Novel π-Extended Thiophene-Fused Electron Acceptors for Organic Metals

Pilar de la Cruz, Nazario Martín,* Fuencisla Miguel, and Carlos Seoane*

Departamento de Química Orgánica, Facultad de Química, Universidad Complutense, 28040 Madrid, Spain

Armando Albert and Félix H. Cano

U.E.I. Cristalografía, Instituto Rocasolano, C.S.I.C. Serrano, 119, 28006 Madrid, Spain

Araceli González and Jose M. Pingarrón

Departamento de Química Analítica, Facultad de Química, Universidad Complutense, 28040 Madrid, Spain

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Novel π-extended thiophene-fused TCNQ-type and DCNQI-type acceptors have been synthesized from the corresponding quinones by reaction with Lehnert's reagent and bis(trimethylsilyl)carbodiimide (BTC), respectively. Additionally, an example of the little-known hybrid TCNQ–DCNQI-type acceptor has also been obtained. The cyclic voltammetric data of the novel acceptors reveal two different behaviors for these molecules. The TCNQ-type derivatives exhibit a two-electron single-wave reduction to the dianion, as confirmed by controlled potential coulometry analysis. The DCNQI-type derivatives display two reduction waves to the corresponding radical anion and dianion. The same behavior is shown by the hybrid TCNQ–DCNQI derivative. The acceptor ability is related to molecular planarity, and a comparative crystallographic study involving TCNQ-type and DCNQI-type derivatives (**6a**, **7a**, and **8a**) has been performed.

Introduction

Since the discovery of one-dimensional electrical conductivity reported for the tetracyano-*p*-quinodimethane–tetrathiafulvalene (TCNQ–TTF)[1] complex, much effort has been devoted to the synthesis of novel donor and acceptor systems.[2] With regard to the acceptor component, synthetic work has been focused mainly on the preparation of substituted-TCNQ derivatives.[3] However, in order to preserve the planarity required to form charge-transfer complexes (CTC), the only substituents which can be tolerated in the ring are those which are non-bulky.[4]

More recently, a new type of acceptor, *N,N'*-dicyanoquinone diimine (DCNQI) (**2**), has been reported to form compounds with a higher degree of planarity, due to the small angle formed by the =NCN group.[5] This new class of acceptor molecules has led to CT complexes and particularly to radical-anion salts with electrical properties exceeding those of the corresponding TCNQ (**1**) derivatives.[4]

Two very interesting structural modifications on these acceptor molecules are the extension of the π-system, leading to a lowering of the intramolecular Coulomb repulsions and, on the other hand, the presence of sulfur atoms in the molecule. Owing to the large size of the sulfur atom, the intrastack as well as the interstack interactions are increased, and as a consequence, the conductivity and stabilization of the metallic state are enhanced.[7]

Recently, we published the synthesis and electrochemical properties of TCNQ derivatives[8] and DCNQI derivatives[9] with fused benzene rings, in which the influence of the π-extension on acceptor ability was studied systematically.

In a preliminary communication we reported[10] the synthesis, electrochemistry, and X-ray data of some π-extended TCNQ-type derivatives containing a thiophene ring, which proved to be highly distorted molecules.

In this paper we describe the synthesis, the electrochemistry, and a comparative crystallographic study of π-extended TCNQ and DCNQI derivatives containing a sulfur atom. Additionally, an example of a TCNQ–DCNQI hybrid system is presented.

Results and Discussion

Synthesis. The preparation of the novel sulfur-containing TCNQ-type acceptors was carried out by reaction of malononitrile with the corresponding quinones by using Lehnert's reagent.[11] The DCNQI-type derivatives were obtained from the appropriate quinones by reaction with bis(trimethylsilyl)carbodiimide (BTC)[12] in the presence of titanium tetrachloride by following the procedure described by Hünig.[13]

The synthesis of the starting quinones involves a multistep process; the exact route employed was dependent upon the particular quinone used. Thus, the preparation of thieno[2,3-*b*]-1,4-naphthoquinones (**5**) was carried out by the cyclization of substituted 2-thenoylbenzoic acids (**4**), obtained from the corresponding phthalic anhydrides (**3**) by reaction with 2-thenoylmagnesium iodide, according to the literature procedure[14] (Scheme I).

On the other hand, thieno[2,3-*b*]-9,10-anthraquinone (**11**) was obtained from thiene-2,3-dicarboxaldehyde (**9**) and 1,4-dihydroxynaphthalene (**10**) according to the method reported by Lepage[15] for the carbocyclic series. It is worth mentioning that the usual preparations of heterocyclic ortho dialdehydes reported in the literature involve multistep processes with low overall yields. We have followed a more expedient procedure for obtaining **9** in a three-step sequence, as depicted in Scheme II.[15] The

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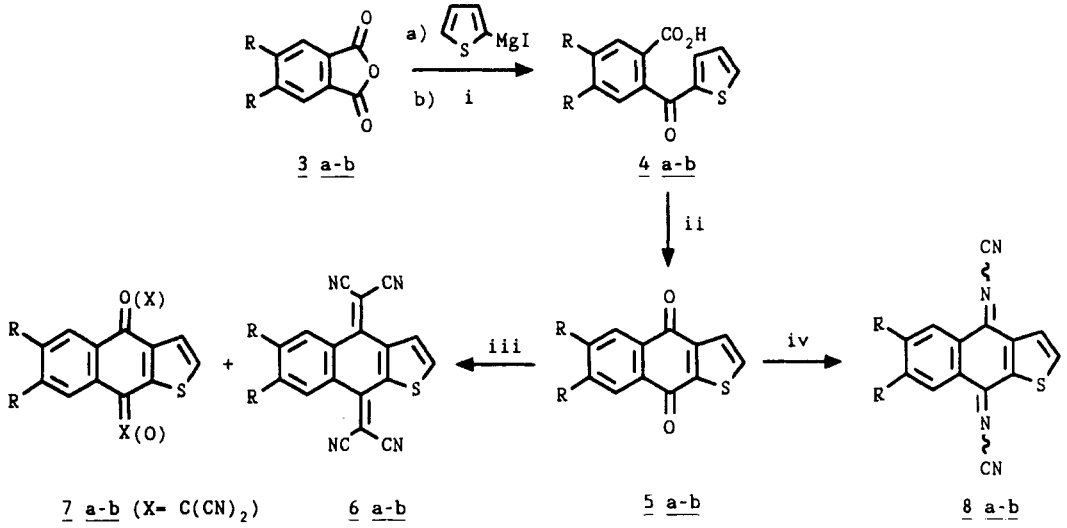
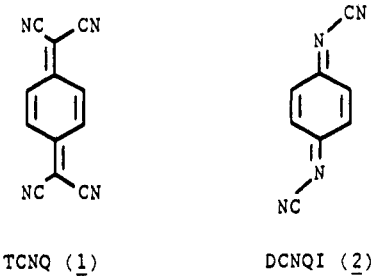
Scheme I[a]



[a] **a**, R = H; **b**, R = Cl. (i) (1) NH_4Cl, (2) HCl (6 N); (ii) PCl_5, $C36H_5NO_2$, $AlCl_3$; (iii) $NCCH_2CN$, $TiCl_4$, pyridine; (iv) $Me_3SiN{=}C{=}NSiMe_3$ (BTC), $TiCl_4$, CH_2Cl_2.



