Preparation of 7-Ethoxy-3-hydroxy-6-methoxy-1-methyl-4-nitroisoquinoline

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This paper reports the large scale preparation of 7-ethoxy-3-hydroxy-6-methoxy-1-methyl-4-nitroisoquinoline (RWJ 19959, **2**) from an available starting material, 4-ethoxy-3-methoxyphenylacetic acid (**9**). Previously **2** was prepared *via* a perchlorate salt which was found to decompose exothermically.

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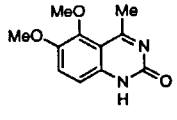
Our Drug Discovery group has been investigating the synthesis and pharmacology of novel quinazolinones for several years in the pursuit of a treatment for congestive heart failure [1]. They have reported on the synthesis [2] and cardiotonic activity [3] of a potent agent in this area, bemarinone (RWJ 16600, **1**). Further investigations led them to a series of compounds isosteric to the quinazolinones [4,5]. The lead compound in these studies proved to be the isoquinoline **2**, which possesses both positive inotropic and systemic peripheral vasodilating activity [6,7]. This type of profile could prove useful in an emergency setting where an immediate increase in myocardial contractility and reduction of cardiac afterload would be beneficial for patients suffering from myocardial infarctions or end-stage congestive heart failure.



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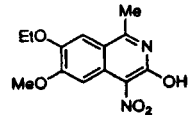
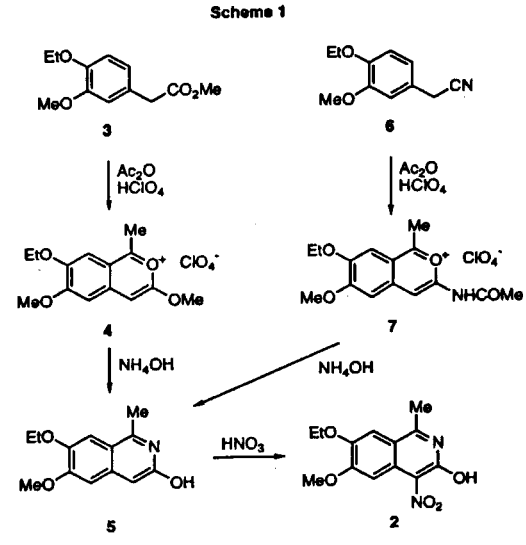


2

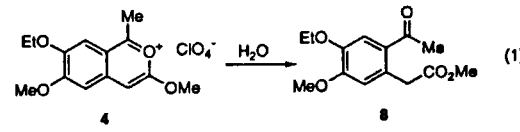
The previous synthesis [7] of **2** shown in Scheme 1 involves the use of 4-ethoxy-3-methoxybenzyl cyanide (**6**) in a Lewis acid-catalyzed acylation to produce the benzopyrilium perchlorate salt **7**. Reaction of **7** with ammonia yields the isoquinoline **5** which is nitrated to give **2**. An alternative to nitrile **6** is ester **3** which can be used in the same fashion to yield perchlorate salt **4** [8]. Because of our concern about the potential for perchlorate decomposition, we had **4** tested by differential scanning calorimetry. Compound **4** was found to undergo a moderately exothermic decomposition above 200° and this, along with the report [5] that salts such as **4** can react explosively with ammonium hydroxide, prompted us to search for an alternative method of preparation.

Hydrolysis of perchlorate salt **4** yielded the acetophenone **8** (Eq. 1) which was easily cyclized to isoquinoline **5**. Therefore, we needed to develop a method to prepare acetophenone **8** which bypassed the perchlorate route (Scheme 2). Dialkoxy-substituted phenylacetic

