acid (**5b**), 1.3 ml of thionyl chloride, 3 drops of pyridine, and 300 ml of anhydrous ether was stirred at room temperature for 3 hr.[16] The reaction mixture was freed from a small amount of insoluble residue by filtration. The solvent was evaporated at 30–40° under reduced pressure, and several small portions of ether were added and likewise removed. A colorless residue of 3.12 g of the crude acid chloride, mp 137–142°; $\tilde{\nu}_{max}$ 1794, 1725 cm^{-1}, was isolated.

The acid chloride prepared as described above was dissolved in 75 ml of cold methylene chloride and added over a period of 20 min to an ice-cold solution of diazomethane, made from 11.48 g of N-nitrosomethylurea and 45 ml of a 40% potassium hydroxide solution in 240 ml of methylene chloride,[17] according to the procedure of Wettstein.[18] The resulting solution was allowed to stand at room temperature overnight, flushed with a stream of nitrogen, and filtered. The solvent was removed under reduced pressure at 40–50°, several small portions of methylene chloride were added and evaporated to leave an oil, 3.73 g, of crude yellow diazo ketone, $\tilde{\nu}_{max}$ 2100, 1720, 1632 cm^{-1}.

A mixture of the above prepared diazo ketone, 20 ml of 2,4,6-trimethylpyridine, and 20 ml of benzyl alcohol in a nitrogen atmosphere was immersed into an oil bath heated to 190–200°[11] and allowed to react for 15 min. The solution was cooled, ether was added, and the ether extract was washed with 2 *N* hydrochloric acid and water, dried, and evaporated to leave a solution of the crude reaction product in benzyl alcohol. This solution was diluted with 80 ml of methyl alcohol and 20 ml of water, 4.00 g of potassium hydroxide was added, and the solution was refluxed for 2 hr. The alkaline reaction mixture was diluted with 500 ml of water and the resulting solution was extracted with ether, the ether solution was extracted with several portions of 0.2 *N* sodium hydroxide solution and water and then discarded. The alkaline phase was made acidic by the addition of 2 *N* hydrochloric acid and warmed on the steam bath for 30 min. The suspension was allowed to cool, the precipitate was collected on a filter, washed with water, and dried at 80° under reduced pressure to yield 1.82 g of cream-colored dihydroxy acid **7a**, mp 219–223° dec.

An analytical sample of **7a** was obtained as a powder from acetone–water: mp 223–225° dec; $\tilde{\nu}_{max}^{Nujol}$ 3600–3100, 2700–2400, 1696 cm^{-1}; nmr (DMSO) 39 (C_{13}-methyl), 45 (C_{10}-methyl), 265 Hz (broad peak, 2 H, exchangeable with D_2O).

Anal. Calcd for $C_{22}H_{36}O_4$: C, 72.49; H, 9.96. Found: C, 72.62; H, 10.09.

3β-Acetoxy-17β-hydroxy-5α-androstane-16α-propionic Acid δ-Lactone (8).—A solution of 0.50 g of the dihydroxypropionic acid **7a** in 9 ml of acetic anhydride and 13 ml of glacial acetic acid was heated on the steam bath for 2 hr.[6] The solution was cooled and slowly diluted with water. The precipitate was collected on a filter, washed with water, and dried under vacuum at 80° to yield 0.41 g of beige solid. The material was chromatographed on a column prepared from 50 g of silica gel in benzene. The residues from the benzene–ethyl acetate (19:1) eluates amounted to 0.32 g of the lactone **8** as a colorless solid. Recrystallization of this substance from acetone–*n*-hexane gave 0.27 g of colorless needles: mp 212.5–213.5°; $[\alpha]^{24}D$ +41° (*c* 1.00); $\tilde{\nu}_{max}$ 1723 cm^{-1}; nmr 50.5 (C_{10}-methyl), 51.5 (C_{13}-methyl), 122 (acetate methyl), 217.5 and 226 (d, J = 8.5 Hz, 17α-H), 285 Hz ($W_{1/2}$ ~20 Hz, 3α-H).

Anal. Calcd for $C_{24}H_{36}O_4$: C, 74.19; H, 9.34. Found: C, 74.47; H, 9.34.

Further elution of the column with benzene–ethyl acetate (9:1, 4:1, and 1:1) gave 0.07 g of a mixture which was shown by tlc to contain the lactone **8** and the diacetoxypropionic acid **7b** described below.

