A second fraction, eluted with 15% ether in hexane, contained a 4:1 mixture of compounds **9** and **10** (400 mg, 0.26% dry weight). The major fraction, eluted with 20% ether in hexane, was a 3:1 mixture of compounds **4** and **5** (700 mg, 0.46% dry weight). The mixture of **4** and **5** was chromatographed on a column (50 cm × 2 cm diameter) of silica gel using 10% ether in hexane as eluant to remove fats. The isomers were separated on μ-porasil using 30% ether in hexane.

(3*E*,5*E*,10*E*)-7-Hydroxy-13-keto-3,7,11,15-tetramethylhexadeca-1,3,5,10,14-pentaene (4): oil; $[\alpha]^{20}_D$ 0; IR (CCl_4) 3470, 1690, 1620 cm^{-1}; UV (hexane) 253 nm (ε 30 000), 261 (ε 41 200), 272 (ε 52 200), 282 (ε 41 200); ^1H NMR ($CDCl_3$) see Table I; ^{13}C NMR (C_6D_6) δ 207.5 (s), 154.8 (s), 142.3 (d), 141.8 (d), 134.8 (s), 131.7 (d), 130.2 (s), 129.7 (d), 124.0 (d), 123.3 (d), 112.2 (t), 73.0 (s), 55.4 (t), 42.7 (t), 28.9 (q), 27.3 (q), 23.6 (t), 20.6 (q), 16.6 (q), 12.1 (q); HRMS, found 302.2246, $C_{20}H_{30}O_2$ requires 302.2246.

(3*Z*,5*E*,10*E*)-7-Hydroxy-13-keto-3,7,11,15-tetramethylhexadeca-1,3,5,10,14-pentaene (5): oil; IR (CCl_4) 3560, 1690, 1620 cm^{-1}; UV (hexane) 248 nm (ε 26 000), 254 (ε 33 850), 264 (ε 38 200), 274 (ε 28 600); ^1H NMR ($CDCl_3$) see Table I; ^{13}C NMR (C_6D_6) δ 207.5 (s), 154.6 (s), 141.1 (d), 133.9 (d), 133.3 (s), 130.2 (d), 129.6 (d), 123.4 (d), 122.9 (d), 114.0 (t), 72.9 (s), 55.4 (t), 42.7 (t), 28.8 (q), 27.2 (q), 23.6 (t), 20.5 (q), 19.9 (q), 16.6 (q) (one signal obscured by C_6D_6); HRMS, found 302.2246, $C_{20}H_{30}O_2$ requires 302.2246.

(3*E*,5*E*,10*E*)-7-Ethoxy-13-keto-3,7,11,15-tetramethylhexadeca-1,3,5,10,14-pentaene (9): oil; IR (CCl_4) 1690, 1620 cm^{-1}; UV (hexane) 254 nm (ε 28 000), 265 (ε 40 000), 275 (ε 51 000), 282 (ε 41 000); ^1H NMR see Table I; ^{13}C NMR (CCl_4) δ 207.1 (s), 153.3 (s), 141.0 (d), 140.0 (d), 134.2 (s), 130.9 (d), 129.4 (s), 129.0 (d), 125.3 (d), 122.7 (d), 112.0 (t), 76.3 (s), 57.0 (t), 55.1 (t), 40.2 (t), 27.3 (q), 22.8 (q), 22.4 (t), 20.2 (q), 16.0 (q), 15.9 (q), 11.8 (q); mass spectrum, *m/e* 330 (1), 284 (5), 201 (5), 186 (8), 86 (100).

(3*Z*,5*E*,10*E*)-7-Ethoxy-13-keto-3,7,11,15-tetramethylhexadeca-1,3,5,10,14-pentaene (10). This compound could not be separated completely from compound **9**. The ^1H NMR data (Table I) were deduced by subtraction.

