stirred suspension of 70.4 g (0.25 mol) of 2,6-dibenzylidenecyclohexanone[5] in 640 mL of MeOH was treated with 41.6 g (0.26 mol) of the above substituted hydrazine and warmed, and the resulting solution was refluxed for 4 h. The solvent was removed on a rotary evaporator and the residual solid was crystallized from 500 mL of CH_3CN to give 72.2 g of pale-yellow base, mp 106–108 °C. Anal. ($C_{27}H_{33}N_3O$) C, H, N.

A stirred suspension of the above base in 360 mL of CH_3CN was treated with 32 mL of 5.6 N HCl in EtOH, and the resulting solution was diluted with 1.8 L of Et_2O to give 72.2 g (62%) of colorless solid, mp 148–151 °C. Recrystallization of this material from 350 mL of MeOH–3.5 L of Et_2O gave 62.0 g (53%) of colorless product, mp 152–154 °C.

Carrageenan-Induced Edema Test and Results. The procedure described by Millonig and Yiakas[6] was used to test agents for antiedema activity. The test compounds were dissolved or suspended in water or 1% aqueous sodium carboxymethylcellulose in a volume of 1 mL and administered orally to adult Charles River Sprague-Dawley rats (seven per group) 2 h prior to injection (footpad) of 0.05 mL of a 1% solution of carrageenan in pyrogen-free saline. Three hours after the injection of carrageenan, the rats were killed, and the paws were removed and weighed. The contralateral paw served as the control. The percentage of inhibition of edema was observed for the following compounds at a dose of 150 mg/kg: 1 (22% inhibition), **5** (0%), **6** (32%), **15** (47%), **16** (26%), **18** (41%), **19** (27%), **26** (17%), **27** (29%), **33** (30%), phenylbutazone (51%).

Ulcerogenic Test. Male Sprague-Dawley rats were deprived of food pellets but allowed free access to water containing 5% dextrose for 48 h before oral administration (via gavage) of the test compound. The compound was dissolved or suspended in water and administered orally to eight rats at each dose. After dosing (six h), the animals were sacrificed, and their stomachs were excised and examined grossly for hyperemia, fresh or tarry blood, and erosions (hemorrhagic or nonhemorrhagic) in the rumen and glandular portions.

Acknowledgment. The authors are indebted to Dr. M. S. Puar for analysis of the NMR data and to the members of the Pharmacology, Experimental Pathology, Toxicology, and Analytical Departments of the Squibb Institute for the data reported herein.

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Synthesis and Preliminary Biological Studies of 4- and 5-[2-Hydroxy-3-(isopropylamino)propoxy]benzimidazoles: Selective β_2 Adrenergic Blocking Agents

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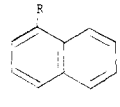
Received July 10, 1978

Benzimidazoles carrying the 2-hydroxy-3-(isopropylamino)propoxy side chain at either the C-4 or C-5 ring positions were synthesized and investigated for β-adrenergic blocking activity. Both compounds demonstrated β_2 selectivity when evaluated in guinea pig atrial and tracheal preparations. The C-4 isomer was 17 times more selective toward tracheal tissue, and its overall potency was roughly comparable to that of propranolol. β_2 selectivity of the C-5 isomer was minimal, with a potency about one-hundredth that of propranolol.

Many heterocyclic analogues of propranolol (**1**) have



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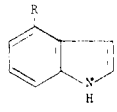
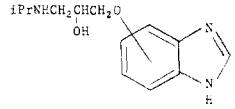


2

R = iPrNHCH$_2$CHCH$_2$O– (OH)

