amorphous solid: mp 149–151 °C dec; IR (KBr) major bands at 3390, 3220, 2920 (br), 1720, 1645, 1535, and 800 (with shoulder at 830) cm^{-1}; EI and CI mass spectra are identical with that of **6**. Anal. Calcd for $C_8H_8Cl_{10}N_4O_3$ (mol wt 562.71): C, 17.08; H, 1.43; Cl^-, 6.03; N, 9.96. Found: C, 17.3; H, 1.7; Cl^-, 5.7; N, 9.7.

(2*S*,4*S*,6*R*)-2,6,7,9-Tetrahydro-2,4,6-tris(trichloromethyl)-8*H*-[1,3,5]triazino[1,2-*c*][1,3,5]oxadiazin-8-one (7). To a stirred mixture of 148.0 g (0.281 mol) of **6** in 2436 mL of dry carbon tetrachloride was added 93.0 g (0.782 mol) of thionyl chloride. The mixture was heated to reflux. After approximately 15 min, a clear solution was obtained. Heating with stirring was continued for 6 h, after which time the precipitate that had formed was removed by filtration. The filter cake was washed with water and dried to give 86.2 g (60.4%) of off-white solid: mp 245 °C dec; IR (KBr) major absorption bands at 3420, 3240, 3090, 2960, 2880 (br), 1690 (with shoulder at 1710), 1490, 850, and 830 cm^{-1}. Anal. Calcd for $C_8H_5Cl_9N_4O_2$ (mol wt 508.23): C, 18.91; H, 0.99; Cl, 62.78; N, 11.02. Found: C, 19.1; H, 1.0; Cl, 62.4; N, 11.2.

X-ray Structure Determination of 7. Compound **7** was recrystallized from *p*-dioxane, resulting in colorless prismatic crystals of $C_8H_5Cl_9N_4O_2$ (plus dioxane solvate). The crystals are orthorhombic: space group *Pccn*, a = 18.94 (3) Å, b = 30.798 (4) Å, c = 11.550 (2) Å, z = 8. A total of 5150 reflections were collected, of which 4413 were considered as statistically significant. Data collection was performed with Cu Kα radiation (λ = 1.541 84 Å) on an Enraf-Nonius CAD4 computer-controlled κ-axis diffractometer equipped with a graphite crystal incident beam monochromator. Data were collected to a maximum 2θ of 112.0°. The structure was solved by direct methods and has been refined anisotropically to give an R factor of 0.12. Hydrogen atoms were not included in the calculations. Two solvent molecules (dioxane) were located and refined. A difference Fourier map suggested the presence of an addition solvent molecule; however, attempts to locate and refine a third solvent molecule were unsuccessful.

Acknowledgment. We thank Dr. Carter Cook, University of Illinois, Urbana, IL, for providing field-desorption mass spectrometry service. The cooperation of the Molecular Structure Corp. in performing the X-ray crystallographic analysis is appreciated.

Registry No. 7, 81956-39-0; cyanoguanidine, 461-58-5; chloral hydrate, 302-17-0.

Supplementary Material Available: Complete X-ray data on compound **7** are available, including tables of fractional atomic coordinates for nonhydrogen atoms, thermal parameters, bond lengths, bond angles, intermolecular contacts, mean planes, and torsion angles (10 pages). Ordering information is given on any current masthead page.

Reaction of Isoquinoline Enamides with Electrophiles

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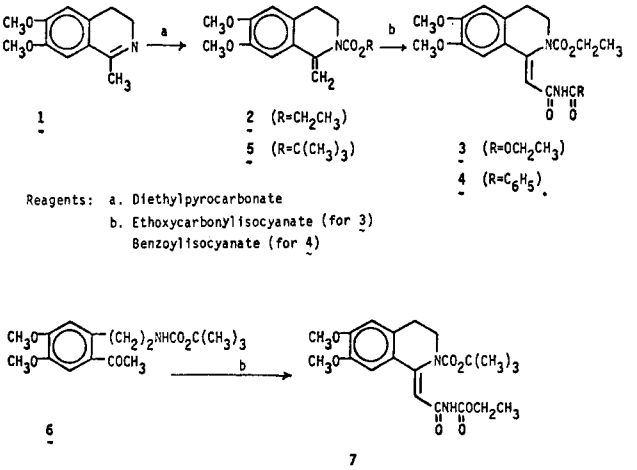
The reaction of isoquinoline enamides with acyl isocyanates yields vinylogous amides through carbon–carbon bond formation between the β carbon of the enamide and the isocyanate carbonyl. Enamide formation occurs between 1-benzyl-3,4-dihydroisoquinolines and phenylacetic anhydride. However, a *N*,*C*-bis(phenylacetyl) derivative is formed with phenylacetyl chloride. The reaction occurs through preferential reaction of phenylketene with the enamine tautomer of the 1-benzyl-3,4-dihydroisoquinoline at the carbon terminus, followed by *N*-acylation. The equilibrium is demonstrated by deuterium NMR.

