Simple Synthesis of Mono- and Bismethyl Ethers of Purpurin (1,2,4-Trihydroxyanthraquinone)

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All possible isomers of mono- and bismethyl ethers of purpurin (1,2,4-trihydroxyanthraquinone) were synthesized starting from purpurin.

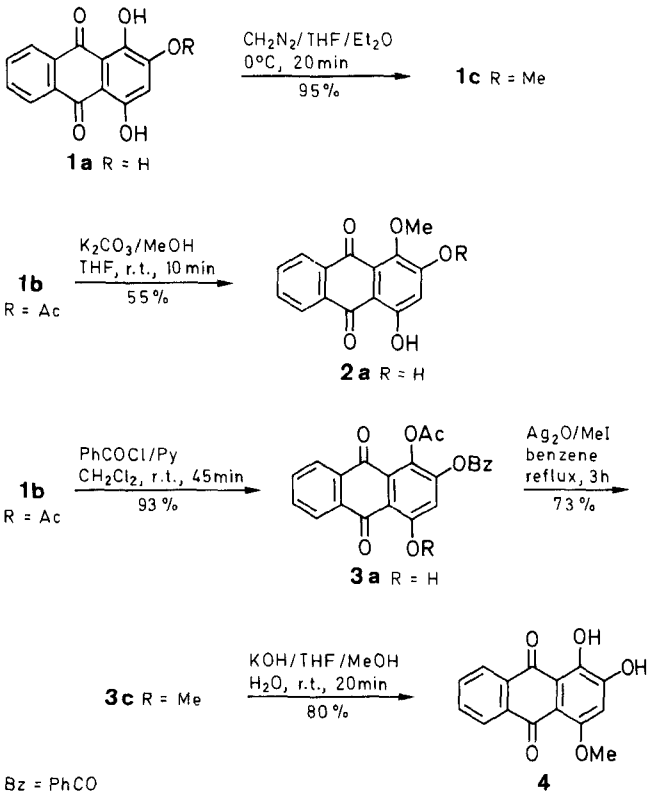
During the course of our work on the chemistry[1,2] and the synthesis[3] of the *C*-glucoside carminic acid by *C*-glucosidation of an appropriate anthraquinone moiety, we have found some unusual reactions of purpurin (1,2,4-trihydroxyanthraquinone, **1a**), which allowed us to obtain in a simple way its mono- **1c, 2a, 4**, (Scheme **1**) and bismethyl ethers **2c, 5a, 6a**, (Scheme **2**).

The results are of interest since two of these simple derivatives of purpurin (**2c**, and **4**) are not reported, and seem difficult to obtain otherwise, two (**2a** and **6a**) have been obtained by total synthesis involving ketene acetals,[4,5] and only two (**1c**, and **5a**) have been obtained from purpurin in two or three steps.[6]

The results reported in the Schemes **1** and **2** show that the derivative **1c** can be prepared directly from purpurin, while the products **2a, 4, 2c, 5a**, and **6a** are all obtained starting from 2-*O*-acetylpurpurin (**1b**)[6] involving some unexpected reactions.

As evident from Scheme **1**, the first unexpected reaction occurred during the treatment of the monoacetate **1b** with potassium carbonate in methanol as normally used for the mild saponification of esters. In this case, during the saponification of the acetyl group, the methylation of the adjacent hydroxy group takes place with the formation of the monomethyl ether **2a**. Treatment of **2a** with diazomethane, gives the bismethyl derivative **2c** (Scheme **2**). The mechanism of the unusual methylation of **1b** was not investigated, however, the evidence that by a similar treatment purpurin was recovered unchanged suggested the involvement of the 2-acetate of **1b** in the methylation of the 1-hydroxy group.

The second unusual result was observed in the reaction of **1b** with methyl iodide and potassium carbonate (Scheme **2**), under the usual conditions for the methylation of phenolic groups. In this case the migration of the acetyl group from the position 2 to the position 1 is accompanied by the quantitative methylation of the 2- and 4-hydroxy groups.[7]