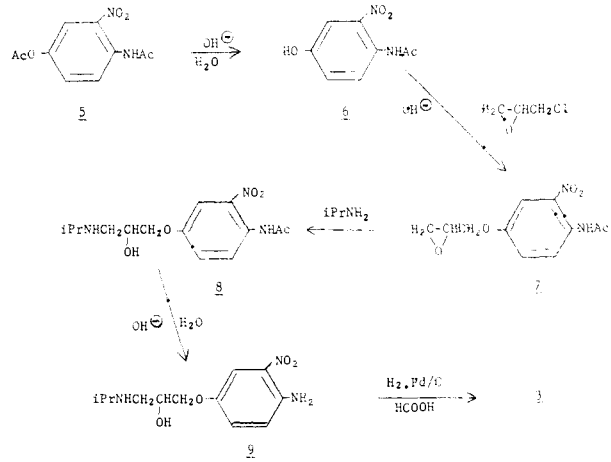
been prepared and some found highly active as β-adrenergic blocking agents.[1-4] Perhaps the most successful drug so far to emerge from these studies is pindolol (**2**), which possesses an indole nucleus and is at least ten times more potent than propranolol.[1,5,6] Despite the close structural resemblance between the indole and benzimidazole ring systems, the benzimidazole analogues **3** and **4** were conspicuously absent from the literature at the beginning of this study.



3 side chain at C-5

4 side chain at C-4

Scheme I



The purpose of this report is to describe the synthesis and initial biological evaluation of two benzimidazole

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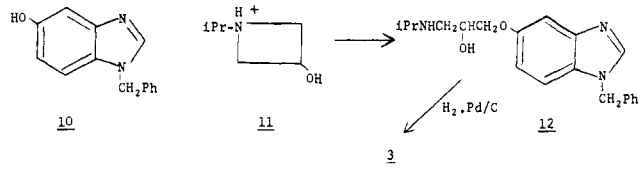
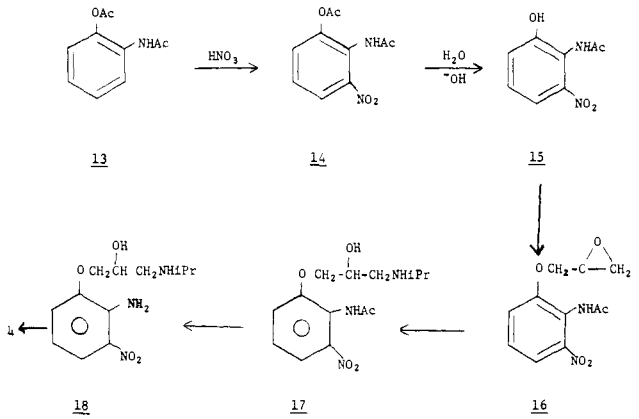
Scheme II



Scheme III



analogues of propranolol in which the side chain is attached at the C-4 and C-5 ring positions, namely, 4- and 5-[2-hydroxy-3-(isopropylamino)propoxy]benzimidazoles **3** and **4**. Investigation of these compounds represents an extension of prior work done by associates.[7-12] Central to this work was the idea of an isosteric relationship between the imidazole ring and the catechol moiety of adrenergic hormones.[12]

Chemistry. The synthesis of **3** is outlined in Scheme I.[13] Initially, other methods of attaching the side chain directly to the benzimidazole nucleus were investigated. These involved the attachment of the epoxide side chain to either 5-hydroxybenzimidazole or protected (*N*-benzyl) derivatives in a manner analogous to the methods reported for the synthesis of **2** and other β blockers.[1,2,4] Failure of these methods in the present synthesis was apparently due to the participation of the nucleophilic imidazole nitrogen(s) in the case of the unprotected and monobenzyl compounds, while that of the *N,N'*-dibenzyl derivative was attributed to the instability of the benzimidazolium ring to base.[14] The yield of **6** from the partial hydrolysis of **5** was increased from a reported 26%[15] to 90% by shortening the exposure time of the product to base, as described under the Experimental Section. Further along in the scheme, unexpected difficulty was encountered with the hydrolysis of **8** to form **9**. Despite repeated recrystallization, **9** could not be obtained with the desired degree of analytical purity, though spectral data (MS, NMR, and IR) was consistent with the structure indicated.

