Synthesis of 2-Amino-L-histidine and 2-Aminohistamine

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While aryldiazonium coupling to *N*-benzoylhistidine esters leads almost entirely to 2,4-bisarylazo derivatives, coupling in the *N*-acetyl series leads predominantly to the 2-arylazo derivative. Similarly, *N*-acetylhistamine couples predominantly at C-2. Catalytic hydrogenolysis of the 2-arylazo derivatives, followed by acid hydrolysis to cleave the side-chain acetamido and ester groups, produced the desired 2-amino-L-histidine and 2-aminohistamine. Success in the synthesis and isolation of these new histidine analogs is dependent on careful chromatographic purification (silicic acid) of the 2-arylazo derivatives. These 2-aminoimidazoles are stable to acid, alkali, and oxygen. Carboxyl derivatives of 2-aminohistidine are hydrolyzed by trypsin, suggesting that the enzyme recognizes the structural similarity between 2-aminohistidine and arginine.

Syntheses of 4-fluorohistamine and of 4-fluorohistidine, based on a photochemical route to ring-fluorinated imidazoles, have been reported from this laboratory recently.[2] Initial studies on the enzymatic and *in vivo* properties of these analogs of histamine and of histidine provided results of sufficient interest to stimulate our pursuit of the corresponding 2-fluoro series. Since we had already obtained 2-fluoroimidazole from 2-aminoimidazole (by irradiation of the corresponding diazonium ion in fluoroboric acid solution),[2] we undertook the synthesis of some 4-substituted 2-aminoimidazoles which might serve as precursors of 2-fluorohistamine and of 2-fluorohistidine, as well as of other members of the series. Since these syntheses proved largely unfeasible, and since the intermediates ultimately used,[3] 2-aminohistamine and 2-aminohistidine, proved to be of considerable biochemical interest in their own right, this report is concerned with the preparation of the latter compounds, as well as with some of the obstacles encountered in general approaches to 2-aminoimidazoles.

In contrast to the very unstable 4-aminoimidazoles, the isomeric 2-aminoimidazoles generally exhibit a high degree of stability.[4,5] Despite this feature, relatively few members of the latter series have been described, and most of these have either a C-aryl substituent or an alkyl substituent at a ring nitrogen atom.[4,6] Our initial efforts were directed toward the synthesis of a 2-aminoimidazole carrying a group such as hydroxymethyl, carboxaldehyde, or carbalkoxy at C-4. Condensation of cyanamide[6] or of *S*-methylisothiourea[6b] with esters of *C*-formylglycine, and of guanidine (or its derivatives)[7] with dihydroxyacetone, ethyl hydroxypyruvate, or ethyl bromopyruvate,[8] invariably led to products other than imidazoles.[9] Attempts to dehydrogenate[10] 2-amino-2-imidazoline-4-carboxylic acid[11] failed, as did efforts to formylate 2-acetaminoimidazole at C-4.[12]

One remaining option was reinvestigation of the classical route to 2-aminoimidazoles, the reduction of 2-arylazo derivatives. While this route had been successful for the synthesis of some simple C-alkylated (or arylated) 2-aminoimidazoles,[13] previous efforts to apply the technique to histidine[14] and to histamine[14,15] failed. This approach was handicapped by reports that aryldiazonium coupling to α-*N*-benzoylhistidine methyl ester results in formation of bisarylazo derivatives almost exclusively,[14,16,17] a result which we confirmed. Variation in reactant ratios, experimental conditions, or in the nature of the aryldiazonium ion failed to repress bis coupling. Surprisingly, however, the principal coupling product of α-*N*-acetylhistidine methyl ester (**1**) proved to be a monoarylazo derivative. Careful chromatography of the crude precipitate of arylazo derivatives on silicic acid produced three homogeneous fractions: the 2-arylazo (**4**, 73–82%) and 4-arylazo (**3**, 13–18%) derivatives, as well as the 2,4-bis derivative (**5**, 5–9%). These results are based on the use of 1 equiv of arylamine. The composition of the precipitate formed during the reaction is not affected significantly by variation in the nature of the diazonium ion or in pH (7.5–9.5); rapid precipitation of the monoazo derivative may be critical, however, in repression of bis coupling.[18] With α-*N*-acetylhistidine, bis coupling again became the major pathway, presumably because the initial product remained in

(1) Associate in the Visiting Program, USPHS, 1971–1973.

