generality of the reaction failed; a number of other mercaptans were tried without success. The structural requirements for the chlorinolytic cleavage without accompanying substitution or oxidation are readily perceived, but the role of the quaternized amino group as a necessary component of the reaction mechanism is not immediately obvious.

The reported reaction provides a straightforward and high-yield synthesis of certain chlorinated amino acid derivatives commonly needed as starting materials for various biologically related compounds containing sulfur or selenium.

Experimental Section[9]

Ethyl 2-Amino-3-Chloropropionate Hydrochloride (4b).—A slurry of cysteine ethyl ester hydrochloride (2)[10] (50.0 g, 0.27 mol) in 300 ml of dry methylene chloride was stirred at −78° for 1 hr while a vigorous stream of chlorine was bubbled through the reaction mixture. The slurry became homogeneous and yellow within 10 min. The solution was held at −20° for 2 days, and then warmed to room temperature. Excess chlorine and approximately one-half of the solvent were removed at room temperature by water aspirator vacuum, and an equal volume of diethyl ether was added. Fine crystals of **4b** formed immediately After being chilled to 0°, the mixture was filtered. The white crystals were washed with ether and air dried: yield 28.9 g (71%); mp 143° dec (sealed evacuated capillary) (lit.[2] mp 141°).

2-Chloroethylamine Hydrochloride.—Cysteamine[10] (2-aminoethanethiol) hydrochloride (10.0 g, 0.088 mol) was stirred in 100 ml of dry methylene chloride for 2 hr at −78° while subjected to a vigorous stream of chlorine gas. After standing for 5 days at −10°, the red-orange heterogeneous reaction mixture was filtered to remove 2.6 g of unreacted cysteamine hydrochloride.

The filtrate was warmed to reflux for 15 min. A white precipitate immediately appeared. An equal volume of diethyl ether was added, and the mixture was cooled to 0°. Filtration of the white crystalline solid followed by ether washing and air drying produced 6.2 g (61% yield, 81% conversion) of 2-chloroethylamine hydrochloride, mp 117–121° (lit.[11] mp 119–123°), confirmed by comparison of the infrared spectrum of this compound with that of an authentic sample.[12]

Registry No.—2b, 868-59-7; 4b, 21615-66-7.

Acknowledgment.—We are grateful to the Joint Awards Council of the Research Foundation of the State University of New York for generous support of this work by Research Grant JA-67-40-006.

(9) All temperature readings were uncorrected. Ir spectra were determined on a Perkin-Elmer Infracord spectrophotometer. Vpc analyses were performed on a Hewlett-Packard chromatograph, Model 5750. Methylene chloride was dried over sodium sulfate.

(10) Aldrich Chemical Co., Inc.

(11) S. Gabriel, *Ber.*, **21**, 573 (1888).

(12) Sadtler Standard Spectrum No. 24369, Sadtler Research Laboratories, Inc., Philadelphia, Pa., 1964.

Synthetic Intermediates Potentially Useful for the Synthesis of Tetrodotoxin and Derivatives

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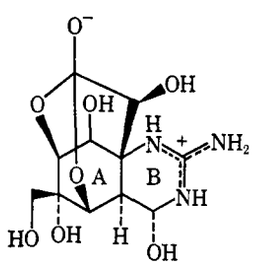
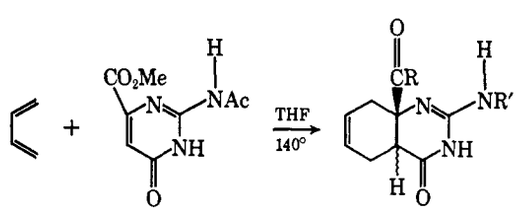
For some time we have been engaged in studies directed toward the total synthesis of the California newt (Taricha Torosa)[1] and Japanese Fugu (puffer fish)[2] poison tetrodotoxin **1** and closely related structural modifications. In the course of this work, we have developed a simple three-step synthetic sequence which permits construction of an intermediate possessing many features of the tetrodotoxin skeleton together with functional groups which ought to be readily alterable to produce ultimately a tetrodotoxin derivative. This paper describes the synthesis of the key intermediate **3**, thereby establishing a new synthetic route to 9-substituted hydroquinazolines.

