A Novel Reaction Type Promoted by Aqueous Titanium Trichloride. Synthesis of Unsymmetrical 1,2-Diols

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Electron-withdrawing substituted carbonyl compounds when allowed to react with 2 equiv of aqueous titanium trichloride in the presence of acetone, acetaldehyde, or benzaldehyde afford unsymmetrical 1,2-diols in high yields under very simple experimental conditions.

Introduction

An aqueous acidic 15% solution of titanium trichloride is a fairly rapid, mild reducing agent ($E^\circ = -0.1$ V). This reagent has no effect on aliphatic or aromatic ketones and aldehydes. It easily couples carbonyl compounds activated toward reduction by an electron-withdrawing group, such as a pyridyl residue,[1] to the corresponding symmetrical diols. These diols are formed through dimerization of the intermediate stabilized capto-dative[2] radicals.

By analogy, benzoyl cyanide, a negatively substituted carbonyl compound, when allowed to react with aqueous titanium trichloride in acetic acid medium affords the expected benzyldicyanohydrin.[3]

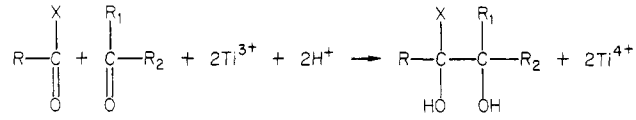
On changing the medium from acetic acid to acetone, a novel reaction type occurs between benzoyl cyanide and acetone, leading to the mixed 1,2-diol as the main product.[3] We have investigated this reaction with the scope to generalize the process which seems to have a wide applicability. We report herein the results obtained with various negatively substituted carbonyl compounds with respect not only to acetone but to acetaldehyde and benzaldehyde also.

Discussion

Titanium trichloride reduction of benzoyl cyanide, benzoylformic acid, methyl benzoylformate, ethyl pyruvate, and 2-acetylpyridine in the presence of either acetone, acetaldehyde, or benzaldehyde affords mixed 1,2-diols in high yields (see Table I) under very simple experimental conditions (e.g., aqueous acidic solution and room temperature). Most of the products synthesized have never been reported before. Each reaction is fairly clean as revealed by NMR and/or GLC analyses of the crude mixture. Back-titration of the amount of unreacted Ti(III) ion shows the equation of Scheme I to account for at least 90% of the reaction products (the excess of the reducing agent was estimated against ferric sulfate solution using potassium thiocyanate solution as indicator). The present reaction is characteristic in several features, mostly regarding the operating mechanism.

(1) It is to be ruled out that mixed 1,2-diol formation is in effect a radical cross-coupling process because a mild reducing agent, such as Ti(III) species, has no effect on acetone, acetaldehyde, or benzaldehyde: actually, these substrates were recovered unchanged in the blank reaction. Only stronger reducing Ti(II) species, generated from $TiCl_4$/Mg amalgama, are able to promote radical cross-coupling to diols between acetone and cyclic saturated ketones.[4]

Scheme I[a]



[a] X = CN, COOH, $COOCH_3$, Py; R = CH_3, Ph; $R_1 = R_2 = CH_3$; R_1 = H, $R_2 = CH_3$; R_1 = H, R_2 = Ph.

(2) It has also been reported that active Ti(O) powder, freshly prepared from $TiCl_3$ dechlorination with potassium[5] or lithium,[6] selectively couples diaryl ketones with acetone to the corresponding mixed olefins. The first operative step of the reaction is believed to proceed through nucleophilic addition of the intermediate dianion to acetone.

(3) The presence of an anion would not be compatible with the aqueous acidic medium (pH ≤ 1) under which Ti(III) species promotes the mixed 1,2-diol synthesis. At most a Ti(IV) anion complex could be proposed as a reaction intermediate, though the formation of a c,d-substituted anion represents matter of speculation: in fact, anions, in contrast to radicals, are destabilized by capto-dative substitution,[2] and furthermore, the very low reducing power of Ti(III) makes difficult a second electron transfer.

On the basis of these observations, an alternative reaction scheme has been tentatively presented[3] as involving a radical addition to the carbonyl carbon atom. Whatever the real mechanism may be, it remains the remarkable outcome that aqueous titanium trichloride provides a potentially useful and simple process for unsymmetrical 1,2-diol synthesis.

