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Short Communication

Natural Product Chemistry, Part 137 [1]: Oxidation of Acridone Alkaloids: Synthesis of 5-Methoxyacronycine

Johannes Reisch* and **Anura Wickramasinghe** [2]

Institut für Pharmazeutische Chemie, Westfälische Wilhelms-Universität, D-4400 Münster, Federal Republic of Germany

Summary. Epoxidation of the acridone alkaloid acronycine (**1**) resulted in hydroxylation at the aromatic ring giving 5-hydroxyacronycine (**3**). The same reaction on 1,3-dimethoxy-10-methyl-9(10*H*)-acridinone (**5**) gave 1,3-dimethoxy-2-hydroxy-10-methyl-9(10*H*)-acridinone (**6**), 1,3-dimethoxy-2-hydroxy-4-peroxy-10-methyl-9(10*H*)-acridinone (**8**), and 1,3-dimethoxy-2,4-diperoxy-10-methyl-9(10*H*)-acridinone (**9**).

Keywords. Acridone alkaloids; Acronycine; Epoxidation.

Naturstoffchemie, 137. Mitt.: Oxidierung von Acridonalkaloiden: Synthese des 5-Methoxyacronycins (Kurze Mitt.)

Zusammenfassung. Die Epoxidierung des Acridonalkaloids Acronycin führte zu einer Hydroxylierung des aromatischen Rings, wobei 5-Hydroxyacronycin (**3**) entstand. Die gleiche Reaktion mit 1,3-Dimethoxy-10-methyl-9(10*H*)acridinon (**5**) ergab 1,3-Dimethoxy-2-hydroxy-10-methyl-9(10*H*)acridinon (**6**), 1,3-Dimethoxy-2-hydroxy-4-peroxy-10-methyl-9(10*H*)acridinon (**8**) und 1,3-Dimethoxy-2,4-diperoxy-10-methyl-9(10*H*)acridinon (**9**).

The acridone alkaloid acronycine (**1**), isolated from several species of Rutaceae [3, 4], exhibits a broad spectrum of antitumor activity [5, 6]. Recently the epoxide of acronycine, acronycine-epoxide (**2**), which could be the active form of acronycine in vivo, has been naturally isolated [7].

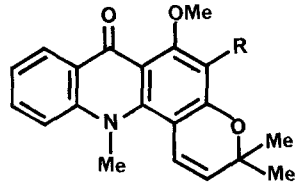
Epoxidation of acronycine resulted in hydroxylation at 5-position. Methylation of this gave 5-methoxyacronycine (**4**). Epoxidation of 1,3-dimethoxy-10-methyl-9(10*H*)-acridinone (**5**) gave 1,3-dimethoxy-2-hydroxy-10-methyl-9(10*H*)-acridinone (**6**) which on methylation gave known 1,2,3-trimethoxy-10-methyl-9(10*H*)-acridinone (**7**) and two other peroxyacridinones.

Acronycine was oxidized with *m*-chloroperbenzoic acid in CH_2Cl_2 in the presence of a phosphate buffer, in order to minimize the opening of the epoxide product by weak acids to yield diols [8]. When one equivalent of the peracid was used the reaction was not complete. However, when another two equivalents were used all

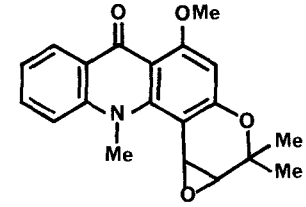
the acronycine was consumed. The product which was isolated in 10% yield was identified as the 5-hydroxyacronycine (**3**). The double bond of the chromene ring of acronycine was resistant to epoxidation. Methylation of this hydroxyacronycine with methyliodide give 5-methoxyacronycine (**4**).

Since the epoxidation of acronycine introduced a hydroxy group to the acridone nucleus, the same reaction was attempted with 1,3-dimethoxy-10-methyl-9(10*H*)-acridinone. The reaction mixture showed the presence of 3 products. The most polar product was identified as the hydroxylated product at 2-position by converting it to known 1,2,3-trimethoxy-10-methyl-9(10*H*)-acridinone (**7**). The least polar compound was shown to be the product with the hydroxy group at 2-position and the peroxy group at 4-position (**8**). The other compound showed peroxy groups at both 2- and 4-positions (**9**). Arene oxides can be assumed as the intermediates in the formation of these phenolic and peroxy acridones.

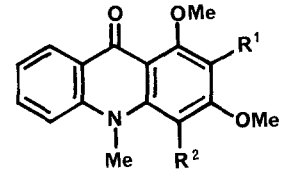
The biogenetic formation of phenols has also been postulated [9] to go via their epoxides.