3β,17β-Diacetoxy-5α-androstane-16α-propionic Acid (7b).—A sample of the dihydroxypropionic acid **7a** was acetylated in acetic anhydride–pyridine and worked up in the usual manner. The product of the reaction was separated into a neutral and an acidic fraction. A small sample of the above described lactone **8** was obtained from the neutral fraction and purified by recrystallization and sublimation, mp 212.5–214°.

The acidic fraction was purified by chromatography on silica gel. The benzene–ethyl acetate (4:1) eluates contained the desired 3β,17β-diacetoxy-5α-androstane-16α-propionic acid (**7b**) which was recrystallized from methanol–water and acetone–hexane. An analytical sample had the following physical constants: mp 156.5–157.5; $[\alpha]^{24}D$ −56° (*c* 0.62); $\tilde{\nu}_{max}$ 2700–2400, 1715 cm^{-1}; nmr 47 (C_{13}-methyl), 49.5 (C_{10}-methyl), 122 and 124 (acetate methyls), 270 and 277 (*d*, J = 7 Hz, 17α-H), 285 Hz ($W_{1/2}$ ~20 Hz, 3α-H).

Anal. Calcd for $C_{26}H_{40}O_6$: C, 69.61; H, 8.99. Found: C, 69.54; H, 8.85.

(16) W. Cole and P. L. Julian, *J. Amer. Chem. Soc.*, **67**, 1369 (1945).
(17) W. E. Bachmann and W. S. Struve, *Org. Reactions*, **I**, 38 (1942).
(18) A. Wettstein, *Helv. Chim. Acta*, **24**, 311 (1941).

Registry No.—**2**, 18039-56-0; **3a**, 18039-57-1; **3b**, 18039-58-2; **7a**, 18039-59-3; **7b**, 18067-04-4; **8**, 18067-05-5.

Acknowledgments.—The authors are indebted to Mrs. Brigitte Fruehwirth for infrared spectra, to Mrs. Ruth Stanaszek for nmr spectra, to Mr. D. E. Williamson for uv spectra, and to Mr. V. Rauschel and his staff for microanalyses. We are grateful to Dr. W. Cole and to Dr. J. Tadanier for stimulating discussions.

Metabolites of *Clitocybe illudens*. IV.[1] Illudalic Acid, a Sesquiterpenoid, and Illudinine, a Sesquiterpenoid Alkaloid

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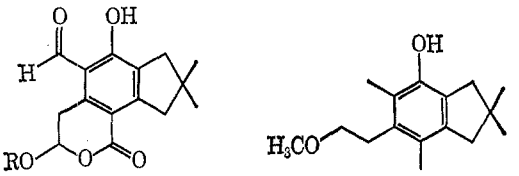
Received September 19, 1968

The structures of illudalic acid (I) and illudinine (II) reported here (Chart I) are both derivable from the same basic "protoilludane" skeleton (III) as those of illudin S and M,[1a,b] illudol[1c] and marasmic acid.[3] Illudalic acid was isolated as "a fourth crystalline compound"[4] accompanying illudin M in culture liquids of the basidiomycete, *Clitocybe illudens*. It was acidic and had a molecular weight (cryoscopic) of 365. However, mass spectrometric determination gave the molecular weight 276. This, together with the elemental analysis, led to the correct formula, $C_{15}H_{16}O_5$. The circumstances of isolation of illudinine suggest that it has a special biogenetic relationship to illudalic acid. The alkaloid was obtained from a strain of the fungus originally selected for enhanced production of illudalic acid. In time, this strain apparently mutated, and, instead of illudalic acid produced a new compound, illudinine.

