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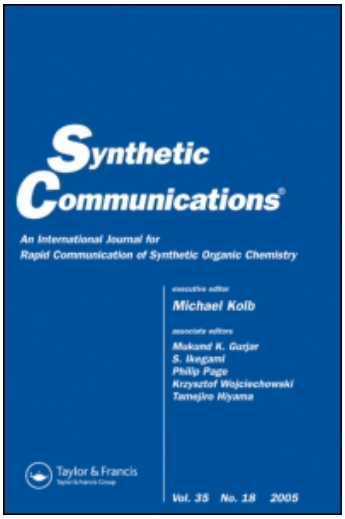

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Synthesis of Some Novel Heteropolyquinanes

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SYNTHESIS OF SOME NOVEL HETEROPOLYQUINANES

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ABSTRACT: Synthesis of structurally novel aza- and oxa-polyquinanes from the abundantly available cis,syn,cis-triquinane dione 1 via transannular nucleophilic additions is reported.

Ready availability[2] of cis,syn,cis-triquinane dione 1 of folded topology and spatially proximal carbonyl groups[3] and the recent report[4] that compounds like 2 derived from 1 can function as effective calcium channel blockers prompts us to report our preparation of some novel heteropolyquinanes containing N and/or O atoms through short, simple methodologies.

Synthesis of the heteropolyquinanes 3-12 from 1 is summarised in the Scheme 1. Of particular interest is

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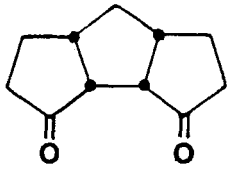
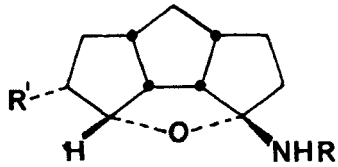


1



2. R= CH_2-C_6H_5, R'= CH_3

the formation of partially reduced 1,4-diazocin and 1,5-diazonine derivatives 5 and 9 through direct condensation of 1 with o-phenylenediamine and 1,3-diaminopropane, respectively, in good yield. Literature reports[5] indicate that the condensation between 1,4-dicarbonyl compounds and o-phenylenediamine take a relatively complex course and in this respect the response of 1 is quite exceptional.

On controlled reduction with sodium borohydride, 5 and 9 undergo facile transannular cyclisation to the spirocyclic diazapolyquinanes 8 and 12, respectively, through intermediate dihydro-compounds 7 and 11. Structures to 7 and 11 have been assigned on the basis of complementary ^{1}H & ^{13}C NMR spectral data summarised in the experimental section. Formation of 3, 4, 6 and 10 involves an intermolecular nucleophilic addition followed by intramolecular displacement as indicated for 4 in Scheme 2.

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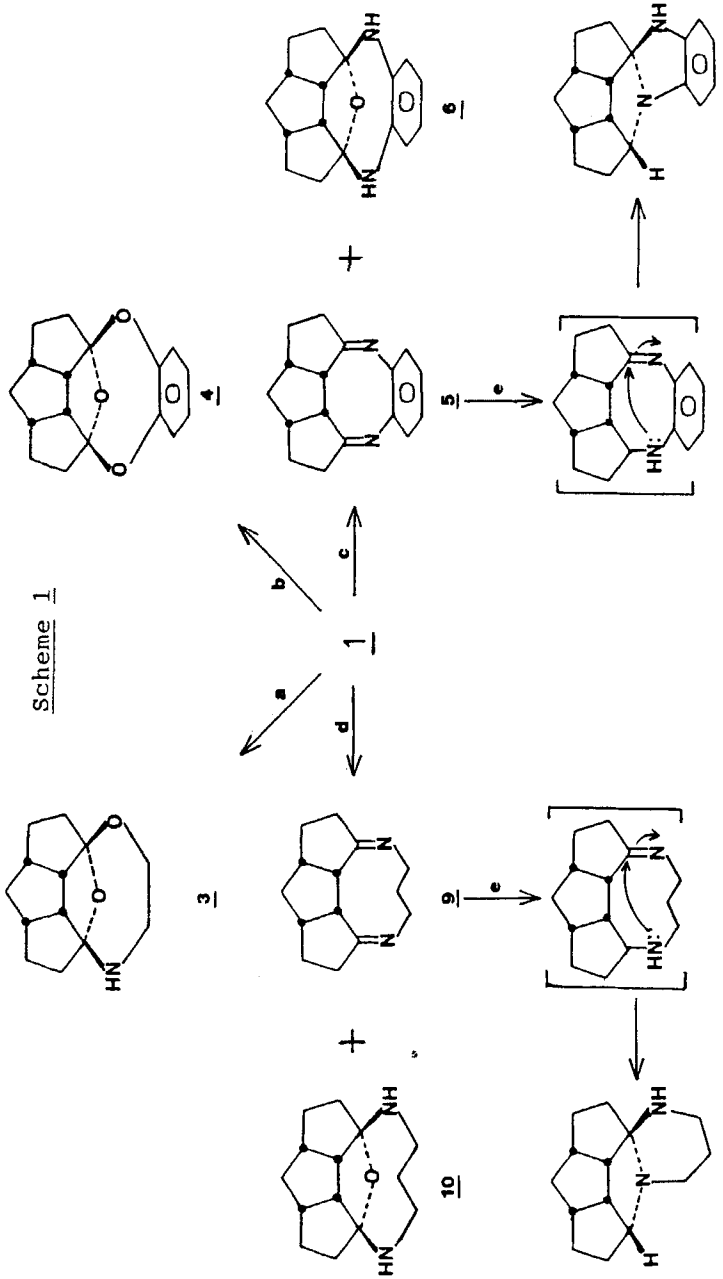
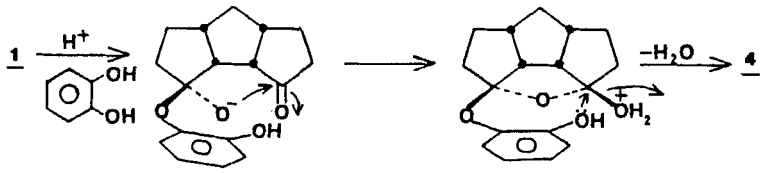
Scheme 1



