(ε 28 400), 293 (sh, 4800); IR (Nujol) 3350, 3220 (OH, NH), 1648 (br, C=O), 1530 (NHCO) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 10.95 (1 H, OH), 8.70, 8.50 (2 H, NH).

Anal. Calcd for $C_{30}H_{29}N_5O_3$: C, 70.99; H, 5.76; H, 13.80. Found: C, 70.71; H, 5.66; N, 13.61.

1,3,4,9a-Tetrahydro-2-hydroxy-*N*,*N*'-diphenyl-1,4-ethano-3,4a-(iminoethano)-4a*H*-carbazole-9,12-(2*H*)-dicarboxamide (13). To a solution of 3.0 g of **10** in 150 mL of absolute methanol was added 1.0 g of potassium borohydride with stirring at 23 °C, and the mixture was allowed to stir overnight. The infrared spectrum showed the absence of the ketone function. The solution was neutralized with acetic acid, and the solvent was removed in vacuo. The residue was taken up with cold water, and the white crystalline material (2.7 g, 90% crude yield) was collected by filtration; mp 253-255 °C dec. Crystallization from acetonitrile-tetrahydrofuran (2:1) gave 2.2 g of the diurea alcohol **13**: mp 256-257 °C dec; UV (ethanol) λ_{max} 249 nm (ε 32 800), 257 (32 280); IR (Nujol) 3420, 3320 (OH, NH), 1679 (C=O, anilide), 1633 (aliphatic NCOAr), 1528 (NHCO) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 8.42 [2 H, $(NH)_2$, D_2O exchangeable], 5.10 (d, $J_{H\text{-}2,OH}$ = 5.0 Hz, OH-3, D_2O exchangeable), 4.92 (m, 1 H, H-2).

Anal. Calcd for $C_{30}H_{30}N_4O_3$: C, 72.85; H, 6.11; N, 11.33. Found: C, 73.15; H, 6.13; N, 11.60.

Acknowledgment. We thank Professor E. L. Eliel for most helpful discussions. We express our thanks to Ms. Randi Eilertsen for very able technical assistance, Mrs. U. Zeek for microanalyses, and Dr. R. C. Greenough and Messrs. R. Puchalski, R. DeSimone, R. E. Saville, and B. R. Scott for the determination of spectra.

Registry No. 1, 79234-11-0; 4, 79234-12-1; 5, 79234-13-2; 6, 79234-14-3; 7, 79234-15-4; 8, 79234-16-5; 9, 79234-17-6; 10d, 79234-18-7; 10e, 79234-19-8; 11a, 79234-20-1; 11b, 79234-21-2; 11c, 79234-22-3; 11d, 79234-23-4; 11e, 79234-24-5; 12, 79234-25-6; 13, 79234-26-7; methyl isocyanate, 624-83-9; ethyl isocyanate, 109-90-0; ethyl isocyanatoacetate, 2949-22-6; cyclohexyl isocyanate, 3173-53-3; phenyl isocyanate, 103-71-9.

Pictet-Spengler Reactions of Epinephrine with Formaldehdye and Acetaldehyde

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Formaldehyde reacts with epinephrine (1) in neutral solution to produce tetrahydroisoquinolines **2** and **3**. Analogously, the reaction between acetaldehyde and epinephrine affords **4a**, **4b**, **5a**, and **5b**. At low pH, cyclization para to the activating hydroxy substituents affords only **2** or **4a** and **4b** regiospecifically. The effect of pH on the rate and products of these reactions was studied.

In 1970, a theory was advanced suggesting that some of the physiological effects of ethanol intoxication, dependence, tolerance, and withdrawal might be caused by tetrahydroisoquinoline derivatives formed in vivo by condensation between endogenous catecholamines and acetaldehyde, the primary metabolite of ethanol.[1] Perfusion of isolated adrenal glands, which contain epinephrine (1), with acetaldehyde produced a mixture of compounds which was thought to consist mainly of 1,2,3,4-tetrahydro-1,2-dimethyl-4,6,7-isoquinolinetriols **4a** or **4b**. The same compounds are formed by the adrenal glands of rats exposed to ethanol and pyrogallol[1f] and also by the simple condensation of acetaldehyde with epinephrine or norepinephrine in the absence of biological material. Low concentrations of these crude condensates cause profound physiological and behavioral changes including complete depletion of guinea pig hypothalamic norepinephrine[1d,1g] and selective degeneration of adrenergic nerves[1h] in laboratory animals. This activity of the mixture suggests that its constituents may indeed be responsible for some of the physiological effects of ethanol. Thus we thought it important to define the precise structure of the compounds present in the mixture.

Structures **4a** and **4b** had never been rigorously proven but merely assumed[1,2] as resulting from a Pictet-Spengler condensation between epinephrine and acetaldehyde. Despite several previous attempts, the preparation of these compounds had not been achieved. Partial purification of the epinephrine-acetaldehyde condensation mixture has been attempted by utilizing preparative TLC, but a pure compound was not isolated.[1d] Synthesis of *N*-demethyl-**4** by an independent route was attempted but afforded only a dark-colored mixture which could not be purified or induced to crystallize.[3]

In this report, we describe isolation and complete characterization of the compounds which result from the reaction between epinephrine and formaldehyde (**2** and **3**) and the reaction between epinephrine and acetaldehyde (**4a**, **4b**, **5a**, and **5b**). In addition, we describe the effect of pH on the rate and product distribution of these reactions.

