6633), from the Pasteur Institue; and *Candida albicans*, grown by the same Institute (Mycology Department).

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Registry No. 4, 10350-10-4; **5a**, 86129-62-6; **5b**, 51146-04-4; **6**, 86129-63-7; **7a**, 86129-64-8; **8**, 86129-65-9; **9**, 86129-66-0; **11a**, 86129-67-1; **11b**, 86129-68-2; **11c**, 86129-69-3; **12**, 70271-80-6; **13**, 18858-06-5; **14b**, 86129-71-7; **15**, 86129-71-7; **16a**, 86129-72-8; **16b**, 86129-73-9; **17a**, 86129-74-0; **17b**, 86129-80-8; **18**, 86129-75-1; **19**, 86129-76-2; **20**, 86129-77-3; **21**, 86129-78-4; **22**, 86129-79-5; thiophenol, 108-98-5; 2-(diethylamino)ethanamine, 100-36-7; 3-(diethylamino)propanamine, 104-78-9; 3-(diethylamino)-2-hydroxypropanamine, 6322-01-6; aniline, 62-53-3.

Synthesis, Evaluation of Chemical Reactivity, and Murine Antineoplastic Activity of 2-Hydroxy-5-(3,4-dichlorophenyl)-6,7-bis(hydroxymethyl)-2,3-dihydro-1*H*-pyrrolizine Bis(2-propylcarbamate) and 2-Acyloxy Derivatives as Potential Water-Soluble Prodrugs[1]

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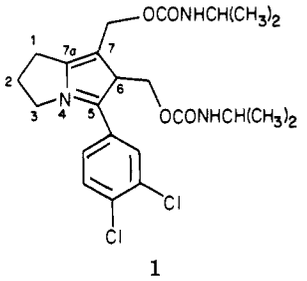
2-Hydroxy-5-(3,4-dichlorophenyl)-6,7-bis(hydroxymethyl)-2,3-dihydro-1*H*-pyrrolizine bis(2-propylcarbamate) (11) was prepared in a multistep synthesis. The 2-hydroxy group was used to prepare ester prodrugs 14 and 15, and the antineoplastic activities of 11, 14, and **15a** were compared to 1 (the 2-deoxy analogue of 11) in murine P388 lymphocytic leukemia and B16 melanocarcinoma. The alcohol 11 showed comparable activity to 1, while 14 was less active and **15a** showed very low activity. The hydrolytic rates of 1, 11, 14, **15a**, and **15b** were compared, and it was found that the two carbamate moieties were much more susceptible toward hydrolysis than the C-2 esters. The salts **15a** and **15b** exhibited good water solubility, 3.0×10^{-2} and 3.88×10^{-2} M, respectively.

In a series of recent publications we have described the design, synthesis, and biological activity of a new class of antitumor agents which we refer to as acylated vinylogous carbinolamines.[2] The continuing antitumor evaluation of selected agents in this class has resulted in the emergence of several compounds that exhibit outstanding activity against a broad spectrum of experimental murine neoplasias and human tumor xenografts in nude mice.[3,4] The pyrrolizine bis(carbamate) 1 is one such compound and is one of the members of this class that has been selected for more extensive preclinical studies.



1

One potential difficulty with 1 is the exhibited lack of any significant water solubility. Thus, the development of water-soluble compounds in this class has emerged as an important goal, and several approaches to this problem are being pursued simultaneously in our laboratories. One approach involves the development of water-soluble prodrugs, in which the hydrophilic moiety can be separated from the parent drug in vivo. This report will describe an approach to a water-soluble prodrug.

The first step in the design of water-soluble analogues of 1 is to determine where changes in the parent compound can be made. The parent compound can be subdivided into four parts: these are the heteroaromatic nucleus, the C-5 aryl moiety, the 6,7-bis[(carbamoyloxy)methyl] groups, and the aliphatic ring (C-1, C-2, and C-3). We chose, as our first point of attack, to modify the aliphatic ring, since this region of the molecule, unlike the other three, is not directly involved as a chemically reactive site in the molecule and it is not implicated in the stabilization of reaction transition states.[2a] Within the aliphatic ring, C-2 was chosen for modification because of its distal location relative to the reactive electrophilic sites at C-6 and C-7 and because of the minimal steric effect C-2 substituents would have upon the C-5 phenyl substituent.

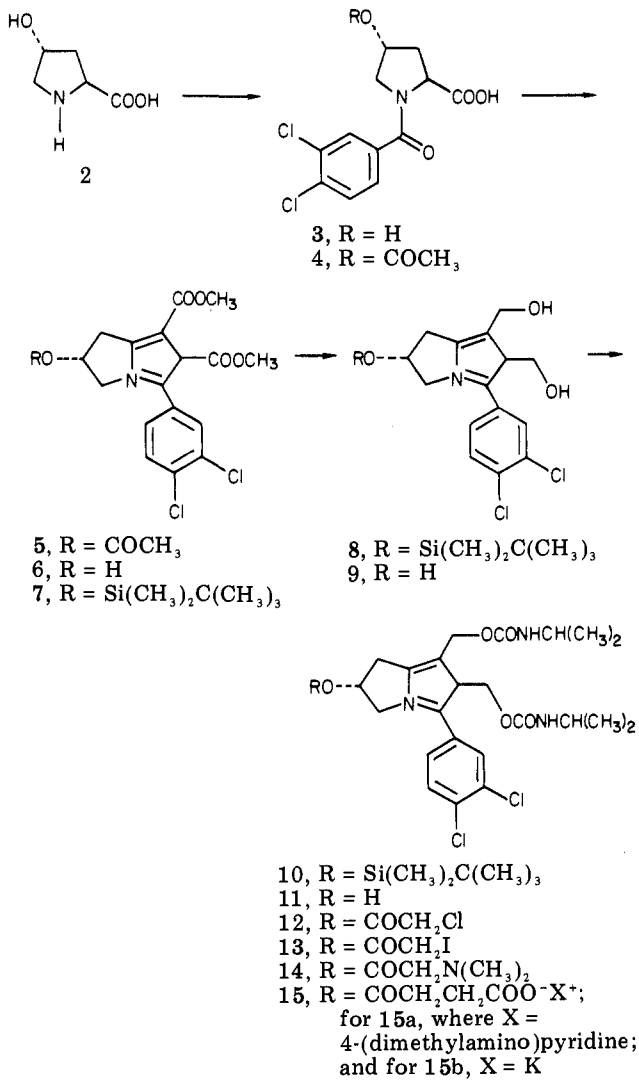
The next step in the design of the prodrug involved selection of an appropriate means to attach the hydrophilic residue to C-2. We chose the hydroxyl group because it is neutral, easily derivatized, and synthetically accessible. Alcohol derivatives, such as carboxylic and phosphoric acid esters, as well as glycosides, can be converted to the parent alcohol in vivo by a variety of enzymatic and/or nonenzymatic processes.