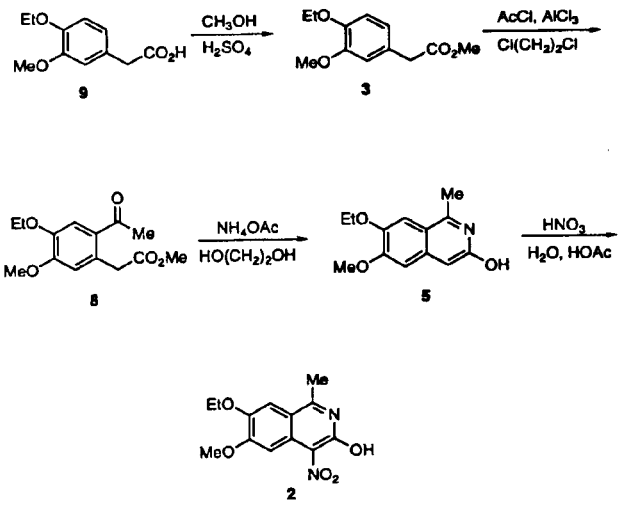
Scheme 1



esters are known to undergo Friedel-Crafts reactions in carbon disulfide [9]. While this method was appealing, we wanted to avoid the use of carbon disulfide on a large scale. Fortunately, the acylation reaction proceeded quite well on ester **3** in 1,2-dichloroethane with aluminum chloride as the catalyst. Ester **3** was easily prepared from the commercially available phenylacetic acid **9**. Cyclization of acetophenone **8** to isoquinoline **5** using ammonium acetate/ethylene glycol was carried out a number of times with good results. The final nitration was reported to be somewhat difficult to reproduce [8] and in fact we also experienced this problem as the nitration was scaled up beyond the size reported here. Larger reaction sizes led to poor filtrations, low yields, and impure product. However, the nitration was run on the scale given (see Experimental) with consistent results eventually producing a total of *ca.* 450 g of **2** for pharmacological and toxicological testing.



Scheme 2



EXPERIMENTAL

Methyl 4-Ethoxy-3-methoxyphenylacetate (**3**) [10].

To a turbid mixture of acid **9** (562.8 g, 2.68 moles) in methanol (4.0 liters) was added concentrated sulfuric acid (25.5 ml). The reaction mixture was heated at reflux (68°) for a total of 21 hours and then cooled to room temperature. To the mixture was added triethylamine (266 ml) and the quenched reaction was allowed to stir for 30 minutes at room tempterature. The solvent was removed at reduced pressure and the residue was taken up in methylene chloride (2.5 liters). This solution was extracted with water (1.5 liters), saturated sodium bicarbonate solution (2.0 liters), and again with water (2 x 1.5 liters). The organic layer was treated with decolorizing carbon and dried over sodium sulfate. Filtration and solvent removal yielded 584.4 g (97%) of **3** as a clear brown liquid [11]; ir (neat): 1738 (ester CO), 1607, 1591, 1514 cm^{-1}; uv (methanol): λ max 232 nm (ε 7478), λ max 281 (ε 2869); nmr (deuteriochloroform): δ 1.43 (t, 3H, CH_3CH_2), 3.55 (s, 2H, CH_2CO), 3.67 and 3.85 (two s, 3H each, CH_3O), 4.06 (q, 2H, CH_3CH_2), 6.78-6.82 (m, 3H,aromatic protons); ms: (chemical ionization) m/z 225 (MH^+).

Methyl 6-Acetyl-4-ethoxy-3-methoxyphenylacetate (**8**).

To a solution of **3** (600.5 g, 2.68 moles) in 1,2-dichloroethane (2.5 liters) cooled to *ca.* 5° was added aluminum chloride (478.0 g, 3.59 moles). The reaction temperature rose to *ca.* 30° and was brought back to 10° before the addition of acetyl chloride (303.8 g, 3.87 moles). Following the addition period (40 minutes) the cooling bath was removed and the reaction mixture was heated at reflux (68°) for a total of 3 hours with evolution of hydrogen chloride. The reaction mixture was allowed to stand at room temperature for 16 hours and then was quenched by pouring into a mixture of 10 kg of ice and 10 liters of 1 *N* hydrochloric acid. This was stirred for 15 minutes and the layers separated. The organic layer was washed with water (2 x 5 liters) and the aqueous layers extrated with methylene chloride (2 x 5 liters). The combined organic layers were treated with decolorizing carbon (75 g) and dried over sodium sulfate. Following fitration the orange solution was evaporated under reduced pressure. To the residue was added hexane (500 ml) and after *ca.* 3 minutes a granular solid precipitated from the solution. This was filtered and redissolved in ethyl acetate (1.25 liters) at 55°. To the solution was slowly added hexane (2.0 liters) with precipitation of yellow needles. The slurry was stirred for 30 minutes and another portion of hexane (2.0 liters) was added. This was cooled to 10° and the solids filtered, washed with hexane (2.0 liters) and dried under vacuum at room temperature to yield 463.6 g (65%) of **8**, mp 89-92°; ir (potassium bromide): 1729 (ester CO), 1675 (ketone CO), 1605, 1567, 1527 cm^{-1}; uv (methanol): λ max 232 nm (ε 21950), λ max 276 nm (ε 9185), λ max 305 nm (ε 5375); nmr (deuteriochloroform): δ 1.49 (t, 3H, CH_3CH_2), 2.55 (s, 3H, CH_3CO), 3.71 and 3.93 (two s, 3H, each, CH_3O), 3.89 (s, 2H, CH_2CO), 4.15 (q, 2H, CH_3CH_2), 6.72 and 7.36 (two s, 1H each, aromatic protons); ms: (chemical ionization) m/z 267 (MH^+).