Results

When 1 equiv of the substrate, 2 equiv of an aqueous acidic 15% solution of $TiCl_3$, and an excess of acetone (runs 2, 4, 8, 11, 13) were allowed to react under N_2 at room temperature according to the times of Table I, the mixed 1,2-diols **2**, **5**, **10**, **14**, and **16** were recovered after workup as the major products. With acetaldehyde (runs 3, 5, and 9), the α-hydroxy ketone **4**, the mixed 1,2-diols **7** and **12**, along with the 1,3-dioxolanes **3**, **6**, and **11** were obtained. Acetaldehyde required the presence of enough acetic acid to produce an homogeneous solution. The α-hydroxy ketone **4** resulted from hydrogen cyanide elimination of the corresponding 1,2-diol during a silica gel chromatography of the crude mixture. Diols **7** and **12** were a mixture of both threo and erythro forms as shown by their ^{1}H NMR spectra. The 1,3-dioxolanes were formed through subsequent condensation of the primary 1,2-diols with the starting acetaldehyde. As revealed by ^{1}H NMR and GLC analyses, 1,3-dioxolane **3** is a mixture of two stereoisomers

(1) Clerici, A.; Porta, O. *Tetrahedron*, in press.
(2) Viehe, H. G.; Mereny, R.; Stella, L.; Jananseck, Z. *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 917.
(3) Clerici, A.; Porta, O.; Riva, M. *Tetrahedron Lett.* **1981**, *22*, 1043.
(4) Corey, E. J.; Danheiser, R. L.; Chandrasekaran, S. *J. Org. Chem.* **1976**, *41*, 260.
(5) Mc Murry, J. E.; Fleming, M. P. *J. Org. Chem.* **1976**, *41*, 896.
(6) Mc Murry, J. E.; Krepski, L. R. *J. Org. Chem.* **1976**, *41*, 3929.

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in a 1.3:1 ratio, while ^1H NMR spectra of the crude 1,3-dioxolanes **6** and **11** showed a mixture of three out of four (*dl* pairs) possible stereoisomers.

Regarding 1,2-diols **7** and **12** and 1,3-dioxolanes **6** and **11**, no attempts were made to separate the isomers and evaluate their ratios. The wide melting point ranges of 1,3-dioxolane **6** and 1,2-diol **7**, despite the apparent purity of the recrystallized products, were consistent with the stereoisomers mixture. When benzaldehyde was used with sufficient acetic acid to keep homogeneous the resulting solution (runs 6 and 10), the α,β-diphenylglyceric acid **8** and its methyl ester **13** were obtained as threo and erythro mixture (see ^1H NMR spectra). In all cases investigated, optimum reaction conditions involve rapid addition of aqueous titanium trichloride. We have observed that dropwise addition of the reducing solution increases the yields of symmetrical diols: their formation occurs through dimerization of the intermediate radical[1,3] formed. Rapid mixing of the reagents, together with an excess of acetone, acetaldehyde, or benzaldehyde, practically eliminates this competitive reaction. Details regarding the symmetrical 1,2-diol formation have been discussed in a previous paper.[1] However, the very good yields and simple experimental conditions under which the symmetrical 1,2-diols **1**, **9**, and **15** were obtained make the process equally interesting from the synthetic point of view as a valuable alternative to the photo- and electrochemical reduction employed to prepare these diols.[7] Furthermore, this reaction can be also extended to the syntheses of unsymmetrical diols. By allowing two different negatively substituted carbonly compounds (runs 14–16) to react in equimolar amounts, a radical cross-coupling process leads to products **17–19**, together with the symmetrical isomers (see Experimental Section). The α-hydroxy ketones **17** and **18** resulted from subsequent hydrogen cyanide loss during workup. The mixed 1,2-diol **19** was directly recovered from the reaction mixture as an insoluble hydrochloride.

Experimental Section

General Data. Infrared spectra were taken on a Perkin-Elmer 177 spectrometer. Proton magnetic resonance spectra were measured with Varian A-90 and HA-100 spectrometers, and chemical shifts are expressed in parts per million downfield from internal standard Me_4Si. Mass spectra were observed with a Hitachi-Perkin-Elmer RMU-6D spectrometer at an ionizing voltage of 70 eV. Gas chromatographic analyses were performed on a Hewlett-Packard 5750-G instrument with a flow rate of 30 mL min^{-1} N_2 on a 5 ft × $^1/_8$ in. column packed with 3% FFAP. Melting points are uncorrected. All chemicals employed were either reagent grade or the best research grade obtainable and were furtherly purified by conventional techniques when necessary.