(2) K. L. Kirk and L. A. Cohen, *J. Amer. Chem. Soc.*, **93**, 3010 (1971); *ibid.*, in press.

(3) Synthesis in the 2-fluoroimidazole series will be reported separately.

(4) (a) K. Hofmann, "Imidazole and Its Derivatives," Interscience, New York, N. Y., 1953, p 141; (b) E. S. Schipper and A. R. Day in "Heterocyclic Compounds," Vol. 5, R. C. Elderfield, Ed., Wiley, New York, N. Y., 1957, p 223; (c) A. F. Pozharskii, A. D. Garnovskii, and A. M. Simonov, *Usp. Khim.*, **35**, 261 (1966); *Russ. Chem. Rev.*, **35**, 125 (1966).

(5) 4-Aminoimidazoles are stable only in the presence of a C-5 substituent capable of resonance interaction with the amino group (carbonyl, sulfonyl, nitro groups, etc.). Whether such a substituent at C-2 confers comparable stability on a 4-amino group has yet to be determined.

(6) For leading references, see (a) A. Lawson, *J. Chem. Soc.*, 307 (1956); (b) B. T. Storey, W. W. Sullivan, and C. L. Moyer, *J. Org. Chem.*, **29**, 3118 (1964); (c) G. C. Lancini and E. Lazzari, *J. Heterocycl. Chem.*, **3**, 152 (1966); (d) G. C. Lancini, E. Lazzari, V. Arioli, and P. Bellani, *J. Med. Chem.*, **12**, 775 (199).

(7) (a) T. Pyl, S. Melde, and H. Beyer, *Justus Liebigs Ann. Chem.*, **663**, 108 (1963); (b) T. Pyl, H. Lahmer, and H. Beyer, *Chem. Ber.*, **94**, 3217 (1961); (c) H. Brederick, R. Sell, and F. Effenberger, *ibid.*, **97**, 3407 (1964); (d) I. Iwai and Y. Yura, Japanese Patent 24,885 (1963); *Chem. Abstr.*, **60**, 4154 (1964).

(8) Ethyl imidazole-4-carboxylate is obtained in 30% yield from the reaction of ethyl bromopyruvate and formamide (L. A. Cohen, unpublished results).

(9) In reactions involving these trifunctional systems, it is likely that six-membered ring formation occurs preferentially.

(10) W. Ried and R. Lantzsch, *Chem. Ber.*, **102**, 378 (1969); P. K. Martin, H. R. Matthews, H. Rapaport, and G. Thyagarajan, *J. Org. Chem.*, **33**, 3758 (1968).

(11) T. Sato, *Bull. Chem. Soc. Jap.*, **35**, 1531 (1962).

(12) W. C. Anthony, *J. Org. Chem.*, **25**, 2049 (1960); I. L. Finar and G. H. Lord, *J. Chem. Soc.*, 3314 (1957).

(13) R. G. Fargher and F. L. Pyman, *J. Chem. Soc.*, **115**, 217 (1919); F. L. Pyman and L. A. Ravold, *ibid.*, **117**, 1426 (1920); R. Burtles and F. L. Pyman, *ibid.*, **127**, 2012 (1925); A. de Cat and A. van Dormael, *Bull. Soc. Chim Belg.*, **59**, 573 (1950); A. Kreutzberger, *J. Org. Chem.*, **27**, 886 (1962).