Mixture of (3*E*,5*E*,10*E*)- and (3*Z*,5*E*,10*E*)-7-Ethoxy-3,7,11,15-tetramethylhexadeca-1,3,5,10,14-pentaene (11 and 12). A 3:1 mixture of geometrical isomers. The spectral data were recorded on the mixture and the ^1H NMR signals assigned according to peak heights (Table I): IR (CCl_4) 1610 cm^{-1}; UV (hexane) 265 nm (ε 38 000), 274 (ε 50 800), 281 (ε 40 000); mass spectrum, *m/e* 271 (1), 270 (1), 255 (11), 228 (11), 69 (100), 55 (75).

Hydrogenation of Ketone 4. A solution of ketone **4** (10 mg, 0.03 mmol) in anhydrous ether (10 mL) containing 10% palladium on carbon catalyst (2 mg) was stirred under an atmosphere of hydrogen for 18 h. The catalyst was removed by filtration and the solvent evaporated to yield the ketone **8** (9.5 mg, 95% theoretical): IR (CCl_4) 1720 cm^{-1}; ^1H NMR δ 0.83 (d, 9 H, *J* = 7 Hz), 0.85 (d, 3 H, *J* = 7 Hz), 0.88 (t, 3 H, *J* = 7 Hz), 0.90 (d, 3 H, *J* = 7 Hz), 1.2–1.3 (m, 16 H), 2.1–2.2 (m, 6 H); mass spectrum, *m/e* 296 (4), 263 (6), 239 (12), 196 (16), 100 (100).

This experiment was repeated with compounds **5**, **9**, and **10** to obtain the same ketone **8** in 85–95% yield.

Treatment of Compound 4 with 4-Phenyl-1,2,4-triazoline-3,5-dione. A solution of ketone **4** (10 mg, 0.033 mmol) and 4-phenyl-1,2,4-triazoline-3,5-dione (6 mg, 0.034 mmol) in dichloromethane (10 mL) was stirred at room temperature for 30 min. The solvent was evaporated in vacuo to obtain an adduct that was purified by preparative TLC on silica gel: yield 11 mg (70% theoretical); IR (CCl_4) 3470, 1770, 1710, 1690, 1610 cm^{-1}; UV (hexane) 234 nm (ε 15 400); ^1H NMR ($CDCl_3$) δ 1.29 (s, 3 H), 1.59 (s, 3 H), 1.64 (t, 2 H, *J* = 7 Hz), 1.82 (s, 3 H), 1.85 (s, 3 H), 2.11 (m, 2 H), 2.13 (s, 3 H), 3.02 (s, 2 H), 4.01 (m, 1 H, *J* = 16, 3, 3 Hz), 4.34 (dd, 1 H, *J* = 16, 4 Hz), 4.73 (bd, 1 H, *J* = 8 Hz), 5.22 (t, 1 H, *J* = 7 Hz), 5.61 (dd, 1 H, *J* = 15, 8 Hz), 5.64 (M, 1 H), 5.98 (d, 1 H, *J* = 15 Hz), 6.09 (bs, 1 H), 7.45 (m, 5 H); mass spectrum, *m/e* 477 (2), 459 (7), 242 (12), 119 (47), 83 (100). The same adduct was obtained from compound **5**.

Acknowledgments. We thank Dr. Klaus Ruetzler for the identification of sponge samples, which were collected during a research cruise on R/V Alpha Helix funded by the National Science Foundation (OCE 76-80874). This research was supported by grants from the National Science Foundation (PCM 77-14946) and the Sea Grant Program, Department of Commerce (04-6-158-44110). The NMR Facility at UCSD is supported by a grant from the National Institutes of Health (RR-00708).

Registry No.—**4**, 68582-63-8; **5**, 68602-58-4; **7**, 68582-67-2; **8**, 68582-68-3; **9**, 68582-64-9; **10**, 68629-49-2; **11**, 68582-65-0; **12**, 68582-66-1; 4-phenyl-1,2,4-triazoline-3,5-dione, 4233-33-4.