TCNQ (1) DCNQI (2)

Figure 1.

reaction of **9** with 1,4-cyclohexanedione led to the pentacyclic quinone **15** as a yellow, highly insoluble compound. Due to the low solubility of **15**, it was not possible to record its NMR spectrum, and therefore, we were unable to distinguish the presence of one or two constitutional isomers (that is, both sulfur atoms cisoid or transoid across the horizontal plane of symmetry) in the reaction product. Furthermore, treatment of **15** with malononitrile or BTC were unsuccessful.

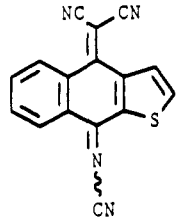
The reaction of quinones **5** with malononitrile in methylene chloride, using $TiCl_4$ and pyridine, led to the corresponding tetracyano derivatives (**6**) as yellow, high-melting solids in moderate yields. The dicyano derivatives (**7**) resulting from the monocondensation reaction were isolated by fractional crystallization from the mother liquors, as a mixture of two constitutional isomers in moderate yield (**7a**, R = H). The dichloro derivatives (**7b**, R = Cl) were also obtained but were contaminated with unreacted starting quinone **5b** and a certain amount of tetracyano derivative **6b**. Attempts to separate them by flash chromatography were unsuccessful due to their instability on silica gel.

The same general behavior was observed in the reaction of quinone **11** with malononitrile, which led to the tetracyano derivative (**12**), together with the dicyano derivative as a mixture of two isomers in about a 1:1 ratio as shown by the high-resolution NMR spectra (Scheme II).

The UV spectra of **6a**, **6b**, and **12** suggest that these molecules are far from planar. The X-ray data for compound **6a** confirm this finding. The high frequencies of the stretching vibrations of the conjugated cyano groups (2219–2232 cm^{-1}, FT-IR) further support this conclusion (see Table I).

Table I. Novel Acceptor Molecules Prepared

compd	λ_{max}, nm (log ε)	ν_{CN}, cm^{-1}	mp, °C	yield, %
5a	325 (3.8)		232–233	56
5b	329 (4.0)		247–248	70
11	390 (2.4)		250–252	55
15	390 (4.2)		380–382	39
6a	374 (4.4)	2219	363–364	26
6b	382 (4.2)	2225	>300	31
12	414 (3.4)	2232	>400	40
8a	354 (4.2)	2160	290–291	68
8b	360 (4.4)	2165	>300	40
14	390 (4.2)	2164	270–272	18
16	365 (4.0)	2210–2160	204–205	65



16

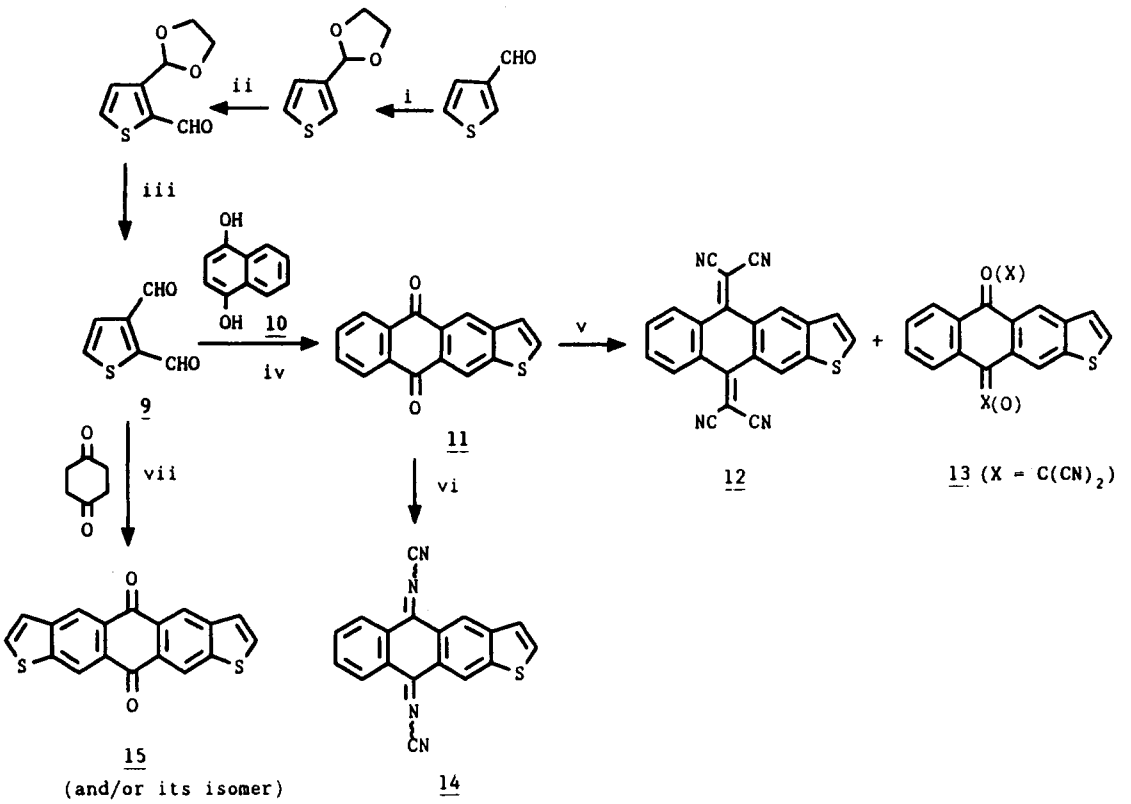
Figure 2.

The synthesis of the heterocyclic DCNQI derivatives was carried out by reaction of bis(trimethylsilyl)carbodiimide (BTC) with the corresponding starting quinones (**5** and **11**) using $TiCl_4$. The reaction led, in all cases, to the dicyanoimine derivative as the only isolated product, in moderate to good yield.