We envisaged construction of the tetrodotoxin skeleton by means of a Diels–Alder reaction between a diene component which would become the carboxylic ring A and a heterocyclic dienophile containing a preformed guanidine ring system which would become ring B of tetrodotoxin (**1**). Heterocycle **2**[3] was readily prepared



1

by condensation of guanidine with dimethyl acetylenedicarboxylate followed by acetylation[4] or, better, by condensation of acetylguanidine with dimethyl acetylenedicarboxylate. When allowed to react with butadiene in tetrahydrofuran solvent at 140° for 2 days, dienophile **2** afforded crystalline adduct **3** in 72% yield. Nmr, ir, mass spectral, and elemental analysis data are all in accord with expression **3** (see Experimental Section for spectral data on all pertinent compounds). Hydrolysis of adduct **3** with aqueous potassium hydroxide in methanol afforded acid amine **4** in high yield, which could be reconverted into starting adduct **3** by esterification with methanolic hydrogen chloride to produce amino ester **5** followed by acetylation with acetic anhydride. Amino ester **5** could also be pre-



2

3, R = OMe, R′ = Ac
4, R = OH, R′ = H
5, R = OMe, R′ = H
6, R = OH, R′ = Ac

(1) H. S. Mosher, F. A. Fuhrman, H. D. Buchwald, and H. G. Fischer, *Science*, **144**, 1100 (1964).

(2) K. Tsuda, *Naturwissenschaften*, **53**, 171 (1966); C. Y. Kao, *Pharmacol. Rev.*, **18**, 997 (1966); R. B. Woodward and J. Z. Gougoutas, *J. Amer. Chem. Soc.*, **86**, 5030 (1964); K. Tsuda, S. Ikuma, M. Kawamura, R. Tachikawa, K. Sakai, C. Tamaura, and O. Amakasu, *Chem. Pharm. Bull* (Tokyo), **12**, 1357 (1964); T. Goto, Y. Kishi, S. Takahashi, and Y. Hirata, *Tetrahedron*, **21**, 2059 (1965); C. Tamura, O. Amakasu, Y. Sasada, and K. Tsuda, *Acta Crystallogr.*, **21**, 219, 226 (1966).

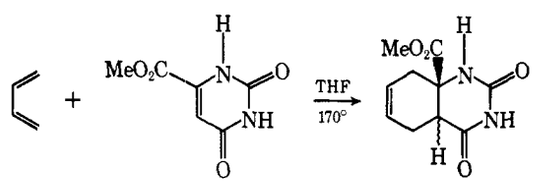
(3) It has not been established which double bond tautomer involving the nitrogen atoms in the heterocyclic rings of **2**, **3**, **4**, **5**, and **6** is the preferred one.

(4) S. Ruhemann and H. Stapleton, *J. Chem. Soc.*, **77**, 804 (1900).

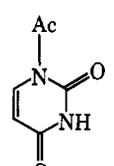
pared by hydrolysis of adduct **3** with hydrochloric acid in methanol. Acetylation of amino acid **4** with acetic anhydride afforded acid **6**.

The rings are probably *cis* fused in adduct **3** in analogy with other Diels–Alder reactions, although definitive proof is lacking. Since in tetrodotoxin the corresponding rings are *trans* fused, an epimerization at the ring juncture of adduct **3** at some point during further elaboration will be necessary. The adjacent carbonyl group should facilitate this step. Further elaboration of adduct **3** is in progress.

To our knowledge, this is the first time heterocycles such as ester **2** have been observed to undergo the Diels–Alder reaction. To test the generality of this new Diels–Alder reaction, we allowed methyl orotate **7** to react with butadiene in tetrahydrofuran at 170° for 2 days.[5] Adduct **8** was obtained in 78% yield, adjusted for recovered starting material. Acetyluracil (**9**), however, failed to react with butadiene under conditions which afforded adduct **8**. Uracil was isolated essentially quantitatively, apparently resulting from hydrolysis of **9** by the inadvertent presence of water.



