6, 91341-03-6; 7a, 115906-95-1; 8, 115906-97-3; 9, 17216-62-5; 10, 10444-11-8; 11, 125847-78-1; MeOH, 67-56-1; EtOH, 64-17-5; *i*-PrOH, 67-63-0; 2-Me-butyl-OH, 137-32-6; 2-Et-hexyl-OH, 104-76-7; c-HexOH, 108-93-0; (−)-menthyl-OH, 2216-51-5; benzyl-OH, 100-51-6; 1-Me-benzyl-OH, 98-85-1; $CO_2(CO)_8$, 10210-68-1; acrylonitrile, 107-13-1; ethyl acrylate, 140-88-5; diethyl maleate, 141-05-9; methyl vinyl ketone, 78-94-4; benzylidene acetone, 122-57-6; diethyl succinate, 123-25-1; diethyl fumarate, 623-91-6; 4-isopropoxybutan-2-one, 32541-58-5; diethyl malonate, 105-53-3; diethyl methylmalonate, 609-08-5.

Supplementary Material Available: Mass spectral data of some byproducts of reactions 3 and 5 (2 pages). Ordering information is given on any current masthead page.

2-Aryl-4-quinolones and Fused Quinolines from β-Chloroarylidenemalonates and Related Chloro Esters

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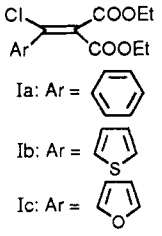
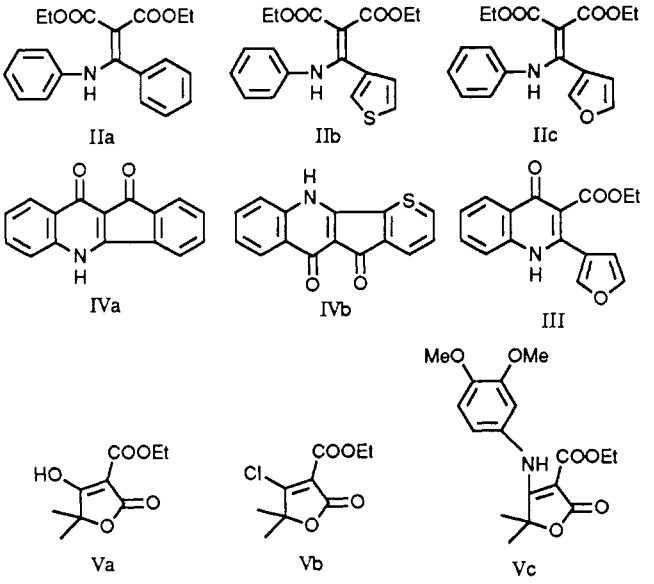
The β-chloroarylidenemalonates I were transformed to the anilinoarylidenemalonates II in 50–70% yield. Thermolysis of the β-anilinofurfurylidenemalonate IIc at 250 °C gave 3-(ethoxycarbonyl)-2-(2-furyl)-4-quinolone III in 85% yield. Treatment of the anilinomalonates IIa and IIb with polyphosphoric acid at 210–230 °C gave the indeno[1,2-*b*]quinoline IVa in 75% yield and its thiophene analogue IVb in 50% yield. The hydroxybutenolide Va was prepared from 2-bromo-2-methylpropanoyl chloride and (ethoxymagnesio)malonate in 72% yield, and Va was then transformed to the chlorobutenolide Vb in 75% yield. The treatment Vb with 3,4-dimethoxyaniline in the presence of triethylamine followed by cyclization of the intermediate anilinobutenolide Vc gave the furo[3,4-*b*]quinolinedione VI in 48% yield.

We have been investigating the utilization of β-chloroarylidenemalonates[1] and related chloro esters I as starting materials in synthetic work, partly because they are accessible in large quantities from readily available acylmalonates[2] and especially because the high level of functionality that is present in these chloro esters leads to chemical reactivity not otherwise attainable. The esters possess three features of functionality: the ester groups, the double bond, and the substituent (Ar in I).



In previous papers we have demonstrated the significance and the powerful nature of the three functionalities. We have shown that the chloro esters can be converted into various substances,[2a,3] some of which are natural products.