Compound **3** was also prepared by a seldom used method for the synthesis of β blockers.[16,17] As seen in Scheme II, 1-benzyl-5-hydroxybenzimidazole (**10**) can be reacted with 1-isopropyl-3-azetidinol (**11**) to attach the side chain in a single step. However, the entire route is only one step shorter than the previous scheme and suffers certain drawbacks: the azetidinol is not easily synthesized, and, in addition, intermediate **12** is difficult to purify.

Synthesis of the C-4 isomer began with 2-aminophenol and proceeded as shown in Scheme III. Subsequent placement of the 2-hydroxy-3-(isopropylamino)propoxy side chain at the C-4 position of benzimidazole was achieved as outlined for the C-5 isomer (Scheme I). Anticipated difficulty in the sequence of **13**–**15** was overcome by nitrating **13** at −15 to −20 °C and then subjecting the crude product to partial hydrolysis followed by sublimation. Thus, **15** was obtained in an overall yield of 41%, this comparing very favorably with reported yields of 6–12%,[18,19] and successfully overcame what was a potential bottleneck early in the scheme.

Table I. β-Blocking Activity in Isolated Atrial and Tracheal Preparations

	pA_2 values (95% confidence limits)		
	atrium		
compd	beat rate	contractile force	trachea relaxation
3	6.00 (5.80-6.28)	6.07 (5.86-6.38)	6.42 (6.14-6.89)
4	7.40 (7.32-7.52)	7.51 (7.31-7.89)	8.64 (8.23-9.37)
1	8.02 (7.68-8.72)	7.85 (7.38-10.51)	7.83 (7.52-8.52)

Table II. β_2 Selectivity

compd	absolute[a]	relative
3	2.63	4.0
4	17.4	27.0
1	0.645	1.0

[a] Antilog of the difference between the atrial rate and tracheal pA_2 values for each antagonist.

Pharmacology.[20] Compounds **3** and **4** were evaluated for both β_1- and β_2-adrenergic blocking activity using isolated guinea pig atrial[21] and tracheal[22,23] preparations, respectively, and assessed by antagonism to isoproterenol-induced responses in these tissues. Activity is expressed as the negative logarithm of the concentration of antagonist needed to reduce the response to 50% of maximum (pA_2 value).[24] The pA_2 values were calculated from log dose–response curves generated in the presence of four different concentrations of each antagonist. Three to five runs were made for each dose in tissues from different animals. Experimental error was determined by linear regression analysis with the aid of a programmed desk calculator according to the statistical methods reviewed by Goldstein.[25]

Results and Discussion

At the initiation of this study, certain predictions had been made concerning the structure–activity relationships of **3** and **4**. Higher blocking activity had been anticipated for **4** because the placement of the side chain relative to the imidazole ring more closely resembles the structures of the potent β-antagonists **1** and **2**. This did prove correct. By converting the pA_2 values in Table I to normal numbers, it may be seen that **4** is 30 times more potent than **3** in guinea pig atrial tissue and about 125 times more active in tracheal tissue. The log dose–response curves from which the pA_2 values were obtained showed slope variations for the several doses of **3** and **4** to be within the range seen with propranolol, a competitive antagonist,[26] which suggests that **3** and **4** both act in a competitive manner.

However, other results were not as expected. It was thought that **3** might show β_1 selectivity, since its side chain is para to an imidazole nitrogen, and some para substituents do impart β_1 selectivity, the *p*-acetamido group of practolol being an example.[27] But to the contrary, **3** was shown to be slightly β_2 selective (Table II). This type of activity was even more pronounced with **4**. Again, this was

not anticipated, mainly because of the close structural resemblance of **4** to compound **2**, a nonselective antagonist.[28]

The high affinity and selectivity shown by **4** for the β_2 receptor are the most interesting results of this study. Not only did **4** have six times the affinity of propranolol toward tracheal tissue (from Table I), it also was 17 times more active in tracheal than atrial tissue (Table II), with a 27-fold difference relative to propranolol.

