TABLE III

PREPARATION OF POLYURETHANS

Polymers[a]	Catalyst[b]	Softening temp., °C.	Solvent[c]	Rel. viscos.[d]	Formulas	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
III	Ba	164–169[e]	P	1.19,C	$C_{10}H_{18}N_2O_4$			12.17			12.12
Va[f]	None[g]	90	D	1.22,F	$C_{27}H_{36}N_2O_6$	66.92	7.45	5.78	66.80	7.54	5.76
Va[h]	Zn	84–93[i]	P	1.07,F	[j]	66.18	7.47	6.10	66.42	7.17	6.27
Vb[k]	Ba	112–136	P	1.06,F	[k]	55.30	6.40	6.99[l]	56.90	6.57	7.14
Vb[m]	Ba + Zn	117–135	P		[m]	56.30	6.21	6.36[n]	57.30	6.60	6.74
VIIa	Ba + Zn	145–147	D	1.21,C	$C_{11}H_{21}NO_2$	66.29	10.62	7.03	66.67	10.67	7.02
VIIb	Ba + Zn	208–215	P	1.12,C	$C_9H_9NO_2$	66.24	5.56	8.58	65.91	5.80	8.82

[a] Numbers refer to labeled compounds in equations. [b] Ba = barium oxide, Zn = zinc borate. [c] Solvent for the polymer. P = N-methyl-2-pyrrolidone, D = dioxane. [d] Relative viscosity in *m*-cresol (C) or dimethylformamide (F). [e] Reported m.p.[4c] for polyurethan from 1,6-hexanediisocyanate and ethylene glycol, 170°. [f] Prepared from 2,2-bis-[4-β-hydroxyethoxyphenyl)-propane and 1,6-hexanediisocyanate. [g] Bulk polymerization at 170–180°. [h] Prepared from 2,2-bis-(4-β-hydroxyethoxyphenyl)-propane and bis-(2-hydroxyethyl)-1,6-hexanedicarbamate. [i] Increasing time of polymerization from 18 to 50 hours changed m.p. to 88–103°, but did not affect the composition of the polymer. [j] Calcd. for 95% $C_{27}H_{36}N_2O_6$ (Va) and 5% $C_{10}H_{18}N_2O_4$ (III). [k] Polymer prepared by heating 4,4′-bis-(2-hydroxyethoxy)-phenyl sulfone and bis-(2-hydroxyethyl)-1,6-hexanedicarbamate for 8 hours. Calcd. for 22% $C_{10}H_{18}N_2O_4$ and 78% $C_{24}H_{30}N_2O_8S$. [l] Also calcd. for S, 4.94. Found: S, 4.90. [m] Polymer from same reactants as in note *k*, heated for 30 hours. Calcd. for 12.5% $C_{10}H_{18}N_2O_4$ and 87.5% $C_{24}H_{30}N_2O_8S$. [n] Also calcd. for S, 5.54. Found: S, 5.86.

thionyl chloride was stirred and refluxed for 3 hours.[16] Then excess thionyl chloride was distilled off, the residue dissolved in a small volume of dioxane and the solution added dropwise to 2 l. of concd. ammonium hydroxide during stirring and cooling. The resulting methyl terephthalamate melted at 204–206° (lit.[17] 201°) after recrystallization from water containing Methyl Carbitol.

Preparation of Polymers.—The polymerization chamber was a heat-jacketed, 30 × 2.5 cm. test-tube attached by a ground-glass joint to a plain distillation head. A fine capillary through which nitrogen was admitted, produced a stirring effect. Ethylene glycol was collected in a Dry Ice trap.

A mixture of 0.1 mole of melted monomer, 0.01–0.02 g. of barium oxide and frequently the same amount of zinc borate was heated in the polymerization apparatus under a pressure of 0.5–2 mm. at the lowest temperature at which ethylene glycol would form. Then the temperature was raised in successive stages to about 220°. Unless the material solidified or discolored badly, the heating was continued as long as the glycol was formed (up to 50 hours). The ethylene glycol was obtained in yields of 80–90%. The polymer was purified by pouring a filtered solution of it into a stirred non-solvent. Precipitation was repeated, the product was dried *in vacuo* and ground repeatedly and often extracted in a continuous extractor with a solvent such as methanol before drying for analysis.

(16) The procedure and the ester were kindly furnished by E. I. du Pont de Nemours and Co., Inc.

(17) P. Kattwinkel and R. Wolffenstein, *Ber.*, **37**, 3223 (1904).

