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AN IMPROVED PROCEDURE FOR THE PREPARATION OF 4,5-DINITROCHRYSAZIN

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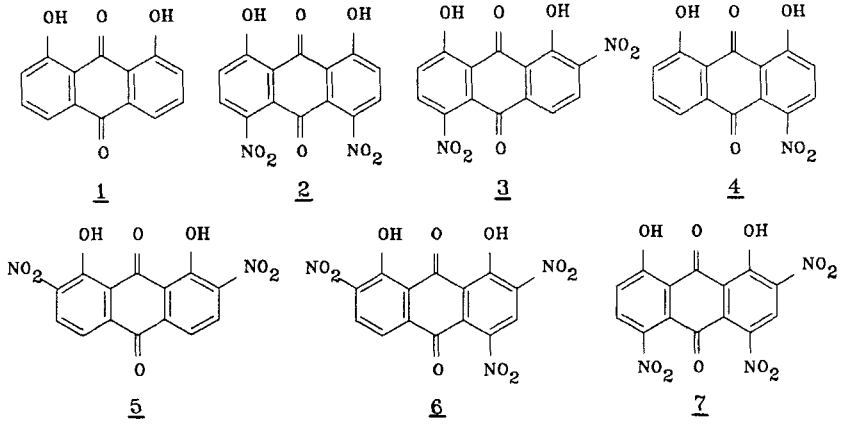
ABSTRACT: Pure 4,5-dinitrochrysazin was prepared by selective nitration of chrysazin, followed by solvent extraction of impurities. This method is suitable for scaling without need of chromatography, and represents a significant improvement over literature methods.

INTRODUCTION

Nitroanthraquinones are important for the synthesis of various dyestuff intermediates, especially, aminoanthraquinones[1]. As an earlier attempt of this laboratory to prepare anticancer anthraquinones, 4,5-dinitrochrysazin (**2**, 1,8-dihydroxy-4,5-dinitroanthraquinone) was prepared as a key intermediate for the synthesis of mitoxantrone[2]. **2** is prepared by nitration of 1,8-dimethoxyanthraquinone followed by acidic cleavage of the methyl groups[3], or directly by nitration of chrysazin (**1**, 1,8-dihydroxyanthraquinone)[4]. The latter procedure is preferred. However, direct nitration results in a mixture of isomers including **2**, **3**, 2,7-dinitrochrysazin (**4**), 2,4,7-trinitrochrysazin (**5**), 2,4,5-trinitrochrysazin (**6**) and 1-nitrochrysazin (**7**)[4] (Scheme 1). Practical methods of purification are not reported.

SCHEME 1



Because of demand highly purified 4,5-dinitrochrysazin in pharmaceutical synthesis, selective nitration and purification methods were studied extensively in this laboratory. This paper describes (1) an efficient procedure with increasing regioselectivity during nitration of chrysazin, and (2) solvent extraction for further purification of the product. This procedure affords high-purity 4,5-dinitrochrysazin with improved yield, and can be applied on large scale. The characteristic IR spectrum of pure 4,5-dinitrochrysazin is discussed.

RESULTS AND DISCUSSION

Direct nitration of chrysazin according to a classical procedure[5], including addition of phosphoric acid[6], resulted in so many regioisomers with unreacted **1** that the desired dinitrochrysazin (**2**) could not be identified. Of other nitrating systems[7], such as nitronium tetrafluoroborate, N-nitropyridinium tetrafluoroborate, isopropyl nitrate-borontrifluoride and trifluoroacetyl nitrate examined. None was a remedy to this problem.

Table 1. Effect of change in mole ratio of fuming nitric acid and sulfuric acid on nitration of chrysazin in different solvents.

HNO_3/H_2SO_4 Mole ratio*	Solvent	Temperature °C	Products 1	2	3§
2 : 3	CCl_4#	reflux	70%	10%	20%
2 : 3	CH_3COOH#	reflux	60%	10%	30%
2 : 2	H_2SO_4#	25	20%	30%	50%
2 : 2	"	60	10%	20%	70%
2 : 2	H_2SO_4	25	10%	40%	50%
2 : 2	"	60	5%	40%	55%
3 : 3	"	25	10%	50%	40%
1.9 : 3.7	10% oleum	25	5%	60%	35%[4a]
2 : 2	"	25		60%	40%
3 : 3	"	25		60%	40%
2 : 2	20% oleum	25		65%	35%
2 : 3	"	25		70%	30%
2 : 4	"	25		65%	35%
2.6 : 4	"	25		65%	35%
3 : 3	"	25		70%	30%
4 : 4	"	25		60%	40%
2 : 3	35% oleum	25		70%	30%
3 : 3	"	25		65%	35%
3 : 3	"	5		65%	35%

* The molar ratio of chrysazin/boric acid was 1 : 1 except entries 1 ~ 4 in which boric acid was not added (#).

§ Including compound **3** and the other products.

