Natural Product Chemistry. Part 153 [1]. Synthesis and Possible Anticancer Activity of 8-Nitronoracronycine

Johannes Reisch* and Peter Dziemba [2]

Institut für Pharmazeutische Chemie der
Westfälischen Willhelms-Universität
Münster, Hittorfstraße 58-62,
4400 Münster, Germany

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Since the strategy for the synthesis of 9-, 10- and 11-nitronoracronycine [3,4] could not be applied to the 8-nitronoracronycine **9**, we here report the preparation of the latter by a fusion of methyl 2-amino-6-nitrobenzoate **2** and phloroglucinol **3**. The fusion of **2** and **3** gave 1,3-dihydroxy-8-nitro-9(10*H*)-acridinone **6**. Subsequent methylation, demethylation and reaction with 2-chloro-2-methyl-3-butyne afforded the desired 8-nitronoracronycine **9**. Compound **9**, 1,3-dimethoxy-10-methyl-8-nitro-9(10*H*)-acridinone **7** and 1,3-dihydroxy-10-methyl-8-nitro-9(10*H*)-acridinone **8** were tested by the National Cancer Institute (NCI) for possible anticancer activity.

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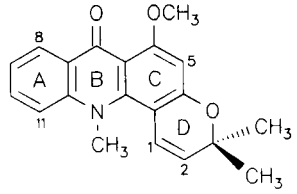
Introduction.

Diseases like cancer, AIDS, ateriosclerosis, tropical diseases and those of the central nervous system (CNS) are as of today not satisfactorily treated by existing medicaments [5]. Since the beginning of the 19th century, cancer related death has steadily increased in the industrialised countries [6,7]. In fact death from cancer ranks second as against seventh a couple of years ago. In former West Germany, 160,000 cases of death from cancer are reported every year, while in the USA 600,000 new occurences of cancer have been diagnosed [8].

It is therefore necessary to have a new research focus with the aim of developing new therapy concepts and drugs to adequately fight against malignant tumors. The problem of resistance and cross-resistance of tumor cells against cytostatic agents should be minimized and also the improvement of already existing drugs and the reduction of many side-effects should be of prime importance in research objectives.

New pharmacologically active substances have been and are continually produced from natural sources. When an active natural product has been isolated, efforts are intensified in the search for synthetic derivatives of this product with better enhancement of activity.

Since 1966 acronycine **1**, a *Rutaceae* alkaloid, which is an angular pyrano-9(10*H*)-acridinone with interesting pharmacological activities has stimulated research into finding other possible synthetic pathways and derivatives [9-19].



