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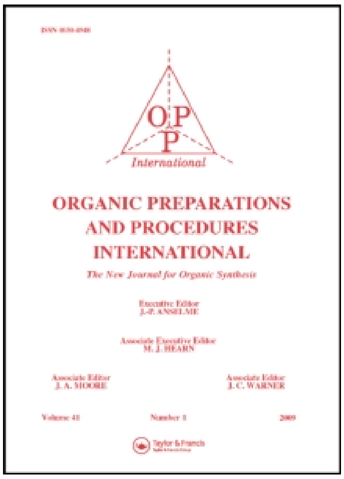

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A SIMPLE REGIOSELECTIVE SYNTHESIS OF (R)-10-HYDROXYAPORPHINE DIRECTLY FROM (R)-10,11-DIHYDROXYAPORPHINE [(R)-APOMORPHINE]

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A SIMPLE REGIOSELECTIVE SYNTHESIS OF (R)-10-HYDROXYAPORPHINE DIRECTLY FROM (R)-10,11-DIHYDROXYAPORPHINE [(R)-APOMORPHINE]

Submitted by (04/28/97)

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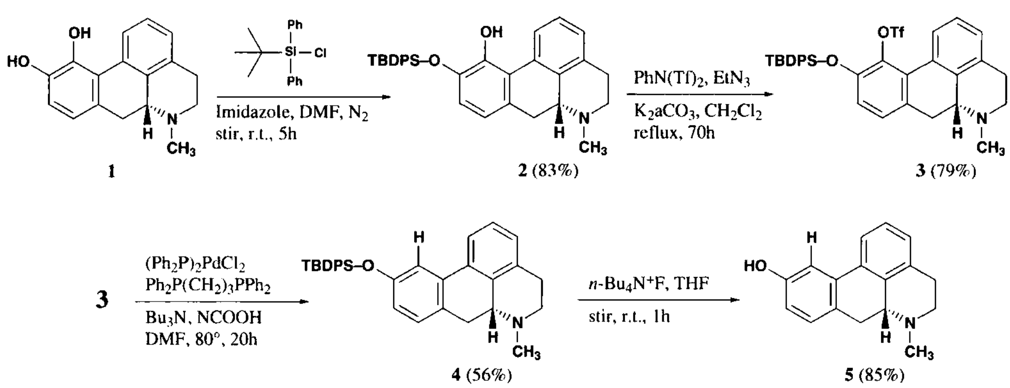
Since the discovery of useful dopamine (DA) agonist activity in hydroxylated aporphine alkaloids such as (R)-apomorphine [(R)-10,11-dihydroxyaporphine] (1),[1] there has been continuing interest in delineating the portions of the apomorphine molecular structure responsible for dopaminergic properties and the structure-activity relationships of this class of conformationally rigid DA analogues at D_1 and D_2 receptors.[2] (R)-11-Hydroxyaporphine (**6**) seems to be a D_1 receptor antagonist.[3] The monophenolic **2** has affinity for D_2 receptors but failed to display agonist activity at D_2 agonist activity in a serum prolactin assay indicating lacking of agonist activity at D_2 receptors.[3] Replacement of the C-10 hydroxy group of **1** with a methyl group, generated a potent 5-hydroxytryptamine ($5\text{-}HT_{1A}$) receptor agonist which did not exhibit any dopaminergic effect in the cat cardiovascular nerve test.[4] These studies have shown that the catechol portion of **1** is not a prerequisite for a potent interaction of aporphines with DA receptors. (R)-11-Hydroxy-N-propylaporphine has been reported by Neumeyer and coworkers2 to be equally potent toward **1** as a DA receptor agonist. In more recent studies, however, compound **4** appears to be more potent than **1**, reportedly having higher affinity toward and efficacy at D_2 receptors.[5] In order to understand the remarkable differences in pharmacological profiles in compounds **1-4**, we needed a quantity of (R)-10-hydroxyaporphine (**5**). Previously, compound **5** had been prepared *de novo* through the Reissert-Pschorr cyclization in a multi-step synthesis.[6,7] This report describes a simple and efficient regioselective synthesis of (R)-10-hydroxyaporphine (**5**) directly from the (R)-10,11-dihydroxyaporphine [(R)-apomorphine] (**1**).

