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Pyridazines and Grignard Reagents

XI. Prototropy, Stereochemistry, and Conformational Stability of 4,5-Di-*t*-butyl-3,6-dimethoxydihydropyridazines

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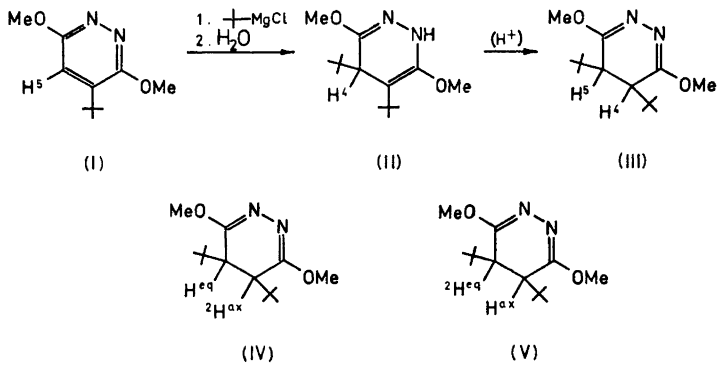
4-*t*-Butyl-3,6-dimethoxypyridazine (I) and *t*-butylmagnesium chloride react to give an adduct, which with water affords 4,5-di-*t*-butyl-3,6-dimethoxy-1,4-dihydropyridazine (II). Acids rapidly convert (II) into *cis*-4,5-*t*-butyl-3,6-dimethoxy-4,5-dihydropyridazine (*cis*-III) and more slowly into (*trans*-III). Stereospecific deuteration of (*cis*-III) at C^4 and C^5 indicates hindered rotation around the C^4-C^5 bond, with a minimum $\Delta G^{\ddagger}$-value of approximately 32 kcal/mol.

Protonation of adducts formed from pyridazines and Grignard reagents have been previously shown to give 1,4-dihydro- or 4,5-dihydropyridazines (see Refs. 1, 2 and literature quoted therein). Addition of *t*-butylmagnesium chloride to 4-*t*-butyl-3,6-dimethoxypyridazine (I), and subsequent protonation by water, gives a 1,4-dihydropyridazine (II), undergoing acid-catalyzed prototropic shifts to *cis*-4,5-dihydropyridazine (III, H^4 and H^5 *cis*) and, observably slower, to the corresponding *trans* isomer.

The structures of (II) and (*cis*-III) follow from the NMR spectra and the observed rearrangements (by NMR). Thus, a broad signal at δ 6 (exchangeable) indicates the presence of an NH group in (II). Upon rearrangement to the 4,5-dihydropyridazine (*cis*-III), an AB-pattern appears, whereas the signals attributable to the methoxy and *t*-butyl groups are only slightly affected. Hence, H^4 and H^5 (in *cis*-III) are diastereotopic and remain so even at 100°. In order to substantiate the observed conformational stability of (*cis*-III), deuterium was specifically introduced to give the isomeric compounds (IV) and (V). This was achieved by carrying out the synthetic reactions, either with (I) as the starting material and deuterium oxide as the decomposing agent or, alternatively, with H^5-deuterated (I) as the substrate and water as the decomposing agent, to give (II) labelled at positions 1 and 4, respectively. Acid-induced rearrangements gave two isomers (formulated as (IV) and (V), respectively) showing singlets at δ-values consistent with those calculated



from the original AB pattern of (*cis*-III). No trace of (IV) or (V) could be detected (NMR) in the preparations of (V) or (IV), respectively, nor could any conversion of (IV) to (V) or of (V) to (IV) be detected when the acid catalysed rearrangements of the deuterated compounds to (*trans*-III, monodeuterated) took place. When, however, the isomer (IV) was heated in *o*-dichlorobenzene to 155° for 15 min, approx. 10 % was obtained (NMR) as (V) and 50 % as (*trans*-III, monodeuterated). This gives a lower limit for $\Delta G^{\ddagger}$ of about 32 kcal/mol for the conversion of (IV) to (V) at 155°.