1

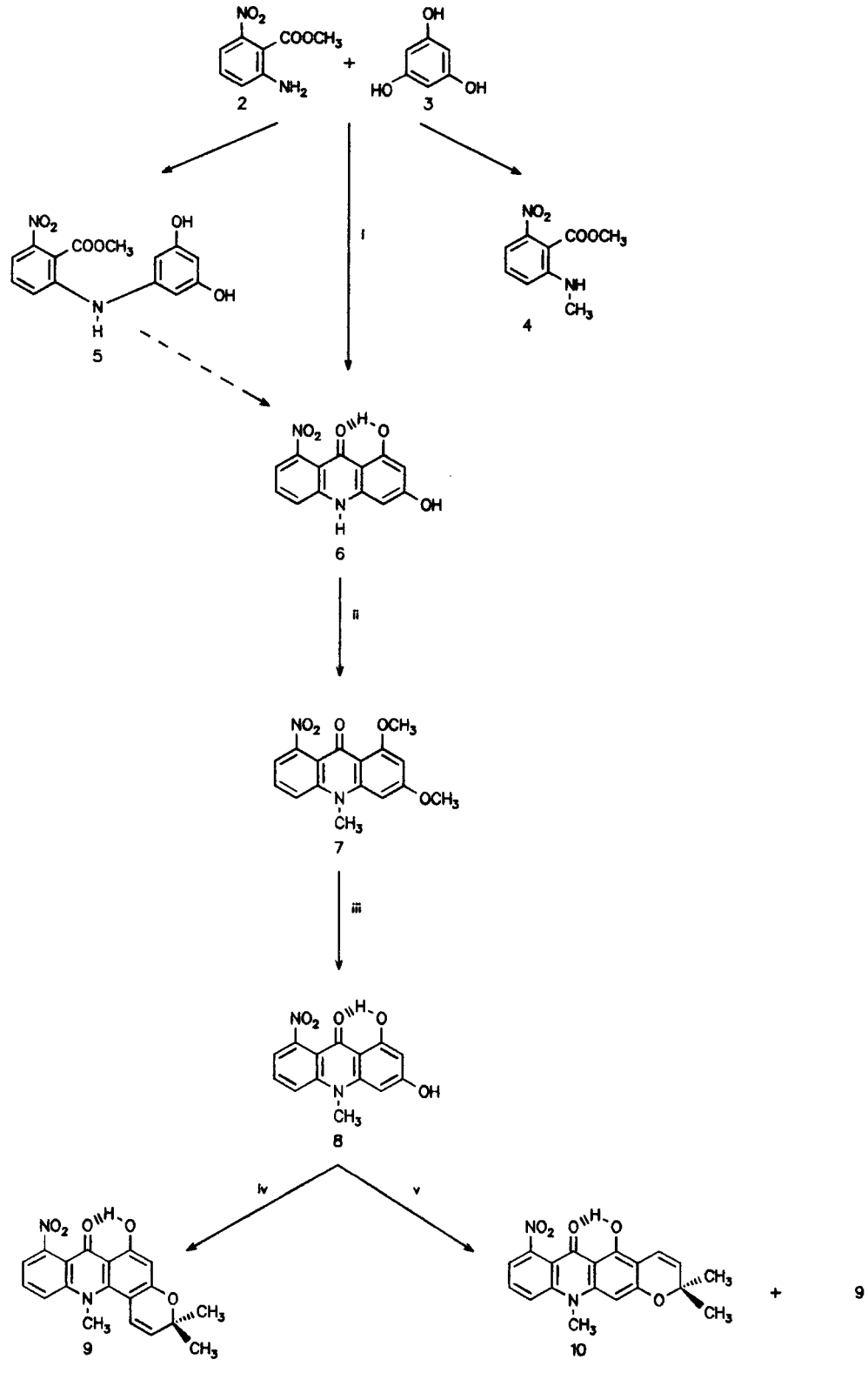
Acronycine

Acronycine is particulary active against a lot of neoplastic incidences of the mouse and shows a wide range of antitumor activity of all known oncolytic active alkaloids [20].

Efforts have been made through molecular variations to improve the cytostatic activity of acronycine. However no significant improvement has been documented recently [21].

Earlier attempts were made to synthesis 8-nitronoracronycine **9** through a modified Ullmann-reaction [22]. This was not possible and probably could be due to the presence of a strong deactivating influence of the nitro group in the 6-position of methyl 2-amino-6-nitrobenzoate **2**. 8-Nitronoracronycine **9** was however synthesized by another method as shown in the first step, which is a fusion of phloroglucinol **3** and methyl 2-amino-6-nitrobenzoate **2** (Scheme 1). In the first reaction step the compounds methyl 2-methylamino-6-nitrobenzoate **4** and methyl 2-(3,5-dihydroxylphenylamino)-6-nitrobenzoate **5** were isolated as side-products. Compound **5** could probably be recognized as a reaction product leading to 1,3-dihydroxy-8-nitro-9(10*H*)-acridinone **6**. Subsequent respective methylation [23] and demethylation [24] of **6** and 1,3-dimethoxy-10-methyl-8-nitro-9(10*H*)-acridinone **7** afforded 1,3-dihydroxy-10-methyl-8-nitro-9(10*H*)-acridinone **8**. After which the potassium salt of **8** was formed using ethanolic potassium hydroxide. The reaction of potassium salt of **8** with 2-chloro-2-methyl-3-butyne in a glass ampoule carried out according to a method developed in our research group yielded mainly **9** [25]. Following Hlubucek's method [12], **9** as well as the isomer 7-nitroisonoracronycine **10** were obtained.