Anal. Calcd. for $C_{14}H_{18}O_5$ (266.3): C, 63.15; H, 6.81. Found: C, 63.27; H, 6.81.

7-Ethoxy-3-hydroxy-6-methoxy-1-methylisoquinoline (**5**).

A mixture of **8** (233.0 g, 0.88 mole), ammonium acetate (2.33 kilograms, 30.2 moles), and ethylene glycol (3.9 liters) was heated to 120-124°. The initial slurry formed a solution which remained at the end of the reaction period of 4.5 hours. The reaction mixture was cooled to 98° and diluted with water (3.9 liters) at which point a yellow precipitate formed. This was cooled to 10° before filtration and the resulting solids washed with water (3 x 0.5 liter) and then with water (3 x 0.5 liter). Following drying at 60° in a vacuum oven, 193.8 g (95%) of crude **5** was obtained.

Two such batches of material were recrystallized by dissolving the crude product (373 g) in dimethylformamide (9.0 liters) at 105-110°. The solution was cooled to 15° and the resulting precipitate filtered. The yellow solid was washed with ethanol (3 x 1.0 liter) and dried for 20 hours at 60° in a vacuum oven to yield 300.1 g (81% recovery) of purified **5**, mp 241-245° dec; ir (potassium bromide): 1644, 1492, 1475, 1230, 1210 cm^{-1}; nmr (trifluoroacetic acid): δ 1.63 (t, 3H, CH_3CH_2), 3.11 (s, 3H, $CH_3C{=}N$), 4.22 (s, 3H, CH_3O), 4.44 (q, 2H, CH_3CH_2), 7.30, 7.34, 7.48 (three s, 1H each, aromatic protons), 11.7 (s, 1H, O*H*).

Anal. Calcd. for $C_{13}H_{15}NO_3$ (233.27): C, 66.94; H, 6.48; N, 6.0. Found: C, 66.73; H, 6.38; N, 5.89.

7-Ethoxy-3-hydroxy-6-methoxy-1-methyl-4-nitroisoquinoline (**2**).

To a slurry of **5** (129.4 g, 0.55 mole) in 1:4 water:acetic acid (1.3 liters) was added a solution of 70% nitric acid (65 ml) in 1:4 water:acetic acid (130 ml) at such a rate that the temperature stayed between 18-20°. Approximately 3/4 of the addition was complete when a solution occurred, the temperature rose to 37°, and a precipitate appeared. Cooling was applied *via* an ice bath to bring the temperature back to 20° and the addition was completed [12]. Stirring at 15-20° was continued for 20 minutes and

then the reaction was diluted with water (1.5 liters) and stirred an additional 30 minutes. The precipitate was filtered, washed with water (3 x 500 ml) and then with ethanol (3 x 500 ml), and dried to yield 107.0 g (70%) of crude **2**.

Several such reactions were combined to give a total of 460 g of crude **2** which was heated in DMF (4.8 liters) to 95°. This was cooled to room temperature slowly and then cooled by an ice bath prior to filtration. The precipitate was washed with ethanol (3 x 500 ml) and dried at 50° under vacuum to give 423 g (92% recovery) of **2**, mp 257-260° dec; ir (potassium bromide): 1650, 1627, 1497, 1468, 1242 cm^{-1}; nmr (trifluoroacetic acid): δ 1.65 (t, 3H, CH_3CH_2), 3.24 (s, 3H, CH_3C=N), 4.34 (s, 3H, CH_3O), 4.45 (q, 2H, CH_3CH_2), 7.68 and 8.70 (two s, 1H each, aromatic protons), 11.7 (s, 1H, O*H*); ms: (chemical ionization) m/z 279 (MH^+).

Anal. Calcd. for $C_{13}H_{14}N_2O_5$ (278.27): C, 56.11; H, 5.07; N, 10.07. Found: C, 56.49; H, 4.80; N, 9.83.

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REFERENCES AND NOTES

† JBL Scientific, Inc., A Subsidiary of Genta, Inc., 277 Granada Drive, San Luis Obispo, CA 93401-7396.

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[10] Essentially prepared by a route obtained from our Medicinal Chemistry Department.

[11] Ester **3** can be distilled (bp 128° @ 0.1 mm) but we found it unnecessary to do so.

[12] **Caution:** Although we never experienced an uncontrollable exotherm, careful addition of the nitric acid, monitoring of the reaction temperature, and suitable safety precautions are advised.