Since X-ray analysis[3] had indicated that the phenolic 11-hydroxyl group of the biphenyl portion in the apomorphine system is apparently strained due to its steric repulsion with 1-peri hydrogen, we have developed a simple and practical method for the conversion of apomorphine **1** into (R)-10-hydroxyaporphine (**5**) in excellent yield. Due to the sterically hindered nature of 11-hydroxyl group of **1**, the use of the bulky (*tert*-butyldiphenyl)silyl chloride led to the exclusive regioselective O-silylation of the 10-hydroxy group (to give **2**), thus leaving the 11-hydroxy group intact.[9] The free 11-hydroxy group in 10-(*tert*-butyldiphenyl)silyloxy-11-hydroxyaporphine (**2**) was then triflated[10] with N-phenyltrifluoromethane sulfonimide and K_2CO_3 under reflux to give (R)-10-(*tert*-butyldiphenyl)silyloxy-11-[(trifluoromethyl)sulfonyl] oxy]aporphine (**3**). The reduced product, 10-(*tert*-butyldiphenyl)silyloxyaporphine (**4**) was prepared from **3** by a palladium-catalyzed hydrogenolysis[11] using the mixture of (diphenyldiphosphino)propane, $(Ph_3P)_2PdCl_2$, tributylamine and formic acid at 80° in DMF. Desilylation of the compound **4** with tetra-(*n*-butyl)ammonium fluoride afforded the desired (R)-10-hydroxyaporphine (**5**) in excellent yield.



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In conclusion, this simple regioselective synthetic procedure is the most practical one for converting (R)-10,11-dihydroxyaporphine (**1**) [(R)-apomorphine] to (R)-10-hydroxyaporphine (**5**) and to the best of our knowledge, it is the first demonstration in the aporphine series, since various other methods failed to effect the direct deoxygenation of apomorphine.

EXPERIMENTAL SECTION

Melting points were determined on an electrothermal capillary melting point apparatus and uncorrected. TLC was performed on glass plates coated with silicone oxide (silica gel $60F_{254}$) and compounds were visualized using a UV lamp. Proton nuclear magnetic resonance and ^{13}C NMR spectra were obtained with a Varian EM-360 spectrophotometer, Varian Gemini 200 MHz, Brucker AM 300 and DPS 200 (solution in DMSO-d_6 with tetramethylsilane as internal standard). Ultraviolet spectra data were measured with a Hitachi 124 spectrometer. Mass spectra were measured with Kratos MS 25 RFA (70eV, E1). The organic solvents and chemicals were obtained from commercial products and purlfied by the appropriate methods before use.

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(R)-10-(*tert*-Butyldiphenyl)silylaxy-11-hydroxyaporphine (2).- To a stirred solution of apomorphine (**1**, 2.79 g, 10.4 mmol) and imidazole (2.04 g, 30 mmol) in dry DMF (10 mL) was slowly added (*tert*-butyldiphenyl)silyl chloride (3 mL, 11.5 mmol) in dry DMF(10 mL) under N_2 atmosphere; the reaction mixture was stirred at r.t for 5h. The mixture was evaporated *in vacuo* to yield a light yellow oily residue, which was chromatographed on silica gel (CH_3OH:$CHCl_3$:NH_4OH 1:19:0.2) to yield **2** as a colorless oil (4.36 g, 83% yield). ^1H NMR ($CDCl_3$): δ 1.06 (s, 9H, *t*-Bu), 2.84 (s, 3H, N-CH_3), 3.25 (m, 7H, aliph-H), 5.90 (broad s, 1H, phenol, exchangeable with D_2O), 7.46-7.22 (m, 10H, SiPh2; 4H, aromat-2H, 3H, 8H, 9H), 8.23 (d, 1H, aromat-1H).