As a complement to our continuing investigations we now describe a utilization of the chloro esters in the synthesis of the 2-(2-furyl)-4-quinolone III, indeno[1,2-*b*]-quinolines and related fused heterocycles IVa and IVb via the intermediate β-anilinoarylidenemalonates II. As a further application of the method we also describe a synthesis of the furoquinoline VI via the anilinobutenolide Vc.



Our interest in the synthesis of the 2-aryl-4-quinolones was stimulated by a recent observation of Chen et al. that only a few examples of the synthesis of 2-aryl-4-quinolones have been described.[4] The authors indicate that problems are encountered during the preparation of the required β-anilinoacrylate intermediates such as the β-anilinoarylidene malonates II.

With our earlier experiences on the nucleophilic vinylic substitution (S_NV) reactions[5] between various chloro esters and nucleophiles in mind we hoped that the anilino esters

(1) We think that it is more convenient and descriptive to use nonsystematic nomenclature for the compounds I and II. Their systematic names are as follows: Ia, ethyl 3-chloro-2-(ethoxycarbonyl)-3-phenylpropenoate; Ib, ethyl 3-chloro-2-(ethoxycarbonyl)-3-(2-thienyl)-propenoate; Ic, ethyl 3-chloro-2-(ethoxycarbonyl)-3-(2-furyl)-propenoate; IIa, ethyl 2-(ethoxycarbonyl)-3-(*N*-phenylamino)-3-phenylpropenoate; IIb, ethyl 2-(ethoxycarbonyl)-3-(*N*-phenylamino)-3-(2-thienyl)propenoate; IIc, ethyl 2-(ethoxycarbonyl)-3-(2-furyl)-3-(*N*-phenylamino)propenoate.

(2) (a) Hormi, O. E. O. *Org. Synth.* **1988**, *66*, 173. (b) Hormi, O. E. O. *Synth. Commun.* **1986**, *16*, 997.

(3) (a) Hormi, O. E. O.; Moisio, M. R. *J. Org. Chem.* **1987**, *52*, 5275. (b) Hormi, O. E. O.; Paakkanen, A. M. *J. Org. Chem.* **1987**, *52*, 5275. (c) Hormi, O. E. O. *J. Org. Chem.* **1988**, *53*, 880.

(4) Chen, B.-c.; Huang, X.; Wang, J. *Synthesis* **1987**, 482. See also: Huang, X.; Chen, B.-c. *Synthesis* **1987**, 480.

(5) Recent reviews of the S_NV mechanism: (a) Rappoport, Z. *Recl. Trav. Chim., Pays-Bas* **1985**, *104*, 309. (b) Bernasconi, C. F. *Tetrahedron* **1989**, *45*, 4017.

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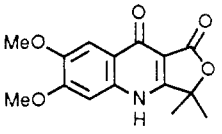
II could result from S_NV reactions between aniline and the appropriate chloro esters I.

Indeno[1,2-*b*]quinolines are of interest because they can be converted into biologically active compounds such as 10-(methylamino)-11*H*-indeno[1,2-*b*]quinolin-11-one (MB 432).[6] They are normally prepared from 3-(ethoxycarbonyl)-2-phenyl-4-quinolones. We hoped that we could find a short synthesis of the indeno[1,2-*b*]quinoline ring system and apply the method to the preparation of related compounds. We were also interested to see whether the strategies could be applied to the synthesis of other fused heterocyclic ring systems, such as the furoquinoline VI.



VI

Although some methods for the synthesis of related furoquinoline ring systems have been developed recently, the previous methods are limited by the availability of suitable aromatic ortho amino carbonyl compounds.[7]

Results and Discussion

Conversion of the β-chloroarylidenemalonates Ia–c into the required β-anilinomalonates IIa–c was achieved by treating the chloro esters with aniline in the presence of triethylamine (12 h, 90 °C). The β-anilinomalonates were produced in 50–70% yield.

Thermolysis of the anilinomalonate IIc was carried out at 250 °C to give the expected 3-(ethoxycarbonyl)quinoline III in 85% yield.

