Natural Product Chemistry. Part 159 [1]. Two Methods for the Synthesis of 4-Azaacronycine as a Potential Antitumor Agent

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Two different methods for the synthesis of 4-azaacronycine (**10**) have been described. One route with a fusion reaction between 1,3-dihydroxy-10-methyl-9(10*H*)-acridinone (**1**) and 2-amino-2-methyl-3-butyne in a glass ampoule and the other by a reaction of 3-amino-1-methoxy-10-methyl-9(10*H*)-acridinone (**9**) with 2-chloro-2-methyl-3-butyne.

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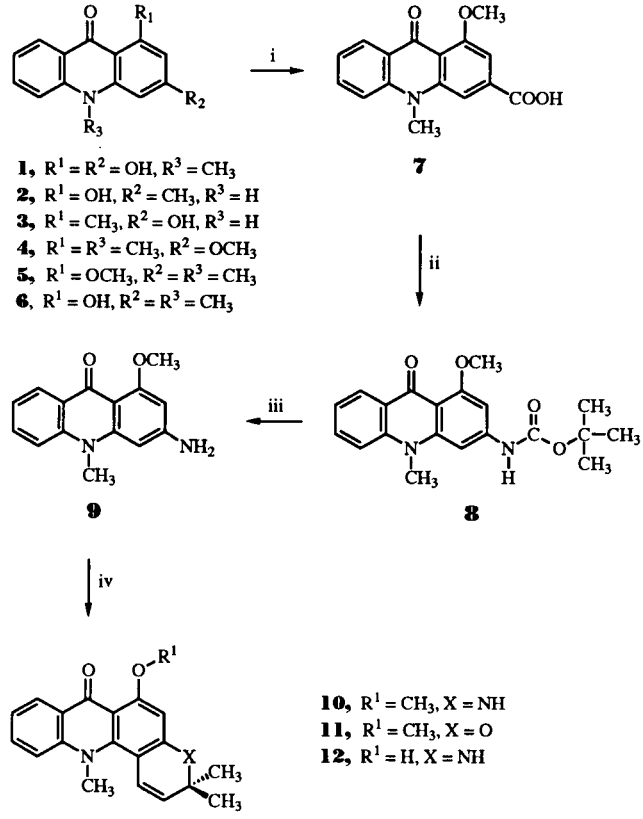
Several planar molecules containing mostly tricyclic structures with different side chains have been reported to possess useful cytotoxic and/or cytostatic potencies. These tricyclic systems include anthraquinone [4], acridine [5], xanthone [6] and 9(10*H*)-acridinone [7]. Some of the derivatives are known drugs like nitracrine, daunomycine, mitoxanthone, *etc.* with excellent cytostatic properties or acronycine (**11**) with a potent antitumor spectrum [8].

In view of the interesting antineoplastic properties of acronycine (**11**), we have been engaged in the synthesis of various analogs of **11** [9]. In an effort to obtain more potent derivatives, it was found worthwhile to modify the D-ring applying the concept of bioisosterism. It has been known that the substitution of oxygen with nitrogen results in enhanced cytostatic properties. This may be attributed to the increased hydrophilicity perhaps due to possible quarternization of the ring nitrogen [10,11].

In the first method a reaction of 1,3-dihydroxy-10-methyl-9(10*H*)-acridinone (**1**) [12] with 2-amino-2-methyl-3-butyne in the presence of cupric chloride in a closed ampoule resulted in 4-azanoracronycine (**12**). Further methylation of the hydroxy group of **11** gave the title compound in a yield of 10%.

The reaction of substituted anilines with 2-chloro-2-methyl-3-butyne following the methods described by Dillard [13] and Barmettler [14] was found to be an alternative route. The synthesis and isomeric separation of 1-hydroxy-3-methyl-9(10*H*)-acridinone (**2**), 3-hydroxy-1-methyl-9(10*H*)-acridinone (**3**) and 3-methoxy-1,10-dimethyl-9(10*H*)-acridinone (**4**), 1-methoxy-3,10-dimethyl-9(10*H*)-acridinone (**5**) was carried out using the reported procedure [12]. Oxidation of **5** using potassium permanganate solution yielded the corresponding 1-methoxy-10-methyl-9(10*H*)-acridinone-3-carboxylic acid (**7**). The conversion of the aryl carboxylic function of **7** to the *N*-substituted aniline **8** was successfully worked out in an one-pot Curtius rearrangement using diphenyl phosphoric azide (DPPA) in



i: pyridine, $KMnO_4$, 100°, 6 hours; ii: toluene, *tert*-butyl alcohol, DPPA, 60°, 8 hours; iii: H^+; iv: DMF, 2-chloro-2-methyl-3-butyne, K_2CO_3, KI, 120°, 8 hours, N_2.

