was turned off, and the flow stopped. After the whole apparatus was isolated from the vacuum pump, dry air was introduced and the traps were warmed to room temperature. Finally, reactant reservoirs and traps were weighed to determine the amount of reactants passed and products collected in traps. Flow rate (r) was calculated from the amount of material lost from the reactant reservoir and the elapsed time during plasmolysis.

Analysis. Analysis of products collected in cold traps was carried out by means of GC. According to the additives, various stationary phases were used for liquid products as follows: silicone SE-30, Carbowax 20M, silicone OV-17, silicone QF-1, and Bentone 34 especially for separation of m- and p-cresols. In either case, the solid support was Chromosorb W-HP, and the percentage of stationary phase was 10%. For gaseous products, Porapak P was used. Identification of products was achieved by coinjection of authentic samples with products mixture, and was confirmed by gas chromatography–mass spectrometry. For the purpose of quantitation, the weight factors of every component in the product mixtures were determined relatively to anisole.

The isotope retention in plasmolysis products of deuterated anisole was determined by comparison of gas chromatographic data and mass spectra obtained from the products and unlabeled standard compounds. In the comparison, after correction for naturally occurring ^{13}C, the molecular ion (M) peak, M − 1 peak, and M − 2 peak were used. As the standard spectra of deuterated compounds were not available except for a few compounds,[18] following assumption was made for the hydrogen loss giving these peaks of interest. For anisole, the hydrogen loss takes place predominantly at methyl. On the other hand, for the other products, all hydrogens are equivalent. In both cases, the isotopic effect is not important. The assumption above was not critical for anisoles, phenols, and singly deuterated cresols. Furthermore, even for multiply deuterated cresols, it seems unlikely to cause considerable error in estimating the isotope retention.

Acknowledgment. Generous support from the National Science Foundation and discussions with H. Suhr are acknowledged. ICR spectra were measured by A. Szabo at Colorado State University.

References and Notes

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(7) The variation in rate with P and r could come from variations in electron distribution, electron energies, rates of interspecies energy transfer, residence time in the plasma region, or simply from the rate law for the specific reactions. Changes in product composition (ratios) could also arise from all of these factors. In addition, the possibility of converting primary products to other materials has often been suggested and a major change in mechanism with conditions is not unlikely.
(8) The above derivation leaves unclear the reasons why $k_1 f(\epsilon)$ is a linear function of P/p. One might suspect that knowing the number density of electrons (Ne^*) with energies greater than some limiting value for a quantized excitation and the average cross section for excitation by these electrons would be useful. Appropriate experimental data for reacting organic plasmas does not appear to be available.
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Synthesis of Parazoanthoxanthins and Pseudozoanthoxanthins

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Contribution from the Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139. *Received September 6, 1977*

Abstract: Parazoanthoxanthin A (**3**) and pseudozoanthoxanthin A (**4**), the least substituted zoanthoxanthins, a group of highly fluorescent marine natural products, have been synthesized by acid-catalyzed oxidative coupling of 2-amino-4(5)-(2-hydroxyethyl)imidazole (**7**), its dibenzoate **8**, 2-benzoylamino-4(5)-vinylimidazole (**16**), and 2-amino-4(5)-(1-hydroxyethyl)imidazole (**26**).

Among the multitude of new natural products isolated from marine organisms[2-5] the zoanthoxanthins[6-10] produced by colonial anthozoans, animals belonging to the order of Zoanthidae, occupy a special position. The highly fluorescent pigments were found to contain new aromatic ring systems and those known today belong to either the parazoanthoxanthin (1,3,5,7-tetrazacyclopent[*f*]azulene) or the pseudozoanthoxanthin (1,3,7,9-tetrazacyclopent[*e*]azulene) group. Within the two structural series the metabolites were shown to differ only in the number and position of N-methyl groups. Chemical transformations and spectral analyses of these pigments provided incomplete insight into their molecular structures and those of zoanthoxanthin (**1**)[6,7] and paragracine (**2**)[11,12] were established by x-ray analyses. The zoanthoxanthins can formally be considered to be dimers of a hypothetical C_5N_3 unit and the Italian investigators[9] were the first to suggest that the monomer used by nature might be arginine derived. To verify the chemical basis of this biogenetic hypothesis we have prepared parazoanthoxanthin A (**3**) and pseudozoanthoxanthin A (**4**) from the four monomers **7, 8, 16,** and **26.** Initial work[13] concentrated on the preparation and use of the primary alcohol **7.** Subsequent studies described in this paper included the secondary alcohol **15** and the vinylimidazole **16.**

Reduction of the commercially available lactone **5** with sodium amalgam in aqueous ethanol[14] yielded a diastereomeric mixture of hemiacetals **6.** The crude product was condensed with cyanamide[15] and the resulting intermediate cyclized and dehydrated to 2-amino-4(5)-hydroxyethylimidazole (**7**). The

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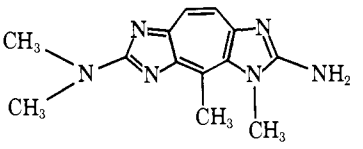

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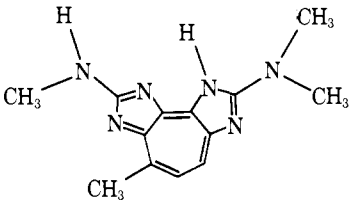

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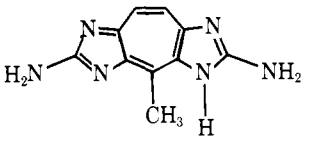

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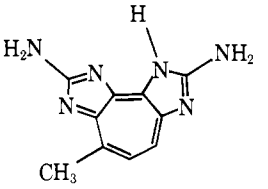
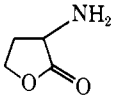


4

oily hydrochloride of this base was found to be hygroscopic but the crystalline picrate[16] can be stored without decomposition even in loosely sealed containers. Benzoylation under Schotten-Baumann conditions followed by hydrolysis with aqueous potassium carbonate gave 2-benzoylamino-4(5)-(2-benzoyloxyethyl)imidazole (**8**).



