was prepared by the general procedure described for **3c**. After workup, an oily residue was obtained. It was purified on an ODS-C_{16} (30–75 μm) column eluted with aqueous methanol to give **3a** in 21% yield; IR 1730, 1240, 1030 cm^{-1}.

Preparation of *N*-[2-[3,4-(Methylenedioxy)phenyl]-ethyl]-*N*-(diethylphosphoryl)glycine (3b). By the general procedure, 3.0 g of **2b** was treated with 2 g (60% oil dispersion) of NaH and then with 2 g of chloroacetic acid. After regular workup, the residue oil was purified on a silica gel column eluted by *n*-hexane/ethanol [3/2 (v/v)]. The compound **3b** (2.23 g) was obtained in 62% yield as a semisolid: IR 1735, 1247, 1020 cm^{-1}; ^1H NMR δ 1.28 (6 H, m), 2.70 (2 H, t), 3.17 (2 H, t), 3.80 (2 H, d, J = 12.5 Hz), 4.05 (4 H, m), 5.84 (2 H, s), 6.58 (3 H, m), 9.70 (1 H, br). Anal. Calcd for $C_{15}H_{22}NO_7P$: C, 50.14; H, 6.17; N, 3.90. Found: C, 50.16; H, 6.64; N, 3.88.

Preparation of *N*-[2-(3-Methoxy-4-ethoxyphenyl)-ethyl]-*N*-(diisopropoxyphosphinyl)glycine (3d).[7] The compound was synthesized from 17.9 g of **2d** in a similar manner as described above. The compound **3d** (17.0 g) was obtained as colorless crystal, mp 83–5 °C, in 81% yield; IR 1730, 1230, 986 cm^{-1}.

Preparation of *N*-[2-[3,4-(Methylenedioxy)phenyl]-ethyl]-*N*-(di-*n*-butoxyphosphinyl)glycine (3e). The compound **2e** (10.7 g), in 90 mL of THF, was treated with 6 g (60%) of NaH and then 6.4 g of chloroacetic acid. After regular workup, **3e** (13.0 g) was obtained as a semisolid. An analytical sample was purified on an ODS-C_{16} (30–75 μm) column eluted with aqueous methanol: IR (max) 1730, 1245, 1035 cm^{-1}; ^1H NMR δ 0.93 (6 H, m), 1.38 (4 H, m), 1.62 (4 H, m), 2.70 (2 H, m), 3.18 (2 H, m), 3.80 (2 H, d, J = 12.0 Hz), 4.0 (4 H, m), 5.86 (2 H, s), 6.60 (3 H, m), 11.08 (1 H, br). Anal. Calcd for $C_{19}H_{30}NO_7P$: C, 54.94; H, 7.23; N, 3.37. Found: C, 54.33; H, 7.45; N, 3.16.

Preparation of 2,3,4,5-Tetrahydro-7,8-(methylenedioxy)-*N*-(diisopropoxyphosphinyl)-3-benzazepin-1-one (4c).[7] The general procedure for the synthesis of **4a–e** was as follows. To a solution of 1.11 g (0.0020 mol) of **3c** in 30 mL of dry chloroform was added 0.80 mL (0.0057 mol) of trifluoroacetic anhydride under a gentle stream of nitrogen and with stirring. After 20 min, the mixture was cooled in an ice bath. A total of 1.0 mL (0.0087 mol) of stannic chloride was introduced with a hyperdermic syringe over 10 min. The mixture was stirred at 15 °C for 4 h. The resultant mixture was poured into a mixture of crushed ice and 6 N HCl. The chloroform layer was seperated, and the aqueous layer was extracted with chloroform. The organic solution was combined, washed with water, dilute sodium bicarbonate solution, and then water, and then dried by $MgSO_4$ and evaporated. Pale yellow crystals of **4c** [0.81 g (77%)] were obtained. An analytical sample was prepared by recrystallization from methanol/water, giving crystals as colorless needles; mp 154–6 °C (73%); IR 1670, 1250, 980 cm^{-1}.