the presence of *t*-butyl alcohol and triethylamine [15]. Acidic hydrolysis of **8** readily resulted in the corresponding free amino derivative, 3-amino-1-methoxy-10-methyl-9(10*H*)-acridinone (**9**). Upon treatment of the amine **9** with 2-chloro-2-methyl-3-butyne in DMF at 120° in the presence of anhydrous potassium carbonate and a catalytic amount of potassium iodide gave the *N*-alkylated product *in situ*, which on further prolongation of heating for 8 hours under a nitrogen atmosphere [9] yielded the title compound (20%).

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. The ir spectra were obtained on a Shimadzu IR 470 spectrophotometer. The uv spectra were obtained on a Shimadzu spectrophotometer UV-160A. The ^1H and ^{13}C nmr spectra were recorded on a Varian Gemini 200 spectrometer with tetramethylsilane as the internal standard. Mass spectra were recorded with a Varian MAT 44S spectrometer. Merck silica gel $60F_{254}$ and silica gel 60 (70-230 mesh) were used for preparative tlc and column chromatography respectively.

1-Hydroxy-3-methyl-9(10*H*)-acridinone (**2**) and 3-Hydroxy-1-methyl-9(10*H*)-acridinone (**3**).

Following the method of Smolders [12] 13.3 g (88 mmoles) of anthranilic acid methyl ester and 12.5 g (100 mmoles) of 5-methylresorcinol were converted into the two isomers **2** and **3** which could not be separated by column chromatography.

1-Methoxy-3,10-dimethyl-9(10*H*)-acridinone (**5**) and 3-Methoxy-1,10-dimethyl-9(10*H*)-acridinone (**4**).

The mixture of **2** and **3** (11.3 g, 50 mmoles) was methylated under phase transfer conditions [12]. The products were separated by column chromatography to give 4.9 g (33%) of **5** and 2.8 g (19%) of **4**.

1-Methoxy-3,10-dimethyl-9(10*H*)-acridinone (**5**).

This compound had mp 159-161° (dichloromethane/methanol), R_f 0.38 (chloroform/ethyl acetate 95:5); uv methanol: λ max (log ε) 394 nm (4.832), 262 (4.758), 215 (4.645); ir (potassium bromide): ν 2850-2975 (C-H), 1623 (C=O), 1593, 1500 (arom, C=C) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.42 (s, 3H, 3-CH_3), 3.70 (s, 3H, N-CH_3), 3.95 (s, 3H, O-CH_3), 6.49 (s, 1H, 4-H), 6.76 (s, 1H, 2-H), 7.19 (ddd, J = 8.0, 7.0 and 1.0 Hz, 1H, 7-H), 7.33 (d, J = 8.6 Hz, 1H, 5-H), 7.57 (ddd, J = 8.4, 7.0 and 1.7 Hz, 1H, 6-H), 8.47 (dd, J = 8.0 and 1.7 Hz, 1H, 8-H); ^{13}C nmr (deuteriochloroform): δ 22.9 (CH_3), 34.64 (N-CH_3), 56.19 (1-OCH_3), 104.35 (C-4), 107.15 (C-2), 111.42 (C-9a), 114.21 (C-5), 121.06 (C-8a), 124.56 (C-7), 127.71 (C-8), 132.83 (C-6), 141.85 (C-10a), 144.76 (C-4a), 145.34 (C-3), 161.53 (C-1), 177.49 (C-9); ms: (70 eV) m/z 253 (100, M^+), 252 (34, M^+ -H), 238 (23, M^+ -CH_3), 224 (93, 252 -CO), 210 (10, 238 -CO), 167 (10, 210 -C_2H_3O), 152 (12, 167 -CH_3).

3-Methoxy-1,10-dimethyl-9(10*H*)-acridinone (**4**).