Results

Since the products resulting from the reaction between epinephrine (1) and acetaldehyde were expected to be mixtures of cis and trans isomers, we turned our attention initially to the reaction between epinephrine and formaldehyde. Previous biological studies[1] utilized low substrate concentrations; however, we found that the same products were formed at the more practical higher concentrations which we employ. The pH at which the reaction was conducted profoundly influenced both the rate

(1) (a) G. Cohen and M. Collins, *Science*, **167**, 1749 (1970); (b) J. E. Rubenstein and M. E. Collins, *Biochem. Pharmacol.*, **22**, 2928 (1973); (c) G. Cohen, *ibid.*, **20**, 1757 (1971); (d) W. Osswald, J. Polonia, and M. A. Polania, *Naunyn-Schmeideberg's Arch. Pharmacol.*, **289**, 275 (1975). (e) R. S. Greenberg and G. Cohen, *J. Pharmacol. Exp. Ther.*, **184**, 119 (1973); (f) M. A. Collins, "Alcohol and Opiates", Academic Press, New York, 1977, p 155; (g) G. Cohen, *ibid.*, p 141; (h) I. Azevedo and W. Osswald, *Naunyn-Schmeideberg's Arch. Pharmacol.*, **300**, 139 (1977); (i) The tetrahydroisoquinoline formed by the reaction of dopamine with 3,4-dihydroxyphenylacetaldehyde has also been proposed as a mediator of alcohol addiction: V. E. Davis and M. J. Walsh, *Science*, **167**, 1005 (1970).

(2) H. Corrodi and N. A. Hillarp, *Helv. Chem. Acta*, **47**, 911 (1964).
(3) M. A. Collins and F. J. Kernozek, *J. Heterocycl. Chem.*, **9**, 1437 (1972).

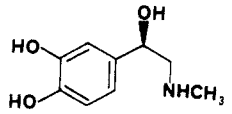
0022-3263/81/1946-4931$01.25/0

Table I. ^{13}C NMR Chemical Shifts[a] of Tetrahydroisoquinolines

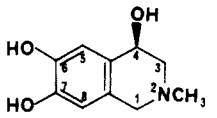
carbon[b]	compd 2	4a	4b	3	5a	5b
1-Me		19.03	15.43		16.69	13.50
N-Me	44.26	43.10	41.12	44.45	42.56	41.90
1	55.16	62.11	58.83	51.82	58.23	56.12
3	59.16	58.15	53.48	58.42	53.70	52.87
4	64.01	63.45	63.94	64.08	63.33	63.76
4a	124.93	125.00	124.16	125.41	125.67	124.28
5	117.19	116.78	117.17	122.26	121.20	122.80
6	146.07	146.18	146.20	116.96	116.77	117.21
7	145.34	144.96	145.38	141.26	141.37	141.17
8	113.84	114.04	114.32	145.32	145.42	145.51
8a	120.79	126.11	127.25	117.37	122.79	122.80

[a] Chemical shifts (δ) in H_2O/D_2O with respect to internal dioxane (δ 67.39). [b] Peaks were assigned as discussed in the text and by comparison with related compounds.[6c] The single-frequency off-resonance decoupled spectra of 2 and 3 displayed the expected multiplicities, and in all spectra, the two proton-bearing aromatic carbon atoms distinguish themselves from the four quaternary aromatic carbon atoms by peak height. Assignments for C-6 and C-7 in 2, 4a, and 4b may be interchanged.

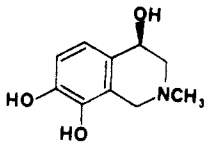
and the products of the reaction. At pH 6.5 the reaction was essentially complete in less than 1 min. Acidic conditions are known to dramatically decrease the rate of similar hydroxy-activated Pictet–Spengler condensations.[4] Thus, the half-lives at pH 2 and 0.5 are approximately 15 min and 12 h, respectively, at 24 °C. At pH 0.5, the product was the expected, but previously elusive,[3,5] 1,2,3,4-tetrahydro-2-methyl-4,6,7-isoquinolinetriol (2). At



1, Epinephrine



2



3

pH 2, this was accompanied by 5% of the isomeric 4,7,8-triol (3), and at pH 6.5, equal amounts of the two isomers were formed. The yield was essentially quantitative in all cases. Though 2 and 3 are extremely polar and unstable in strong acid or dilute base, we were able to chromatographically separate, crystallize, and fully characterize the two isomers.