β-Adrenergic antagonists that possess such a high degree of β_2 affinity and selectivity have seldom been reported. A survey of the literature did reveal that *N*-isopropyl- and *N*-*tert*-butyl-substituted *o*-nitrilophenoxypropanolamines are comparable to **4** in activity.[29] Recently, a high degree of β_2 activity has been shown for several aromatic oxime ethers.[30]

β_2 selective antagonists do have great potential importance, not only from the viewpoint of clinical applicability in the treatment of hypertension[31] but as useful tools in the characterization of the β receptor. It is for these reasons that the benzimidazole compound **4** may prove to be of interest.

Experimental Section

Melting points are corrected and were determined with a Thomas-Hoover melting point apparatus. IR spectra were determined with a Perkin-Elmer Model 257 grating infrared spectrophotometer. NMR (proton) spectra were taken with either a JEOLCO C-60HL high-resolution or a Varian Model T-60 spectrometer using tetramethylsilane as an internal standard in the specified solvent. Mass spectra were determined on a DuPont 21-490 mass spectrometer interfaced with a DuPont 21-094 data system; fragmentation was by electron impact at an ionizing voltage of 70 eV. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn., or Heterocyclic Chemical Corp., Harrisonville, Mo.

4-Acetamido-3-nitrophenol (6). Compound **5**[15] (44.4 g, 0.186 mol) was stirred in cold water maintained at 5 °C with an ice bath. A solution of 4 N NaOH was added dropwise at a rate which kept the temperature below 15 °C. After exactly 5 min, the mixture was filtered and the unreacted material washed with cold water. The combined filtrate and wash was kept cold, and concentrated HCl was slowly added until an orange solid had completely precipitated. After the entire process was repeated three times, only a small amount (1.2 g) of starting material remained unreacted. The orange precipitates were combined, filtered, washed with cold water, and crystallized from 50% ethanol to yield 31.9 g (89.7%, based on recovered starting material) of product, mp 221.5–222.5 °C (lit.[15] mp 218–220 °C).

1-(4-Acetamido-3-nitrophenoxy)-2,3-epoxypropane (7).[32] Made as previously described:[32] yield 65%; mp 121–122 °C (lit.[32] mp 117–118 °C).

1-(4-Acetamido-3-nitrophenoxy)-3-(isopropylamino)-2-propanol (8). A mixture of the epoxide **7** (2.5 g, 0.01 mol), isopropylamine (25 mL, 0.29 mol), and water (5 mL) was stirred and gently heated to reflux for 15 min. Stirring was continued for 45 min at room temperature, and then the solvents were evaporated. The residue was crystallized twice from ethyl acetate to yield a yellow solid: 1.5 g (48.2%); mp 149.5–150.0 °C. A small amount was recrystallized as the HCl salt, mp 163–165 °C. Anal. ($C_{14}H_{21}N_3O_5$) C, H, N.

1-(4-Amino-3-nitrophenyl)-3-(isopropylamino)-2-propanol (9). A suspension of **8** (1.3 g, 0.0042 mol) was stirred in boiling 4 N NaOH (15 mL) for 2 h. A red precipitate formed upon cooling. Crystallization from benzene yielded 0.70 g (62%) of fine, red crystals, mp 109–111 °C (173–174 °C as the HCl salt). Anal. ($C_{12}H_{19}H_3O_4$) C: calcd, 55.49; found, 53.39; H: calcd, 6.82; found, 7.50; N.

