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Natural Product Chemistry, Part 136 [1]: A Convenient Synthesis of Rutacridone and Isorutacridone

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Summary. C-alkylation of phenolic acridones with 1,4-dibromo-2-methyl-2-butene under different conditions was studied. Condensations with 1,3 dihydroxy-10-methyl-acridin-9(10*H*)-one gave an O-alkylated product together with rutacridone and isorutacridone through C-alkylation. The aluminiumoxide and the ion exchange resin method offered the best yields for rutacridone and isorutacridone, respectively. Attempts with 4-hydroxy-10-methylacridin-9(10*H*)-one yielded several O-alkylated products including a dimer.

Keywords. Aluminiumoxide; C- and O-Alkylation; 1,4-Dibromo-2-methyl-2-butene; Hydroxyacridones; Ion exchange resin; Isorutacridone; Rutacridone.

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Zusammenfassung. Die C-Alkylierung von phenolischen Acridonen mit 1,4-Dibrom-2-methyl-2-buten wurde unter verschiedenen Bedingungen studiert. Die Kondensation mit 1,3-Dihydroxy-10-methyl-acridin-9(10*H*)-on ergibt ein O-alkyliertes Produkt zusammen mit Rutacridon und Isorutacridon, die über eine C-Alkylierung entstehen. Die Aluminiumoxid- und die Ionenaustauscher-Methode lieferten die besten Ausbeuten an Rutacridon und Isorutacridon. Versuche mit 4-Hydroxy-10-methyl-acridin-9(10*H*)-on führten zu einigen O-alkylierten Produkten, darunter ein Dimeres.

Introduction

The alkaloid rutacridone (**4**) has been isolated [2] from the roots of *Ruta graveolens* (Rutaceae) as the first member of a series of dihydrofuranoacridones. The antimicrobial activity of its epoxides [3], rutacridone-epoxide and hydroxyrutacridone-epoxide, which have also been isolated [4, 5], has increased the synthetic and the pharmacological interest in this member of the furanoacridones. Rutacridone has already been synthesized [6] in 15% yield together with its linear isomer, isorutacridone (**5**) in 5%, using the procedure of Nickl [7].

In continuation of our studies on the synthesis of acridone derivatives in order to investigate their activities, several methods were employed in the synthesis of rutacridone because it is the implicating precursor for the synthesis of other furanoacridones.

Results and Discussion

The yields of rutacridone and isorutacridone obtained in different methods are given in Table 1. By stirring a mixture of 1,3-dihydroxy-10-methyl-acridin-9(10*H*)-one (**1**) and 1,4-dibromo-2-methyl-2-butene (dibromoisoprene) in acetone with K_2CO_3 and KI, rutacridone was isolated in low yield (9%). The major product, however, was the O-alkylated product **3**. The use of a phase transfer catalyst gave no better results. Using N-(*p*-trifluoromethylbenzyl)-cinchoniumbromide as catalyst, the formation of neither rutacridone nor isorutacridone was observed. These results confirm earlier results [8], in which acridones reacted differently from other aromatic systems in attempted C-alkylations under PTC-conditions. When a crown ether was used in a single phase system, rutacridone and isorutacridone were obtained in 8% and 2% yields respectively.

When **1** was first adsorbed on basic in Al_2O_3, as used for TLC, and then stirred with dibromoisoprene in *THF* the furanoacridones were obtained in satisfactory yields. This offers the best yield for rutacridone (25%). Al_2O_3 has already been used for C-alkylation of acridones with allylic halides [9].

In recent years functionalized insoluble polymers have been developed for a variety of sequential and simple one step organic syntheses [10] including a number of C- and O-alkylations. We have therefore attempted to use basic anion exchange resins to carry out C-alkylation of phenolic acridones with dibromoisoprene leading to dihydrofuranoacridones. Commercially available Amberlite IRA-68 anion exchange resin has an unusually high capacity for large organic molecules. A solid solvate was formed with this resin by adding it to **1** dissolved in *THF* and stirring for 2 h. Then dibromoisoprene was added and stirred further.

