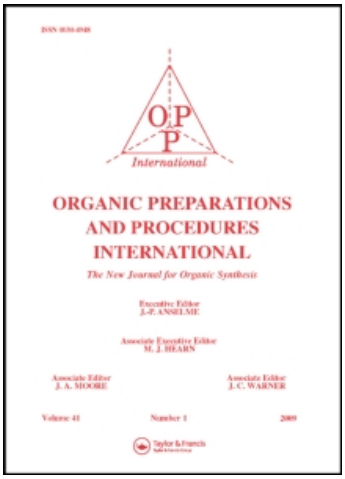


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

STUDIES IN THE SYNTHESIS OF HALOGENATED ANTHRAQUINONES. I. A CONVENIENT PREPARATION OF 1,4-DICHLORO-5-HYDROXY-9,10-ANTHRACENEDIONE

Judith L. Johnson[a]; H. D. Hollis Showalter[a]
[a] Chemistry Department, Warner-Lambert/Parke-Davis Pharmaceutical Research, Ann Arbor, MI

To cite this Article Johnson, Judith L. and Showalter, H. D. Hollis(1984) 'STUDIES IN THE SYNTHESIS OF HALOGENATED ANTHRAQUINONES. I. A CONVENIENT PREPARATION OF 1,4-DICHLORO-5-HYDROXY-9,10-ANTHRACENEDIONE', Organic Preparations and Procedures International, 16: 2, 85 — 89
To link to this Article: DOI: 10.1080/00304948409356170
URL: http://dx.doi.org/10.1080/00304948409356170

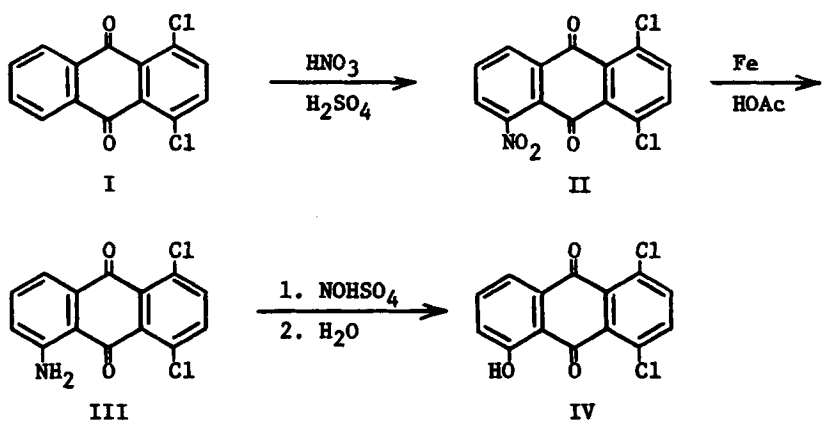
ORGANIC PREPARATIONS AND PROCEDURES INT. 16(2), 85-89 (1984)

STUDIES IN THE SYNTHESIS OF HALOGENATED ANTHRAQUINONES. I. A CONVENIENT PREPARATION OF 1,4-DICHLORO-5-HYDROXY-9,10-ANTHRACENEDIONE

Judith L. Johnson* and H. D. Hollis Showalter

Chemistry Department, Warner-Lambert/Parke-Davis
Pharmaceutical Research, Ann Arbor, MI 48105

During the course of some investigations into the synthesis of 1,4-dihalo-9,10-anthracenediones, substantial quantities of 1,4-dichloro-5-hydroxy-9,10-anthracenedione (IV) were needed. Existing methods[1-3] for the synthesis of IV involve controlled chlorination of inexpensive, commercially available 1-amino-9,10-anthracenedione followed by diazotization and hydrolysis. Unfortunately, after trying several of the described chlorination procedures we were unable to synthesize 5-amino-1,4-dichloro-9,10-anthracenedione (III) of sufficient purity for further use. Described herein is a convenient, high-yielding procedure from readily available 1,4-dichloro-9,10-anthracenedione (I)[4] to multigram quantities of IV (Scheme).