We next examined the synthesis of the indenoquinoline IVa and its thiophene analogue IVb. Since β-anilinoarylidenemalonates undergo heat-induced cyclizations to give the expected 2-aryl-3-(ethoxycarbonyl)-4-quinolones and since 3-(ethoxycarbonyl)-2-phenyl-4-quinolone is reported to undergo ring closure in polyphosphoric acid at elevated temperatures to give the target indenoquinoline, we were attracted to the use of polyphosphoric acid as the solvent to carry out the transformation II directly to IV at elevated temperatures. We found that the desired double cyclization proceeded smoothly at 210–220 °C, giving a 75% yield of the indenoquinoline IVa and a 50% yield of its thiophene analogue IVb.

We also made several attempts at various temperatures to apply the polyphosphoric acid cyclization to the β-anilinofurfurylidenemalonate IIc, but we were unable to obtain the desired product. Our attempts to cyclize the ethoxycarbonylquinoline III in polyphosphoric acid or trifluoroacetic acid/trifluoroacetic anhydride were also unsuccessful. Our cyclization experiments with IIc and III were frustrated by total decomposition of the furan ring.

We next expanded the scope of the methodology to the synthesis of other fused heterocyclic ring systems. We chose to investigate the anilinobutenolide Vc because we hoped that it could easily be transformed into the furoquinoline VI.

A good synthesis of the hydroxybutenolide Va was required since it was the key intermediate in the synthesis of Vb. Prompted by a preliminary report of Bloomer and Kappler[8] of alkaline ring closure of ethyl 4-bromo-2-(ethoxycarbonyl)-4-methyl-3-oxopentanoate to give the target butenolide we treated 2-bromo-2-methylpropanoyl chloride with diethyl (ethoxymagnesio)malonate to give the crude ethyl 4-bromo-2-(ethoxycarbonyl)-4-methyl-3-oxopentanoate. Treatment of the crude bromo ester with aqueous potassium carbonate followed by hydrochloric acid resulted in replacement of bromine by a hydroxy group and in ring closure of the intermediate ethyl 2-(ethoxycarbonyl)-4-hydroxy-4-methyl-3-oxopentanoate to give the butenolide Va in 72% yield over the two steps.

Chlorination of Va to the chlorobutenolide Vb was achieved by heating Va with phosphorus oxychloride in the presence of diisopropylethylamine. The yield of the crude Vb was 75%.

Replacement of the chlorine by 3,4-dimethoxyaniline was affected by treatment of Vb with the desired aniline in the presence of triethylamine. Although the anilinobutenolide Vc could be purified, it was more convenient to cyclize it directly to the target furoquinoline VI in 48% yield over the two steps.

Experimental Section

Melting points are uncorrected and they were determined on a Gallenkamp melting point apparatus. Homogenity of all final products was monitored by thin-layer chromatography (TLC), which was performed on precoated silica gel plates (Kiselgel 60 F_{254}, Merck, 0.25 mm thick). The developed plates were air-dried and exposed to UV light. NMR spectra were measured with JEOL 90 Q spectrometer and chemical shifts are reported relative to internal Me_4Si. IR spectra were obtained on a Perkin-Elmer 297 IR spectrometer and wave numbers are reported in cm^{-1}. Mass spectra were recorded by Markku Reunanen and Kirsti Viinamäki on a WG 7070 E instrument.

Preparation of β-Anilinomalonates II: Diethyl β-Anilinofurfurylidenemalonate (IIc). Diethyl β-chlorofurfurylidenemalonate (Ic) (5.44 g, 20 mmol), aniline (2.24 g, 24 mmol) and triethylamine (2.13 g, 26 mmol) were heated at 90 °C in an oil bath overnight (12 h) with efficient stirring. The solution was cooled to room temperature, 50 mL chloroform was added, and the mixture was washed with water. The chloroform phase was dried with anhydrous sodium sulfate and concentrated on a rotary evaporator. Methanol (40 mL) was added to the residue, and the mixture was placed in a refrigerator to give 2.7 g of the product. The mother liquid was concentrated to 10 mL on a rotary evaporator, and the solution was placed in a refrigerator to give additional 1.8 g of the product, totally 4.5 g (66%): mp 70–71 °C; TLC R_f 0.42 (7:3 pentane–diethyl ether); ^1H NMR ($CDCl_3$) δ 1.12 (t, 3 H, J = 6.84 Hz), 1.30 (t, 3 H, J = 6.84 Hz), 4.05 (q, 2 H, J = 6.85 Hz), 4.26 (q, 2 H, J = 6.84 Hz), 6.30–7.40 (total 8 H) 6.35, 6.75, 7.36 (J = 1.95 Hz), 6.40, 6.49, (J = 3.41 Hz); IR (Nujol) 3050 (w), 1715 (s), 1655 (s), 1600 (s), 1570 (s), 1500 (s), 1420 (w), 1300–1000 (several bands); MS calcd for $C_{18}H_{19}NO_5$ 329.1262, M^+ 329.1262 (82), 284 (30), 283 (10), 257 (18), 256 (100), 255 (36), 238 (20), 211 (17), 210 (88), 209 (10), 184 (17), 183 (36), 182 (14), 170 (64), 154 (16), 77 (25).