Scheme 1

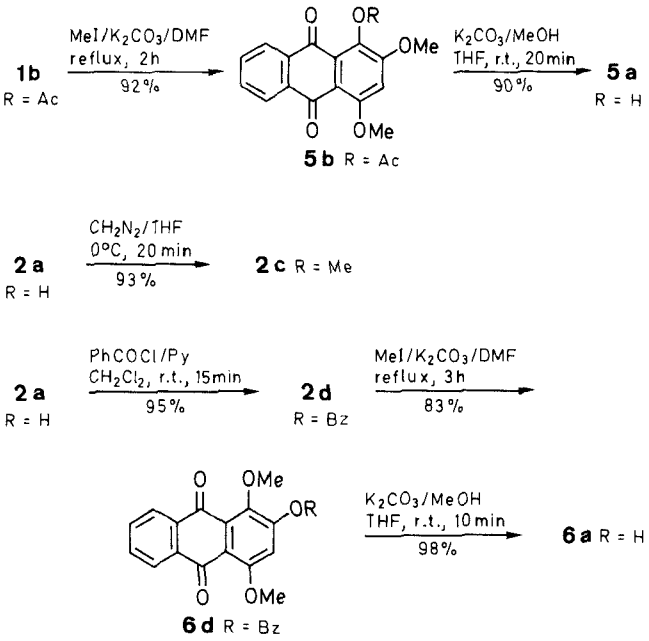
A third reaction affording unusual results, that, however, has a precedent in the alizarin chemistry,[6] was observed in the treatment of **1b** with benzoyl chloride and pyridine, under conditions of usual benzoylation (Scheme **1**). In fact, the migration of the acetyl group from the position 2 to the position 1 occurs, probably under the influence of pyridine, and the benzoyl group enters the place of the acetate to give only (^{1}H-NMR of the crude product of the reaction) the 1-*O*-acetyl-2-*O*-benzoylpurpurine (**3a**), which by methylation and saponification affords the 4-*O*-methylpurpurin (**4**) (Scheme **1**).

The structures of the methyl ethers obtained **1c, 2a, 5a**, and **6a** were assigned on the basis of their physico-

Table 1. Compounds Involved in the Synthesis of Monomethyl Ethers of Purpurin (**1a**)

Product	Yield (%)	mp (°C) (MeOH)	Molecular Formula[a] or Lit. mp (°C)	IR ($CHCl_3$) ν (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS) δ	MS (70 eV) *m/z* (%)
1b	70	170–172	179–180[6]	1780, 1760, 1630	2.38 (s, 3H, $COCH_3$), 7.08 (s, 1H, H-3), 12.90 (s, 1H, OH-1 or OH-4), 12.98 (s, 1H, OH-4 or OH-1)	298 (M^+, 5), 256 (100)
1c	95	232–234	232–233[6]	1620	3.98 (s, 3H, OCH_3), 6.70 (s, 1H, H-3), 13.43 (s, 1H, OH-1 or OH-4), 13.53 (s, 1H, OH-4 or OH-1)	270 (M^+, 100), 241 (12), 227 (18), 210 (1)
2a	55	224–225	230[4] 219–221[5]	1670, 1630	3.96 (s, 3H, OCH_3), 6.84 (s, 2H, OH-2, H-3), 13.50 (s, 1H, OH-4)	270 (M^+, 100), 241 (25), 227 (60), 210 (46)
3a	93	174–176	$C_{23}H_{14}O_7$ (402.4)	1770, 1750, 1675, 1640	2.33 (s, 3H, $COCH_3$), 7.34 (s, 1H, H-3), 13.20 (s, 1H, OH-4)	402 (M^+, 2), 105 (100)
3c	73	197–199	$C_{24}H_{16}O_7$ (416.4)	1765, 1740, 1670	2.35 (s, 3H, $COCH_3$), 4.09 (s, 3H, OCH_3), 7.40 (s, 1H, H-3)	416 (M^+, 2), 105 (100)
4	80	235–238	$C_{15}H_{10}O_5$ (270.24)	1675, 1630	3.85 (s, 3H, OCH_3), 7.00 (s, 1H, H-3)[b]	270 (M^+, 90), 241 (100), 227 (11), 210 (0)

[a] Satisfactory microanalyses obtained: C ±0.4, H ±0.4.
[b] In DMSO-d_6.