7 **8**



9

Experimental Section

Infrared spectra were recorded with a Beckman IR-5 spectrophotometer. The small letters in parentheses found after infrared maxima refer to the relative intensities of the peaks. Weak, moderate, and strong are referred to as w, m, and s, respectively. Nmr spectra were determined on a Varian Associates Model A-60 high-resolution spectrometer. Chemical shifts are recorded in parts per million downfield from internal TMS. Elemental analyses were performed by either Micro-Tech Laboratories, Skokie, Ill., Alfred Bernhard Laboratories, Mülheim, Germany, or Chemalytics, Inc., Tempe, Ariz. Mass spectra were determined either by Morgan Schaeffer Co., Quebec, Canada, or on a CEC-110 spectrometer at the University of Oregon. Melting points are uncorrected.

2-Amino-6-carbomethoxy-4(3H)-pyrimidone.—A modification of Ruhemann's procedure[4] was followed. To a suspension of 8.9 g (0.050 mol) of guanidine carbonate in 175 ml of absolute methanol under nitrogen was added dropwise with stirring a solution of 5.4 g (0.10 mol) of sodium methoxide in 50 ml of absolute methanol. As the guanidine carbonate reacted, it was replaced by a precipitate of sodium carbonate which was not removed. When addition was complete, a second solution consisting of 14.2 g (0.100 mol) of dimethyl acetylenedicarboxylate (distilled) and 50 ml of absolute methanol was added dropwise with stirring with concurrent yellow-orange coloration of the mixture. The reaction mixture was stirred overnight, and then 200 ml of water was added followed by excess acetic acid. The resulting precipitate was collected and dried, affording 4.5 g (27% yield) of a tan solid, mp 345° dec (preheated block). Two recrystallizations from methanol afforded the analytical specimen as a white microcrystalline powder: mp >345° dec; λ_{max}^{KBr} 2.99 (s), 3.16 (m), 3.33 (m), 5.83 (s), 5.97 (s), 6.19 (m), 6.86 (s), 7.83 (s), 8.21 (s), 8.89 (s), and 9.64 μ (s); λ_{max}^{EtOH} 270 (ϵ 1.7 × 10^4) and 316 mμ (ϵ 9.2 × 10^3).

Anal. Calcd for $C_6H_7N_3O_3$: C, 42.61; H, 4.17; N, 24.84. Found: C, 42.8; H, 4.3; N, 24.7.

2-Acetamido-6-carbomethoxy-4(3H)-pyrimidone (2). A.—A suspension of 1.00 g (5.92 mmol) of unpurified amine obtained in the previous experiment and 10 ml of acetic anhydride under nitrogen was placed in an oil bath at 130°. The mixture remained heterogeneous, and after 40 min the mixture was allowed to cool to 25° and filtered, and the solid was washed with carbon tetrachloride and dried to yield 1.1 g (88% yield, 24% over-all, based on dimethyl acetylenedicarboxylate) of a tan solid, mp *ca.* 280° (preheated block). Three recrystallizations from ethyl acetate afforded the analytical specimen as white needles: mp 278° dec; λ_{max}^{KBr} 2.96 (m), 3.46 (m), 3.79 (m), 5.76 (s), 5.90 (s), 6.25 (s), 6.60 (s), 6.97 (m), 8.19 (s), and 9.06 μ (m); λ_{max}^{EtOH} 273 (ϵ 1.4 × 10^4) and 322 mμ (ϵ 1.2 × 10^4). The nmr spectrum (DMSO-d_6) showed a singlet (3 H) at δ 2.21 (acetate protons), a broad singlet (1 H) at 3.1–3.7 (NH), a singlet (3 H) at 3.75 (methyl ester protons), and a singlet (1 H) at 5.84 (vinyl proton).

Anal. Calcd for $C_8H_9N_3O_4$: C, 45.50; H, 4.30; N, 19.90. Found: C, 45.3; H, 4.3; N, 19.7.