Chemistry. The 2-hydroxypyrrolizine 11 was synthesized from 4-hydroxyproline (2) in 19% overall yield (Scheme I). N-Benzoylation of 2, followed by acetylation of the secondary alcohol in 3, gave the requisite α-amido acid precursor 4 for the ensuing cycloaddition reaction. It

(1) Vinylogous Carbinolamine Tumor Inhibitors. 11. For part 10 in this series, see Anderson, W. K.; McPherson, H. L., Jr. *J. Med. Chem.* **1982**, *25*, 84.
(2) (a) Anderson, W. K.; Corey, P. F. *J. Med. Chem.* **1977**, *20*, 812. (b) Anderson, W. K.; Corey, P. F. *Ibid.* **1977**, *20*, 1691. (c) Anderson, W. K.; Halat, M. J. *Ibid.* **1979**, *22*, 977. (d) Anderson, W. K.; Halat, M. J.; Rick, A. C. *Ibid.* **1980**, *23*, 87. (e) Anderson, W. K.; New, J. S.; Corey, P. F. *Arzneim.-Forsch.* **1980**, *30*(1), 765.
(3) (a) Anderson, W. K. *Cancer Res.* **1982**, *42*, 2168. (b) Anderson, W. K.; Chang, C.-P.; Corey, P. F.; Halat, M. J.; Jones, A. N.; McPherson, H. L., Jr.; New, J. S.; Rick, A. C. *Cancer Treat. Rep.* **1982**, *66*, 91.
(4) Lomax, N. R.; Narayanan, V. L. "Chemical Structures of Interest to the Division of Cancer Treatment", Drug Synthesis and Chemistry Branch, Developmental Therapeutics Program, National Cancer Institute, January 1983; Vol III.

0022-2623/83/1826-1333$01.50/0

Scheme I[a]



[a] Reagents: 2 → 3, 3,4-dichlorobenzoyl chloride; 2 → 4, (i) acetic anhydride, (ii) 3,4-dichlorobenzoyl chloride; 4 → 5, acetic anhydride-dimethyl acetylenedicarboxylate; 5 → 6, methanol-HCl; 6 → 7, *tert*-butyldimethylsilyl chloride; 7 → 8, lithium aluminum hydride; 8 → 9, tetra-*n*-butylammonium fluoride; 8 → 10, isopropyl isocyanate, 10 → 11, tetra-*n*-butylammonium fluoride; 11 → 12, chloroacetyl chloride; 12 → 13, sodium iodide; 13 → 14, dimethylamine; 11 → 15a, succinic anhydride-4-(dimethylamino)pyridine; 15a → 15b, KCl-H_2O.

was necessary to acetylate the secondary alcohol to avoid the formation of *N*-(3,4-dichlorobenzoyl)-2-aza-5-oxabicyclo[2.2.1]heptan-6-one during the cycloaddition reaction. Treatment of **4** with acetic anhydride–dimethyl acetylenedicarboxylate gave **5**, which on treatment with methanolic HCl gave **6**. The sequence of steps from **3** to **6** could be carried out with a minimum of purification of the intermediates **4** and **5**. The secondary alcohol was protected as the *tert*-butyldimethylsilyl ether, and the diester **7** was reduced with lithium aluminum hydride to give the diol **8**. The diol **8** was converted to the bis(2-propylcarbamate) **10**, and the silyl ether was cleaved with anhydrous tetra-*n*-butylammonium fluoride in tetrahydrofuran to give **11**.

Two different ester derivatives of **11** were chosen for synthesis, the (dimethylamino)acetate **14** and the hemisuccinate **15**. In the synthesis of **14**, the alcohol **11** was converted to the chloroacetate **12**, which was converted to the iodide **13**; subsequent displacement of iodide by dimethylamine afforded the (dimethylamino)acetate **14**.

Table I. Water Solubility[a] and HPLC Assays of Solvolytic Half-Lives of Compounds 1, 11, 14, 15a, and 15b[a]

no.	water solubility, M	elution solvent H_2O-CH_3CN	flow rate, mL/min	t_R, min	half-life, min
1	1.26×10^{-6}	3:7	2.0	5.8	13
11	4.02×10^{-5}	3:7	2.0	2.8	31
14	1.96×10^{-5}	3:7	2.5	4.7	248
15a	3.0×10^{-2}	3:2	1.5	2.7	153
15b	3.88×10^{-2}	3:2	1.5	2.5	92

[a] See Experimental Section for a description of the assay conditions.

Preliminary attempts to prepare a water-soluble acid salt of the (dimethylamino)acetate **14** were unsuccessful. Treatment of **14** with anhydrous hydrogen chloride or hydrogen bromide led to excessive decomposition of the (carbamoyloxy)methyl groups. Therefore, preliminary biological evaluation of **14** was carried out with the free amine.

Treatment of the alcohol **11** with succinic anhydride and 4-(dimethylamino)pyridine gave the hemisuccinate **15**, isolated as the 4-(dimethylamino)pyridinium salt **15a**. The 4-(dimethylamino)pyridinium counterion was easily exchanged for potassium by treatment of **15a** with aqueous potassium chloride. The potassium ion was considered more desirable because of the known toxicity of the 4-(dimethylamino)pyridine.[5]

The hydrolytic labilities of the bis(carbamate)s prepared were studied. The reactivity of **1** is compared with the reactivities of **11**, **14**, **15a**, and **15b**, and the data are summarized in Table I. The half-lives were not affected by the chromatographic conditions; for example, the half-life of **15b** was unchanged over the elution solvent composition range (water–acetonitrile) of 60:40, 55:45, and 35:65. Changes in the flow rate had no effect on the measured half-life either. The products from the hydrolysis of **1** and **11** were the diol derived from **1** and the triol **9**, respectively. The identities were established by comparison of the retention times of the authentic alcohols with the retention times of the hydrolysis products and by adding authentic alcohols to the hydrolysis mixture before an HPLC injection to effect direct comparisons. The end products in the hydrolyses of **14**, **15a**, and **15b** were diols (with hydroxymethyl groups at C-6 and C-7) that had the C-2 ester intact. This was inferred from the HPLC retention times of the hydrolysis products and from the fact that no triol (**9**) was produced.