While the photochemistry of enamides has been well studied and has led to a variety of preparatively useful reactions,[1] the thermal reactions of simple enamides have been relatively neglected. Brossi has described the facile hydration of isoquinoline enamides to form [(acetylphenyl)ethyl]acetamides,[2] and Ninomiya has successfully brominated the β carbon of an enamide using *N*-bromosuccinimide.[3] Barton has shown that the β carbon of enamides is successfully acetoxylated using lead tetraacetate,[4] while other enamides undergo rearrangements with thallium(III).[5] In this report we describe the reactions of enamides with strongly electrophilic acyl isocyanates and their putative reaction with phenylketene.

Scheme I



The reaction between 3,4-dihydro-6,7-dimethoxy-1-methylisoquinoline (**1**) and diethyl pyrocarbonate gave an excellent yield of the enamide **2** as the only product. Enamide **2** was treated with ethoxycarbonyl isocyanate in an inert solvent, and a product rapidly crystallized in 56%

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(4) (a) Boar, R. B.; McGhie, J. F.; Robinson, M.; Barton, D. H. R.; Horwell, D. C.; Stick, R. V. *J. Chem. Soc., Perkin Trans 1* **1975**, 1237. (b) Boar, R. B.; McGhie, J. F.; Robinson, M.; Barton, D. H. R. *Ibid.* **1975**, 1242.

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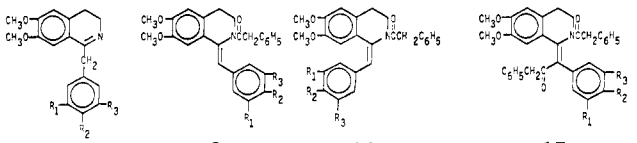
0022-3263/82/1947-3049$01.25/0

Chart I



8, $R_1 = OCH_3$; $R_2 = OCH_3$; $R_3 = H$
11, $R_1 = R_2 = OCH_2O$; $R_3 = H$
14, $R_1 = OCH_3$; $R_2 = OCH_3$; $R_3 = OCH_3$

9	10	17
12	13	18
15	16	19

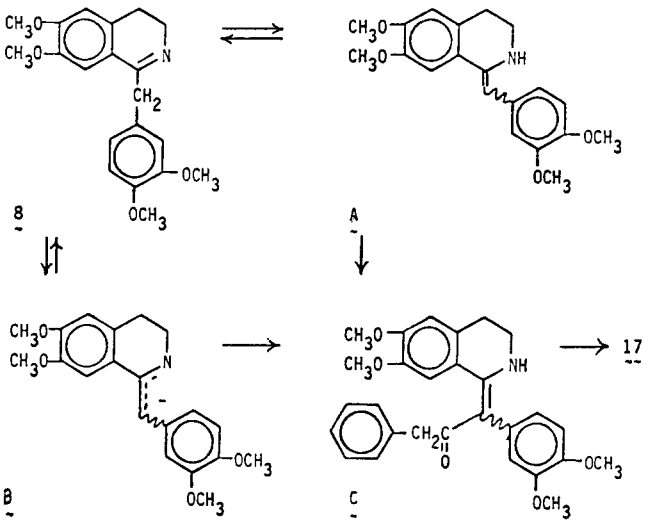
yield. The elemental analysis and spectral properties of the adduct **3** indicated the structure. In particular the NMR spectrum of **3** indicated the position of bonding when only one of the exocyclic methylene protons in **2** was still present. The absence of a significantly deshielded aromatic proton in **3** indicated the usual *Z* stereochemistry.[6] The probable mechanism is indicated in Scheme I, where the strongly polarized acyl isocyanate induces addition by the carbon–carbon double bond of the enamide to form the acylimminium zwitterion. Intramolecular proton abstraction by the ambident anion completes formation of the product. There were no observations of either [2 + 2] or [4 + 2] cycloadditions with this reagent as is commonly observed in other cases.[7] A similar reaction of enamide **2** with benzoyl isocyanate yielded the adduct **4** in 72% yield.

When the dihydroisoquinoline **1** was treated with di-*tert*-butyl pyrocarbonate in toluene, the products of enamide formation, **5**, and subsequent hydrolysis **6**, were obtained.[2,8] Treating [(acetylphenyl)ethyl]urethan **6** with excess ethoxycarbonyl isocyanate led to the isolation of the *tert*-butyl ester analogue **7** of adduct **3** in 59% yield. The isolation of compound **7** indicates that the isocyanate can act as a dehydrating agent to form the enamide **5**, which in turn undergoes addition with a second mole of isocyanate to form the observed product **7**.

Reaction of dihydropapaverine **8** with phenylacetic anhydride in pyridine led to an *E*/*Z* mixture of enamide isomers. Separation was effected by a combination of crystallization and flash chromatography.[9] Structural characterization was done by UV and NMR studies as previously described,[10-12] as well as by iodine-catalyzed isomerization of the *E* isomer to its more stable *Z* isomer. The compounds prepared are collected in Chart I.