Anal. Calcd. for $C_{31}H_{35}NO_2Si$: C, 77.29; H, 7.39; N, 2.91. Found C, 77.21; H, 7.29; N, 2.94

(R)-10-(*tert*-Butyldiphenyl)silylaxy-11-[(trifluoromethyl)sulfonyloxy]aporphine (3).- A slurry of **2** (2.19 g, 8.7 mmol) and Et_3N (3.71 mL, 26.7 mmol) in CH_2C1_2 (110 mL) kept under N_2 was stirred for 1h at reflux. N-Phenyltrifluoromethanesulfonimide (3.72 g, 10.4 rnmol) and K_2CO_3 (1.23 g, 9.23 mL) was added. After being stirred for 1h, additional portions of N-phenyltrifluoromethanesufonimide (0.4 g, 1.1 mmol and 0.33 g, 0.9 mmol) were added after 30h and 40h. After 70h, the heating was interupted and the reaction mixture was extracted with 10% aq. $NaHCO_3$. The organic layer was dried (K_2CO_3), filtered and concentrated *in vacuo*. The oily residue was chromatographed on silica gel (CH_3OH:$CHCl_3$:NH_4OH 1:19:0.2) to yield **3** as a pure oil (2.71 g, 79% yield). ^1H NMR ($CDCl_3$): δ 1.06 (s, 3H, t-Bu), 2.51-2.63 (m, 2H), 2.56 (s, 3H), 2.77 (dd, 1H), 2.84 (s, 3H, N-CH3), 3.05 (ddd, 1H), 3.13-3.25 (m, 3H), 7.14 (app d, 1H), 7.13-7.16 (m, 4H), 7.79 (app d, 1H); ^{13}C NMR ($CDCl_3$): δ 29.1, 35.0, 44.1, 52.8, 61.5, 118.5(g), 121..4, 126.0, 126.6, 128.1, 128.3, 128.7, 128.3, 129.2, 133.3, 135.2, 139.7, 146.4.

Anal. Calcd. for $C_{32}H_{34}F_3NO_3SSi$: C, 68.66; H, 6.12; N, 2.50. Found C, 68.83; H, 6.19; N, 2.62

(R)-10-(*tert*-Butyldiphenyl)silyloxyaporphine (4).- Formic acid (40.33 μl, 1.0 mmol) was added to a stirred mixture of **4** (0.14 g, 0.3 mmol), 1,3-*bis*(diphenylphosphino)propane (0.02 g, 50.1 mmol),

$(Ph_3P)_2PdCl_2$ (0.014 g, 20.7 mmol) and tributylamine (0.34 mL, 1.4 mmol) in DMF (5 mL). The mixture was stirred at 80° for 20h. The volatiles were evaporated *in vacuo*, and the residue was partitioned between CH_2Cl_2 and 10% aq. $NaHCO_3$. The organic layer was dried (K_2CO_3) filtered and concentrated. The residue was chromatographed on silica gel (hexane:EtOAc 7:3) to yield **4** as a semisolid (0.007 g, 56% yield). ^{1}H NMR($CDCl_3$): δ 1.06 (s, 9H, t-Bu), 2.84 (s, 3H, N-CH_3), 3.25 (m. 7H, aliphat-H), 7.40-7.72 (m, 10H, $SiPh_2$; 4H, aromat-2H, 3H, 8H, 9H, 11-H), 8.23 (d, 1H, aromat-1H); ^{13}C NMR ($CDCl_3$): δ 29.2, 31.0, 34.6 44.1, 52.9, 61.7, 126.48, 126.8, 127.4, 128.7, 130.1, 131.7, 133.0, 133.5, 137.0, 137.2, 139.9.