Reagents, Conditions & Yields: a) 2-amino ethanol, benzene, PTSA, Δ , 12h, 80%; b) Catechol, benzene, PTSA, Δ , 14h, 87%; c) o-phenylenediamine, benzene, PTSA, Δ , 3h, 68% of 5 and 6% of 6; d) 1,3-diaminopropane, benzene, PTSA, Δ , 1h, ~90%; e) $NaBH_4$, methanol, 0-30°C, 62% of 8 and 50% of 12.

Scheme 2



Experimental Section[6]

Reaction between 1 and 2-aminoethanol. Formation of 3:

A mixture of dione 1 (100 mg, 0.6 mmol), 2-aminoethanol (75 mg, 1.3 mmol) and p-toluenesulphonic acid (5 mg) in dry benzene (25 ml) was refluxed for 12h and the contents were diluted with benzene (15 ml), washed with aq.$NaHCO_3$, brine and dried over anhydrous Na_2SO_4. The crude product obtained after removal of solvent was chromatographed on a silica gel (10 g) column. Elution with 80% ethyl acetate-pet ether furnished 3 (100 mg, 80%) and was recrystallised from pet ether dichloromethane mixture, mp.: 86°C, IR (KBr): 3350, 2950, 1450, 1310, 1150, 1040 cm^{-1}; ^1H NMR: δ 3.9-3.3 (m, 3H), 3.2-2.4 (m, 6H), 2.0-1.2 (m, 10H); ^{13}C NMR: δ 117.4, 106.7, 66.0, 61.5, 54.0, 45.7, 44.7, 42.8, 40.6, 38.0, 36.3, 32.8, 32.3; MS: m/z 221 (M^+); Anal. Calcd. for $C_{13}H_{19}O_2N$: C, 70.55; H, 8.65; N, 6.33. Found: C, 70.24; H, 8.71; N, 6.42.

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Reaction between 1 and catechol. Formation of 4:

Into a 25 ml RB flask fitted with a Dean-Stark water separator, reflux condenser and mercury seal, the dione (100 mg, 0.6 mmol), catechol (70 mg, 0.65 mmol) and p-toluenesulphonic acid (2 mg) in dry benzene (10 ml) were placed. The reaction mixture was refluxed for 14h and the contents were diluted with benzene (10 ml), washed with aq. $NaHCO_3$, brine and dried over anhydrous Na_2SO_4. The crude product obtained after removal of the solvent was chromatographed on a silica gel column (10 g). Elution with 10% ethyl acetate-pet ether resulted in the removal of less polar impurities and further elution with 30% ethyl acetate-pet ether furnished the bis-acetal ether 4 (130 mg, 87%), which was recrystallised from hexane-benzene mixture, mp. 143°C, IR (KBr): 3050, 2950, 1580, 1490, 1170, 870, 760 cm^{-1}; ^1H NMR: δ 7.2-6.7 (m, 4H), 3.0-1.2(m, 14H); ^{13}C NMR: δ 146.5, 123.0, 122.5, 122.0, 56.9, 46.1, 38.5, 35.7, 31.7; MS: m/z 270 (M^+). Anal. Calcd. for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.58; H, 6.78.