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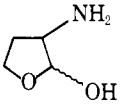

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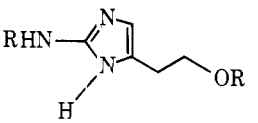
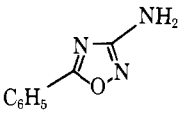


7, R = H
8, R = COC_6H_5

2-Amino-4(5)-(1-hydroxyethyl)imidazole and its derivatives were prepared by two different methods. The first made use of the 1,2,4-oxadiazole-imidazole rearrangement.[17] Oxadiazole **9**,[18] readily available from *N*-cyanobenzamidine and hydroxylamine, was condensed with 4-methoxybut-3-en-2-one to give the enamino ketone **10.** Treatment of **10** with 1 equiv



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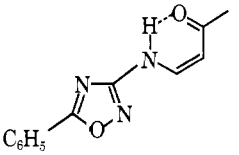

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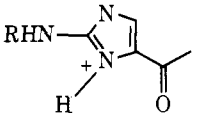
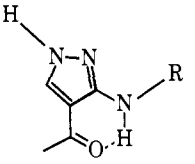
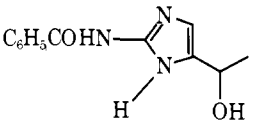


11, R = COC_6H_5
12, R = H



13, R = COC_6H_5
14, R = H

of sodium hydride in dimethylformamide caused isomerization to a mixture of the anticipated imidazole **11** and what turned out to be the isomeric pyrazole **13** in a ratio of 1:3, respectively. The structure of the latter was established by acid hydrolysis to 3-amino-4-acetylpyrazole **14** followed by deamination with nitrite to the known 4-acetylpyrazole (**17**).[19] The formation of a pyrazole in this isomerization was not anticipated because an earlier report on the behavior of oxadiazoles **18** and **19** claimed clean conversion to imidazoles **20** and **21.** We have verified the smooth transformation of **18** to **20** using sodium



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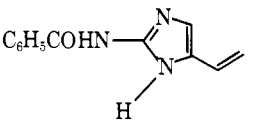

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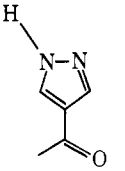

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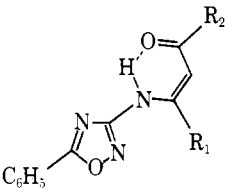
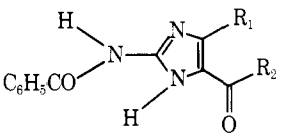
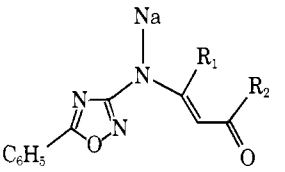


18, 19



20, 21



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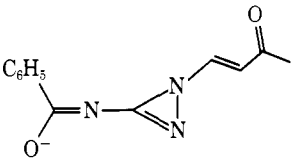
18, 20, 22, $R_1 = R_2 = CH_3$
19, 21, $R_1 = C_6H_5$; $R_2 = OC_2H_5$



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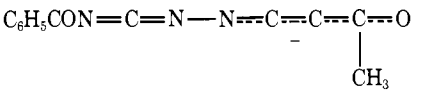


24

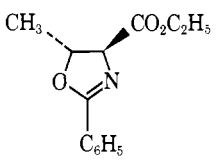
hydride rather than sodium methoxide in dimethylformamide. Approximately ten such mononuclear rearrangements are known and a generalized mechanistic scheme has been presented[20] but a rearrangement of the type leading from **10** to **13** appears to be without precedent. It can be rationalized if the original anion isomerizes to the diazirine (**23**) in which an O-N bond has been traded for a N-N bond. A further change might lead to the carbodiimide **24** and thence to the pyrazole **13.** The striking difference in behavior between β-substituted and unsubstituted ketones can perhaps be attributed to a difference in stereochemistry of the corresponding sodium salts. Imidazole formation cannot occur if the salts retain the configurations of the original hydrogen bonded enaminocarbonyl compounds **10, 18,** and **19.** The change should be facile, however, in the stereoisomeric salts such as **22.** Space-demanding R_1 substituents causing nonbonding interactions with the oxadiazole ring should thus facilitate isomerization to salts of type **22** and consequently imidazole formation.

Reduction of the ketone **11** with sodium borohydride gave the alcohol **15** and its dehydration with *p*-toluenesulfonic acid in hot toluene afforded the vinylimidazole **16.** The acid- and base-sensitive 2-amino-4(5)-(1-hydroxyethyl)imidazole (**26**), not available by hydrolysis of the amide **15,** was synthesized as follows. *d,l*-Threonine ethyl ester hydrochloride was condensed with benziminoethyl ether hydrochloride in the presence of aqueous ethanolic ammonia.[21] Reduction of the carboethoxy group in the resulting oxazoline **25** was accomplished with diisobutylaluminum hydride. The crude aldehyde was then immediately hydrolyzed with mineral acid and the hydrolysate condensed with cyanamide. Product **26** was difficult to separate from urea formed by hydrolysis of cyanamide. It was obtained in only 10% overall yield and an analytically pure sample remains to be prepared.

Table I. Synthesis of Parazoanthoxanthin A (**3**) and Pseudozoanthoxanthin A (**4**)

Starting material	Acid	Time, h	Yield, %	3, %	4, %
7	*a*	50	50	100	0
	b	16	27	65	35
8	*a*	21	25	65	35
	b	6	25	50	50
16	*b*	4	10	Trace	100
26	*a*	25	21	25	75
	b	12	27	Trace	100

[a] 35% HCl-H_2O, 90-100 °C. [b] Concentrated H_2SO_4, 90-100 °C.