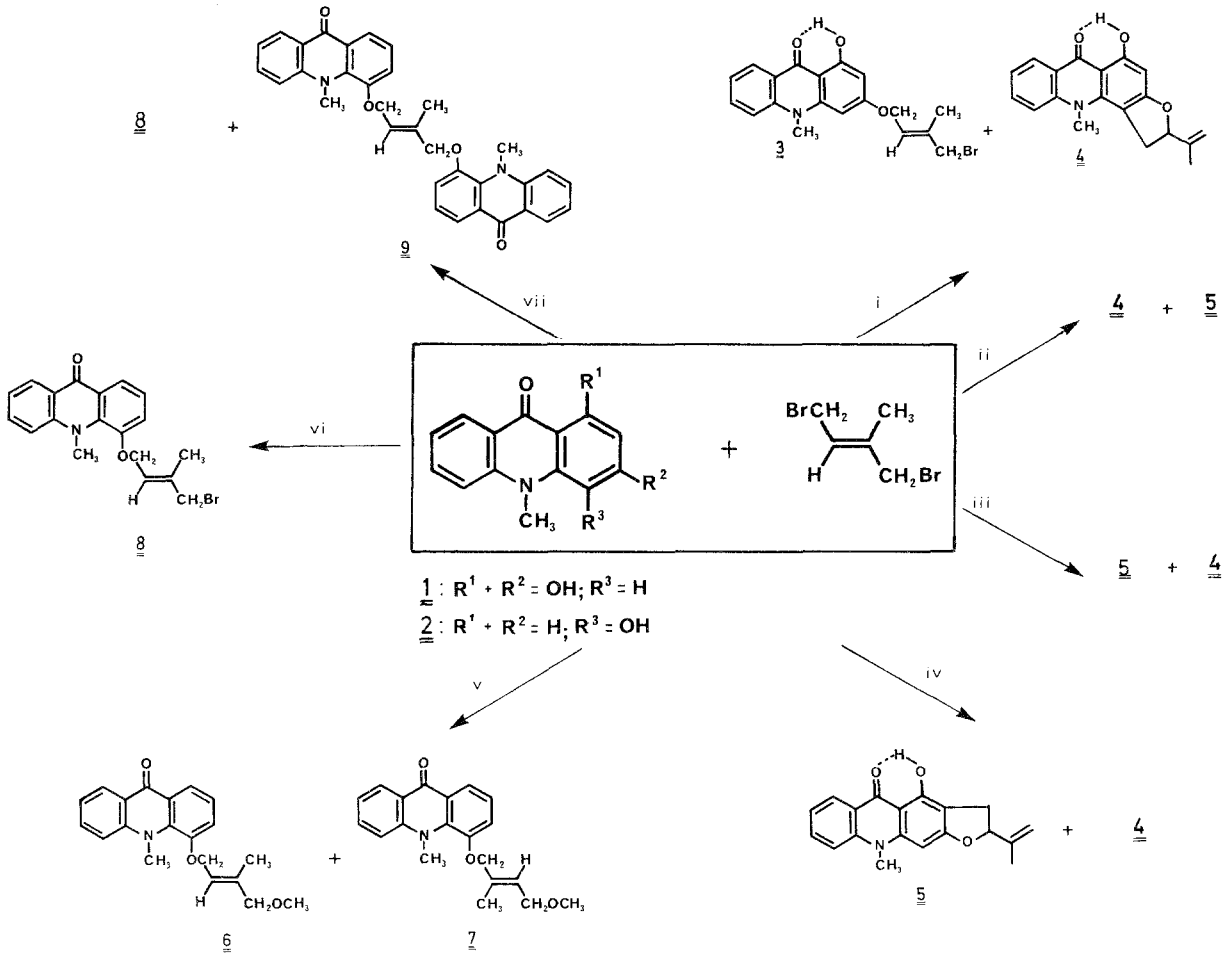
In contrast to the other methods, more isorutacridone (61%) was isolated than rutacridone (16%) by this method.

