of 50 mM potassium pyrophosphate buffer, pH 8.5, containing 5 mM α-ketoglutarate. Controls for each concentration of **3** (X = F) excluding enzyme were run concurrently. After a 60-min incubation period, a 550-μL aliquot of each sample was removed and added to 550 μL of a total ionic strength adjusting buffer (57 mL of glacial acetic acid, 58 g of NaCl, and 0.30 g of sodium citrate diluted to 500 mL with H_2O; pH 5.25) in a plastic vial and the concentration of fluoride ion measured with a fluoride ion electrode. Kinetic constants (K_m and V_{max}) were determined from linear regression analyses (correlation coefficients > 0.99) of Lineweaver–Burk plots.[37]

Time-Dependent Fluoride Ion Release from 3 (X = F). Pig brain GABA-T (0.11 unit) was incubated at 25 °C in 5.0 mL of a solution containing 0.12 mM **3** (X = F), 5 mM α-ketoglutarate, 50 mM potassium phosphate, and 5 mM β-mercaptoethanol at pH 7.0. A similar sample containing no enzyme served as a control. At various time intervals, 550-μL aliquots of the reaction mixture were removed, quenched by addition to an equal volume of total ionic strength adjusting buffer, and analyzed for fluoride ion concentration. Virtually no fluoride ion was released in the control after 60 min. The concentration of fluoride ion in the reaction mixture was plotted as a function of time.

Acknowledgment. We thank the National Institutes of Health (Grant NS 15703) for financial support of this work.

Registry No. GABA, 56-12-2; GABA-T, 9037-67-6; (*Z*)-**3** (x = Cl), 100702-76-9; (*Z*)-**3** (x = Cl), free base, 100702-84-9; (*Z*)-**3** (x = F), 100702-78-1; (*Z*)-**3** (x = F), free base, 100702-86-1; (*E*)-**3** (x = OH), 100702-77-0; (*E*)-**3** (x = OH), free base, 100702-85-0; **7** (R = Bu-*t*), 5105-79-3; **8** (R = Bu-*t*), 100702-79-2; **9** (R = Bu-*t*), 100702-80-5; (*E*)- **10** (R = Bu-*t*), 100702-81-6; (*Z*)-11 (R = Bu-*t*), 100702-82-7; (*Z*)-12 (R = Bu-*t*), 100702-83-8; PhSeBr, 34837-55-3; $PhCONHCH_2CH{=}C(CH_2OH)CO_2Me$-(*E*), 100702-87-2.

Improved Glucose Tolerance in Rats Treated with Oxazolidinediones

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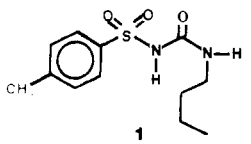
5-(2-Chloro-6-methoxyphenyl)oxazolidine-2,4-dione (**49**) is the most potent agent selected from a series of 5-substituted oxazolidinediones that were found to cause improvements in glucose tolerance in previously fasted rats and potentiation of insulin release in response to a glucose challenge. These compounds were unique in not producing hypoglycemia below the normal fasting glycemia levels. Substituent effects at positions 2–6 of the phenyl ring were investigated. Optimal positions for substitution were found to be the 2-, 5-, and 6-positions. Variations in the oxazolidinedione ring generally lead to loss of activity. The synthesis and structure–activity relationships of this series are detailed.

The search for drugs to treat non-insulin-dependent diabetes mellitus (NIDDM), recently estimated as 2.1% diagnosed in the population of the United States,[1] has been widely pursued for the past four decades. The culmination of early efforts was reported in the milestone papers of Haack[2a] and Ruschig[2b] describing the sulfonylurea (SU) drugs, e.g., tolbutamide (**1**), and was more recently reviewed by Sarges[1] and others.[3] However, after nearly 30 years of research, therapy for diabetics of this type remains largely restricted to the sulfonylureas[4] (SUs). Although SUs are valuable therapy, they possess disadvantages, e.g., primary or secondary failure of efficacy and induction of hypoglycemia, which have stimulated scientists to seek better antidiabetic drugs. Numerous other non-sulfonylurea classes of compounds have been clinically investigated in NIDDMs, with the most promising agents being varieties of aromatic and aliphatic carboxylic acids. Unfortunately, none of these has been sufficiently efficacious or well tolerated in man to have reached market status.