Conformations and mechanisms. The proposed stereochemistry of the individual compounds is based on the following considerations: protonation (or deuteration) of (II) takes place, for stereoelectronic reasons, at position 5 axially and *trans* to the pseudoaxial *t*-butyl group at position 4 to give (*cis*-III) or (IV), respectively, in a kinetically controlled reaction.[2,3] If a (small) percentage of the protonation does take place *cis* to the *t*-butyl group, the thermodynamically more stable form (*trans*-III) is formed. Conversion of *cis* to *trans* forms may thus involve the acid catalysed reactions:

$$(cis\text{-III}) \rightleftharpoons (\text{II}) \rightleftharpoons (trans\text{-III})$$

This implies a transition state for the formation of (*trans*-III) with two nearly axially oriented protons. The preferred conformation of (*trans*-III), however, is more likely to be that of (III) with the *t*-butyl groups pseudodiaxially placed, partly because of the favourable *anti* arrangement, which, admittedly, must involve repulsive *t*-butyl-π orbital interactions, and partly because the δ-value (2.06) of H^4 and H^5 in (*trans*-III) is closer to the δ-value 2.32 of (IV, H^{eq}) than to the δ-value 2.65 of (V, H^{ax}). Furthermore, a sharp signal from the ring proton of (*trans*-III, monodeuterated) indicates a small coupling ($J < 0.4$ cps) between H and D. Recently, the somewhat analogous tetrahydropyridazine system has been subject of detailed conformational studies.[4]

The considerable barrier to rotation of the C^4-C^5 bond in (*cis*-III), as compared with that in *cis*-1,2-di-*t*-butylcyclohexane,[5] (minimum 32 kcal/mol and 16 kcal/mol, respectively), suggests significant contribution to the rigidity of the molecule from the nitrogens and the π electron system. The diaza analogous of cyclohexenes do show a substantial increase in activation energies

to ring inversion relative to cyclohexene itself (*cf.* Ref. 6). A "ring twisting" process with $\Delta G^{\ddagger} \simeq 23$ kcal/mol has been suggested for 1,2-diethoxycarbonyl-3,6-diphenyl-1,2-dihydropyridazine.[7]

EXPERIMENTAL

Melting points are uncorrected. NMR spectra were recorded on a Varian A-60 instrument using deuteriochloroform as a solvent. The positions of signals are given in ppm (δ-values) relative to tetramethylsilane.

3,6-Dimethoxy-4,5-dideuteriopyridazine. 3,6-Dimethoxypyridazine (2.80 g), sodium methoxide (from *ca.* 100 mg of sodium) and monodeuteriomethanol [8] (4 ml) were kept at 100° for 48 h.[9] Addition of water and extraction with chloroform gave a crude, partly deuterated dimethoxypyridazine. Two more exchange reactions and one recrystallization from a mixture of water (10 ml) and ethanol (1 ml) gave 3,6-dimethoxypyridazine (1.90 g, m.p. 106 – 107°) with 92 % deuterium (NMR; integral of aromatic H, triplet, $J = 1.2$ cps, compared with integral of the methoxy protons).

*4-*t*-Butyl-3,6-dimethoxy-5-deuteriopyridazine (I, deuterated at H^5).* The deuterated dimethoxypyridazine (1.90 g), ether (20 ml), and *t*-butylmagnesium chloride (30 ml, 0.8 M) were heated to reflux for 5 min and subsequently decomposed with methanol (2 ml in 20 ml of ether). The suspension was kept at 3 – 4° while a mixture of bromine (2 ml), pyridine (2 ml), and chloroform (20 ml) was added. Addition of ice, extractions with chloroform, and removal of solvents *in vacuo* gave the bromo compound, which was dehydrobrominated on reflux for 5 min in sodium methoxide (from 2 g of sodium in 20 ml of methanol). Addition of water, extractions with chloroform, and distillation (54 – 76°/0.2 mm) gave a crude product (2.39 g), which was purified by dissolving in petroleum ether (50 ml) and adsorbing the pyridazine on silica gel (Merck, 0.05 – 0.20 mm, 24 g). Impurities, revealed by NMR signals between δ 0.92 and 1.06, were removed by washing the silica gel with petroleum ether (50 ml). Extraction with ether gave deuterated (I), 2.14 g. NMR analysis showed a content of 30 % H (integral of peak at δ 6.56 relative to that of methoxy groups at δ 3.88 and 3.96 and that of the *t*-butyl group at 1.30).

No deuterium exchange took place at position 5 when (I) was treated with sodium methoxide in monodeuteriomethanol at 100° as above.