References and Notes

(1) For recent reviews, see D. J. Faulkner, *Tetrahedron*, **33**, 1421 (1977); and W. H. Fenical in "Marine Natural Products: Chemical and Biological Perspectives", Vol. II, P. J. Scheuer, Ed., Academic Press, New York, 1979.
(2) B. J. Burreson, C. Christopherson, and P. J. Scheuer, *Tetrahedron*, **31**, 2015 (1975).
(3) J. J. Sims and J. A. Pettus, Jr., *Phytochemistry*, **15**, 1076 (1976).
(4) E. Fattorusso, S. Magno, L. Mayol, C. Santacroce, D. Sica, V. Amico, G. Oriente, M. Piattelli, and C. Tringali, *Tetrahedron Lett.*, 937 (1976).
(5) C. Francisco, G. Combaut, J. Teste, and M. Prost, *Phytochemistry*, **17**, 1003 (1978).
(6) Cf. Mesityl oxide, "Aldrich Library of NMR Spectra", Vol. 2, C. J. Pouchert and J. R. Campbell, Eds., Aldrich Chemical Co., Milwaukee, p 113B.

Pyrimidine Derivatives and Related Compounds. 32.[1] Acid-Catalyzed Hydrolysis of 1,3-Disubstituted 6-Carbamoyl(or Cyano)uracils. N(1)- and N(3)-Dealkylation of Uracils[2]

Shigeo Senda,* Kosaku Hirota, and Tetsuji Asao

Gifu College of Pharmacy, Mitahora-Higashi, Gifu 502, Japan

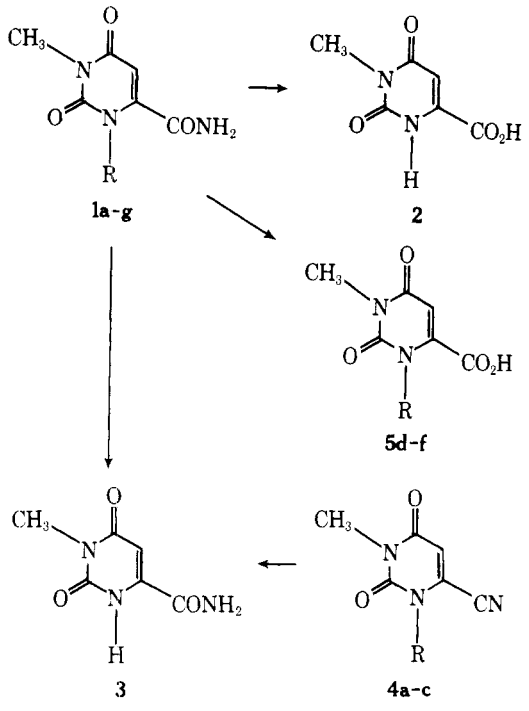
Received September 5, 1978

Acid-catalyzed hydrolysis of 1-*sec*-alkyl-6-carbamoyl-3-methyluracil in refluxing 48% hydrobromic acid causes dealkylation at the 1 position to afford 3-methylorotic acid. 1-*sec*-Alkyl-6-carbamoyl(or cyano)-3-methyluracils undergo a similar N(1)-dealkylation when treated in 98% sulfuric acid, yielding 6-carbamoyl-3-methyluracil. In the case of 3-cyclohexyl-6-carboxyl(or carbamoyl)uracils, the N(3)-dealkylation is observed. It is clarified that the N(1)-dealkylation takes place, in general, more readily than the N(3)-dealkylation does.

We previously reported the synthesis of 6-cyano- and 6-carbamoyluracils by the reaction of 5-bromouracils with sodium cyanide.[3] Prior to that, in our laboratory[4] it was demonstrated that 5-cyanouracils undergo acid-catalyzed hydrolysis and decarboxylation, yielding 5-carbamoyluracils, 5-carboxyuracils, or uracils, depending upon the acidic conditions employed. In this connection we investigated the acid-catalyzed hydroysis of 6-cyano- and 6-carbamoyluracils. This paper describes that N-dealkylation of *N-sec*-alkyl-6-cyano(or carbamoyl)uracils readily proceeds together with

0022-3263/79/1944-0970$01.00/0

Scheme I



a, R = c-C_6H_{11}; b, R = *i*-C_3H_7; c, R = *sec*-C_4H_9; d, R = CH_3; e, R = C_3H_7; f, R = C_4H_9; g, R = $C_6H_5CH_2$

hydrolysis of the cyano or carbamoyl group.

