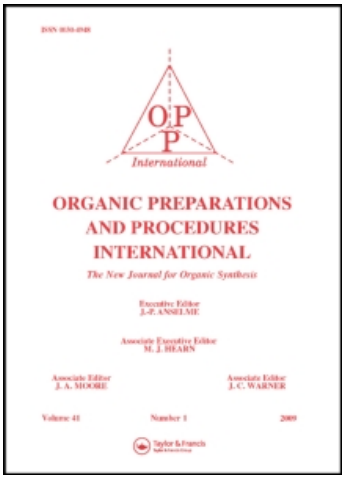

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SYNTHESIS OF A NOVEL ASARONE DIMER

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washed with ether, basified with aqueous sodium hydroxide and extracted with ether. The ethereal extract yielded 6.05 g. (87%) of 1-benzylpyrazole-2-^{15}N, bp. 77-80°/0.5 mm, lit.,[1] bp. 255-257°/750 mm.

NMR (CCl_4): δ 5.2 (2H, s, CH_2), 6.17 (1H, t, 4-H), 7.2 (6H, m,5-H and Ph), and 7.37 (1H, d, J=2 Hz,3-H); δ_N ($CDCl_3$) - 74.433 (2-N) and - 168.617 ppm (1-N).

REFERENCES

1. R. G. Jones, J. Am. Chem. Soc., 71, 3994 (1949).
2. F. Sommer, O. F. Schultz and M. Nassau, Z. anorg. allgem. Chem., 147, 142 (1925) [Chem. Abs., 19, 3249 (1925)].
3. H. J. Abendroth, Angew. Chem., 73, 67 (1961).
4. E. Schmitz and D. Habisch, Chem. Ber., 95, 680 (1962).
5. H. J. Matsuguma and L. F. Audrieth, Inorg. Synth., 5 122 (1957).

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SYNTHESIS OF A NOVEL ASARONE DIMER

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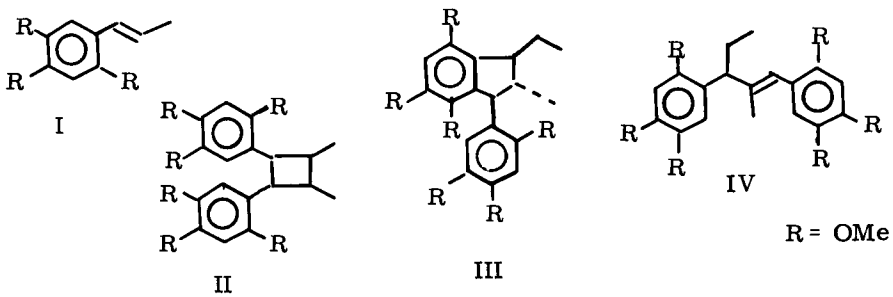
It has been recently claimed[1] that asarone (I), the main constituent of Guatteria goumeri, a plant used in southeast Mexico for the treatment of gallstones, has potentially useful

hypocholesteremic properties.[2] In fact, when administered to rats and dogs, it causes a noticeable reduction in the corresponding serum cholesterol levels.[2,3]

As part of our studies directed towards the synthesis of asarone-like hypocholesteremic agents, we became interested in the work of Szeki[4,5] who reported the isolation of an asarone dimer, mp. 101.5°, from the direct hydrogen chloride treatment of an ethereal solution of I; the cyclobutane structure II was proposed for this compound based solely on chemical evidence,[4,5] such as lack of bromine addition. Kovacs[6] subsequently proposed the indane-derived structure III for a dimer, mp. 98-99°, resulting from the sodium iodide treatment of asarone dibromide, but no direct comparison with the Szeki dimer was reported. However, in our hands, treatment of I according to either of the reported conditions[4-6] resulted exclusively in the isolation of dimer III, which was fully characterized by analytical and spectroscopic methods. Based on the observed coupling constants $J_{1,2}$ = 4.2 Hz and $J_{2,3}$ = 9 Hz, the Williamson-Johnson equation[7] provides dihedral angles of 121° and 138.5° respectively, thus suggesting the relative configurations shown.



Moreover, if asarone (I) is allowed to react with an equivalent amount of PBr_3 under carefully controlled conditions in dry chloroform for 3 hrs. at room temperature, a novel unsaturated dimer, mp. 96-97° can be isolated in 87% yield. From its spectroscopic properties, the E-2-methyl-1,3-bis(2,-4,5-trimethoxyphenyl)-1-pentene (IV) is proposed. Furthermore, dimer IV cleanly isomerizes to III in chloroform solution at room temperature in the presence of a catalytic amound of hydrogen bromide. In fact, if rigorously controlled anhydrous conditions are not observed during the PBr_3 treatment, varying amounts of III are also obtained. Based on the fact that upon prolonged PBr_3 treatment dimer IV converts readily into III, we have assumed the former to be the kinetically controlled product, whereas the latter should be to the thermodynamic one.

Both dimers III and IV are being tested for hypocholesteremic activity and the full pharmacological evaluation will be reported independently.