Biological Results and Discussion

The antitumor activity of **11**, **14**, and **15a** have been compared to compound **1** in Tables II–IV. The first consideration involves a comparison of **11** and **1**, since **11** is the parent compound for subsequent derivatization. Does the 2-hydroxyl function have an adverse effect on antitumor activity?

The data in Tables II (P388 lymphocytic leukemia) and III (B16 melanocarcinoma) show that **11** is slightly less active than **1**, while the toxicities of the compounds are comparable. Regardless of these differences, the 2-hydroxypyrrolizine, **11**, does show good antitumor activity in the two tumor systems examined, and **11** has been scheduled for study in a broader panel of experimental

(5) Rosskamp, G.; Schöbel, C.; Günzel, P., unpublished data cited by Höjle, G.; Steglich, W.; Vorbrüggen, H. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 569.

Table II. Activity of 1, 11, and 15a against P388 Lymphocytic Leukemia in Mice[a,b]

no.	dose,[c] mg/kg	wt diff (T − C), g	% T/C[d,e]	log cell kill[f]
1	100	−5.6	110	−1.40
11		−6.3	166	2.16
15a		−1.8	125	−1.08
1	50	−5.3	205	5.25
11		−5.6	150	0.85
15a		−2.2	111	−1.39
1	25	−3.9	179	3.16
11		−3.8	145	0.46
15a		−1.2	107	−1.44
1	12.5	−3.4	160	1.70
11		−2.7	147	0.62
15a		−1.3	106	−1.45
1	6.25	−2.8	164	2.01
11		−2.1	140	0.08

[a] Determined under the auspices of the National Cancer Institute, National Institutes of Health. For general screening procedures and data interpretation, see Geran, R. I.; Greenberg, N. H.; MacDonald, M. M.; Schumacher, A. M.; Abbott, B. J. *Cancer Chemother. Rep., Part 3* 1972, *3*(2), 1. [b] Ascitic fluid containing ca. 6×10^6 cells was inoculated into male CDF_1 mice (ip route), and administration of the test compounds was initiated 24 h later; a total of five doses of the test compounds were given on a daily schedule. Acute toxicities were evaluated on day 5 (toxicity day), and, unless noted otherwise, all of the test animals survived beyond that day. [c] The compounds were administered by intraperitoneal injection; compounds 1 and 11 were given as suspensions in Klucel (hydroxypropylcellulose), and 15a was given as an aqueous solution. [d] Test results were evaluated on day 30; the median survival times of the test animals compared to controls are expressed as percent T/C. The activity threshold is a T/C > 120% (i.e., minimal activity). [e] The data were all obtained at the same time with a single control. [f] The log cell kill is the log of the tumor cell population at the end of the treatment relative to its size at the beginning of treatment.

murine neoplasias and human tumor xenografts.

The activities of the two ester derivatives of **11** are given in the tables. The hemisuccinate **15a** showed only slight antileukemic activity at a dose of 100 mg/kg and was inactive at lower doses (Table II); **15a** was toxic at a dose of 200 mg/kg. The (dimethylamino)acetate, **14**, was less active than **1** against P388 lymphocytic leukemia (Table IV) and B16 melanocarcinoma (Table III). Compound **14** also appeared to be less active than the parent 2-hydroxypyrrolizine, **11**, against B16 melanocarcinoma.

Several reasons can be advanced to explain the low activity of **15a** relative to either **1** or **11**. In any case, the data in Table I show that **15a** is not acting as a prodrug for **11**, because the carbamate moieties are hydrolyzed much faster than the hemisuccinate ester. It seems unlikely that the low level of activity of **15a** is due to the increased hydrophilicity per se because many very hydrophilic compounds have been shown to possess good activity against P388 lymphocytic leukemia. A more plausible reason for the weak activity of **15a** is that **15a** was given as a solution, and the entire dose of the soluble drug underwent facile hydrolysis. Compounds **1** and **11**, by way of contrast, were very insoluble and were given as suspensions.

The differences in the half-lives ($t_{1/2}$) of the compounds described in Table I may be due to two factors. First, an electronic effect would be predicted to alter the $t_{1/2}$ of **1**, **11**, and **14** in the direction that was observed. Second, compounds with a polar function at C-2 can form micelles, and the stability of the micelle would play a definite role in stability of the compound toward hydrolysis if the carbamate moieties were located in the hydrophobic core of the micelle. Both of these factors suggest future points of modification of **1** to control the chemical reactivity of the compound.

In conclusion it is apparent that water-soluble analogues of **1** can be made but that these analogues are too unstable. It is the current objective of our research to prepare stable, water-soluble prodrugs of **1**.

Table III. Activity of 11 and 14 (Compared to 1) against B16 Melanocarcinoma in Mice[a-c]

no.	dose,[d] mg/kg	wt diff (T − C), g	% T/C[e]	cures[f]
11	80	−2.4 (−1.2)	101 (319)	0 (4)
14	80	−1.5 (−1.8)	<100 (106)	0 (0)
11	40	−0.9 (−0.7)	223 (256)	4 (1)
14	40	−0.8 (−0.7)	174 (235)	1 (1)
11	20	0.0 (−0.1)	196 (209)	0 (1)
14	20	0.5 (0.3)	152 (209)	0 (0)
11	10	0.2 (0.3)	143 (175)	0 (0)
14	10	0.2 (0.3)	152 (153)	0 (0)
11	5[g]	0.1 (−0.2)	129 (158)	0 (0)
14	5	0.2 (0.7)	106 (134)	0 (0)

[a] See footnote *a* in Table II. [b] In each of the assays, **1** was assayed in parallel with **11** or **14** as a positive control; the data for **1** are given in parentheses. [c] Tumor homogenate (0.5 mL of a dilution containing 1.0 g of tumor tissue per 10 mL of brei) was inoculated intraperitoneally into female BDF_1 mice. The test compounds were administered 24 h later; a total of nine doses were given on a daily schedule. Acute toxicity was evaluated on day 5 (toxicity day) and, unless otherwise specified, all of the test animals survived beyond that day. [d] The test compounds were given by intraperitoneal injection; **1** and **11** were given as suspensions in Klucel (hydroxypropylcellulose), and **14** was given as a suspension in water/Tween-80. [e] Test results were evaluated on day 60; the median survival times of the test animals compared to controls are expressed at percent T/C. The activity threshold (i.e., minimum activity) is a T/C > 125%. [f] The number of cures is the number of animals in the 10-animal test group that were designated as cures on day 60. [g] 9/10 toxicity day survivors.

