8**, **9**, and **10** are given in Fig. 1. No significant change in chemical shift for the 2a-methyl group is observed. Their comparative ^{13}C nmr chemical shift data are shown in Table 2. The ^{13}C nmr chemical shifts of the three carbonyl carbons of the β-triketone system and also the 2a-methyl of the 2-acetyldimedone (**5**) are profoundly affected by substitutions of amino functions on the 2a carbonyl as well as the 1 or 3 carbonyl as illustrated in Table 2.



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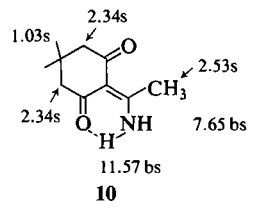

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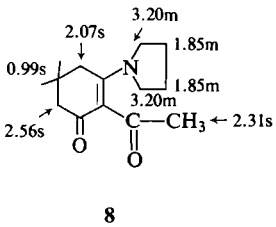

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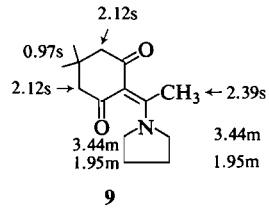

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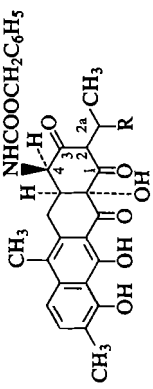
FIG. 1. Comparative nmr chemical shift data (given in ppm with spectra taken in DMSO-d_6) of 2-acetyldimedone (**5**) and substituted 2-acetyldimedones.

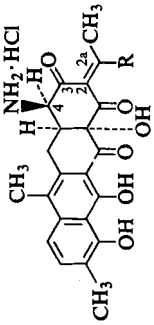
When the substitution of the amino group is on the 2a carbonyl (e.g. **9** and **10**), the C(2a) and C(2a)-methyl carbon resonances undergo substantial *upfield* shifts. On the other hand, when the substitution of the amino group is on the 1 or 3 carbonyl, the C(2a)-methyl carbon resonance undergoes substantial *downfield* shift. This observation in chemical shifts in ^{13}C nmr is extremely useful in the determination of the location of the substitution of amino reagents to chelocardin (**1**) or its *N*-protected derivatives.

All the amino-chelocardin derivatives obtained according to the route described (3) show an additional absorption at approximately 307–312 nm in their uv spectra, indicating the formation of a vinylogous imide system (6). Their mass spectra show the presence of several fragments normally found in the mass spectrum of chelocardin; the most important and prominent ion can be assigned to structure B shown in Fig. 2 (*m/e* 270, $C_{16}H_{14}O_6$) (2). This suggests that substitution of the amino group is not located in the B, C, and D rings.

In order to establish the position of the substitution, an analysis of the ^{13}C nmr spectra of the amino-chelocardin derivatives and also those of 2-acetyldimedone and its amino analogues was studied. The comparative ring A ^{13}C nmr chemical shift data of chelocardin hydrochloride (**1**), *N*-carbobenzoxychelocardin (**3**), and their amino derivatives **11**, **12**, **13**, **14**, **15**, and **16** are shown in Table 3. An excellent correlation was observed when their

TABLE 3. Comparative ring A ^{13}C nmr chemical shift data[a] of chelocardin (**1**), *N*-carbobenzoxychelocardin (**3**), and their derivatives





Assignments	1	11	12	3	13	14	15	16
	R = OH	R = *p*-NHC$_6$H$_4$—SO$_2$NH$_2$	R = NH—	R = OH	R = NH$_2$	R = N	R = NHCH$_2$C$_6$H$_5$	R = NHNHAc
C(1)	190.6	189.2	189.0	190.6	190.8	184.1	191.3	190.8
C(3)	191.1	191.1	191.0	196.0	192.0	185.6	191.3	192.1
C(2)	110.7	106.7	106.4	111.2	105.0	109.0	106.4	104.7
C(2a)[b]	200.0	173.9	174.1	200.5	174.5	176.6	173.8	169.4
C(2a)CH_3[b]	26.5	20.3	19.8	26.3	23.8	23.6	17.8	16.5

[a]See corresponding footnote to Table 1.
[b]Substantial upfield shift observed.

