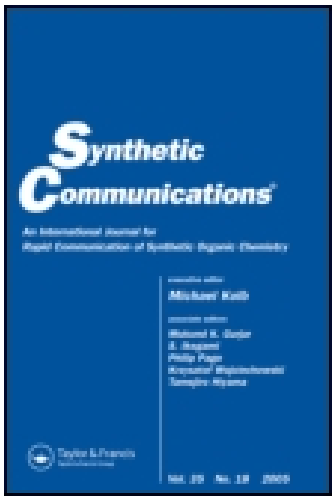

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Maxime Robin [a] , Robert Faure [a] , Alain Périchaud [b] & Jean-Pierre Galy [a]

[a] Laboratoire de Valorisation de la Chimie Fine , Faculté des Sciences et Techniques de Saint Jérôme , Université d'Aix-Marseille III , Av. Escadrille Normandie-Niemen, Marseille Cedex 3, Marseille, 13397, France

[b] Laboratoire de Chimie Macromoléculaire , 3 Place Victor Hugo, Marseille Cedex 3, Marseille, 13331, France

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SYNTHESIS OF NEW TETRACYCLE FUSED ACRIDINE ANALOGUES BEARING OXAZOLE RING

Maxime Robin,[1,*] Robert Faure,[1] Alain Périchaud,[2] and Jean-Pierre Galy[1]

[1]Laboratoire de Valorisation de la Chimie Fine, Faculté des Sciences et Techniques de Saint Jérôme, Université d' Aix-Marseille III, Av. Escadrille Normandie-Niemen, 13397 Marseille Cedex 3, France
[2]Laboratoire de Chimie Macromoléculaire, 3 Place Victor Hugo, 13331 Marseille Cedex 3, France

ABSTRACT

New acridine derivatives have been prepared via Ullman condensation involving benzoxazole (**5**) and 2-bromo-benzoic acid. Linear products were obtained. The structure of oxazolo[4,5-*b*]acridine was determined by NMR spectroscopy.

In our effort to synthesize acridine derivatives with a wide range of properties we investigated the opportunities to introduce the oxazole ring on the acridine skeleton. Many heterocycle-fused acridines have been synthesized bearing a five[1] or six[2]-membered heterocycle. These compounds

*Corresponding author.

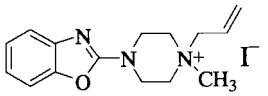
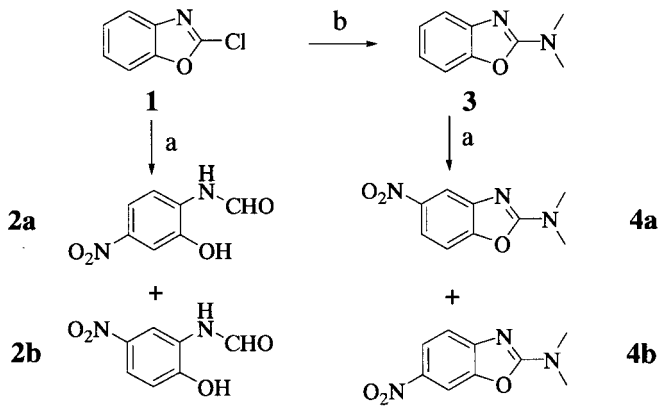


Figure 1. Allyl-1-methyl-4-(2-benzoxazolyl)piperazinium iodide CP2289.

possess a variety of biological properties, such as antiviral, antimicrobial, antitumor properties, enzyme inhibitors and DNA-intercalation.[3] Benzoxazoles are important intermediates for the synthesis of fluorescent whitening agents,[4] *o*-sulfonamidophenol dye-releasers[5] in instant color photography, biological interests in polyethers antibiotics,[6] and new 5-HT_3 receptor ligand (Figure).[7–10]