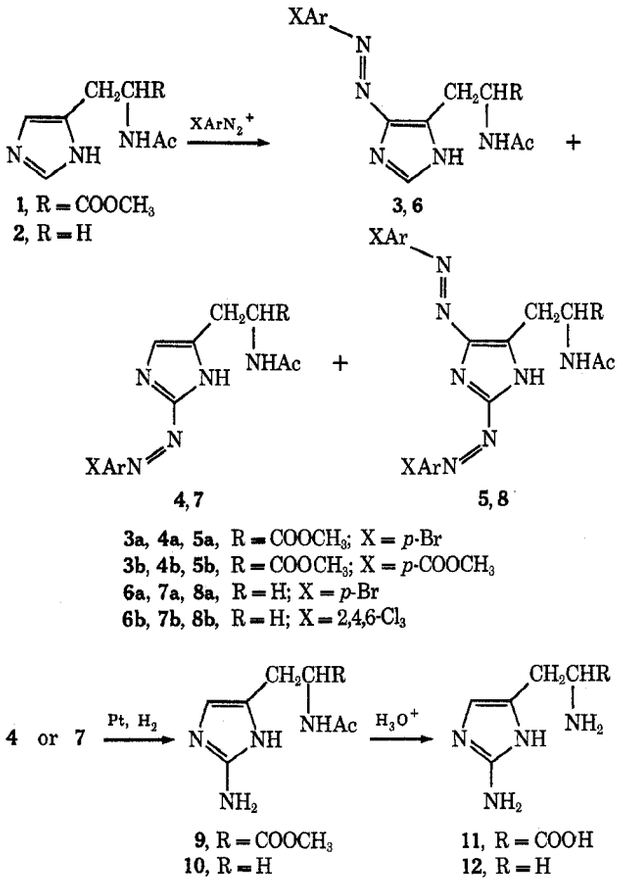
(14) W. Diemair and H. Fox, *Ber.*, **71**, 2493 (1938).

(15) L. Kesztyüs, *Arch. Exp. Pathol. Pharmakol.*, **205**, 287 (1948).

(16) S. Koshimura, *Jap. J. Exp Med.*, **21**, 343 (1951).

(17) Diazonium coupling to histidine itself produces at least seven products: W. Diemair and H. Fox, *Biochem. Z.*, **298**, 38 (1938).

(18) We have no obvious explanation for the striking difference in behavior between the *N*-acetyl- and *N*-benzoylhistidine esters, although rate of precipitation may be a factor.



solution. Assignments of structure to the isomeric monoarylazo derivatives were based on their nmr spectra (Table I),[19] and on the fact that each species assigned a 2-arylazo structure produced a *stable* aminoimidazole. Visible spectra for the arylazo compounds are given in Table II; it is interesting and useful to note that λ_{max} for each 2-arylazo derivative is consistently 30–40 nm higher than that for its 4-arylazo isomer.

TABLE I

NMR SPECTRA OF IMIDAZOLE DERIVATIVES[a]

Compd	δ, ppm H2	δ, ppm H4
1	7.58 (8.76)	6.85 (7.41)
2	7.56 (8.73)	6.83 (7.36)
3a	7.83	
4a		7.20
3b	7.86	
4b		7.30
6a	7.83 (8.57)	
7a		7.26 (7.36)
6b	7.87 (8.45)	
7b		7.35 (7.45)
9		6.56
10		6.23

[a] All spectra were recorded on a Varian A-60 spectrometer in DMSO-d_6 solution; values in parentheses refer to CD_3COOD solution.

(19) The chemical shift of a proton at C-2 invariably appears further downfield than that of a proton at C-4: G. L. Schmir, W. M. Jones, and L. A. Cohen, *Biochemistry*, **4**, 539 (1965).

Although aryldiazonium coupling to histamine and to its α-*N*-acyl derivatives had been reported to produce principally monoarylazo derivatives,[14,15] the heterogeneous composition of these products and their resistance to purification by direct crystallization had not been recognized. In parallel with our results with **1**, α-*N*-acetylhistamine (**2**) afforded, after silicic acid chromatography of the crude precipitate of coupling products, 87% of the 2-arylazo derivative (**7a**), 5% of the 4-arylazo derivative (**6a**), and 8% of the 2,4-bisarylazo derivative (**8a**). Coupling of **2** with 2,4,6-trichlorophenyldiazonium ion produced a significantly greater fraction of the 4-arylazo derivative (34%). Since the aryldiazonium ion shows a decided preference for C-2 (when positions 2 and 4 are both available), as is apparent from the results above as well as from numerous earlier studies,[4] the behavior of the trichlorophenyldiazonium ion is surprising and warrants further study.

Prior to reductive cleavage of the azo linkage, it is essential that the 2-arylazo derivative be as free as possible of contamination by either the 4-arylazo or the 2,4-bisarylazo derivative. Reduction at the 4-arylazo site leads to unstable 4-aminoimidazoles, which are subject both to air oxidation and to hydrolytic imidazole ring cleavage.[14,15] Separation of the highly polar products of these decompositions from the equally polar 2-aminoimidazoles is tedious and unnecessary. Accordingly, exhaustive purification at the arylazo stage is preferable to that at any subsequent step.