4-Hydroxy-10-methyl-9(10*H*)-acridinone (**2**) was investigated as an example to show how hydroxy acridones, which do not tend to undergo C-alkylation, react with dibromoisoprene under different conditions. In the presence of sodium methoxide (analog [6]), under which **1** reacted to give **4** and **5**, **2** gave 4-(4′-methoxy-3′-methyl-2′-butenyloxy)-10-methyl-9(10*H*)-acridinone (**6**) and 4-(4′-methoxy-2′-methyl-2′-butenyloxy)-10-methyl-9(10*H*)-acridinone (**7**).

In the ^{1}H-NMR spectra of both reaction products the methylene signals are shifted in a way than in both cases an aromatic and an aliphatic ether linkage can be concluded. Since the typical peaks for isotopes of bromine are missing in the mass spectrum, an exchange of bromine must have taken place on both sides. Aliphatic protons were identified from coupling patterns.

Table 1

Method	Rutacridone	Isorutacridone
carbonat-method	9%	–
PTC-method	–	–
with crown ether	8%	2%
aluminiumoxide-method	25%	6%
ionexchange-method	16%	61%



Scheme 1

Reagents: i: **1**, K_2CO_3, KI, acetone, room temperature, 8 h, yield: **3** (73%), **4** (9%); ii: **1**, Amberlite IRA-68, *THF*, room temperature, 96 h, yield: **4** (60%), **5** (16%); iii: **1**, Al_2O_3, CH_2Cl_2, room temperature, 24 h, yield: **5** (25%), **4** (6%); iv: **1**, KOH, crown ether toluene, room temperature, 12 h, yield: **5** (84%), **4** (2%); v: **2**, CH_3ONa, CH_3OH, room temperature, 96 h, yield: **6** (6%), **7** (4%); vi: **2**, K_2CO_3, KI, acetone, room temperature, 24 h, yield: **8** (90%); vii: **2**, TBACl, 50% aqueous NaOH, toluene, room temperature, 2 h, yield: **8** (17%), **9** (15%)

In **6** the *Ar*-O $-CH_2$-group ($\delta = 4.75$) appeared as a doublet by coupling with an olefinic proton and the $-CH_2-OCH_3$ group as a singlet at δ 3.90 ppm. In **7** these signals appeared as a singlet at δ 4.55 ppm and as a doublet at δ 4.05 ppm, respectively. Therefore the only difference in structures of both isomers is the substitution at olefinic carbons. In ^{1}H-NMR spectra of both **6** and **7**, 3 H singlets appeared at δ 3.40 ppm for aliphatic methoxy groups. This indicates that one alkylbromide function had reacted with sodium methoxide.

The usual method of O-alkylation is the reaction of a phenolic OH group with an alkylhalide and K_2CO_3 in acetone under reflux. Under this condition **2** reacted with dibromoisoprene almost quantitatively within 24 h to give **8**.

Under *PTC*-conditions **2** reacted with dibromoisoprene to give 4-(4′-bromo-3′-methyl-2′-butenyloxy)-10-methyl-9(10*H*)-acridinone (**8**) and 2-methyl-1,4-bis-(10′-methyl-9′-oxo-9,10′-dihydro-4′-acridinyloxy)-2-butene (**9**). For compound **9** a molecular mass of 516 and the presence of 14 aliphatic and 14 aromatic protons were observed. The product **8** may have further reacted with **2** to give **9** by the heat evolved when the reaction mixture was neutralized with HCl to separate the catalyst.

Since the other structural isomer of **8** (which is analogous to **7**) is missing, the substitution at C-4 of dibromoisoprene follows the Hoffmann-orientation.

The reactivity of C-1 in dibromoisoprene against nucleophilic substitution is reduced as compared to C-4 due to the positive inductive effect of the CH_3 group. Therefore formation of the ether linkage on C-1 takes place as the second step.