The hybrid compound **16** (Figure 2) was obtained in good yield by reaction of the dicyanomethylene derivative (**7a**) with BTC. Thus, the free carbonyl group opens the way to the little-known hybrid tricyano derivatives recently reported,[3] the electrochemical properties of which render them good candidates for CT complexes. The presence of a sulfur atom in the ring prevents the unfavorable steric interaction found in the TCNQ-type derivatives, between the cyano groups and the *peri*-hydrogens of the π-system.[8]

Electrochemistry. The CV measurements of the new compounds were carried out in acetonitrile at room temperature with tetrabutylammonium perchlorate as the supporting electrolyte. The half-wave redox potentials of the quinones as well as the TCNQ and DCNQI π-extended

Scheme II[a]



[a] (i) $HOCH_2CH_2OH$, C_6H_6, *p*-TsOH; (ii) (1) *n*-BuLi/ether; (2) DMF/ether; (3) H_2O; (iii) HCl (2 M); (iv) pyridine, reflux; (v) $NCCH_2CN$, $TiCl_4$, CH_2Cl_2, rt; (vi) BTC, CH_2Cl_2, rt; (vii) 5% KOH, ETOH.

Table II. Cyclic Voltammetry Data of Novel Acceptors (V vs SCE)[a]

compd	$E^1_{1/2}$, V	$E^2_{1/2}$, V	ΔE, V	log K
1 (TCNQ)	+0.08	−0.48	0.56	9.65
2 (DCNQI)	+0.08	−0.43	0.51	8.79
	+0.23[b]	−0.43		
5a	−0.78	−1.42	0.64	11.03
5b	−0.53	−1.12	0.69	11.89
11	−0.93	−1.50	0.57	9.82
15	−0.97	−1.49	0.52	8.96
7a	−0.33	−0.64	0.31	5.34
13	−0.86	−1.00	0.14	2.41
6a	−0.18 ($2e^-$)			
6b	−0.10 ($2e^-$)			
12	−0.37 ($2e^-$)			
8a	−0.11	−0.61	0.50	8.62
8b	−0.04	−0.50	0.46	7.93
14	−0.33	−0.68	0.35	6.03
16	−0.07	−0.31	0.24	4.13

[a] Versus Ag wire as a Ag/Ag^+ quasireference electrode; electrolyte $Bu_4N^+ClO_4^-$; solvent MeCN; scan rate 20 mV s^{-1}. [b] In DMF.

sulfur-containing derivatives are summarized in Table II.

In contrast to the other compounds, the tetracyano TCNQ-type derivatives (**6a,b** and **12**) show only a two-electron single-wave reduction to the dianion. The separation of their cathodic and anodic peaks, less than 60 mV, suggests a two-electron transfer. The number of electrons was confirmed by controlled potential coulometric analysis of this redox wave in compound **6b**, using a platinum sheet macroelectrode. Thus, the redox wave in the CV of these molecules is indicative of an overall process leading to the dianion ($A + 2e^- \rightleftharpoons A^{2-}$). This result is in good agreement with previously described data for 11,11,12,12-tetracyano-9,10-anthraquinodimethane (TCAQ), which shows a two-electron single-wave reduction to the corresponding dianion.[16,17] However, from the ESR study carried out on TCAQ,[16] a coproportionation reaction ($A + A^{2-} \rightleftharpoons 2A^{\bullet-}$) could also be operative to some extent.

Substitution on the molecule allows the modulation of the acceptor ability. Thus, the presence of two electron-withdrawing chlorine atoms in **6b** significantly decreases the reduction potential. The effect of the sulfur atom on the acceptor ability is noticeable in the tetracyclic TCNQ-type acceptor (**12**), which also exhibits a two-electron single-wave reduction. This finding contrasts with the behavior of the tetracarbocyclic acceptor 13,13,14,14-tetracyano-5,12-naphthacenequinodimethane which shows, under the same experimental conditions, two quasi-reversible reduction waves ($E^1_{1/2} = -0.44$, $E^2_{1/2} = -0.93$ V)[8] with a more negative first reduction potential. Dicyanomethylene derivatives (**7a, 13**) exhibit two reduction waves to the corresponding radical anion and dianion. As expected, the first reduction potentials are more negative than the corresponding tetracyano derivatives (Table II).

On the other hand, the *N,N'*-dicyano diimine derivatives (**8a, 8b, 14**) present two quasi-reversible single-wave reductions to the corresponding radical anion and dianion. Substitution on the parent compound (**8a**) with chlorine atoms (**8b**) yields better acceptors. However, extension of the conjugation by fusion of another benzene ring (**14**) leads to poorer acceptors, probably due to the large influence of the molecular distortion, which overcomes the electronic effect.

Finally, the hybrid compound (**16**) also exhibits two quasi-reversible reduction waves to the radical anion and dianion. Compared with the nonsubstituted tetracyano (**6a**) and *N,N'*-dicyano diimine (**8a**) analogues, the hybrid

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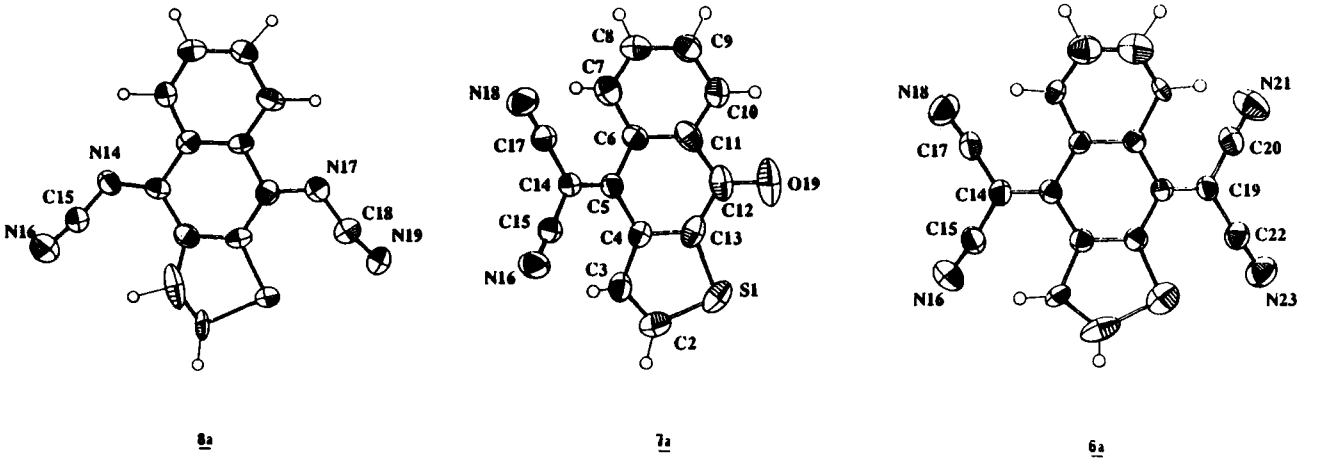

8a 7a 6a

Figure 3. A view[20] of the molecular structure of the compounds, showing the atomic numbering.