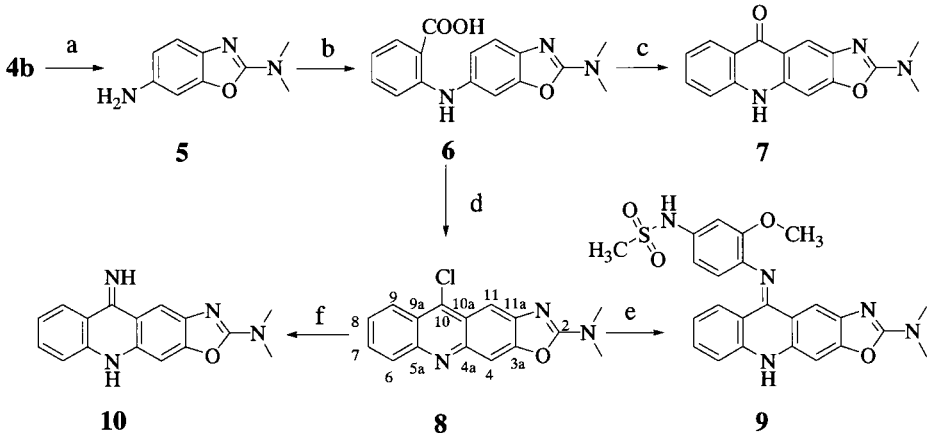
Our synthesis of oxazoloacridine starts with 2-*N*-dimethylbenzoxazole **3** because the nitration of the commercial 2-chlorobenzoxazole **1** (Scheme 1) resulted in the formation of 2-hydroxy-4-nitro- and 2-hydroxy-5-nitro-formanilides (**2a**, **2b**).



Scheme 1. Reagents: (a) HNO_3/H_2SO_4, $-15°C$, 1 h; (b) Dimethylamine in aqueous solution 40% (10 eq.), rt, 2 h.

The ^1H and ^{13}C NMR spectra of **2a** and **2b** were consistent with their structures and identical to those reported for these compounds.[11] 2-*N*-Dimethylbenzoxazole (**3**)[12] instead was not hydrolyzed under Katz[13] nitration conditions. We obtained 5- and 6-nitro compounds **4a** and **4b** in

a ratio 2/8 respectively. The major 6-nitro-2-*N*,*N*-dimethylbenzoxazole (**4b**) was obtain by crystallization from ethanol (52% yield). Hydrogenation of **4b** using Pd/C as catalyst at rt[14] afforded **5** (93%). The subsequent Ullman–Goldberg condensation to anthranilic acid (Scheme 2) was usually done using Copper catalyst for 12 h with poor yield (40–50%).[15]



Scheme 2. Reagents: (a) EtOH, Pd/C, H_2, rt; (b) *o*-Bromo bezoic acid, 2-butanone, Cu/Zn, Ultrasonic irradiation, 80°C, 3 h; (c) H_2SO_4, 120°C, 2 h; (d) $POCl_3$, reflux, 1 h; (e) *N*-(4-amino-3-methoxy phenyl) methane sulfonamide, EtOH, rt, 12 h; (f) Ammonium carbonate, Phenol, 80°C, 2 h.

This *N*-substitution reaction could be improved using the ultrasound.[16,17] When ultrasound was applied, the reaction of **5** with *o*-bromo benzoic acid and Cu/Zn as catalyst[18] yielded **6** in 90% (Scheme 2). The cyclisation of anthranilic acid (**6**) to acridine derivatives can give two isomers as described in the literature.[1] In our case, we obtained oxazolo[4,5-*b*]acridines, the linear compounds (**7–8**), using a PPA, H_2SO_4 and $POCl_3$ in 60, 67 and 80% respectively as the sole product. The structure of these compounds was established using a combination of 1D- and 2D-NMR techniques. The occurrence of "linear" skeleton follows from the multiplet pattern analysis of 1H data (two singulets for H-4 and H-11 resonances).[19,21] Using compound **8** we synthesized an analogue (**9**) of *m*-Amsacrine,[22,23] which is now known to target the enzyme topoisomerase II (Topo II).[24–26] The reaction of **8** with carbonate ammonium in hot phenol produced in excellent yield (65%) the imino derivatives **10**.[27]

EXPERIMENTAL

2-Chlorobenzoxazole and *o*-bromo benzoic acid were obtained from commercial suppliers. *N*-(4-amino-3-methoxy phenyl) methane sulfonamide was synthesized according to the published procedure.[28] All reagents and solvents were used as received without further purification. Melting points were determined with an Electrothermal 9300 apparatus and were uncorrected. The NMR spectra were recorded on a Bruker AC 200 spectrometer operating at 200 MHz for ^{1}H and ^{13}C. Two-D NMR spectra, both of homonuclear (COSY) and heteronuclear (HMBC, HMQC) correlation, were obtained with a Bruker AMX 400. In all cases TMS was used as an internal standard.