Among the different derivatives of **2** the product **9** is of special interest. With this new example, the phase transfer catalysis offers approaches to compounds which are not accessible by conventional methods (e.g. carbonate-method). The compound **9** could be of pharmacological interest, because the dimeric acridones coupled through an alkyl chain are potentially cytostatic substances. In the series of acridines the bifunctionalisation increases the ability to intercalate with *DNA* [11].

Acknowledgement

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Experimental Part

For instrumental and chromatographic methods see: Reisch J., Probst W. (1987) Arch. Pharm. (Weinheim) **320**: 1065.

Reaction of 1,3-Dihydroxy-10-methylacridin-9-(10H)-one (**1**) *with 1,4-Dibromo-2-methyl-2-butene*

i. *Carbonate Method*

A mixture of **1** (80 mg, 0.33 mmol), dibromoisoprene (114 mg, 0.5 mmol), dry K_2CO_3 (207 mg, 1.5 mmol) and KI (8.3 mg, 0.05 mmol) in 10 ml of dry acetone were stirred at room temperature for 18 h. The reaction mixture was filtered and the filtrate was evaporated. The residue on chromatographic separation gave 12 mg of unreacted **1**, 8 mg (9.2%) rutacridone and 80 mg (73%) of the ether, 1-hydroxy-3-(4-bromo-3-methyl-2-butenyloxy)-10-methyl-acridin-9(10*H*)-one (**3**). The latter was recrystallised from *EtOAc* as yellow cubes, m.p. 155°C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ (ppm) = 1.92 (3 H, d, J = 1.2 Hz; $=C-CH_3$), 3.69 (3 H, s, $N-CH_3$), 4.01 (2 H, s, H-4′), 4.61 (2 H, d, J = 5.8 Hz; H-1′), 5.88 (1 H, dt, J = 5.8 and 1.2 Hz; H-2′), 6.16 and 6.19 (each 1 H, d, J = 2.2 Hz; H-2 and 4), 7.23 (1 H, ddd, J = 8.0, 7.0 and 1.0 Hz; H-7), 7.40 (1 H, br. d, J = 8.7 Hz; H-5), 7.66 (1 H, ddd, J = 8.7, 7.0, and 1.7 Hz; H-6), 8.35 (1 H, dd, J = 8.0 and 1.7 Hz; H-8), 14.78 (1 H, s, −OH). ^{13}C NMR ($CDCl_3$, 50.29 MHz): δ (ppm) = 15.5 (3′-CH_3), 34.1 (C-4′), 39.5 (N-*Me*), 65.2 (C-1′), 90.6 (C-4), 94.9 (C-2), 105.6 (C-9a), 114.9 (C-5), 121.4 (C-8a), 121.8 (C-7), 125.3 (C-2′), 127.0 (C-8), 134.4 (C-6), 137.4 (C-3′), 142.6 (C-4a), 145.1 (C-5a), 165.4 (C-1), 166.3 (C-3), 181.2 (C-9). MS: *m*/e (%) = 389.044959 (M^+ 6; $C_{19}H_{18}NO_3Br$ requires 389.045148), 387 (6), 319, 321 (8), 308 (78), 292 (18), 266 (20), 241 (30), 212 (34), 67 (100).

ii. *PTC-Method*

A mixture of 40 mg (0.17 mmol) **1**, 38 mg (0.17 mmol) dibromoisoprene, 9 mg (0.017 mmol) N-(*p*-trifluoromethylbenzyl)-cinchoniumbromide, 5 ml of 50% aq. NaOH and 10 ml toluene was stirred at room temperature. Even after 48 h no formation of furanoacridones was observed through TLC.

iii. *With Crown Ether*

A mixture of 80 mg (0.33 mmol) **1**, 92 mg (0.4 mmol) dibromoisoprene, 88 mg dicyclohexyl-18-crown-6-ether, 400 mg KOH and 20 ml toluene was stirred at room temperature. After 12 h the reaction mixture was washed with water and evaporated. The residue on chromatographic separation gave 6.2 mg (8%) rutacridone and 1.6 mg (2%) isorutacridone.