Preparation of 2,3,4,5-Tetrahydro-7,8-(methylenedioxy)-*N*-(dimethoxyphosphinyl)-3-benzazepin-1-one (4a). Following the general procedure, 0.311 g of **3a** was treated with 0.6 mL of trifluoroacetic anhydride and 0.7 mL of $SnCl_4$ at 0 °C for 2 h and then at 5 °C for 12 h. After regular workup, 0.23 g (74%) of **4a** were obtained. Recrystallization from ether gave 0.135 g (44%) of colorless crystals: mp 128–9 °C; IR 1670, 1240, 1030 cm^{-1}; ^1H NMR δ 2.93 (2 H, t), 3.40 (8 H, m), 3.90 (2 H, d, J = 11 Hz), 5.97 (2 H, s), 6.61 (1 H, s), 7.17 (1 H, s). Anal. Calcd for $C_{13}H_{16}NO_6P$: C, 49.84; H, 5.11; N, 4.47. Found: C, 50.07; H, 5.18; N, 4.48. MS, M^+ 313 (100), M + 1 (17.2), 298 (4.9) 285 (13.6), 270 (4.9), 254 (2.2), 188 (44), 176 (52.3).

Preparation of 2,3,4,5-Tetrahydro-7,8-(methylenedioxy)-*N*-(diethoxyphosphinyl)-3-benzazepin-1-one (4b). Following the general procedure, 0.718 g of **3b** was treated with 1.2 mL of trifluoroacetic anhydride and 1.3 mL of $SnCl_4$ in 20 mL of $CHCl_3$. After workup, 0.38 g (56%) of light yellow solid was obtained. Recrystallization from ether gave 0.23 g (34%) of **4b** as colorless crystals: mp 92–3 °C; IR 1670, 1240, 1030 cm^{-1}; ^1H NMR δ 1.16 (6 H, m), 2.93 (2 H, m), 3.44 (2 H, m), 3.65 (2 H, m), 3.84 (2 H, m), 3.91 (2 H, d, J = 12.5 Hz), 5.97 (2 H, s), 6.62 (1 H, s), 7.17 (1 H, s). Anal. Calcd for $C_{15}H_{20}NO_6P$: C, 52.79; H, 5.87; N, 4.11. Found: C, 52.54; H, 5.76; N, 3.91.

Preparation of 2,3,4,5-Tetrahydro-7-methoxy-8-ethoxy-*N*-(diisopropoxyphosphinyl)-3-benzazepin-1-one (4d).[7] Compound **4d** was prepared according to the method for the synthesis of **4c**. The crude product was recrystallized from ethyl ether, giving colorless needles: mp 92–4 °C (60%); IR 1670, 1250, 980 cm^{-1}.

Preparation of 2,3,4,5-Tetrahydro-7,8-(methylenedioxy)-*N*-(di-*n*-butoxyphosphinyl)-3-benzazepin-1-one (4e). **3e** (1.16 g) was treated with 1.8 mL of trifluoroacetic anhydride and 2.2 mL of $SnCl_4$ at 15 °C for 4 h and then at 5 °C for 24 h. After workup, the product was recrystallized from $CHCl_3$/*n*-hexane, giving 0.17 g (16%) of colorless crystals: mp 73–5 °C; IR 1675, 1240, 1030, 990 cm^{-1}; ^1H NMR δ 0.87 (6 H, m), 1.26 (4 H, m), 1.47 (4 H, m), 2.92 (2 H, t), 3.43 (2 H, m), 3.55 (2 H, m), 3.75 (2 H, m), 3.91 (2 H, d, J = 10.0 Hz), 5.97 (2 H, s), 6.63 (1 H, s), 7.17 (1 H, s). Anal. Calcd for $C_{19}H_{28}NO_6P$: C, 57.43; H, 7.05; N, 3.52. Found: C, 57.65; H, 7.15; N, 3.39.

Keto Amine–HCl Salt 5a. A solution of 0.245 g of **4c** in 10 mL of dry THF was saturated with dried HCl(g). After being kept overnight at 20 °C, the precipitate was filtered and washed with ether, giving 0.136 g (85%) of **5a** as colorless crystals. Compound **4a** (0.028 g), after the same treatment, gave 0.016 g of **5a** (77%). Compound **4b** (0.023 g) gave 0.013 g (78%) of **5a**. Compound **4e** (0.030 g) gave 0.014 g (75%) of **5a**. All these salts have the same IR: 1650, 1560, 2350–2800 cm^{-1}. ^1H NMR in trifluoroacetic acid: 3.31 (2 H, t), 3.80 (2 H, t), 4.46 (2 H, s), 6.09 (2 H, s), 6.82 (1 H, s), 7.26 (1 H, s).