Dilute solution viscosities (η_r) were done in an Ostwald viscosimeter at 25°, using 0.4000 g. of polymer in 100 ml. of dimethylformamide or 1.000 g. of polymer in 100 ml. of *m*-cresol.

Polymers Va and Vb (Table III) formed weak films or fibers; the others were brittle powders. All the polyurethans showed strong infrared absorption at approximately 6.00 and 6.54 μ.[4d]

Polyurea from N-Isobutyl-1,6-hexanediamine and Ethylene Carbonate.—A mixture of 0.2 mole of the diamine and 0.2 mole of ethylene carbonate was heated gently until an exothermic reaction took place. After an interval of cooling and standing, the glycol elimination reaction was carried out in the usual way, using barium oxide. The product, precipitated from N-methyl-2-pyrrolidone with ice, and from methanol with water, softened at 81–96°. Weak fibers could be drawn.

Anal. Calcd. for $C_{11}H_{22}N_2O$: C, 66.62; H, 11.18; N, 14.13. Found: C, 65.77; H, 11.16; N, 13.95.

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[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF MARYLAND]

An Example of a Ring Closure Yielding a 5-Methoxyoxazole in Preference to a Dihydroisoquinoline

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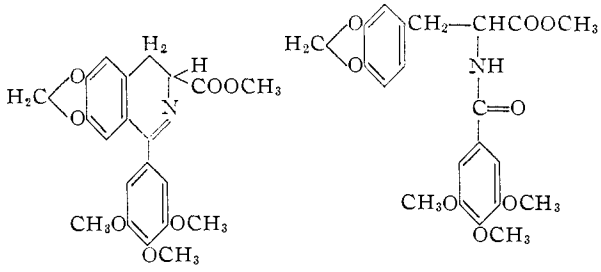
An example is given of a substituted α-benzamidohydrocinnamate ester (II) which, on treating with phosphorus oxychloride under the usual Bischler–Napieralski conditions, cyclizes predominately to a 5-methoxyoxazole (III) instead of to a dihydroisoquinoline (I).

The synthesis of 3,4-dihydro-6,7-methylenedioxy-1-(3,4,5-trimethoxyphenyl)-3-isoquinolinecarboxylic acid (free acid of I) was originally undertaken because it has certain structural features of podophyllotoxin, a tumor-damaging agent,[1] and because the corresponding dihydroisoquinoline without the carboxylic acid group has been found to have tumor-damaging properties. The synthesis employed is of interest from the chemical standpoint because one intermediate, methyl 3,4-methylenedioxy-α-(3,4,5-trimethoxybenzamido)-hydrocinnamate (II), can cyclize either *via* the classical Bischler–Napieralski reaction to the de-

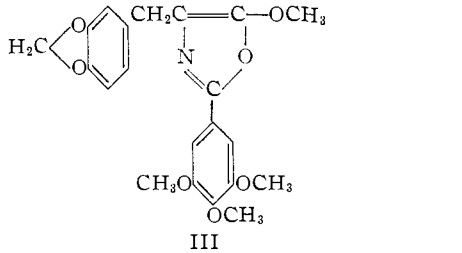
(1) M. G. Kelly and J. L. Hartwell, *J. Nat. Cancer Inst.*, **14**, 967 (1954); J. L. Hartwell and A. W. Schrecker, THIS JOURNAL, **73**, 2909 (1951).

sired dihydroisoquinoline (I) or by an alternative route to yield a substituted 5-methoxyoxazole (III). Seven substituted β-aryl-α-acylamidohydrocinnamates, similar to structure II, are listed in the literature as cyclizing to substituted dihydroisoquinolines,[2-4] and evidence is presented in two of these cases to show that a dihydroisoquinoline is actually formed rather than an oxazole.[3,4] Karrer and co-workers have shown that α-acylamido esters will cyclize to 5-alkoxyoxazoles under Bischler–Napieralski reaction conditions,[5-8] but a Bischler–Napieralski reaction was not possible in any of the esters which they examined since the esters contained no β-aryl group.



I

II



III

In the present work methyl 3,4-methylenedioxy-α-(3,4,5-trimethoxybenzamido)-hydrocinnamate (II) was prepared in excellent yield by standard reactions involving the preparation of 3,4,5-trimethoxybenzoylglycine, condensation with piperonal and concurrent cyclization to an azlactone, opening of the azlactone ring with methanol to form methyl 3,4-methylenedioxy-α-(3,4,5-trimethoxybenzamido)-cinnamate, and hydrogenation of this ester to compound II. In addition to the methyl ester, the isopropyl ester and the diethylamide were prepared in the hope that they would cyclize preferentially to the substituted dihydroisoquinoline, but initial attempts to cyclize them were unsuccessful.