Illudalic acid (I) had $\lambda_{max}^{H_2O}$ 247, 270 (sh) and 332 mμ (ε 29,000, 12,000 and 760) shifting to 260 and 347 mμ (ε 16,000 and 2000) in sodium hydroxide solution. The compound dissolved in sodium bicarbonate solution with evolution of carbon dioxide. Potentiometric titration in 80% methyl Cellosolve gave pK_a 7.85. The nmr spectrum showed two low-field proton signals, one at τ −2.4 (singlet, which disappeared on adding D_2O) and the other at −0.2 (singlet). The first could be assigned to a strongly chelated phenol, and the second to an aldehyde. Acetylation of illudalic acid

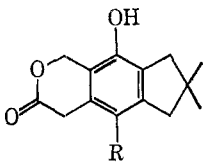
(1) (a) Part I, T. C. McMorris and M. Anchel, *J. Amer. Chem. Soc.*, **85**, 831 (1963); (b) part II, T. C. McMorris and M. Anchel, *ibid.*, **87**, 1594 (1965); (c) part III, T. C. McMorris, M. S. R. Nair, and M. Anchel, *ibid.*, **89**, 4562 (1967).
(2) Department of Chemistry, Tohoku University, Sendai, Japan.
(3) J. J. Dugan, P. de Mayo, M. Nisbet, J. R. Robinson, and M. Anchel, *J. Amer. Chem. Soc.*, **88**, 2833 (1966).
(4) M. Anchel, A. Hervey, and W. J. Robbins, *Proc. Natl. Acad. Sci., U. S.*, **38**, 927 (1952).

CHART I

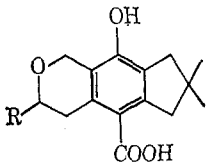


I, R = H
IV, R = Ac

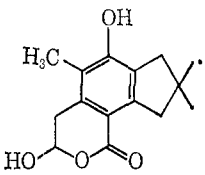
V



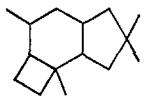
VI, R = COOH
VII, R = H



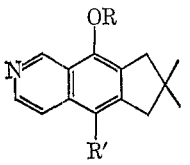
VIII, R = H
IX, R = OH



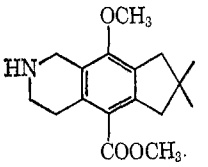
X



III



II, R = CH_3; R′ = COOH
XI, R = CH_3; R′ = $COOCH_3$
XII, R = CH_3; R′ = CH_2OH
XIV, R = H; R′ = H



XIII

with acetic anhydride–pyridine at room temperature gave a mixture of products. From this, a crystalline monoacetate (IV) in which the phenolic function was intact was isolated. In the nmr spectrum of IV, a triplet at 3.1 (J = 6 cps), resulting from a shift of the one at 4.2 in the parent compound, indicated the presence in I of a proton α to a secondary hydroxyl. This methine proton was coupled to a methylene group which gave a doublet at τ 6.58. Illudalic acid gave carbonyl bands at 1683 and 1649 cm^{-1}, and characteristic aromatic absorption at 1624 and 1580 cm^{-1} in its ir spectrum. The 1649-cm^{-1} band was compatible with an *o*-hydroxyaldehyde. The position of the band, and the nmr signal (τ −2.4) for the chelated phenol, are in good agreement with values found for *o*-hydroxybenzaldehydes.[5] The band at 1683 cm^{-1} [6] was shifted to 1727 cm^{-1} in the monoacetate which also exhibited bands at 1767 and 1187 cm^{-1}. This, in conjunction with the nmr evidence (signal at τ 4.2 shifting to τ 3.1 on acetylation) and reaction with sodium bicarbonate, was best explained by a δ-lactol structure.

The evidence thus far accounted for 10 of the 15 carbon atoms. The other 5 carbon atoms were accounted for by the remaining signals in the nmr spectrum: singlets at τ 6.88 and 7.28, two protons each, and a singlet at τ 8.33, six protons, were compatible only with a cyclopentane possessing a *gem*-dimethyl group, and fused to the benzene ring. The values are similar to those of 2,2-dimethylindanes, *e.g.*, the indanol derivative V.[1a,b]

On treatment with strong alkali, illudalic acid afforded an isomeric lactonic acid. The ir spectrum (ν_{max} 1740, 1680 cm^{-1}) and the nmr spectrum [singlets at τ 7.22, 6.78, 5.55 and 4.47 (two protons each) and a singlet at τ 8.82 (six protons)] indicated structure VI.

Formation of VI clearly involves a Canizzaro-type reaction of the aromatic aldehyde and the aldehyde derived from the opening of the lactol ring.[7] Since the aromatic aldehyde has been shown to be *ortho* to the phenolic hydroxyl, the formation of a δ-lactone allows a complete definition of orientation of substituents in the aromatic ring of I. On heating, acid VI was decarboxylated, and the resulting lactone VII (ν_{max} 1725 cm^{-1}) gave a one-proton singlet at τ 3.2.