16 shows the best acceptor ability. Replacing the benzene ring with the thiophene ring leads, in all cases, to better acceptors, due both to electronic factors as well as to reduced steric hindrance.

Increasing benzannulation in the different series leads to a diminishing of the thermodynamic stability of the radical anions (lower values in log K, see Table II). The least stable radical anions were found in the tetracyano derivatives, which exhibited a single two-electron reduction wave to the dianion.

Tetrasubstituted TCNQ derivatives deviate significantly from planarity[18,19] due to the steric interaction between the dicyanomethylene groups and the *peri*-hydrogen atoms. To overcome this difficulty, a thiophene ring, with no *peri*-hydrogen atoms, was fused to TCNQ-type system, as well as to the DCNQI system, which is substantially more planar. A comparative crystallographic study on the novel tetracyano, dicyanomethylene and *N,N*-dicyano diimine derivatives thus obtained was then performed.

Structural Study. The molecular structures of compounds **7a** and **8a** are shown in Figure 3[20] together with their atomic numbering schemes. The structure of compound **6a**[10] is also presented for comparison purposes.

The planarity of the molecules can be described, firstly, in terms of the angles between the central plane (C4, C5, C11, C13) and the external ones (S1, C2, C3, C4, C13 and C6, C7, C8, C9, C10, C11) and, secondly, in terms of the angle of that plane with those that involve the substituent groups.[10,19]

Molecules **6a** and **7a** present a butterfly shape centered at the two substituted C atoms, while compound **8a** is quite planar (see Table III, supplementary material). The butterfly shapes may be due to the steric hindrance between the cyano groups and the peri-hydrogens on the benzene ring; compounds **6a** and **7a** present a 1–4 boat conformation at the central ring (C4, C5, C6, C11, C12, C13), but the distance of C12 from the least square plane formed by C4, C5, C11, C13 is larger in compound **6a** than in compound **7a** (0.328 (4) Å vs 0.122 (3) Å). However, the central ring in compound **8a** does not deviate significantly from planarity.[21] These geometrical features, and the fact that all bond distances lie in the range between single and double bond (1.54–1.30 Å), suggest some electronic delocalization in the molecules. This effect is less important at the substituents and at the thiophene ring.

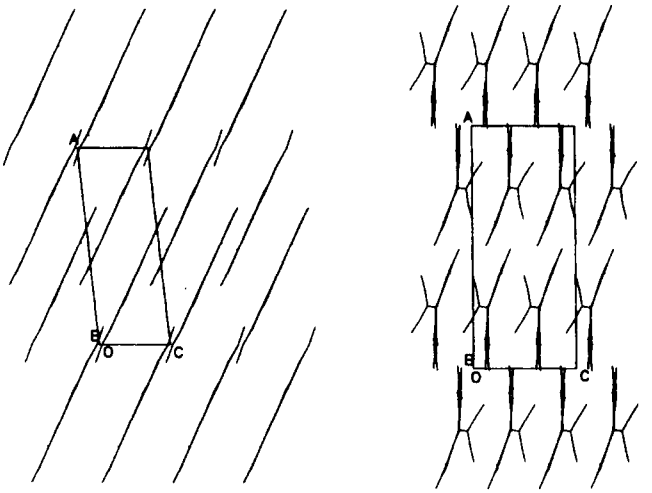

Figure 4. The crystal packing of the compounds **8a** and **7a**, as projected along the axis,[24] showing the intermolecular interactions.

The crystal packing of the three molecules presents a stacking pattern of interactions (interplanar angle around 0°) with contacts between the aromatic rings. In compounds **7a** and **8a** the interactions involve all the molecules, while in compound **6a** there is a chain system that involves only one ring at each interaction (see Figure 4).[22-24]

The crystal structures presented by compounds **7a** and **8a** fulfill all the requirements for a good candidate to form a charge-transfer complex.[25] This is not the case for **6a**, due to the volume of the substituents which induces distortions in the planarity of the molecule and does not allow the formation of suitable stack patterns in the crystal packing.[10]

In conclusion, looking to the design of new CT complexes, we have carried out a systematic and comparative synthetic, electrochemical, and structural study on a model structure and carried out modifications on the number and nature of the acceptor functional groups present in the structure. Modulation of the acceptor ability of these

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molecules can also be achieved by varying the substituents on the carbon framework.

Experimental Section

All melting points were measured on a Gallenkamp melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 257 and FTIR spectra on a Bruker IFs 114 c spectrometer. UV spectra were recorded on a Perkin-Elmer Lambda 3 instrument. ^1H and ^{13}C NMR spectra were determined with a Varian XL-300 spectrometer, and elemental analyses were performed on a Perkin-Elmer CHN 2400 apparatus.

Cyclovoltammetric and coulometric measurements were performed on a EG & G PAR Versabtat potentiostat using 250 Electrochemical Analysis software. A Metrohm 6.0804.C10 glassy carbon electrode was used as indicator electrode in voltammetric studies.

X-ray Crystallographic Measurements. Crystal data for compound 8a: $C_{14}N_4S_1H_6$, MW = 234.275, monoclinic, $P2_1$, a = 10.609 (1) Å, b = 14.043 (1) Å, c = 3.8176 (1) Å, β = 96.647 (4)°, V = 564.9 (1) Å^3, D_c = 1.38 g/cm^3, z = 2, $F(100)$ = 240, μ = 22.80 cm^{-1}, refined cell parameters were obtained from setting angles of 62 reflections. A prismatic brown (0.4 × 0.1 × 0.05 mm) sample was used for the analysis.

Crystal data for compound 7a: $C_{15}N_2O_1S_1H_6$, MW = 250.274, monoclinic, $P2_1/c$, a = 17.441 (1) Å, b = 8.8826 (3) Å, c = 7.4816 (2) Å, β = 90.44 (1)°, V = 1159.0 Å^3, D_c = 1.4343 g/cm^3, z = 2, $F(100)$ = 512, μ = 23.24 cm^{-1}, refined cell parameters were obtained from setting angles of 72 reflections. A prismatic brown (0.3 × 0.12 × 0.03 mm) sample was used for the analysis.

Data collection was similar for both compounds: by use of an automatic four circle diffractometer (Philips PW 1100) with graphite oriented monochromated and Cu Kα radiation. The intensity data were collected using the $\omega/2\theta$ scan mode, with $2 < \theta$ 65°; two standard reflections were measured every 90 min with no intensity variation. For compound 7 a total of 1008 reflections were measured and 983 were considered as observed ($I > 3\sigma(I)$ criterium for both compounds). For compound 6, 2124 reflections were measured and 1902 were considered as observed. The data were corrected for Lorentz and polarization effects.