If dihydropapaverine **8** is treated with phenylacetyl chloride in place of phenylacetic anhydride, a new compound, **17**, is now isolated as the major product (Scheme II). Its elemental analysis and spectral properties indicated that **17** was the result of the addition of two molecules of phenylketene to dihydroisoquinoline **8**. The gross structure of **17** was indicated by ^{13}C NMR to be the result of addition of the second mole of phenylketene to the benzylidene carbon of enamide **9**. In particular, the presence and positions of the four triplets and fifteen doublets in the off-resonance spectrum of **17** readily distinguished it from the plausible alternatives where the

Scheme II



second mole of phenylketene condensed with the active methylene of the phenylacetyl group in enamide **9**.

The stereochemistry about the double bond in **17** was determined by a combination of 60- and 270-MHz proton magnetic resonance. The 60-MHz spectrum of **17** was not particularly informative except to show a strongly shielded methoxyl methyl group similar to that observed with enamide **10**, which possesses the *E* configuration, and a strongly deshielded ethylene-bridge hydrogen in a position close to that observed in the *Z*-enamide **9**. However the isoquinoline 7-methoxy methyl group was not being shielded because the bis-adducts **18** and **19**, prepared from the methylenedioxy- and trimethoxydihydroisoquinolines **11** and **14** and phenylacetyl chloride, did not show any shielded methoxyl groups and two shielded methoxyls as a single resonance, respectively. This proved that it was the meta-methoxyl group in the isoquinoline benzylidene ring that was being shielded. Inspection of a Dreiding model of bis-adduct **19** indicates that the aromatic ring of the phenylacetyl group attached to carbon should shield the meta-methoxy methyls on the benzylidene ring and the carbonyl group should deshield the 8-hydrogen on the isoquinoline ring, which is also observed. It is unlikely that the aromatic ring of the nitrogen-substituted phenylacetyl group is responsible for the observed shielding since it is not observed in the *Z*-enamide **9**. However, the axial 4-hydrogen of the isoquinoline ring in **19** is deshielded analogously to enamide **9** and the methylene protons of the *N*-phenylacetyl substituent in **19** appear as a shielded AB quartet, again analogously to enamide **9**. In summary, the shielding and deshielding effects, as well as the ethylene-bridge splitting pattern, are only consistent with the *E* stereochemistry in the bis-adducts **17–19**.

The similarity of structure of the bis-adduct **17** to that derived from the isocyanate enamide adducts of type **3** indicated that a like mechanism for their formation could be operative. In this mechanism, phenylketene would add to the initially formed enamide, followed by prototropic rearrangement to generate **17**. However, when either enamide **9** or **10** was treated with phenylacetyl chloride, no bis adduct was obtained and the enamides were recovered in high yield. The mechanism outlined in Scheme II explains the formation of the bis adducts. Since the enamides are not involved in bis adduct formation, it is obvious that acylation occurs on carbon first whether through the intermediacy of enamine A in equilibrium with the imine in **8** or through an enamine anion B formed by deprotonation of **8** to form C. The unobserved interme-

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diate C then undergoes acylation on nitrogen.[13]

The facile benzylic oxidation of 1-benzyldihydroisoquinolines is well-known,[14] as is the benzylic methylene deuterium exchange.[15] The former has been attributed to an electron-exchange mechanism between singlet oxygen and an equilibrium concentration of the enamine form of the dihydroisoquinoline.[16] To the best of our knowledge, there have been no direct investigations of these equilibria among the 1-benzyldihydroisoquinolines although ultraviolet spectral evidence indicates that it exists.[16] The *N*-methylimine of desoxybenzoin, which may serve as a model system for the dihydroisoquinolines, undergoes imine–enamine tautomerism as a function of solvent polarity.[17]

The NMR proton spectrum of dihydropapaverine 8 was investigated with the same solvent composition used in the acylation experiments to look for the presence of the imine–enamine equilibrium. However the complexity of the spectrum precluded any meaningful conclusions. So that the problem could be simplified, the benzylic protons in 8 were exchanged for deuterium,[15] and the deuterium NMR spectrum was recorded in chloroform–pyridine (5:2 v/v). The benzylic deuterons appeared as a broad singlet at δ 4.15 while a second signal, which we ascribe to the vinylic deuteron of the enamine form A (Scheme II), appeared as a broad singlet at δ 5.4.[18] Integration indicated a ratio of 78:22 for the imine–enamine equilibrium. This is good evidence for the equilibrium, and indicates that A probably has *E* stereochemistry.[18,20] This point is being investigated in these laboratories and will be the subject of a future communication. It appears therefore that the bis-adducts **17–19** are formed by initial reaction of the enamine form A with phenylketene to generate the vinylogous amide C, which subsequently undergoes *N*-acylation.

