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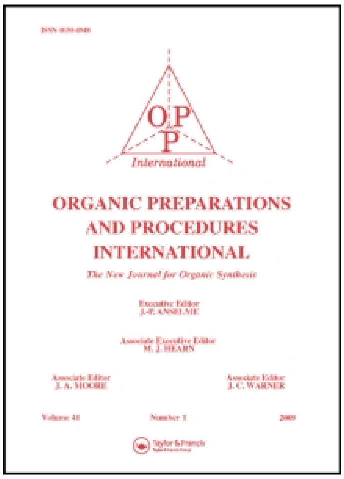

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AN IMPROVED SYNTHESIS OF 5,5,9,9-TETRAMETHYL-5*H*, 9*H*-QUINO[3,2,1-DE]ACRIDINE

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AN IMPROVED SYNTHESIS OF 5,5,9,9-TETRAMETHYL-5H,9H-QUINO[3,2,1-DE]ACRIDINE

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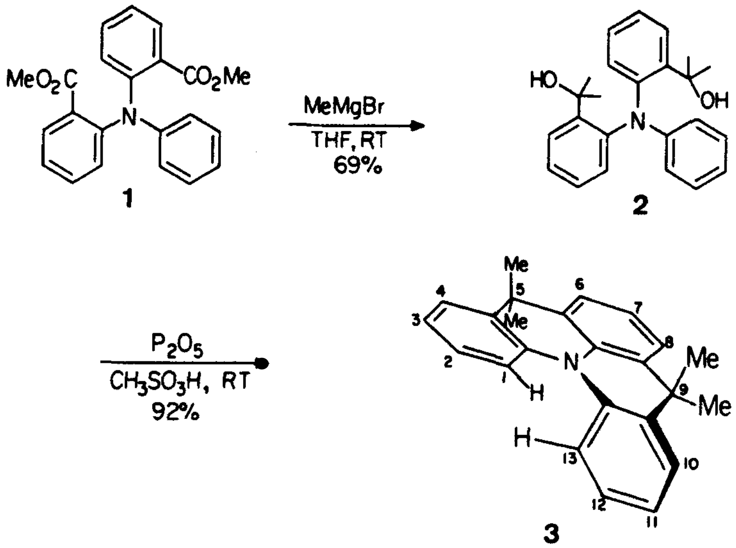
5,5,9,9-Tetramethyl-5H,9H,quino[3,2,1-de]acridine (3) has been shown by X-ray analysis to have in its bridged structure a totally flattened nitrogen lying only 0.03 Å outside the plane formed by the three linking carbons.[1] This interesting molecule also has a C_2 element of symmetry in which the two acridine subunits are folded away from each other so as to alleviate the interaction between H_1 and H_{13}. These results,



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coupled with the unusually high barrier of racemization (>22 kcal/mole)[1] obtained from the variable-temperature ^{1}H NMR studies, suggest that this molecule is, in principle, resolvable. Working toward this goal necessitated a large amount of pure, racemic 3. Although the preparation of 3 has been reported,[1] the yield was poor and the procedure was nonreproducible. We report here an improved synthesis of 3 in 64% overall yield from 2,2'-bis(carbomethoxy)triphenylamine (1).

Exhaustive methyllithiation of 1 in refluxing ether according to the literature procedure produced the biscarbinol 2 in only 10-20% yield, depending on the scale of the experiment. The purity of 2 isolated from this reaction also influenced the subsequent ring closure with 85% phosphoric acid. Although yields up to 55% have been reported,[1] in our hands the yields of this cyclodehydration varied from 18% to 43%.

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Variations such as using excess methyllithium in ether with low amounts of halides, changing the solvent from ether to THF, and varying the temperature and time of the reactions failed to improve the yield of 2, which invariably was accompanied by at least four byproducts (TLC assay). Separation by fractional recrystallization was also inadequate.

When excess methylmagnesium bromide was used in place of MeLi in THF, after hydrolysis, the biscarbinol 2 was obtained as the major product, which was readily isolated in pure form (69% yield) by recrystallization from EtOH. The MeMgBr was added dropwise to 1 at ambient temperature, and the mixture was warmed at 40° for 70 min, after which time TLC showed the reaction to be complete. Varying the reaction temperature did not appreciably affect the yield of 2. One notable difference between the MeMgBr and MeLi reactions in THF was that the former was completely homogeneous throughout, whereas in the MeLi reaction, the lithium alkoxide intermediate quickly precipitated. Presumably, the divalent magnesium cation intramolecularly complexes with the lone pair of the nitrogen atom, which would otherwise deactivate the intermediate methyl ketone toward further additions.