Structure Solution and Refinements. Both structures were solved by direct methods using SIR88[26] and successive Fourier synthesis. The molecules present disorder (populations of 0.54 (1) and 0.46 (1) for compound 7, and 0.68 (1) and 0.32 (1) for compound 6); most H of compound 7 were included in mixed refinement (see the supplementary material); H atoms were located geometrically,[27] except for hydrogens of the phenyl rings which were located from difference Fourier synthesis; U parameters of those atoms were considered as fixed in the refinement contributors. A convenient weighting scheme was applied to obtain flat dependence in $\langle w\Delta^2F\rangle$ vs $\langle F_0\rangle$ and $\langle \sin\theta/\lambda\rangle$.[28] Final R (R_w) values were 3.7 (3.9) and 6.1 (7.3). According to space group polarity of compound 7, the Y coordinate of the S1A atom was fixed. Atomic scattering factors were taken from ref 29, and calculations were performed using XRAY-80,[30] XTAL,[31] and PARST.[21]

2-(2-Thenoyl)benzoic Acid (4a). This compound was obtained by following the procedure previously reported[14] in 68% yield: mp 144–145 °C (lit.[14] mp 145 °C).

2-(2-Thenoyl)-4,5-dichlorobenzoic Acid (4b). To a mixture of magnesium (1.2 g, 50 mmol) in 25 mL of dry ether, under argon atmosphere, was added dropwise a solution of 2-iodothiophene (5.5 g, 50 mmol) in 20 mL of dry ether. During the addition of 2-iodothiophene, the reaction mixture was warmed until the magnesium shavings were consumed. The Grignard reagent was slowly added to a suspension of 4,5-dichlorophthalic anhydride (10.85 g, 50 mmol) in 100 mL of dry ether cooled in an ice bath. The reaction mixture was kept under vigorous stirring for 24 h and then treated with a saturated solution of ammonium chloride (50 mL) and 6 N hydrochloric acid (10 mL). The solid that precipitated in the organic phase was dissolved with 15% sodium carbonate (100 mL). To the basic phase was added 6 N hydrochloric acid (100 mL) dropwise with vigorous stirring, and a brown solid was obtained in 94% yield. Further purification was accomplished by recrystallization from water to give white needles: mp 198–199 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 8.16 (s, 1 H, Ar-H), 7.74 (q, 1 H, J = 4.6 Hz, J' = 1.0 Hz, thiophene), 7.57 (s, 1 H, Ar-H), 7.29 (q, 1 H, J'' = 4.1 Hz, thiophene-H), 5.55 (bs, 1 H, CO_2H); IR (KBr) 3000, 1690, 1650, 1590, 1560, 1520, 1420, 1300, 1260, 1250, 940, 910 cm^{-1}. Anal. Calcd for $C_{12}H_6Cl_2O_3S$: C, 47.84; H, 1.99. Found: C, 47.72; H, 1.94.

Syntheses of Quinones. Thieno[2,3-*b*]-1,4-naphthoquinone (**5a**) was obtained according to a previously reported procedure.[14] However, no spectroscopic data were available, and this compound is now described. The 6,7-dichlorothieno[2,3-*b*]-1,4-naphthoquinone (**5b**) has not been previously reported. The novel thieno[2,3-*b*]-9,10-anthraquinone (**11**) and dithieno[2,3-*b*][6,7-*b*]-9,10-anthraquinone (**15**) were obtained following the methods previously reported for the carbocyclic series.[32,33]

Thieno[2,3-*b*]-1,4-naphthoquinone (5a). To a solution of 2-(2-thenoyl)benzoic acid (0.6 g, 2.6 mmol) and phosphorus pentachloride (0.8 g, 4 mmol) in 20 mL of dry nitrobenzene was added aluminum trichloride (0.5 g, 4 mmol). The mixture was kept at room temperature for 1 h and then at 140 °C for 4 h. The solvent was distilled under vacuum (65 °C, 0.007 mbar), and a solid was obtained. Further purification was accomplished by column chromatography and recrystallization. Thus, a yellow solid was obtained in 56% yield: mp 232–233 °C (lit.[14] mp, 228 °C); ^1H NMR (300 MHz, $CDCl_3$) δ 8.23 (m, 2 H, Ar-H), 7.86 (m, 2 H, Ar-H), 7.73 (dd, 2 H, J = 5 Hz thiophene-H); IR (KBr) 3100, 1660, 1590, 1580, 1510, 1425, 1390, 1320, 1300, 1275, 1245, 870, 700 cm^{-1}; UV (CH_2Cl_2) λ_{max} (log ϵ) 325 (3.78), 280 (4.19), 272.6 (4.13), 250.0 (4.44), 255.4 (4.41), 214.9 (4.69); MS m/e (%) 214 (M^+, 100), 186 (56), 158 (41), 114 (19). Anal. Calcd for $C_{12}H_6O_2S$: C, 67.29; H, 2.80. Found: C, 67.14; H, 2.52.

6,7-Dichlorothieno[2,3-*b*]-1,4-naphthoquinone (5b). This compound was obtained in 70% yield by following the same procedure described above: mp 247–248 °C (from DMF or sublimation at 100 °C (0.1 mbar); ^1HNMR (300 MHz, $CDCl_3$) δ 8.29 (s, 2 H, Ar-H), 7.82–7.70 (dd, 2 H, J = 5.1 Hz, thiophene-H); IR (KBr) 3100, 1675, 1580, 1510, 1430, 1400, 1370, 1310, 1260, 1190, 950, 900, 730 cm^{-1}; MS m/e (%) 286 (M^+ + 2, 71), 282 (M^+, 100), 254 (57), 226 (36), 219 (12), 191 (25), 149 (20). Anal. Calcd for $C_{12}H_4Cl_2O_2S$: C, 50.98; H, 1.41. Found: C, 50.97; H, 1.45.

Thieno[2,3-*b*]-9,10-anthraquinone (11). 2,3-Thiophenedicarboxaldehyde[15] (**9**) (2.8 g, 20 mmol) and 1,4-dihydroxynaphthalene (3.2 g, 20 mmol) were dissolved in 25 mL of dry pyridine under argon atmosphere. The reaction mixture was refluxed for 24 h (TLC) and then cooled to room temperature. The solid that separated was filtered off and washed with hexane. A second crop was obtained from the mother liquors to give a 55% yield: mp 250–252 °C; ^1H NMR (300 MHz, CD_3–$SOCD_3$) δ 8.92 (s, 1 H, Ar-H), 8.75 (s, 1 H, Ar-H), 8.27–8.24 (m, 2 H, Ar-H), 8.21 (d, 1 H, J = 5.5 Hz, thiophene-H), 7.96–7.93 (m, 2 H, Ar-H), 7.83 (d, 1 H, J = 5, 5 Hz, thiophene-H); IR (KBr) 3120, 1690, 1610, 1590, 1490, 1420, 1340, 1305, 1180, 975, 920, 830, 780, 720, 700 cm^{-1}; UV (CH_2Cl_2) λ_{max} (log ϵ) 390.0 (2.40), 383.1 (2.34), 282.1 (3.20), 250.0 (3.20); MS m/e (%) 269 (M^+, 100), 236 (24), 208 (39), 163 (15), 104 (11). Anal. Calcd for $C_{16}H_8O_2S$: C, 72,73; H, 3.03. Found: C, 72.74; H, 3.31.