EXPERIMENTAL

Melting points were determined on a Kofler hot stage and are uncorrected. UV and IR spectra were recorded on a Perkin Elmer 202 and 567 spectrophotometers respectively. Nmr spectra were obtained using Varian HA-100 and EM-390 spectrometers. Mass spectra were determined on a AEI-MS-902 high resolution mass spectrometer. Elemental analyses were done at Dr. F. Pasher's Laboratory, Bonn (Germany).

E-2-Methyl-1,3-bis-(2,4,5-trimethoxyphenyl)-1-pentene (IV).- A solution of PBr_3 (1.152 g, 4.4 mmol) in dry chloroform (10 ml) was added dropwise to a solution of asarone (I) (1 g, 4.8 mmol) in the same solvent (30 ml). After 3 hrs. stirring at room temperature the reaction mixture was diluted with cold water (40 ml) and the layers separated. The chloroform extract was

washed with saturated $NaHCO_3$, water, and dried over anh. Na_2SO_4. Evaporation of the solvent under reduced pressure left a solid residue which was recrystallized from MeOH to give 0.875 g (87%) of dimer IV, mp. 96-97°. UV (EtOH): λ max 214 (ε 35,846), 256 (ε 15,047), 298 nm (ε 11,860); IR (KBr): ν max 2825, 1610, 825 cm^{-1}; nmr ($CDCl_3$): δ 0.93 (3H, t, J=7.5 Hz, $\underline{CH_3}$-CH_2), 1.67 (3 H, s, $\underline{CH_3}$-C=C), 1.85 (2 H, m, $\underline{CH_2}CH_3$), 3.83 (9 H, s, Ar-$\underline{OCH_3}$), 3.90 (9 H, s, Ar-$\underline{OCH_3}$), 6.50 (1 H, s, $\underline{H}$-C=C), 6.61 (2 H, s, Ar-$\underline{H}$ 3 and 3'), 6.84 (1 H, s, Ar-$\underline{H}$ 6 and 6'); MS m/e 416.2197 M^+ (calculated for $C_{24}H_{32}O_6$, 416.2199), 385, 356, 341, 296, 278, 262, 248, 220, 219.

Anal. Calcd. for $C_{24}H_{32}O_6$: C, 69.21; H, 7.74; O, 23.05.
Found: C, 69.29; H, 7.65; O, 23.13.

Prolonged PBr_3 Treatment of Dimer IV.- Prolonged treatment of IV (obtained as described above) under the above described conditions, using a reaction time of 24 hrs., gave 0.783 g (78%) of dimer III, mp. 100-101° UV (EtOH): λ max 211 (ε 23,590), 234 (ε 14,965), 286 nm (ε 7,663); IR ($CHCl_3$): ν max 2925, 2885, 1600 cm^{-1}; nmr ($CDCl_3$): δ 0.85 (3 H, t, J=7 Hz, $\underline{CH_3}CH_2$), 1.16 3H, d, J=7 Hz, $\underline{CH_3}CH$), 1.65 (2 H, m, $\underline{CH_2}CH_3$), 2.05 (1 H, m, $\underline{CH}$-CH_3), 2.68 (1 H, td J=7, 9 Hz $\underline{CH}C_2H_5$), 3.37 (3H, s, $O\underline{CH_3}$), 3.62 (3H, s, $O\underline{CH_3}$), 3.81 (3 H, s, $O\underline{CH_3}$), 3.83 (6H, s, $2O\underline{CH_3}$), 3.86 (3H, s, $O\underline{CH_3}$), 4.27 (1 H, d, J=4.2 Hz, CH-$(\emptyset)_2$), 6.36 (1 H, s, Ar-$\underline{H}$) 6.41 (1 H, s, Ar-$\underline{H}$), 6.54 (1 H, s, Ar-H); MS (m/e): M^+, 401, 387, 385, 356, 341, 247, 233, 219, 208, 204, 201, 195, 196.

Anal. Calcd. for $C_{24}H_{32}O_6$: C, 69.21; H, 7.74; O, 23.05.
Found: C, 69.30; H, 7.78; O, 22.94.

Acid-catalyzed Interconversion of Dimer IV to III.- A solution

of (IV) (0.1 g, 0.48 mmole) in dry chloroform (10 ml) was treated with a 40% (w/w) solution of HBr in glacial acetic acid (0.1 ml) and stirred at room temperature for 24 hrs. The reaction mixture was poured into ice (20 g) and thoroughly extracted with ether. Evaporation of the organic extracts left a residue which was recrystallized from MeOH to give dimer (III) (0.070 g; 70%), mp. 100-101°.

REFERENCES

1. R. G. Enriquez, M. A. Chavez and J. F. Jauregui, Phytochem., 19, 2024 (1980).

2. J. Sanchez and L. C. Ruiz, La Homeopatia en Mexico, 32, 4 (1975).

3. J. J. Mandoki, Department of Pharmacology, IV Mexican Meeting of Pharmacology, Mexico 1980.

4. T. Szeki, Ber., 39, 2422 (1906).

5. J. Haraszti and T. Szeki, Ann., 507, 197 (1933).

6. J. Kovacs, Magyar Kem. Folyoirat, 56, 392 (1950); Chem. Abs., 46, 7556h (1952).

7. K. L. Williamson and W. S. Johnson, J. Am. Chem. Soc., 83, 4623 (1961).