B.—To a solution of 2.0 g (0.02 mol) of acetylguanidine,[6] mp 177–180°, and 175 ml of *dry* methanol was added dropwise with stirring at 0° over 3 hr a solution of 2.8 g (0.02 mmol) of dimethyl acetylenedicarboxylate (freshly distilled) in 25 ml of dry methanol. After addition was complete, the mixture was allowed to warm to 25° and then stand overnight. The precipitate was filtered, affording 2.6 g of yellowish ester **2**, mp 275–277° (preheated bath). Concentration of the mother liquor afforded an additional 0.58 g, mp 250–260°, of material (69% combined yield) suitable for the next reaction.

3,4,5,8,9,10-Hexahydro-2-acetamido-9-carbomethoxyquinazolen-4-one (3).—A 50-ml glass liner was placed into a 127-ml stainless steel pressure reactor and charged with 2.00 g (9.44 mmol) of ester **2**, mp 263–265°, 20 ml of tetrahydrofuran (freshly distilled from lithium aluminum hydride), 10 ml (55 mmol) of 1,3-butadiene, and *ca.* 10 mg of hydroquinone. The system was flushed with nitrogen and then sealed and heated at 140 ± 2° for 48 hr (optimum conditions). The reaction vessel was allowed to cool to 25° and then opened to reveal a light yellow solution above a small quantity of yellow solid. The solid was removed by centrifugation, washed with fresh tetrahydrofuran, and dried, affording 340 mg (17% yield), mp *ca.* 260° dec, of starting dienophile suitable for reuse. The mother liquor and washes were combined and the solvent was removed under vacuum, affording 2.38 g of a solid. Trituration with 30 ml of hexane yielded 2.17 g of a light yellow solid which was dissolved in 75 ml of hot ethyl acetate, treated with Norit, and filtered. Concentration to 10 ml followed by a cooling period produced 1.17 g of a white solid, mp 200–202° (first crop), 150 mg, mp 199–202° (second crop), and 180 mg, mp 194–201° (third crop). The combined yield was thus 60%, or, based on starting material consumed, 72%. Two further recrystallizations from ethyl acetate–hexane afforded the analytical sample as white needles: mp 200–202°; λ_{max}^{KBr} 2.97 (m), 3.2–3.4 (br), 3.60 (m), 5.82 (s), 6.27 (s), 6.54 (s), and 7.00 μ (m). No maximum in the uv spectrum was observed. The nmr spectrum ($CDCl_3$) displayed a complex multiplet (6 H) at δ 1.8–4.0 (NH, allylic protons, and methine proton), a singlet (3 H) at 2.50 (acetate protons), a singlet (3 H) at 3.67 (methyl ester protons), a broadened singlet (2 H) at 5.82 (vinyl protons), and a broad singlet (1 H) at 10.5–11.5 (NH). The mass spectrum included, in addition to a prominent parent ion peak at *m/e* 265, the following prominent peaks: *m/e* 250 (M − 15, loss of CH_3), 206 (M − 59, loss of O_2CCH_3), 196 (M − 69, loss of CH_3 plus butadiene), 191 (M − 74, loss of CH_3 plus $NHCOCH_3$), 190 (M − 75, loss of CH_3 plus NH_2COCH_3), and 164 (M − 101, loss of CO_2CH_3 plus ketene).

Anal. Calcd for $C_{12}H_{15}N_3O_4$: C, 54.33; H, 5.70; N, 15.84. Found: C, 54.5; H, 5.86; N, 15.6.

3,4,5,8,9,10-Hexahydro-2-amino-9-carboxyquinazolin-4-one (4).—A solution of 223 mg (0.84 mmol) of adduct **3**, mp 196–201°, 10 ml of methanol, 326 mg (5.8 mmol) of potassium hydroxide, and 1 ml of water was gently refluxed under nitrogen for 24 hr. Then all solvent was evaporated under vacuum, 2 ml

(5) Initial experiments were performed by Mr. Joel Van Ornum of this laboratory.