(1) R = H
(3) R = OH
(4) R = OMe



(2)



(5) $R^1 = R^2 = H$
(6) $R^1 = OH$, $R^2 = H$
(7) $R^1 = OMe$, $R^2 = H$
(8) $R^1 = OH$, $R^2 = -OOH$
(9) $R^1 = R^2 = -OOH$

Dank

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Experimental Part

Melting points were recorded on a Kofler hot-stage apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were measured on a Varian Gemini 200 MHz spectrometer using *TMS* as internal standard. Mass spectroscopic analyses were carried out on a MAT 44S spectrometer. Merck silica gel 60 F_{254} coated on aluminium sheets and glass plates was used for analytical and preparative (2 mm) chromatography.

5-Hydroxyacronycine (**3**)

To a stirred solution of acronycine (107 mg, 0.33 mmol) in CH_2Cl_2 phosphate buffer (the buffer was prepared by adding sufficient aq. 0.1 *M* Na_2HPO_4 to 0.1 *M* Na_2HPO_4 until the *pH* was 8.0) (20 ml, 1 : 1) was added *m-CPBA* (57.5 mg, 0.33 mmol) in small portions over a 10 min period at 0°C. After stirring for 4 h at room temperature 57.5 mg of *m-CPBA* was added in small portions to the mixture at 0°C over a second 10 min period. The mixture was stirred at room temperature for 4 h and the organic layer was separated, washed with saturated $Na_2S_2O_3$ solution and water, dried over Na_2SO_4 and evaporated. The residue was chromatographed over silica gel (CH_2Cl_2 : *Me*OH; 19 : 1) to give **3** (12 mg, 10%), m.p. 181–182°C.

^{1}H NMR ($CDCl_3$): δ = 1.62 (s, 6 H, 2 × $-CH_3$), 3.85 (s, 3 H, N$-CH_3$), 4.06 (s, 3 H, $-OCH_3$), 5.63 (d, *J* = 9.8 Hz, 1 H, 2-H), 6.63 (d, *J* = 9.8 Hz, 1 H, 1-H), 7.26 (ddd, *J* = 8.5, 8.0 and 1.2 Hz, 1 H, 9-H), 7.38 (dd, *J* = 8.7 and 1.2 Hz, 1 H, 11-H), 7.66 (ddd, *J* = 8.7, 8.5 and 1.7 Hz, 1 H, 10-H), 8.41 (dd, *J* = 8.0 and 1.7 Hz, 1 H, 8-H).

^{13}C NMR ($CDCl_3$): δ = 27.1 (2 × $-OCH_3$), 44.5 (N$-CH_3$), 62.4 ($-OCH_3$), 76.4 (C-3), 101.2 (C-12 b), 116.4 (C-11), 116.5 (C-6 a), 122.0, 122.1 (C-2 and 9), 124.6 (C-7 a), 125.2 (C-1), 127.5 (C-8), 133.3 (C-10), 134.3, 134.7 (C-5 and 12 a), 146.9 (C-11 a), 147.7 (C-6), 153.7 (C-4 a), 177.4 (C-7).

MS (70 eV): *m*/e (%) = 337 (100) [M^+], 322 (80) [$M^+ - CH_3$], 294 (72), 277 (50), 268 (48). $C_{20}H_{19}NO_4$: calcd. 337.3787; found 337.3796 (MS).

5-Methoxyacronycine (**4**)

Hydroxyacridone **3** (10 mg, 0.03 mmol) and *Me*I (21 mg, 0.15 mmol) were refluxed in dry aceton (5 ml) for 1 h with anhydrous K_2CO_3 (40 mg, 0.3 mmol). The reaction mixture was filtered and the filtrate concentrated. The product on crystallisation from ethylacetate gave yellow needles of 5-methoxyacronycine (**4**) (9 mg, 86%), m.p. 164–166°C.

^{1}H NMR ($CDCl_3$): δ = 1.64 (s, 6 H, 2 × $-CH_3$), 3.84, 3.91 and 4.05 (each 3 H, s, 2 × $-OCH_3$ and N$-CH_3$), 5.61 (d, *J* = 9.8 Hz, 1 H, 2-H), 6.59 (d, *J* = 9.8 Hz, 1 H, 1-H), 7.23–7.31 (m, 1 H, 9-H), 7.38 (br, d, *J* = 8.5 Hz, 1-H, 11-H), 7.67 (ddd, *J* = 8.5, 8.3 and 1.8 Hz, 1 H, 10-H), 8.40 (dd, *J* = 8.0 and 1.8 Hz, 1 H, 8-H).