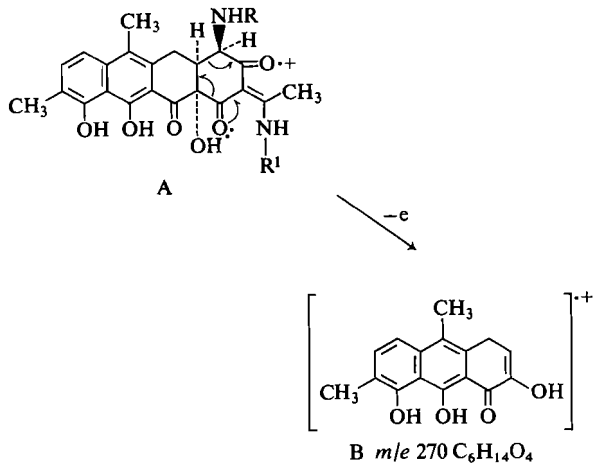


FIG. 2. Major fragmentation of chelocardin and analogues.

^{13}C nmr chemical shift values were compared with those of aminoacetyldimedones. (**13** vs. **10** and **14** vs. **9**). All the derivatives show substantial *upfield* shifts for their corresponding C(2a) and C(2a)-methyl carbon resonances. Using the previous observations with 2-acetyldimedone (**5**) and its amino analogues, all the amino-chelocardin analogues would have their amino substitutions at the 2a-carbonyl group. This confirms our previous finding that reaction of chelocardin hydrochloride (**1**) or *N*-carbobenzoxychelocardin (**3**) with amino reagents always gives rise to 2a-amino substituted chelocardin derivatives **2** or **4**.

In summary, we have provided a confirmation of the structures of the chemical reaction products obtained with the highly functionalized and reactive chelocardin and various amines. It further establishes a general reaction that a β-triketone having an exocyclic carbonyl function reacts with amines to give β,β′-diketoenamines having substitution exclusively on the exocyclic carbonyl.

Experimental

Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. The infrared spectra were recorded on a Beckman Model IR8 infrared spectrophotometer. The nmr spectra were recorded on Varian Associates EM-360 and HA-100 spectrometers in deuterated solvents; resonance positions are given on the δ scale (ppm) relative to internal tetramethylsilane. The mass spectra were recorded on an AEI MS-902 double-focussing mass spectrometer. The uv spectra were recorded on a Unican SP-800A spectrometer in 0.1 *N* methanolic hydrogen chloride solution. The ^{13}C nmr spectra were recorded on a Varian Associates XL-100-15/TT-100 spectrometer system in Me_2SO; resonance positions are given in ppm relative to internal tetramethylsilane. Parameters used were pulse width (30°) 3.5/μs, pulse delay 0.5–1.0, 6K sweep width, and 8K data table.

Preparation of Amino Derivatives of Chelocardin

2a-Amino-substituted analogues of chelocardin were prepared according to the procedure reported previously (3, 4). The general procedure for the preparation of these analogues was to add a slight excess of 1 mole equivalent of the corresponding hydrazine, hydrazide, or aniline to a solution of chelocardin hydrochloride (**1**) or its free base or *N*-carbobenzoxychelocardin (**3**) in 98% aqueous tetrahydrofuran or methanol. (In the case of anilines, one to two mole equivalents of acetic acid was also added.) The reaction mixture was allowed to stand for at least 1 h at room temperature (a few compounds required a longer reaction time). The product was isolated by precipitation, filtration, and recrystallization.

Amino Derivatives of 2-Acetyldimedone

The 2-acetyl-5,5-dimethyl-3-*N*-pyrrolidylcyclohex-2-en-1-one (**8**) was prepared according to the method of Alt and Speziale (6). The preparation of 2-aminoacetyldimedone (**10**) was reported recently (7).

Pyrrolidylacetyldimedone (9)

Pyrrolidylacetyldimedone was prepared as follows. Pyrrolidine (71 mg, 1 mmol) was added to a solution of 2-acetyldimedone (182 mg, 1 mmol) in benzene (25 mL). After it was refluxed with removal of water for 8 h, the benzene was removed to give a yellow solid. Column chromatography on silica gel using chloroform/methanol (9:1) as eluent yielded 210 mg pure product **9** (90% yield). The nmr and ^{13}C nmr data are given in the text. *Anal.* calcd. for $C_{14}H_{21}NO_2$: C 71.45, H 8.99, N 5.95; found: C 71.15, H 9.10, N 5.91.

Acknowledgements

We thank the staff of the microanalytical department of Abbott Laboratories for the elemental analyses and Sandra L. Mueller for recording the mass spectra.

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