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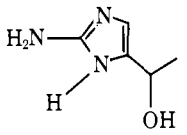
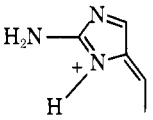


26

The four monomers **7**, **8**, **16**, and **26** on treatment with concentrated sulfuric acid at 90 °C or with concentrated aqueous hydrochloric acid at the same temperature all afforded zoanthoxanthins. The ratio of parazoanthoxanthin A (**3**) to pseudozoanthoxanthin A (**4**) in these oxidative dimerizations depended mainly on the starting material used (see Table I). Pseudozoanthoxanthin A (**4**) was the major if not exclusive dimer formed when the vinylimidazole **16** or the highly acid-sensitive secondary alcohol **26** served as starting materials. We assume that precursor **29** of pseudozoanthoxanthin (**4**) is the



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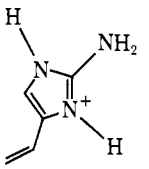

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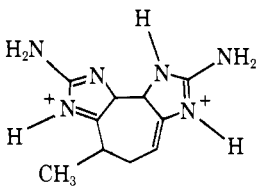

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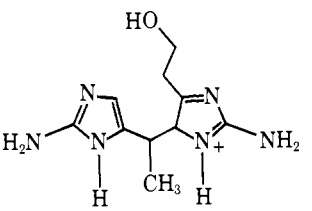

30

result of a concerted [4 + 6] cycloaddition[22] in which the more nucleophilic carbon atom of the diene **28** becomes attached to the exocyclic carbon atom of the diazafulvene **27**.[23] Sulfuric acid not only serves as an acid catalyst in these dimerizations but also causes oxidation of the cycloadduct **29** to pseudozoanthoxanthin A (**4**) with concomitant formation of sulfur dioxide.

The possibility that parazoanthoxanthin A (**3**), best prepared from the primary alcohol **7** in hydrochloric acid, is also the result of a [4 + 6] cycloaddition cannot be excluded by the available evidence. Perhaps it seems more reasonable to postulate other intermediates, e.g., **30** formed by combination of the diazafulvene **27** with starting materials **7**, **8**, or **26** rather than with a vinylimidazole which should be present in only low concentrations in this particular reaction medium. Concentrated sulfuric acid, a far better dehydrating agent than aqueous hydrochloric acid, on the other hand, produced substantial proportions of pseudozoanthoxanthin A (**4**) even from the primary alcohol **7** and its dibenzoyl derivative **8**. These oxidative dimerizations could be accelerated by added oxidants and ferric chloride served well when the dimerizations were performed in hydrochloric acid. Methods for alkylation of both ring and side-chain nitrogens have been devised[8] and homologous zoanthoxanthins can thus be prepared by total synthesis from the two archetypes **3** and **4**.

Experimental Section

Nuclear magnetic resonance (NMR) spectra were determined on a Varian T-60 instrument, a Perkin-Elmer R-24 B, or a Perkin-Elmer R-22 spectrometer. Chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane as an internal standard unless otherwise stated. Mass spectra were determined on Hitachi Perkin-Elmer RMU-6E and Varian MAT-44 spectrometers. Ultraviolet (UV) and visible spectra were recorded on Cary Model 14 and Perkin-Elmer 202 spectrometers. Infrared (IR) spectra were obtained on Perkin-Elmer 247 or 237 B grating spectrometers. Melting points were determined on a Reichert hot stage microscope and are corrected. Progress of most reactions was followed by thin layer chromatography (TLC) using Baker-flex silica gel GF analytical plates or Analtech precoated silica gel GF plates. Ultraviolet light, iodine, or sprays such as Weber reagent[24] were used to visualize spots. Woelm silica gel (0.063-0.02 mm) was used for column chromatography. The trifluoroacetic acid used was reagent grade purchased from Aldrich Chemical Co. and no further purification was necessary. Microanalyses were performed by the Robertson Laboratory, Florham Park, N.J.

2-Amino-4(5)-(2-hydroxyethyl)imidazole Picrate (7). α-Amino-γ-butyrolactone (20.0 g, 0.11 mol) was dissolved in a mixture of 200 mL of absolute ethanol and 450 mL of water. The solution was placed in a 4-L beaker equipped with a mechanical stirrer, a thermometer, and a calomel electrode connected to a pH meter. The solution was stirred in an ice bath for 30 min, and 1.5 kg of 2.5% sodium amalgam (1.67 mol of sodium) was then added in large pieces with vigorous stirring over ca. 4 h. During addition, the pH was maintained between 1.5 and 2.0 by dropwise addition of 15% hydrochloric acid, and the temperature was held at 3-7 °C.[14] When the amalgam had completely decomposed, the solution was decanted from the mercury and brought to pH 4.5 by addition of 1 N sodium hydroxide. An aqueous solution of 50% cyanamide (44 mL, 0.56 mol) was added, and the mixture was heated to 60-70 °C for 2 h.[15] The solvent was removed in vacuo and the dry residue was washed with ether (200 mL) and was extracted with absolute ethanol (3 × 200 mL). Concentration of the ethanol fractions afforded an oil which was dissolved in 600 mL of 15% hydrochloric acid and placed on a steam bath for 2 h. Neutralization with 4 N sodium hydroxide followed by evaporation to dryness, extraction of the residue with absolute ethanol, and concentration of the ethanolic extracts gave crude **7** as an oil. This was dissolved in 220 mL of water and added to a boiling solution of 22 g of picric acid in 440 mL of water. The resulting solution was allowed to cool overnight and the precipitate was collected. The ethanol-soluble fraction was recrystallized from absolute ethanol to give 16.2 g (41%) of the picrate of **7**: mp 177-179 °C; NMR (CF_3CO_2H, $CDCl_3$) δ 9.33 (s, 2, picrate ArH), 6.60 (br, s, 1, imidazole H), 4.10 (t, 2, J = 7 Hz, imidazole $-CH_2CH_2OH$), 2.93 (t, 2, J = 7 Hz, imidazole $-CH_2CH_2OH$).