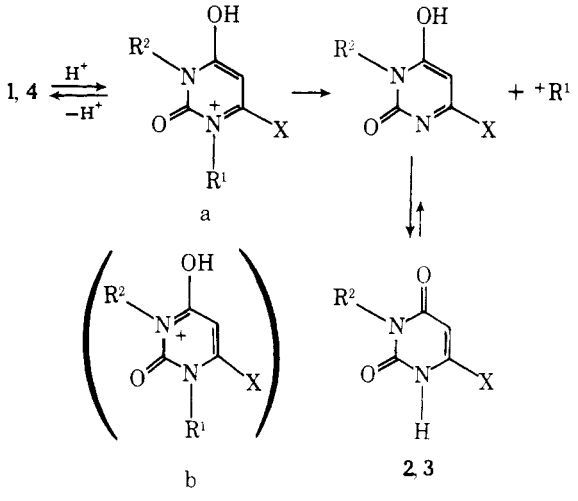
Results and Discussion

N(1)-Dealkylation of Uracils. When 6-carbamoyl-1-cyclohexyl-3-methyluracil (**1a**) was refluxed in 48% hydrobromic acid for 1 h, 3-methylorotic acid (**2**) was obtained in quantitative yield (Scheme I). Compound **2** was identical with an authentic sample[5] prepared by the methylation of orotic acid. Similary, 1-isopropyl- (**1b**) and 1-*sec*-butyl-6-carbamoyl-3-methyluracil (**1c**), having a secondary alkyl group at the 1 position, underwent dealkylation of the *N*(1)-alkyl group and hydrolysis of the carbamoyl group to give the same product (**2**) quantitatively. However, N(1) normal alkyl derivatives (**1d–f**) were not dealkylated under such conditions, but gave 1,3-disubstituted orotic acids (**5d–f**) in good yields.

An attempt was made to determine the effect of acid on such a dealkylation. Thus, heating of **1a–c** in 98% sulfuric acid at 80–90 °C caused the N(1)-dealkylation without hydrolysis of the carbamoyl group to afford 6-carbamoyl-3-methyluracil (**3**), which was also obtained from 1-*sec*-alkyl-6-cyano-3-methyluracils (**4a–c**) by the same treatment. Compound **1a** was also dealkylated by heating in 70% perchloric acid to yield **3**. However, refluxing of **1a** in 35% hydrochloric acid, acetic acid, or trifluoroacetic acid caused neither dealkylation nor hydrolysis, and only the starting material was recovered. No dealkylation occurred, too, when **1a** was allowed to stand at room temperature in 98% sulfuric acid for several days or heated in sulfuric acid diluted with equivolume water or acetic acid.

1-Cyclohexyl-3-methyluracil or 1-cyclohexyl-3,6-dimethyluracil underwent no dealkylation under acidic conditions. 5-Bromo-1-cyclohexyl-3-methyluracil (**6**) and 1-cyclohexyl-5,6-dihydrouracil (**7**) also remained unchanged. Incidentally, it was already known[4] that the 5-substituted 1-cyclohexyl-3-methyluracils, in which an electron-withdrawing group such as CN, $CONH_2$, or CO_2H is present at the 5 position, undergo acid-catalyzed hydrolysis and/or decarboxylation of the 5 substituent to give the corresponding uracils without the N(1)-dealkylation. These results imply that C-6 electron-withdrawing groups such as CN, $CONH_2$, and CO_2H are necessary for the N(1)-dealkylation.

Scheme II



The N(1)-dealkylation would involve a carbocation process because the reaction was observed in the N(1) secondary alkyluracils but not in the normal alkyluracils. Therefore, we examined the hydrolysis of 1-benzyl-6-carbamoyl-3-methyluracil (**1g**), which can produce a stable benzyl cation by the fission of the N–C bond. Thus, refluxing of **1g** in 48% hydrobromic acid readily caused the expected debenzylation to yield **2** and benzyl bromide. A mechanism for the N(1)-dealkylation is shown in Scheme II.