Table IV. Comparative Activity of 1 and 14 against P388 Lymphocytic Leukemia in Mice[a]

no.	dose,[b] mg/kg	wt diff (T − C), g	% T/C[c]	log cell kill[d]
1	80	−4.0	126	−1.64
14		−3.4	110	−1.84
1	40	−2.6	155	−1.25
14		−3.1	144	−1.41
1	20	−1.8	144	−1.41
14		−1.9	146	−1.37
1	10	−0.7	141	−1.44
14		−2.0	128	−1.61
1	5	−0.8	127	−1.63
14		−1.3	117	−1.76
1	2.5	−0.5	135	−1.52
14		0.1	101	−1.96

[a] See footnotes *a* and *b* of Table II: except in this test, **1** and **14** were given in nine daily doses. [b] The test compounds were given as suspensions (**1** in Klucel, and **14** in water) by intraperitoneal injection. [c] See footnotes *d* and *e* of Table II. [d] See footnote *f* of Table II.

Experimental Section

Melting points (uncorrected) were taken in open capillary tubes on a Thomas-Hoover melting point apparatus. For compounds that decomposed on melting, the oil bath was heated to within 5–10 °C where decomposition was rapid, and the sample was

inserted into the bath as the temperature was raised. Infrared spectra were determined as KBr wafers, unless specified otherwise, on a Perkin-Elmer Model 337. NMR spectra were determined on a Varian T60A for chloroform-*d* solutions, unless otherwise specified, containing approximately 1% tetramethylsilane. Optical rotations were determined with a Perkin-Elmer 141 polarimeter. Elemental analyses were performed by Atlantic Microlabs, Inc., Atlanta, GA. All of the compounds gave satisfactory analysis for C, H, and N (±0.4%) unless otherwise noted.

HPLC studies were carried out with a microprocessor controlled Spectra-Physics 8000 equipped with a printer/plotter, a helium degas ternary solvent delivery system, and a Varian Vari-Chrom UV-visible detector. An Alltech 600 RP C-18 reversed-phase HPLC column (25 cm × 4.5 mm i.d.) packed with 10 μm irregularly shaped particles was used; the column had approximately 25 000 theoretical plates/m.

***N*-(3,4-Dichlorobenzoyl)-4-hydroxy-L-proline (3).** A solution of 3,4-dichlorobenzoyl chloride (170.0 g, 0.81 mol) in anhydrous ether (350 mL) was added dropwise to a stirred, cooled (8–10 °C) mixture of L-4-hydroxyproline (110.0 g, 0.84 mol) in water (500 mL) and ether (200 mL). Portions of 19% aqueous sodium hydroxide solution were added during the addition to maintain an alkaline reaction mixture. The mixture was stirred for 14 h after the addition was completed, the ether layer was separated, and the aqueous layer was acidified with dilute hydrochloric acid. The heavy gum that separated from the aqueous phase was dissolved in ethyl acetate, and the aqueous phase was extracted with two portions of ethyl acetate. The combined ethyl acetate solution was washed with water, dried (Na_2SO_4), and concentrated in vacuo to yield a thick syrup. The thick syrupy residue was dissolved in hot ethyl acetate (500 mL), and the solution was diluted with hot chloroform (500 mL) and allowed to cool (seed crystals are of benefit). The mixture was filtered to yield 179 g (73%) of *N*-(3,4-dichlorobenzoyl)-4-hydroxy-L-proline (3) as a white powder, mp 158–161 °C; concentration of the mother liquor gave an additional 15.86 g (6%) of product (mp 156–159 °C). Further concentration of the mother liquor gave 3,4-dichlorobenzoic acid (mp 199–203 °C). The material at this stage was used directly in the next step. A small sample was recrystallized one more time to give an analytical sample of 3 as tiny white needles: mp 161–162 °C; IR 3175, 2947, 1761, 1613, 1435, 1244, 1085, 864 cm^{-1}; NMR (Me_2SO-d_6/Me_3Si) δ 2.00–2.67 (br m, 2 H), 3.27–4.05 (br m, 2 H), 4.33–4.83 (br m, 2 H), 7.50–8.00 (m, 3 H) (the two exchangeable protons appeared as a very broad hump in the base line): $[\alpha]^{25}_D$ −107.7° (*c* 0.02, Me_2SO). Anal. ($C_{12}H_{11}NO_4Cl_2$) C, H, N.

Dimethyl 5-(3,4-Dichlorophenyl)-2-hydroxy-2,3-dihydro-1*H*-pyrrolizine-6,7-dicarboxylate (6). A mixture of 3 (189.0 g, 0.62 mol), acetic anhydride (600 mL), and pyridine (100 mL) was stirred at room temperature for 2 days. The mixture was distilled to dryness in vacuo. The residue was diluted with cold water, stirred for 2 h, and extracted with ethyl acetate. The ethyl acetate solution was washed with water, 3 N HCl, and finally with water. The ethyl acetate solution was dried (Na_2SO_4) and concentrated to dryness in vacuo to yield crude 4 as a thick syrup.

The syrup was treated with acetic anhydride (1400 mL) and dimethyl acetylenedicarboxylate (135.0 g, 0.95 mol), and the stirred mixture was slowly heated to reflux. The solution became light yellow in color, and carbon dioxide was evolved. The solution was heated for an additional 1 h after the carbon dioxide evolution had ceased. The solution was cooled and concentrated to dryness in vacuo. The tan-colored residue was treated with water (1000 mL), and the mixture was stirred for 1 day and then extracted with benzene. The benzene extract was washed with 5% aqueous sodium hydroxide solution and then with water; the extract was dried (Na_2SO_4) and concentrated to dryness in vacuo to yield crude 5 as a tan syrup.