Anal. Calcd for $C_{11}H_{12}N_6O_8$: C, 37.08; H, 3.40; N, 23.59. Found: C, 36.90; H, 3.43; N, 23.69.

2-Amino-4(5)-(2-hydroxyethyl)imidazole Hydrochloride (7). A 2.0-g (5.61 mmol) quantity of the picrate of **7** was heated in a refluxing mixture of 60 mL of 15% hydrochloric acid and 80 mL of benzene for 10 min, the benzene layer was decanted, and the aqueous phase was washed with benzene (4 × 60 mL).[16] Evaporation of the aqueous phase gave an oily product which was dried in a desiccator over phosphorus pentoxide at 0.1 mm to give 0.92 g (100%) of the hydrochloride of **7** as an oil: UV max (EtOH) 216 nm (ϵ 8150); IR (neat) 3200 (br), 1675, 1050 cm^{-1}; NMR (D_2O, sodium 2,2,3,3-tetradeuterio-3-trimethylsilylpropionate internal standard) δ 6.55 (s, 1, imidazole H), 3.80 (t, 2, J = 7 Hz, imidazole CH_2CH_2OH), 2.75 (t, 2, J = 7 Hz, imidazole $-CH_2CH_2OH$); mass spectrum (70 eV) *m/e* (rel intensity) 127 M^+ of free base (55), 110 (18), 109 (19), 97 (96), 96 (100), 69 (35), 55 (21), 54 (46).

2-Benzoylamino-4(5)-(2-benzoyloxyethyl)imidazole (8). Five grams

(14.0 mmol) of the picrate of **7** was dissolved in 150 mL of 15% hydrochloric acid and 200 mL of benzene and refluxed for ca. 15 min. The layers were separated and the aqueous layer was washed with benzene (4 × 100 mL) and basified to pH 10 with 4 N sodium hydroxide. Benzoyl chloride (total amount 30 mL (0.26 mol)) and 4 N sodium hydroxide were added in small portions with vigorous stirring so that the pH was maintained between 7 and 10. When the pH of the reaction mixture remained basic, the aqueous solution was extracted with chloroform (3 × 150 mL), and the combined organic fractions were dried (Na_2SO_4) and concentrated in vacuo to give an oil which was dissolved in 250 mL of ether and allowed to stand overnight. The white solid obtained was stirred in 150 mL of saturated potassium carbonate for 1 h followed by filtration and drying to give 3.25 g (67% from picrate) of **8.** Recrystallization from benzene yielded the product as white plates: mp 171–173 °C; UV max (EtOH) 226 nm (ε 29 200), 273 (sh) (11 200), 281 (11 500), 295 (sh) (9400); UV max (EtOH, 1 N HCl) 229 nm (ε 26 000), 266 (16 200); IR ($CHCl_3$) 3430, 1715, 1665, 1600, 1275, 1090 cm^{-1}; NMR ($CDCl_3$) δ 8.15–7.90 (m, 4, ortho ArH), 7.60–7.30 (m, 6, meta and para ArH), 6.45 (s, 1, imidazole H), 4.20 (t, 2, J = 7 Hz, $ArCO_2CH_2$–), 2.80 (t, 2, J = 7 Hz, –CH_2– imidazole); mass spectrum (70 eV) *m/e* (rel intensity) 336 M + 1 (4), 335 M^+ (16), 213 (100), 122 (12), 106 (12), 105 (98), 77 (54), 51 (12); *m/e* exact mass 335.124 05 (calcd for $C_{19}H_{17}N_3O_3$, 335.126 99).[25]

5-Phenyl-*N*-(1,2,4-oxadiazol-3-yl)-4-but-3-en-2-one (10). A mixture of 1.00 g (6.20 mmol) of oxadiazole **9**[18] and 2.00 g (20.0 mmol) of 4-methoxy-3-buten-2-one was placed in a 50-mL flask under a nitrogen atmosphere. The reaction flask was placed in an oil bath maintained at 90 °C and the mixture was stirred vigorously for 50 min. A 40-mL quantity of hexane was added to the reaction mixture and after refluxing for 15 min the hexane was decanted and the procedure repeated. The combined hexane fractions were concentrated to ca. 30 mL and allowed to cool to afford 1.07 g (75%) of crystalline **10.** Recrystallization from hexane followed by sublimation at 90 °C (0.1 mm) gave a white solid: mp 110–111 °C; UV max (CH_3OH) 249 nm (ε 16 000), 256 (16 300), 288 (26 700); IR ($CHCl_3$) 3620, 1655, 1600, 1550, 1450, 1400, 1260 cm^{-1}; NMR ($CDCl_3$) δ 11.50 (br d, 1, J = 11 Hz, D_2O exchangeable, NH), 8.20–8.00 (m, 2, ortho ArH), 7.60–7.20 (m, 4, meta ArH, para ArH, and –NCH=), 5.47 (d, 2, J = 8 Hz, –NCH=C*H*–), 2.21 (s, 3, CH_3); mass spectrum (70 eV) *m/e* (rel intensity) 229 M^+ (40), 214 (25), 105 (100), 77 (40), 43 (31).

Anal. Calcd for $C_{12}H_{11}N_3O_2$: C, 62.87; H, 4.84; N, 18.33. Found: C, 62.81; H, 4.91; N, 18.18.