Procedures for Unsymmetrical Diol Formation. Runs 2, 4, 8, and 11. The substrate (10 mmol) in acetone (60 mL) and a 15% aqueous solution off $TiCl_3$ (20 mmol) added all at once were allowed to react at room temperature under N_2 for the times reported in Table I. After evaporation of the excess acetone, the mixture was extracted with ethyl acetate (three times). The combined extracts, washed with H_2O, dried over $MgSO_4$, and concentrated to dryness in vacuo, afforded the mixed diols **2**, **5**, **10**, and **14** as the major products.

Run 13. After evaporation of acetone, the residual mixture was added of 20 mL of 30% dibasic ammonium citrate solution, and the pH was adjusted to 8–9 by addition of a 10% NaOH solution. The resulting mixture, washed with H_2O and evaporated to dryness, afforded the diol **16** as an oil in almost quantitative yield.

Runs 3, 5, and 9. Reaction conditions and workup were in accordance with runs 2, 4, 8 and 11, except that, instead of acetone, acetaldehyde (60 mL) and glacial acetic acid (20 mL) as cosolvent were used. Dioxolanes **3**, **6**, and **11** were separated from adducts **4**, **7**, and **12**, respectively, by column chromatography on silica gel (eluent hexane/ethyl acetate, 7:3).

Runs 6 and 10. Reaction conditions and workup were as described for runs 2, 4, 8, and 11, expect that benzaldehyde (20 mL) and glacial acetic acid (30 mL) were used. The excess of benzaldehyde was distilled off. The diols **8** and **13** were recovered as crystalline products by addition of an ether/petroleum ether mixture to the residue.

General Procedure for Symmetrical Diol Coupling. Runs 1, 7, and 12. To a well-stirred solution of the substrate (10 mmol) in glacial acetic acid (10 mL) was added dropwise a 15% aqueous solution of $TiCl_3$ (10 mmol) under N_2. The reaction mixture was allowed to react at room temperature until the blue color of $TiCl_3$ was barely kept in the reaction flask for the times reported in Table I. Adequate workup[1,3] afforded the diols **1** and **15**. The methyl diphenyltartarate **9** (meso and *dl* forms) was obtained after extraction of the reaction mixture with chloroform, followed by evaporation in vacuo to dryness of the organic solvents: 1.3:1.0 ratio of meso/*dl* by ^1H NMR analysis of the crude mixture.

General Procedure for Unsymmetrical Diol Coupling. Runs 14–16. To a well-stirred solution of pyridine aldehydes or ketones (10 mmol) and benzoyl cyanide (10 mmol) in glacial acetic acid (10 mL) was added dropwise a 15% aqueous solution of $TiCl_3$ (20 mmol) at room temperature while N_2 was bubbled through. The crude mixture was extracted (three times) with ether. The combined extracts, dried over anhydrous Na_2SO_4 and concentrated in vacuo, afforded benzildicyanohydrin and unreacted benzoyl cyanide. The residual aqueous solution (20 mL of a 30% dibasic ammonium citrate solution was added to prevent hydrolytic precipitation of Ti(IV) dioxide hydrate) was carefully neutralized with a saturated aqueous solution of K_2CO_3 and extracted with chloroform. The organic layers, dried and concentrated to dryness in vacuo, afforded the products **17** and **18**. The adduct **19** was directly recovered from the reaction mixture as an insoluble hydrochloride. The symmetrical diols of pyridine aldehydes and ketones were recovered by ethyl acetate extraction of the residual aqueous solution at higher pH (9–10).

Spectroscopic Data. The structures of the products obtained were deduced from the following data.

Benzyldicyanohydrin (1). See ref 3.

1-Phenyl-1-cyano-2-methyl-1,2-propanediol (2). See ref 3.