The tan syrup was dissolved in anhydrous methanol (1200 mL), and anhydrous hydrogen chloride gas was bubbled into the stirred solution for several minutes. The solution was then stirred at room temperature for 4 days and concentrated to dryness in vacuo. The residue was diluted with water and extracted with ethyl acetate. The ethyl acetate combined extract was washed several times with 4% aqueous sodium hydroxide solution and then with water; it was then dried (Na_2SO_4) and filtered. The ethyl acetate solution was reduced in volume and allowed to stand to give 134.7 g (56%) of 6 as a cream-colored solid (mp 143–145 °C); further concentration of the mother liquor gave an additional 11.08 g (5%) of product (mp 142–144 °C). The product was recrystallized from a minimum volume of ethyl acetate to give 6 as fine colorless prisms: mp 143.8–144.5 °C; IR 3521, 2945, 1714, 1698, 1473, 1450, 1223, 1174, 1122, 833 cm^{-1}; NMR δ 3.17–3.67 (m, 2 H), 3.78 (s, 3 H), 3.83 (s, 3 H), 3.75–4.33 (m, 3 H), 5.00 (br s, 1 H, OH), 7.17–7.67 (m, 3 H); $[\alpha]^{25}_D$ −8.70° (*c* 0.2, Me_2SO). Anal. ($C_{17}H_{15}NO_5Cl_2$) C, H, N.

***N*-(3,4-Dichlorobenzoyl)-2-aza-5-oxabicyclo[2.2.1]heptan-6-one.** A 19% yield of this lactone was obtained when 3 was treated at 120 °C for 1 h with acetic anhydride–dimethyl acetylenedicarboxylate. The white solid (chloroform–isopropyl ether) had the following physical properties: mp 194–195 °C; IR 2945, 1783, 1640, 1423, 1100, 992, 837, 749 cm^{-1}; NMR (Me_2SO-d_6/Me_3Si) δ 2.28 (s, 2 H), 3.30–4.07 (m, 2 H), 4.83 (br s, 1 H), 5.38 (br s, 1 H), 7.50–8.00 (m, 3 H); $[\alpha]^{25}_D$ −85.32° (*c* = 0.02, Me_2SO). Anal. ($C_{14}H_{17}NO_6$) C, H, N.

Dimethyl 2-*O*-(*tert*-Butyldimethylsilyl)-5-(3,4-dichlorophenyl)-2,3-dihydro-1*H*-pyrrolizine-6,7-dicarboxylate (7). A mixture of 6 (97.5 g, 0.254 mol) and imidazole (41.46 g, 2.4 equiv) in dry DMF (200 mL) was stirred at 0 °C. A solution of *tert*-butyldimethylsilyl chloride (45.9 g, 1.2 equiv) in dry DMF (250 mL) was added dropwise to the mixture. After the addition was completed, the mixture was stirred at room temperature for 12 h and then poured into 500 mL of water. A white precipitate formed immediately, and the aqueous solution was extracted with benzene (3 × 150 mL). The benzene solution was washed with 1% NaOH (50 mL, cold) and then with water (2 × 50 mL) and dried (Na_2SO_4). The mixture was filtered, and the filtrate was concentrated to dryness in vacuo to give a light yellow oily residue, which was crystallized from hexanes to yield 7 (120.1 g, 95%) as colorless needles: mp 97–97.5 °C; IR 2950, 2859, 2882, 1710, 1470, 1400, 1305, 1260, 1120, 990, 840, 780 cm^{-1}; NMR δ 0.10 (s, 6 H), 0.88 (s, 9 H), 3.07 (q, *J* = 6 Hz, 2 H), 3.70 (s, 3 H), 3.73 (s, 3 H), 3.93–4.40 (m, 2 H), 4.70–5.20 (br m, 1 H), 7.03–7.50 (m, 3 H). Anal. ($C_{23}H_{39}NO_5Cl_2Si$) C, H, N.

2-*O*-(*tert*-Butyldimethylsilyl)-5-(3,4-dichlorophenyl)-6,7-bis(hydroxymethyl)-2,3-dihydro-1*H*-pyrrolizine (8). A solution of 7 (134.4 g, 0.27 mol) in anhydrous ether (800 mL) was added dropwise to a stirred, cooled (0 °C) suspension of lithium aluminum hydride (23.53 g, 2.3 equiv) in anhydrous ether (400 mL). After the addition was completed, the mixture was stirred at room temperature for 30 min, and the excess hydride was decomposed by the addition of water (23.5 mL), 15% NaOH (23.5 mL), and water (67.5 mL). The mixture was filtered, and the inorganic residue was put in soxhlet extraction tube and extracted with dichloromethane overnight. The combined dichloromethane solution was concentrated to dryness in vacuo. The residue was dissolved in dichloromethane (200 mL) and dried (Na_2SO_4). The solution was evaporated to dryness in vacuo, and the product was crystallized from hexanes to give 8 (95.43 g, 80%) as fine colorless prisms: mp 98–100 °C; IR 3430, 1620, 1465, 1380, 1260, 1100, 1000, 840, 780 cm^{-1}; NMR δ 0.1 (s, 6 H), 0.88 (s, 9 H), 2.77–3.67 (m, 2-CH, 2-OH), 3.70–4.30 (m, 2 H), 4.33–4.70 (br s, 4 H), 4.72–5.20 (m, 1 H), 7.07–7.63 (m, 3 H). Anal. ($C_{21}H_{30}NO_3Cl_2Si$) H, N; C: calcd, 57.01; found, 55.76.

2-Hydroxy-5-(3,4-dichlorophenyl)-6,7-bis(hydroxymethyl)-2,3-dihydro-1*H*-pyrrolizine (9). A solution of 6 (1.33 g, 3.46 mmol) in dry dichloromethane (10 mL) was added dropwise to a mechanically stirred mixture of lithium aluminum hydride (0.289 g, 2.2 equiv) in anhydrous ether (40 mL) at 0 °C. After the addition was completed, the mixture was stirred at room temperature for 30 min and cooled in an ice bath. The excess hydride was cautiously destroyed by the sequential addition of water (0.3 mL), 15% NaOH (0.3 mL), and water (0.9 mL); the mixture was filtered, and the inorganic residue was washed with several portions (ca. 25 mL) of dichloromethane. The filtrate was concentrated to dryness in vacuo and the solid residue was dissolved in dichloromethane (50 mL) and dried (Na_2SO_4). The solution was concentrated to dryness in vacuo, and the residue was crystallized from ethyl acetate to yield 9 (0.97 g; 85%) as colorless needles: mp 163–164 °C; IR 3368 (OH), 3230 (OH), 2880, 2400, 1595, 1460, 1085, 1000 cm^{-1}; NMR δ 2.92–3.60 (m, 2 H), 3.60–4.60 (m, 2 H), 4.03 (s, 3-OH, overlap with δ 3.60–4.60), 4.53 (s, 2 H), 4.57 (s, 2 H), 4.70–5.17 (br m, 1 H), 7.07–7.67 (m, 3 H).