2-*N*,*N*-Dimethylaminobenzoxazole (3): 2-Chlorobenzoxazole (2 g, 13 mmol) and 10 ml of 40% aqueous dimethylamine solution were stirred at rt for 1 h. The white precipitate formed was filtered and washed with water to give **3** as pure product (1.88 g, 11.6 mmol, yield 90%, m.p. 85°C (lit.,[9] m.p. 83–84°C), mol. wt.: 162). ^{1}H NMR ($CDCl_3$, δ): 3.12 (s, 6H, $2CH_3$), 6.94 (ddd, 1H, $J = 1.1$, 6.6, 7.7 Hz, C-H_5), 7.10 (ddd, 1H, $J = 1.1$, 6.6, 7.7 Hz, C-H_6), 7.20 (dd, 1H, $J = 1.1$, 7.7 Hz, C-H_7), 7.31 (dd, 1H, $J = 1.1$, 7.7 Hz, C-H_4). ^{13}C NMR ($CDCl_3$, δ): 37.5 (C-α), 108.4 (C-7), 115.8 (C-6), 120.4 (C-4), 123.7 (C-5), 143.5 (C-3a), 149.0 (C-7a), 162.9 (C-2).

2-*N*,*N*-Dimethylamino-6-nitro-benzoxazole (4b): This compound was prepared according to the method described by Katz,[13] by nitration of **3** (1.5 g, 9.3 mmol) with 5 ml of HNO_3 in 10 ml of H_2SO_4 at 0°C. The yellow reaction mixture was poured into ice water and neutralized with 16% NH_4OH; the yellow precipitate which formed was collected by filtration to give 1.8 g of 5-, and 6-nitro compounds (**4a** and **4b**) 20/80, yield 93%. The mixture was crystallized from ethanol (10 ml) to give **4b** (1 g, 4.8 mmol, yield 52%, m.p. 182°C, mol. wt.: 207). ^{1}H NMR (Cd-Cl_3, δ): 3.21 (s, 6H, $2\alpha CH_3$), 7.21 (d, 1H, $J = 8.25$ Hz, C-H_4), 8.03 (d, 1H, $J = 2.2$ Hz, C-H_7), 8.13 (dd, 1H, $J = 2.2$, 8.8 Hz, H_5). ^{13}C NMR (Cd-Cl_3, δ): 37.6 (C-α), 104.8 (C-7), 114.5 (C-4), 121.3 (C-5), 140.9 (C-6), 148.0 (C-7a), 150.4 (C-3a), 165.5 (C-2). Anal. calcd for $C_9H_9N_3O_3$: C, 52.17; H, 4.38; N, 20.28. Found: C, 52.18; H, 4.42; N, 20.35.

2,6-*Bis*(*N*,*N*-Dimethylamino)benzoxazole (5): (**4b**) (1 g, 4.8 mmol), 0.1 g of Pd/C catalyst was placed in 85 ml of ethanol. The solution was placed under hydrogen atmosphere and vigorously stirred for 2 h. The reaction was monitored by TLC (CH_2Cl_2/MeOH 9/1). After complete consumption of starting materials, the resulting solution was filtered and the filtrate was concentrated under vacuum to give **5** as pure product (0.8 g, yield 93%, m.p. 165°C, mol. wt.: 177). ^{1}H NMR (DMSO-d_6, δ): 3.01 (s, 6H, $2\alpha CH_3$),

4.84 (s, 2H, NH_2), 6.40 (dd, 1H, $J = 2.2$, 8.25 Hz, C-H_5), 6.63 (d, 1H, $J = 2.2$ Hz, C-H_7), 6.94 (d, 1H, $J = 8.25$ Hz, C-H_4). ^{13}C NMR (DMSO-d_6, δ): 37.6 (C-α), 95.6 (C-7), 110.5 (C-4), 115.7 (C-5), 133.7 (C-3a), 143.6 (C-6), 149.9 (C-7a), 161.3 (C-2). Anal. calcd for $C_9H_{11}N_3O$: C, 61.00; H, 6.26; N, 23.71. Found: C, 59.87; H, 6.31; N, 23.56.