The proton NMR spectra of 2 and 3 readily distinguish the two isomers. The two aromatic protons in 2 appear as uncoupled singlets at δ 6.72 and 6.97 ppm[6a] while the aromatic protons in 3 coincidentally display the same chemical shift, affording a two-proton singlet at δ 6.97.[6b] Analysis of coupling constants reveals that the 4-hydroxy group in 2 and 3 exists preferentially in the pseudoaxial

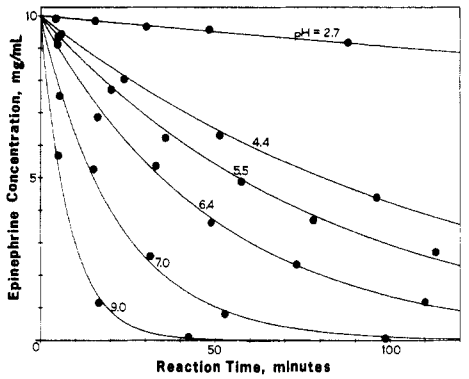


Figure 1. Reaction rate of epinephrine (10 mg/mL) with excess acetaldehyde at 24 °C as a function of pH.

Table II. Rate of Epinephrine–Acetaldehyde Reaction[a] and Product Distribution as a Function of pH

pH	$t_{1/2}$, min	log k_{obsd}[b]	% yield 4a	4b	5a[c]	5b
0.4	1530	−3.343	51	49	0	0.5
1.0	2890	−3.620	51	46	1	2
2.0	1440	−3.318	56	29	5	10
2.7	702.3	−3.006	51	29	7	12
4.4	80.8	−2.067	32	27	16	24
5.5	56.7	−1.913	23	15	16	46
6.7	34.7	−1.700	27	19	14	40
7.0	15.25	−1.342	47	27	11	15
9.0	5.77	−0.920	40	26	16	18

[a] Reaction conditions as in Figure 1. [b] $k_{obsd} = -d[1]/dt[1]$; t = minutes. [c] Percentages of 5a below 5% are estimates.

conformation presumably because of allylic strain destabilization in the pseudoequatorial conformer. The ultraviolet absorption maximum of 2 occurs at longer wavelength than that of 3 (Table III) due to the presence of alkyl substituents para to both aromatic hydroxyl groups in 2.[7] The ^{13}C NMR spectra tabulated in Table I also support the assigned structures.[6c] Carbon 5 of compound 3 which lacks an *o*-hydroxyl group absorbs downfield of C-6 in 3 or C-5 and C-8 in 2.

The reaction between epinephrine (1) and acetaldehyde, previously reported to give **4a** and **4b**,[1] was now reinvestigated. When the reaction was carried out in neutral solution, four distinct products were formed under the dilute conditions employed in previous investigations or in more concentrated solution. Like the formaldehyde–epinephrine reaction, the rate of the acetaldehyde–epinephrine reaction was strongly influenced by pH. As displayed in Figure 1, and tabulated in Table II, the reaction rate was greatest at high pH and decreased at low pH, except below pH 1 where a slight acceleration occurred. Above pH 2, the reaction rate of epinephrine with acetaldehyde is several orders of magnitude slower than the reaction with formaldehyde.

At low pH, the product consisted almost exclusively of the expected *cis*- and *trans*-tetrahydro-4,6,7-isoquinolinetriols **4a** and **4b** in approximately 95% yield. Though these two isomers comigrated on TLC, they were distinguishable by ^1H and ^{13}C NMR and analytical reverse-phase liquid chromatography and were separated by preparative reverse-phase liquid chromatography. The ultraviolet, ^1H NMR, ^{13}C NMR, and mass spectra correlate well with the spectra of 2. The aromatic protons absorb

(4) (a) W. M. Whaley and T. R. Govindchari, *Org. React.*, 6, 151 (1951); (b) J. H. Robbins, *Clin. Res.*, 16, 305 (1968); (c) C. Schöpf and W. Salzer, *Justus Liebigs Ann. Chem.*, 544, 1 (1940); (d) G. Hahn and F. Rumpf, *Chem. Ber.*, 71, 2141 (1938); (e) M. R. Falco, J. X. de Vries, E. Marchelli, and H. C. de Lorenzo, *Tetrahedron*, 28, 5999 (1972).

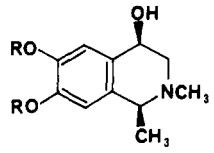
(5) R. Sarges, *J. Hetercycl. Chem.*, 11, 599 (1974).

(6) (a) For related NMR spectra see ref. 3 and 5. (b) The NMR signals due to H-5 and H-6 coincide in related compounds.[5] (c) For ^{13}C NMR spectra of related tetrahydroisoquinolines, see: D. Hughes, H. Holland, and D. MacLean, *Can. J. Chem.*, 54, 2252 (1976).

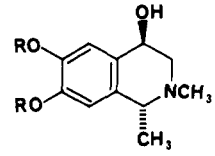
(7) T. Kametani, K. Kigasawa, M. Hiiragi, and H. Ishimaru, *J. Chem. Soc. C*, 2632 (1971).

as two singlets in each case,[6a] and the ^{13}C chemical shifts of the sp^2 carbons indicate hydroxyl substituents at C-6 and C-7 (Table I). Introduction of the methyl group at C-1 causes the expected downfield shift in the signals assigned to C-1 and C-8a and an upfield shift in the γ C-3 and *N*-methyl carbons relative to **2**.

