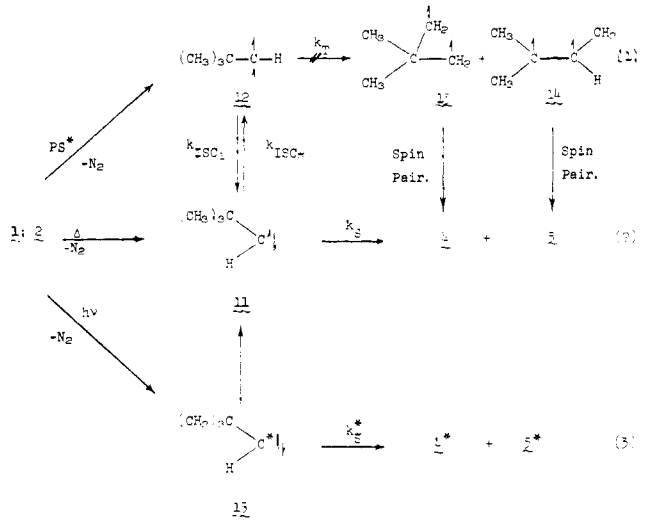

8 as a major product strongly supports the presumption that intersystem crossing of **12** to **11** occurs.[19] It would thus appear that, along with rearrangement, insertion results from reaction of **11**. Without further information, however, it can not be concluded that conversion into **4** and **5** is the exclusive province of singlet **11**.[19]

Direct photolysis and singlet photosensitization of **1** and **2** occur with absorption of ~82–90 kcal/mol of energy. Electronically excited singlets **1–2*** and/or possibly excited **15*** are thus highly energetic and their conversions into **4*** and **5*** are spin allowed. Rearrangement to **5*** is now extensive and the product does not undergo alteration as occurs when derived from vibrationally excited intermediates in the gas phase.[7e] Finally, triplet photosensitization of diazo compounds and diazirines as in the present systems may give advantage over thermolysis and direct photolysis for specific synthesis.

Acknowledgment. Support of this research by the National Science Foundation is gratefully acknowledged.

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(9) Diazirines are of advantage because they are readily purified and protected against cationic decomposition.

(10) In the gas phase (250 mm) at 160 °C, **1** also thermolyzes to **4** (92%) and **5** (8%).[7g]

(11) Effected at 302.5, 313, and 334 nm with a Hanovia lamp (679A) through Pyrex.

(12) In diglyme containing lithium *tert*-butoxide, **2** photolyzes at 20 °C to **4** (51.6%), **5** (46.6%), and **7** (1.8%).

(13) Extension of subsequent theory of this manuscript raises the question that such gas-phase decompositions involve electronically excited intermediates.

(14) 10-Thioxanthone effects efficient photosensitization of larger ring azo analogues of **1** and **3**: P. S. Engel, *J. Am. Chem. Soc.*, **91**, 6903 (1969).

(15) (a) Hanovia 679A lamp, Corning 7380 filter; 10-thioxanthone, ε 2800 (349 nm). (b) Reaction mixtures were samples at <20% conversion. (c) Hanovia 679A lamp, potassium chromate filter.

(16) Neopentane (~1%) formed upon photosensitizations in cumene possibly arises by hydrogen abstraction by **12** and then the neopentyl radical.

(17) Isomerizations of **12** with spin preservation to **13** and **14** apparently are higher energy demanding processes.[2d]

(18) (a) P. F. Zittel, G. B. Ellison, S. V. O'Neil, E. Herbert, W. C. Lineberger, and W. P. Reinhardt, *J. Am. Chem. Soc.*, **98**, 3731 (1976).[18b] (b) Prior experimental values for the triplet–singlet energy gap for methylene range from 6 to 10 kcal/mol.[18c] (c) H. M. Frey, *J. Chem. Soc., Chem. Commun.*, 1024 (1972); W. L. Hase, R. J. Phillips and J. W. Simons, *Chem. Phys. Lett.*, **12**, 161 (1971); F. S. Rowland, C. McKnight, and E. K. C. Lee, *Ber. Bunsengess.*, **72**, 236 (1968).