Other β-anilinomalonates using this procedure include the following.

Diethyl β-anilino-2-thenylidenemalonate (IIb): yield 58%; mp 57–58 °C; R_f 0.45 (7:3 pentane–diethyl ether); ^1H NMR ($CDCl_3$) δ 0.98 (t, 3 H, J = 7.08 Hz), 1.30 (t, 3 H, J = 7.08 Hz), 3.95 (q, 2 H, J = 7.08 Hz), 6.69–7.40 (total 8 H), 10.89 (s, 1 H); IR (Nujol) 3050 (w), 1715 (s), 1650 (s), 1600 (s), 1580 (s), 1530 (w), 1500 (w), 1440 (w), 1410 (w), 1300–1000 (several strong bands); MS m/e calcd for $C_{18}H_{19}NSO_4$ 345.1034, M^+ 345.103 (80), 300 (27), 299 (16), 273 (15), 272 (78), 271 (39), 254 (12), 230 (27), 227 (19), 226 (100), 200 (17), 199 (43), 198 (19), 187 (11), 186 (80).

Diethyl β-anilinobenzylidenemalonate (IIa): yield 57%; mp 74–75 °C (lit.[9] mp 75 °C).

(6) (a) Bala, M.; Michankow, M.; Chojnacka-Wojcik, B.; Wiczynska, E. *Pol. J. Pharmacol. Pharm.* **1983**, *35*, 523. (b) Bala, M. *Pol. J. Chem.* **1981**, *55*(1), 121. (c) Zankowska-Jasinska, W.; Bala, M.; Boksa, J. *Roczniki Chem.* **1974**, *48*, 2253.

(7) Schmidt, D. G.; Seemuth, P. D.; Zimmer, H. *J. Org. Chem.* **1983**, *48*, 1914. See also: Ellis, G. P. Synthesis of Fused Heterocycles. In *The Chemistry of Heterocyclic Compounds*; Taylor, E. C., Ed.; John Wiley and Sons Interscience: New York, 1987; Vol. 47, p 255.

(8) Bloomer, J. L.; Kappler, F. E. *Tetrahedron Lett.* **1973**, *2*, 163.

(9) Just, F. *Ber.* **1885**, *18*, 2632.

Preparation of 3-(Ethoxycarbonyl)-2-(2-furyl)-4-quinolone (III). The anilinomalonate IIc (3.2 g, 10 mmol) was heated with stirring in an oil bath at 250 °C until the mixture had solidified completely. The reaction mixture was cooled to 160 °C and dissolved in 10 mL of dimethylformamide. The solution was cooled to room temperature. Filtration with suction gave 2.4 g (85%) of III: mp >250 °C, TLC; R_f 0.72 (9:1 chloroform–methanol); ^{1}H NMR (DMSO-d_6) δ 1.30 (t, 3 H, J = 7.32 Hz), 4.31 (q, 2 H, J = 7.32 Hz), 6.80 (dd, 1 H, J = 1.46, 3.66 Hz), 7.32 (d, 1 H, J = 3.66 Hz) 7.40–8.25 (total 5 H); IR (Nujol) 1725 (s), 1635 (m), 1610 (m), 1570 (s), 1510–40 (s), 1400–1000 (several strong bands); MS m/e calcd for $C_{16}H_{13}NO_4$ 283.0844, M^+ 283.0849 (35), 238 (18), 237 (100).