The reagent most generally used for reductive cleavage of arylazo compounds, stannous chloride, proved only partially satisfactory for the present cases; although the desired aminoimidazoles were formed, benzidine rearrangements and other side reactions[13] served to complicate purification and to reduce yields sizeably. Reduction with sodium dithionite proved even less satisfactory, leading to water-soluble products (possibly sulfinic or sulfonic acids). The desired 2-aminoimidazoles (**9**, **10**) were obtained, however, by simple platinum-catalyzed hydrogenolysis, cleanly and in good yield. The side-chain acetamido and ester groups were cleaved by acid hydrolysis, resulting in the formation of the new histidine analogs 2-amino-L-histidine (**11**) and 2-aminohistamine (**12**). Neither compound gave evidence of instability in acid or alkali, or upon exposure to air. Both compounds give positive Pauly tests for the imidazole ring, and positive Sakaguchi tests for the guanidine moiety. On the amino acid analyzer, 2-aminohistidine coincides with arginine in its retention time.

The realization that 2-aminohistidine may be viewed as a cyclic analog of arginine led us to consider its derivatives as substrates for trypsin. Indeed, trypsin readily cleaves the ester bond in **9**, and liberates ammonia from α-*N*-acetyl-2-aminohistidineamide. In addition to implications regarding the geometry of the active site of trypsin, these observations suggest the possibility of creating a new site for the tryptic cleavage of polypeptides and proteins.[20] The behavior of these analogs of histamine and of histidine toward other enzymes, as well as their pharmacological properties, is under investigation.

(20) Studies in these directions are in progress and will be reported separately.

TABLE II

PHYSICAL AND ANALYTICAL DATA

Compd	Yield,[a] %	Mp, °C	S[b]	λ_{max}, nm[c] (log ε)	Formula	Calcd, % C	H	N	Br/Cl	Found, % C	H	N	Br/Cl
3a	13	138–140	B	354 (4.39)	$C_{15}H_{16}N_5O_3Br$	45.70	4.09	17.76	20.27	45.34	4.20	17.40	19.53
4a	82	173–175	B	387 (4.41)	$C_{15}H_{16}N_5O_3Br$	45.70	4.09	17.76	20.27	45.89	4.15	17.80	20.18
5a	5	155–158	C	428 (4.44)	$C_{21}H_{19}N_7O_3Br_2$	43.70	3.32	16.99	27.68	43.40	3.38	16.63	27.34
3b	18	132–133	E	358 (4.45)	$C_{17}H_{19}N_5O_5 \cdot H_2O$	52.17	5.41	17.89		52.27	5.32	18.19	
4b	73	187–188	E	388 (4.44)	$C_{17}H_{19}N_5O_5$	54.69	5.13	18.76		54.60	5.13	18.70	
5b	9	150–151	C	435 (4.49)	$C_{25}H_{25}N_7O_7$	56.07	4.71	18.31		55.83	4.82	17.89	
6a	5	214–215[d]	C	353 (4.37)	$C_{13}H_{14}N_5OBr$	46.44	4.20	20.83	23.77	46.14	4.08	20.93	23.99
7a	87	221–223[d]	C	388 (4.46)	$C_{13}H_{14}N_5OBr$	46.44	4.20	20.83	23.77	45.77	4.14	20.66	23.66
8a	8	225[d]	C	427 (4.47)	$C_{19}H_{17}N_7OBr_2$	44.04	3.31	18.92	30.65	43.81	3.21	19.00	30.99
6b	34	203–204	C	327 (4.27)	$C_{13}H_{12}N_5OCl_3$	43.30	3.36	19.42	29.49	42.73	3.29	19.39	29.21
7b	55	189–190	C	365 (4.33)	$C_{13}H_{12}N_5OCl_3$	43.30	3.36	19.42	29.49	42.94	3.15	19.46	28.84
8b	11	203–204	C	385 (4.23)	$C_{19}H_{13}N_7OCl_6$	40.17	2.31	17.26	37.45	39.39	2.20	16.95	37.79
9		183–184	EE		$C_9H_{14}N_4O_3 \cdot 2H_2O$	41.21	6.92	21.36		41.20	6.79	21.14	
10[e]		220–227[d]	E		$C_{13}H_{15}N_7O_8$	39.30	3.81	24.68		39.15	3.89	24.94	
11			MA		$C_6H_{10}N_4O_2 \cdot 2HCl$	29.64	4.98	23.05		29.56	5.16	23.21	
12[f]		220–223[d]	E		$C_{17}H_{16}N_{10}O_{14}$	34.94	2.76	23.97		35.23	2.95	24.09	