Scheme 1


NO2
COOCH3
NH2
2
+
OH
HO
OH
3
NO2
COOCH3
OH
N
H
OH
5
i
NO2
COOCH3
NH
CH3
4
NO2
O
H
O
N
H
OH
6
ii
NO2
O
OCH3
N
CH3
OCH3
7
iii
NO2
O
H
O
N
CH3
OH
8
iv
v
NO2
O
H
O
N
CH3
O
CH3
CH3
9
NO2
O
H
O
N
CH3
O
CH3
CH3
10
+
9

The compounds **7**, **8**, and **9** were sent to National Cancer Institute (NCI) for cytostatic activity test on transplantation tumor Leukaemia P388. The results of the test showed no significant activity (**7** (NSC 647750), **8** (NSC 647749) and **9** (no NSC number)).

EXPERIMENTAL

Melting points were determined on a Lofler hot-stage apparatus and were uncorrected. Infrared spectra (ir) were recorded on a Pye Unicam Sp3-200 spectrophotometer. The ^1H and ^{13}C nmr spectra were obtained on a Varian Gemini 200 spectrometer with tetramethylsilane as internal standard. Mass spectra were recorded with a Varian MAT 44S spectrometer. Merck Silica gel 60 F_{254} and Merck Silica gel 60 (70-230 mesh) were used for preparative thin layer chromatography and column chromatography respectively.

To a 5 g (25.5 mmoles) methyl 2-amino-6-nitrobenzoate **2** heated to 195°, was added carefully 15 g (119 mmoles) phloroglucinol **3** over a period of 15 minutes in small portions with stirring. The temperature was then increased to 220° and held at this temperature for 20 minutes. After cooling to room temperature, column chromatography (dichloromethane:methanol 95:5) was used to separate and purify the products. Methyl 2-amino-6-nitrobenzoate (2 g, 10.2 mmoles) was recovered together with methyl 2-*N*-methylamino-6-nitrobenzoate **4**, methyl 2-(3,5-dihydroxyphenylamino)-6-nitrobenzoate **5** and 1,3-dihydroxy-8-nitro-9(10*H*)-acridinone **6**.

Methyl 2-Methylamino-6-nitrobenzoate **4**.

This compound had mp 71-72°; ir (potassium bromide): ν 3400 (NH), 1701 (C=O), 1605, 1563 (C=C), 1514, 1348 (NO), 1180 (COC) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.91 (d, 3H, NCH_3), 3.81 (s, 3H, OCH_3), 6.64 (br s, 1H, N-H), 6.85 (dd, J = 8.9, 1 Hz, 1H, 3-H), 6.94 (dd, J = 7.8, 1 Hz, 1H, 5-H), 7.38 (t, 8.5 Hz, 1H, 4-H); ^{13}C nmr (deuteriochloroform): δ 30.23 ($N-CH_3$), 52.74 (OCH_3), 106.45 (C-1), 110.92 (C-5), 114.97 (C-3), 133.00 (C-4), 150.84 (C-6) , 152.59 (C-2), 167.01 (C=O); ms: m/z 210 (100% M^+), 209 (44, M^+-H), 179 (17, 210-CH_3O), 160 (69), 149 (15, 179-NO), 134 (28, 149-CH_3), 121 (30), 104 (77), 93 (33).

Methyl 2-(3,5-Dihydroxyphenylamino)-6-nitrobenzoate **5**.

This compound had mp 211-213°; ir (potassium bromide): ν 3395 (OH), 3355 (NH), 2950 (CH aliphatic), 1709 (C=O), 1604, 1564 (C=C), 1519, 1340 (NO), 1065, 1030 (COC) cm^{-1}; uv (methanol): λ max (log ϵ) = 379.0 (3.40), 271.5 (4.22), 208.5 (4.43); ^1H nmr (acetone-d_6): δ 3.85 (s, 3H, OCH_3), 6.17 (t, J = 2.1 Hz, 4'-H), 6.23 and 6.24 (each d, each J = 2.1 Hz, each 1H, 2'-H and 6'-H), 7.34 (dd, J = 7.2, 1.7 Hz, 1H, 3-H), 7.51 (dd, J = 8.5, 0.5 Hz, 1H, 5-H), 7.59 (dd, J = 8.5, 1.7 Hz, 1H, 4-H), 7.85 (br s, 1H, NH), 8.52 (br s, 1H, OH); ^{13}C nmr (acetone-d_6): δ 53.47 (OCH_3), 99.77 (C-4'), 101.10 (C-2', C-6'), 113.30 (C-1), 115.25 (C-5), 122.25 (C-3), 133.16 (C-4), 143.70 (C-2), 146.66 (C-6), 152.03 (C-1'), 160.75 (C-3', C-5'), 167.05 (C=O); ms: m/z 304 (100% M^+), 272 (26, M^+-CH_4 O), 255 (10, 272-OH), 244 (37, 272-CO), 230 (44), 227 (83), 199 (59), 186 (22), 170 (44).