iv. *Aluminiumoxide-Method*

1 (80 mg, 0.33 mmol) in *THF* (10 ml) was added to a slurry of 4 g Al_2O_3 (Merck, neutral Type T for thin layer chromatography) in ether. The solvent was evaporated and dibromoisoprene (76 mg, 0.33 mmol) in CH_2Cl_2 (10 ml) was added. After stirring for 12 h, the same quantity of dibromoisoprene was added again and stirred for another 12 h. Al_2O_3 was filtered off and washed with 1% HO*Ac* – *Et*O*Ac*. The combined organic layer was evaporated and the residue was chromatographed over silica gel to give 21 mg of **1**, 19 mg (25%) rutacridone, and 4.5 mg (6%) isorutacridone.

v. *Ionexchange-Method*

180 mg (0.99 mmol) of Amberlite IRA-68 were added to a solution of **1** (80 mg, 0.33 mmol) in *THF* (25 ml) and stirred for 2 h at room temperature. After addition of dibromoisoprene (152 mg, 0.66 mmol) the mixture was further stirred for 48 h. The same quantities of Amberlite IRA-68 and dibromoisoprene were added again and stirred for further 48 h. The resin was filtered off and washed with CH_2Cl_2. The combined filtrate was evaporated and the residue on chromatographic separation gave 62 mg (61%) of isorutacridone and 16.5 mg (16%) of rutacridone.

Reaction of 4-Hydroxy-10-methylacridin-9-(10H)-one (**2**) *with 1,4-Dibromo-2-methyl-2-butene*

i. *Method of Nickl* [7]

500 mg (2.2 mmol) of **2** and 580 mg (2.5 mmol) of dibromoisoprene were added to 0.174 *N* solution of sodium in methanol (10 ml) and kept for 4 days at room temperature. The reaction mixture was diluted with water, extracted with *Et*O*Ac* and the ethyl acetate phase dried over Na_2SO_4 and evaporated. The oily residue on chromatographic separation gave 4-(4′-methoxy-3′-methyl-2′-butenyloxy)-10-methylacridin-9(10*H*)-one (**6**) (44 mg, 6.1%) and 4-(4′-methoxy-2′-methyl-2′-butenyloxy)-10-methylacridin-9(10*H*)-one (**7**) (25 mg, 3.5%) both as brown yellow oils.

4-(4′-Methoxy-3′-methyl-2′-butenyloxy)-10-methylacridin-9(10H)-one (**6**)

IR (film): 3070 (CH, aromat.), 2950 (CH, aliphat.), 1635 (C=O), 1600 (C=C), 1090, 1060 cm^{-1}. ^1H NMR: ($CDCl_3$, 60 MHz: δ (ppm) = 1.75 (3 H, s, $=CCH_3$), 3.40 (3 H, s, CH_2OCH_3), 3.90 (2 H, s, CH_2OCH_3), 4.05 (3 H, s, NCH_3), 4.75 (2 H, d, $J = 6$ Hz; $OCH_2CH=$), 5.90 (1 H, t, $J = 6$ Hz; $OCH_2CH=$), 7.05–8.30 (6 H aromat., m), 8.50 (1 H, dd, $J = 2/8$ Hz; 8-H). ^{13}C NMR: ($CDCl_3$, 90 MHz): δ (ppm) = 14.2 ($=CCH_3$), 41.6 (NCH_3), 58.0 (CH_2OCH_3), 66.4 (*Ph*OCH_2), 77.0 (CH_2OCH_3), 116.1 (C-1), 117.3 (C-5), 119.5 (C-3), 121.1 (HC=), 121.3 (C-7), 121.9 (C-2), 122.8 (C-8a), 125.7 (C-9a), 127.1 (C-8), 133.6 (C-6), 137.8, 138.1 (C-4a, $=CCH_3$), 145.7 (C-5a), 149.0 (C-4), 178.4 (C-9). MS: *m*/e (%) = 323.1521 (M^+, 10; $C_{20}H_{21}NO_3$ requires 323.1522), 225 (86, M^+-$C_6H_{10}O$),

224 (68, M^+-$C_6H_{11}O$), 210 (18, 225-CH_3), 196 (25, 224-CO), 167 (24, 196-CHO), 139 (10, 167-CH_2N), 99 (60, $C_6H_{11}O^+$), 67 (100, $C_5H_7^+$).