This compound had mp 139-141° (dichloromethane/methanol), R_f 0.63 (chloroform/ethyl acetate 95:5); ir (potassium bromide): ν 2850-2960 (C-H), 1627 (C=O), 1592, 1497 (arom, C=C) cm^{-1}; uv (methanol): λ max (log ε) 386 nm (3.694), 269 (4.691), 216 (4.757); ^1H nmr (deuteriochloroform): δ 2.95 (s, 3H, 1-CH_3), 369 (s, 3H, N-CH_3), 3.89 (s, 3H, O-CH_3), 6.57 (d, J = 1.3 Hz, 1H, 4-H), 6.59 (d, J = 1.3 Hz, 1H, 2-H), 7.2 (ddd, J = 8.0, 7.0 and 1.0 Hz, 1H, 7-H), 7.33 (d, J = 8.6 Hz, 1H, 5-H), 7.59 (ddd, J = 8.6, 7.0 and 1.8 Hz, 1H, 6-H), 8.43 (dd, J = 8.0 and 1.7 Hz, 1H, 8-H); ^{13}C nmr (deuteriochloroform): δ 24.95 (1-CH_3), 34.49 (N-CH_3), 55.29 (O-CH_3), 96.41 (C-4), 112.33 (C-2), 114.23 (C-9a), 115.99 (C-5), 120.91 (C-8a), 124.09 (C-7), 127.54 (C-8), 132.32 (C-6), 142.11 (C-10a), 145.18 (C-4a), 146.32 (C-1), 162.42 (C-3), 178.93 (C-9); ms: (70 eV) m/z 253 (100, M^+), 252 (59, M^+ -H), 238 (12, M^+ -CH_3), 224 (38, 252 -CO), 210 (37, 238 -CO), 167 (37, 210 -C_2H_3O).

1-Hydroxy-3,10-dimethyl-9(10*H*)-acridinone (**6**).

After only 7 hours of methylation 150 mg (1%) of **6** could also be isolated, mp 200-202° (chloroform/ethyl acetate), R_f 0.59 (acetone); ir (potassium bromide): ν 3600-3200 (OH), 2960-2850 (C-H), 1627 (C=O), 1588, 1549 (arom, C=C) cm^{-1}; uv (methanol): λ max (log ε) 407 nm (3.639), 263 (4.764), 215 (4.791); ^1H nmr (deuteriochloroform): δ 2.39 (s, 3H, 3-CH_3), 3.68 (s, 3H, N-CH_3), 6.40 (s, 1H, 4-H), 6.54 (s, 1H, 2-H), 7.20 (m, 1H, 7-H), 7.40 (d, J = 8.8 Hz, 1H, 5-H), 7.66 (ddd, J = 8.7, 7.0 and 1.6 Hz, 1H, 6-H), 8.35 (d, J = 8.0 Hz, 1H, 8-H), 14.30 (s, 1H, 1-OH); ^{13}C nmr (deuteriochloroform): δ 23.04 (3-CH_3), 33.98 (N-CH_3), 104.14 (C-4), 108.02 (C-2), 108.67 (C-9a), 114.64 (C-5), 121.00 (C-8a), 121.23 (C-7), 126.65 (C-8), 134.15 (C-6), 142.28 (C-10a), 143.50 (C-4a), 147.50 (C-1), 163.36 (C-3), 181.52 (C-9); ms: (70 eV) m/z 239 (100, M^+), 238 (16, M^+ -H), 224 (5, M^+ -CH_3), 210 (15, M^+ -CHO).

Anal. Calcd. for $C_{15}H_{13}NO_2$ (239.27): C, 75.29; H, 5.47; N, 5.85. Found: C, 74.98; H, 5.63; N, 5.86.

1-Methoxy-10-methyl-9(10*H*)-acridinone-3-carboxylic Acid (**7**).