In a strong acid, initial protonation occurs upon the C-4 carbonyl group, leading to the formation of a.[6] Subsequently, fission of the N–C bond at the 1 position of a affords the product **2** or **3**. The secondary alkyl residue dissociated thereby forms a carbonium ion which is more stable than that of the normal alkyl residue. The electron-withdrawing groups at the 6 position should play a significant role in accelerating the fission of the N–C bond.

It is well known[7] that pyrimidine nucleosides are hydrolyzed at the *N*(1)-glycosyl bond in acid to yield the corresponding pyrimidines and degraded sugar. The mechanisms of these processes have been established to involve an A-1 or A-2 path.[8] We found that *sec*-alkyl groups can also be cleaved from the 1 position of uracils by a A-1 or A-2 mechanism. This would offer further corroborating evidence for the hydrolysis mechanism of nucleosides.

N(3)-Dealkylation of Uracils. As compared with the N(1)-dealkylation, a few examples of the N(3)-dealkylation of uracils have appeared in the literature. Shetler et al.[9] reported the photo-N(3)-dealkylation of 1,3-diethyluracil, yielding 1-ethyluracil. This dealkylation selectively occurred at the N-3 position via the Norrish type II reaction caused by the photoexcited C-4 carbonyl group. Ries et al.[10] studied the pyrolysis and acid-catalyzed hydrolysis of 3-alkyl-5-halo-6-methyluracils. They took *N*(3)-alkyl derivatives which remained unoccupied at the 1 position and observed that only 3-*tert*-butyl-5-halo-6-methyluracils underwent the acid-catalyzed N(3)-dealkylation.

Now, we have investigated the hydrolysis, in strong acid, of *N*(3)-*sec*-alkyluracils having an electron-withdrawing group such as CO_2H and $CONH_2$ at the 6 position. Heating of 3-cyclohexylorotic acid (**8**) in 98% sulfuric acid at 90 °C led to N(3)-dealkylation to afford orotic acid (**9**) (Scheme III). Similar treatment of 6-carbamoyl-3-cyclohexyl-1-methyluracil (**10**) gave 6-carbamoyl-1-methyluracil (**11**). Compound **10**, however, was not dealkylated on refluxing in 48% hydrobromic acid, but gave 3-cyclohexyl-1-methylorotic acid (**12**).

Table I. Acid-Catalyzed Hydrolysis of 6-Substituted 1,3-Dialkyluracils

starting material	acid	temp, °C	time	product	yield, %
1a	48% HBr	reflux	1 h	**2**	98
	98% HBr	90	30 min	**3**	89
	70% $HClO_4$	90	1 h	**3**	30
1b	48% HBr	reflux	2 h	**2**	96
	98% H_2SO_4	90	1 h	**3**	49
1c	48% HBr	reflux	2 h	**2**	80
	98% H_2SO_4	90	1 h	**3**	62
1d	48% HBr	reflux	1 h	**5d**[a]	75
1e	48% HBr	reflux	2 h	**5e**	98
1f	48% HBr	reflux	2 h	**5f**	93
1g	48% HBr	reflux	1 h	**2**	95
4a	98% H_2SO_4	90	30 min	**3**	65
4b	98% H_2SO_4	90	1 h	**3**	49
4c	98% H_2SO_4	90	1 h	**3**	49
4d	98% H_2SO_4	45–50	3 h	**1d**	68
8	98% H_2SO_4	90	30 min	**9**[b]	82
10	98% H_2SO_4	90	30 min	**11**	56
	48% HBr	reflux	2 h	**12**	56
13	48% HBr	reflux	4 h	**14**[c]	86

[a] Identified by comparison with an authentic sample prepared from orotic acid by dimethylation: K. A. Chkhikvadze, N. E. Britikova, and O.Yu. Magidson, *Biol. Akt. Soedin., Akad. Nauk SSSR*, **22** (1965); *Chem. Abstr.*, **63**, 18080f (1965). [b] Identified by comparison with a commercial orotic acid, manufactured by Wako Pure Chemical Industries, Ltd. [c] Identified by comparison with an authentic sample: W. V. Gurran and R. B. Angier, *J. Org. Chem.*, **31**, 201 (1966).