Acknowledgment. Preliminary account of this work was presented at the International Conference of Phosphorus Chemistry, Nice, France, Sept 1983. Thanks to Prof. T. H. Chan at McGill University for reading this manuscript.

Registry No. **2a**, 87261-13-0; **2b**, 92269-46-0; **2c**, 87212-43-9; **2d**, 87212-42-8; **2e**, 92241-51-5; **3a**, 87212-45-1; **3b**, 92241-52-6; **3c**, 87212-49-5; **3d**, 87212-48-4; **3e**, 92241-53-7; **4a**, 89815-74-7; **4b**, 92241-54-8; **4c**, 87212-50-8; **4d**, 87212-53-1; **4e**, 92241-55-9; **5a**, 87212-52-0; chloroacetic acid, 79-11-8.

An Extremely Facile Carbon Epimerization

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Received June 4, 1984

In connection with studies of the methylenecyclopropane rearrangement,[2] optically active *trans*-2,3-dicyanomethylenecyclopropane (1) was prepared. Attempts to measure the optical rotation of **1** in methanol led to the discovery of the rapid epimerization reported herein. The polarimeter reading was observed to decrease rapidly with time, leading to the pseudo-first-order plot shown in Figure 1. Similar behavior was observed in distilled water but not in benzene, chloroform, or acetonitrile. When **1** was dissolved in methanol that had previously been saturated with sodium bicarbonate, no optical rotation was observed. Liquid chromatography of the product mixtures showed the presence of **1** and a more polar material, later identified as the cis isomer **2**. Epimerization of **1** in methanol-*O-d* led to considerable diminution of protium on the ring carbons as shown by NMR.

The latter experiment rules out an alternative mechanism involving reversible ring-opening. Also in contradiction to that possibility is the known[2] overwhelming thermodynamic preference for the rearranged methylenecyclopropanedinitriles, ((*Z*)- and (*E*)-2-cyanocyclopropylidene)acetonitrile (**3** and **4**). If ring-opening

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0022-3263/84/1949-4551$01.50/0

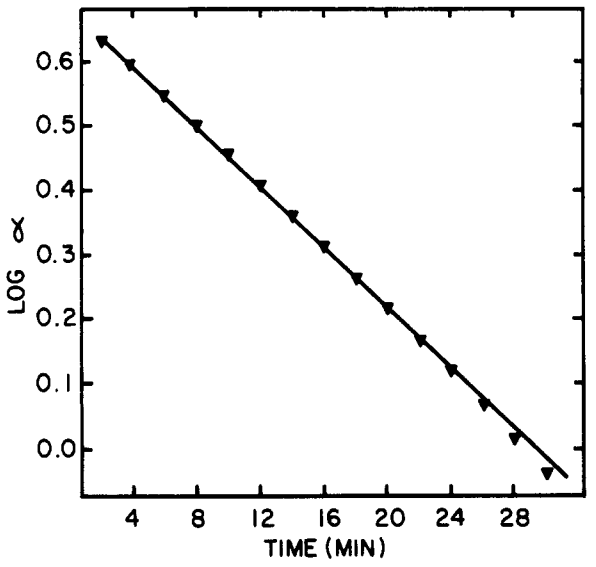
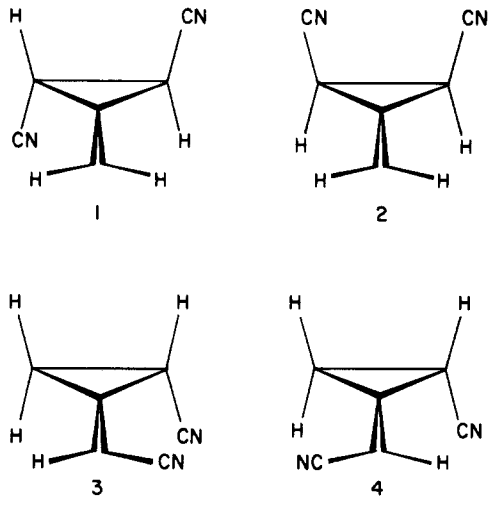


Figure 1. Racemization of 1 (0.288 M in MeOH) at 26 °C.

Chart I



had occurred under these conditions, these isomers would have been detected.