Hydrogenation of illudalic acid with reduced platinum oxide catalyst in acetic acid gave the acid VIII, $C_{15}H_{18}O_4$, ν_{max} 1682 cm^{-1}. The nmr spectrum showed singlets at τ 5.33, 7.03 and 7.3 (two protons each), two triplets at 7.03 (superimposed on the two-proton singlet) and 6.25, and a singlet at 8.85 (6 H) for the *gem*-dimethyl. It is interesting to note that another metabolite of *Clitocybe illudens*, illudoic acid, $C_{15}H_{18}O_5$, resembles this compound closely. Examination of the spectral characteristics of illudoic acid and of its (methylated and acetylated) derivatives led to the tentative structure IX.

On hydrogenation over 30% palladized carbon, illudalic acid gave the lactol X in which the aldehyde group is reduced to a methyl. It showed ν_{max} at 1680 cm^{-1} for the lactol, and the hydrogen-bonded aldehyde absorption at 1649 cm^{-1} had disappeared. Nmr signals at τ 8.85 (6 H, singlet), 7.84 (3 H, singlet), 7.29 (2 H, singlet), 7.0–6.9 (4 H, a singlet superimposed on a doublet), and 4.25 (1 H, triplet) were in full agreement with this proposed structure.

Illudinine, II [mp 228–229° dec; mol wt 271 (mass spectrum); ν_{max} 1690, 1640, 1605 and 1565 cm^{-1}], analyzed for $C_{16}H_{17}O_3N$, and had one O-methyl group. Its ultraviolet absorption spectrum varied with pH as shown in Table I. On treatment with diazomethane it formed a methyl ester (XI) which could be reduced to a primary alcohol (XII), indicating the presence of a carboxyl group. Illudinine showed nmr signals at τ 1.73 (1 H, doublet), 1.47 (1 H, doublet) and 0.6 (1 H, singlet), characteristic of pyridine ring protons of an isoquinoline.[8] Absence of any other low-field signals, and presence of two methylene singlets (6.97, 6.91) and a two-methyl singlet (8.83) suggested the presence of a *gem*-dimethyl cyclopentane ring fused to the benzene ring of the isoquinoline.

Catalytic hydrogenation of XI yielded the tetrahydro derivative XIII in which the low-field signals had disappeared, and there was a singlet (τ 5.59) and a multiplet (τ 6.60) for protons adjacent to nitrogen.

On pyridine hydrochloride cleavage of the methoxyl

(5) R. W. Hay and P. P. Williams, *J. Chem. Soc.*, 2270 (1964).

(6) *Cf.* isocoumarin IV, in D. C. Aldrich, J. F. Grove, and W. B. Turner, *J. Chem. Soc., C*, 126 (1966).

(7) For other examples of a similar reaction, see ref 3 and (a) J. F. Grove, *Biochem. J.*, **50**, 648 (1952); (b) J. H. Birkinshaw, H. Raistrick, D. J. Ross, and C. L. Stickings, *ibid.*, **50**, 610 (1952).

(8) Varian High Resolution Nmr Spectra Catalog, Vol. I and II, Varian Associates, Palo Alto, Calif., 1962 and 1963.

TABLE I

Compound	Solvent[a]	λ_{max}	$\epsilon \times 10^{-3}$
II	N	232.5, 300, 332	45.0, 4.7, 4.9
	A	228 (sh), 251, 295, 360	22.0, 41.0, 3.6, 5.2
	B	238, 298, 332	52.0, 7.0, 4.5
XI	N	231, 298, 332	45.0, 2.6, 2.6
	A	252, 360	37.5, 2.5
XIII	N	250, 280	
XIV	N	238, 330	58.0, 4.9
	A	253, 378	51.0, 5.3
	B	252, 325, 375	41.0, 5.3, 6.4
Methiodide of XIV	A	217, 256, 320, 380	41.0, 60.0, 3.8, 6.24
	B	271, 343, 465	37.0, 4.8, 4.8
8-Hydroxyisoquinoline[b]	N	233, 304, 334	29.5, 3.7, 6.1
	A	247, 310, 378	29.5, 2.45, 5.25
	B	247, 328, 370	19.0, 4.5, 6.0
8-Hydroxyisoquinoline methiodide[b]	A	217, 250, 315, 378	30.2, 20.0, 1.6, 4.7
	B	263, 347, 460	16.20, 3.8, 4.8