Anal. Calcd. for $C_{14}H_{12}N_2O_6 \cdot \frac{1}{2}H_2O$: C, 53.68; H, 4.18; N, 8.94. Found: C, 53.53; H, 4.36; N, 8.84.

1,3-Dihydroxy-8-nitro-9(10*H*)-acridinone **6**.

This compound had mp >345° dec; ir (potassium bromide): ν 3425 (OH), 3315 (NH), 1641 (C=O), 1592 (C=C), 1526, 1329 (NO), 1060 (C=C); uv (methanol): λ max (log ϵ) 398.5 (3.56), 272.5 (4.44), 245.5 (4.33), 225.0 (4.36); ^1H nmr (dimethyl sulfoxide-d_6): δ 6.09 (d, J = 2.1 Hz, 1H, 2-H), 6.38 (d, J = 2.1 Hz, 1H, 4-H), 7.47 (d, J = 7.3 Hz, 1H, 5-H), 7.68 (dd, J = 8.5, 1 Hz, 1H, 7-H), 7.84 (dd, J = 8.5, 7.3 Hz, 1H, 6-H), 12.22 (br s, 1H, NH), 13.41 (s, 1H, 1-OH); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 91.20 (C-2), 96.72 (C-4), 103.63 (C-9a), 108.78 (C-8a), 115.12 (C-7), 119.70 (C-5), 133.41 (C-6), 141.41 (C-5a), 142.77 (C-4a), 148.23 (C-8), 163.20 (C-3), 164.93 (C-1), 176.88 (C-9); ms: m/z 272 (100% M^+), 243 (10, M^+-CHO), 242 (8, 272-NO), 226 (46, 272-NO_2), 214 (10, 243-CHO), 214 (10, 242-CO), 198 (71, 226-CO), 197 (20, 198-H), 186 (6, 214-CO), 159 (40, 186-HCN).

Anal. Calcd. for $C_{13}H_8N_2O_5 \cdot \frac{1}{3}H_2O$: C, 56.12; H, 3.14; N, 10.07. Found: C, 56.36; H, 3.26; N, 10.04.

1,3-Dimethoxy-10-methyl-8-nitro-9(10*H*)-acridinone **7**.

To 1.5 g (5.5 mmoles) 1,3-dihydroxy-8-nitro-9(10*H*)-acridinone **6** and 1.6 g (27 mmoles) of anhydrous potassium carbonate in 150 ml of absolute acetone was added 3 ml (55 mmoles) of methyl iodide in 3 ml of absolute acetone. The reaction mixture was then stirred at room temperature for 6 hours. Removal of acetone and excess methyl iodide *in vacuo* was followed by adding the resulting mixture in 50 ml of water. Filtration and recrystallization from methanol afforded yellow needles of 1,3-dimethoxy-10-methyl-9(10*H*)-acridinone **7**, 1.6 g (93%), mp 264-266°; ir (potassium bromide): ν 3080 (CH aromatic), 2930 (CH aliphatic), 1633 (C=O), 1615 (C=C), 1532, 1321 (NO), 1038 (C=C); uv (methanol): λ max (log ϵ) 404.5 (3.67), 332.0 (3.84), 274.5 (4.59), 251.0 (4.44), 225.0 (4.36); ^1H nmr (deuteriodichloromethane): δ 3.72 (s, 3H, 3-OCH_3), 3.85 (s, 3H, N-CH_3), 3.87 (s, 3H, 1-OCH_3), 6.26 (d, J = 2.1 Hz, 1H, 2-H), 6.36 (d, J = 2.1 Hz, 1H, 4-H), 7.09 (dd, J = 7.3. 1.3 Hz, 1H, 5-H), 7.48 (dd, J = 8.8, 1.3 Hz, 1H, 7-H), 7.58 (dd, J = 8.8, 7.3 Hz, 1H, 6-H); ^{13}C nmr (deuteriodichloromethane): δ 35.20 (N-CH_3), 55.01 (1-OCH_3), 55.56 (3-OCH_3), 90.45 (C-2), 92.56 (C-4), 108.37 (C-9a), 110.02 (C-8a), 115.05 (C-7), 116.75 (C-5), 131.64 (C-6), 142.54 (C-5a), 146.23 (C-4a), 148.74 (C-8), 162.75 (C-3), 164.43 (C-1), 174.84 (C-9); ms: m/z 314 (15% M^+), 297 (60, M^+-OH), 268 (20, 297-CHO), 267 (100, 297-NO), 239 (31, 267-CO), 238 (49, 267-CHO), 210 (11, 239-CHO), 195 (12), 167 (19).