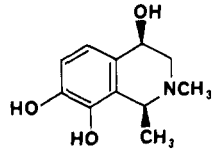
The stereochemistry in structures **4a** and **4b** was assigned as follows: Examination of proton–proton coupling constants reveals that the 4-hydroxyl group in **4a** and **4b**



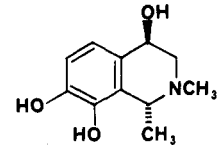
4a, R = H
6a, R = CH_3



4b, R = H
6b, R = CH_3



5a



5b

preferentially occupies the pseudoaxial position as it does in **2**. That these three compounds have the same conformation at C-4 is also supported by the constancy of the ^{13}C NMR chemical shift at C-4. The 1-methyl group in **4b** occupies the pseudoaxial position based on the dramatic γ-gauche induced upfield position of the 1-methyl, *N*-methyl, and C-3 ^{13}C NMR signals compared to those for **4a**.[8] Thus **4a** is cis and **4b** is trans. These conclusions were substantiated by examination of the proton NMR spectra in which the pseudoequatorial 1-methyl of **4a** (δ 1.75) is deshielded with respect to the pseudoaxial 1-methyl (δ 1.53) of **4b**, and the pseudoaxial 1-proton of **4a** (δ 4.40) is shielded with respect to the pseudoequatorial 1-proton of **4b** (δ 4.54). Considerable precedent for this effect exists for nitrogen heterocycles[8b] including tetrahydroisoquinolines.[9,10] Finally, the structural assignments were verified by transforming **4a** and **4b** into dimethyl ethers **6a** and **6b**, respectively, the structures of which had been independently established.[10]

Under mildly acidic, neutral, or alkaline conditions, the reaction of epinephrine with acetaldehyde affords, in addition to **4a** and **4b**, the two new compounds which were determined to be *cis*- and *trans*-tetrahydro-4,7,8-isoquinolinetriols **5a** and **5b**. The proportion of **5a** and **5b** produced is maximum at pH 5.5 (Table II). Analytical or preparative chromatography on silica gel successfully separated **5a** and **5b** from **4a** and **4b**, but the cis/trans pairs were separable only by reverse-phase liquid chromatography. After preparative liquid chromatography, each isomer was characterized by UV, ^1H NMR, ^{13}C NMR, and mass spectroscopy, and assignment of the cis and trans stereochemistry to **5a** and **5b**, respectively, was accomplished by examination of the ^{13}C NMR (Table I) and ^1H NMR spectra as described above.

Like most catechols, the tetrahydroisoquinolinols described in this study are sensitive to oxidation in alkaline solution. At neutral pH or as solids, tetrahydro-4,6,7-isoquinolinetriols **2**, **4a**, and **4b** are quite stable, but the isomeric tetrahydro-4,7,8-isoquinolinetriols **3**, **5a**, and **5b** are prone to air oxidation. The benzylic 4-hydroxyl groups displayed the expected instability to acid. Thus **4a** and **4b** interconvert by epimerization in less than 1 day at pH 1.5. Likewise, **5a** and **5b** interconvert under the same conditions. Substantial epimerization and racemization, therefore, certainly occur during the isolation procedure involving chromatography on silica gel utilizing a strongly acidic solvent. However, no epimerization is detectable under the conditions employed for reverse-phase liquid chromatography.

Discussion

The Pictet–Spengler reaction between aldehydes and alkoxyphenethylamines generally requires acid catalysis, and cyclization occurs para to the alkoxy group (unless that position is blocked). In contrast, when the aromatic ring is activated by a hydroxyl substituent, the reaction is quite facile at neutral pH.[4] That the nucleophilic species in this case is the phenoxide is consistent with our observation that the logarithm of the rate constant increases linearly with pH between 1 and 4.

There is ample precedent for the Pictet–Spengler reaction of (aminoethyl)phenols with formaldehyde proceeding with cyclization both ortho and para to the activating hydroxyl group.[4a,11] Thus **2** and **3** are the expected products of the epinephrine–formaldehyde reaction. In contrast, aldehydes other than formaldehyde generally give only para cyclization.[4a,7,11a,12,13] Our observation that the epinephrine–acetaldehyde reaction affords ortho cyclization products **5a** and **5b** as the major products at pH 5.5–6.4 is, therefore, quite unusual. The lack of regioselectivity observed when the Pictet–Spengler reaction of (aminoethyl)phenols is performed at neutral pH has been attributed to the low activation energy of the ring closure caused by high electron density in the partially deprotonated phenolic aromatic ring.[4a] The regiospecificity which we observe when the same reaction is performed under acidic conditions might be ascribed to the decreased reactivity of the fully protonated phenol. Under these conditions, the reaction rate and regiospecificity are similar to the acid-catalyzed Pictet–Spengler reaction in which the aromatic ring is activated by alkoxy groups. This evidence, as well as the increase in rate observed below pH 1, suggests that distinct mechanisms are operative when a Pictet–Spengler reaction is conducted under neutral vs. acidic conditions.