[a] Calculated as weight per cent of total material recovered after silica gel chromatography. [b] Solvents for crystallization: B, benzene; C, chloroform; E, 95% ethanol; EE, ethanol–ether; MA, methanol–acetonitrile. [c] Measured in ethanol. [d] Decomposition. [e] Crystallized and analyzed as picrate. [f] As dipicrate.

Experimental Section[21]

α-*N*-Acetyl-L-histidine Methyl Ester (1).—Dry hydrogen chloride was passed into a stirred solution of 12 g (0.056 mol) of *N*-acetyl-L-histidine (Sigma or Aldrich Chemical Co.) in 500 ml of methanol. Introduction of hydrogen chloride was continued for 10 min, and the solvent was removed at reduced pressure (without heat). To the residual oil was added 50 ml of saturated aqueous sodium bicarbonate and an additional 8 g of solid sodium bicarbonate, to produce a final pH of 8.5–9. The mixture was extracted with three 50-ml portions of chloroform, and the combined extracts were dried (Na_2SO_4) and evaporated to give 6.4 g (54%) of colorless, crystalline material. The product was recrystallized from ethyl acetate to give 4.3 g of **1** as needles, mp 124–125°.

Anal. Calcd for $C_9H_{13}N_3O_3$: C, 51.18; H, 6.20; N, 19.90. Found: C, 50.89; H, 6.30; N, 19.67.

More prolonged contact of *N*-acetylhistidine with hydrogen chloride, or the use of heat during evaporation of the solvent, resulted in partial loss of the acetyl group. Acetylation of L-histidine methyl ester proved an even less effective procedure.

α-*N*-Acetyl-2-(*p*-bromophenylazo)-L-histidine Methyl Ester (4a).—A solution of 1.44 g (0.021 mol) of sodium nitrite in 20 ml of water was cooled to 0–2° and was added gradually to a stirred, ice-cold solution of 3.44 g (0.02 mol) of *p*-bromoaniline in 100 ml of 2.3 *N* hydrochloric acid. The solution of diazonium salt was stored at ice temperature for 40 min and was then added gradually to a stirred, ice-cold solution of 4.22 g (0.02 mol) of α-*N*-acetyl-L-histidine methyl ester (**1**) in 200 ml of 0.2 *M* sodium carbonate. The mixture was refrigerated for 2 hr and the yellow-orange precipitate was collected and dried (6.0 g). A solution of 3.78 g of the crude product in the minimum volume of chloroform–methanol (15:1) was applied to a column of silicic acid (600 g, 100 mesh), and the column was eluted with chloroform–methanol (15:1). The mixture of azo compounds was resolved into three bands: the fastest moving consisted of 147 mg of dark red crystals, mp 155–158° ($CHCl_3$), which were identified as the bis product **5a** by nmr (Table I) and by elemental analysis (Table II); the second fraction consisted of 2.6 g of bright yellow crystals, mp 173–175° (benzene), which were identified as the 2-arylazo derivative **4a** by nmr and mass spectra and by elemental analysis; the third fraction consisted of 406 mg of light yellow crystals, mp 138–140° (benzene), which were identified as the 4-arylazo derivative **3a**.

When this diazonium coupling reaction was repeated with *N*-benzoyl-L-histidine methyl ester, only the bis adduct could be detected chromatographically and was isolated as orange crystals, mp 136–137° (acetone).

Anal. Calcd for $C_{26}H_{21}O_3N_7Br_2$: C, 48.84; H, 3.31; N, 15.34; Br, 25.00. Found: C, 48.42; H, 3.49; N, 14.94; Br, 24.44.

For the *p*-carbomethoxyphenyl series **3b–5b**, the diazonium salt was added to a solution of **1** in 0.01 *M* sodium tetraborate, the pH being maintained at 9–9.5 by addition of 1 *N* sodium hydroxide. Physical and analytical data for the coupling products, separated by silicic acid chromatography, are given in Table II.