2-{[2-(Dimethylamino)-benzoxazole-6-yl]amino}-benzoic acid (6): (**5**) (0.7 g, 6 mmol), *o*-bromobenzoic acid (1.41 g, 7 mmol), anhydrous potassium carbonate (1.11 g, 8 mmol), powdered copper catalyst (0.05 g), and ethyl methyl ketone (15 ml) were placed in a 250 ml round-bottomed flask. This mixture was sonicated in a bath (80°C) for 3 h. The solution was concentrated in vacuo, the brown residue stirred in hot water (80 ml), filtered, and the filtrate acidified to pH 5 with 2N aqueous hydrochloric acid. The green precipitate was filtered and washed with water to give pure (**6**) without any further purification (1.6 g, yield 90%, m.p. 224°C, mol. wt.: 297). ^{1}H NMR (DMSO-d_6, δ): 3.09 (s, 6H, 2αCH_3), 6.67 (ddd, 1H, $J = 1.1$, 7.7 Hz, C-H_{11}), 6.98 (m, 2H, C-H_5, C-H_{10}), 7.28 (m, 2H, C-H_4, C-H_9), 7.30 (s, 1H, C-H_7), 7.86 (dd, 1H, $J = 7.7$ Hz, C-H_{12}), 9.54 (s, 1H, N-H_8). ^{13}C NMR (DMSO-d_6, δ): 37.5 (C-α), 105.3 (C-4), 111.6 (C-12a), 113.2 (C-9), 115.8 (C-5), 116.7 (C-11), 120.2 (C-7), 132.0 (C-12), 133.3 (C-6), 134.5 (C-10), 140.5 (C-3a), 149.0 (C-7a), 149.3 (C-8a), 163.1 (C-2), 170.4 (C-13). Anal. calcd for $C_{16}H_{15}N_3O_3$: C, 64.64; H, 5.09; N, 14.13. Found: C, 64.51; H, 5.10; N, 14.26.

2-(Dimethylamino)-oxazolo[4,5-*b*]acridin-10(5*H*)-one (7): Compound (**6**) (0.22 g, 0.75 mmol) in H_2SO_4 (5 ml) was stirred at 120°C for 2 h. The solution was poured onto ice water and neutralized with (10%) ammonia, the resulting green precipitate was filtered off, washed with water, and crystallized from ethanol to give (**7**) (0.15 g, yield 67%, m.p. >260°C, mol. wt.: 279). ^{1}H NMR (DMSO-d_6, δ): 3.13 (s, 6H, 2αCH_3), 7.19 (ddd, 1H, $J = 1.1$, 7.25 Hz, C-H_8), 7.41 (s, 1H, C-H_{11}), 7.45 (dd, 1H, $J = 8.25$ Hz, C-H_6), 7.65 (ddd, 1H, $J = 1.1$, 7.3 Hz, C-H_7), 7.90 (s, 1H, C-H_4), 8.20 (dd, 1H, $J = 7.95$ Hz, C-H_9), 11.75 (s, 1H, N-H_5). ^{13}C NMR (DMSO-d_6, δ): 37.6 (C-α), 96.7 (C-4), 109.5 (C-11), 117.1 (C-6), 118.4 (C-10a), 119.6 (C-9a), 120.8 (C-8), 126.0 (C-9), 133.0 (C-7), 136.3 (C-11a), 137.2 (C-4a), 140.7 (C-5a), 153.7 (C-3a), 161.9 (C-2), 176.2 (C-10). Anal. calcd for $C_{16}H_{12}N_3O_2$: C, 69.06; H, 4.35; N, 15.10. Found: C, 69.24; H, 4.21; N, 15.04.

10-Chloro-2-*N*,*N*-dimethylamino-oxazolo[4,5-*b*]acridine (8): Compound (**6**) (0.6 g, 2 mmol) and $POCl_3$ (20 ml, 220 mmol) were introduced into a 100 ml round-bottomed flask and heated at 80°C for 15 min, and then the solution was heated to 120°C for 30 min. The solution was allowed to cool to rt and the excess of $POCl_3$ was eliminated with petroleum spirit (60–80°C, 200 ml). The resulting orange syrupy oil was poured onto ice (100 g) and

neutralized with 10% ammonia. The precipitate was collected by filtration, dried, to give (**8**) as a red powder (0.5 g, yield 80%, m.p. 218°C, mol. wt.; 298). ^{1}H NMR (Cd-Cl$_3$, δ): 3.24 (s, 6H, 2αCH$_3$), 7.53 (dt, 1H, $J = 7.5$ Hz, C-H$_8$), 7.66 (dt, 1H, $J = 6.4$ Hz, C-H$_7$), 7.85 (s, 1H, C-H$_4$), 8.04 (s, 1H, C-H$_{11}$), 8.12 (d, 1H, $J = 7.85$ Hz, C-H$_6$), 8.33 (d, 1H, $J = 8.8$ Hz, C-H$_9$). ^{13}C NMR (Cd-Cl$_3$, δ): 37.9 (C-α), 105.1 (C-4), 106.1 (C-11), 123.6 (C-9a), 123.7 (C-10a), 124.4 (C-9), 129.0 (C-6), 129.4 (C-7), 126.3 (C-8), 139.3 (C-10), 146.1 (C-11a), 146.5 (C-4a), 147.1 (C-5a), 153.6 (C-3a), 165.0 (C-2). Anal. calcd for $C_{16}H_{12}ClN_3O$: C, 64.54; H, 4.06; N, 14.11. Found: C, 64.62; H, 4.11; N, 14.08.