I II III IV

Nitration of 1,4-dichloro-9,10-anthracenedione (I) by a slight modification of a known procedure[5] gave 1,4-dichloro-5-nitro-9,10-anthracenedione (II) in 79% yield. The regiochemistry of nitration, previously determined by transformation of II to known derivatives, was confirmed by 200 MHz ^{1}HNMR. In an attempt to abbreviate the overall sequence, we subjected commercially available 1-nitro-9,10-anthracenedione to controlled chlorination as described in the patent literature.[2] However, in our hands II was obtained only in very poor yield and of low purity.

Reduction of nitro compound II to amino derivative III was attempted initially by the previously described procedure utilizing Sn/AcOH[5] or by $NaBH_4$/10% aq THF.[6] Both procedures proved unsatisfactory with the former giving product of poor purity and the latter various intractable side products. However, reduction with iron filings in refluxing AcOH by a recently described procedure for the reduction of nitroarenes[7] provided III in high yield (94%) and of excellent purity. Conversion of III to target product IV was then carried out by a simple adaptation of the literature procedure.[1] Instead of the traditional method of generating nitrosylsulfuric acid in situ for the diazotization of III, commercially available 40% nitrosylsulfuric acid in sulfuric acid was utilized to give the desired product in 95% yield following hydrolysis.

In summary, the sequence in the Scheme can be carried out without chromatography in a 70% overall yield, and is easily adapted to large-scale operations. The utilization of IV for the synthesis of biologically active molecules will be described in due course.

EXPERIMENTAL

Melting points were taken on a Thomas-Hoover Unimelt capillary melting point apparatus and are uncorrected. Infrared (IR) spectra were determined on a Nicolet FT-3600 instrument. ^{1}H nuclear magnetic resonance (^{1}H NMR) spectra were recorded at 200 MHz on a Varian XL-200 instrument.

Chemical shifts are reported as δ units downfield from internal tetramethylsilane on samples of ca. 1% w/v. Combustion analyses were performed on a Perkin-Elmer 240 elemental analyzer.

1,4-Dichloro-5-nitro-9,10-anthracenedione (II).- A mixture of 293.6 g (1.06 mol) of 1,4-dichloro-9,10-anthracenedione,[4] 2.12 ℓ of 90% HNO_3, and 53 ml of 20% oleum was placed into a 5 ℓ three-neck round bottom flask equipped with a motorized stirrer and an efficient condensor connected to a gas scrubber. After heating over a steam bath for 30 min, the mixture was cooled, then poured carefully into 6 ℓ of ice water. The collected solids were washed well with water, and dried at 50° (200 mm) to leave 326 g of crude product. Crystallization from 11 ℓ of toluene afforded 222.5 g (65%) of analytically pure product as a yellow solid, mp. 253-255°, lit.[1,5] mp. 247-256° and 238°.

^1H NMR ($CDCl_3$): δ 7.70 (s, 2, H-2,3), 7.84-7.97 (m, 2, H-7,8), 8.38 (dd, 1, $J_{6,7}$ = 7.2 Hz, $J_{6,8}$ = 1.9 Hz, H-6); IR (KBr): 1684, 1545, 1305, 1248 cm^{-1}.

Anal. Calcd for $C_{14}H_5Cl_2NO_4$: C, 52.21; H, 1.56; N, 4.35, Cl, 22.01

Found: C, 51.95; H, 1.67; N, 4.33; Cl, 22.31

The filtrate was reduced to 1 ℓ, then cooled for 3 days. The collected solids were recrystallized from 800 ml of toluene to afford 48 g (14%) of additional product, mp. 245° (dec.), containing a small amount of higher R_f impurity.

5-Amino-1,4-dichloro-9,10-anthracenedione (III).- A mixture of 125 g (388 mmol) of 1,4-dichloro-5-nitro-9,10-anthracenedione (II), 80 g (1.43 mole) of iron filings (40 mesh), and 3.1 ℓ of glacial AcOH was stirred at reflux for 6 hr. The hot solution was filtered through Celite and the Celite pad was washed with 300 ml of hot AcOH. The filtrate was diluted with 800 ml of H_2O, then allowed to crystallize at 5° overnight. The precipitated solids were collected by filtration, washed with H_2O

and then 2-propanol, and dried overnight at 50° (200 mm) to leave 100 g (88%) of pure product as a deep red-brown solid, mp. 207-208°. Crystallization of a small portion from AcOH gave an analytical sample, mp. 212-214°, lit.[2,5] mp. 209-214° and 199°.