2-Benzoylamino-4(5)-acetylimidazole (11) and 3-Benzoylamino-4-acetylpyrazole (13). A suspension of 600 mg (25.0 mmol) of sodium hydride in 80 mL of dry dimethylformamide was stirred under argon in a 250-mL, three-necked, round-bottomed flask equipped with a thermometer and a dropping funnel. A solution of 5.31 g (23.2 mmol) of **10** in 20 mL of dimethylformamide was added to the suspension over 5 min (hydrogen evolution), and the mixture was stirred for 1.5 h at room temperature, during which time it became a clear, dark solution. After additional stirring for 3.5 h at 135 °C, the solution was cooled, poured into 200 mL of water, neutralized with 1 N hydrochloric acid, and evaporated to dryness. The dark residue was extracted with ethyl acetate, and the ethyl acetate solution was treated with activated carbon, filtered, and concentrated in vacuo to give 3.29 g (62%) of a crude mixture. Analysis of this product by NMR showed a 1:3 mixture of **11** and **13**, respectively. Recrystallization from chloroform–ether gave pure compounds. The initial compound that precipitated was identified as **11**: mp 214–216 °C; UV max (CH_3OH) 225 nm (ε 10 000), 285 (17 000); IR ($CHCl_3$) 3370, 3000, 1665, 1600, 1525, 1190, 945 cm^{-1}; NMR ($CDCl_3$) δ 12.0–10.7 (m, 1, NH), 8.12–7.46 (m, 5, ArH), 7.10 (s, 1, imidazole H), 2.38 (s, 3, $-CH_3$); mass spectrum (70 eV) *m/e* (rel intensity) 230 M + 1 (9), 229 M^+ (56), 201 (11), 106 (17), 105 (100), 77 (34), 51 (38).

Anal. Calcd for $C_{12}H_{11}N_3O_2$: C, 62.87; H, 4.84; N, 18.33. Found: C, 62.83; H, 4.87; N, 18.20.

The second compound that precipitated from solution was identified as **13**: mp 170–172 °C; UV max (CH_3OH) 234 nm (ε 17 000), 283 (11 000), 290 (sh) (10 700); IR ($CHCl_3$) 3400, 3280, 2970, 1675, 1635, 1580, 1270, 930 cm^{-1}; NMR ($CDCl_3$) δ 11.5–11.2 (m, 1, NH), 8.10–7.50 (m, 6, ArH with pyrazole hydrogen singlet at δ 7.87), 2.50 (s, 3, $-CH_3$); mass spectrum (70 eV) *m/e* (rel intensity) 230 M + 1 (21), 229 M^+ (100), 106 (26), 105 (100), 77 (50), 51 (22).

Anal. Calcd for $C_{12}H_{11}N_3O_2$: C, 62.87; H, 4.84; N, 18.33. Found: C, 63.04; H, 4.89; N, 18.36.

2-Amino-4(5)-acetylimidazole (12) and 3-Amino-4-acetylpyrazole (14). A 327-mg (1.43 mmol) quantity of a mixture of **11** and **13** (1:3 ratio, respectively) in 20 mL of ethanol and 2 mL of concentrated hydrochloric acid was refluxed for 30 h. The solvent was removed in vacuo and the dry residue was dissolved in water. The aqueous solution was washed with ether (2 × 20 mL), neutralized with 1 N sodium hydroxide, and evaporated to dryness. Extraction with ethanol and evaporation of the solvent gave 166 mg (93%) of a crude mixture of compounds **12** and **14** in ca. 1:3 ratio, respectively. A 100-mg quantity was chromatographed on a 2-mm silica gel plate (chloroform–methanol, 50:50). The more polar isomer was identified as **12**: R_f 0.7; 23 mg; sublimed 150 °C (0.1 mm); mp 210–215 °C; UV max (EtOH) 300 nm (ε 14 000); UV max (EtOH, 1 N HCl) 268 nm (ε 10 000); UV max (EtOH, 1 N NaOH) 244 nm (ε 3300), 317 (12 000); IR (Nujol) 3300, 1620, 1550 cm^{-1}; NMR (D_2O, methanol internal standard) δ 7.77 (s, 1, imidazole H), 2.30 (s, 3, $-CH_3$); mass spectrum (70 eV) *m/e* (rel intensity) 126 M + 1 (15), 125 M^+ (55), 110 (100), 83 (70), 54 (100), 53 (35), 52 (55), 43 (55); *m/e* exact mass 125.059 68 (calcd for $C_5H_7N_3O$, 125.058 91).[25]

The less polar isomer was shown to be **14**: R_f 0.8; 47 mg; sublimed 130 °C (0.1 mm); mp 148–150 °C; UV max (EtOH, HCl salt) 232 nm (sh) (ε 4800), 281 (6500); UV max (EtOH, 1 N NaOH) 260 nm (ε 12 000), 292 (sh) (6150); IR ($CHCl_3$) 3450, 1650, 1200 cm^{-1}; NMR (D_2O, methanol internal standard) δ 8.10 (s, 1, pyrazole H), 2.30 (s, 3, $-CH_3$); mass spectrum (70 eV) *m/e* (rel intensity) 126 M + 1 (9), 125 M^+ (55), 111 (9), 110 (100), 54 (68), 53 (23), 52 (41), 43 (41); *m/e* exact mass 125.058 45 (calcd for $C_5H_7N_3O$, 125.058 91).