Anal. ($C_{15}H_{15}NO_3Cl_2$) C, H, N.

2-*O*-(*tert*-Butyldimethylsilyl)-5-(3,4-dichlorophenyl)-6,7-bis(hydroxymethyl)-2,3-dihydro-1*H*-pyrrolizine Bis(2-propylcarbamate) (10). A solution of **8** (31.3 g, 0.071 mol) and dry triethylamine (6 mL) in dry dichloromethane 500 mL) was treated with freshly distilled isopropyl isocyanate (13.85 g, 2.3 equiv) and refluxed for 3 days (protected from moisture). The mixture was concentrated to dryness in vacuo and the residue was dissolved in a small amount of ethyl acetate. The isopropylurea byproduct, which precipitated from ethyl acetate, was removed by filtration. The filtrate was concentrated to dryness in vacuo, and the residue was crystallized from ethyl acetate–hexanes to give **9** (24.7 g, 57%) as colorless needles: mp 121–121.5 °C; IR 3450 (NH), 2965, 2900, 1720 (C=O), 1480, 1415, 1140, 845 cm^{-1}; NMR δ 0.1 (s, 6 H), 0.88 (s, 9 H), 1.15 (d, J = 6 Hz, 12 H), 2.77–3.27 (m, 2 H), 3.30–4.20 (br m, 4 H), 4.30–4.60 (br m, 2 H), 4.73–5.20 (br 5 H), 5.00 (s, 2 H), 5.07, (s, 2 H), 7.07–7.63 (m, 3 H). Anal. ($C_{27}H_{43}N_3Cl_2O_5Si$) C, H, N.

2-Hydroxy-5-(3,4-dichlorophenyl)-6,7-bis(hydroxymethyl)-2,3-dihydro-1*H*-pyrrolizine Bis(2-propylcarbamate) (11). A mixture of **10** (130 g, 0.212 mol) in THF (250 mL) was treated with 1.1 equiv of tetrabutylammonium fluoride (234 mL of 1 M solution in THF). The reaction mixture was stirred at room temperature for 12 h, the mixture was concentrated to dryness in vacuo, and the residue was dissolved in dry dichloromethane (400 mL). The solution was washed with water (3 × 200 mL), dried (Na_2SO_4), and filtered. The solution was concentrated in vacuo to give a pale yellow residue, which was crystallized from ethyl acetate–chloroform–hexanes to yield **11** (99.4 g, 94%) as fine colorless needles: mp 143–145 °C dec; IR 3350 (NH), 2995, 1690 (C=O), 1540, 1470, 1260, 1080 cm^{-1}; NMR δ 1.15 (d, J = 6 Hz, 12 H), 2.83–3.30 (m, 2 H), 3.33–4.33 (m, 5 H, NCH_2, OH), 4.35–4.80 (m, 3 H), 4.98 (s, 2 H), 5.04 (s, 2 He, 7.07–7.63 (m, 3 H). Anal. ($C_{23}H_{29}N_3O_5Cl_2$) C, H, N.

2-(Chloroacetoxy)-5-(3,4-dichlorophenyl)-6,7-bis(hydroxymethyl)-2,3-dihydro-1*H*-pyrrolizine Bis(2-propylcarbamate) (12). A mixture of **11** (2.99 g, 6 mmol) in dry dichloromethane (50 mL) was stirred at 0 °C, and a solution of chloroacetylchloride (0.813 g, 1.2 equiv) in dry dichloromethane (20 mL) was added dropwise to the mixture. After the addition was completed, the mixture was stirred at room temperature for 15 min. The color of the solution changed to pale yellow. The solution was concentrated in vacuo, and the residue was washed through a small column [SiO_2, 50 g, 3 (o.d.) × 18 cm (long) column] with ethyl acetate. The eluate was collected and concentrated. The product was crystallized from ethyl acetate–isopropyl ether–hexanes to give **12** (3.2 g, 94%) as pale yellow crystals: mp 142–146 °C dec; IR (mineral oil) 3302 (NH), 1750, 1680 (C=O), 1530, 1265, 1160, 1065, 725 cm^{-1}; NMR δ 1.15 (d, J = 6 Hz, 12 H), 3.08–3.50 (m, 2 H), 3.50–4.77 (m, 7 H), 4.05 (s, 2 H, overlap with δ 3.50–4.77), 5.00 (s, 2 H), 5.07 (s, 2 H), 5.50–6.03 (br m, 1 H), 7.07–7.63 (m, 3 H). Anal. ($C_{25}H_{30}N_3Cl_3O_6$) C, H, N.

2-(Iodoacetoxy)-5-(3,4-dichlorophenyl)-6,7-bis(hydroxymethyl)-2,3-dihydro-1*H*-pyrrolizine Bis(2-propylcarbamate) (13). A mixture of **12** (3.2 g, 5.57 mmol) and sodium iodide (1.0 g, 1.2 equiv) in dry acetone (50 mL) was stirred vigorously at room temperature for 24 h. The solid sodium chloride was filtered, and the filtrate was concentrated to dryness in vacuo. The residue was dissolved in a small amount of dry dichloromethane, and the insoluble sodium iodide was removed by filtration. The solution was concentrated, and the residue was eluted through a small silica gel column with ethyl acetate. The eluate was collected, and the product was crystallized from ethyl acetate–hexanes to give **13** (3.34 g, 90%) as brown needles: mp 123–125 °C dec; IR 3420 (NH), 2980, 1690 (C=O), 1520, 1380, 1250, 1075, 780 cm^{-1}; NMR δ 1.15 (d, J = 6 Hz, 12 H), 3.08–3.50 (m, 2 H), 3.50–4.50 (m, 4 H), 3.68 (s, H overlap with δ 3.50–4.50), 4.50–4.87 (m, 2 H), 5.00 (s, 2 H), 5.07 (s, 2 H), 5.53–6.00 (br m, 1 H), 7.07–7.63 (m, 3 H). The product was not analyzed but was submitted directly to the next step.