[a] N = MeOH, A = 0.1 *N* HCl–MeOH, B = 0.1 *N* NaOH. [b] Reference 10.

group[9] illudinine underwent simultaneous decarboxylation to yield an isoquinoline (XIV). Comparison of the ultraviolet absorption spectra of XIV and its methiodide in neutral, acidic and alkaline solution with those of 5-, 6-, 7-, and 8-isoquinolinols under similar conditions[10] established XIV as an 8-hydroxyisoquinoline. It has been possible to obtain this same isoquinoline by treatment of illudalic acid with ammonia and subsequent decarboxylation. This reaction demonstrates the relationship between XIV and I and establishes the structure of illudinine as II. It suggests that illudinine may be derived biogenetically from the protoilludane skeleton III *via* illudalic acid. This would be in harmony with the observation that illudalic acid could no longer be isolated from the culture that produced illudinine. Like other members of this family of metabolites, illudinine incorporated mevalonic acid-2-C^{14}.

Experimental Section[11]

Illudalic Acid (I).—The isolation of I was described in ref 4. The acid, after recrystallization from ethanol, had mp >200° dec; $[\alpha]_D$ 0 (EtOH); pK_a 7.85; $\lambda_{max}^{H_2O}$ 247, 270 (sh), and 332 mμ (ε 29,000, 12,000, 760); λ_{max}^{NaOH} 260 and 347 mμ (ε 6000 and 2000); ν_{max} 3300, 1683, 1649, 1624, and 1575 cm^{-1}; τ (DMSO-d_6) 8.89 (6 H, singlet), 7.37 (2 H, singlet), 6.93 (2 H, singlet), 6.6 (2 H, doublet, J = 6 cps), 4.27 (1 H, triplet, J = 6 cps), 2.43 (1 H, broad), −0.2 (1 H, singlet), and −1.93 (1 H, broad) (the signals at 2.43 and −1.93 shifted to 8.48 and −2.4, respectively, in $CDCl_3$ solution, and disappeared when D_2O was added); mass spectrum M^+ 276. *Anal.* Calcd for $C_{15}H_{16}O_5$: C, 65.20; H, 5.84. Found:[4] C, 65.07; H, 5.88.

Acetylation of Illudalic Acid.—Illudalic acid (I, 50 mg) was mixed with acetic anhydride (0.5 ml) and pyridine (2 ml) and the colorless solution was left overnight at room temperature. Excess reagents were removed under reduced pressure and the resultant gum, which showed four spots on tlc, was separated on a preparative thin layer plate. The major component of the mixture (IV) crystallized from methanol: mp 168–169.5°; ν_{max} 1763, 1727, 1652, 1626, 1574, and 1187 cm^{-1}; τ ($CDCl_3$) 8.82 (6 H, singlet), 7.92 (3 H, singlet), 7.23 (2 H, singlet), 6.72 (2 H, singlet), 6.40 (2 H, doublet, J = 6 cps) 3.10 (1 H, triplet, J = 6 cps), −0.40 (1 H, singlet), and −2.50 (1 H, singlet); mass spectrum M^+ 318. The parent compound could be regenerated from this acetate by cold alkaline hydrolysis and subsequent acidification. The uv spectrum of the acetate was the same as that of I.

Reaction of Illudalic Acid with Potassium Hydroxide.—Illudalic acid (I, 50 mg) was heated for 5 min on a steam bath with 50% aqueous potassium hydroxide (5 ml). Acidification and filtration yielded a yellowish powder (VI) which crystallized from ethyl acetate: mp 225–228° (sublimed around 190° and gave off carbon dioxide on melting); λ_{max}^{EtOH} 255 mμ and strong end absorption; ν_{max} 3400, 1742, 1675, 1613, and 1587 cm^{-1}; τ (pyridine-d_5), 8.95 (6 H, singlet), 7.22 (2 H, singlet), 6.78 (2 H, singlet), 5.55 (2 H, singlet), 4.47 (2 H, singlet); mass spectrum M^+ 276.