(19) (a) R. C. Friedmann of this laboratory has observed that photosensitization of 4-methyl-1-pyrazoline with benzophenone and with 10-thioxanthone in tetrahydrofuran at −78 to 25 °C yields **7** (97.0–98.0%) and **8** (1.5–2.8%). Direct photolysis of 4-methyl-1-pyrazoline in tetrahydrofuran at −78 to 25 °C results in **7** (84.4–88.0%), **8** (10.0–15.4%), and 1-butene (0.3–1.0%). The behavior of 4-methyl-1-pyrazoline and its presumed photolytic intermediates,[19b] triplet and singlet 2-methyl-1,3-propane diradicals, is quite different from that for photosensitization, thermolysis, and photolysis of **3** and argues strongly (1) against triplet and singlet β-C–H abstraction reactions for 2-methyl-1-propylidenes from **3** as a major source of **8** (and probably **7**) and (2) for spin inversion of triplet to singlet 2-methyl-1-propylidene and then to **8** (and probably **7**). Further, triplet photosensitization of 4,4-dimethyl-1-pyrazoline to give **4** (94–98%) and 2-methyl-1-butene (trace) as the only intramolecular products supports the conversion of **12** from **1** into **11** and then **5** (and probably **4**). (b) For summary of the experimental results and the theory of decomposition of various 1-pyrazolines, see G. Koga, N. Koga, and J.-P. Anselme and R. J. Drewer in "The Chemistry of the Hydrazo, Azo, and Azoxy Groups, Part 2", S. Patai, Ed., Wiley, New York, 1978, Chapters 19 and 20.

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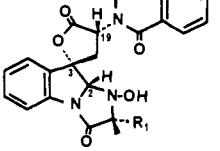
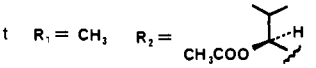
Received November 21, 1978

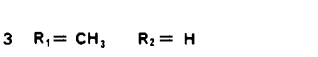
Total Synthesis of Tryptoquivaline G

Sir:

A strain of the fungus *Aspergillus clavatus* collected from mold damaged rice produced a group of toxic, tremor inducing metabolites with novel structures. Tryptoquivaline (**1**) was found to be the major metabolite, and a transformation product containing a δ-lactone ring was used to determine its structure and relative configuration by X-ray crystallography.[1] Comparison of circular dichroism and ^{1}H NMR spectra with those of nortryptoquivaline[2] suggested structure **2** for this companion metabolite. Tryptoquivaline G (**3**) is a representative of a more recently discovered group of mycotoxins produced by *Aspergillus fumigatus*.[3-5] It, as well as tryptoquivaline L (**17**), an artefact, lacks the isobutyl side chain. The total synthesis of tryptoquivaline G (**3**) outlined here confirms the proposed







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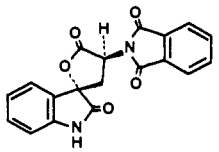
structure and establishes both relative and absolute configuration.

The synthesis relied heavily on a new method for the conversion of *N*-acyltryptophans to spirolactones and the steric course of the reaction was explored with a model compound.[6] Oxidation of *N*-phthalimido-L-tryptophan with 2 equiv of trichloromethanesulfonyl chloride–dimethyl sulfoxide[7] (CH_2Cl_2, −20 °C) gave a 65% yield of two diastereomeric lactones (**4** and **5**) in a ratio of 7:3. The major isomer **4**, mp



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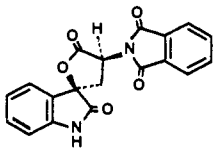
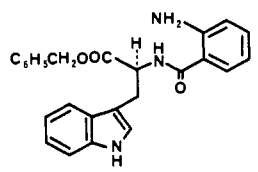


5

275–277 °C, $[\alpha]^{25}_D$ −133° (*c* 1.7, acetone), was recovered unchanged after treatment with sodium hydride or imidazole in dimethylformamide. The minor isomer **5**, mp 279–281 °C, $[\alpha]^{24}_D$ −206° (*c* 1.4, acetone), under the same conditions was converted into the *enantiomer* of **4**, $[\alpha]^{25}_D$ +132° (*c* 1.4, acetone), demonstrating different configurations at the spiro atom in the two diastereomers. Since the epimerization of tryptoquivaline G (**3**) to tryptoquivaline L (**17**) is accompanied by a large negative shift in optical rotation, the absolute configurations at C_3 and C_{19} should be opposite those of the model compound **5**. The major, and thermodynamically more stable, epimer formed in the oxidative lactonization thus has the correct stereochemistry at the spiro center.