The identity of the active base is of interest. Presumably, sodium bicarbonate would buffer out any adventitious strong base. The apparent effect of the bicarbonate was to increase the rate sufficiently that the racemization was complete in the time required (ca. 1 min) to load the solution into the polarimeter. Whether the active base in the absence of bicarbonate is solvent or the dinitriles themselves has not been established, but two observations suggest that the latter is in fact the case. First, the rate increased slightly with time (Figure 1), which would be consistent with the increase in concentration of **2**, presumably a slightly stronger base than **1**. Second, the rate in water increased when the initial concentration of 1 was increased (see Table I).

The facile epimerization of **1** is explicable as a combination of the known effects of the exocyclic double bond and the nitrile groups. Bottini and Davidson[3] reported that the α-proton exchange of two cyclopropanecarboxylates was at least 10^3 times slower than that for the corresponding methylenecyclopropanecarboxylates. Also, Breslow[4] found that a cyclopropyl nitrile was 10^4 times slower to exchange than a similarly substituted methylenecyclopropane. Regarding the effect of nitrile groups alone, Cram[5] has noted that the kinetic acidity of nitriles is considerably greater than that of other compounds of comparable equilibrium acidity.

Table I. Rates of Racemization of 1

concn (M)	0.288	0.077	0.115
solvent	MeOH	H_2O	H_2O
temp (°C)	26	28	28
k_α[a] (10^4 s^{-1})	9.02	1.84	5.45

[a] From the slope of log α vs. time, e.g., Figure 1.

Experimental Section

(+)-*trans*-2,3-Dicyanomethylenecyclopropane[2] [$[\alpha]_{546}$ +172° (*c* 0.59, $CHCl_3$); NMR ($CDCl_3$) δ 2.35 (t, 2 H), 6.01 (t, 2 H)] in 1 mL of reagent grade solvent or distilled water (glass still) was placed in a thermostated 1-dm cell in a Perkin-Elmer 141 polarimeter. The optical rotation at 546 nm was monitored. The starting material and product were separated by LC (Waters Associates, Corasil II, 0.375 in. × 4 ft, 32% reagent $CHCl_3$ in cyclohexane, 3.5 mL/min). The product was identified as *cis*-2,3-dicyanomethylenecyclopropane[2] by IR, MS, and NMR: ($CDCl_3$) δ 2.71 (t, 2 H), 6.08 (t, 2 H). When the epimerization was done in MeOD, NMR for the mixture was as follows: ($CDCl_3$) δ 2.35 (m, 1.1 H), 6.01 (m, 2 H).

Acknowledgment. I express appreciation for the guidance and encouragement of Prof. William Doering, in whose laboratory this work was performed, and for the support of a Graduate Fellowship from the National Science Foundation (1969–1971).

Registry No. (+)-*trans*-2,3-Dicyanomethylenecyclopropane, 92396-92-4.

(3) Bottini, A. T.; Davidson, A. J. *J. Org. Chem.* **1965**, *30*, 3302.
(4) Nathan, E., unpublished results cited by Breslow, R. *Acc. Chem. Res.* **1973**, *6*, 393.
(5) Cram, D. J. "Fundamentals of Carbanion Chemistry"; Academic Press; New York, 1965; p 11.

Synthesis of Tetrahydro-4,6,7-isoquinolinetriols and Tetrahydro-4,7,8-isoquinolinetriols

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Received April 17, 1984

Reaction between certain endogenous catecholamines and acetaldehyde, the primary metabolite of ethanol, affords physiologically active products which may be responsible for some effects of ethanol consumption.[1] We recently established that the reactions of the catecholamines epinephrine and norepinephrine with formaldehyde and acetaldehyde produced tetrahydro-4,6,7-isoquinolinetriols (**5**) and tetrahydro-4,7,8-isoquinolinetriols (**13**), resulting from Pictet–Spengler cyclizations para and ortho to the activating hydroxyl group.[2] At neutral pH, a mixture of **5** and **13** was formed quite rapidly, while in strongly acidic solution, **5** was essentially the exclusive product of a slower reaction. Accordingly, under the appropriate acidic conditions, the tetrahydro-4,6,7-isoquinolinetriols (**5**) may be prepared in good yield via Pictet–Spengler cyclization. On the contrary, only minute

(1) (a) Cohen, G.; Collins, M. *Science (Washington, D. C.)* **1970**, *167*, 1749. (b) See also footnote 1 of ref 2a.
(2) (a) Bates, H. A. *J. Org. Chem.* **1981**, *46*, 4931. (b) Bates, H. A. *J. Org. Chem.* **1983**, *48*, 1932.

0022-3263/84/1949-4552$01.50/0