Dithieno[2,3-*b*][6,7-*b*]-9,10-anthraquinone and/or Dithieno[2,3-*b*][6,7-*d*]-9,10-anthraquinone (15). To a solution

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of 2,3-thiophenedicarboxaldehyde (9) (4 g, 28.6 mmol) and 1,4-cyclohexanedione ((1.5 g, 14.3 mmol) in 87 mL of ethanol was added 3 mL of 5% sodium hydroxide. The reaction turned progressively darker, and a yellow solid precipitated in the reaction medium. It was collected by filtration and washed with hexane. Further purification was accomplished by recrystallization from a large volume of DMF to give a yellow solid in 39% yield: mp 380–382 °C; IR (KBr) 3100, 1680, 1586, 1500, 1410, 1355, 1330, 1200, 1190, 1000, 930, 840, 770, 750, 720, 705 cm^{-1}; UV (CH_2Cl_2) λ_{max} (log ϵ) 390.0 (4.16), 293.3 (4.90), 246.7 (4.60); MS m/e (%) 320 (M^+, 100), 292 (20), 264 (25), 219 (9), 132 (8). Anal. Calcd for $C_{18}H_8O_2S_2$: C, 67.50; H, 2.50; S, 20.00. Found: C, 67.62; H, 2.80; S, 19.85.

Condensation of Quinones with Malononitrile. General Procedure. To a solution of the corresponding quinone (1.4 mmol) and malononitrile (0.23 g, 3.5 mmol) in 40 mL of dry methylene chloride, were added dropwise titanium tetrachloride (0.38 mL, 3.5 mmol) under argon atmosphere and, then, anhydrous pyridine (0.57 mL, 7 mmol). The reaction was stirred at room temperature for 24 h (TLC). The solid formed in the reaction medium was filtered off and washed with plenty of water. The mother liquors were concentrated, and a second crop was obtained.

The solid thus obtained was a mixture of tetracyano derivative and the two isomeric dicyano derivatives, resulting from the monocondensation reaction. By fractional crystallization in acetonitrile, the more insoluble tetracyano derivative precipitated first in all cases and was thus isolated. A mixture of the dicyano isomers was isolated from the mother liquors.

9,9,10,10-Tetracyanothieno[2,3-*b*]-1,4-naphthoquinodimethane (6a). This compound was obtained by following the above general procedure by fractional crystallization from the crude mixture as a yellow solid in 26% yield: mp 363–364 °C (from acetonitrile); ^{1}H NMR (300 MHz, CD_3SOCD_3) δ 8.55–8.25 (m, 3 H, Ar-H), 8.00 (d, 1 H, thiophene-H), 7.95–7.80 (m, 2 H, Ar-H); IR (KBr) 3093, 2220, 1539, 1480, 1421, 1387, 764, 746 cm^{-1}; UV (CH_2Cl_2) λ_{max} (log ϵ) 374 (4.4), 318 (4.0), 280 (4.2), 216 (5.0); MS m/e (%) 310 (M^+, 100), 283 (M^+ – HCN, 18), 262 (24), 234 (15). Anal. Calcd for $C_{18}H_6N_4S$: C, 69.67; H, 1.93; N, 18.06. Found: C, 69.82; H, 1.93; N, 17.76.

The monocondensation isomers (7a) were obtained from the mother liquors as yellow solids in 39% yield: mp 246–248 °C (from acetonitrile); ^{1}H NMR (300 MHz, CD_3SOCD_3) δ 8.55–8.45 (m, 1 H, Ar-H), 8.38–8.33 (m, 1 H, Ar-H), 8.25–8.18 (m, 1 H, Ar-H), 8.11–8.06 (m, 1 H, Ar-H), 7.95–7.83 (m, 2 H, thiophene-H); IR (KBr) 3100, 2215, 1650, 1590, 1570, 1535, 1420, 1400, 1200, 760, 700 cm^{-1}; UV (CH_2Cl_2) λ_{max} (log ϵ) 332 (4.3), 266 (4.3), 226 (4.2), 218 (4.1); MS m/z (%) 262 (M^+, 100), 234 (56), 207 (13), 189 (13), 163 (19), 117 (13), 104 (19). Anal. Calcd for $C_{15}H_{16}N_2OS$: C, 68.70; H, 2.29; N, 10.69. Found: C, 68.24; H, 2.09; N, 10.77.

9,9,10,10-Tetracyano-6,7-dichlorothieno[2,3-*b*]-1,4-naphthoquinodimethane (6b). This compound was obtained by following the general procedure as a yellow solid in 31% yield: mp > 300 °C; ^{1}H NMR (300 MHz, CD_3SOCD_3) δ 8.75–8.62 (m, 1 H, Ar-H), 8.4–8.3 (m, 1 H, Ar-H), 8.0 (bs, 1 H, thiophene-H), 7.98 (bs, 1 H, thiophene-H); IR (KBr) 3100, 2225, 1560, 1540, 1520, 1470, 1440, 1370, 1320, 1210, cm^{-1}; UV (CH_2Cl_2) λ_{max} (log ϵ) 382 (4.2), 326 (4.0), 297 (4.2), 282 (4.2), 229 (4.3). Anal. Calcd for $C_{18}H_4Cl_2N_4S$: C, 57.01; H, 1.06; N, 14.77. Found: C, 56.69; H, 1.54; N, 14.33.

11,11,12,12-Tetracyanothieno[2,3-*b*]-9,10-anthraquinodimethane (12). This compound was obtained by following the general procedure as a yellow solid in 40% yield: mp >400 °C (from acetonitrile); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.74 (s, 1 H, Ar-H), 8.66 (s, 1 H, Ar-H), 8.26 (m, 2 H, Ar-H), 7.85 (d, 1 H, thiophene-H), 7.74 (m, 2 H, Ar-H), 7.57 (d, 1 H, thiophene-H); IR (KBr) 3096, 2232, 1583, 1555, 1477, 1342, 1308, 1283, 1223, 918, 783, 762, 729 cm^{-1}; UV (CH_2Cl_2) λ_{max} (log ϵ) 319 (3.9), 295 (3.9), 264 (3.7); MS m/z (%) 360 (M^+, 100), 333 (M^+ – HCN, 11). Anal. Calcd for $C_{22}H_8N_4S$: C, 73.33; H, 2.22; N, 15.56; S, 8.89. Found: C, 73.43; H, 2.24; N, 15.48; S, 8.50.