2,4-Dimethyl-5-cyano-5-phenyl-1,3-dioxolane (3). The mixture of the two stereoisomers was separated by preparative gas chromatography on 10% FFAP. One stereoisomer: NMR ($CDCl_3$) δ 1.4 (3 H, CH_3, d), 1.6 (3 H, CH_3, d), 3.86 (1 H, CH, q), 5.42 (1 H, CH, q), 7.3–7.6 (5 H, Ph H, m). The other stereoisomer: NMR ($CDCl_3$) δ 0.9 (3 H, CH_3, d), 1.46 (3 H, CH_3, d), 4.48 (1 H, CH, q), 5.32 (1 H, CH, q), 7.24–7.6 (5 H, Ph H, m); MS, *m/e* 203 (M), 159, 115 (base peak), 105, 77, 43; IR (film) ν_{max} 2220 (CN), 1170, 1145, 1070, 1020 (five characteristic bands of dioxolane ring[8]) cm^{-1}.

Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.93; H, 6.40; N, 6.89. Found: C, 70.9; H, 6.6; N, 6.7.

2-Hydroxy-1-phenyl-1-propanone (4): NMR ($CDCl_3$)[9] δ 1.4 (3 H, CH_3, d), 3.8 (1 H, OH, br, exchanged with D_2O), 5.16 (1 H, CH, q), 7.2–7.6 (3 H, Ph H, m), 7.8–8.0 (2 H, Ph H, m); IR (film) ν_{max} 3450, 1680, 1590 cm^{-1}; MS, *m/e* 150 (M), 133, 107, 105 (base peak), 77, 45, 43.

2-Phenyl-2,3-dihydroxy-3-methylbutanoic acid (5): mp 91–2 °C (from ether/petroleum ether, 1:1); NMR ($CDCl_3$) δ 1.2 (3 H, CH_3, s), 1.3 (3 H, CH_3, s), 6.34 (3 H, 3 OH, br, exchanged with D_2O), 7.32 (3 H, Ph H, m), 7.7 (2 H, Ph H, m); IR (Nujol) ν_{max} 3440, 3360, 1710 cm^{-1}.

Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.86; H, 6.67. Found: C, 63.0; H, 6.7.

2,4-Dimethyl-5-phenyl-5-carboxyl-1,3-dioxolane (6): mixture of three stereoisomers; mp 79–85 °C (from ether/petroleum ether, 8:2); NMR ($CDCl_3$) δ 0.8–1.65 (6 H, 2 CH_3, 6 d), 4.0–5.7

(7) (a) Raaen, V. F. *J. Org. Chem.* **1966**, *31*, 3310. (b) Juday, R. E. *Ibid.* **1958**, *23*, 1010. (c) Bencze, V. L.; Burckhardt, C. A.; Yost, W. L. *Ibid.* **1962**, *27*, 2865. (d) Stocker, J. H.; Jenevein, R. M. *Ibid.* **1969**, *34*, 2807.

(8) Barker, S. A.; Bowrne, E. J.; Pinkard, R. M.; Whiffen, D. H. *J. Chem. Soc.* **1959**, 807.

(9) Hung, S.; Wehner, G. *Chem. Ber.* **1979**, *112*, 2067.

Table I. Reaction Conditions and Product Yields

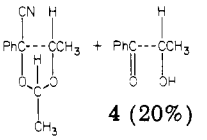
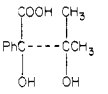
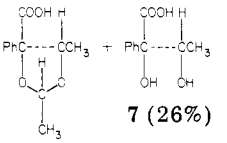
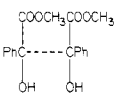
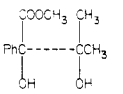
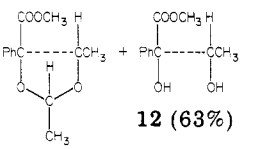
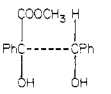
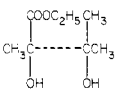
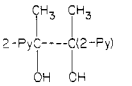
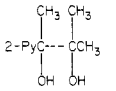
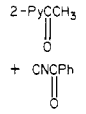
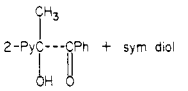
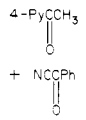
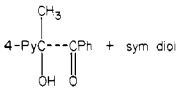
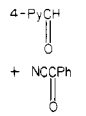
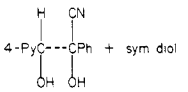
run	substrate	solvent	conditions	product isolated yield[a] (%)
1		acetic acid	1 h; sa[c]	 **1** (75%)
2		acetone	1 h; ra[d]	 **2** (54%)
3		acetaldehyde (acetic acid)[e]	4 h; ra	 **4** (20%) **3** (53%)
4		acetone	0.5 h; ra	 **5** (85)
5		acetaldehyde (acetic acid)[e]	1 h; ra	 **7** (26%) **6** (70%)
6		benzaldehyde (acetic acid)[e]	4 h; ra	 **8** (58%)
7		acetic acid	4 h; sa	 **9** (meso/*dl*, 1.3:1)[f] (61%)
8		acetone	1 h; ra	 **10** (85%)
9		acetaldehyde (acetic acid)[e]	5 h; ra	 **12** (63%) **11** (28%)
10		benzaldehyde (acetic acid)[e]	6 h; ra	 **13** (55%)
11		acetone	10 h; ra	 **14** (83%)
12		acetic acid	7 h; sa	 **15** (meso/*dl*, 0.59:1)[f] (72%)