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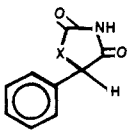

2 X=O
2a X=S

Because the greatest majority of hypoglycemic drugs discovered thus far have been acidic,[5] our research began a number of years ago to focus on acidic substances, excluding, however, the sulfonylurea class and the carboxylic acid functionality.[6] Attention was focused initially on heterocyclic acids and β-dicarbonyl structures. Among a group of simple aromatic acidic heterocycles chosen empirically for testing in the fasted rat glucose tolerance test, compounds **2** and **2a** showed remarkable improvements in iv glucose tolerance. Unique to **2**, as compared to **1**, was the powerful control of glycemia without a subsequent hypoglycemic effect commonly found with sulfonylureas[7] and carboxylic acids (Figure 1). Because of the significance of this observation and the attractive toleration profile found upon further pharmacological experimentation, **2** was selected as a lead to pursue extensive structure–activity relationship (SAR) studies. Some of the results of these investigations are reported here.

Chemistry. Recent advances in the synthesis of oxazolidinediones,[8] as well as earlier synthetic procedures,[9] were used to prepare the target molecules.[10] The method shown in Figure 2, starting with the readily available aldehydes, generally was found most expedient and reliable.

(1) Sarges, R. *Prog. Med. Chem.* **1981**, *18*, 191.
(2) (a) Haack, E. *Arzneim.-Forsch.* **1958**, *8*, 444. (b) Ruschig, H.; Korger, G.; Aumüller, N.; Wagner, H.; Weyer, R.; Bander, A.; Scholz, J. *Arzneim.-Forsch.* **1958**, *8*, 448.
(3) Other reviews: Keller, U.; Berger, W. *Schweiz. Med. Wochenschr.* **1983**, *113*, 645. Rasmussen, C. R. Maryanoff, B. E.; Tutwiler, G. F. *Ann. Rep. Med. Chem.* **1981**, *16*, 173 and references therein.
(4) The extent of biguanide therapy is minor and limited to some foreign markets; see ref 1.
(5) The pK_a of tolbutamide, **1**, is 7.14 in 1:1 dioxane–H_2O; other drugs are metabolized to acids.[1]
(6) The Sarges review summarizes the outcome of many of these clinical drug candidates.[1] Wreber, H.; Aumüller, W.; Muth, K.; Weyer, R.; Heerdt, R.; Fauland, E.; Bander, A.; Pfaff, W.; Schmidt, F. H.; Stork, H. *Arzneim.-Forsch.* **1969**, *19*, 1326. Rufer, C.; Biere, H.; Ahrens, H.; Loge, O.; Schroder, E. *J. Med. Chem.* **1974**, *17*, 708.
(7) Latter time points of Figure 1. The dangers of unpredictable hypoglycemic episodes involve coma and sometimes death.
(8) Schnur, R. C.; Sarges, R.; Peterson, M. J. *J. Med. Chem.* **1982**, *25*, 1451 and references therein.
(9) The chemistry of oxazolidinediones has been reviewed: Clark-Lewis, J. W. *Chem. Rev.* **1958**, *58*, 63.
(10) Schnur, R. C. U.S. Patent 4 399 296, 1983; 4 407 811, 1983; 4 448 971, 1984.

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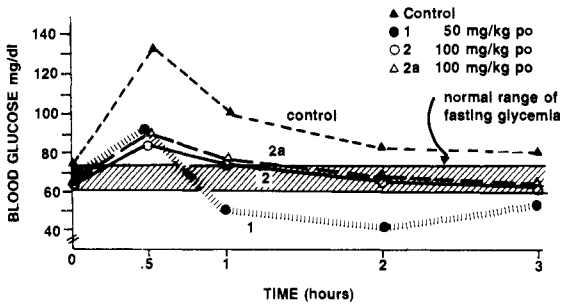


Figure 1. Rat blood glucose levels vs. time after an ip glucose tolerance test as described in the Biological Procedures section.