1-(5-Benzimidazoloxy)-3-(isopropylamino)-2-propanol (3). Method A. The HCL salt of **9** (6.5 g, 0.021 mol) and 97% formic acid (38 mL, 1.0 mol) were cooled in a hydrogenation bottle until frozen. Air was displaced with nitrogen, and 10% Pd/C (0.5 g) was quickly added. (These precautions were necessary due to the extreme flammability of formic acid in the presence of the catalyst.) The bottle was mounted on a Parr hydrogenator (low-pressure shaker type) equipped with a steam jacket, and the mixture was hydrogenated (2.8 kg/cm^2) at room temperature until hydrogen uptake ceased (1.5 h). The pressure was released, and the reaction was continued for 1.5 h under steam heat. The catalyst was removed by filtration and immediately washed with a small amount of water to prevent its combustion, and the filtrate was evaporated. The residue was dissolved in water, and 0.5 N NaOH was added to bring the solution to pH 10–11, resulting in an oily precipitate which formed a white solid after standing overnight at room temperature. Crystallization from 20% ethanol yielded 0.5 g (9.4%) of **3**, mp 166–168 °C. The mass spectrum (*m/e*) was consistent with the benzimidazole structure.

Method B. The dihydrochloride of **12** (4.0 g, 9.8 mmol) and 10% Pd/C (0.2 g) in 25% ethanol (20 mL) were hydrogenated under steam heat for 3.5 h. Catalyst was removed by filtration, and the solvents were evaporated. The residue was dissolved in a minimum amount of ethanol, and the solution was made basic with a slight excess of NaOH in methanol. Inorganic material was precipitated by the addition of ether and removed by filtration. Solvents were evaporated from the filtrate, and the remaining brown oil was crystallized from acetonitrile. Several recrystallizations from either acetonitrile or nitromethane gave a white solid (0.4 g, 17%), mp 164–166 °C. A small amount was converted to the monohydrochloride salt, mp 218 °C. Free base: IR (KBr) 1630 (s), 1585 (m), 1490 (s), 1445 (s), 1435 (s) cm^{-1} (bands characteristic of benzimidazoles[33]); NMR (Me_2SO-d_6) δ 8.03 (s, H_2, shifts to 9.39 ppm with DCl, indicates imidazole ring formation). Anal. ($C_{13}H_{19}N_3O_2$) C, H, N.

***N*-(4-Methoxy-2-nitrophenyl)benzylamine.** 4-Methoxy-2-nitroaniline (84 g, 0.50 mol), benzyl bromide (60 mL, 0.50 mol), K_2CO_3 (42 g, 0.30 mol), and toluene (500 mL) were stirred vigorously (overhead stirrer) and heated under reflux for 18 h. The mixture was then filtered hot using a steam-jacketed funnel. Once cool, the remaining red material in the funnel was washed into the filtrate with $CHCl_3$, leaving only inorganic residue. The filtrate was then evaporated and the resulting red oil crystallized from methanol. Recrystallization gave the pure product (56.2 g). Additional product (7.9 g) was obtained from the mother liquors by evaporating the methanol and extracting the remaining oil with dilute HCl/$CHCl_3$. Unreacted methoxynitroaniline was soluble in the aqueous phase, leaving impure product in the organic phase for eventual crystallization from methanol. The total yield was 64.1 g (50%), mp 105–106 °C (lit.[34] mp 105 °C).

1-Benzyl-5-methoxybenzimidazole. A mixture of *N*-(4-methoxy-2-nitrophenyl)benzylamine (19.7 g, 0.0764 mol) and 83% PtO_2 (0.7 g) in 97% formic acid (100 mL) (**Caution**: see method A for compound **3**) was hydrogenated (2.8 kg/cm^2) for 2 h. The reaction bottle was then heated, in place, with steam for 11 h. The catalyst was removed by filtration and the formic acid evaporated. The residue was dissolved in $CHCl_3$, treated with activated charcoal, and crystallized twice from CCl_4 to yield 12.2 g (67.0%) of white crystals, mp 111–113 °C. Anal. ($C_{19}H_{14}N_2O$) C, H, N.

1-Benzyl-5-hydroxybenzimidazole (10). 1-Benzyl-5-methoxybenzimidazole (14.1 g, 0.0592 mol) in 48% HBr (75 mL) was heated under reflux for 9 h. The solution was evaporated to dryness, and the residue was dissolved in hot water and neutralized with $NaHCO_3$. After cooling, the resulting precipitate was filtered and crystallized as the HCl salt with a 93.9% yield, mp 205–207 °C (HBr salt, mp 206–207 °C). The free base, mp 247–249 °C, was conveniently prepared by triturating the halide salt with 5% $NaHCO_3$ and thoroughly washing the white solid with water. Anal. ($C_{14}H_{12}N_2O$) C, H, N.