Experimental Section

General Procedures. Proton NMR spectra were recorded at 80 MHz with a Varian CFT-20 spectrometer in D_2O with DSS [sodium 3-(trimethylsilyl)propanesulfonate] as an internal standard. Coupling constants are expressed in hertz. The HDO peak was suppressed by utilizing the inversion–recovery technique when necessary. ^{13}C NMR spectra were recorded with a Varian

(8) Recent references concerning the gamma gauche effect in heterocycles include: (a) F. Ungemach, D. Soerens, R. Weber, M. DiPierro, O. Campus, P. Mokry, J. Cook, and J. Silverton, *J. Am. Chem. Soc.*, **102**, 6976 (1980). (b) F. Vierhapper, E. Eliel, and G. Zuniga, *J. Org. Chem.*, **45**, 4844 (1980). (c) See also ref 12.

(9) A. Brossi, A. Focella, and S. Teitel, *Helv. Chim. Acta*, **55**, 15 (1972).

(10) G. Grethe, M. Uskokovic, T. Williams, and A. Brossi, *Helv. Chim. Acta* **50**, 2397 (1967). The ^1H NMR spectra of our dimethyl ethers **5a** and **5b** are in full agreement with the literature spectra. Though our absolute TLC R_f values differ from the reported values, the relative mobilities are consistent.

(11) (a) S. N. Quessy and L. R. Williams, *Aust. J. Chem.*, **32**, 1317 (1979); (b) G. S. King, B. L. Goodwin, and M. Sandler, *J. Pharm. Pharmacol.*, **26**, 478 (1974); (c) R. L. Ranieri and J. L. McLaughlin, *J. Org. Chem.*, **41**, 319 (1976).

(12) T. Hudlicky, T. M. Kutchan, G. Shen, V. E. Sutliff, and C. J. Cosica, *J. Org. Chem.*, **46**, 1738 (1981).

(13) For exceptions to this statement see ref 11b and: (a) M. R. Falco and J. X. de Vries, *Z. Chem.*, **13**, 56 (1973); (b) T. Kametani, A. Ujiie, M. Ihara, K. Fukumoto, and S. Lu, *J. Chem. Soc., Perkin Trans. 1*, 1218 (1976); (c) S. Rachlin, K. Worning, and J. Enemark, *Tetrahedron Lett.*, 4163 (1968); (d) G. Kapadia, G. Rao, E. Leete, M. Fayez, and Y. Vaishnav, H. Fales, *J. Am. Chem. Soc.*, **92**, 6943 (1970).

Table III. UV and Chromatographic Properties of Epinephrine (1) and Tetrahydroisoquinoline Hydrochlorides

compd	λ_{max}, nm	R_f[a]	V_e, mL[b]
1	277 (H_2O)	0.48	6.00
2	283	0.40	8.10
3	278.5	0.50	8.40
4a	282	0.45	9.12
4b	282	0.45	14.40
5a	280	0.52	8.64
5b	280	0.52	18.02

[a] R_f on silica gel eluted with 2-butanol–14 M formic acid (60:40). [b] Elution volume on 30 × 0.39 cm μ-Bondapak C_{18} eluted with 0.01 M KH_2PO_4.

CFT-20 spectrometer in pH 4–5 water or D_2O by using dioxane (δ 67.39) as an internal standard. UV spectra were recorded in aqueous solution by using a Beckman DB-GT spectrophotometer. IR spectra of samples as KBr pellets were recorded with a Unicam SP1000 spectrophotometer. Low-resolution mass spectra were recorded with a Hewlett-Packard 5984A spectrometer. High-resolution mass spectra were recorded with a Kratos MS-30 spectrometer.

Analytical TLC was performed on EM 5539 silica gel 60 plates, and preparative chromatography was performed by using EM silica gel 60 (E. Merck). Dowex 2-X8 Cl^- resin (Dow Chemical) was rinsed with ethanol, 1 M HCl, and water before use. Epinephrine and the tetrahydroisoquinolinols were visualized by spraying with $FeCl_3$ (10 mg/mL of acetone–water, 3:2). The $K_3Fe(CN)_6$ spray previously employed[1a,b] was unsatisfactory in our hands. R_f values are given in Table III.

(–)-Epinephrine-free base was prepared by treating (–)-epinephrine bitartrate (Boehringer Ingelheim) with aqueous sodium carbonate. Acetaldehyde was redistilled and stored at 5 °C. Aqueous solutions were rotary evaporated in vacuo with a bath temperature of 50 °C or less.

Liquid Chromatography. A Waters 6000-A pump and a Perkin-Elmer LC-55 variable-wavelength detector generally at 252 nm were used. For quantitative work, the output was analyzed with a HP3380A integrator. The eluting solvent was 0.01 M KH_2PO_4 (pH 4.5). Analytical chromatography was performed by using a 30 × 0.39 cm 10-μm Waters μ-Bondapak C_{18} column with a flow rate of 2.0 mL/min. The retention volumes are listed in Table III.