The oxidation of 2.5 g (9.9 mmoles) of 1-methoxy-3,10-dimethyl-9(10*H*)-acridinone (**5**) following a reported method [12] gave a yield of 470 mg (18%) of **7**, mp 269-271°; ir (potassium bromide): ν 3700-2500 (COOH, O-H), 1698 (C=O), 1605, 1560 (arom, C=C) cm^{-1}; uv (methanol): λ max (log ε) 413 nm (3.812), 263 (4.758), 215 (4.683); ^1H nmr (dimethyl sulfoxide-d_6): δ 3.85 (s, 3H, N-CH_3), 3.95 (s, 3H, O-CH_3), 7.23 (s, 1H, 2-H), 7.24 (d, 1H, 4-H), 7.67 (m, 3H, 7-H, 6-H, 5-H), 8.20 (d, J = 7.7 Hz, 1H, 8-H); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 34.79 (N-CH_3), 55.96 (1-OCH_3), 102.55 (C-4), 108.77 (C-2), 114.22 (C-9a), 115.73 (C-5), 121.44 (C-8a), 123.91 (C-7), 126.36 (C-8), 133.54 (C-6), 135.13 (C-10a), 141.67 (C-4a), 144.53 (C-1), 160.86 (C-3), 166.75 (COOH), 175.83 (C-9); ms: (70 eV) m/z 283 (100, M^+), 282 (37, M^+ -H), 267 (14, 282 -CH_3), 254 (88, 282 -CO), 239 (14, 254 -CH_3), 238 (32, 282 -CO_2); hrms: Calcd. for $C_{16}H_{13}NO_4$: 283.084459. Found: 283.0850467.

3-*tert*-Butoxycarbonylamino-1-methoxy-10-methyl-9(10*H*)-acridinone (**8**).

Following Shioiri's method [15] 330 mg (1.2 mmoles) of **7** was taken in 5 ml of dry toluene and 5 ml of *t*-butyl alcohol, 0.2 g of triethylamine and 0.4 g (1.5 mmoles) of diphenylphosphoric ester azide (DPPA) were added. The mixture was heated to 60° for 30 minutes. The temperature was raised to 100° and kept for 8 hours. The residue was separated by column chromatography to give 161 mg (40%) of **8**, mp 124-126° (dichloromethane/methanol), R_f 0.25 (chloroform/ethyl acetate 95:5); ir (potassium bromide): ν 3255 (N-H), 2850-2960 (C-H), 1720 (C=O), 1565 and 1596 (arom, C=C) cm^{-1}; uv (methanol): λ max (log ε) 389 nm (4.002), 322 (4.129), 271 (4.954), 216 (4.820); ^1H nmr (deuteriochloroform): δ 1.50 (s, 9H, 3 x CH_3), 3.70 (s, 3H, N-CH_3), 3.90 (s, 3H, O-CH_3), 6.76 (s, 1H, 4-H), 7.30 (s, 1H, 2-H), 7.17 (ddd, J = 7.9, 7.0 and 0.8 Hz, 1H, 7-H), 7.33 (d, J = 8.2 Hz, 1H, 5-H), 7.58 (ddd, J = 8.6, 7.0 and 1.7 Hz), 7.66 (s, 1H, N-H), 8.48 (dd, J = 7.9 and 1.5 Hz, 1H, 8-H); ^{13}C nmr (deuteriochloroform): δ 28.31 (3 x CH_3), 34.74 (N-CH_3), 56.07 (O-CH_3), 81.08 (*tert*-C), 94.29 (C-4), 95.15 (C-2), 109.21 (C-9a), 114.24 (C-5), 121.12 (C-7), 124.50 (C-8a), 127.62 (C-8), 132.77 (C-6), 141.92 (C-3), 144.07 (C-10a), 146.27 (C-4a), 152.52 (N-*C*=O), 162.50 (C-1), 176.90 (C-9); ms: (70 eV) m/z 354 (8, M^+), 297 (9, M^+ -$C(CH_3)_3$), 269 (8, 297 -CO), 254 (3, 269 -CH_3), 253 (7, 254 -H), 225 (6, 254 -CO).

Anal. Calcd. for $C_{20}H_{22}N_2O_4 \cdot 2/3H_2O$ (354.39): C, 65.60; H, 6.42; N, 7.65. Found: C, 65.20; H, 6.26; N, 7.45.

3-Amino-1-methoxy-10-methyl-9(10*H*)-acridinone (**9**).