1-(1-Benzyl-5-benzimidazoloxy)-3-(isopropylamino)-2-propanol (12). The HCl salts of **10** (7.8 g, 0.030 mol) and **11**[35] (6.0 g, 0.039 mol) were dissolved in ethanol (75 mL) and heated at 115 °C in a sealed pressure container for 40 h. The ethanol was evaporated, and an aqueous solution of the residue was made basic with 1 N NaOH solution. Unreacted azetidinol was removed by azeotropic distillation with water. The remaining aqueous solution (about 100 mL) was refrigerated, and a solid, white precipitate was formed. The precipitate was filtered, washed with cold water, and then stirred in boiling water and filtered hot to remove some of the insoluble, unreacted hydroxybenzimidazole. The desired product was crystallized as the dihydrochloride salt:

8.1 g (65.8%); mp 238–240 °C. Free base, oil. Anal. ($C_{20}H_{27}Cl_2N_3O_2$) C, H, N.

***N,O*-Diacetyl-*o*-aminophenol (13).** *o*-Aminophenol (32.7 g, 0.0300 mol) was slowly added, with stirring, to acetic anhydride (62 mL, 0.65 mol), cooled with a dry ice–2-propanol bath. The mixture was then heated under reflux for 2.5 h. Solvent was removed by vacuum distillation, and the remaining yellow-brown solid was crystallized three times from toluene to yield 36.0 g (62.2%) of product: mp 126–127 °C (lit.[36] mp 123–124 °C).

***N,O*-Diacetyl-2-amino-3-nitrophenol (14).** Compound 13 (48.4 g, 0.251 mol) was suspended in acetic anhydride (150 mL) and cooled to −8 °C with a dry ice–2-propanol bath. Nitric acid (15.1 mL of 90%, 0.314 mol) in acetic anhydride (60 mL) was slowly added to the stirred suspension over a 15-min period. During this time, the temperature was allowed to slowly increase, and 24 min after the addition of nitric acid was begun a precipitate first appeared. After 34 min, the temperature had risen to almost 15 °C, and the reaction was terminated by filtering the precipitate through a cold sintered glass funnel and washing the residue with cold acetic anhydride (30 mL). The solid residue was crystallized four times from acetonitrile. The product (10.2 g, 17.2%) melted at 182–186 °C (lit.[18] mp 183 °C).

2-Acetamido-3-nitrophenol (15). Method A. The procedure was the same as that for 6. In this case, however, almost all starting material was consumed within 5 min, so the process was completed in a single step. Compound 15 was obtained from 14 in 95% yield, mp 170–173 °C (lit.[18] mp 169 °C).

Method B. Compound 13 (19.3 g, 0.1 mol) was suspended in acetic anhydride (125 mL), cooled to −45 °C, and stirred using an overhead stirrer with a large paddle. Nitric acid (14.1 mL of 90%, 0.30 mol) in acetic anhydride (25 mL) was slowly added over a 15-min period. The temperature of the mixture was allowed to slowly increase to −15 to −20 °C over a period of 2 h. The precipitate was then filtered with a sintered glass funnel and washed with a small amount of cold acetic anhydride and then cold water (200 mL). NMR analysis of the solid indicated the presence of 80–90% of the 3-nitro isomer by integration of the acetyl protons. The solid was then subjected to partial hydrolysis as described in method A. Crude compound 15 formed was mixed with iron filings and sublimed [100 °C (0.05 mm)]. An orange solid was collected and recrystallized from water to yield 8.0 g (41%) of long, orange crystals, mp 166 °C.