Anal. Calcd. for $C_{16}H_{14}N_2O_5$: C, 61.15; H, 4.42; N, 8.91. Found: C, 61.03; H, 4.38; N, 8.98.

1,3-Dihydroxy-10-methyl-8-nitro-9(10*H*)-acridinone **8**.

To 900 mg (3 mmoles) 1,3-dimethoxy-10-methyl-8-nitro-9(10*H*)-acridinone **7** was added 60 ml of 47% hydrogen bromide and gradually heated to reflux. The reaction mixture was stirred and maintained at reflux for 7 hours. The hydrobromide salt, which crystallized at 0° overnight was stirred for 4 hours in distilled water in order to obtain the free base. Recrystallization from ethanol/water gave brown needles, 650 mg (76%), mp 307-309°; ir (potassium bromide): ν 3425 (OH), 3090 (CH aromatic), 2920 (CH aliphatic), 1634 (C=O), 1591 (C=C), 1522, 1337 (NO), 1234 (C=C) cm^{-1}; uv (methanol): λ max (log ϵ) 398.5 (3.65), 335.5 (3.76), 274.5 (4.54), 250.0 (4.41), 226.0 (4.32); ^1H nmr (dimethylformamide-d_7): δ 3.96 (s, 3H, N-CH_3), 6.27 (d, J = 2 Hz, 1H, 2-H), 6.60 (d, J = 2 Hz, 1H, 4-H), 7.57 (dd, J = 7.5, 1 Hz, 1H, 5-H), 7.98 (dd, J = 9, 1 Hz, 1H, 6-H), 8.12 (dd, J = 9, 7.5 Hz, 1H, 7-H), 14.03 (s, 1H, 1-OH); ^{13}C nmr (dimethylformamide-d_7): δ 35.86 (N-CH_3), 92.84 (C-2), 97.91 (C-4), 105.52 (C-9a), 111.78 (C-8a), 116.74 (C-7), 119.66 (C-5), 134.97 (C-6), 144.25 (C-5a), 146.23

(C-4a), 150.41 (C-8), 166.19 (C-3), 167.25 (C-1), 178.21 (C-9); ms: m/z 286 (100% M^+), 256 (6, M^+-NO), 240 (37, M^+-NO_2), 228 (9, 256-CO), 212 (60, 240-CO), 184 (44, 212-CO), 169 (14, 184-CH_3), 154 (22), 140 (18), 128 (22).

Anal. Calcd. for $C_{14}H_{10}N_2O_5$: C, 58.42; H, 3.50; N, 9.79. Found: C, 58.07; H, 3.60; N, 9.49.

Syntheses of 8-Nitronoracronycine **9** and 7-Nitroisonoracronycine **10**.

Ethanolic potassium hydroxide 0.1 *N* was added to 600 mg (2.1 mmoles) 1,3-dihydroxy-10-methyl-8-nitro-9(10*H*)-acridinone **8** at 60° for 1 hour. Removal of ethanol *in vacuo* gave the reddish-brown potassium salt of 1,3-dihydroxy-10-methyl-8-nitro-9(10*H*)-acridinone.

A) Reaction in a Glass Ampoule.

Anhydrous potassium iodide (320 mg, 2 mmoles), 224 mg of anhydrous potassium carbonate and 200 mg (2.2 mmoles) of 2-chloro-2-methyl-3-butyne were added to 360 mg (1.1 mmoles) of potassium salt of 1,3-dihydroxy-10-methyl-8-nitro-9(10*H*)-acridinone **8** in 10 ml of absolute DMF. The reaction mixture was heated at 120° for 48 hours. After cooling to room temperature, the ampoule was carefully opened and the crude brown product was dissolved in chloroform, washed with 2% sodium hydroxide, brine and water and dried over anhydrous sodium sulfate. Removal of chloroform *in vacuo* followed by pcs (4 x toluene) and recrystallization from chloroform gave red needles of 8-nitronoracronycine **9** in 21% (83 mg) yield.