*4,5-Di-*t*-butyl-3,6-dimethoxy-1,4-dihydropyridazine (II) and* cis- *and* trans-*4,5-di-*t*-butyl-3,6-dimethoxy-4,5-dihydropyridazine (III).* 4-*t*-butyl-3,6-dimethoxypyridazine (I) (196 mg), ether (10 ml), and *t*-butylmagnesium chloride (4 ml 0.8 M) was mixed and kept at 20° (evacuated system) for 4 h. Addition of water (0.6 ml) gave a precipitate and a clear solution of the dihydropyridazine (II), only characterized by its NMR spectrum: δ 0.90 and 1.18 (two *t*-butyl groups), 2.93 (allylic hydrogen), 3.61 and 3.66 (two methoxy groups) and approx. 6 (NH), all singlets. A trace of the starting material (I) was discernible. After an hour at room temperature, the spectrum of (II) was partly replaced by that of (*cis*-III). Addition of acid (*e.g.* acetic acid, see below) catalyzed the reaction and (*cis*-III) was formed together with a trace of (*trans*-III). NMR: (*cis*-III), δ 0.99 and 1.20 (two *t*-butyl groups), 2.32 and 2.65 (AB system of H^4 and H^5, $J = 5.6$ cps), 3.75 and 3.81 (two methoxy groups). Addition of acetic acid (0.2 mmol) to (II) (1 mmol in 0.5 ml deuteriochloroform) resulted in an instant formation of the *cis* form of (III) and subsequent conversion to the *trans* form (only trace of (*cis*-III) observable after one hour). The stable tautomer (*trans*-III) was recrystallized in low yield from petroleum ether at – 80°, colorless crystals, m.p. 68 – 70°. (Found: C 65.85; H 10.25; N 11.21. Calc. for $C_{14}H_{26}N_2O_2$: C 66.11; H 10.30; N 11.01.) NMR: δ 0.89 (two *t*-butyl groups), 2.06 (H^4 and H^5) and 3.75 (two methoxy groups), all singlets. Hydrobromic acid at 100° hydrolyzed (III) to 4,5-di-*t*-butyl-3-methoxy-1,4,5,6-tetrahydro-6-oxopyridazine, m.p. 196 – 198° (colorless needles from ligroin or ethanol). (Found: C 64.97; H 10.07; N 11.66. Calc. for $C_{13}H_{24}N_2O_2$: C 65.10; H 9.75; N 11.82.) NMR: δ 0.97 and 1.00 (two *t*-butyl groups), 2.23 (slightly broadened singlet, H^4 and H^5), 3.64 (methoxy), and 8.64 (broad, NH).

Specifically deuterated dihydropyridazines, (IV) and (V). Addition of deuterium oxide instead of water to the Grignard reagent – pyridazine adduct (I, above) gave (II), NH deuterated. The latter product (1 mmol in 0.5 ml of deuteriochloroform) was tauto-

merized by the addition of monodeuterioacetic acid (approx. 20 μl of a solution in carbon tetrachloride) to give (IV). NMR showed the same resonances as (III, *cis*), see above, expect for the AB system of H^4 and H^5, which now had collapsed to a peak at δ 2.32. A trace of the AB system was discerned above the noise, but there was no resonance at δ 2.65. The isomer (V) was similarly prepared, only the starting material was now (I, H^5 deuterated), and the adduct was decomposed with water as in the preparation of (II) and (III), above. NMR showed both the AB system of (III, *cis*) (from the 30 % undeuterated (I)) and a peak at δ 2.65; the peak of (IV) at δ 2.32 was absent. Both the *cis* dihydropyridazines (IV) and (V) rearranged to the *trans* form. The latter compound (III, *trans*, H^4=D), prepared from (IV) and dissolved in *o*-dichlorobenzene, revealed in NMR (Varian A-100; sweep width 50 cps) a small splitting of the H^5 signal at δ 2.23. The half hight width of the signal was 1.05 cps as compared to 0.45 cps of a standard signal of *o*-dichlorobenzene, suggesting a coupling constant of about 0.3 cps.

Added in proof. A hexadeutero-*t*-butyl group has been introduced on reaction of (I) with $(CD_3)_2CH_3CMgCl$,[10] and is revealed by a signal at δ 0.99 in the resulting (*cis*-III) Provided H^4 assumes a pseudoaxial position, *t*-butyl signals at δ 0.99 and δ 1.20 are indicative of pseudoaxial and pseudoequatorial orientation at C^5 and C^4, respectively. Hence, the observed signal in (*trans*-III) (δ 0.89) suggests pseudodiaxial orientation, in support of the proposed conformation.

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