Decarboxylation of Acid VI. Preparation of VII.—The lactonic acid (VI) in an evacuated flask was immersed in a bath preheated to 230°, and the sublimate of the decarboxylation product (VII) was separated: mp 214° (sublimes at 190°); ν_{max} 1725, 1614, and 1585 cm^{-1}; τ (DMSO-d_6) 8.87 (6 H, singlet), 7.3 (4 H, singlet), 6.37 (2 H, singlet), 4.65 (2 H, singlet), and 3.2 (1 H, singlet).

Hydrogenation of I.—Illudalic acid (55 mg) was hydrogenated in 50 ml of ethanol over 30% palladized carbon (55 mg) for 30 min at room temperature and atmospheric pressure. The reaction product (X), separated from its less polar impurities by preparative tlc, crystallized from ethanol: mp 213–216°; λ_{max}^{EtOH} 270 mμ (ε ~4000), λ_{max}^{NaOH} 280 (sh) and 295 mμ (ε ~4000); ν_{max} 1680 and 1590 cm^{-1}; τ (DMSO-d_6) 8.85 (6 H, singlet), 7.84 (3 H, singlet), 7.29 (2 H, singlet), 7.01–6.90 (4 H, a singlet superimposed on a doublet), 4.25 (1 H, triplet).

Illudalic acid (50 mg) was hydrogenated in 40 ml of glacial acetic acid over reduced platinum oxide catalyst (40 mg) for 4.5 hr at room temperature and atmospheric pressure. The catalyst was filtered off and the solvent evaporated to obtain the reduction products as an amorphous powder. This mixture was separated on preparative tlc. The major of the three components, VIII, crystallized from ethanol: mp 217°; λ_{max}^{EtOH} 260 mμ (ε 4400); $\lambda_{max}^{EtOH-NaOH}$ 273–283 mμ (broad) (ε 4000); ν_{max} 1682, 1610, and 1580 cm^{-1}; τ (acetone-d_6) 8.85 (6 H, singlet), 7.3 (2 H, singlet), 7.03 (4 H, a 2 H singlet superimposed on a 2 H triplet), 6.25 (2 H, triplet), 5.33 (2 H, singlet).

Illudoic Acid (IX, Tentative).—Illudoic acid, mp 135°, had λ_{max} 216 and 260 mμ (ε 23,000 and 7300), shifting to 270–280 mμ (ε *ca.* 7500) at alkaline pH; ν_{max} 1670, 1610, and 1582 cm^{-1}.

On brief treatment with diazomethane, a monomethylated product was obtained: mp 80°; ν_{max} 1712, 1614, and 1587 cm^{-1}; τ (acetone-d_6) 8.85 (6 H, singlet), 7.25 (2 H, singlet), 7.1 (2 H, singlet), 7.0 (2 H, broad), 6.5 (1 H, broad, exchanges with D_2O), 5.15 (2 H, doublet), 4.72 (1 H, triplet).

On treatment with acetic anhydride–pyridine at room temperature, a diacetate was obtained: mp 153–154°; ν_{max} 1775, 1720, 1614, and 1580 cm^{-1}; τ (acetone-d_6) 8.87 (3 H, singlet), 8.83 (3 H, singlet), 8.12 (3 H, singlet), 7.7 (3 H, singlet), 7.42 (2 H, singlet), 6.92 (2 H, singlet), 6.67 (2 H, broad), 5.27 (2 H, singlet), 3.67 (1 H, triplet).

Illudinine (II).—Ethyl acetate extracts of the culture liquid were taken to dryness *in vacuo* and the residue was subjected to a 50-tube countercurrent distribution between chloroform and water. The chloroform phases of tubes 6–20 were combined. On removal of most of the solvent, illudinine was obtained as a partly crystalline precipitate. After crystallization from ethanol, it had mp 228–229° dec; ν_{max} 1690, 1640, 1605 and 1565 cm^{-1}; τ (DMSO-d_6) 8.83 (6 H, singlet), 6.97 (2 H, singlet), 6.91 (2 H, singlet), 5.95 (3 H, singlet), 1.72 (1 H, doublet), 1.47 (1 H, doublet), and 0.60 (1 H, singlet); mass spectrum M^+ 271. *Anal.* Calcd for $C_{16}H_{17}O_3N$: C, 70.83; H, 6.32; O, 17.69; N, 5.16; 1 methoxyl, 11.44. Found: C, 69.88; H, 6.38; O, 18.45; N, 5.35; $-OCH_3$, 11.99.