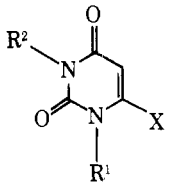
Table II. Some Physical Properties of Orotic Acid Derivatives

compd	mp, °C (solvent of recrystn)	NMR (Me_2SO-d_6), δ (C5-H)	UV, λ_{max} ($\epsilon \times 10^{-3}$) 0.1 N HCl	UV, λ_{max} ($\epsilon \times 10^{-3}$) 0.1 N NaOH	formula	analyses[a]
2	>300 (H_2O)[b]	6.17	283 (6.83)	298 (6.97)	$C_6H_6O_4N_2$	C, H, N
3	>300 (H_2O)	6.37	280 (5.97)	313 (6.63)	$C_6H_7O_3N_3$	C, H, N
5d	146–148 (benzene)[c]	6.02	272 (8.00)	271 (8.73)	$C_7H_8O_4N_2$	C, H, N
5e	165–167 (benzene)	6.05	273 (8.32)	272 (8.79)	$C_9H_{12}O_4N_2$	C, H, N
5f	172–174 (H_2O)	6.01	274 (9.02)	270 (9.39)	$C_{10}H_{14}O_4N_2$	C, H, N
11	>300 (H_2O)	6.23	273 (8.51)	271 (6.38)	$C_6H_7O_3N_3$	C, H, N
12	195–197 (H_2O)	5.95	275 (8.52)	274 (8.90)	$C_{12}H_{16}O_4N_2 \cdot H_2O$	C, H, N
14	230–231 (MeOH)[d]	6.17	284 (6.26)	300 (6.90)	$C_{12}H_8O_3N_2 \cdot H_2O$	C, H, N

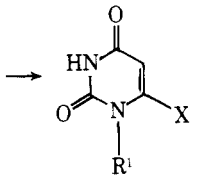
[a] Analyses were within 0.3% of theoretical values. [b] Lit.[5] mp 316–323 °C (EtOH). [c] Lit. mp 150–151 °C; footnote *a* in Table I. [d] Lit.[5] mp 226–227.5 °C (EtOH).

In order to make sure of the difference of facility of the dealkylation between the 1 and 3 positions, we examined the hydrolysis of 6-carbamoyl-1,3-dibenzyluracil (**13**). Thus, when **13** was refluxed in 48% hydrobormic acid for 1 h, only the N(1)-dealkylation proceeded to afford 3-benzylorotic acid (**14**), so it is apparent that the N(1)-dealkylation takes place more readily than the N(3)-dealkylation. This difference would be due to stability of the protonated uracil a and b, in which an intermediate a is more stable than b[11] (Scheme II).

Scheme III



8, R^1 = H; R^2 = c-C_6H_{11}; X = CO_2H
10, R^1 = CH_3; R^2 = c-C_6H_{11}; X = $CONH_2$
12, R^1 = CH_3; R^2 = c-C_6H_{11}; X = CO_2H
13, R^1 = R^2 = $C_6H_5CH_2$; X = $CONH_2$
14, R^1 = H; R^2 = $C_6H_5CH_2$; X = CO_2H



9, R^1 = H; X = CO_2H
11, R^1 = CH_3; X = $CONH_2$

Experimental Section

Melting points were determined on a Yanagimoto hot-stage apparatus and are uncorrected. ^1H NMR spectra were recorded on a Hitachi Perkin-Elmer R-20B 60-MHz spectrometer; chemical shifts were reported in ppm downfield from a tetramethylsilane internal standard (δ scale). Infrared spectra were recorded on a Hitachi Model 215 spectrometer as KBr pellets. Ultraviolet spectra were obtained on a Hitachi 323 spectrophotometer.

Acid-Catalyzed Hydrolysis of 6-Substituted 1,3-Dialkyluracils. General Procedure. Hydrolysis in 48% Hydrobromic Acid. A suspension of 6-substituted 1,3-dialkyluracil (1 mmol) in 20 mL of hydrobromic acid was refluxed as specified in Table I. Depending on the solubility of the product in the solvent, the orotic acid derivative was either isolated by filtration or by evaporation followed by recrystallization (see Tables I and II).