Table I (*Continued*)

run	substrate	solvent	conditions	product isolated yield[a] (%)
13		acetone	6 h; ra	 **16** (95%)
14		acetic acid	4 h; sa	 **17** (44%)
15		acetic acid	4 h; sa	 **18** (44%)
16		acetic acid	2 h; sa	 **19** (40%)

[a] Yields are based on the starting substrate. [b] See ref 3. [c] sa = slow addition of $TiCl_3$. [d] ra = rapid addition of $TiCl_3$. [e] Added as cosolvent. [f] Determined by ^1H NMR spectroscopy. [g] See ref 1.

(2 H, 2 CH, 6 q), 7.3–7.8 (5 H, Ph, H, m), 10.1 (1 H, COOH, s, exchanged with D_2O); IR (Nujol) ν_{max} 3300–2500, 1700, 1160–1020 (five characteristic bands of dioxolane ring[8]) cm^{-1}; MS, *m/e* 221 (M – 1), 178, 133, 115, 105 (base peak) 77, 43.

2-Phenyl-2,3-dihydroxybutanoic acid (7): threo and erythro mixture; mp 158–165 °C (from chloroform); NMR (acetone-d_6) δ 0.9 and 1.2 (3 H, CH_3, 2 d), 4.5 (1 H, CH, q), 6.0 (3 H, 3 OH, br, exchanged with D_2O), 7.3 (3 H, Ph H, m), 7.7 (2 H, Ph H, m); IR (Nujol) ν_{max} 3300, 1690, 1250, 700 cm^{-1}.

Anal. Calcd for $C_{10}H_{12}O_4$: C, 61.22; H, 6.12. Found: C, 61.3; H, 6.4.

α,β-Diphenylglyceric acid (8): threo and erythro mixture; mp 184–9 °C;[10] NMR (acetone-d_6) δ 5.0 (3 H, 3 OH, br, exchanged with D_2O), 5.46 and 5.50 (1 H, CH, 2 s), 7.0–8.0 (10 H, Ph H, m); IR (Nujol) ν_{max} 3520, 3450, 3100–2500, 1690 cm^{-1}; MS, *m/e* 258 (M), 240, 152 (base peak), 107, 105, 79, 77.

Methyl *meso*-diphenyltartarate (9): mp 153 °C (from ether) (lit.[7b] mp 151–153 °C); NMR ($CDCl_3$) δ 3.75 (6 H, 2 OCH_3, s), 5.0 (2 H, 2 OH, s, exchanged with D_2O) 7.0–7.2 (10 H, Ph H, m); IR (Nujol) ν_{max} 3500, 1710 cm^{-1}.

Methyl *dl*-diphenyltartarate (9): mp 120–121 °C (from methanol) (lit.[7b] mp 119–121 °C); NMR ($CDCl_3$) δ 3.7 (6 H, 2 OCH_3, s), 5.5 (2 H, 2 OH, br, exchanged with D_2O), 7.0–7.5 (10 H, Ph H, m).

Anal. Calcd for $C_{18}H_{18}O_6$: C, 65.45; H, 5.45. Found: C, 65.6; H, 5.7.