α-*N*-Acetyl-2-(*p*-bromophenylazo)histamine (7a).—Using a procedure analogous to that for coupling with **1**, 9.30 g (0.06 mol) of α-*N*-acetylhistamine (California Biochemical Co.) was coupled with the diazonium salt obtained from 10 g of *p*-bromoaniline. The crude orange-red product, 17.0 g, was resolved into three fractions by chromatography on 900 g of silicic acid (eluent, chloroform–methanol, 15:1). The coupling products were eluted in the same order as in the case of the histidine derivatives; their properties are summarized in Table II.

A similar procedure was used for coupling with 2,4,6-trichloroaniline. The results differed from those above in that the per cent by weight of **6b** was significantly greater than that of **6a**.

α-*N*-Acetyl-2-amino-L-histidine Methyl Ester (9).—A suspension of 5.0 g (0.013 mol) of **4b** in 200 ml of absolute ethanol containing 0.5 g of platinum oxide was subjected to catalytic hydrogenation at ambient temperature and at an initial hydrogen pressure of 40–45 psi (Paar bomb). A hydrogen pressure of 30–40 psi was maintained throughout the reduction process. After the reaction mixture had been shaken overnight, solution was complete; an additional 0.5 g of platinum oxide was added; and reduction was continued for an additional 18 hr. The catalyst was removed by filtration and the solvent was evaporated *in vacuo*. The residual material was dissolved in 100 ml of water, the solution was filtered from a brown precipitate, and the filtrate was extracted with three 100-ml portions of ether. The aqueous layer was evaporated, with minimal heat, to give 2.88 g of yellow-brown crystals (contaminated with resinous material). The crude product was dissolved in 35 ml of ethanol and 80 ml of ether was added. This turbid solution was refrigerated overnight to give 1.43 g of almost colorless, crystalline material, mp 166–169°. Following recrystallization from ethanol–ether, a colorless, crystalline sample of **9** (dihydrate) was obtained, mp 183–184°.

The *p*-bromophenylazo derivative **4a** was subjected to a similar hydrogenolysis procedure. The aryl–bromine bond was also cleaved, leading to the hydrobromide of **9**. In an attempt to obtain the free base by ion-exchange chromatography, the methyl ester group of **9** was partially lost during the ammonia elution step. For direct conversion of **4** to **11** (without isolation of **9**), this incident is of little consequence.

2-Amino-L-histidine Dihydrochloride (11 2HCl).—A solution of 360 mg of **9** in 10 ml of 6 *N* hydrochloric acid was heated on

(21) Microanalyses, nmr spectra, and mass spectra were provided by the Microanalytical Services and Instrumentation Section of this laboratory, under the direction of Dr. D. F. Johnson. Homogeneities of all compounds were confirmed by tlc; identities of all compounds, except bisarylazo derivatives, were checked by mass spectroscopy. Under the conditions necessary for their volatilization, the latter compounds decomposed without appearance of a parent ion. All melting points are uncorrected.

steam for 20 hr. The solvent was evaporated *in vacuo*, the residue was dissolved in 10 ml of water, and the solvent was again evaporated; this process was repeated twice more, and the crystalline residue was twice recrystallized from methanol–acetonitrile to give **11** as the dihydrochloride, $[\alpha]^{25}D$ −7.7 (*c* 1.4, H_2O), −13.4 (*c* 1, 0.2 *M* acetate buffer, pH 5).

α-*N*-Acetyl-2-aminohistamine (10).—A suspension of 5.7 g of **7a** in 200 ml of ethanol was subjected to catalytic hydrogenation, as described above for **4b**. Following removal of the catalyst, the solvent was evaporated *in vacuo* and the residual material was dissolved in 100 ml of water. The solution was extracted with three 100-ml portions of ether and the aqueous layer, containing **10** as its hydrobromide, was applied to a column of Dowex 50W. The column was eluted with dilute ammonium hydroxide, and the effluent was evaporated to dryness. The residual oil was dissolved in ethanol, the solution was decolorized partially with Norit, and the solvent was removed to give 2.3 g of a red-brown, noncrystalline solid. This material could not be crystallized and **10** was characterized as its picrate (Table II).