Hydrolysis in 98% Sulfuric Acid. A suspension of 6-substituted 1,3-dialkyluracil (1 mmol) in 1 mL of 98% sulfuric acid was heated at 85–90 °C as specified in Table I. After cooling, the mixture was poured into 5 mL of water and the resulting precipitate was collected by filtration and recrystallized (see Tables I and II).

Hydrolysis in 70% Perchloric Acid. A suspension of 100 mg (0.4

mmol) of 6-carbamoyl-1-cyclohexyl-3-methyluracil (**1a**) in 1 mL of 70% perchloric acid was heated at 85–90 °C as specified in Table I. After cooling, the precipitate was collected by filtration, washed with water, and recrystallized from water to give **3** (see Tables I and II).

Hydrolysis of 1-Benzyl-6-carbamoyl-3-methyluracil (1g) in Hydrobromic Acid. A suspension of 520 mg (2 mmol) of **1g** in 10 mL of hydrobromic acid was refluxed as specified in Table I. After cooling, the separated irritating oil was extracted with ether and the extract was washed with aqueous sodium bicarbonate and water, dried (Na_2SO_4), and evaporated under reduced pressure to give 300 mg (88%) of benzyl bromide, which was identified by comparison of its IR spectrum with that of a commercial product. The aqueous layer was evaporated under reduced pressure, and the residue was triturated with water. The insoluble solid was collected by filtration and recrystallized (see Tables I and II).

Registry No.—**1a,** 53293-13-3; **1b,** 55643-12-4; **1c,** 55643-13-5; **1d,** 2019-20-7; **1e,** 55643-15-7; **1f,** 55643-16-8; **1g,** 55643-14-6; **2,** 705-36-2; **3,** 55643-21-5; **4a,** 53293-09-7; **4b,** 55643-19-1; **4c,** 55643-20-4; **4d,** 49846-86-8; **5d,** 4116-38-5; **5e,** 55643-17-9; **5f,** 55643-18-0; **8,** 68843-56-1; **9,** 65-86-1; **10,** 68843-57-2; **11,** 68843-59-4; **12,** 68843-60-7; **13,** 68843-58-3.

References and Notes

(1) For Part 31, see S. Senda, K. Hirota, T. Asao, and K. Maruhashi, *J. Am. Chem. Soc.*, **100,** 7661 (1978).
(2) A part of this work was presented as a communication: S. Senda, K. Hirota, and T. Asao, *Heterocycles*, **3,** 213 (1975).
(3) (a) S. Senda, K. Hirota, and T. Asao, *J. Org. Chem.*, **40,** 353 (1975); (b) *Yakugaku Zasshi*, **95,** 1250 (1975).
(4) S. Senda, K. Hirota, and J. Notani, *Chem. Pharm. Bull.*, **20,** 1389 (1972).
(5) W. V. Curren and R. B. Angier, *J. Org. Chem.*, **31,** 201 (1966).
(6) It is known that uracil derivatives accept a proton on the 4-carbonyl group in strong acidic media: C. D. Poulter and R. B. Anderson, *Tetrahedron Lett.*, 3823 (1972), and references therein.
(7) (a) A. M. Michelson, "The Chemistry of Nucleosides and Nucleotides", Academic Press, New York, N.Y., 1963, p 26; (b) N. K. Kochetkov and E. I. Budowsky, "Organic Chemistry of Nucleic Acids", Plenum Press, New York, N.Y., 1972, Chapter 8.
(8) (a) R. Shapiro and S. Kang, *Biochemistry*, **8,** 2219 (1969); (b) E. R. Garrett, J. K. Seydel, and A. J. Sharpen, *J. Org. Chem.*, **31,** 2219 (1966).
(9) M. D. Shetler and P. J. S. Koo, *Tetrahedron Lett.*, 2015 (1975).
(10) Z. D. Tadic, M. B. Pesic, and S. K. Ries, *J. Agric. Food Chem.*, **21,** 108 (1973).
(11) J. Elguero, C. Marzin, A. R. Katitzky, and P. Linda, "The Tautomerism of Heterocycles", Supplement I in the series "Advances in Heterocyclic Chemistry", A. R. Katritzky and A. J. Boulton, Ed., Academic Press, New York, N.Y., 1976, p 131.