Intermediate **6** was prepared by condensation of L-tryptophan with *o*-nitrobenzoyl chloride to give the amide, mp



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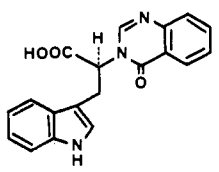

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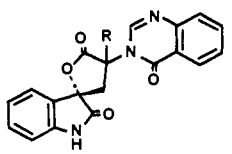
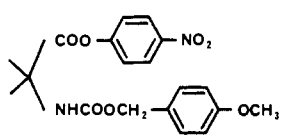


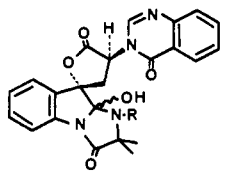
8 R = α−H

9 R = β−H



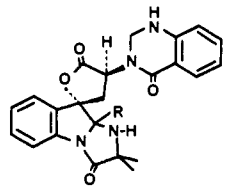
10

212–214 °C, esterification with phenyldiazomethane to the benzyl ester, mp 148–150 °C, and reduction with iron (HCl, ethanol, reflux). The formamide, mp 140–142 °C (HCOOH, benzene, reflux), on dehydration (TsOH, xylene, reflux) gave a quinazolinone which was hydrogenolyzed to the acid **7**, mp 238–240 °C, over palladium on carbon in ethanol (overall yield from L-tryptophan was 50%). Oxidation of **7** with 2 equiv of methanesulfonic anhydride–dimethyl sulfoxide (CH_2Cl_2, −20 °C, 5 h) gave 56–66% spirolactone **8**, mp 321–322 °C dec, $[\alpha]^{25}_D$ −377 ° (*c* 0.07, CH_3CN), in addition to <10% epimer differing in configuration at the spiro center. To confirm the stereochemistry, **8** was exposed to potassium hydride in THF–DMF (20 °C, 3 min), and the resulting enolate was protonated with 1% HCl in THF (−70 °C). Product **9** (40%), mp 315–318 °C dec, $[\alpha]^{25}_D$ +320° (*c* 0.02, CH_3CN), was the enantiomer of the minor product formed in the oxidative lactonization. Owing to the exceptional lability of **9** to base, the synthesis was continued with **8**. Derivative **10**, mp 82–83 °C, was prepared from α-methylalanine and *p*-methoxybenzyl-8-quinolyl carbonate[8] with the aid of triethylamine, followed by esterification with *p*-nitrophenol and dicyclohexylcarbodiimide. Lactone **8** was then silylated with bis(trimethylsilyl)acetamide[9] and the crude product condensed with **10** in DMF containing tetramethylammonium chloride. Treatment of the crude imide with triethylamine gave the highly insoluble cyclol **11**, mp 243–245 °C, in 81% overall yield. Transforma-