(6) R. Greenhalgh and R. A. B. Bannard, *Can. J. Chem.*, **39**, 1017 (1961).

of water was added, and the evaporation was repeated, affording a clear yellow syrup. This was dissolved in 5 ml of water and centrifuged, and the clear supernatant liquid was treated with 348 mg (5.8 mmol) of glacial acetic acid and cooled to 5°. After 2 hr, the white crystals were collected, washed with water, and dried. Concentration of the mother liquor afforded a second crop which was combined with the first crop, affording 162 mg (92% yield) of white needles, mp 263–265°. Recrystallization from methanol–water produced the analytical specimen as white needles, mp 270–271° (gas evolution).

Anal. Calcd for $C_9H_{11}N_3O_3$: C, 51.67; H, 5.27; N, 20.09. Found: C, 51.5; H, 5.3; N, 20.1.

3,4,5,8,9,10-Hexahydro-2-amino-9-carbomethoxyquinazolin-4-one (5). A.—To a solution of 524 mg (1.98 mmol) of adduct **3**, mp 197–200°, in 30 ml of methanol was added 0.5 ml (6 mmol) of concentrated hydrochloric acid. The solution was refluxed for 11 hr, after which the solvent was evaporated at reduced pressure. The resulting cloudy syrup was taken up in 10 ml of water, filtered, and concentrated to 5 ml. Addition of 0.5 ml of concentrated ammonium hydroxide caused crystalline amino ester **5** to separate after a few minutes. There was isolated 345 mg (mp 245–255°) after combination of several crops. Two recrystallizations from water afforded the analytical specimen as white needles, mp 259–260° dec. The mass spectrum included, in addition to an intense parent ion peak at *m/e* 223, the following intense peaks: *m/e* 192 (M − 31, loss of OCH_3), 191 (M − 32, loss of $HOCH_3$), 169 (M − 54, loss of butadiene), and 164 (M − 59, loss of O_2CCH_3).

Anal. Calcd for $C_{10}H_{13}N_3O_3$: C, 53.81; H, 5.83. Found: C, 53.5; H, 5.84.

B.—To 5 ml of methanol saturated with hydrogen chloride was added 100 mg (0.480 mmol) of amino acid **4**, mp 269–272°, and the resulting mixture was refluxed for 6 hr. Evaporation of the solvent at reduced pressure afforded a foam which was dissolved in 2 ml of water, filtered, and concentrated to 1 ml. Addition of three drops of concentrated ammonium hydroxide caused the amino ester to crystallize upon cooling. There was isolated 100 mg (84%) of amino ester **5**, mp 240–255°. Recrystallization from water afforded a sample, mp 258–260°, admixture of which with authentic **5** showed no melting point depression.

A 42-mg sample of **5**, mp 254–255°, was heated at 100° in 0.2 ml of acetic anhydride until solution was effected. Excess solvent was then removed under vacuum and the crystalline residue was triturated with ether. Removal of the solvent afforded 44 mg (88%) of adduct **3**, mp 198–199°, admixture of which with authentic **3** showed no melting point depression.

3,4,5,8,9,10-Hexahydro-2-acetamido-9-carboxyquinazolin-4-one (6).—A mixture of 500 mg (2.39 mmol) of amino acid **4**, mp 267–270°, and 3 ml of acetic anhydride was heated with stirring under nitrogen until solution was effected (30 min). Removal of the solvent under reduced pressure produced a foam which was dissolved in 3 ml of chloroform and vigorously stirred for 6 hr in the presence of 3 ml of water. The resulting solid was isolated by centrifugation, washed with carbon tetrachloride, and dried, affording 482 mg (90%) of the title compound as a white powder, mp 159–163° dec. Two recrystallizations from ethyl acetate afforded the analytical specimen as a white microcrystalline powder, mp 171–173° (solvate containing 0.5 mol of acetic acid per mol of **6**). The mass spectrum included, in addition to an intense parent ion peak at *m/e* 251, the following prominent peaks: *m/e* 207 (M − 44, loss of HO_2C), 197 (M − 54, loss of butadiene), and 60 (acetic acid).