Methyl 2-phenyl-2,3-dihydroxy-3-methylbutanoate (10): mp 98 °C (from ether); NMR ($CDCl_3$) δ 1.2 (3 H, CH_3, s), 1.3 (3 H, CH_3, s), 3.0 (2 H, 2 OH, br, exchanged with D_2O), 3.9 (3 H, OCH_3, s), 7.3 (3 H, Ph H, m), 7.7 (2 H, Ph H, m); IR (Nujol) ν_{max} 3500, 3300, 2580 and 2500 (intramolecular H bond with carbonyl), 1700, 1250; MS, *m/e* 225 (M + 1),[11] 166, 106, 105 (base peak), 77, 59.

2,4-Dimethyl-5-phenyl-5-(methoxycarbonyl)-1,3-dioxolane (11): mixture of three stereoisomers; NMR ($CDCl_3$) δ 0.9–1.6 (6 H, 2 CH_3, 6 d), 3.65–3.92 (3 H, OCH_3, 3 s), 4.15–5.7 (2 H, CH, 6 q), 7.3–8.1 (5 H, Ph H, m); IR (film) ν_{max} 1730, 1160–1000 (characterisitic bands of dioxolane ring[8]) cm^{-1}; MS, *m/e* 192 (M – 44), 178, 133, 105 (base peak), 79, 77, 59, 51, 43.

Methyl 2-phenyl-2,3-dihydroxybutanoate (12): threo and erythro mixture; NMR ($CDCl_3$) δ 0.9 and 1.15 (3 H, CH_3, 2 d) 3.4 (2 H, 2 OH, br, exchanged with D_2O), 3.68 and 3.7 (3 H, OCH_3, 2 s), 4.3–4.7 (1 H, CH, 2 q), 7.3 (3 H, Ph H, m), 7.65 (2 H, Ph H, m); IR (film) ν_{max} 3480, 1730, 1250 cm^{-1}.

Methyl *erythro*-α,β-diphenylglycerate (13): mp 165–167 °C (from ether) (lit.[10] 153 °C); NMR ($CDCl_3$) δ 2.7 (2 H, 2 OH, br, exchanged with D_2O), 3.8 (3 H, OCH_3, s), 5.4 (1 H, CH, s), 7.3–7.5 (8 H, Ph H, m), 7.7–7.9 (2 H, Ph H, m); IR (Nujol) ν_{max} 3500, 1720, 1260 cm^{-1}; MS, *m/e* 273 (M + 1),[11] 255, 254, 195, 166, 107, 106, 105 (base peak), 79, 77, 51.

Anal. Calcd for $C_{16}H_{16}O_4$: C, 70.57; H, 5.93. Found: C, 70.5; H, 5.8.

Methyl *threo*-α,β-diphenylglyerate (13): mp 142–144 °C (from ether/petroleum ether) (lit.[10] mp 144 °C); NMR ($CDCl_3$) δ 3.6 (3 H, OCH_3, s), 4.3 (2 H, 2 OH, br, exchanged with D_2O), 5.4 (1 H, CH, s), 7.0–7.8 (10 H, Ph H, m); IR (Nujol) ν_{max} 3300, 1710, 1260.

Ethyl 2,3-dimethyl-2,3-dihydroxybutanoate (14): NMR ($CDCl_3$) δ 1.2–1.45 (12 H, 4 CH_3, m), 4.3 (2 H, CH_2 q), 4.5 (2 H, 2 OH, s, exchanged with D_2O); IR (film) ν_{max} 3500, 1725 cm^{-1}.

Anal. Calcd for $C_8H_{16}O_4$: C, 54.54; H, 9.09. Found: C, 54.4; H, 9.2.

2,3-Bis(2-pyridyl)-2,3-butanediol (15). See ref 1.

2-(2-Pyridyl)-3-methyl-2,3-butanediol (16): NMR ($CDCl_3$) δ 1.07 (6 H, 2 CH_3, s), 1.6 (3 H, CH_3, s), 4.0 (1 H, OH, br, exchanged with D_2O), 5.1 (1 H, OH, br, exchanged with D_2O), 7.1–7.25 (1 H, Py γ-H, m), 7.5–7.7 (2 H, Py β-H, m), 8.45 (1 H, Py α-H, m); MS, *m/e* 182 (M + 1),[11] 164, 146, 122 (base peak), 79, 59, 43.