1-(2-Acetamido-3-nitrophenoxy)-2,3-epoxypropane (16). *N*-Acetyl-2-amino-3-nitrophenol (15) (5.9 g, 0.030 mol) and epichlorohydrin (24 mL, 0.31 mol) in 1.1 N NaOH (30 mL, 0.033 mol) were stirred at room temperature for 18 h. The resulting solid was crystallized twice from 20% ethanol to yield 3.6 g (47%) of product, mp 141–142 °C. Anal. ($C_{11}H_{12}N_2O_5$) C, H, N.

1-(2-Acetamido-3-nitrophenoxy)-3-(isopropylamino)-2-propanol (17). 1-(2-Acetamido-3-nitrophenoxy)-2,3-epoxypropane (16) (5.0 g, 0.020 mol), isopropylamine (50 mL, 0.59 mol), and water (5 mL) were stirred together at room temperature for 1.5 h. The solvents were evaporated, and the remaining yellow solid was crystallized from 20% ethanol to yield 5.3 g (85%) of product, mp 161–162 °C. Anal. ($C_{14}H_{21}N_3O_5$) C, H, N.

1-(2-Amino-3-nitrophenoxy)-3-(isopropylamino)-2-propanol (18). 1-(2-Acetamido-3-nitrophenoxy)-3-(isopropylamino)-2-propanol (17) (5.3 g, 0.017 mol) was stirred in boiling 4 N HCl (50 mL) for 2.5 h. The resulting solution was evaporated to dryness, and the remaining orange solid was crystallized from ethanol to yield 4.6 g (89%) of the HCl salt, mp 171–172 °C. Anal. ($C_{12}H_{20}ClN_3O_9$) C, H, N.

1-(4-Benzimidazoloxy)-3-(isopropylamino)-2-propanol (4). 1-(2-Amino-3-nitrophenoxy)-3-(isopropylamino)-2-propanol (18) hydrochloride (1.4 g, 0.0044 mol) and 10% Pd/C (0.1 g) in 97% formic acid (19 mL, 0.5 mol) (**Caution**: See method A for compound 3) were hydrogenated at room temperature until hydrogen uptake ceased. The mixture was then steam heated for 3 h. The catalyst was removed and the solution evaporated, leaving a red-brown oil. The crude product was crystallized as the dihydrochloride salt (ethanolic HCl–ether) and recrystallized twice from ethanol–ether to yield 0.6 g (43%) of fine grayish crystals, mp 218–221 °C (lit.[13] mp 202–203 °C); IR (KBr) 1620 (s), 1590 (m), 1465 (m), 1435 (s), and 1415 (s) cm^{-1} (bands characteristic of benzimidazoles[31]). Free base (oil): NMR (Me_2SO-d_6) δ 7.61 (s, H_2, shifts to 9.59 ppm with DCl, indicating ring closure). Mass spectrum (m/e) was consistent with the benzimidazole structure. Anal. ($C_{13}H_{21}Cl_2N_3O_2$) C, H, N.

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Book Reviews

Annual Reports on Fermentation Process. Volume 1. Edited by David Perlman. Academic Press, New York, N.Y. 1977. xi + 386 pp. 16 × 25 cm. $19.50.

This volume, the first in a new series edited by David Perlman, aims at a "critical account of significant developments published during the past 2 to 3 years concerning fermentation processes". In spite of this stated "goal" the volume includes several broad (and useful) chapters which would be well suited to a textbook, together with a second group which is devoted to quite specific subjects (chosen possibly by the availability of authors). The sections vary greatly, with the authors supposedly being asked to answer the question "what are the *major developments* in the field published recently". This question is answered well in some chapters (e.g., genetics and β-lactams) and virtually ignored in others (e.g., aeration and macrolides) where an encyclolpedic coverage and/or an undifferentiated listing of nearly all recently published literature is given.