Illudinine Methyl Ester (XI).—Illudinine (110 mg) in 20 ml of methanol was esterified by adding an excess of an ethereal solution of diazomethane at room temperature. The ester obtained by the removal of the solvents, and purified by sublimation and crystallization from petroleum ether (bp 60–70°), had mp 83–84°; ν_{max} 1725, 1640, 1624, 1595, and 1570; τ ($CDCl_3$) 8.82 (6 H, singlet), 7.00 (2 H, singlet), 6.88 (2 H, singlet), 5.98 (3 H, singlet), 5.90 (3 H, singlet), 1.72 (1 H, doublet), 1.47 (1 H, doublet), and 0.62 (1 H, singlet); mass spectrum M^+ 285. *Anal.* Calcd for $C_{17}H_{19}O_3N$: C, 71.56; H, 6.71. Found: C, 70.99; H, 6.70.

Illudinine Alcohol (XII).—Ester XI (30 mg) was reduced in 40 ml of anhydrous ether with lithium aluminum hydride (100

(9) V. Prey, *Ber.*, **74**, 1219 (1941); **75**, 350 (1942).

(10) K. Nakanishi, M. Ohashi, S. Kumasaki, and H. Koike, *Bull. Soc. Chem. Jap.*, **34**, 533 (1961).

(11) Melting points were taken on a Kofler hot stage and are uncorrected. Ir spectra were determined as KBr pellets on a Perkin-Elmer Model 21 spectrometer; nmr spectra were recorded on a Varian A-60A spectrometer with TMS as internal standard and uv spectra on a Perkin-Elmer Model 45 spectrophotometer. Elemental analyses were carried out by Dr. Franz Pascher of Bonn, and some of the mass spectra measurements by Morgan-Shaffer Corp., Montreal. Preparative tlc was carried out on 1-mm plates of silica gel PF 254 (E. Merck AG, Darmstadt) using a benzene–acetic acid 9:1 system, unless otherwise indicated.

mg) at reflux for 2 hr. The alcohol, purified by preparative tlc (EtOAc), had ν_{max} 1640, 1610, 1590, and 1570 cm^{-1}; τ ($CDCl_3$) 8.80 (6 H, singlet), 7.20 (1 H, broad, disappears on shaking the solution with D_2O), 7.00 (4 H, singlet), 5.97 (3 H, singlet), 4.97 (2 H singlet).

Tetrahydroilludinine Methyl Ester (XIII).—Methyl ester XI (100 mg) was hydrogenated at room temperature and atmospheric pressure in 50 ml glacial acetic acid containing reduced platinum oxide catalyst (100 mg) for 2 hr. The solution was made alkaline with sodium bicarbonate and extracted with ethyl acetate, from which the tetrahydro derivative was obtained as a yellow gum. Sublimation and crystallization from petroleum ether afforded the pure ester XIII: mp 83–84°; ν_{max} 1725 and 1575 cm^{-1}; τ ($CDCl_3$) 8.87 (6 H, singlet), 7.13 (4 H, singlet), 6.95 (2 H, multiplet), 6.60 (2 H, multiplet), 61.7 (6 H, singlet), 5.59 (2 H, singlet).

Pyridine Hydrochloride Cleavage and Decarboxylation of Illudinine. Isoquinolinol XIV.—Illudinine (I, 40 mg) was mixed with pyridine hydrochloride (400 mg) and heated in a sealed tube at 220° for 4 hr. The reaction mixture was cooled, dissolved in water, and extracted with ethyl acetate. The extract on evaporation gave isoquinolinol XIV as a reddish residue, which crystallized from methanol: mp 207–210°; ν_{max} 1640, 1612, and 1575 cm^{-1}; τ ($CDCl_3$) 8.84 (6 H, singlet), 7.16 (4 H, singlet), 2.92 (1 H, singlet), 1.61 (1 H, broad), 1.32 (1 H, broad), 0.73 (1 H, broad); mass spectrum M^+ 213. On refluxing with methyl iodide in an acetone–benzene solution, XIV formed the methiodide, mp 230–233° (EtOH).