Preparative liquid chromatography was accomplished with two Waters 37–75-μm Porasil B C_{18} 60 × 0.78 cm columns in series and a flow rate of 2–5 mL/min.

Kinetics. Solutions of (A) epinephrine free base dissolved in water plus 1 M HCl and then basified to pH 3 with $NaHCO_3$ (0.400 mL, 20 mg/mL), (B) buffer consisting of 0–1 M $NaHCO_3$ or 0.1 M pH 6 NaOAc buffer (0.200 mL), and (C) aqueous acetaldehyde (0.200 mL, 100 mg/mL) were mixed together at 24 °C. Thus, the initial concentrations were as follows: epinephrine, 10 mg/mL (0.0546 M); acetaldehyde, 25 mg/mL (0.568 M). The pH of an aliquot was determined, and the progress of the reaction was monitored by liquid chromatography, following disappearance of epinephrine. The logarithm of the concentration was fitted via linear least squares versus time to obtain rate constants and the exponential curves displayed in Figure 1 were plotted utilizing a Hewlett-Packard 9820A calculator and a 9862A plotter.

1,2,3,4-Tetrahydro-2-methyl-4,6,7-isoquinolinetriol Hydrochloride (2). (–)-Epinephrine free base (500 mg, 2.73 mmol) was dissolved in water (1 mL) plus 1 M HCl (2.4 mL), and 1 M $NaHCO_3$ was added to pH 2.0, followed by water to give a final volume of 4.0 mL. After purging with nitrogen, aqueous formaldehyde (1.0 mL, 37 wt %, 13.3 mmol, 490 mol %) was added. After 18 h[14] at 20 °C, the water was evaporated in vacuo, and absolute ethanol (10 mL) and celite were added. The brown precipitate was removed by filtration. The solvent was evaporated from the filtrate, and the residue was dissolved in absolute ethanol (2.0 mL). Acetone (3.0 mL) was added, the precipitate was removed, and the solvent was evaporated from the filtrate to afford a solid which was triturated with acetone and dried to afford 310 mg (49% yield) of a white powder which was recrystallized from 10:1 acetone–ethanol: mp 165 °C dec; ^1H NMR (D_2O) δ 3.08 (3 H, s, NCH_3), 3.58 (2 H, br AB q, J = 12, NCH_2), 4.33 (2 H, ABq J = 16, $PhCH_2$), 5.02 (1 H, br t, J = 3, CHOH), 6.72 (1 H, s, arom), 6.97 (1 H, s, arom); mass spectrum, m/e 195 (19, M^+), 176 (19), 152 (56), 151 (100). Anal. Calcd for $C_{10}H_{13}NO_3 \cdot HCl$: C, 51.84; H, 6.09; N, 6.04. Found: C, 51.73; H, 6.18; N, 5.92.

1,2,3,4-Tetrahydro-2-methyl-4,7,8-isoquinolinetriol Hydrochloride (3). (–)-Epinephrine free base (100 mg, 0.55 mmol) was suspended in water, and 1 M HCl was added until the solid dissolved. The solution was basified to pH 6.5 with 1 M $NaHCO_3$ and adjusted to a final volume of 1 mL with water, and formaldehyde (0.2 mL, 37 wt %, 2.6 mmol, 470 mol %) was added. After 1 h[14] the reaction was acidified to pH 4.3 with 1 M HCl, the solvent was evaporated, and the residue was redissolved in absolute EtOH and filtered. Most of the ethanol was evaporated from the filtrate, and acetone was added to afford a precipitate, a 1:1 mixture of **2** (R_f 0.4) and **3** (R_f 0.5) plus some polyformaldehyde.

The mixture was separated by flash chromatography, purified on Dowex 2, and triturated with 95% EtOH as described below for **5a** and **5b** to afford 29 mg (22% yield) of **3** as the HCl salt: mp 152–160 °C dec; ^1H NMR (D_2O) δ 3.13 (3 H, s, NCH_3), 3.57 (2 H, d, J = 3.5, NCH_2), 4.17 (1 H, d, J = 16, $PhCH_2$), 4.65 (1 H, D, J = 16, $PhCH_2$), 5.04 (1 H, t, J = 3.5, CHOH), 6.97 (2 H, s, arom); mass spectrum, m/e 195 (27, M^+), 176 (32), 152 (49), 151 (100).

***cis*- and *trans*-1,2,3,4-Tetrahydro-1,2-dimethyl-4,6,7-isoquinolinetriol Hydrochloride (4a,b).** Dilute HCl was added to (–)-epinephrine free base (100 mg, 0.55 mmol) until it dissolved and the pH reached 1.0, and then water was added to give 0.8 mL total volume, followed by acetaldehyde (150 mg, 3.4 mmol, 620 mol %). After 11 days at 20 °C, 1 M $NaHCO_3$ was added to pH 3, the solution was concentrated, triturated with 95% EtOH, and filtered, and the filtrate was evaporated to dryness. The residue was triturated with acetone to afford 125 mg (93% yield) of a solid, a 60:40 mixture of **4a** and **4b**, mp 88–90 °C. LC, TLC, ^1H NMR, and ^{13}C NMR revealed no impurities.