Although the predominant reaction of 1-substituted dihydroisoquinolines with acylating agents is enamide formation,[1] there are scattered reports in the literature indicating bond formation at the α carbon instead. Russian workers reported that the reaction of 1-substituted dihydroisoquinolines with α,β-unsaturated esters, nitriles, and ketones gave exclusive 1,4-addition at the α carbon.[21] Subsequently, several other reports have appeared illustrating the same phenomenon with 1-substituted dihydroisoquinolines and dihydro-β-carbolines.[22] Although none of these reports have involved reaction with a ketene as in this study, all seem to have given cleanly the carbon-bonded product. In contrast, the reaction of dihydroisoquinoline **11** with phenylacetyl chloride gave besides the major product, the bis-adduct **18**, the *Z*-enamide **12**, which was observed as a byproduct by NMR and LPLC in a ratio of 72:28, indicating competing *N*- vs. *C*-acylation. The reason for competing *C*-acylation with phenylketene may be the lessened steric bulk of the phenylketene vs. the phenylacetyl pyridinium intermediate formed from the anhydride and pyridine.

Experimental Section

General. Melting points were taken on a Thomas-Hoover Unimelt capillary apparatus and are not corrected. Infrared spectra were run in KBr, and ultraviolet and visible spectra were determined in methanol. A Varian Associates T-60, A-60, or FT-80 NMR spectrometer or a Bruker 270-MHz spectrometer was used to record the spectra of all the compounds in deuteriochloroform with tetramethylsilane as an internal standard. The NMR results are reported in chemical shifts (δ), followed by the signal shape: s, singlet; d, doublet; t, triplet; m, multiplet. The multiplicity is followed by the coupling constant where applicable and then the integrated signal intensity. The deuterium spectra were obtained at 55.27 MHz with a 360-MHz Nicolet NMR, either by using $CDCl_3$ as an external reference or by diluting the pyridine–chloroform (2:5) solutions of the dihydroisoquinolines with deuteriochloroform for an internal standard. Microanalysis were determined by the Searle Laboratories Microanalyical Department under the direction of E. Zielinski.

Formation of Enamide 2 from Dihydroisoquinoline 1 and Diethyl Pyrocarbonate. A solution of 7.8 g of 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline (1) in 200 mL of toluene was refluxed under argon and dried with use of a Dean–Stark Trap.[23] When the mixture cooled to approximately 50 °C, 10 mL of diethyl pyrocarbonate (Fluka) was introduced, which was followed by immediate gas evolution. After approximately 10 min, the majority of the solvent was removed, and after dilution with ether and petroleum ether, crystallization was induced by scratching to yield 8.9 g (32.1 mmol, 85%) of enamide **2**; mp 89–91 °C; IR 1705, 1615, 1515 cm^{-1}; UV 277 (min, ϵ 6500), 263 (11 500), 286 (min, 4000), 302 (6000), 312 nm (sh, 4500); NMR δ 7.13 (s, 1 H), 6.58 (s, J = 1 Hz), 5.53 (s, 1 H), 5.38 (s, 1 H), 4.23 (q, 2 H), 3.93 (t, 2 H), 3.88 (s, 3 H), 3.85 (s, 3 H), 2.8 (t, 2 H), 1.3 (t, 3 H).

Anal. Calcd for $C_{15}H_{19}NO_3$: C, 64.96; H, 6.91; N, 5.05. Found: C, 65.03; H, 6.86; N, 5.08.

Reaction of Enamide 2 with Ethoxycarbonyl Isocyanate. A solution of enamide **2** (1.00 g, 4.08 mmol) in 10 mL of toluene, under argon, was stirred magnetically and 1 mL of ethoxycarbonyl isocyanate added. Within a short time a precipitate had formed. After 4 h, ether was added, and the precipitate was collected and recrystallized from methylene chloride–ethyl acetate–petroleum ether to yield 900 mg (2.30 mmol (56%)) of adduct **3**; mp 155–158 °C; IR 3200 (br), 1770, 1720, 1600, 1520 cm^{-1}; UV 225 (ϵ 18 500), 245 (11 500), 263 (min, 4000), 293 (sh, 10 000), 336 nm (17 500); NMR δ 7.77 (s, 1 H, NH, exchanges with D_2O), 7.25 (s, 1 H), 7.15 (s, 1 H), 6.62 (s, 1 H), 4.23 (q, 2 H), 4.17 (q, 2 H), 3.93 (s, 3 H), 3.90 (t, 2 H), 3.88 (s, 3 H), 2.87 (t, 2 H), 1.3 (t, 3 H), 1.23 (t, 3 H).

Anal. Calcd for $C_{19}H_{24}N_2O_7$: C, 58.15; H, 6.17; N, 7.14. Found: C, 57.93; H, 6.23; N, 7.02.

Reaction of Enamide 2 with Benzoyl Isocyanate. A solution of 1.00 g (4.08 mmol) of **2** in 50 mL of benzene was dried by refluxing with a Dean–Stark trap. After the mixture cooled, 1.5 mL of benzoyl isocyanate was added. TLC on silica (1:1 ethyl acetate–toluene) indicated the reaction was complete almost immediately after mixing. Nevertheless the reaction mixture was stirred for 16 h when aqueous citric acid was added to decompose excess isocyanate. After separation, drying of the organic layer,

(13) We have observed acylation on nitrogen in similar cases: Lenz, G. R., unpublished observations.