Preparation of 5,10-Dihydro-11*H*-indeno[1,2-*b*]quinoline-10,11-dione (IVa). Polyphosphoric acid (50 g) was heated to 210 °C in an oil bath, and the β-anilinomalonate IIa (3.42 g, 10 mmol) was added to the hot solution. The mixture was heated for 5 min with stirring at 210–230 °C and was then poured into hot water (150 mL). The solution was cooled to room temperature. Filtration with suction and recrystallization from dimethylformamide gave 1.9 g (75%) of IVa: mp >250 °C (lit.[9] mp 350 °C); TLC R_f 0.54 (9:1 chloroform–methanol); ^{1}H NMR (DMSO-d_6) δ 7.25–8.30 (m, total 8 H); IR (Nujol) 1710–1695 (several strong bands), 1630 (s), 1580 (s), 1540 (s), 760 (s), 710 (s); MS m/e calcd for $C_{16}H_9NO_2$ 247.0633, M^+ 247.0639 (100), 248 (18), 219 (14), 190 (17).

Preparation of 5,10-Dihydro-4*H*-cyclopenta[*b*]thieno-[6,5-*b*]quinoline-4,5-dione (IVb). Utilization of the above described cyclization procedure on 2.5 g of IIb gave 0.9 g (50%) of IVb: mp >250 °C; TLC R_f 0.47 (9:1 chloroform–methanol); ^{1}H NMR (DMSO-d_6) δ 7.29 (d, 1 H, J = 4.39 Hz), 7.35–7.78 (m, 3 H, J = 8.06, 4.39 Hz), 7.90 (d, 1 H, J = 5.13 Hz), 8.20 (d, 1 H, J = 8.06 Hz); IR (Nujol) 1700 (s), 1635 (s), 1570 (s), 1530 (s), 1435 (w), 1355 (w), 1230–1170 (weak bands), 835–625 (several strong bands); MS m/e calcd for $C_{14}H_7NO_2S$ 253.0197, M^+ 253.0237 (100), 254 (17), 196 (12).

Preparation of 5,5-Dimethyl-3-(ethoxycarbonyl)-4-hydroxy-2(5*H*)-furanone (Va). 2-Bromo-2-methylpropanoyl chloride (5.6 g, 30 mmol) was added slowly with stirring and cooling (cold water bath) to diethyl (ethoxymagnesio)malonate[10] (30 mmol) in 50 mL of toluene. The mixture was stirred for 2 h at room temperature and was then acidified with 2 M hydrochloric acid. The toluene phase was dried with sodium sulfate and concentrated on a rotary evaporator to give the crude product (8 g) that was used without further purification.

The crude product was dissolved in 70 mL of water containing 3.7 g (26 mmol) of potassium carbonate, and the mixture was heated until the evolution of carbon dioxide had subsided. The mixture was acidified with hydrochloric acid and extracted with chloroform. The chloroform phase was dried with sodium sulfate and concentrated on a rotary evaporator to give 4.4 g (72%) of the product that solidified with time: mp 83–84 °C; TLC R_f 0.35 (8:2 chloroform–methanol); ^{1}H NMR ($CDCl_3$) δ 1.40 (t, 3 H, J = 7.08 Hz), 1.59 (s, 6 H), 4.42 (q, 2 H, J = 7.08 Hz), 8.90 (s, 1 H); IR (Nujol) 1760 (s), 1720 (w), 1610 (s), 1315 (s), 1200–800 (several strong bands); MS calcd for $C_9H_{12}O_5$ 200.0684, M^+ 200.0695 (24), 156 (83), 155 (23), 154 (36), 142 (12), 139 (21), 138 (20), 126 (12), 114 (43), 86 (38), 69 (11), 67 (16), 59 (100), 58 (48), 55 (11), 45 (46).

Preparation of the Crude 4-Chloro-5,5-dimethyl-3-(ethoxycarbonyl)-2(5*H*)-furanone (Vb). The hydroxybutenolide Va (4.4 g) was dissolved in 20 mL of phosphorus oxychloride, and diisopropylethylamine (2.8 g) was added. The mixture was refluxed for 3 h, and the excess of phosphorus oxychloride was then removed with an evaporator. The residue was extracted three times with ether, and the combined ether layers were concentrated on a rotary evaporator to give 3.5 g (75%) of Vb: ^{1}H NMR ($CDCl_3$) δ 1.40 (t, 3 H, J = 7.08 Hz), 1.62 (s, 6 H), 4.40 (q, 2 H, J = 7.08 Hz); MS calcd for 218.0345, M^+ 218.0354 (14).