The monocondensation isomers (13) were obtained as a mixture from the mother liquors as yellow solids in 19% yield: mp 274–276 °C (from acetonitrile); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.80 (m, 1 H, Ar-H), 8.74 (s, 1 H, Ar-H), 8.34–8.31 (m, 2 H, Ar-H), 7.84–7.86 (m, 3 H, 2Ar-H + thiophene-H), 7.58 (d, 1 H, thiophene-H); IR (KBr) 3094, 2216, 1674, 1636, 1593, 1576, 1541, 1516, 1346, 1335, 756, 720, 702 cm^{-1}; UV (CH_2Cl_2) λ_{max} (log ϵ) 407 (3.0), 229 (3.6), 255 (3.7); MS m/z (%) 312 (M^+, 100), 284 (M^+ – HCN, 32), 257 (6), 212 (4), 142 (7), 115 (7). Anal. Calcd for $C_{19}H_8N_2OS$: C, 73.06; H, 2.58. Found: C, 72.77; H, 2.46.

Condensation of Quinones with Bis(trimethylsilyl)carbodiimide (BTC). General Procedure. To a solution of the corresponding quinone (1.2 mmol) in dry methylene chloride (20–50 mL), under argon atmosphere, were added dropwise titanium tetrachloride (0.4 mL, 4.2 mmol) and then bis(trimethylsilyl)carbodiimide (BTC) (0.94 mL, 3.5 mmol). The reaction mixture was stirred at room temperature for a variable time (24–96 h). After this time, 100 g of crushed ice was added, and the reaction mixture was vigorously stirred until room temperature was reached. The organic phase was dried over magnesium sulfate and concentrated to half its volume. A yellow solid precipitated and was collected by filtration. [For compound 14 the solvent was eliminated almost to dryness, and when petroleum ether (50–70 °C) was added, a solid precipitated.] The solid thus obtained was purified by recrystallization from acetonitrile.

***N,N'*-Dicyanothieno[2,3-*b*]-1,4-naphthoquinone Diimine (8a).** This compound was obtained in 68% yield by following the general procedure and stirring for 96 h: mp 290–291 °C (from acetonitrile); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.0–8.9 (m, 1 H, Ar-H), 8.58–8.46 (m, 2 H, Ar-H), 8.08–8.00 (m, 1 H, Ar-H), 7.88–7.78 (m, 2 H, thiophene-H); IR (KBr) 3120, 2160, 1553, 1472, 1423, 1379, 1339, 1300, 700 cm^{-1}; UV (CH_2Cl_2) λ_{max} (log ϵ) 354 (4.2), 266 (4.1), 225 (4.0); MS m/z (%) 262 (M^+, 100), 234 (40), 207 (14), 72 (19), 59 (30). Anal. Calcd for $C_{14}H_6N_4S$: C, 64.12; H, 2.29; N, 21.37. Found: C, 64.11; H, 2.24; N, 21.28.

***N,N'*-Dicyano-6,7-dichlorothieno[2,3-*b*]-1,4-naphthoquinone Diimine (8b).** This compound was obtained in 24 h as an orange solid in 40% yield: mp >300 °C (from acetonitrile); ^{1}H NMR (300 MHz, CD_3SOCD_3) δ 8.28 (s, 1 H, Ar-H), 8.23 (s, 1 H, Ar-H), 7.84 (d, 1 H, thiophene-H), 7.75 (d, 1 H, J = 5 Hz, thiophene-H); IR (KBr) 3110, 2170, 1650, 1555, 1460, 1430, 1375, 1320, 1280, 920, 700 cm^{-1}; UV (CH_2Cl_2) λ_{max} (log ϵ) 360 (4.4), 285 (4.3), 275 (4.3), 228 (4.3). Anal. Calcd for $C_{14}H_4Cl_2N_4S$: C, 50.75; H, 1.21; N, 16.92. Found: C, 50.82; H, 1.43; N, 16.60.

***N,N'*-Dicyanothieno[2,3-*b*]-9,10-anthraquinone Diimine (14).** This compound was obtained in 18% yield by following the above general procedure in 48 h reaction time: mp 270–272 °C (from acetonitrile); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.0 (s, 1 H, Ar-H), 8.80 (s, 1 H, Ar-H), 8.34–8.24 (m, 2 H, Ar-H), 8.02–7.96 (m, 2 H), 7.88–7.83 (m, 2 H); IR (KBr) 2164, 1611, 1587, 1553, 1474, 1410, 1352, 1339, 1223, 1013, 889, 824, 772, 723 cm^{-1}; UV (CH_2Cl_2) λ_{max} (log ϵ) 390 (4.2), 283 (4.9), 250 (4.9); MS m/z (%) 312 (M^+, 100), 285 (19), 184 (11), 156 (10). Anal. Calcd for $C_{18}H_8N_4S$: C, 69.23; H, 2.56; N, 17.95. Found: C, 68.71; H, 2.78; N; 17.49.

***N*,10,10-Tricyanothieno[2,3-*b*]-1,4-naphthoquinomethane Imine (16).** To a solution of 7a (66 mg, 0.25 mmol) in methylene chloride (40 mL) was added dropwise titanium tetrachloride (0.049 mL, 0.45 mmol) followed by bis(trimethylsilyl)carbodiimide (BTC) (0.085 mL, 0.38 mmol). After 12 h the same quantities of titanium tetrachloride and BTC were added, and this operation was repeated at 18 and 25 h. Methylene chloride (40 mL) was added to the reaction mixture and then poured in 100 g of crushed ice. The crude solid was crystallized from acetonitrile, and yellow crystals were obtained in 65% yield: mp 204–205 °C; ^{1}H NMR (300 MHz, CD_3SOCD_3) δ 8.56–8.47 (m, 2 H), 8.44–8.38 (m, 1 H), 8.18–8.12 (m, 1 H), 8.0–7.84 (m, 2 H); IR (KBr) 3080, 2210, 2160, 1550, 1390, 1330, 1305, 1260, 770, 700, 690 cm^{-1}; UV (CH_2Cl_2) λ_{max} (log ϵ) 365 (4.0), 305 (3.4), 270 (3.9), 226 (4.0). Anal. Calcd for $C_{16}H_6N_4S$: C, 67.12; H, 2.11; N, 19.57. Found: C, 66.87; H, 2.42; N, 18.80.