***cis*-1,2,3,4-Tetrahydro-1,2-dimethyl-4,6,7-isoquinolinetriol Hydrochloride (4a).** The mixture of **4a** and **4b** (15 mg) was applied to a column of C-18 Porasil B (37–75 μm, 120 × 0.78 cm) and eluted with 0.01 M KH_2PO_4 (2.0 mL/min). Compound **4a** was eluted between 30 and 50 mL. The eluate was passed through a short column of Dowex 2-X8 Cl^- (1 mL, 20–50 mesh), concentrated, and triturated twice with 95% EtOH to afford 8 mg of **4a** as a white solid: mp 102–105 °C dec; ^1H NMR (D_2O) δ 1.75 (3 H, d, J = 6.7, 1-CH_3), 3.12 (3 H, s, NCH_3), 3.58 (2 H, t, J = 2.7, NCH_2), 4.40 (1 H, q, J = 6.7, PhCH), 4.90 (1 H, t, J = 2.7, CHOH), 6.80 (1 H, s, arom), 6.92 (1 H, s, arom); mass spectrum, m/e (relative intensity) 209 (1, M^+), 194.0814 (100, M – CH_3; calcd m/e 194.0817), 191 (10, M – H_2O), 176 (57, M – CH_3 – H_2O), 166 (8, M – $H_2C{=}NCH_3$).

***trans*-1,2,3,4-Tetrahydro-1,2-dimethyl-4,6,7-isoquinolinetriol Hyrochloride (4b).** Continued elution of the Porasil column afforded **4b** in the next 65 mL. The eluate was passed through a short column of Dowex 2-X8 Cl^- (1.5 mL, 20–50 mesh), concentrated, and triturated twice with 95% EtOH to afford 3 mg of **4b** as a white solid: ^1H NMR (D_2O) δ 1.53 (3 H, d, J = 6.9, 1-CH_3), 3.01 (3 H, s, NCH_3), 3.38 (1 H, dd, J = 3.6, 14, NCH_2), 3.79 (1 H, dd, J = 3.6, 14, NCH_2), 4.54 (1 H, q, J = 6.9, PhCH), 4.96 (1 H, t, J = 3.6, CHOH), 6.77 (1 H, s, arom), 6.94 (1 H, s, arom); for the mass spectrum, see that for **4a**.

***cis*- and *trans*-1,2,3,4-Tetrahydro-1,2-dimethyl-4,7,8-isoquinolinetriol Hydrochloride (5a,b).** Dilute HCl was added to (–)-epinephrine free base (200 mg, 1.09 mmol) until it dissolved, the pH was adjusted to 6.5 with 1 M $NaHCO_3$, water was added to 2 mL total volume, and then acetaldehyde (400 mg, 9 mmol, 830 mol %) was added. After 18 h at 20 °C, the dark orange solution was extracted three times with ether, acidified to pH 4.5 with 1 M HCl, concentrated, and triturated with 95% EtOH. The

(14) The rate of the formaldehyde–epinephrine reaction under the same conditions as employed for the acetaldehyde–epinephrine reaction was determined by liquid chromatography. The half-lives are 12 h (pH 0.5), 15 min (pH 2), and less than 0.5 min (pH 6.5). The relative amount of 2 and 3 produced was determined by LC and TLC and is reported in the Results. Combined yields according to LC were essentially quantitative.

filtrate was concentrated, dissolved in a small volume of 2-butanol–14 M formic acid (70:30), and flash chromatographed on silica gel (60 g, 3 × 15 cm, EM silica gel 60, 40–63 μm) eluted with the same solvent. Compounds **5a** and **5b** were eluted in the yellow fractions 15–35 mL after the void volume while **4a** and **4b** were eluted in the pale yellow fractions 35–80 mL after the void volume. The eluate containing **5a** and **5b** was concentrated, dissolved in water, cautiously basified to pH 6.0 with 1 M $NaHCO_3$, filtered through Dowex 2-X8 Cl^- (2 mL, 20–50 mesh), and extracted twice with ether. The aqueous phase was concentrated, triturated with 95% EtOH, filtered through Celite, and concentrated, redissolved in 95% EtOH (2 mL), treated with chloroform (2 mL), and filtered. The filtrate was concentrated to afford 100 mg (37% yield) of a reddish solid, a 1:1 mixture of **5a** and **5b**. LC, TLC, ^1H NMR, and ^{13}C NMR revealed no impurities other than a small amount of formate.