Anal. Calcd. for $C_{31}H_{35}NOSi$: C, 79.95; H, 7.58; N, 3.01. Found C, 79.79; H, 7.52; N, 3.01

(R)-10-Hydroxyaporphine (5).- A mixture of (R)-10-(*tert*-Butyldiphenyl)silyloxyaporphine (**4**) (3.55 g, 10.5 mmol) and 1.0M *tetra*-(*n*-butyl)ammonium fluoride (11.32 mL, 11.3 mmol) in THF (75 mL) was stirred at r.t. for 1h under a N_2 atmosphere and the resulting reaction mixture was concentrated to dryness under reduced pressure. The foamy residue was chromatographed on silica gel (hexane:EtOAc 7:3) to yield **5** (2.49 g, 85% yield). mp. 274° dec. ^{1}H NMR($CDCl_3$): δ 2.29 (s, 3H), 2.63-2.81 (m, 2H), 2.60 (s, 3H) 2.80 (dd, 1H), 3.08 (ddd, 1H), 3.12-3.28 (m, 3H), 7.07-7.65 (m, 6H); ^{13}C NMR ($CDCl_3$): δ 29.1 34.1, 43.8, 53.4, 62.0, 121.2, 123.7, 126.8, 127.3, 127.5, 128.0 133.4, 133.5, 133.8, 134.4, 135.3.

Anal. Calcd for $C_{17}H_{17}NO$: C, 81.24; H, 6.81; N, 5.57. Found C, 81.41; H, 6.89; N, 5.58

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A NEW SYNTHESIS OF 6,7-DICHLORO-DIBENZO[c,f][2,7]-NAPHTHYRIDINES *via* PHOTOCYCLIZATION

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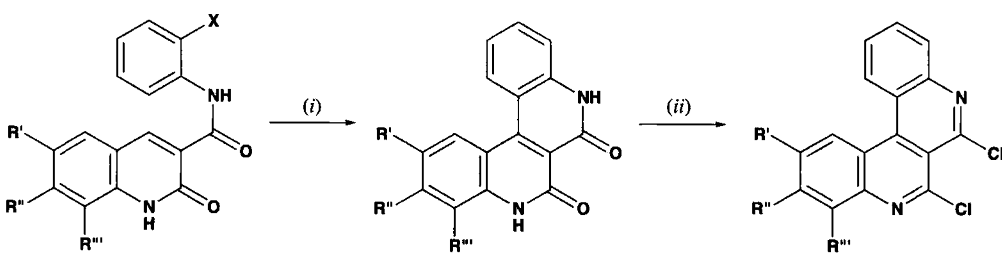
Substituted naphthyridines are of importance because of their bactericidal and fungicidal properties.[1-3] Many of the benzo and dibenzonaphthyridines exhibit chemotherapeutic behavior.[4] Earlier reports[5,6] showed that dibenzo[c,f][2,7]naphthyridines were synthesized from *N*-phenylcarbamoyl coumarins by the action of Grignard reagents and ketones followed by the annulation with cyclohexanone. We now report a new photochemical method which can be extended to the synthesis of derivatives of this system.

Our synthesis starts from *o*-halo-3-carboxanilidoquinolin-2(1H)ones (**1a-g**),[7] which were obtained from 2-oxoquinoline-3-carboxylic acids. The carboxanilides (**la-g**), on eliminative photocyclization afforded dibenzo[c,f][2,7]naphthyridin-6,7-(5H,8H)diones (**2a-g**), which on treatment with $POCl_3$ in presence of N,N-dimethylaniline,gave 6,7-dichlorodibenzo[c,f][2,7]naphthyridines (**3a-g**).



i) hν, MeOH, Et_3N, 35h *ii*) $POCl_3$, $PhNMe_2$

a) R' = R'' = R''' = H b) R' = OCH_3; R'' = R''' = H c) R' = CH_3; R'' = R'''= H d) R' = R''' = H; R'' = OCH_3
e) R' = R''' = H; R'' = CH_3 f) R' = R'' = H; R''' = CH_3 g) R' = H; R'' = R''' = -CH=CH-CH=CH-