Compound II on cyclization with phosphorus oxychloride under a variety of conditions gives a 35 to 50% yield of the substituted 5-methoxyoxazole (III) as the major product, and about 0 to 3% yield of the expected dihydroisoquinoline (I). An examination of models gives no clue as to why the formation of a methoxyoxazole should be favored in this case more so than in the other cases reported to yield dihydroisoquinolines. There can be no doubt that the compound assigned the methoxyoxazole structure does in fact have this structure. The results of elementary analysis and a molecular weight determination require the formation of a new cycle in the compound. The presence of the methoxy group follows from the methoxyl analysis. Reaction with a boiling alcoholic sodium ethoxide solution yields the intermediate hydrocinnamic acid and proves the absence of a dihydroisoquinoline ring. However, the material was inert to refluxing aqueous 1 *N* potassium hydroxide solution which shows no ester group is present and establishes that the ester group has entered into the formation of the cycle. Oxidation with potassium permanganate in an acid solution yields trimethylgallamide and proves cyclization has not occurred so as to involve the trimethoxyphenyl ring. Accordingly, an oxazole structure is the only possibility.

With phosphorus oxychloride as the condensing agent, the use of toluene or xylene as solvents, instead of no solvent, did not change the course of the reaction except that none of the substituted isoquinoline could be isolated. No reaction occurred when benzene was used as the solvent, even at the refluxing temperature. Using phosphorus pentachloride as the condensing agent and toluene as the solvent, chlorination followed by dehydrochlorination apparently occurred since a 60% yield of the unsaturated azlactone, 4-piperonylidene-2-(3,4,5-trimethoxyphenyl)-2-oxazolin-5-one, was the only product obtained.

Experimental

All melting points are corrected. Analyses are by Mrs. Mary Aldridge and Miss Kathryn Gerdeman of this Laboratory.

N-(3,4,5-Trimethoxybenzoyl)-glycine.—To 48 g. (0.63 mole) of glycine dissolved in 300 ml. of 10% aqueous sodium hydroxide and cooled in an ice-bath were added simultaneously with constant stirring over an hour period 145 g. (0.63 mole) of trimethylgalloyl chloride,[9] dissolved in 300 ml. of dioxane and 300 ml. of a 10% sodium hydroxide solution to maintain a basic medium. After stirring an additional half-hour, the chilled mixture was acidified with cold concentrated hydrochloric acid and the crude product filtered off and dried. There was obtained 155 g. (91% yield), m.p. 214–216°. Recrystallization from water gave an analytical sample, m.p. 221.5–223°. *Anal.* Calcd. for $C_{12}H_{15}O_6N$: C, 53.53; H, 5.61; N, 5.20; $-OCH_3$, 34.58. Found: C, 53.53; H, 5.67; N, 5.49; $-OCH_3$, 34.31.

4-Piperonylidene-2-(3,4,5-trimethoxyphenyl)-2-oxazolin-5-one.—This follows an "Organic Syntheses" procedure for a similar compound.[10] Sixty grams (0.40 mole) of piperonal, 108 g. (0.40 mole) of the trimethoxybenzoylglycine, 32 g. (0.60 mole) of powdered sodium acetate and 120 g. (1.2 moles) of acetic anhydride were stirred together by hand and heated over a hot-plate to 80° for a few minutes until the mass liquefied. A yellow solid immediately began to precipitate. The mixture was heated for an hour on a steam-bath, 300 ml. of ethanol then slowly added, the mixture chilled, and the yellow azlactone filtered off. The yield was 128 g. (83%), m.p. 197–198°. An analytical sample, m.p. 203–204°, was obtained by successive recrystallizations from acetic acid and benzene. *Anal.* Calcd. for $C_{20}H_{17}O_7N$: C, 62.65; H, 4.48; N, 3.65; $-OCH_3$, 24.28. Found: C, 62.42; H, 4.44; N, 3.94; $-OCH_3$, 24.29.

A dioxane solution of this azlactone could not be hydrogenated to the saturated azlactone at room temperature and

(2) M. Hartmann and H. Kagi, U. S. Patent 1,437,802 (Dec. 5, (1922).

(3) H. J. Harwood and T. B. Johnson, THIS JOURNAL, **56**, 468 (1934).