(14) Buck, J. S.; Haworth, R. D.; Perkin, W. H., Jr. *J. Chem. Soc.* **1924**, 2176.

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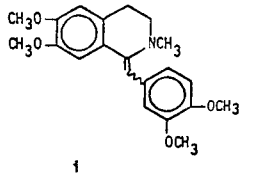
(18) In a 5:2 deuteriochloroform–deuteropyridine solvent mixture, the vinylic stilbene proton of the predominant *Z* isomer of the *N*-methylenamine tautomer i of dihydropapaverine appears at δ 6.02 while the *E*-isomer proton appears at δ 5.40.[19]



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(20) Albrecht, H. *Tetrahedron* **1970**, *26*, 4783.

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(22) (a) Danielli, B.; Lesma, G.; Palmisano, G. *J. Chem. Soc., Chem. Commun.* **1980**, 109. (b) *Ibid.* **1980**, 860. (c) Atta-ur-Rahman *J. Chem. Soc.; Perkin Trans. 1* **1972**, 731.

(23) (a) Spath, E.; Polgar, N. *Monatsh. Chem.* **1929**, *51*, 198. (b) Walker, G. N. *J. Am. Chem. Soc.* **1954**, *76*, 3999.

and evaporation, the residue was recrystallized from ethyl acetate to yield 1.30 g of adduct **4** (2.94 mmol (72%)): mp 163–167 °C; IR 3300, 1710, 1685, 1670 1600, 1515 cm^{-1}; UV 243 (ϵ 21 700), 276 (min, 6600), 345 nm (16 900); NMR δ 8.68 (s, 1 H, NH, exchanges with D_2O), 7.87 (m, 2 H), 7.3–7.6 (m, 5 H), 6.58 (s, 1 H), 4.17 (q, 2 H), 4.00 (t, 2 H), 3.96 (s, 3 H), 3.90 (s, 3 H), 2.87 (t, 2 H), 1.20 (t, 3 H).

Anal. Calcd for $C_{23}H_{24}N_2O_6 \cdot H_2O$: C, 62.43; H, 5.92; N, 6.33. Found: C, 62.72; H, 5.62; N, 6.23.

Preparation and Hydrolysis of Enamide 5. To a solution of 15.0 g (73 mmol) of 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline (**1**) in 100 mL of dry toluene at 40 °C, 16 g of di-*tert*-butyl pyrocarbonate (Fluka) was added. The solution cooled to room temperature and stirred overnight. The solvent was removed and the oil dissolved in ether and filtered. The residue was crystallized from ethyl acetate–petroleum ether to yield the hydrolyzed enamide **6** (12.0 g, 37.1 mmol (51%)): mp 111.5–113 °C; IR 3385 (sharp), 1690, 1610, 1573, 1530, 1520 cm^{-1}; UV 230 (ϵ 21 600), 248 (min, 2650), 273 (8410), 292 (min, 4800), 305 nm (5100); NMR δ 7.20 (s, 1 H), 6.72 (s, 1 H), 4.95 (br s, 1 H, NH, exchanges with D_2O), 3.92 (s, 6 H), 3.36 (m, 2 H), 3.01 (m, 2 H), 2.56 (s, 3 H), 1.42 (s, 9 H).

Anal. Calcd for $C_{17}H_{25}NO_5$: C, 63.14; H, 7.79; N, 4.33. Found: C, 63.00; H, 7.83; N, 4.34.

Reaction of the Hydrolyzed Enamide 6 with Ethoxycarbonyl Isocyanate. To a suspension of 1.00 g (3.09 mmol) of **6** in 10 mL of toluene was added 0.75 mL of ethoxycarbonyl isocyanate. After the mixture stirred for 3 h, the solvent was evaporated and the residue crystallized from methanol to yield 550 mg of adduct **7**. A further 230 mg (total 780 mg, 1.82 mmol (59%)) was obtained by flash chromatography using 1:1 ethyl accetate–methylene chloride. Data for adduct **7** is as follows: mp 170–174 °C; IR 3340, 1770, 1705, 1685, 1630 (w), 1605, 1520 cm^{-1}; UV 245 (12 900), 266 (min, 4400), 295 (sh, 10 300), 335 nm (17 800); NMR δ 7.71 (br s, 1 H, NH, exchanges with D_2O), 7.17 (s, 1 H), 6.93 (s, 1 H), 6.56 (s, 1 H), 4.19 (q, 2 H), ~2.90 (t, 2 H, resonates under methoxyl methyl protons), 3.92 (s, 3 H), 3.88 (s, 3 H), 2.82 (t, 2 H), 1.44 (s, 9 H), 1.30 (t, 3 H).

Anal. Calcd for $C_{21}H_{28}N_2O_7 \cdot 0.5H_2O$: C, 58.72; H, 6.81; N, 6.52. Found: C, 58.83; H, 6.60; N, 6.64.