Reaction of 1 with o-phenylenediamine. Formation of 5 and 6:

A mixture of dione 1 (178 mg, 1 mmol), o-phenylenediamine (120 mg, 1.1 mmol) and catalytic amount of

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PTSA in dry benzene (30 ml) was refluxed for 3h with azeotropic removal of water using a Dean-Stark trap. The reaction mixture was cooled and diluted with more benzene, washed with $NaHCO_3$, brine and dried over Na_2SO_4. Removal of solvent gave 290 mg of crude material which was chromatographed on a silica gel column. Elution with 40% ethylacetate-hexane gave products 5 (170 mg, 68%) and 6 (15 mg, 6%). 5: mp. 153-54°C; IR (KBr): 1680, 1480, 1190, 970 cm^{-1}; ^1H NMR: δ 6.8-7.1 (m, 4H), 2.24-3.0 (m, 8H), 1.2-2.18 (m, 6H); ^{13}C NMR: δ 186.3, 143.0, 123.9, 121.2, 51.1, 45.7, 36.4, 33.2, 26.0. Anal. Calcd. for $C_{17}H_{18}N_2$: C, 81.56; H, 7.24; N, 11.19. Found: C, 81.17; H, 7.23; N, 11.01. 6: mp. 173-74°C, IR (KBr): 3360, 2950, 1600, 1480, 1340, 760 cm^{-1}; ^1H NMR: δ 6.70 (s, 4H), 3.4-4.1 (br, 2H), 1.2-3.0 (m, 14H); ^{13}C NMR: δ 136.6, 120.8, 120.7, 105.0, 59.4, 47.0, 38.8, 38.5, 33.6; MS: m/z 268 (M^+).

$NaBH_4$ reduction of 5. Formation of 8:

To a solution of 5 (100 mg, 0.39 mmol) in methanol (10 ml), maintained at 0°C, was added $NaBH_4$ (20 mg, 0.53 mmol). The reaction mixture was sitrred for 2h and 1 ml of H_2O was added. Methanol was removed under reduced pressure and the residue extracted with ethyl acetate (25 ml x 2). The organic extract was washed

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with brine and dried over Na_2SO_4 and concentrated to give 80 mg of crude product. Purification over neutral alumina column gave 8 (62 mg, 62%), mp. 139-140°C, IR (KBr): 3360, 2960, 2920, 1610, 1460, 1240, 740 cm^{-1}; ^1H NMR: δ 6.5-6.8 (m, 4H), 1.4-4.0 (series of m, 16H); ^{13}C NMR: δ 144.1, 142.7, 122.6, 119.5, 114.1, 108.8, 103.6, 75.8, 61.4, 55.5, 46.7, 46.2, 42.1, 37.3, 36.1, 32.0, 31.6; MS: m/z 252 (M^+); Anal. Calcd. for $C_{17}H_{20}N_2$: C, 80.91; H, 7.99; N, 11.10; Found: C, 80.72; H, 8.07, N, 10.93.

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Reaction of 1 with 1,3-diaminopropane. Formation of 9 and 10:

To a solution of dione 1 (50 mg, 0.28 mmol) and 1,3-diamino propane (42 mg, 0.57 mmol) in 25 ml dry benzene was added catalytic amount of PTSA and the mixture refluxed for 1h using a Dean-Stark trap. The reaction mixture was cooled, diluted with benzene, washed with $NaHCO_3$, brine and dried over Na_2SO_4. Removal of solvent gave 75 mg of crude material which could not be purified through chromatography on silica gel column. The presence of a mixture 9 and 10 was revealed through the spectral data. IR (KBr): 3180, 2980, 2880, 1620, 1580, 1400, 760 cm^{-1}; ^1H NMR: s 1.4-3.4 (series of m); ^{13}C NMR: s 179.2, 106.2, 89.7, 59.5,

57.6, 46.5, 45.7, 40.4, 39.0, 36.6, 36.3, 33.3, 32.1, 24.5, 21.8; MS: m/z 216 (M^+ for 9), m/z 234 (M^+ for 10).

$NaBH_4$ reduction of 9 and 10. Formation of 12:

50 mg of the mixture 9 and 10 was dissolved in methanol (5 ml) and cooled to 0oC. $NaBH_4$ (8 mg; 0.21 mmol) was added and the reaction was stirred for 30 min. at 0oC, and then for 2h at room temperature. Water (1 ml) was added and methanol was removed under reduced pressure. Extraction with ethyl acetate (15 ml x 2), washing and drying furnished 40 mg of crude material. Chromatography on neutral alumina column and elution with 5% methanol-ethyl acetate as gave 12 (25 mg, 50%). IR (KBr): 3400, 2950, 1400, 840 cm^{-1}; ^1H NMR: s 6.3 (s, 1H), 3.9 (m, 1H), 1.2-3.4 (series of m, 20H); ^{13}C NMR: s 90.1, 68.1, 60.7, 52.4, 47.2, 45.5, 42.3, 39.8, 37.0, 34.2, 33.5, 32.7, 32.4, 18.0; Anal. Calcd. for $C_{14}H_{22}N_2$: C, 77.06; H, 10.09, N, 12.84; Found: C, 77.62; H, 9.65, N, 12.85.

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