***N*-4-[(*N*,*N*-Dimethyl-2-amine-oxazolo[4,5-*b*]acridin-11(6*H*)-ylidene) amino]-3-methoxy phenyl methane sulfonalide (9):** (**8**) (1 g, 3.3 mmol) and *N*-(4-amino-3-methoxyphenyl)methanesulfonamide (0.76 g, 3.5 mmol) were mixed in ethanol (100 ml) overnight and stirred at rt. The orange precipitate obtain was filtered to give (**9**) as an orange powder (1.2 g, yield 75%, m.p. > 260°C, mol. wt.; 478). ^{1}H NMR (DMSO-d$_6$, δ): 3.09 (s, 3H, (CH$_3$)$_{20}$), 3.15 (s, 6H, 2(CH$_3$)$_{23}$), 3.48 (s, 3H, (CH$_3$)$_{21}$), 7.00 (d, 1H, $J = 7.15$ Hz, C-H$_{17}$), 7.02 (s, 1H, C-H$_{15}$), 7.37 (dt, 1H, $J = 6.6$ Hz, C-H$_8$), 7.45 (d, 1H, $J = 8.8$ Hz, C-H$_6$), 7.76 (s, 1H, C-H$_{11}$), 7.84 (d, 1H, C-H$_{18}$), 7.92 (dt, 1H, $J = 6.6$ Hz, C-H$_7$), 8.12 (d, 1H, $J = 8.8$ Hz, C-H$_9$), 10.10 (s, 1H, N-H$_{19}$), 10.71 (s, 1H, N-H$_5$). ^{13}C NMR (DMSO-d$_6$ + TFA, δ): 37.6 (C-23), 39.4 (C-20), 55.8 (C-21), 96.9 (C-4), 104.2 (C-15), 106.9 (C-11), 111.7 (C-10a), 112.0 (C-17), 112.7 (C-9a), 118.9 (C-6), 123.6 (C-8), 124.5 (C-9), 124.8 (C-13), 127.9 (C-18), 134.3 (C-7), 136.7 (C-4a), 138.6 (C-5a), 139.6 (C-16), 142.8 (C-11a), 154.3 (C-14), 154.5 (C-10), 154.5 (C-3a), 164.2 (C-2). Anal. calcd for $C_{24}H_{23}N_5O_4S$: C, 60.36; H, 4.85; N, 14.67. Found: C, 60.54; H, 4.69; N, 14.31.

10-Imino-2-*N*,*N*-dimethylamino-5,10-dihydro-oxazolo[4,5-*b*]acridine (10): To a stirred solution of **8** (0.6 g, 2 mmol) in phenol (2 g, 21 mmol) heated at 80°C was added ammonium carbonate (0.21 g, 2.2 mmol), and then the solution was heated to 120°C for 2 h. The reaction mixture was allowed to cool rt, acetone (40 ml) was introduced and stirred for 2 h. The green precipitate formed was collected and washed in hot water, filtered to afford (**10**) as green powder (0.36 g, yield 65%, m.p. > 260°C, mol. wt.; 278). ^{1}H NMR (DMSO-d$_6$ + TFA, δ): 3.13 (s, 6H, 2(CH$_3$)$_{13}$), 7.45 (dt, 1H, $J = 6.5$ Hz, C-H$_8$), 7.69 (s, 1H, C-H$_4$), 7.82 (m, 2H, C-H$_{6,7}$), 8.23 (s, 1H, C-H$_{11}$), 8.59 (d, 1H, $J = 8.1$ Hz, C-H$_9$), 9.65 (bs, 1H, N-H$_{12}$), 13.99 (s, 1H, N-H$_5$). ^{13}C NMR (DMSO-d$_6$ + TFA, δ): 37.8 (C-13), 97.1 (C-4), 107.2 (C-10a), 109.6 (C-11), 109.7 (C-9a), 118.6 (C-6), 123.7 (C-8), 124.8 (C-9), 134.7 (C-7), 136.3 (C-4a), 138.7 (C-5a), 141.7 (C-11a), 154.5 (C-3a), 154.8 (C-10), 163.7 (C-2). Anal. calcd for $C_{16}H_{14}N_4O$: C, 69.05; H, 5.07; N, 20.13. Found: C, 69.12; H, 5.14; N, 20.47.

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