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Registry No. **3b**, 942-06-3; **4a**, 46496-80-4; **4b**, 143746-69-4; **5a**, 4968-81-4; **5b**, 143746-70-7; **6a**, 143034-10-0; **6b**, 143746-73-0; **7a** isomer 1, 143034-08-6; **7a** isomer 2, 143773-89-1; **8a**, 143746-74-1; **8b**, 143746-75-2; **11**, 143034-07-5; **12**, 143034-11-1; **13** isomer

1, 143034-09-7; 13 isomer 2, 143773-90-4; 14, 143746-76-3; 15, 143746-71-8; 16, 143746-77-4; 2-iodothiophene, 3437-95-4; 1,4-dihydroxynaphthalene, 571-60-8; 2,3-thiophenedicarboxaldehyde, 932-41-2; dithieno[2,3-*b*][6,7-*b*]-9,10-anthraquinone, 143746-72-9; 1,4-cyclohexanedione, 637-88-7; malononitrile, 109-77-3.

Supplementary Material Available: X-ray data for $C_{14}N_4S_1H_6$ and $C_{15}N_2O_1S_1H_6$ (17 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Cytotoxic Polyketides from *Annona densicoma* (Annonaceae): 10,13-*trans*-13,14-*erythro*-Densicomacin, 10,13-*trans*-13,14-*threo*-Densicomacin, and 8-Hydroxyannonacin

Jing Guang Yu, David K. Ho, and John M. Cassady*

Division of Medicinal Chemistry and Pharmacognosy, College of Pharmacy, The Ohio State University, Columbus, Ohio 43210

Lizhen Xu and Ching-jer Chang

Department of Medicinal Chemistry and Pharmacognosy, School of Pharmacy and Pharmacal Sciences, Purdue University, West Lafayette, Indiana 47907

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Three new linear polyketides, 10,13-*trans*-13,14-*erythro*-densicomacin (1), 10,13-*trans*-13,14-*threo*-densicomacin (2), and 8-hydroxyannonacin (3), and a known polyketide goniothalamicin were isolated from the stem bark of the Peruvian plant *Annona densicoma* Mart (Annonaceae). Their structures were elucidated on the basis of UV, IR, ^1H and ^{13}C NMR, and mass spectrometry data of the natural compounds and their derivatives. These polyketides are cytotoxic against human tumor cells in culture. In particular, densicomacins (1 and 2) were significantly active against the lung carcinoma (A-549) and the colon adenocarcinoma (HT-29) cell lines with ED_{50} at 4×10^{-4} and 1×10^{-5} μg/mL, respectively.

In earlier studies we reported four cytotoxic polyketides, annonacin,[1] annonacin-10-one, isoannonacin, and isoannonacin-10-one,[2] from the Peruvian plant *Annona densicoma* Mart. These polyketides possess a C_{35} skeleton with one tetrahydrofuran ring, one lactone moiety, and several hydroxyl groups. In this paper[3] we report the discovery of three novel cytotoxic polyketides from the stem bark of *A. densicoma*: 10,13-*trans*-13,14-*erythro*-densicomacin (1), 10,13-*trans*-13,14-*threo*-densicomacin (2), and 8-hydroxyannonacin (3) as well as a known polyketide (goniothalamicin (4)) which was first isolated from *Goniothalamus giganteus* Hook, f., Thomas (Annonaceae) by Alkofahi et al.,[4] (Chart I). Compounds 1 and 2 represented the first two examples of C_{35} polyketides with the tetrahydrofuran ring located between C-10 and C-13.

Results and Discussion

Densicomacin was isolated as white crystals, mp 83–4 °C, $[\alpha]_D$ +26° (*c* 0.05, MeOH). The molecular formula was established to be $C_{35}H_{64}O_7$ by high resolution CI-MS: obsd 597.4716 (MH^+), calcd 597.4730. The IR absorption band at 1748 cm^{-1}, the UV absorption at λ_{max} (MeOH) 209.5 nm (log ϵ, 3.85), the proton signals at δ 7.19, 5.05, and 1.43, and the carbon signals at δ 174.59, 151.85, 131.11, and 19.06 were characteristic for the α,β-unsaturated lactone moiety typical of the annonacin-type[1] of polyketides (Table I). The EI-MS ions of 227, 239, 281, 297, 333, 351, and others suggested the position of the tetrahydrofuran ring to be at C-10 and C-13 and those of the hydroxyl groups at C-4, C-14, C-17, and C-18 as shown (Scheme I, Table II). The conversion of densicomacin to its isomer[5] with KOH/*t*-BuOH confirmed the presence of a hydroxyl group at C-4. By ^1H–^1H 2D-COSY, H-13 of densicomacin was found to be coupled to H-14 while H-10 was not coupled to any hydroxyl methine proton. This pattern was also observed in the ^1H NMR spectra of the tetraacetate (5), acetonide (6), and acetonide diacetate (7) derivatives. The assignment of the last two hydroxyl groups at C-17 and C-18 was substantiated by the formation of the acetonide 6, the acetonide diacetate 7, and pentadecanoic acid by treatment with sodium periodate. In compound 6, the *gem*-dimethyl signal appeared as a singlet at δ 1.38 (6 H). Downfield shifts were observed for the H-17 (from δ 3.43 to 3.58) and H-18 (from δ 3.40 to 3.58) protons. The conversion of 6 to 7 induced downfield shifts at H-4 (from δ 3.85 to 5.10) and H-14 (From δ 3.41 to 4.89) but not at H-17 or H-18).

From the ^{13}C and ^1H NMR data (Table I), densicomacin was observed as a mixture of two stereoisomers. These isomers were resolvable by preparative TLC as the mesitoates 8 and 9. The H-13 and H-14 signals of the me-

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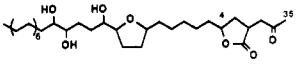
(5) Densicomacin (4 mg) was treated with 2% KOH in *t*-BuOH (0.5 mL) at room temperature for 24 h. The reaction mixture was acidified with dilute HCl and extracted with CH_2Cl_2. The extract was purified by preparative TLC to give isodensicomacin (1 mg): CI-MS *m/z* (rel int) 597 (MH^+, 100), 579 (12), 561 (30); EI-MS *m/z* (rel int) 351 (2), 333 (2), 315 (0.3), 297 (3), 281 (55), 263 (5), 245 (8), 239 (50), 221 (15), 141 (15), 123 (30); ^1H NMR (250 MHz in $CDCl_3$) δ 4.39 (m, H-4 of 2,4-cis isomer), 4.54 (m, H-4 of 2,4-trans isomer), 2.20 (s, H-35).



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