Preparation of 4-(3,4-Dimethoxyanilino)-5,5-dimethyl-3-(ethoxycarbonyl)-2(5*H*)-furanone (Vc). The chlorobutenolide Vb (1.32 g, 6 mmol), 3,4-dimethoxyaniline (1.02 g, 6 mmol), and 0.73 g of triethylamine were heated at 90 °C in an oil bath over night (12 h) with efficient stirring. The solution was cooled to room temperature, and 50 mL of chloroform was added. The chloroform solution was washed twice with water, dried with anhydrous sodium sulfate, and concentrated on a rotary evaporator. Methanol (10 mL) was added to the crude product, and the mixture was placed in a refrigerator to give the product, 0.84 g (41%): mp 145–146 °C; TLC R_f 0.17 (6:1 benzene–EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.4 (s + t, total 9 H), 3.88 (s, 3 H), 3.91 (s, 3 H), 4.40 (q, 2 H, J = 6.84 Hz), 6.70–7.92 (total 3 H), 10.13 (s, 1 H); IR (Nujol) 3215 (w), 1755 (s), 1670 (s), 1600 (s), 1590 (s), 1520 (s), 1415 (w), 1400–1000 (several strong bands); MS calcd for $C_{17}H_{21}NO_6$ 335.1369, M^+ 335.1384 (17), 290 (19), 289 (100), 274 (19), 203 (28).

Preparation of 6,7-Dimethoxy-3,3-dimethyl-1*H*,3*H*,4*H*,9*H*-furo[3,4-*b*]quinoline-1,9-dione (VI). The chlorobutenolide Vb (3.5 g, 16 mmol) was treated with 3,4-dimethoxyaniline (2.5 g, 16 mmol) and 1.7 g of triethylamine in toluene as described before to give the crude anilinobutenolide Vc, 3.2 g (59%), that was then cyclized by the method used for the preparation of III to give 2.3 g (48% over the two steps) of VI: mp >250 °C; TLC R_f 0.48 (9:1 chloroform–methanol); ^{1}H NMR (DMSO-d_6) δ 1.7 (s, 6 H), 3.93 (s, 3 H), 4.02 (s, 3 H), 7.10 (s, 1 H), 7.62 (s, 1 H); IR (Nujol) 3250–3050 (several weak bands), 1760 (s), 1725 (s), 1630 (s), 1610 (w), 1595 (w), 1575 (w), 1550 (w), 1500 (s), 1400–1000 (several strong bands); MS calcd for $C_{15}H_{15}NO_5$ 289.0949, M^+ 289.0989 (97), 274 (41), 272 (11), 271 (63), 270 (23), 256 (16), 240 (10).

Acknowledgment. We thank M. Reunanen and K. Viinamäki for mass spectra and P. Pennanen for drawing the illustrations.

Registry No. Ia, 106536-15-6; Ib, 106536-17-8; Ic, 106536-16-7; IIa, 125610-66-4; IIb, 125610-67-5; IIc, 125610-68-6; III, 125610-69-7; IVa, 79522-49-9; IVb, 125610-70-0; Va, 55473-58-0; Vb, 125610-71-1; Vc, 125610-73-3; VI, 125610-72-2; $PhNH_2$, 62-53-3; $(CH_3)_2C(Br)COCl$, 20469-89-0; diethyl (ethoxymagnesio)malonate, 35227-78-2; 3,4-dimethoxyaniline, 6315-89-5.

(10) For the preparation of diethyl (ethoxymagnesio)malonate, see, for example: Price, J. A.; Tarbell, D. S. *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol. IV, p 285.

First Preparation of Mitomycins Specifically Labeled with Deuterium at the C^6-Methyl Position

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The C^6-methyl group of mitomycins was specifically labeled with deuterium. 7,7-(Ethylenedioxy)mitomycin (8), a masked quinonoid compound derived from mitomycin A (2), played an important role in this methodology.

Mitomycins are well known to be potent antitumor antibiotics,[2] produced by various *Streptomyces* cultures. Among these compounds, mitomycin C (1) has been used extensively in cancer chemotherapy against a variety of

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