Preparation of Intermediates for Coproporphyrin Synthesis

Luis Diaz, Graciela Buldain, and Benjamin Frydman*

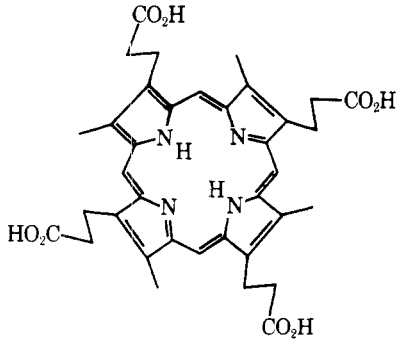
Facultad de Farmacia y Bioquímica, Universidad de Buenos Aires, Junin 956, Buenos Aires, Argentina

Received September 11, 1978

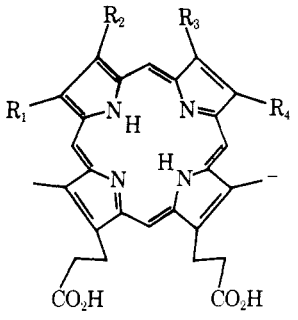
The synthesis of dipyrrylmethanes necessary for the obtention of coproporphyrins I–IV (**1–4**) is described. The synthesis of the former was designed so as to avoid isomeric mixtures in order to obtain pure samples of the latter. The asymmetric dibenzyl-3,4′-bis(β-ethoxycarbonylethyl)-4,3′-dimethyl-5,5′-dipyrrylmethane as well as the symmetric dibenzyl 3,3′-dimethyl-4,4′-bis(β-ethoxycarbonylethyl)-5,5′-dipyrrylmethanedicarboxylate were obtained. Hydrogenolysis of the dibenzyloxycarbonyl groups and condensation of the 5,5′-dicarboxydipyrrylmethanes with a 5,5′-diformyldipyrrylmethane gave **3** and **4**. Conversion of *tert*-butyl 3,4′-dimethyl-4,3′-bis(β-ethoxycarbonylethyl)-5′-(benzyloxycarbonyl)-5-dipyrrylmethanecarboxylate into a (*tert*-butyloxycarbonyl)-5′-formyldipyrrylmethane was followed by treatment of the latter with hydrogen bromide. By a self-condensation of the resulting product, **1** was obtained in good yield.

Coproporphyrins are important natural products since several of their reduced derivatives (coproporphyrinogens) are metabolic intermediates in protoporphyrin biosynthesis. The four coproporphyrin isomers I–IV, structures **1–4**, respectively, have been prepared by synthesis using different methods. All four coproporphyrin isomers were originally prepared by Fischer and co-workers following his method of fusion of dipyrrylmethenes.[1] They were also prepared by thermal decarboxylation of the corresponding uroporphyrins,[1] and **2** was prepared by condensation of a 5,5′-dipyrrylmethanedicarboxylic acid with formic acid.[1] Fischer's method was again used by Morsingh and MacDonald[2] to prepare **3** and **4**. The latter were also prepared by Kenner and co-workers[3] using the α-oxobilane route to porphyrins. They again described the synthesis of **1** following Fischer's method of fusion in succinic acid of a dipyrrylmethene which was in turn obtained by the self-condensation of a pyrrole acid.[3] We found that the simplest approach to obtain the four coproporphyrin isomers in a pure form is to use MacDonald's original approach[4] in its simplified form,[5] which consists in the condensation of a diformyldipyrrylmethane with a dicarboxydipyrrylmethane.

The synthesis of **1** was achieved by the self-condensation



1



2, $R_1 = R_4 = CH_3$; $R_2 = R_3 = CH_2CH_2CO_2H$
3, $R_1 = R_3 = CH_3$; $R_2 = R_4 = CH_2CH_2CO_2H$
4, $R_1 = R_4 = CH_2CH_2CO_2H$; $R_2 = R_3 = CH_3$

0022-3263/79/1944-0973$01.00/0