Scheme 2

chemical properties, which altogether are diagnostic and identical to that shown by the same compounds prepared by different routes.[4,6]

The structure of the unreported compound **2c** was derived from the analysis of its IR and ^{1}H-NMR spectra and from its easy preparation by treatment of **2a** with diazomethane; that of the monomethyl derivative **4** was in agreement with spectral data and was confirmed by transformation of **4** into the bismethyl derivative **5a** by diazomethane. Some differences observed in the mass spectrometry analysis, summarized in Tables 1 and 2, are of interest for possible identification of small amounts of these methyl ethers of purpurin in biological sources. In fact, some of them are present in very small amounts in many species of the *Rubiacea* family[8] and in callus cultures of *Cinchona ledgeriana*[9] where, in some cases,[8,9] their identification was proved incorrect.[4] Our results confirm their incorrect identification and clarify other literature discrepancies.[7]

All reagents were of commercial quality from freshly opened containers. Reagent quality solvents were used without further purification. 1-*O*-Acetylpurpurin (**1b**) was prepared according to literature.[6]

Melting points were determined on a Büchi melting point apparatus. Mass spectra were obtained using a Hewlett-Packard 5890 spectrometer (direct inlet). IR spectra were obtained using a Perkin-Elmer 1420 spectrophotometer. ^{1}H-NMR spectra were obtained using a Bruker AM-500 spectrometer.

Methylation of Purpurin and Derivatives; General Procedures:

With CH_2N_2, for compounds **1a,2a**: A solution of **1a** or **2a** (10 mmol) in THF (60 mL) is treated with ethereal diazomethane (25 mmol) at 0°C. After 20 min, the excess of diazomethane is destroyed by AcOH (0.9 mL) and the solvent is evaporated under reduced pressure. Crystallization of the residue from MeOH gives **1c**; yield: 95%, or **2c**; yield: 93%.

With K_2CO_3,MeOH/THF, for compound **1b**: To a solution of the anthraquinone **1b** (2.98 g, 10 mmol) in THF (350 mL) is added a hot suspension of K_2CO_3 (70 mmol) in MeOH (350 mL) and the mixture is kept at r.t. for 10 min. The mixture is acidified with 4 N HCl (36 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The organic layers are washed with water, dried (Na_2SO_4), and evaporated. The residue is chromatographed on silica gel (eluent: CH_2Cl_2/EtOAc, 8/2), to afford **2a**; yield: 1.5 g (55%).

With K_2CO_3/MeI/DMF, for compounds **1b,2d**: To a stirred solution of **1b** or **2d** (10 mmol) in DMF (100 mL) are added K_2CO_3 (30 mmol) and MeI (80 mmol). The mixture is refluxed for 2 h or 3 h, cooled and acidified with 4 N HCl (16 mL). Evaporation of the solvent affords a residue which is extracted with CH_2Cl_2 (3 × 50 mL). The combined CH_2Cl_2 layers are washed with water, dried (Na_2SO_4) and evaporated to afford the bismethylated anthraquinones **5b**; yield: 92%, or **6d** yield: 83%.

With Ag_2O/MeI for compound **3a**: To a stirred solution of **3a** (4.02 g, 10 mmol) in benzene (100 mL) are added Ag_2O (30 mmol) and MeI (80 mmol) and the mixture is refluxed for 3 h. The mixture is filtered on a pad of Celite and the solvent evaporated to afford **3c**; yield: 3.04 g (73%).

2-*O*-Benzoyl-1-*O*-methylpurpurin (2d) and 1-*O*-Acetyl-2-*O*-benzoylpurpurin (3a):

To a solution of the anthraquinone **2a** or **1b** (10 mmol) in CH_2Cl_2 (100 mL) containing benzoyl chloride (2.11 g, 15 mmol), is added

Table 2. Compounds Involved in the Synthesis of Bismethyl Ethers of Purpurin (**1a**)

Product	Yield (%)	mp (°C) (solvent)	Molecular Formula[a] or Lit. mp (°C)	IR ($CHCl_3$) ν (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS) δ	MS (70 eV) *m/z* (%)
2c	93	202–203 (MeOH)	$C_{16}H_{12}O_5$ (284.3)	1670, 1630	3.92 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 6.72 (s, 1H, H-3), 13.62 (s, 1H, OH-4)	284 (M^+, 100), 269 (20), 255 (71), 170 (10)
2d	95	154–155 (*i*-Pr_2O/CH_2Cl_2)	$C_{22}H_{14}O_6$ (374.4)	1748, 1675, 1640	3.88 (s, 3H, OCH_3), 7.22 (s, 1H, H-3), 13.24 (s, 1H, OH-4)	374 (M^+, 2), 105 (100)
5a	90	187–200 (MeOH)	186–189[6]	1660, 1640	3.99 (s, 6H, OCH_3), 6.79 (s, 1H, H-3), 13.50 (s, 1H, OH-1)	284 (M^+, 100), 269 (5), 255 (74), 170 (28)
5b	92	187–189 (EtOH)	189–190[6]	1760, 1670	2.44 (s, 3H, $COCH_3$), 3.93 (s, 3H, OCH_3), 4.01 (s, 3H, OCH_3), 6.82 (s, 1H, H-3)	326 (M^+, 4), 284 (100)
6a	98	227–229 (MeOH)	229.5[4]	1670	3.96 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 6.77 (s, 1H, OH-2), 6.95 (s, 1H, H-3)	284 (M^+, 100), 269 (8), 255 (19), 170 (17)
6d	83	175–177 (*i*-Pr_2O/CH_2Cl_2)	$C_{23}H_{16}O_6$ (388.4)	1740, 1670	3.90 (s, 3H, OCH_3), 4.00 (s, 3H, OCH_3), 7.25 (s, 1H, H-3)	388 (M^+, 3), 105 (100)