4-Acetylpyrazole (17). A 33-mg (0.26 mmol) quantity of **14** was chilled and dissolved in a solution of 0.1 mL of concentrated hydrochloric acid and 0.03 mL of water. The flask was immersed in an ice–salt bath and the temperature was maintained at −5 to 0 °C while a 20-mg (0.30 mmol) quantity of sodium nitrite dissolved in 0.04 mL of water was added dropwise. The resulting solution was stirred for 45 min before 0.3 mL of 50% hypophosphorous acid was added slowly. The reaction mixture was stirred for 1 h at −5 to 0 °C followed by placing it in the refrigerator overnight. The resulting mixture was extracted with chloroform (3 × 1 mL), and the aqueous solution was concentrated in vacuo. The crude residue was extracted with ethanol and the combined ethanolic solution was concentrated in vacuo to give 70 mg of white solid which was extracted with chloroform. The chloroform solution was filtered and concentrated in vacuo to give 20 mg (69%) of previously known compound **17**: mp 110–113 °C (lit.[19] mp 111 °C); IR ($CHCl_3$) 3450 (sh), 3200 (br), 1671, 1550, 940 cm^{-1}; NMR ($CDCl_3$) δ 11.7–10.3 (br, 1, NH), 8.20–8.00 (br s, 2, ArH), 2.50 (s, 3, $-CH_3$); mass spectrum (70 eV) *m/e* (rel intensity) 111 M + 1 (6), 110 M^+ (25), 95 (100), 68 (12), 43 (19), 40 (15).

2-Benzoylamino-4(5)-(1-hydroxyethyl)imidazole (15). A suspension of 303 mg (7.97 mmol) of sodium borohydride in 60 mL of isopropyl alcohol was heated to reflux in a 250-mL, three-necked, round-bottomed flask equipped with a reflux condenser, a dropping funnel, and a magnetic stirrer. Within 5 min, a solution of 233 mg (1.02 mmol) of **11** in 40 mL of isopropyl alcohol was added to the boiling solution. After 1 h of refluxing, the solution was allowed to cool to room temperature, acidified to pH 5 by cautious addition of 1 N hydrochloric acid, and then neutralized with 1 N sodium hydroxide. The solid which precipitated during the neutralization coagulated when the solution was heated for a few minutes on the steam bath. The precipitate was then removed by filtration, the filtrate was evaporated to give a solid, which was dissolved in methanol, and the solution was again evaporated to dryness. This procedure was repeated four times, and the resulting residue was then extracted with ethanol. After filtration, the ethanolic filtrate was concentrated to give 209 mg (89%) of compound **15.** Recrystallization from benzene–ethyl acetate yielded the product as white plates: mp 181–183 °C; UV max (95% EtOH) 226 nm (ε 11 900), 281 (9500), 295 (sh) (8600); UV max (95% EtOH, 1 N HCl) 240 nm (ε 10 700), 265 (13 650); IR (Nujol) 3250 (br), 1665, 1070 cm^{-1}; NMR (Me_2SO-d_6, $CDCl_3$) δ 11.6 (m, 2, NH), 8.20–8.00 (m, 2, ortho ArH), 7.60–7.40 (m, 3, meta and para ArH), 6.61 (s, 1, imidazole H), 4.79 (q, 1, J = 7 Hz, –C*H*(OH)CH_3), 3.90–3.20 (br, 1, OH), 1.42 (d, 3, J = 7 Hz, $-CH_3$); mass spectrum (70 eV) *m/e* (rel intensity) 231 M^+ (13), 216 (6), 213 (10), 105 (100), 77 (58), 51 (19).

Anal. Calcd for $C_{12}H_{13}N_3O_2$: C, 62.32; H, 5.67; N, 18.17. Found: C, 62.06; H, 5.72; N, 17.88.

2-Benzoylamino-4(5)-vinylimidazole (16). A 2-L round-bottomed

flask, equipped with a magnetic stirrer and a Soxhlet extractor containing ca. 20 g of molecular sieves (4A), was charged with 590 mg (2.55 mmol) of **15** and 1.3 L of dry toluene. The mixture was refluxed briefly, the resulting solution was cooled slightly, and 680 mg (3.57 mmol) of *p*-toluenesulfonic acid monohydrate was added in one portion. After 8 h of vigorous refluxing under the Soxhlet extractor, the solution was cooled, transferred into a separatory funnel, diluted with 200 mL of ethyl acetate, and washed with 50 mL of 1 N sodium hydroxide. The sodium hydroxide solution was extracted with ethyl acetate (3 × 50 ml). The combined organic layers were washed with water, dried (Na_2SO_4), and evaporated to give a crystalline, crude product. Recrystallization (chloroform–ether) provided 370 mg of **16.** The mother liquor was concentrated and purified by thin layer chromatography on 1-mm silica gel plates (chloroform–ethanol; 95:5), R_f 0.6, to give another 108 mg of **16**, raising the yield to 478 mg (88%): sublimed 140 °C (0.1 mm); mp 158–160 °C; UV max (95% EtOH) 228 nm (ε 13 000), 259 (9650), 283 (sh) (9300), 296 (9700); IR ($CHCl_3$) 3380, 2950 (br), 1660, 1590, 1520, 1280, 1110, 980, 885 cm^{-1}; NMR ($CDCl_3$) δ 11.33 (m, 2, D_2O exchangeable, NH) 8.10–7.83 (m, 2, ortho ArH), 7.67–7.33 (m, 3, meta and para ArH), 6.50 (s, 1, imidazole H), 6.43 (dd, 1, J_{trans} = 18, J_{cis} = 11 Hz, imidazole -C*H*=CH_2), 5.33 (d, 1, J_{trans} = 18 Hz, imidazole -CH=$CH_{trans}H_{cis}$), 5.03 (d, 1, J_{cis} = 11 Hz, imidazole -CH=C$H_{trans}H_{cis}$); mass spectrum (70 eV) *m/e* (rel intensity) 213 M^+ (40), 106 (11), 105 (100), 77 (63), 51 (19), 43 (27).