However, when fuming nitric acid was used, instead of nitric acid, and boric acid was added to the reaction[4], nitration was greatly facilitated within 1 h at room temperature. Compounds **2** and **3** were produced primarily in a ratio 5 : 4 [4]. At this point, it was decided to optimize conditions for selective nitration of chrysazin at room temperature.

After numerous efforts it was found that altering the molar ratio of nitrating reagent and the reaction solvent had an effect on the selective

Table 2. Effect of change in mole ratio of boric acid on nitration of chrysazin in 20 % oleum, fuming HNO_3/H_2SO_4 = 2 : 3.

Boric acid Mole ratio	Time h	Temperature °C	Products 2	Products 3§
1	1	25	70%	30%
1	0.6	60	60%	40%
2	1	25	80%	20%
2.2	1	25	85%	15%
2.2	1.5	5	85%	15%
2.5	1	25	85%	15%
3	1.3	25	80%	20%

§ Including compound **3** and the other products.

preparation of **2**; the results are summarized in Table 1. The best molar ratio of chrysazin / fuming nitric acid / sulfuric acid was 1 : 2 : 3 with 20% oleum as the solvent (**2**, 70%, **3** and others, 30%). In the absence of oleum the selectivity of the preparation of **2** was lost 15%.

The effect of change in molar ratio of boric acid and the effect of temperature on the best reaction conditions were evaluated under a fixed nitration mixture with 20% oleum as the solvent. According to the results summarized in Table 2, the best molar ratio for chrysazin/boric acid was 1 : 2.2 (**2**, 85%), and the reaction conditions maintained below 25 °C were favored to yield **2**. These results clearly indicate a remarkable effect of the exact molar ratio of boric acid, fuming nitric acid and oleum in the selective preparation of **2**.

Although the present method provided **2** as the predominant product in the reaction mixture, the solubility of the product led to tedious purification, and constituted a limitation on large-scale preparation. However, it

was found that most by-products were washed away by 90% sulfuric acid. The remaining impurities in **2** were separated by extraction with a solvent system containing ethanol/benzene/ DMF, which was discovered during the effort to recrystallize **2**. In this way, the resultant product was washed thoroughly with acid, followed by the solvent extraction. After that, pure 4,5-dinitrochrysazin (>99%) was yielded. It should be noted that throwing the product into ice water upon reaction–the classical procedure–causes failure in selective preparation of **2**.

Structures of synthetic products were assigned on the basis of instrumental analysis, and data are presented in the experimental section. Yields were based on materials isolated or TLC. Crude **2** provided an IR spectrum fully in agreement with that reported in the literature[8]. Nevertheless, 4,5-dinitrochrysazin synthesized according to the present method created significant variations in absorption in the region 650 - 900 cm^{-1}, and minor variations elsewhere[9]. This fact may be attributed to interference by impurity in a small proportion, such as 2,5-dinitrochrysazin, remaining in the crude product. The absorption pattern at small wavenumber was of little use to determine the nature of nitro-group substitution, but it would be useful to identify the purity of 4,5-dinitrochrysazin (**2**).

EXPERIMENTAL

Preparation of 4,5-dinitrochrysazin (**2**)

Chrysazin (**1**, Aldrich) (52 g, 0.217 mol) was slowly added to an agitated solution of boric acid (30 g, 0.485 mol) in 20% oleum (600 g). A mixed acid (93 g, containing 31% by weight nitric acid, i.e. 29 g, 0.460 mol) was added dropwise into the reaction mixture over l h. The reaction temperature was controlled by an ice bath and not allowed to exceed 25 °C

during the addition, while the color changed from purple to dark brown. Reaction was quenched with water (105 mL). The resulting suspension was filtered through a glass sinter, and the filtered cake washed with 90% sulfuric acid (~250 mL) until the washings became pale yellow. The residue was washed free from acid with water and dried. Then, the golden-yellow product was added into a mixed solvent (2.5 L) containing EtOH/C_6H_6/DMF (25:5:1), and heated under reflux for 2 h with stirring. The product was filtered off and dried to give 4,5-dinitrochrysazin (54 g, 76 %), m.p.> 300 °C (Lit.[9] 296 - 297 °C); R_f 0.47, Silica gel G, $CHCl_3$/ $(CH_3)_2CO$/CH_3OH(40:2:1); ^{1}H-NMR ($CDCl_3$, 100 MHz): δ(ppm) 12.02 (2H, s, peri- OH), 7.86 (2H, d, H-3 & -6, J = 9.2 Hz), 7.47 (2H, d, H-2 & -7, J = 9.2 Hz); IR (KBr, cm^{-1}): 1681, 1630, 1549, 1442, 1370, 1260, 1177, 1101, 851 (Ar-N), 804, 787, 764, 730, 673; MS (EI, m/z): 330 (M^+, 100%), 228, 200, 150, 106, 89, 57.

Analysis: $C_{14}H_6N_2O_8$: Calcd.: C, 50.9; H, 1.8; N, 8.5

Found : C, 50.8; H, 1.9; N, 8.4

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