Reaction of Dihydropapaverine 8 with Phenylacetic Anhydride. A solution of phenylacetic anhydride in toluene was prepared from 6.0 g of phenylacetic acid (44 mmol) and 2.44 g of 1-(*N*,*N*-diethylamino)propyne in 50 mL of toluene.[24] To this solution was added 3.15 g of dihydropapaverine **8** (9.24 mmol) in 50 mL of chloroform and 10 mL of pyridine.[14,25] The solution was stirred for 16 h under nitrogen and then washed three times with water. The organic layer was dried with sodium sulfate and evaporated. Crystallization of the residue from ethyl acetate containing a little ether yielded 1.75 g (3.81 mMol (41%)) of the *Z*-enamide **9**: mp 189–192 °C; IR 1655, 1635, 1615, 1520 cm^{-1}; UV 225 (ϵ 30 000), 264 (min, 8500), 302 (sh, 17 500), 331 nm (29 000); NMR δ 6.7–7.2 (m, 9 H), 6.63 (s, 1 H), 6.51 (s, 1 H), 5.02 (m, 1 H), 3.92 (s, 3 H), 3.89 (s, 3 H), 3.87 (s, 6 H), 3.58 (d, AB q, J = 14 Hz, 1 H), 3.27 (d, AB q, J = 14 Hz, 1 H), 2.5–3.25 (m, 3 H).

Anal. Calcd for $C_{28}H_{29}NO_5$: C, 73.18; H, 6.36; N, 3.05. Found: C, 72.73; H, 6.38; N, 2.95.

The mother liquor from the crystallization of the *Z*-isomer **9** was evaporated and the residue flash chromatographed with use of 1:9 ethyl acetate–methylene chloride to give 1.60 g (3.49 mmol (38%)) of the *E*-enamide **10**: mp 121.5–123 °C; IR 1655, 1635, 1605, 1510 cm^{-1}; UV 220 (ϵ 27 000), 265 (min, 8500), 296 (13 500), 315 nm (13 000); NMR δ 7.2 (m, 6 H), 6.65–6.80 (m, 2 H), 6.57 (m, 2 H), 6.34 (s, 1 H), 4.00 (t, 2 H), 3.94 (s, 2 H), 3.84 (s, 6 H), 3.70 (s, 3 H), 3.42 (s, 3 H), 2.88 (t, 2 H).

Anal. Calcd for $C_{28}H_{29}NO_5$: C, 73.18; H, 6.36; N, 3.05. Found: C, 73.07; H, 6.47; N, 3.04.

Isomerization of the *E*-Enamide 10 to Its *Z*-Isomer 9. Iodine crystals (30 mg) were added to a solution of 300 mg of the *E*-enamide **10** in 30 mL of dry benzene, and the solution was refluxed overnight. The iodine was reduced with dilute sodium bisulfite solution, and the organics were dried with sodium sulfate. Evaporation and crystallization of the residue from ether yielded 260 mg of the *E*-isomer **9**.

Condensation of 1-(3′,4′-Methylenedioxybenzyl)-3,4-dihydro-6,7-dimethoxyisoquinoline (11) with Phenylacetic Anhydride. Phenylacetic anhydride was prepared by using the enamine condensation method as described above and isolated as a crystalline solid by using flash chromatography (3:97 ethyl acetate–methylene chloride). The dihydroisoquinoline **11** (2.28 g, 7.00 mmol)[26] was dissolved in 10 mL of chloroform and placed under nitrogen. To this stirred solution was added 5 mL of pyridine followed by 5.0 g of phenylacetic anhydride. After stirring overnight, the solution was diluted with chloroform and washed three times with water. The organic layer was dried with sodium sulfate and evaporated. The residue was flash chromatographed by using 1:9 ethyl acetate–methylene chloride. The *Z*-enamide **12** (695 mg, 1.57 mmol (23%)) eluted first; mp 193.5–5.196 °C; IR 1645, 1605, 1515 cm^{-1}; UV 220 (ϵ 31 000), 262 (min, 7700), 297 (sh, 14 000), 333 nm (26 000); NMR δ 6.7–7.1 (m, 9 H), 6.62 (s, 1 H), 6.51 (s, 1 H), 4.96 (s, 2 H), 4.97 (m, 1 H), 3.89 (s, 3 H), 3.85 (s, 3 H), 3.65 (*AB*, J = 15 Hz, 1 H), 3.35 (*AB*, J = 15 Hz, 1 H), 2.5–3.25 (m, 3 H).

Anal. Calcd for $C_{27}H_{25}NO_5$: C, 73.12; H, 5.68; N, 3.16. Found: C, 72.79; H, 5.67; N, 3.10.

The *E*-enamide **13** eluted next (1.46 g, 3.30 mmol (47%)) and was isolated as a noncrystalline oil. After approximately 10 days the oil nucleated, and seed crystals thus obtained were used to crystallize the remainder from ether. **13** crystallized slowly over a period of several hours; mp 111.5–114 °C; IR 1640, 1610, 1510 cm^{-1}; UV 220 (ϵ 32 300), 262 (min, 8400), 297 (13 600), 317 nm (13 200); NMR δ 7.20 (s, 5 H), 6.5–6.75 (m, 5 H), 6.34 (s, 1 H), 5.90 (s, 2 H), 3.99 (t, 2 H), 3.93 (s, 2 H), 3.85 (s, 3 H), 3.47 (s, 3 H), 2.87 (t, 2 H).