8-Nitronoracronycine **9**.

This compound had mp 276-278°; ir (potassium bromide): ν 3420 (br OH), 2970 (CH aromatic), 2930 (CH aliphatic), 1620 (C=O), 1597 (C=C), 1536, 1328 (NO), 1264, 1137 (COC) cm^{-1}; uv (methanol): λ max (log ϵ) = 425.5 (3.49), 287.0 (4.50), 206.0 (4.37); ^1H nmr (deuteriochloroform): δ 1.53 (s, 6H, 2 x $-CH_3$), 3.93 (s, 3H, N-CH_3), 5.57 (d, J = 9.75 Hz, 1H, 2-H), 6.31 (s, 1H, 5-H), 6.52 (d, J = 9.75 Hz, 1H, 1-H), 7.26 (dd, J = 7.5, 1 Hz, 1H, 11-H), 7.59 (dd, J = 8.5, 1 Hz, 1H, 9-H), 7.79 (dd, J = 8.5, 7.5 Hz, 1H, 10-H), 13.64 (s, 1H, 6-OH); ^{13}C nmr (deuteriochloroform): δ 27.03 (2 x $-CH_3$), 44.56 (N-CH_3), 75.33 (C-3), 94.86 (C-12b), 99.12 (C-5), 115.31 (C-6a), 116.32 (C-9), 116.96 (C-7a), 118.83 (C-11), 120.72 (C-1), 124.25 (C-2), 133.27 (C-10), 145.49 (C-8), 161.54 (C-12a), 162.13 (C-11a), 164.56 (C-6), 164.83 (C-4a), 179.81 (C-7); ms: m/z 352 (31% M^+), 337 (100, M^+-CH_3), 291 (17, 337-NO_2), 263 (27, 291-CO), 248 (22, 263-CH_3), 220 (8, 248-CO), 191 (15, 220-CHO).

Anal. Calcd. for $C_{19}H_{16}N_2O_5$: C, 64.77; H, 4.55; N, 7.95. Found: C, 64.40; H, 4.49; N, 7.62.

B) Reaction According to Hlubucek.

To 360 mg (1.1 mmoles) of the potassium salt of 1,3-dihydroxy-10-methyl-8-nitro-9(10*H*)-acridinone **8** and 200 mg of 2-chloro-2-methyl-3-butyne in 100 ml of absolute DMF was added 320 mg (2 mmoles) of anhydrous potassium iodide, 224 mg of potassium carbonate and gradually heated to 90° under nitrogen for 12 hours. The work-up procedure was essentially the same as described above, which gave 8-nitronoracronycine **9** (62 mg, 16%) and 7-nitroisonoracronycine **10** (97 mg, 25%).

7-Nitroisonoracronycine **10**.

This compound had mp 285-287°; ir (potassium bromide): ν 3415 (br OH), 2980 (CH aromatic), 2910 (CH aliphatic), 1634 (C=O), 1589 (C=C), 1533, 1322 (NO), 1127 (COC) cm^{-1}; uv (methanol): λ max (log ϵ) 426.5 (3.48), 309.5 (4.60), 260.5 (4.34), 206 (4.28); ^1H nmr (deuteriochloroform): δ 1.48 (s, 6H, 2 x $-CH_3$), 3.81 (s, 3H, N-CH_3), 5.59 (d, J = 10 Hz, 1H, 3-H), 6.30 (s, 1H, 12-H), 6.74 (d, J = 10 Hz, 1H, 4-H), 7.15 (dd, J = 7.3, 1.2 Hz, 1H, 10-H), 7.60 (dd, J = 9, 1.2 Hz, 1H, 8-H), 7.71 (dd, J = 9, 7.3 Hz, 1H, 9-H), 14.04 (s, 1H, 3-OH); ^{13}C nmr (deuteriochloroform): δ 28.52 (2 x $-CH_3$), 35.03 (N-CH_3), 78.71 (C-2), 91.97 (C-12), 103.56 (C-4a), 105.62 (C-5a), 112.34 (C-11a), 115.39 (C-8), 115.63 (C-10), 116.96 (C-4), 127.36 (C-9), 133.13 (C-3), 142.74 (C-6a), 143.72 (C-10a), 149.60 (C-7), 159.42 (C-5), 160.71 (C-12a), 177.31 (C-6); ms: m/z 352 (34% M^+), 337 (100, M^+-CH_3), 291 (31, 337-NO_2), 276 (5, 291-CH_3), 263 (32, 291-CO), 248 (6, 263-CH_3), 220 (8, 248-CO), 191 (5, 220-CHO).