(4) A. Galat, *ibid.*, **73**, 3654 (1951).

(5) P. Karrer and C. Granacher, *Helv. Chim. Acta*, **7**, 763 (1924).

(6) P. Karrer, E. Miyamichi, H. C. Storm and R. Widmer, *ibid.*, **8**, 205 (1925).

(7) C. Granacher, *ibid.*, **8**, 211 (1925).

(8) E. Miyamichi, *J. Pharm. Soc. Japan*, No. 548, 863 (1927), from *C. A.*, **22**, 782 (1928).

(9) W. Reeve and J. D. Sterling, THIS JOURNAL, **71**, 3657 (1949).

(10) J. S. Buck and W. S. Ide, "Organic Syntheses," Coll. Vol. II, John Wiley & Sons, Inc., New York, N. Y., 1943, p. 55.

atmospheric pressure over platinum or palladium catalysts, presumably because of the presence of the extended conjugation system.

N,N-Diethyl-3,4-methylenedioxy-α-(3,4,5-trimethoxybenzamido)-cinnamamide.—This was obtained by refluxing 5.5 g. of the 2-oxazolin-5-one with 75 ml. of diethylamine for 1.5 hours. The excess diethylamine was distilled off, the residue dissolved in ether and washed first with dilute hydrochloric acid and then with water. The ether was removed and the product crystallized from methanol. There was obtained 4.8 g. (73% yield) of the crude product, m.p. 198–201°. A sample for analysis was further purified by repeated crystallizations from 60–80° petroleum ether–tetrahydrofuran solutions and from petroleum ether–ethanol solutions. It then melted at 231.5–232.5°. *Anal.* Calcd. for $C_{24}H_{28}N_2O_7$: C, 63.14; H, 6.18; N, 6.14; $-OCH_3$, 20.35. Found: C, 63.00; H, 6.43; N, 6.02; $-OCH_3$, 21.39.

The substituted hydrocinnamamide was obtained by hydrogenating the cinnamamide in an acetic acid solution over a 20% palladium-on-carbon catalyst. The hydrogenation was sluggish at room temperature and atmospheric pressure and fresh catalyst had to be added after 24 hours. The material melted at 129–130° after crystallization from a small amount of methanol. *Anal.* Calcd. for $C_{24}H_{30}O_7N_2$: C, 62.86; H, 6.60; N, 6.12; $-OCH_3$, 20.30. Found: C, 62.62; H, 6.73; N, 6.41; $-OCH_3$, 20.06.

Methyl 3,4-Methylenedioxy-α-(3,4,5-trimethoxybenzamido)-cinnamate.—Thirty-one grams of the recrystallized 2-oxazolin-5-one, 200 ml. of dry methanol and 0.8 g. of anhydrous sodium carbonate were refluxed for 15 minutes at which time the yellow color of the oxazolone had disappeared and a white solid was precipitating. It was chilled for several hours and the crude product was filtered and dried. After crystallizing from ethanol the white product weighed 29 g. (89% yield) and melted at 174–175°. Two more crystallizations from ethanol gave an analytical sample, m.p. 176–177°. *Anal.* Calcd. for $C_{21}H_{21}O_8N$: C, 60.71; H, 5.09; N, 3.37; $-OCH_3$, 29.88. Found: C, 60.58; H, 4.91; N, 3.38; $-OCH_3$, 30.20.

Methyl 3,4-Methylenedioxy-α-(3,4,5-trimethoxybenzamido)-hydrocinnamate (II).—This was prepared by the room temperature hydrogenation of the cinnamate ester over a 20% palladium-on-carbon catalyst using acetic acid as a solvent. The solvent was evaporated off and the product crystallized from ethanol. Ten grams of the cinnamate ester yielded 9.8 g. of the hydrogenated product, m.p. 152–154°. Two more crystallizations from ethanol gave an analytical sample, m.p. 155.5°. *Anal.* Calcd. for $C_{21}H_{23}O_8N$: C, 60.42; H, 5.56; N, 3.36; $-OCH_3$, 29.73. Found: C, 60.56; H, 5.61; N, 3.84; $-OCH_3$, 29.52.

The free acid was prepared by refluxing 2 g. of the methyl ester with 70 ml. of 5% sodium hydroxide solution for an hour, acidifying, and recrystallizing the 1.75 g. of crude product from ethyl acetate twice. It melted at 195–196°. *Anal.* Calcd. for $C_{20}H_{21}O_8N$: C, 59.55; H, 5.24; N, 3.47; $-OCH_3$, 23.07. Found: C, 59.58; H, 5.34; N, 3.69; $-OCH_3$, 22.78.