2-[(Dimethylamino)acetoxy]-5-(3,4-dichlorophenyl)-6,7-bis(hydroxymethyl)-2,3-dihydro-1*H*-pyrrolizine Bis(2-propylcarbamate) (14). A mixture of **13** (3.2 g, 4.8 mmol) in dichloromethane–ether (1:5, 30 mL) was stirred at 0 °C. A solution of dimethylamine in ether (4 equiv, 4.3 mL, 100 g/500 mL of solution) was added dropwise to the mixture, and, after the addition was completed, the mixture was stirred at room temperature for 10 h. The dimethylamine hydrogen iodide salt was removed by filtration, and the solution was concentrated in vacuo. The excess dimethylamine was evaporated under high vacuum overnight, and the residue was crystallized from ethyl acetate–hexanes to give 14 (2.1 g, 75%): mp 141–142 °C dec; IR 3335 (NH), 2980, 1690 (C=O), 1525, 1460, 1250, 1060 cm^{-1}; NMR δ 1.15 (d, J = 6 Hz, 12 H), 2.37 (s, 6 H), 2.77–3.47 (m, 2 H), 3.03 (s, 2 H, overlap with δ 2.77–3.47), 3.47–3.93 (m, 2 H), 3.93–4.33 (m, 2 H), 4.33–4.80 (m, 2 H), 5.00 (s, 2 H), 5.07 (s, 2 H), 5.57–6.00 (br m, 1 H), 7.07–7.67 (m, 3 H). Anal. ($C_{27}H_{36}N_4Cl_2O_6$) C, H, N.

4-(Dimethylamino)pyridinium 5-(3,4-Dichlorophenyl)-6,7-bis(hydroxymethyl)-2-[(carboxylatoethyl)carbonyl]-2,3-dihydro-1*H*-pyrrolizine Bis(2-propylcarbamate) (15a). A mixture of **11** (4.984 g, 0.01 mol), succinic anhydride (1.00 g, 0.01 mol), and 4-(dimethylamino)pyridine (1.221 g, 0.01 mol) in dry dichloromethane (200 mL) was stirred at room temperature for 18 h. The solvent was evaporated in vacuo, and the residue was dissolved in a small amount of ethyl acetate and crystallized to yield **15a** (7.06 g, 98%) as colorless chunky prisms: mp 122–124 °C dec; IR 2950, 1720, 1640, 1560, 1480, 1440, 1220, 1160, 1110, 920, 820, 730 cm^{-1}; NMR δ 1.17 (d, J = 6 Hz, 12 H), 2.60 (s, 4 H), 2.90–3.40 (br m, 2 H), 3.10 (s, 6 H, overlap with δ 2.90–3.40), 3.53–3.90 (m, 2 H), 3.90–4.33 (m, 2 H), 4.73–5.4 (br m, 2 H), 5.00 (s, 2 H) 5.05 (s, 2 H), 5.40–6.00 (br m, 1 H), 6.40–6.77 (br d, 2 H) 7.05–7.67 (m, 3 H), 7.90–8.40 (br d, 2 H), 14.77 (br s, 1 H). Anal. ($C_{34}H_{43}N_3O_8Cl_2$) C, H, N.

Potassium 5-(3,4-Dichlorophenyl)-6,7-bis(hydroxymethyl)-2-[(carboxylatoethyl)carbonyl]-2,3-dihydro-1*H*-pyrrolizine Bis(2-propylcarbamate) (15b). A saturated potassium chloride aqueous solution (5 mL) was added to a solution of **15a** (200 mg) in ethanol (5 mL). A white precipitate formed immediately, and the solution was stirred vigorously at room temperature for 10 min. The solid was filtered and dissolved in small amount of absolute ethanol; the potassium chloride was precipated and separated. The ethanol solution was concentrated to a syrup in vacuo, and ethyl acetate was added. The potassium salt **15b** (120 mg, 65%) was formed as yellow chunky prisms that contained 1 mol each of KCl and water: mp 155–157 °C dec; IR 3300 (NH), 2960, 1680 (C=O), 1540, 1390, 1235, 1050 cm^{-1}; NMR (CD_3OD/Me_3Si) δ 1.17 (d, J = 6 Hz, 12 H), 2.50 (s, 4 H), 2.70–3.40 (m, 2 H), 3.40–3.90 (m, 2 H), 3.93–4.46 (m, 2 H), 4.85 (br s, 4 H), 4.90–5.13 (br m, 2 H), 5.40–5.90 (br m, 1 H), 7.05–7.67 (m, 3 H). Anal. ($C_{27}H_{32}N_3O_8Cl_2K \cdot 1KCl \cdot 1H_2O$) H, N; C: calcd, 44.48, found, 44.90.

Hydrolysis of the Bis(carbamates). Acetonitrile (5.0 mL, HPLC grade) was added to a vial containing the bis(carbamate) (0.002 mol). The solution was agitated (Vortex-Genie) for 1 min and filtered through a 0.5-μm filter (Millix-SR PTFE membrane, Millipore Co., Bedford, MA). Water (1.0 mL) was added to an aliquot (1.0 mL) of the acetonitrile solution, and the mixture was agitated (Vortex-Genie) for 30 s and immediately injected into the HPLC column through a 10-μL injection loop. The acetonitrile–water solution was kept in a water bath at 25.0 ± 1 °C, and 10-μL aliquots were analyzed on the HPLC at time intervals such that a minimum of 7 injections were made for the faster reactions and about 15 injections were made for the slower reactions. The solutions were not buffered, but the pH of the solutions was monitored and was 7.4 ± 0.4 during the entire reaction.

The HPLC column was eluted with water–acetonitrile (3:7) at a flow rate of 2.0 mL/min for 1 and 11 and 2.5 mL/min for 14. The polar salts **15a** and **15b** were eluted with water–acetonitrile (3:2) at flow rates of 1.5 mL/min. The HPLC effluent was monitored for the disappearance of starting bis(carbamate) at a wavelength of 291 nm. The peak heights and retention times were measured with an Alltech Peakometer. Logarithmic values of peak heights were plotted against time (minutes), and the slope was the observed rate constant of the pseudo-first-order hydrolysis reaction. The faster reactions were followed for 10 half-lives, while the slower reactions were followed for a minimum of 6 half-lives. All of the assays were done in triplicate, and the half-lives given in Table I are mean values based on the three determinations.