3-*tert*-Butoxycarbonylamino-1-methoxy-10-methyl-9(10*H*)-acridinone (**8**) (420 mg, 1.2 mmoles) was dissolved in 2.2 ml of cold trifluoroacetic acid. After shaking for 1 hour at room temperature, the acid was removed *in vacuo* and the residue poured into 150 ml of cold water. The *p*H of the solution was brought to 7 using ammonia solution. The solid product that separated was filtered. On recrystallization from ethanol, 200 mg (67%) of **9** was obtained, mp 115-117° (ethanol), R_f 0.22 (chloroform/ethyl acetate 95:5); ir (potassium bromide): ν 3195, 3385 (N-H), 2850-2960 (C-H), 1624 (C=O), 1610, 1569 (arom C=C) cm^{-1}; uv (methanol): λ max (log ϵ) 344 nm (3.726), 293 (4.084), 269 (4.391), 216 (4.722); ^1H nmr (dimethyl sulfoxide-d_6): δ 3.69 (s, 3H, N-CH_3), 3.79 (s, 3H, O-CH_3), 6.12 (d, J = 1.3 Hz, 1H, 4-H), 6.25 (d, J = 1.3 Hz, 1H, 2-H), 6.96 (s, 2H, NH_2), 7.18 (ddd, J = 7.8, 6.2 and 1.6 Hz, 1H, 7-H), 7.53 (d, J = 9.0 Hz, 1H, 5-H), 7.60 (ddd, J = 9.1, 6.7 and 1.6 Hz, 1H, 6-H), 8.16 (dd, J = 8.2 and 1.3 Hz); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 34.25 (N-CH_3), 55.29 (O-CH_3), 89.38 (C-2), 91.73 (C-4), 104.2 (C-9a), 114.75 (C-5), 120.22 (C-8a), 123.36 (C-7), 126.12 (C-8), 132.21 (C-6), 141.52 (C-10a), 146.76 (C-4a), 154.26 (C-3), 162.28 (C-1), 173.34 (C-9); ms: (70 eV) m/z 254 (100, M^+), 238 (14, M^+ -NH_2), 210 (16, 238 -CO), 195 (12, 210 -CH_3), 167 (8, 195 -CO); hrms: Calcd. for $C_{15}H_{14}N_2O_2$: 254.105528. Found: 254.1051541.

4-Azaacronycine (**10**).

To 100 mg (0.4 mmole) of **9** and 71 mg (0.7 mmole) of 2-chloro-2-methyl-3-butyne in 2.6 ml of absolute DMF, 115 mg of potassium iodide and 81 mg of potassium carbonate were added. The mixture was gradually heated to 120° under nitrogen for 48 hours. Removal of the solvent gave an oily residue, which on separation by column chromatography gave 25 mg (20%) of **10**, mp 137-139°, R_f 0.27 (dichloromethane/methanol 95:5); ir (potassium bromide): ν 3270 (N-H), 2955 (C-H), 1620 (C=O), 1588, 1554 (arom, C=C) cm^{-1}; uv (methanol): λ max (log ϵ) 350 nm (4.245), 320 (4.574), 283 (4.681), 274 (4.699), 210 (4.705); ^1H nmr (deuteriochloroform): δ 1.40 (s, 6H, 2 x CH_3), 3.83 (s, 3H, N-CH_3), 3.90 (s, 3H, O-CH_3), 4.62 (s, 1H, N-H), 5.35 (d, J = 9.6 Hz, 1H, 2-H), 5.93 (s, 1H, 5-H), 6.50 (d, J = 9.5 Hz, 1H, 1-H), 7.22 (m, 1H, 9-H), 7.32 (d, J = 8 Hz, 1H, 11-H), 7.60 (ddd, J = 8.0, 6.9 and 1.3 Hz, 1H, 10-H), 8.38 (dd, J = 7.8 and 1.4 Hz, 1H, 8-H); ^{13}C nmr (deuteriochloroform): δ 29.34 (2 x CH_3), 44.62 (N-CH_3), 56.20 (O-CH_3), 71.37 (C-3), 91.20 (C-5), 92.70 (C-12b), 100.21 (C-6a), 113.90 (C-11), 115.85 (C-9), 121.25 (C-7a), 122.70 (C-1), 127.08 (C-8), 132.11 (C-2), 144.83 (C-10), 147.63 (C-12a), 150.11 (C-11a), 162.47 (C-6), 162.81 (C-4a), 176.61 (C-7); ms: (70 eV) m/z 320 (23, M^+), 305 (100, M^+ -CH_3), 290 (22, 305 -CH_3), 275 (10, 290 -CH_3), 260 (22, 275 -CH_3), 232 (9, 260 -CO), 204 (5, 232 -CO); hrms: Calcd. for $C_{20}H_{20}N_2O_2$: 320.152478. Found: 320.1532817.

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