Anal. Calcd for $C_{12}H_{11}N_3O$: C, 67.59; H, 5.20; N, 19.71. Found: C, 67.62; H, 5.20; N, 19.31.

2-Amino-4(5)-(1-hydroxyethyl)imidazole (26). A 3.39-g (14.5 mmol) quantity of **25**[21] was dissolved in 30 mL of dry toluene, placed under a nitrogen atmosphere, and cooled in a dry ice–acetone bath. The solution was stirred while 19.5 mL (29 mmol) of diisobutylaluminum hydride in toluene was added dropwise (15 min). Following addition the reaction mixture was stirred at −78 °C for 25 min. The reaction was slowly quenched with saturated ammonium chloride (25 mL) and allowed to warm to 25 °C when 50 mL of ether was added. After vigorous stirring for ca. 15 min the entire solution turned to a gel. This was filtered through Celite and the layers were separated. The aqueous layer was washed with ether (2 × 50 mL), and the combined ether layers were washed with saturated sodium chloride (50 mL) and concentrated in vacuo to an oil that was dissolved in 14.5 mL (14.5 mmol) of 1 N hydrochloric acid and left standing overnight at 25 °C. Concentration of the acidic solution gave 2.9 g of a white solid. A separately prepared 6.6-g sample of this white solid was dissolved in 30 mL of water. To this was added 8 mL of 50% cyanamide and the pH was adjusted to 4.5 with 1 N sodium hydroxide. The mixture was heated to 65–70 °C for 2 h while the pH was maintained at 4.5. After cooling to 25 °C the aqueous solution was washed with ether (70 mL) and was concentrated in vacuo to an oily product. This crude product was washed with ether (3 × 50 mL) and extracted with absolute ethanol. The ethanol was removed in vacuo and the crude products were chromatographed on 70 g of silica gel (chloroform–methanol, 80:20) to give 1.44 g of impure imidazole **26** as an oil. A 475-mg quantity of the crude product was again submitted to chromatography on 40 g of silica gel (chloroform–methanol, 85:15) to give 135 mg (10% from **15**) of imidazole **26**: IR (neat) 3500–2700 (br), 1680, 1610, 1265, 1050, 700 cm^{-1}; NMR (D_2O, CF_3CO_2H, methanol internal standard) δ 6.72 (s, 1, imidazole H), 4.53 (q, 1, J = 7 Hz, imidazole -C*H*(OH)CH_3), 1.47 (d, 3, J = 7 Hz, CH_3).

The picrate of **26** was precipitated as a yellow, crystalline compound from an aqueous solution of picric acid and **26**: mp 157–160 °C; NMR (CF_3CO_2H, $CDCl_3$) δ 9.10 (s, 2, aromatic H), 7.00 (s, 1, imidazole H), 6.05 (q, 1, J = 7 Hz, imidazole -C*H*(OH)CH_3), 1.80 (d, 3, J = 7 Hz, CH_3).

Parazoanthoxanthin A (3) from 7. A 10.0-g (28.0 mmol) quantity of the picrate of **7** was dissolved in a mixture of 300 mL of 15% hydrochloric acid and 400 mL of benzene and was refluxed for ca. 15 min. The layers were separated and the aqueous layer was washed with benzene (4 × 200 mL). The aqueous solution was concentrated in vacuo and the resulting oil dissolved in 40 mL of concentrated hydrochloric acid containing 400 mg (1.47 mmol) of $FeCl_3 \cdot 6H_2O$. The reaction mixture was heated to 100 °C and the progress of the reaction was monitored by determining the ultraviolet spectrum of equal samples diluted with constant volumes of water. After 45 h, the absorption at 285 nm reached a maximum and the reaction mixture was allowed to cool to 25 °C followed by neutralization with 4 N sodium hydroxide. The resulting yellow precipitate was collected by filtration and dried under vacuum over phosphorus pentoxide. This solid was applied to the top of a silica gel column (80 g) and slowly leached through with a 2-L solution of chloroform–methanol–25% ammonium hydroxide (80:20:2). A total of 1.5 g (50%) of parazoanthoxanthin A (**3**)[6] was obtained as the sole product: mp >310 °C; UV max (MeOH) 285 nm (ε 31 500), 295 (37 500), 405 (15 100); UV max (MeOH, 1 N HCl) 293 nm (ε 43 700), 390 (11 300); UV max (MeOH, 1 N NaOH) 295 nm (ε 65 400), 402 (17 800); IR (KBr) 3500–2800 (br), 1680, 1550, 1405, 1260, 1190 cm^{-1}; NMR (CF_3CO_2H) δ 8.94 (s, 2, aromatic H), 3.32 (s, 3, CH_3); mass spectrum *m/e* exact mass 214.095 56 (M^+, base peak) (calcd for $C_{10}H_{10}N_6$, 214.096 69).[25]

Pseudozoanthoxanthin A (4) from 26. A 200-mg (1.57 mmol) quantity of **26** was heated in 2 mL of concentrated sulfuric acid at 100 °C for 12 h. After cooling to room temperature, the solution was poured into 50 mL of water. Basification with aqueous barium hydroxide suspension to pH 10–11, removal of barium sulfate by filtration through Celite, and concentration in vacuo gave 103 mg of brown solid. Purification by column chromatography on 49 g of silica gel (chloroform–methanol–25% ammonium hydroxide, 80:20:2) afforded a trace (<1 mg) of parazoanthoxanthin A (**3**) and 45 mg (27%) of pseudozoanthoxanthin A (**4**):[9] mp 280 °C dec; UV max (MeOH) 245 nm (ε 6000), 296 (27 700), 363 (4900), 402 (6600); UV max (MeOH, 1 N HCl) 230 nm (ε 9500), 288 (29 400), 357 (br), 395 (9100); UV max (MeOH, 1 N NaOH) 227 nm (ε 8400), 296 (33 300), 364 (4600), 404 (7350); NMR (CF_3CO_2H) δ 8.61 (s, AB quartet J = 11 Hz, aromatic H), 3.13 (s, 3, CH_3); mass spectrum *m/e* exact mass 214.096 31 (calcd for $C_{10}H_{10}N_6$, 214.096 69).