4-(4'-Methoxy-2'-methyl-2'-butenyloxy)-10-methylacridin-9(10H)-one (**7**)

IR: (film) 3080 (CH, aromat.), 1630 (C=O), 1600 (C=C), 1270, 1250, 1090, 1060 cm^{-1} (COC). ^1H NMR: ($CDCl_3$, 60 MHz): δ (ppm) = 1.85 (3H, s, $CH_3C=$), 3.40 (3H, s, CH_2OCH_3), 4.05 (5H, s and d, J = 6 Hz; NCH_3 and $=CHCH_2$), 4.55 (2H, s, $PhOCH_2$), 5.85 (1H, t, J = 6 Hz; $=CHCH_2$), 7.15–8.30 (6H, aromat., m), 8.45 (1H, dd, J = 2/8 Hz; 8-H). ^{13}C NMR: ($CDCl_3$, 90 MHz): δ (ppm) = 14.3 ($CH_3C=$), 41.4 (NCH_3), 58.0 (CH_2OCH_3), 68.4 ($PhOCH_2$), 74.9 (CH_2OCH_3), 116.0 (C-1), 116.9 (C-5), 119.2 (C-3), 121.1 (C-7), 121.6 (C-2), 122.5 (C-8a), 125.0 ($=CHCH_2$), 125.3 (C-9a), 126.8 (C-8), 133.4 (C-6), 134.1, 135.6 ($CH_3C=$, C-4a), 145.4 (C-5a), 148.8 (C-4), 178.1 (C-9). MS: m/e (%) = 323.1521 (M^+, 16; $C_{20}H_{21}NO_3$ requires 323.1522), 225 (M^+-$C_6H_{10}O$, 74), 224 (M^+-$C_6H_{11}O$, 100), 210 (225-CH_3,7), 196 (224-CO, 12), 167 (196-CHO, 8), 99 ($C_6H_{11}O^+$, 34), 67 ($C_5H_7^+$, 40).

ii. *Carbonate-Method*

20 mg (0.088 mmol) of **2**, 25 mg (0.1 mmol) of dibromoisoprene, 10 mg of dry K_2CO_3 (0.07 mmol) and a trace of KI in dry acetone were stirred at room temperature. After 24 h a complete conversion to 4-(4'-bromo-3'-methyl-2'-butenyloxy)-10-methylacridin-9(10*H*)-one (**8**) was observed by TLC.

iii. *PTC-Method*

A mixture of **2** (500 mg, 2.2 mmol), dibromoisoprene (580 mg, 2.5 mmol), *TBA*Br (500 mg, 1.6 mmol) in 50% aq. NaOH (10 ml) and toluene (20 ml) was stirred for 2 h at room temperature. The organic phase was separated, washed with water, dried over Na_2SO_4 and evaporated. The residue on chromatographic separation gave 4-(4'-bromo-3'-methyl-2'-butenyloxy)-10-methylacridin-9(10*H*)-one (**8**) (120 mg, 16.5%) as pale yellow crystals and 2-methyl-1,4-bis-(10'-methyl-9'-oxo-9',10'-dihydro-4'-acridinyloxy)-2-butene (**9**) (84 mg, 14.7%) as green yellow needles.