Anal. Calcd for $C_{11}H_{13}N_3O_4 \cdot {}^1/_2CH_3CO_2H$: C, 51.24; H, 5.38. Found: C, 51.2; H, 5.20.

1,2,3,4,5,8,9,10-Octahydro-9-carbomethoxyquinazolin-2,4-dione (8).—To 1.00 g (5.72 mmol) of methyl orotate (**7**),[7] mp 240–241°, in a 40-ml glass liner was added 30 ml of dry tetrahydrofuran, 10 mg of hydroquinone, and 10 ml of 1,3-butadiene. Care was taken to exclude water. The glass liner was then placed in a 127-ml stainless steel pressure reactor and heated at 165 ± 2° for 48 hr, after which time the resulting slightly yellow solution was evaporated to dryness and then treated with three 25-ml portions of boiling hexane, which removed butadiene-derived hydrocarbons. The resulting white gummy solid was boiled with 75 ml of chloroform for 30 min and filtered, affording 52 mg (5%) of starting methyl orotate, mp 235–238°. Concentration of the filtrate followed by cooling afforded 1.19 g of a white solid, two recrystallizations of which from ethyl acetate produced 1.02 g (78%) of adduct **8**: mp 201–203°; λ_{max}^{KBr} 2.9–3.6 (s), 5.7–6.2 (s), 6.64 (w), 6.98 (s), 7.65 (m), 8.37 (m), and 9.36 μ (m). The nmr spectrum ($CDCl_3$) displayed a complex multiplet (5 H) at δ 2.3–2.8 (allylic and methine protons), a singlet (3 H) at 3.70 (methyl ester protons), and a multiplet (2 H) at 5.6 (vinyl protons). The mass spectrum included, in addition to a prominent parent ion peak at *m/e* 224, prominent peaks at *m/e* 170 (M − 54, loss of butadiene) and 165 (M − 59, loss of O_2CCH_3).

Anal. Calcd for $C_{10}H_{12}N_2O_4$: C, 53.47; H, 5.36. Found: C, 53.3; H, 5.33.

Under the above reaction conditions, acetyluracil (**9**) afforded uracil in near-quantitative yield.

(7) J. J. Fox, N. Yung, and I. Wempen, *Biochim. Biophys. Acta*, **28**, 295 (1957).

Registry No.—**2**, 21615-58-7; **3**, 21615-59-8; **4**, 21615-60-1; **5**, 21615-61-2; **6**, 21615-62-3; **8**, 21615-63-4; 2-amino-6-carbomethoxy-4(3H)-pyrimidone, 21615-64-5.

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Alkylation by Alcohols in the Presence of Dicyclohexylcarbodiimide.[1] Alkylation of Thymine, Uracil, Thymidine, and Uridine by Alcohols

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In a previous publication[2] from this laboratory it was shown that methanol could be used to methylate thymidine. This reaction occurred in the presence of N,N′-dicyclohexylcarbodiimide (DCC); it resulted in the synthesis of 3-methylthymidine (2′-deoxy-3,5-dimethyluridine). We now wish to present evidence that alkylation of the N-3 position of thymidine and uridine, or of the N-1 and N-3 positions of thymine and uracil by a variety of alcohols in the presence of DCC can be considered to be a general reaction.

The synthesis of alkyl aryl ethers from alcohols and phenols in the presence of DCC was shown to occur by Vowinkel in 1962.[3] In 1965 Bach studied this reaction with the use of ^{18}O ethanol and was able to show that none of the ^{18}O was found associated with the alkyl aryl ether but rather that all the ^{18}O was found associated with the DCU formed as a by-product of the reaction.[4] Consequently, Bach suggested that the original attack on DCC is by the ethanol. The resultant

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(2) R. T. Markiw and E. S. Canellakis, *Tetrahhdron Lett.*, 657 (1968).

(3) E. Vowinkel, *Chem. Ber.*, **95**, 2997 (1962).

(4) F. L. Bach, *J. Org. Chem.*, **30**, 1300 (1965).