Parazoanthoxanthin A (3) and Pseudozoanthoxanthin A (4) from 7. A solution of 80 mg (0.49 mmol) of **7** in 2 mL of concentrated sulfuric acid was heated to 95 °C while being monitored as described previously. After ca. 16 h, the reaction was complete and continued heating showed no decomposition of product. After cooling to room temperature, the solution was poured into 40 mL of water. Normal workup and chromatography on 1-mm silica gel plates (chloroform–methanol–25% ammonium hydroxide, 80:20:2) afforded two products, The more polar isomer was identical with parazoanthoxanthin A (**3**), R_f 0.18, 11 mg, 19% yield, recrystallized from ethanol. The less polar isomer was identical with pseudozoanthoxanthin A (**4**), R_f 0.24, 4 mg, 8% yield, recrystallized from ethanol.

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Biomimetic Transformations among Monomeric Macroline-Related Indole Alkaloids[1]

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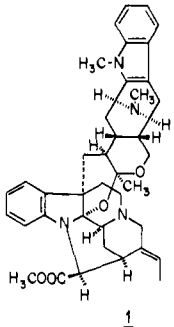
Abstract: The monomeric base macroline **5**, previously utilized in biomimetic syntheses of the *Alstonia* bisindole alkaloids villalstonine (**1**), alstonisidine (**2**), macralstonine (**3**), and macralstonidine (**4**), was converted to the monomeric alkaloid alstonerine (**10**) by an epoxidation–dehydration sequence. Alstonerine (**10**) was converted by reduction followed by acid-catalyzed rearrangement into N_b-methyl-N_b,21-secotalpinine (**20**), and alstonisine (**21**) into talpinine (**18**) by twofold reductive rearrangement. Model experiments bearing upon these interconversions are described. The nature of the biogenetic "macroline equivalent" is discussed in the light of these results. During model reactions performed to develop a biomimetic pathway to the pyridinoindole base suaveoline (**30**), a new, potentially general synthesis of 2-alkyl- and 3-alkylpyridines, utilizing dihydropyran as starting material, was developed.

In previous work in our laboratory, the *Alstonia* bisindole alkaloids villalstonine (**1**),[2] alstonisidine (**2**),[2] macralstonine (**3**),[3] and macralstonidine (**4**)[4] were synthesized by acid-cat-



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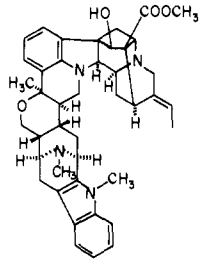

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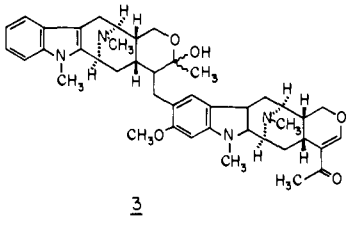

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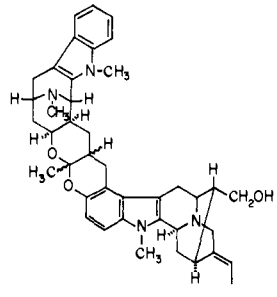
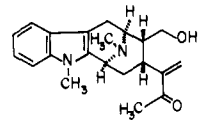


4

alyzed Michael-type and vinylogous Michael-type reactions between macroline **5** and respectively pleiocarpamine (**6**), quebrachidine (**7**), alstophylline (**8**), and N_a-methylsarpagine (**9**). Although macroline itself has not been encountered as a natural product, the notable directness and stereospecificity of these syntheses have led us to consider macroline or an "equivalent" as a likely biogenetic precursor of the bisindoles **1–4**, and to regard the syntheses therefore as biomimetic. In this paper we report our work on biomimetic transformations



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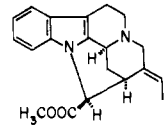

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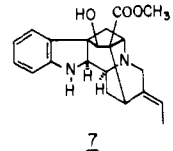

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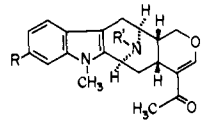
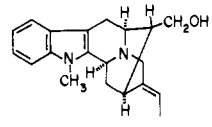


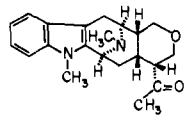
8; R = OCH_3, R' = CH_3
10; R = H, R' = CH_3
24; R = H, R' = $COCF_3$
25; R = H, R' = $COCH_3$



9

among some monomeric alkaloids. First we consider alkaloids closely related to macroline itself by virtue of carbon skeleton and natural occurrence, and then we discuss interconversions connecting the macroline bases with other indole alkaloids so as to suggest the likelihood of biogenetic relationships.

Alstophylline (**8**) and alstonerine (**10**) are the known alkaloids closest to macroline (**5**), so we investigated first the conversion **5** → **10.** In view of the importance of Michael-type reactions in the bisindole syntheses, we envisaged a Michael-type ring closure of macroline followed by dehydrogenation to give **10.** Macroline was recovered unchanged after exposure



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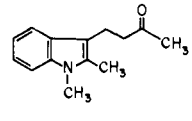

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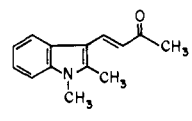

13

to various aqueous acid conditions (0.2 N HCl, 20 °C for 12 h, or 2 N HCl, reflux, 4 h) but was converted by methanolic sodium methoxide into an approximately 1:1 equilibrium mixture of **5** and a new compound, $C_{21}H_{26}N_2O_2$. This com-

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