Reaction of this acid with thionyl chloride in refluxing toluene yielded the unsaturated azlactone, 4-piperonylidene-2-(3,4,5-trimethoxyphenyl)-2-oxazolin-5-one.

The amide was prepared by treating 0.5 g. of the methyl ester, dissolved in 10 ml. of dioxane, with 25 ml. of concd. ammonium hydroxide on a steam-bath for 20 minutes. The amide (0.4 g., 82% yield) separated on chilling, and was recrystallized from ethanol. It melted at 220–220.5°. *Anal.* Calcd. for $C_{20}H_{22}O_7N_2$: C, 59.70; H, 5.51; N, 6.96; $-OCH_3$, 23.14. Found: C, 59.57; H, 5.34; N, 6.99; $-OCH_3$, 23.37.

The isopropyl ester was prepared by refluxing 8.5 g. of the free acid with 200 ml. of isopropyl alcohol and 1.5 ml. of concd. sulfuric acid for 27 hours. On standing at 0° for two days, 8.2 g. (88% yield) separated and was recrystallized from ethanol. It melted at 156.5–157.5°. *Anal.* Calcd. for $C_{23}H_{27}O_8N$: C, 62.02; H, 6.11; N, 3.14; $-OCH_3$, 27.84. Found: C, 62.28; H, 6.01; N, 3.38; $-OCH_3$, 27.61.

Cyclization of Methyl 3,4-Methylenedioxy-α-(3,4,5-trimethoxybenzamido)-hydrocinnamate (II).—One and six-tenths grams (0.004 mole) of the methyl ester II and 7 ml. of freshly distilled phosphorus oxychloride were heated in an oil-bath at 90–95° for 20 minutes, and the temperature then slowly raised to the refluxing temperature of 106° over a 40-minute period. The flask was chilled in an ice-bath and its contents poured into 100 ml. of ice-water. The mixture settled to the bottom as an oil which changed into a suspension of a solid upon vigorous stirring. On warming to room temperature, the solid changed to a pasty brown gum insoluble in the acid solution. This was the crude oxazole; the yellow supernatant liquid contained the substituted dihydroisoquinoline hydrochloride in solution.

The solution of the dihydroisoquinoline hydrochloride was extracted with ether to remove any neutral material, make alkaline with ammonium hydroxide and the dihydroisoquinoline extracted with ether. The ether extracts were washed thoroughly with water and the ether then evaporated off. The residual **methyl 3,4-dihydro-6,7-methylenedioxy-1-(3,4,5-trimethoxyphenyl)-3-isoquinolinecarboxylate** (I) was crystallized from aqueous alcohol after which it melted at 101–102°. *Anal.* Calcd. for $C_{21}H_{21}O_7N$: C, 63.13; H, 5.30; $-OCH_3$, 31.07. Found: C, 62.50; H, 5.55; $-OCH_3$, 30.99. The yield was about 3%.

The crude oxazole, **5-methoxy-4-piperonyl-2-(3,4,5-trimethoxyphenyl)-oxazole** (III) was recrystallized from aqueous alcohol, and the 0.55 g. (35% yield) obtained melted at 89–90°. Further recrystallization from aqueous alcohol raised the m.p. to 92–93°. *Anal.* Calcd. for $C_{21}H_{21}O_7N$: C, 63.13; H, 5.30; N, 3.50; $-OCH_3$, 31.07; mol. wt., 399. Found: C, 63.32; H, 5.34; N, 3.36; $-OCH_3$, 31.11; mol. wt., from f.p. depression in acetic acid, 359.

Using 225 ml. of toluene as a solvent, 25.5 g. of the substituted methyl hydrocinnamate (II) on treatment with 90 ml. of phosphorus oxychloride at the refluxing temperature gave 14 g. (55% yield) of the oxazole III, m.p. 84–85° before recrystallization. None of the dihydroisoquinoline was obtained.

The oxidation of the oxazole to trimethylgallamide involved treating 0.5 g. of the oxazole with 30 ml. of 0.5 *N* sulfuric acid and 0.1 g. of potassium permanganate in 20 ml. of water at 50 to 60° for half an hour. The solution was made alkaline with ammonia, extracted with ethyl acetate, and 0.1 g. of the gallamide, m.p. 176–179°, isolated on evaporation of the ethyl acetate. The material was identified by m.p., and by carbon–hydrogen, nitrogen and methoxyl analyses.

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