2-(2-Pyridyl)-2-hydroxy-1-phenyl-1-propanone (17): mp 96–97 °C (from petroleum ether/ether); NMR ($CDCl_3$) δ 1.86 (3 H, CH_3, s), 6.05 (1 H, OH, s, exchanged with D_2O), 7.2–7.7 (6 H, Ph H and Py H, m), 7.9 (2 H, Ph H, dd), 8.6 (1 H, Py α-H, m); IR (Nujol) ν_{max} 3200, 1690, 1590, 1240, 710 cm^{-1}; MS, *m/e* 228 (M + 1),[11] 227, 226, 217, 210, 199, 182, 181, 167, 154, 122 (base peak), 105, 104, 77.

2-(4-Pyridyl)-2-hydroxy-1-phenyl-1-propanone (18): mp 205 °C (from aqueous ethanol); NMR (Me_2SO) δ 1.65 (3 H, CH_3, s), 6.75 (1 H, OH, br, exchanged with D_2O), 7.2–7.5 (5 H, Ph H and Py β-H, m), 7.9 (2 H, Ph H, dd), 8.5 (2 H, Py α-H, m); IR (KBr) ν_{max} 3150, 1670, 1600, 1255, 1050, 1000 cm^{-1}; MS, *m/e* 227 (M), 167, 122, 105 (base peak), 77.

Anal. Calcd for $C_{14}H_{13}NO_2$: C, 72.5; H, 6.0; N, 6.5. Found: C, 74.13; H, 5.9; N, 6.16.

1-(4-Pyridyl)-2-cyano-2-phenyl-1,2-ethanediol hydrochloride (19): mp 214 °C dec (from aqueous ethanol); NMR (Me_2SO) δ 5.1 (1 H, CH, s), 7.0–8.0 (2 H, 2 OH, br, exchanged with D_2O), 7.2–7.7 (5 H, Ph H and Py β-H, m), 8.0 (2 H, Ph H,

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(11) This compound shows a very abundant M + H parent ion due to intramolecular reactions occurring at low pressure into the mass spectrometer. A study of this particular behavior is underway.

d), 8.9 (2 H, Py α-H, d); IR (Nujol)[12] ν_{max} 3200, 2800–2300 (NH^+ stretching), 1640, 1500, 1065, 750 cm^{-1}; MS,[13] m/e 213, 183, 108, 107, 106, 105 (base peak), 77, 36 (HCl), 27 (HCN); ^{13}C NMR (Me_2SO_4; 25.2 MHz) δ 76.0 (C-OH, d), 76.9 (C-CN, s), 119.0 (CN, s), 126.1 (Py β-C, d), 127.4 (d), 128.1 (d), 128.8 (d), 138.5 (Ph, s), 141.0 (Py α-C, d), 158.6 (Py γ-C, s).

(12) The apparent absence of the CN group absorption may be explained by its triple-bond character which can be greatly modified by interaction with neighboring hydroxyl groups: Raaen, V. R. *J. Org. Chem.* **1966**, *31*, 3310, note 9.

(13) The mass spectrum of **19** does not show the molecular ion because of the complete loss of HCN due to its thermal decomposition. The presence of the CN group is confirmed by the very intense m/e 27 ion corresponding to HCN loss.

Anal. Calcd for $C_{13}H_{13}N_2O_2Cl$: C, 58.97; H, 4.91; N, 10.58. Found: C, 59.0; H, 4.8; N, 10.6.

Registry No. **1**, 10425-22-6; **2**, 78387-03-8; **3**, 81390-08-1; **4**, 5650-40-8; **5**, 81390-09-2; **6**, 81390-10-5; *erythro*-**7**, 63031-61-8; *threo*-**7**, 81390-11-6; *erythro*-**8**, 81390-12-7; *threo*-**8**, 81390-13-8; *meso*-**9**, 81390-14-9; *dl*-**9**, 81390-15-0; **10**, 81390-16-1; **11**, 81390-17-2; *erythro*-**12**, 63031-62-9; *threo*-**12**, 81390-18-3; *erythro*-**13**, 81390-19-4; *threo*-**13**, 81390-20-7; **14**, 81390-21-8; *meso*-**15**, 20445-38-9; *dl*-**15**, 20445-39-0; **16**, 81390-22-9; **17**, 81390-23-0; **18**, 81390-24-1; **19**, 81390-25-2; $TiCl_3$, 7705-07-9; benzoyl cyanide, 613-90-1; benzoylformic acid, 611-73-4; methyl benzoylformate, 15206-55-0; ethyl pyruvate, 617-35-6; 2-acetylpyridine, 1122-62-9; acetone, 67-64-1; acetaldehyde, 75-07-0; benzaldehyde, 100-52-7; 4-acetylpyridine, 1122-54-9; 4-pyridinecarboxaldehyde, 872-85-5.