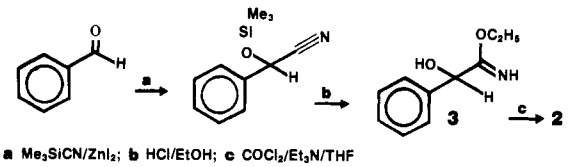


Figure 2.

Several advantages of this procedure make it ideal for preparing laboratory quantities of oxazolidinediones. Imidate salts **3** are prepared rapidly and in high yield from the crude, easily obtained silyl cyanohydrins, and they are separable from minor neutral contaminants very conveniently by trituration with organic solvents. These salts then can be converted cleanly under mild conditions to the bicarbonate-soluble, crystalline oxazolidinediones, e.g., **2**, which are readily purified by extraction. A more detailed description of the rationale and versatility of this scheme has been reported previously.[8] Alternative large-scale, optimized procedures were developed for preparing certain examples, e.g., compound **49**, and in these cases, aldehydes were converted to oxazolidinediones by adaptation of the Stoughton method[9] (Figure 3).

The oxazolidinedione ring proved to be stable to a large variety of reaction conditions used to prepare analogues. In the majority of cases of derivatization no attempt was made to optimize product yields. Nucleophilic substitution of aromatic fluorine by alkoxides, amide anion, or mercaptide often was used in analogue synthesis strategies with products being obtained in high yield and purity. The oxazolidinedione ring was also resistant to strong acid hydrolytic conditions (for example, hot concentrated HCl/formic acid) necessary to convert nitriles to amides and amides to acids. Reduction of nitro groups in hot acid with iron was also uneventful. Finally, chlorosulfonation of the aromatic ring proceeded smoothly without involvement of the oxazolidinedione. Thus, nucleophilic aromatic substitution was used in the prevention of **49** in high yield from **57**, **51** and **73–75** from **60**, **55** from **57**, **61** and **81–84** from **57**, **79** from **76**, and finally **42** from **38**. The chlorosulfonation and subsequent derivatization of oxazolidinedione **12** led to **45**, **66**, and **72**. Selective acid hydrolysis of nitrile **42** afforded either **43** or **44** by a controlled treatment with concentrated HCl/formic acid. Reduction of the nitro compounds **20**, **40**, and **52** was accomplished with iron/HCl to afford **22**, **46**, and **56**, respectively.

Members of this class of oxazolidinediones are chiral. One example, **34**, was resolved by complexation with L-cinchonidine to afford enantiomers **68**(−) and **69**(+), which were shown to be 73% ee and >99% ee, respectively, by rotation and chiral shift reagent NMR analysis.[11] Since tautomerism may occur by the equilibria shown in Figure 4, giving **4** and/or **5**, an attempt to estimate the rate of racemization was made. A 25 mM solution of **69** in 5% $NaHCO_3$ at room temperature was monitored for loss of rotation.[12] A half-racemization time of ca. 7 days without hydrolysis was observed.

For these studies, the novel aldehyde precursors[10] for compounds of Tables I and II generally were prepared by the Reiche[13] formylation procedure using α,α-dichloromethyl methyl ether and titanium tetrachloride with the appropriate aromatic substrate. Other aldehydes were obtained by metalation of the aromatic with *n*-butyllithium followed by treatment with DMF or *N*-methylformanilide.

Biological Procedures. The glucose tolerance improving activity of these oxazolidinediones was evaluated in male albino rats given a glucose tolerance test (GTT) in a modification of the method of Hoffman.[14] Test animals, in groups of five or six, were fasted 18–24 h and then dosed intraperitoneally with glucose (1 g/kg rat) and orally with either water (controls) or drug (ranging from 0.1 to 100 mg/kg). Blood glucose levels (mg/100 mL), sampled from the tail vein over a 0–3-h period were measured by the Technicon Autoanalyser ferricyanide method. The results shown as a percent lowering of blood glucose vs. controls[14] at 0.5 h are found in Table I. Clinically useful hypoglycemic drugs, e.g., **1**, show activity in this test. In general a blood glucose lowering of ≥9% is required before statistical significance at $P = 0.05$ is achieved. A few congeners had delayed hypoglycemic effect and are so noted.