The more general chapters of the volume include the following: a fine comprehensive and useful survey of genetic studies and approaches recently employed with industrial strains of microorganisms used for the production of antibiotics as well as other chemical and pharmaceutical products (Elander, Chang, and Vaughn); a brief section on culture maintenence which will at least serve as a useful guide to the literature (Perlman and Kikuchi); a thorough section on the complex problem of suitable (cost, availability, etc.) substrates for industrial-scale fermentations (Ratledge) together with another on the economic status of fermentation processes (Nyiri and Charles); an extremely detailed treatment of aeration (Tsao and Lee); and brief surveys of continuous fermentation (Dawson) and computer use in conuection with industrial fermentations (Dobry and Jost). The specific treatments include the following: single-cell protein (Laskin); enzymes of industrial interest (Aunstrup); immobilized cells (Abbott) and enzymes (Bernath, Venkatasubramanian, and Vieth); microbial transformation (Sebek and Kieslich); aminoglycoside (Nara); and β-lactam (Gorman and Huber) and macrolide antibiotics.

Published rapidly by a photo-offset process, this book will serve a useful purpose for many medicinal chemists and students. The general topics are excellent for students and others wishing knowledge of fermentation processes. The specific sections compete with many other review publications (Annual Reports in Medicinal Chemistry, etc.), and their interest to both students and research workers will be variable.

Northwestern University Medical and Dental Schools **John W. Corcoran**

Polymeric Drugs. Edited by L. Guy Donaruma and Otto Vogl. Academic Press, New York, N.Y. 1978. xii + 397 pp. 16 × 23 cm. $19.50.

"Polymeric Drugs" is the collected papers presented at the International Symposium on Polymeric Drugs, 173rd National Meeting of the American Chemical Society, March 20-25, 1977. It adds interesting and informative material to the rapidly accumulating literature dealing with biomedically useful polymers. The book opens with a general discussion of the benefits of polymeric drug delivery systems by Alejandro Zaffaroni and Pieter Bonsen of Alza Corp. who illustrate these benefits with three examples, two of which are the Ocusert and Progestasert (both Alza devices) and both of which use an inert polymer to control diffusion of the nonpolymeric drugs to the target organs.

However, the remainder of the book does not address this use of polymers; there is no discussion of systems which use either biodegradable or nonbiodegradable inert polymers either in reservoir or matrix devices. This is a rather surprising omission, as the editors have chosen a rather broad definition of the term drug: "... any compond, substance, or composition which when applied upon or introduced into a living system elicits a physiological response".

"Polymeric Drugs" does impress the reader with the breadth of its coverage, including papers on synthesis and structure–activity relationships, and a variety of specific applications including, but not limited to, UV absorbers, food additives, chemotherapy of microbial infections, antithrombogenic polymers, and interferon inducers.

The lack of certain emphases is surprising; very little attention is given to blood–tissue reactions to these materials or to the relation of biocompatibility to polymer structure and properties of polymeric excipients.

Finally, it is difficult to find either a specific thrust of the collection or organization of the material. All articles but one deal with human applications; the exception deals with a herbicide. It can be argued that this falls within the editors' definition of a drug, and, indeed, it does, but it hardly does justice to the agricultural/environmental applications of controlled delivery technology.

The order of the 14 papers following the introductory paper appears to be somewhat random. The material falls broadly into three convenient categories: structure-activity relationships (five papers), synthesis (three papers), and applications (six papers). Even though there is necessarily some overlapping of these categories, the editors have neglected an opportunity to present the reader with a more satisfying arrangement.

Dynatech Corporation **Joseph D. Gresser**
D. L. Wise

Saturated Heterocyclic Chemistry. Volume 5. Specialist Periodical Reports. By G. Pattenden, Senior Reporter. The Chemical Society, Burlington House, London. 1978. ix + 314 pp. 13.5 × 21.5 cm. $52.00.

A guide to the literature, "Saturated Heterocyclic Chemistry". Volume 5, is organized as the previous volumes, and the 1975 coverage is extensive. This final volume of the series retains the quality, excellent reporting, and concise review characteristic of Volumes 1-4 and is very useful to the medicinal chemist. The series will be missed.

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