Water Solubility Studies. Excess bis(carbamate) (30–60 mg) was placed in a small vial containing distilled water (2 mL). The vial was stoppered and agitated (Vortex-Genie) for 10 min. The

mixture was filtered through a Teflon–wool plug and diluted to a suitable concentration for the UV measurement. A Beer's law calibration curve was made with the salt **15b**, and the UV absorption maximum (291 nm) plotted against concentration gave a straight line (correlation coefficient = 0.998). Unknown concentrations were determined by linear regression analysis using the derived equation (eq 1), where y is the UV absorbance and x is the concentration.

$$y = (2.844 \times 10^4)x + (1.808 \times 10^{-2}) \quad (1)$$

Acknowledgment. This investigation was supported by Public Health Service Grants CA 22935 and CA 09166 awarded by the National Cancer Institute, DHHS. The authors thank Paul A. Corey for his initial work leading to the preparation of **9** and Dr. Louis Malspeis, College of Pharmacy, The Ohio State University, for showing us his unpublished data concerning the hydrolysis of **1** and the details of his HPLC assay.

Registry No. 1, 74296-42-7; **2**, 51-35-4; **3**, 86421-96-7; 4, 86421-97-8; **5**, 86421-98-9; **6**, 86421-99-0; **7**, 86422-00-6; **8**, 86422-01-7; **9**, 86422-02-8; **10**, 86422-03-9; 11, 86422-04-0; **12**, 86422-05-1; **13**, 86422-06-2; 14, 86422-07-3; **15a**, 86422-09-5; **15b**, 86422-10-8; 3,4-dichlorobenzoyl chloride, 3024-72-4; dimethyl acetylenedicarboxylate, 762-42-5; (−)-*N*-(3,4-dichlorobenzoyl)-2-aza-5-oxabicyclo[2.2.1]heptan-6-one, 86422-11-9; *tert*-butyldimethylsilyl chloride, 18162-48-6; isopropyl isocyanate, 1795-48-8; chloroacetyl chloride, 79-04-9; dimethylamine, 124-40-3; succinic anhydride, 108-30-5.

Book Reviews

Drugs and the Pharmaceutical Sciences. Volume 14. Novel Drug Delivery Systems. Edited by Yie W. Chien. Marcel Dekker, New York. 1982. xii + 633 pp. 15.5 × 23.5 cm. $65.00.

Fourteenth in the series of *Drugs and the Pharmaceutical Sciences*, this volume addresses the physicochemical principles, developmental concepts, and biomedical applications of controlled-release drug-delivery systems. One chapter is devoted to each of the following routes of drug administration: ocular, intravaginal, intrauterine, transdermal, parenteral, and subcutaneous implantation. The remaining four chapters discuss veterinary medicine applications, general pharmacokinetic principles, and the physical parameters governing drug release from capsule, matrix, and sandwich-type drug-delivery systems. The table of contents and author and subject indexes are very complete and thus allow the text to be easily utilized as a reference book.

Chapters dealing with a particular route of drug administration usually include historical development, a brief overview of anatomy and physiology, a comprehensive description of physical and pharmacokinetic principles of drug release, followed by examples of the clinical performance of several different drugs. The text is amply augmented by graphs and tables of research data from primary journal articles or directly from the investigator. A large majority of the primary reference citations are dated prior to 1979. As a result, the text discusses recent applications in this rapidly growing technology in a cursory fashion or not at all. For instance, transdermal nitroglycerin is only briefly discussed under governmental regulations. Routes of administration that are omitted are intranasal, subbuccal, and bronchial aerosal. A reader might expect the latter topics to be included in a book about "novel" drug-delivery systems.

This book would serve the investigator in academia or industry who is contemplating research and development of controlled drug-delivery systems or the educator who wishes to include principles of rate-controlled drug dosage in a graduate pharmaceutics course. Because of the pharmaceutical industry's recent intensive development in this field, the book should not be relied upon to provide a comprehensive description of all novel drug-delivery systems.

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Behavioral Models and the Analysis of Drug Action. Edited by M. V. Spiegelstern and Aharon Levy. Elsevier, Amsterdam and New York. 1982. xvii + 498 pp. 19 × 25 cm. ISBN 0-444-42125-4. $139.50.

This excellent volume will make medicinal chemists appreciate the sophistication that has been developed in behavioral pharmacology in the relatively short time the discipline has been practiced. It comprises the proceedings of the 27th OHOLO conference, held in Israel in March 1982. There are manuscripts representing 22 invited papers grouped under the following subject headings: "Theoretical Issues in the Use of Animal Models"; "Memory, Learning, and Performance"; "Behavioral Toxicology and Addiction"; and "Behavioral Models Induced by Brain Manipulation". In addition, summaries of seven poster papers included at the conference are given.

The most significant theme appearing in the papers in the book appears to be the remarkable success achieved in developing specific animal models for various human behavioral anomalies. For example, the following techniques were reported to have been developed to represent the human condition shown in parentheses: an animal model of attention (schizophrenia), manipulation of brain cholinergic mechanisms by ethylcholine aziridinium (Alzheimer's disease), toxicity and self-administration (drug abuse liability), stress tolerance in rats (human behavioral depression), and threshold for brain reward stimulation (drug abuse potential). Also, techniques to measure hitherto unexplored behaviors such as attention, tardive dyskinesia, and aggression, are presented, as are references to social effects on behavioral experiments. Of particular interest to medicinal chemists are the several papers devoted to biochemical correlates of abnormal behavior. Examples include dopamine and rotational behavior, catecholamines and learning, and catecholamines and self-stimulation.

This book contains much information which should be highly useful to medicinal chemists engaged in design of drugs to alter CNS neurochemistry or behavior.

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Solid-State Chemistry of Drugs. By Stephen R. Byrn. Academic Press, New York. 1982. xii + 346 pp. 16 × 23.5 cm. ISBN 0-12-148620-6. $55.00.

Though it is common to consider solids as being inert, such is not always the case. There are instances where certain environmental conditions can initiate a reaction in or on a solid. In this monograph, S. R. Byrne has provided a fairly extensive overview of the types of reactions that take place in organic solids, especially drugs.

The subject is introduced by a brief description of the solid state (crystal forces, habits, crystalline and noncrystalline states) and the sequence of events that take place in a solid-state reaction. In the second chapter, the methods that are used to study solids and solid-state reactions are outlined: microscopy, X-ray diffraction, thermal methods, infrared, and analytical procedures for detecting chemical products. The various equations commonly used to treat solid-state kinetic data are presented in Chapter