Anal. Calcd. for $C_{19}H_{16}N_2O_5$: C, 64.77; H, 4.55; N, 7.95. Found: C, 64.49; H, 4.61; N, 7.87.

REFERENCES AND NOTES

[1] Part **152**: J. Reisch and S. H. Achenbach, *Phytochemistry*, submitted for publication.

[2] Part of the Ph. D. Thesis, Peter Dziemba, University of Münster.

[3] J. Reisch and P. Dziemba, *Arch. Pharm. (Weinheim)*, **324**, 67 (1991).

[4] J. Reisch and W. Probst, *Arch. Pharm. (Weinheim)*, **322**, 31 (1989).

[5] H.-E. Radunz, *Pharm. Unserer Zeit*, 161 (1988).

[6] L. F. Tietze, *Nachr. Chem. Tech. Lab.*, **36**, 28 (1988).

[7] G. Franz, *Pharm. Unserer Zeit*, 257 (1990).

[8] V. Schirrmacher, Krebs-Tumoren, Zellen, Gene, V. Schirrmacher, ed, Spektrum der Wissenschaft Verlagsgesellschaft mbH & Co, Heidelberg, 1989, p 7.

[9] J. H. Adams, P. M. Brown, P. Gupta, M. S. Khan and J. R. Lewis, *Tetrahedron*, **37**, 209 (1981).

[10] J. R. Beck, R. N. Booher, A. C. Brown, R. Kwok and A. Pohland, *J. Am. Chem. Soc.*, **89**, 3934 (1967).

[11] J. R. Beck, R. Kwok, R. N. Booher, A. C. Brown, L. E. Patterson, P. Pranc, B. Bockey and A. Pohland, *J. Am. Chem. Soc.*, **90**, 4706 (1968).

[12] J. Hlubucek, E. Ritchie and W. C. Taylor, *Aust. J. Chem.*, **23**, 1881 (1970).

[13] F. N. Lahey and R. V. Stick, *Aust. J. Chem.*, **26**, 2311 (1973).

[14] W. M. Bandaranayake, M. J. Begley, B. O. Brown, D. G. Clarke, L. Crombie and D. A. Whiting, *J. Chem. Soc., Perkin Trans. 1*, 109 (1976).

[15] J. H. Adams, P. Gupta and J. R. Lewis, *Chem. Ind. (London)*, 109 (1976).

[16] S. Blechert, K.-E. Fichter and E. Winterfeldt, *Chem. Ber.*, **111**, 43 (1978).

[17] M. Watanabe, A. Kurosaki and S. Furukawa, *Chem. Pharm. Bull.*, **32**, 1264 (1984).

[18] M. H. Bahar and B. K. Sabata, *Indian J. Chem.*, **26B**, 782 (1987).

[19] J. Reisch, A. A. W. Voerste, M. Top and P. Dziemba, *Monatsh. Chem.*, in press.

[20] D. Gröger, Biosynthese der Alkaloide, K. Mothers and H. R. Schütte, eds, VEB Deutscher Verlag der Wissenschaften, Berlin (DDR), 1968, p 564.

[21] J. Reisch and S. M. El-Moghazy Aly, *Arch. Pharm. (Weinheim)*, **319**, 25 (1986).

[22] Peter Dziemba, M. Sc Thesis, University of Münster, 1989.

[23] L. Claison and O. Eilers, *Liebigs Ann. Chem.*, **401**, 29 (1913).

[24] H. Brockmann, H. Muxfeld and G. Haese, *Chem. Ber.*, **90**, 44 (1957).

[25] J. Reisch, I. Mester and S. M. El-Moghazy Aly, *Liebigs Ann. Chem.*, 31 (1984).