^{1}H NMR ($CDCl_3$): δ 6.61 (br s, exchanges D_2O, 2, NH), 6.94 (dd, 1, $J_{6,7}$ = 6.9 Hz, $J_{6,8}$ = 2.6 Hz, H-6); 7.41-7.49 (m, 2, H-7,8), 7.58 (d, 1, $J_{2,3}$ = 8.7 Hz, H-3), 7.64 (d, 1, $J_{2,3}$ = 8.7 Hz, H-2); IR (KBr): 3458, 3337, 1668, 1641, 1610, 1546, 1300, 1243 cm^{-1}.

Anal. Calcd for $C_{14}H_7Cl_2NO_2$: C, 57.56; H, 2.42; N, 4.80, Cl, 24.27

Found: C, 57.34; H, 2.54; N, 4.82; Cl, 24.55

The filtrate was diluted with additional H_2O to precipitate 6.6 g (6%) of a second crop, mp 160-178°.

1,4-Dichloro-5-hydroxy-9,10-anthracenedione (IV).- A mixture of 180 g (616 mmol) of 5-amino-1,4-dichloro-9,10-anthracenedione (III), and 1.8 ℓ of conc. H_2SO_4 was placed into a 5 ℓ three-neck round bottom flask equipped with a motorized stirrer, a dropping funnel, and an efficient condenser connected to a gas scrubber. The solution was maintained below 30° during dropwise addition of 142 ml (850 mmol) of nitrosylsulfuric acid (Dupont, 40% in 87% H_2SO_4) over 30 min followed by dropwise addition (two drops/sec) of 450 ml of H_2O during which the temperature was maintained at 30-40°. The mixture was stirred at 35-37° for 40 min, then treated dropwise with 465 ml of H_2O. During the addition the temperature rose to 70°. The mixture was brought to 125° over 1 hr, maintained there for 1 hr, then allowed to cool to 25° overnight. The collected solids were washed to neutrality with H_2O and dried at 60° (200 mm) for 3 days to give 172.1 g (95%) of analytically pure product as a deep orange solid, mp. 224-226°, lit.[1] mp. 229°.

^{1}H NMR ($CDCl_3$): δ 7.30 (dd, 1, $J_{6,7}$ = 7.8 Hz, $J_{6,8}$ = 1.6 Hz, H-6), 7.69 (s, 2, H-2,3) overlapping 7.63-7.77 (m, 2, H-7,8), 12.18 (br s, exchanges D_2O, 1, OH); IR (KBr): 1670, 1635, 1455, 1305, 760 cm^{-1}.

Anal. Calcd for $C_{14}H_6Cl_2O_3$: C, 57.36; H, 2.06; Cl, 24.19

Found: C, 57.18; H, 2.38; Cl, 24.44

Acknowledgement.- We thank the WL/PD analytical staff for the acquisition of spectral and combustion data and Ms. Jean Hoftiezer for scale-up syntheses.

REFERENCES

1. W. Hohmann, British Patent 1029448 (1966); CA 65:10707c.

2. H. Vollmann, W. Hohmann, and F. Baumann, British Patent 1033773 (1966); CA 65:9065e.

3. O. Bayer, "Methoden Der Organischen Chemie", Houben-Weyl, 4th Edit., Vol. 7, Pt. 3, p. 187, G. Thieme, Stuttgart, 1979.

4. Synthesized by a patent procedure [M. Grelat, US Patent 3703533 (1972); CA 72:122929s] in 55% overall yield by PCl_5 chlorination of commercially available 1,4,9,10-anthracenetetrol (leucoquinizarin) followed by 1-pentanol solvolysis of the derived 1,4,9,9,10,10-hexachloro-9,10-dihydroanthracene to I.

5. G. M. Walsh and C. Weizmann, J. Chem. Soc., 97, 685 (1910).

6. J. O. Morley, Synthesis, 528 (1976).

7. D. C. Owsley and J. J. Bloomfield, ibid., 118 (1977).

(Received December 12, 1983; in revised form February 23, 1984)