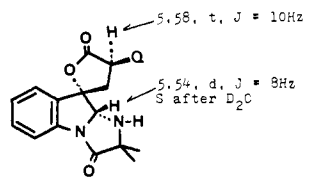
11 R = $COOCH_2$–⟨⟩–OCH_3

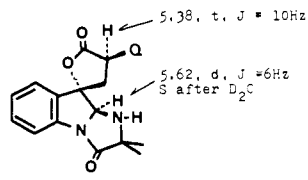
12 R = H



13 R = β−H

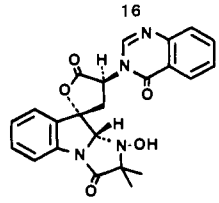
14 R = α−H





15 Q = quinazolinyl

16



17

tion to the aminals **15** and **16** could be accomplished by consecutive treatment of **11** with sodium cyanoborohydride, DDQ, and trifluoroacetic acid, but the two epimers were obtained in a ratio of 1:1. In a more stereoselective sequence, the *p*-methoxybenzyloxycarbonyl group was first removed by treatment of a suspension of the cyclol **11** in ethyl acetate with trifluoroacetic acid in the presence of anisole (0 °C, 30 min).[10] The deprotected cyclol **12**, mp 268–270 °C (76%), was reduced with sodium cyanoborohydride (THF, H_2O, HCl, pH ~3, 20 °C, 1 h) to give a 4:1 mixture of dihydroquinazolinones **13**, mp 248–250 °C, and **14**, mp 243–245 °C. Reoxidation to the corresponding quinazolinones **15**, mp 250–251 °C (acetone), $[\alpha]^{25}_D$ −260° (*c* 0.01, acetone), and **16**, mp 172–174 °C (AcOEt–hexane), $[\alpha]^{25}_D$ −67° (*c* 0.12, $CHCl_3$), was accomplished in 89% and 80% yield, respectively, with DDQ in chloroform. ^1H NMR spectra of the two isomers were used to establish the configurations at C_2, and the major isomer on oxidation with *m*-chloroperbenzoic acid[2] gave tryptoquivaline L (**17**, 85%), mp 275–277 °C dec, $[\alpha]^{25}_D$ −230° (*c* 0.02, acetone), with spectral properties in accord with those published.[4,5] Contrathermodynamic epimerization, as in the conversion of **8** into **9**, gave tryptoquivaline G identical (melting point, $[\alpha]_D$, IR, ^1H NMR and chromatographic behavior) with material isolated from *A. fumigatus*.[11] The tryptoquivalines are thus derived from D-tryptophan.

The configuration of nortryptoquivaline (**2**) was established by X-ray analysis[12] and reduction of this metabolite with zinc followed by hydrolysis which yielded L-alanine.[3,5] The absolute configuration of the metabolite (**2**) thus agrees with that of tryptoquivaline G (**3**) determined by synthesis.

Acknowledgments. This work was supported by Grant GM 09686 awarded by the Institute of General Medical Sciences,

Department of Health, Education and Welfare, the Hoffmann-La Roche Foundation, and Sankyo Ltd. Tokyo. All high resolution mass spectra were measured in the National Institutes of Health supported facility at Massachusetts Institute of Technology (Grant FR 00317) under the direction of Professor K. Biemann.

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General Acid Catalysis in the Hydrolysis of Benzo[*a*]pyrene 7,8-Diol 9,10-Epoxides

Sir:

The most studied of the carcinogenic hydrocarbons is the ubiquitous environmental contaminant benzo[*a*]pyrene (BP). Studies from several laboratories[1] have recently allowed the identification of the metabolite (+)-7β,8α-dihydroxy-9α,10α-epoxy-7,8,9,10-tetrahydro BP ((+)-**2**, Figure 1) as an ultimate carcinogen of BP in newborn mice.[2] Two diastereomeric 7,8-diol 9,10-epoxides of BP are metabolically possible, each capable of existing in enantiomeric forms. Although (±)-**1** is >30-fold more hydrolytically reactive in the physiological pH range[5] and more susceptible to attack by nucleophiles in nonaqueous solution relative to (±)-**2**,[6] only (+)-**2** is tumorigenic in newborn mice. Both **1** and **2** alkylate the phosphate backbone of nucleic acid and effect the strand scission of DNA.[7] Because alkylation at phosphate may play an important role in the mutagenic and carcinogenic activities of **1** and **2**, the mechanisms of reaction of **1** and **2** with hydrogen phosphate species (and other general acids) in aqueous dioxane solutions were determined and are reported in this study.[8]

The rates of reaction of **1** and **2** in 10% dioxane–water solutions at a given pH exhibit a marked first-order dependence on concentration of phosphate buffer (Figure 2).[9,10] The rate data for series of serially diluted buffer solutions of constant pH were fit to

$$k_{obsd} = k_{HA}[HA] + k_{H^+}a_{H^+} + k_0 \qquad (1)$$

where $k_{H^+}a_{H^+}$ and k_0 represent contributions by the acid catalyzed and spontaneous hydrolysis mechanisms, respectively,[5] and HA refers to the dihydrogen phosphate ion ($H_2PO_4^-$). Values of $k_{H_2PO_4^-}$ for hydrolysis of **1** and **2**, obtained from plots of k_{obsd} vs. [$H_2PO_4^-$] for solutions at a given pH, were found to be constant within experimental error over the pH range studied (6.3–7.6, Table I). These data indicate that $H_2PO_4^-$ is the only catalytic or reactive phosphate species in the hydrolysis of **1** and **2** under these conditions.