2-Aminohistamine (12).—A solution of 1.0 g of **10** in 50 ml of 6 *N* hydrochloric acid was heated on steam for 14 hr. The solvent was removed *in vacuo;* to the residual oil was added 50 ml of ethanol and the solvent was evaporated, the process being repeated. The residual oil was dissolved in 100 ml of ethanol, the solution was decolorized with Norit, and the solvent was removed to give 750 mg of a colorless, noncrystalline solid. The amine **12** was characterized as its dipicrate, mp 200–223° dec (95% ethanol).

Registry No.—**1**, 36097-48-0; **3a**, 39037-16-6; **3b**, 39037-17-7; **4a**, 39037-18-8; **4b**, 39004-81-4; **5a**, 39037-19-9; **5b**, 39037-20-2; **6a**, 39050-06-1; **6b**, 39050-07-2; **7a**, 39050-08-3; **7b**, 39050-09-4; **8a**, 39050-10-7; **8b**, 39050-11-8; **9**, 39037-21-3; **10** picrate 39050-12-9; **11**, 39037-22-4; **11** 2HCl, 39037-23-5; **12**, 39050-13-0; **12** dipicrate, 39050-14-1; *N*-acetyl-L-histidine, 2497-02-1; *p*-bromoaniline, 106-40-1; α-*N*-acetylhistamine, 673-49-4.

A Total Synthesis of Camptothecin and Deethyldeoxycamptothecin[1]

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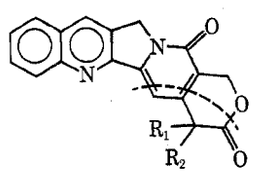
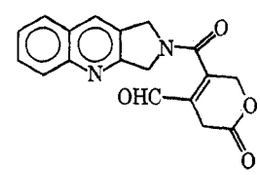
The synthesis of the plant antitumor agent camptothecin, is described. More significantly, the synthesis leads to the pentacyclic lactone **2** in preparative quantities suitable for further study and modification. The scheme involves conversion of the readily available amine **8** to an oxazine amide **7**, which underwent Michael addition with the unsaturated ester **26** leading to the completely functionalized precursor **27**. Borohydride reduction to the tetrahydro-1,3-oxazine **28** followed by cleavage to the aldehyde **29** produced, after borohydride reduction, the hydroxy ester **30**. Acylation of the latter afforded the acetate derivative **41** (R = Me), which was stable to dioxolane cleavage ($BF_3 \cdot Et_2O$) and led to the aldehyde **42** (R = Me). Cyclodehydration of the aldehyde to the pyrrole nucleus gave the dihydropyridone **43** (R = Me), which was aromatized with DDQ to the appropriate pyridone system **45**. Acid hydrolysis then produced the pentacyclic lactone **2** ($R_1 = R_2 = H$), which was converted to racemic camptothecin. A variety of interesting side reactions were encountered during the study, resulting in novel heterocyclic ring systems (*e.g.*, pyrrole oxazines **21**, and *N*-alkyl pyrroles **25**). Certain model experiments having meaningful bearing on the synthesis of camptothecin analogs are also described.

The extensive effort by many groups toward a total synthesis of the plant antitumor agent camptothecin (**1**) has recently culminated in four successful achievements.[3–6] The literature also contains a large number of studies directed toward a total synthesis[7–11] which show varying degrees of promise.

We describe our effort which led to the title compound **1** and is based upon initially obtaining deethyldeoxycamptothecin (**2**) which has already been readily converted to camptothecin by alkylation and hydroxylation of the active methylene group present in the molecule.[6] Construction of **2** was considered most efficient by linking two major units as designated by the dotted line. The precursor **3** was therefore highly desirable, since a cyclodehydration process of the aldehyde to the active methylene group (2 position of quinoline) should produce **2**. Formation of **3** was envisioned as being derived from the open-chain aldehyde **4** and the link-up to form the latter (dotted line) represented the key synthetic transformation in the total synthesis. The formation of **4** required that a Michael addition be performed using the unsaturated ester **5** and the hydroxy amide **6** (or in a masked form, *i.e.*, **7**). Since it is quite unreasonable to expect



1, R_1 = Et; R_2 = OH
2, $R_1 = R_2$ = H



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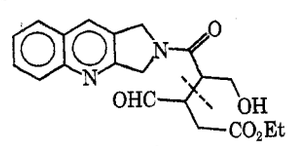

4

(1) This study was supported by the National Institutes of Health.

(2) Please direct all communications concerning this paper to Department of Chemistry, Colorado State University, Fort Collins, Colo. 80521.

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