Anal. Calcd for $C_{27}H_{25}NO_5$: C, 73.12; H, 5.68; N, 3.16. Found: C, 72.92; H, 5.68; N, 3.26.

Reaction of 1-(3′,4′,5′-Trimethoxybenzyl)-3,4-dihydro-6,7-dimethoxyisoquinoline (14) with Phenylacetic Anhydride. Phenylacetic anhydride (2.00 g) and dihydroisoquinoline **14**[27] (0.98 g, 2.71 mmol) were condensed analogously to the method for methylenedioxydihydroisoquinoline **11**. Workup and flash chromatography using 5:95 ethyl acetate–methylene chloride yielded 0.45 g (0.92 mmol (34%)) of the *Z*-enamide **15**: 150–154 °C; IR 1660, 1640, 1610, 1580, 1520 cm^{-1}; UV 330 nm (ϵ 25 000); NMR δ 6.8–7.2 (m, 6.8–7.2 (m, 6 H), 6.77 (s, 2 H), 6.62 (s, 1 H), 6.53 (s, 1 H), 5.03 (m, 1 H), 3.93 (s, 3 H), 3.87 (s, 6 H), 3.84 (s, 6 H), 3.57 (AB, J = 16 Hz, 1 H), 3.31 (AB, J = 16 Hz, 1 H), 2.5–3.7 (m, 3 H).

Anal. Calcd for $C_{29}H_{31}NO_6$: C, 71.15; H, 6.38; N, 2.86. Found: C, 71.46; H, 6.42; N, 2.81.

Continued elution gave 0.72 g (1.47 mmol (54%)) of the *E*-isomer **16** as a noncrystallizable oil: IR ($CHCl_3$) 1650, 1630, 1605, 1510 cm^{-1}; UV 292 (ϵ 9900), 312 nm (10 500); NMR δ 7.25 (m, 5 H), 6.62 (s, 1 H), 6.58 (s, 1 H), 6.40 (s, 2 H), 6.34 (s, 1 H), 3.97 (s, 2 H), 3.85 (s, 3 H), 3.82 (s, 3 H), 3.72 (s, 6 H), 3.44 (s, 3 H), 2.38 (t, 2 H). The remaining two protons of the ethylene bridge are under the methoxyl resonances by integration. Isomerization using the iodine method described above converted *E*-**16** into its *Z*-isomer **15**.

***N*,*C*-Diacylation of Dihydropapaverine 8 with Phenylacetyl Chloride.** A solution of 14 g (41 mmol) of dihydropapaverine **8** in 100 mL of methylene chloride and 50 mL of pyridine was placed under nitrogen and cooled in an ice bath. To this rapidly stirred solution was added 20 mL of commercial phenylacetyl chloride (Aldrich or Fluka) in 25 mL of methylene chloride. The mixture warmed to room temperature overnight and was diluted with 250 mL of methylene chloride and washed three times with water. The organic layer was dried with sodium sulfate and evaporated. The residue was chromatographed with 1:9 ethyl acetate–methyl acetate. Combination of the appropriate fractions gave 9.0 g (16 mmol (40%)) of the bis-adduct **17**: mp 180–182 °C (ethyl acetate–methylene chloride); IR 1655, 1615, 1520 cm^{-1}; UV 231 (ϵ 28 000), 281 nm (ϵ 10 800); NMR δ 7.38 (s, 5 H), 7.25 (s, 5 H), 6.82 (s, 1 H), 6.60 (d, J = 8 Hz, 1 H), 6.57 (s,

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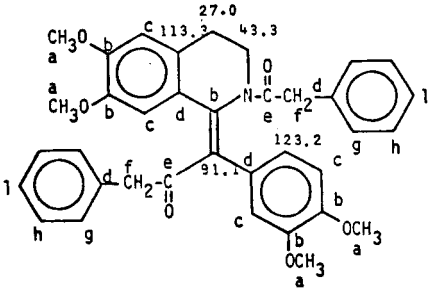
1 H), 6.30 (dd, J = 8, 1.5 Hz, 1 H), 6.03 (d, J = 1.5 Hz, 1 H), 4.02 (m, 1 H), 3.89 (s, 3 H), 3.87 (s, 3 H), 3.80 (s, 3 H), 3.70 (AB, $J \approx 15$ Hz, 1 H), 3.59 (s, 3 H), 3.4–3.6 (m, 1 H), 3.44 (AB, $J \approx 15$ Hz, 1 H), 2.4–2.9 (m, 3 H), 1.8–2.25 (m, 1 H). CMR: ^{13}C NMR spectroscopy data are shown in I.



I

carbon atom(s)	δ
a	55.7, 55.8, 56.0, 56.1
b	148.2, 148.5, 148.9, 149.6
c	109.5, 110.7, 111.1, 114.0
d	133.8, 136.5
e	160.2, 162.1
f	37.9, 38.0
g	129.6, 131.4
h	127.0, 127.7

Anal. Calcd for $C_{36}H_{35}NO_6$: C, 74.85; H, 6.11; N, 2.42. Found: C, 74.75; H, 6.17; N, 2.52.