4-(4'-Bromo-3'-methyl-2'-butenyloxy)-10-methylacridin-9(10H)-one (**8**)

M.p. 137–137°C (diethyl ether). IR: 3050 (CH, aromat.), 2960 (CH, aliphat.), 1635 (C=O), 1600 (C=C), 1265, 1075 (COC), 765 cm^{-1} (CH_2Br). ^1H NMR: ($CDCl_3$, 60 MHz): δ (ppm) = 1.90 (3H, s, $=CCH_3$), 4.00 (5H, s, NCH_3, CH_2Br), 4.70 (2H, d, J = 7 Hz; $PhOCH_2$), 6.00 (1H, t, J = 7 Hz; $CH_2CHC=$), 7.10–8.20 (6H aromat., m), 8.45 (1H, dd, J = 2/8 Hz; 8-H). ^{13}C NMR: ($CDCl_3$, 90 MHz): δ (ppm) = 15.3 ($=CCH_3$), 39.2 (CH_2Br), 41.5 (NCH_3), 66.5 ($PhOCH_2$), 116.1 (C-1), 117.3 (C-5), 119.8 (C-3), 121.3 (C-7), 121.8 (C-2), 122.8 (C-8a), 124.8 (CH=), 125.6 (C-9a), 127.1 (C-8), 133.6 (C-6), 136.8 (C-4a), 137.1 ($C=CCH_3$), 145.6 (C-5a), 148.7 (C-4), 178.3 (C-9). MS: m/e (%) = 371, 373 (M^+, 2), 292 (M^+-Br, 6), 224 (292-C_5H_8, 100), 196 (224-CO, 18), 167 (196-CHO, 16), 139 (167-CH_2N, 6). $C_{19}H_{18}Br \cdot \frac{1}{2}H_2O$. Calc. C 59.9, H 5.02, N 3.7; found C 59.6, H 4.99, N 3.8.

2-Methyl-1,4-bis(10'-methyl-9'-oxo-9',10'-dihydro-4'-acridinyloxy)-2-butene (**9**)

(84 mg, 14.7%), m.p. 95°C (yellow green needles, petrol ether/CH_2Cl_2). IR: 3050 (CH, aromat.), 2920 (CH, aliphat.), 1630 (C=O), 1600 (C=C), 1260, 1240, 1060 cm^{-1} (COC). ^1H NMR: ($CDCl_3$, 60 MHz): δ (ppm) = 1.95 (3H, s = CCH_3), 4.00 (6H, 2s, 2 × NCH_3), 4.60 [2H, s, $=C(CH_3)CH_2$], 4.80 (2H, d, J = 6 Hz; $=CHCH_2$), 6.00 (1H, t, J = 6 Hz; $=CHCH_2$), 7.05–8.30 (12H, m, aromat.), 8.45 (2H, dd, J = 2/8 Hz; 2 × 8'-H). ^{13}C NMR: (*DMSO-d_6*, 200 MHz): δ (ppm) = 14.3 ($=CCH_3$), 41.4 (2 × NCH_3), 66.1 [$CH_2C(CH_3)=$], 74.3 ($=CHCH_2$), 117.3 (2 × C-5'), 118.1, 118.3 (2 × C-3'),

118.5, 118.6 (2 × C-1′), 121.7 (2 × C-2′), 122.1, 122.4 (2 × C-7′, 2 × C-8a′), 123.0 (=CH), 125.0 (2 × C-9a′), 126.3 (2 × C-8′), 134.3 (2 × C-6′), 135.9 (2 × C-4a′), 136.4 (=CCH_3), 145.6 (2 × C-5a′), 149.1 (2 × C-4′), 177.4 (2 × C-9′). MS: *m*/e (%) = 516.2049 (M^+, 3, $C_{33}H_{28}N_2O_4$ requires 516.2047), 292 (M^+-$C_{14}H_{10}NO_2$, 48), 291 (M^+-$C_{14}H_{11}NO_2$, 82), 276 (291-CH_3, 68), 225 ($C_{14}H_{11}NO_2$, 82), 210 (225-CH_3, 100), 196 (225-HCO, 12), 167 (196-CHO, 14).

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