Blood obtained after decapitation, bleeding, chilling, and centrifugation was assayed for insulin by the alcohol precipitation method of Hedding[15] using a rat radioimmunoassay kit and rat insulin standard (Novo Research Institute).

Results and Discussion

The oxazolidinedione ring substituted with a phenyl group at the C-5 position was selected as a lead for detailed structure–activity relationships (SAR) after investigating a number of heterocyclic ring variations, some of which are shown in Table II. The thiazolidinedione **2a**, while showing good efficacy at 100 mg/kg, proved not to be as potent as **2** in glucose-tolerance testing. Other examples of this class were similarly less active. The isosteric hydantoin **95** was inactive. Alkylation at N-3 or C-5 of the oxazolidinediones **92** and **93** resulted in loss of activity. Exchanging a carbonyl unit for an imine or thione, **94** and **96**, gave decreased or absent activity, while separation of the phenyl ring from the heterocycle by, for example, a methylene unit as in **97**, led to diminished or no activity.

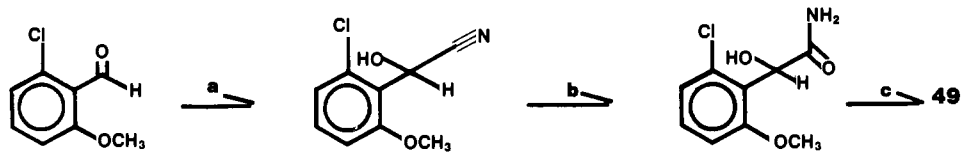
Members of the oxazolidinedione class cause glucose-tolerance improvement with a potency range greater than 3 orders of magnitude (**10** inactive at 100 mg/kg vs. **49** active at 0.63 mg/kg). Since wide ranges in activity were demonstrated among simple monosubstituted phenyl derivatives (**12** vs. **10**), a thorough study of substituent kind and position was undertaken. None of the compounds

(11) The chiral shift reagent experiment used tris[3-[(heptafluoropropyl)hydroxymethylene]-*d*-camphorato]europium(III) (Aldrich Chemical Co.) and **68** (or **69**) in a 0.66 to 1.0 ratio dissolved $CDCl_3$.

(12) A 0.025 M solution of compound **68** in 5% $NaHCO_3$ was monitored for loss in optical rotation during a 3-day period at room temperature. The half-racemization time as determined by extrapolation was ca. 7 days. No evidence of decomposition of **68** by ring opening was detectable.

(13) This method was found superior to the Vilsmeier procedure in all cases where the comparison was made. Rieche, A.; Gross, H.; Hoft, E. *Chem. Ber.* **1960**, *93*, 88.

(14) Hoffman, W. S. *J. Biol. Chem.* **1937**, *120*, 51; % BG lowering = [control blood glucose] − [treated blood glucose] × 100%/[control blood glucose].



a 1. $NaHSO_3$; 2. KCN/CH_2Cl_2; b HCO_2H/concHCl; c $(MeO)_2CO$/MeO-/MeOH

Figure 3.

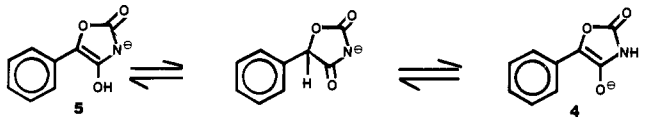


Figure 4.

with para substitution was superior to **2**. Some small electron-withdrawing substituents in the meta position enhanced activity, **27**, or left it essentially unchanged, **26** and **30**, while electron-donating groups and large groups had negative effects. A number of ortho moieties, particularly methoxy, **12**, caused enhanced activity.