[a] Satisfactory microanalyses obtained: C ±0.4, H ±0.4.

dropwise pyridine (3 mL). After the appropriate time (0.25 h for **2a** and 0.75 h for **1b**) the solvent is evaporated and the residue triturated with MeOH (100 mL) to afford a crystalline product: **2d**; yield: 95%, or **3a**; yield: 93%.

2,4-Di-*O*-Methylpurpurin (5a) and 1,4-Di-*O*-methylpurpurin (6a):
Compounds **5b** and **6d** (10 mmol) are hydrolysed under the same conditions described above for the methylation of **1b**. However, at the end of the saponification the recovery of **5a** in 90% yield requires the heating of the acidified mixture for 10 min. Compound **6a** is obtained in 98% yield.

4-*O*-Methylpurpurin (4):
A solution of the ester **3c** (4.16 g, 10 mmol) in THF (250 mL) and MeOH (3 mL) is stirred with 1 M aq KOH (50 mL) at r.t. for 20 min. The solution is acidified with 2 N aq HCl (26 mL) and concentrated under reduced pressure to 100 mL. The product is filtered and washed with water; yield: 2.16 g (80%).

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(5) Purpurin 1-methyl ether (**2a**) was also obtained, with some difficulty (in 0.1% yield) by converting purpurin into its 2-benzyl ether, followed by partial methylation with MeI/Ag_2O, and debenzylation:
Brew, E.J.C.; Thomson, R.H. *J. Chem. Soc.* **1971**, 2001.
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(7) The migration of the acyl group from the 2 to the 1 position of partly acylated polyhydroxyanthraquinones by action of diazomethane is well documented,[6] however, no report concerning a similar migration under methylation with MeI is reported. We have found that, in one cases, this reaction occured unnoticed by the authors, during the treatment of 2,4-di-*O*-acetylpurpurin with MeI/Ag_2O to afford 1,4-di-*O*-acetyl-2-*O*-methylpurpurin in place of the 2,4-di-*O*-acetyl-1-*O*-methylpurpurin reported:
Hirose, Y. *Chem. Pharm. Bull.* **1960**, *8*, 417.
The same methylation in our hands afforded a mixture (80:20) of 1,4-di-*O*-acetyl-2-*O*-methylpurpurin [(mp 202–204°C, Lit.[7] mp 170–172°C; ^{1}H-NMR ($CDCl_3$/ TMS): δ = 2.47 (s, 3H, $COCH_3$), 2.48 (s, 3H, $COCH_3$), 3.96 (s, 3H, OCH_3), 6.93 (s, 1H, H-3), 7.67–7.74 (m, 2H, H-6, H-7), 8.11–8.17 (m, 2H, H-5, H-8)] and 2,4-di-*O*-acetyl-1-*O*-methylthylpurpurine; [(mp 174–176°C, Lit.[7] mp 202–204°C; ^{1}H-NMR ($CDCl_3$/TMS): δ = 2.37 (s, 3H, $COCH_3$), 2.45 (s, 3H, $COCH_3$), 3.95 (s, 3H, OCH_3), 7.20 (s, 1H, H-3), 7.70–7.75 (m, 2H, H-6, H-7), 8.13 (dd, 1H, J = 6.3 Hz, H-5 or H-8), 8.17 (dd, 1H, J = 6.3 Hz, H-8 or H-5)]. Both compounds are identical to that obtained by the acetylation of 1- and 2-*O*-methylpurpurine.
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