Action of Ammonia on Illudalic Acid.—Illudalic acid (40 mg) was heated on a steam bath for 10 min with 20 ml of 15% ammonia solution. The solution was evaporated to dryness, extracted with acetic acid and the acetic acid was then removed under reduced pressure. Partition of the residue between water and ethyl acetate (1:10) yielded the isoquinolinol XIV identical with that obtained from II: mp and mmp 208–210°; mass spectrum M^+ 213; ir, nmr, and uv spectra, superimposable.

Registry No.—I, 18508-77-5; II, 18500-63-5; IV, 18508-78-6; VI, 18500-64-6; VII, 18500-65-7; VIII, 18500-66-8; IX, 18508-79-7; methyl ester of IX, 18508-80-8; diacetate of IX, 18508-81-1; X, 18508-82-2; XI, 18500-67-9; XII, 18500-68-0; XIII, 18500-60-2; XIV, 18500-61-3; methiodide of XIV, 18500-62-4.

Acknowledgment.—This work was supported by grants AI-00226 and GM 12150 from the National Institutes of Health. The nmr spectra were done on a Varian A60A nuclear magnetic resonance spectrometer, the purchase of which was made possible by a General Research Support Grant, 5-S01-FRO-5621, to The New York Botanical Garden. The authors are indebted to Drs. A. K. Bose and K. S. Khanchandani of the Stevens Institute for some of the mass spectra. We thank Mr. Francis Manginelli and Mrs. Hulda Holness for technical assistance.

Preparation of N-Carboxy-α-amino Acid Anhydrides by the Reaction of Copper(II)–Amino Acid Complexes with Phosgene

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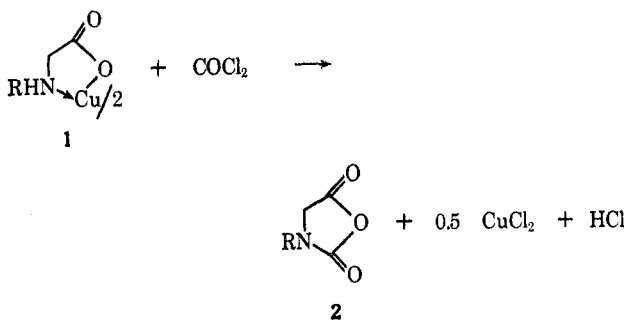
Received July 22, 1968

N-Carboxy-α-amino acid anhydrides (2), which are widely used as precursors for polypeptides, are generally prepared by reacting phosgene directly with amino acids, their hydrochlorides, or their sodium salts in an inert, polar solvent.[1] They are also obtained by treatment of N-alkoxycarbonyl-α-amino acids with thionyl chloride,[2] phosphorous pentachloride,[3] and oxalyl chloride,[4] and by the reaction of thionyl chloride or phosgene with the disodium salts of N-carboxy-amino acids.[5]

We have now found that N-carboxy-α-amino acid anhydrides are obtained in good yields when finely ground copper(II)–amino acid complexes (1) are suspended in tetrahydrofuran and treated with phosgene at room temperature for 1–2 hr. The copper atom is expelled as copper(II) chloride. The first



1

2

stage of the reaction probably involves attack by the nitrogen atom on the carbonyl carbon atom of phosgene, even though the nucleophilicity of the nitrogen atom is greatly diminished because of its coordination with copper. Subsequent cleavage of the covalent[6,7] N–Cu bond and ring closure with elimination of copper(II) chloride would lead to 2. The rate of the reaction is related to the nature of the R group, the N–Cu bond, and the solubility of the complex in the solvent. The influence of the metal atom was not studied (the order of stability of complex formation between amino acids and metals is Cu > Ni > Zn > Co > Cd > Fe^{2+} > Mn > Mg).[8]

Preparation of N-carboxyanhydrides of amino acids which are purified only with difficulty might be facilitated by this reaction—*i.e.*, the complex could be prepared, readily purified (in contrast to the amino acid itself), and reacted directly with phosgene to afford the desired N-carboxyanhydride.

Experimental Section[9]

Amino Acid–Copper(II) Complexes.—The general procedure used to prepare these complexes was as follows. The amino acids (0.1 mol) were dissolved in hot water (150 ml for sarcosine and 500 ml of DL-alanine and glycine), and a 10% excess of solid cupric carbonate was slowly added with stirring to give deep blue

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(9) All melting points are corrected. Analyses were performed by the Stanford University Microanalytical Laboratories, Stanford, Calif.