***cis*-1,2,3,4-Tetrahydro-1,2-dimethyl-4,7,8-isoquinolinetriol Hydrochloride (5a).** The mixture of **5a** and **5b** (40 mg) was applied to a column of C-18 Porasil B (37–75 μm, 120 × 0.78 cm) and eluted with 0.01 M KH_2PO_4 (5.0 mL/min). Compound **5a** was eluted between 50 and 100 mL. Ion exchange and EtOH trituration as before afforded 12 mg of **5a** as a yellow-brown solid: ^1H NMR (D_2O) δ 1.71 (3 H, d, J = 6.7, 1-CH_3), 3.07 (3 H, s, NCH_3), 3.52 (2 H, t, J = 5.7, NCH_2), 4.69 (1 H, q, J = 6.7, PhCH), 5.05 (1 H, t, J = 5, CHOH), 7.01 (2 H, s, arom); mass spectrum, m/e 194.0857 (100, M-CH_3, calcd 194.0817), 191 (6), 176 (68), 166 (5), 165 (12).

***trans*-1,2,3,4-tetrahydro-1,2-dimethyl-4,7,8-isoquinolinetriol Hydrochloride (5b).** Continued elution of the Porasil column afforded **5b** in the next 100 mL. Ion exchange and EtOH trituration as before afforded 14 mg of **5b** as a yellow-brown solid: ^1H NMR (D_2O) δ 1.53 (3 H, d, J = 6.9, 1-CH_3), 3.05 (3 H, s, NCH_3), 3.42 (1 H, dd, J = 1.9, 14, NCH_2), 3.82 (1 H, dd, J = 3.5, 14, NCH_2), 4.65 (1 H, q, J = 6.9, PhCH), 5.00 (1 H, dd, J = 1.9, 3.7, CHOH) 6.98 (2 H, s, arom); for the mass spectrum, see that for **5a**.

***cis*-1,2,3,4-Tetrahydro-6,7-dimethoxy-1,2-dimethyl-4-isoquinolinol (6a).** Compound **4a** (35 mg, 0.14 mmol) in methanol (2 mL) was treated with ethereal diazomethane (3 mL, 0.25 M, 0.75 mmol, 500 mol %). After 5 h, the solvent was evaporated, methanol (2 mL) was added, and the pH was adjusted to 1-2 with conc HCl. More diazomethane (2 mL, 330 mol %) was added, and after 18 h the sample was concentrated, dissolved in water and saturated sodium carbonate, extracted into chloroform, and dried over magnesium sulfate. Evaporation of the solvent afforded 20 mg (60% yield) of **5a**. TLC (cyclohexane–chloroform–diethylamine, 50:40:10) R_f 0.18 (lit.[10] R_f 0.48). The ^1H NMR was consistent with the literature.[10]

***trans*-1,2,3,4-Tetrahydro-6,7-dimethoxy-1,2-dimethyl-4-isoquinolinol (6b)** was prepared from **4b** according to the above procedure; TLC R_f 0.15 (lit.[10] R_f 0.39). The ^1H NMR was consistent with literature.[10]

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Registry No. 1, 51-43-4; 2, 79254-31-2; 2·HCl, 79254-32-3; 3, 79201-21-1; 3·HCl, 79201-22-2; 4a, 79201-23-3; 4a·HCl, 79201-24-4; 4b, 79201-25-5; 4b·HCl, 79201-26-6; 5a, 79201-27-7; 5a·HCl, 79201-28-8; 5b, 79201-29-9; 5b·HCl, 79201-30-2; 6a, 79254-33-4; 6b, 79254-34-5; formaldehyde, 50-00-0; acetaldehyde, 75-07-0.

Cycloaddition of *tert*-Butylcyanoketene to Isocyanides

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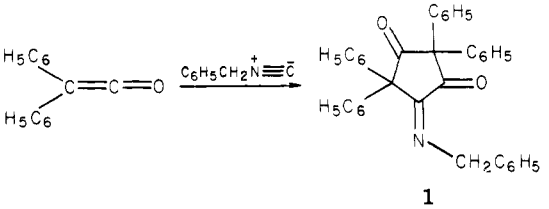
The reaction of *tert*-butylcyanoketene with a series of isocyanides results in an unusual mode of addition involving the carbonyl bond of the ketene. The scope and mechanism of these cycloadditions are discussed.

Reported here is a study of the cycloaddition of *tert*-butylcyanoketene (TBCK) to isocyanides, a reaction which proceeds anomalously when compared to other ketene/isocyanide additions. Specifically, it is shown that 2 mol of the ketene react with 1 mol of isocyanide to give good yields of the previously unobserved imino lactones **5a–e**. Such products result from a reaction mode in which the cycloaddition takes place across the carbonyl bond of the ketene components. This is unusual since all other reported examples of ketene/isocyanide cycloadditions give products arising from reactions involving addition to the alkene bond of the cumulene. For example, the 1-imino-2,4-cyclopentanedione (1) was obtained in 90% yield when benzyl isocyanide was treated with diphenylketene at −20 °C.[1] °C.[1]

The cycloadditions reported here were accomplished by the addition of a benzene solution of TBCK[2] to a slight excess of the isocyanides at ambient temperature. The reactions were complete within a few minutes and the products isolated by standard methods. Although the yields differed slightly, the same products were obtained when the mode of addition was reversed or if the temperature of the reaction was maintained at −20 °C. In one case, the ketene was slowly added to an excess of neat *tert*-butylisocyanide in an attempt to obtain products incorporating more than 1 equiv of the isocyanide. However,



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