Crystal Structure of "Homoaromatic" 6-Ethyl-3-phenyl-1,6-dihydro-1,2,4,5-tetrazine[1a]

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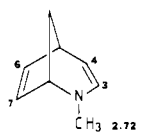
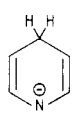
The crystal structure of 6-ethyl-3-phenyl-1,6-dihydro-1,2,4,5-tetrazine (**3**) was elucidated by X-ray structure analysis. This analysis revealed that the molecule is in a boat conformation with C(6) and C(3) pointing upward with dihydral angles of 49.3° and 26.7°, respectively. N(1) was found to be sp^2 hybridized, and the N(1)–N(2), N(2)–N(3), C(3)–N(4), and N(4)–N(5) bond distances were found to be between single and double bond length, in agreement with the expected electron delocalization.

^1H NMR spectroscopy[2] revealed that 1,6-dihydro-1,2,4,5-tetrazines are homoaromatic[3,4] species. The aromatic sextet is formed by the four electrons in the two double bonds and the lone pair of N(1); therefore, a 1,6-dihydro-1,2,4,5-tetrazine can be considered as a monohomotetrazole. In order to enable electron delocalization in the aromatic part, homoaromatic compounds have to be nonplanar with one methylene group pointing out of the plane; consequently, the p_z orbitals of the atoms adjacent to the methylene bridge are canted. Therefore, the overlap here becomes restricted to single lobes at the side of the molecule opposite the bridging atom. For this reason 1,6-dihydro-1,2,4,5-tetrazines were considered[2] to contain an approximately planar tetrazine ring (see Figure 1) with a shortened N(1)–N(5) distance with respect to the corresponding distance in 1,2,4,5-tetrazine, so that overlap and delocalization are possible.

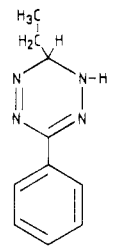
There are very few reports in the literature about homoaromatic compounds containing heteroatoms in their ring: e.g., the UV spectrum of *N*-methyl-2-azabicyclo-[3.2.1]octa-3,6-diene (**1**)[5] can be explained by the assumption of a homoaromatic contribution; the 1,4-dihydropyridyl anion (**2**)[6], on the contrary, was not found to be a homoaromatic species. By use of ^1H NMR spectroscopy, 6-ethyl-3-phenyl-1,6-dihydro-1,2,4,5-tetrazine (**3**) was found to exist in one conformation in solution.[2] The



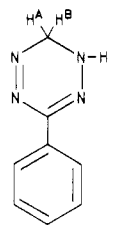
1



2



3



4

hydrogen at the sp^3 carbon atom is above the tetrazole ring, and the alkyl group is in the exo position. In contrast, at room temperature, 3-phenyl-1,6-dihydro-1,2,4,5-tetrazine (**4**) undergoes an inversion between two conformations, one with the methylene group pointing upward and the other with the methylene downward.[2] Since **3** is easily obtained in crystalline form, it is possible to obtain direct information about the correctness of the assumed conformation by a crystal structure determination.

Results and Discussion

The crystals of **3** (from pentane/ether) are orthorhombic, with space group P_{bca}. The unit cell which has dimensions a = 8.349 (1), b = 10.252 (1), and c = 23.041 (2) Å and contains eight molecules of **3**, leading to a calculated density of 1.267 g cm^{-3}. A total of 1454 reflections were collected at 223 K (because the compound decomposes at room temperature) on a Nonius CAD-4 automatic fractometer by using graphite-monochromatized Cu Kα radiation. No absorption correction was applied (crystal

(1) (a) Part 6 on 1,2,4,5-tetrazines and their derivatives. For part 5 see: Counotte-Potman, A.; Van der Plas, H. C.; Van Veldhuizen, A.; Landheer, C. A. *J. Org. Chem.* **1981**, *46*, 5102. (b) Laboratory of Crystallography, J. H. van't Hoff Institute, University of Amsterdam, Nieuwe Achtergracht 166, 1018 WS Amsterdam, The Netherlands.

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