MS (70 eV): *m*/e (%) = 351 (38) [M^+], 336 (100) [$M^+ - CH_3$], 306 (14). $C_{21}H_{21}NO_4$: calcd. 351.4058; found 351.4027 (MS).

Treatment of 1,3-Dimethoxy-10-methyl-9(10H)-acridinone (**5**) *with m-Chloroperbenzoic Acid*

1,3-Dimethoxy-10-methyl-9(10*H*)-acridinone (**5**) (90 mg, 0.33 mmol) was oxidized with *m-CPBA* (172.5 mg, 1 mmol) using the above described method. Chromatographic separation of the reaction mixture gave 1,3-dimethoxy-2-hydroxy-10-methyl-9(10*H*)-acridinone (**6**) (6 mg, 6.5%), m.p. 168–170°C, 1,3-dimethoxy-2,4-diperoxy-10-methyl-9(10*H*)-acridinone (**9**) (15 mg, 13.5%), m.p. 138°C (decomp.) and 1,3-dimethoxy-2-hydroxy-4-peroxy-10-methyl-9(10*H*)-acridinone (**8**) (20 mg, 18.8%), m.p. 157–158°C.

1,3-Dimethoxy-2-hydroxy-10-methyl-9(10H)-acridinone (**6**)

^{1}H NMR ($CDCl_3$): δ = 3.88, 3.94, 4.07 (each, s, 3 H, 2 × $-OCH_3$ and N$-CH_3$), 6.70 (s, 1 H, H-4), 7.25–7.32 (m, 1 H, 7-H), 7.50 (br, d, *J* = 8.8 Hz, 1 H, 5-H), 7.65–7.74 (m, 1 H, 6-H), 8.50 (dd, *J* = 8.0 and 1.4 Hz, 1 H, 8-H).

MS (70 eV): *m*/e (%) = 285 (50) [M^+], 270 (48), 267 (70), 266 (100), 242 (44), 238 (40), 199 (40).

1,3-Dimethoxy-2,4-diperoxy-10-methyl-9(10H)-acridinone (**9**)

^{1}H NMR ($CDCl_3$): δ = 3.37, 3.82 and 4.14 (each, s, 3 H, 2 × $-OCH_3$ and $N-CH_3$), 7.34–7.46 (m, 1 H, 7-H), 7.57 (br, d, J = 8.5 Hz, 1 H, 5-H), 7.81 (ddd, J = 8.5, 8.6 and 2.5 Hz, 1 H, 6-H), 8.53 (dd, J = 8.4 and 2.5 Hz, 1 H, 8-H).

MS (70 eV): m/e (%) = 333 (30) [M^+], 245 (100), 216 (50), 189 (35), 174 (95), 146 (32).

$C_{16}H_{15}NO_7$: calcd. 333.0848; found 333.0826 (MS).

1,3-Dimethoxy-2-hydroxy-4-peroxy-10-methyl-9(10H)-acridinone (**8**)

^{1}H NMR ($CDCl_3$): δ = 3.37, 3.57 and 4.17 (each, s, 3 H, 2 × $-OCH_3$ and $N-CH_3$), 7.40 (ddd, J = 8.0, 8.5 and 1.7 Hz, 1 H, 7-H), 7.59 (br, d, J = 8.6 Hz, 1 H, 5-H), 7.78 (ddd, J = 8.5, 8.6 and 1.7 Hz, 1 H, 6-H), 8.57 (dd, J = 8.0 and 1.7 Hz, 1 H, 8-H).

MS (70 eV): m/e (%) = 317 (45) [M^+], 274 (30), 258 (28), 230 (100), 215 (30), 159 (28).

$C_{16}H_{15}NO_6$: calcd. 317.0900; found 317.0958 (MS).

Methylation of 1,3-Dimethoxy-2-hydroxy-10-methyl-9(10H)-acridinone (**6**)

Hydroxyacridone **6** (5 mg, 0.018 mmol) and *Me*I (13 mg) were refluxed in dry acetone (5 ml) for 2 h with anhydrous K_2CO_3 (25 mg). The reaction mixture was filtered and the filtrate concentrated. The product on crystallisation from $CHCl_3$/petrolether gave yellow needles of 1,2,3-trimethoxy-10-methyl-9(10*H*)-acridinone (**7**) (4.5 mg, 85%), m.p. 119–120°C (Ref. [10] 116–118°C); on the basis of spectroscopic data the substance corresponds with the natural product described in Ref. [11].

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