For the final cyclization, we tried polyphosphoric acid (PPA), since 85% phosphoric acid per se was not a good dehydrating agent. The result, however, was discouraging, presumably because of the poor solubility of 2 in the extremely viscous PPA medium, which had to be heated to 100° to allow adequate mixing. A milder cyclodehydrating agent, prepared by dissolving ca. 10% P_2O_5 in methanesulfonic acid (MSA),[2] was an excellent medium for the desired cyclodehydration. Pure 3 (~92%) was obtained in gram-scale quantities. The workup entailed stirring at ambient temperature, followed by pouring into water, from which 3 was precipitated and readily purified by recrystallization. The entire sequence is thus highly conducive to large-scale preparation. The overall yield of 3 from the bisester 1 was ~64%.

EXPERIMENTAL SECTION

Melting points (uncorrected) were determined with a Thomas-Hoover capillary melting-point apparatus. ^1H NMR spectra were recorded on a Bruker WH 270-MHz spectrometer, with Me_4Si as internal standard. Field-desorption mass spectra were obtained on an MAT-731 mass spectrometer. Microanalyses were done by the Analytical Sciences Division, Kodak Research Laboratories.

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2,2-Bis(1-hydroxy-1-methylethyl)triphenylamine (2). - To a solution of 1 (3.61 g, 0.01 mole) in 100 mL of dry THF at room temperature was added dropwise by syringe 17.2 mL (0.05 mole) of methylmagnesium bromide in ether (2.9 M). The solution was warmed to 40° and stirred for 70 min. The solution was cooled to 0°, 5 mL of 1 N aqueous NH_4Cl was added dropwise over 10 min, and 100 mL of Et_2O was added. The organic phase was washed twice with 50 mL of H_2O and dried ($MgSO_4$), and the solvent was evaporated. Trituration of the yellow solid (4.1 g) with 15 mL of hot hexanes and filtration yielded 2.62 g of a pale yellow solid. Recrystallization from 12 mL of EtOH yielded 2.51 g (69%) of 2 as transparent crystals: mp 184-186° (lit.[1] mp 183-184°); field-desorption mass spectrum, m/e 361 (M^+); ^1H NMR ($CDCl_3$): δ 1.35 (s, 6 H, CH), 1.48 (s, 6 H, CH_3), 6.80-7.35 (m, 12 H, ArH).

Anal. Calcd for $C_{24}H_{27}NO_2$: C, 79.7; H, 7.5; N, 3.8
Found: C, 79.4; H, 7.4; N, 3.8

5,5,9,9-Tetramethyl-5H,9H-quino[3,2,1-de]acridine (3). - To a solution of 18 mL of 10% P_2O_5 in methanesulfonic acid was added 1.75 g (4.8 mmole) of the biscarbinol 2 at room temperature. The mixture was stirred rapidly for 1 h and then poured into 150 mL of ice water. The colorless precipitate was filtered and washed with water. Recrystallization of the crude product from 70 mL of isopropyl alcohol gave, after drying, 1.31 g (83%) of 3: mp 196-197° (lit.[1] mp 196°). An additional 0.125 g of pure 1 (TLC assay) was obtained from the concentrated mother liquors; total yield, 92%: field-desorption mass spectrum, m/e 325 (M^+); ^1H NMR ($CDCl_3$): δ 1.2 (s, 6 H, CH_3), 1.9 (s, 6 H,

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CH_3), 7.07-7.22 (m, 5 H, ArH), 7.32 (d, 2 H, *J* = 7.5 Hz, H_1 and H_{13}), 4.01 (dd, 4 H, *J* = 7.5 Hz, H_4/H_{10} and H_6/H_8).

Anal. Calcd for $C_{24}H_{23}N$: C, 88.6; H, 7.1; N, 4.3.
Found: C, 88.5; H, 7.1; N, 4.2.

When unrecrystallized 2 was used for the cyclization, the final recrystallized 3 was greenish, apparently because of a cocrystallized impurity. To purify by sublimation, 6.8 g of crude 3 was placed in a 200-mL recovery flask with a small stirring bar. A 0.4-torr vacuum was applied, and the flask was immersed in a 200° oil bath; the crude product melted and recondensed on the walls of the flask. After 30 min, the oil bath was removed, and the flask was allowed to cool to room temperature under reduced pressure. The pressure was slowly released, and the colorless crystals were removed from the flask so as not to disturb the solidified, dark pot residue; yield 6.3 g (93%).

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