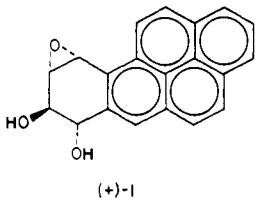

Figure 1. Diastereomeric BP 7,8-diol 9,10-epoxides.[3] The enantiomers of each diastereomer shown are those found bound to nucleic acid when BP is applied to mouse skin.[4]

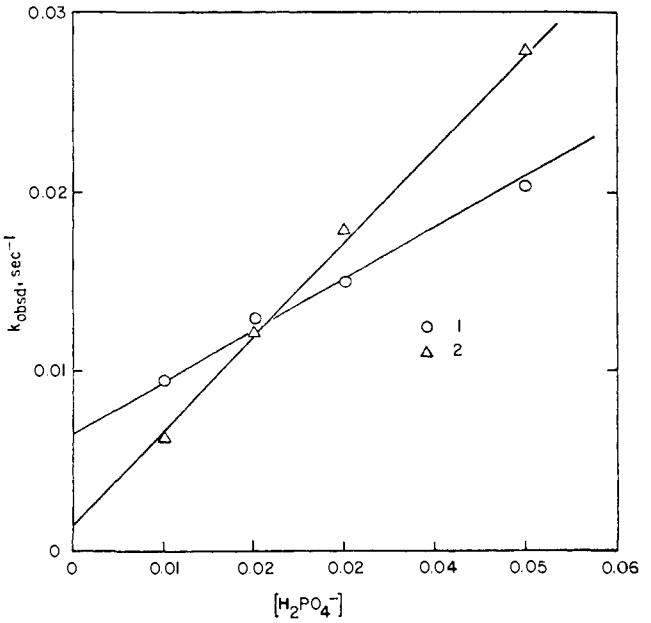

Figure 2. Plots of k_{obsd} vs. [$H_2PO_4^-$] for the hydrolysis of **1** and **2** in 10% dioxane-water solutions at 25 °C, ionic strength 0.2 ($NaClO_4$), pH 7.02.

Table I. Values of k_{HA} for the General Acid Catalyzed Hydrolysis of **1** and **2** in 10% Dioxane–Water[a] at 25 °C[b]

HA	pH	k_{HA}(**1**), M^{-1} s^{-1}	k_{HA}(**2**), M^{-1} s^{-1}
HOAc	4.81	0.72 ± 0.06	1.32 ± 0.02
	5.11	0.71 ± 0.04	1.33 ± 0.03
$H_2PO_4^-$	6.34	0.31 ± 0.01	0.48 ± 0.03
	6.70	0.28 ± 0.03	0.49 ± 0.01
	7.02	0.27 ± 0.01	0.48 ± 0.02
	7.10	0.28 ± 0.01	0.54 ± 0.02
	7.60	0.25 ± 0.01	0.49 ± 0.02
Tris-H^+	7.94	0.055 ± 0.006	0.026 ± 0.001
	8.54	0.056 ± 0.005	0.020 ± 0.002
$HO(CH_2)_2NH_3^+$	8.68	0.048 ± 0.004	0.0043 ± 0.0003
	8.94	0.048 ± 0.002	0.0044 ± 0.0004
phenol	9.22	0.19 ± 0.02	0.046 ± 0.003
	9.58	0.17 ± 0.01	0.046 ± 0.002

[a] Volume/volume; ionic strength, 0.2 ($NaClO_4$). [b] Rates were monitored by observing the absorbance change of the reaction solutions at 348 nm in the thermostated cell compartment (25.0 ± 0.1 °C) of a Gilford 2400 spectrophotometer. Rate constants were determined from least-squares plots of k_{obsd} vs. [HA] for solutions of constant pH but varied buffer concentrations.

Several kinetically indistinguishable mechanisms might account for the $H_2PO_4^-$ term in eq 1. One possibility is the specific acid–general base mechanism outlined in Scheme I (arbitrarily shown for the reaction of **1**). This mechanism involves attack of hydrogen phosphate ion (HPO_4^{-2}) on the protonated epoxide **3** to yield phosphate ester **4**.

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