Reaction of the *Z*-Enamide 9 with Phenylketene. To a solution of 1. g of *Z*-enamide **9** in 5 mL of chloroform and 5 mL of pyridine, 3 mL of phenylacetyl chloride in 3 mL of chloroform was added over 0.5 h. The resultant reaction mixture was diluted with 50 mL of chloroform and washed with water and dilute hydrochloric acid. The organic layer was dried with sodium sulfate and evaporated to an oil, which was diluted with ether and a little ethyl acetate and scratched to return 1.0 g of *Z*-enamide **9** by TLC and NMR.

Reaction of the *E*-Enamide 10 with Phenylketene. To a solution of 0.5 g of *E*-enamide **10** in 2.5 mL of chloroform and 2.5 mL of pyridine, 1.5 mL of phenylacetyl chloride in 2.5 mL of chloroform was added during 0.5 h. After the solution was stirred overnight, 45 mL of chloroform was added and the resultant solution washed with water and extracted with dilute hydrochloric acid. After being dried with sodium sulfate, the solvent was removed and the oily residue crystallized from ether to return 0.30 g of the *E*-enamide **10**. The mother liquors from the crystallization were chromatographed with 5:95 ethyl acetate–methylene chloride to yield 0.13 g of *E*-enamide **10** contaminated with a little of its *Z*-isomer **9**. Comparisons were made by TLC and NMR.

***N,C*-Diacylation of 1-(3′,4′-Methylenedioxybenzyl)-3,4-dihydro-6,7-dimethoxyisoquinoline (11) with Phenylketene.** To a solution of 4.5 g (13.8 mmol) of dihydroisoquinoline **11** in 20 mL of methylene chloride and 10 mL of pyridine was added, during 0.5 h, 7 mL of phenylacetyl chloride in 10 mL of methylene chloride. The solution was diluted with 100 mL of methylene chloride, washed with water, and extracted with dilute hydrochloric acid. After evaporation, the residue was flash chromatographed with 1:9 ethyl acetate–methylene chloride, and the appropriate fractions were combined and crystallized from ether and a little ethyl acetate and finally from methanol to yield 3.7 g (6.60 mmol (48%)) of bis-adduct **18**: mp 157–158.5 °C; IR 1647, 1610, 1520 cm^{-1}; UV 232 (ε 27 700), 261 (min, 5800), 284 nm (10 700); NMR δ 7.37 (s, 5 H), 7.23 (s, 5 H), 6.72 (s, 1 H), 6.51 (d, J = 8 Hz, 1 H), 6.48 (d, J = 1.5 Hz, 1 H), 6.12 (dd, J = 8, 1.5 Hz, 1 H), 6.08 (s, 1 H), 5.82 (s, 2 H), 4.18 (m, 1 H), 3.86 (s, 3 H), 3.83 (s, 3 H), 3.63 (AB, J = 15 Hz, 1 H), 3.55 (m, 1 H), 3.43 (AB, J = 15 Hz, 1 H), 2.80 (m, 3 H), 2.0–2.5 (m, 1 H).

Anal. Calcd for $C_{35}H_{31}NO_6$: C, 74.85; H, 5.56; N, 2.49. Found: C, 74.67; H, 5.56; N, 2.48.

***N,C*-Diacylation of 1-(3′,4′,5′-Trimethoxybenzyl)-3,4-dihydro-6,7-dimethoxyisoquinoline (14) with Phenylketene.** To a solution of 3.0 g (7.8 mmol) of dihydroisoquinoline **14** in 35 mL of chloroform and 10 mL of pyridine under nitrogen, 6 mL of phenylacetyl chloride in 20 mL of chloroform was added through an addition funnel. After stirring at room temperature for 18 h, the reaction mixture was diluted with 100 mL of chloroform and then washed with water and extracted with dilute hydrochloric acid. After being dried with sodium sulfate and evaporation, the residue was subjected to low-pressure liquid chromatography using Woelm silica and eluting with 1:1 ethyl accetate–toluene. Combination of the appropriate fractions gave 2.20 g (3.6 mmol (46%)) of bis-adduct **19** from methanol: mp 168–171 °C (methylene chloride–ethanol); IR 1650, 1590, 1520, 1510 cm^{-1}; UV 232 (ε 27 500), 262 (min, 5500), 280 nm (9000); NMR δ 7.38 (s, 5 H), 7.23 (s, 5 H), 6.83 (s, 1 H), 6.48 (s, 1 H), 5.87 (s, 2 H), 4.05 (m, 1 H), 3.88 (s, 3 H); 3.85 (s, 3 H), 3.58 (s, 6 H), ~3.6 (2 H), 2.70 (m, 3 H), 2.05 (m, 1 H).

Anal. Calcd for $C_{37}H_{37}NO_7$: C, 73.13; H, 6.14; N, 2.30. Found: C, 72.88; H, 6.09; N, 2.27.

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