The influence of substitution at positions 2 through 6 of the benzene ring may be deduced from selected di- and trisubstituted phenyl derivatives if the assumption of additivity for substituent effects is accurate. For this analysis of SAR the authors have adopted the convention that the *o*-methoxy has been ascribed position 2 (P-2) of the phenyl oxazolidinedione and a systematic investigation was made of positions 3, 5, and 6 (P-3, P-5, and P-6). Thus chlorine at P-3 caused decreased potency, **89** vs. **36**, while at P-5 and P-6, it resulted in substantially increased activity, **34** and **49** vs. **12**. Fluorine at P-3 resulted in essentially the same activity, **91** vs. **39**, and at P-5 and P-6 markedly enhanced effects, **36** and **50** vs. **12**. Bromine had effects like chlorine at P-5. Ethoxy, **13**, at P-2 was similar to methoxy, but higher alkoxy substitution at P-2 led to decreased activity, **16**, **73**, and **82–84**. Methyl at P-2 enhanced activity, **17** vs. **2**, but not as markedly as methoxy, **17** vs. **12**. Methyl at P-3, P-5, and P-6 lowered activity, **85** vs. **34**, **39** vs. **12**, and **80** vs. **12**, respectively. Other larger alkyl or electron-withdrawing, electron-donating, acidic, basic or neutral polar groups at the P-3, P-5, and P-6 resulted in diminished, though sometimes respectable, activity. The best compounds to emerge from this study were **34**, **49**, and **50**.

The blood glucose lowering effects of the resolved oxazolidinediones **68** and **69** were measured and revealed only a twofold stereoselectivity for the (−) rotating isomer **68**. Maximally effective oxazolidinediones of this class generally elicit a blood sugar lowering of ca. 35%, representing a flattening of the glucose tolerance test curve. Figure 1 shows that after fasting and drug treatment, the glucose load causes the blood sugar to rise to the normal fed level (ca. 100 mg/dL) but not above. Thereafter, blood glucose falls slowly but does not fall below the normal fasting level. More potent analogues of the series, e.g., **49**, show similar GTT curves (Figure 5). Measurement of circulating insulin during a similar GTT experiment showed that **49** caused markedly enhanced insulin levels (Figure 6) in the blood in response to the glucose challenge during a time frame that would be expected to effect a rapid lowering of blood sugar.

These results suggest that oxazolidinediones enhance natural metabolic processes, while glucose homeostasis as a whole is not overridden. Further reports are in preparation on extensions of this SAR work and on more detailed investigations into the mechanism of action of these compounds.

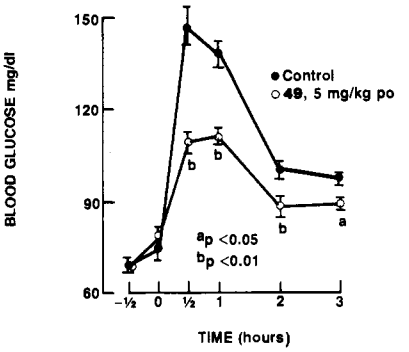


Figure 5. Compound **49** was administered 30 min prior to glucose (1 g/kg ip), which was given at 0 time. Values are ±SEM, n = 5.

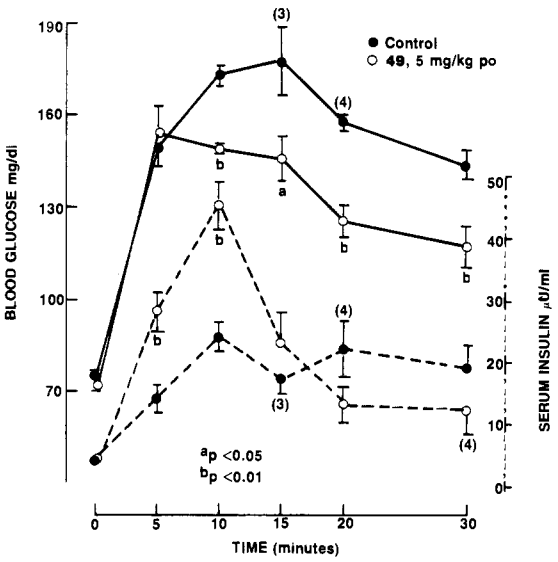


Figure 6. Compound **49** was administered 1 h prior to glucose (1 g/kg ip), which was given at 0 time. Values are ±SEM, n = 5 except where noted in parentheses.

Experimental Section

All melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. Microanalyses were performed by the Pfizer Central Research microanalysis laboratory, and results obtained for specified elements are within ±0.4% of the theoretical values unless otherwise denoted. IR spectra were obtained on a Perkin-Elmer Model 21 spectrophotometer using the stipulated solvents and are reported in reciprocal centimeters. ^1H NMR spectra of $CDCl_3$, CD_3OD, or $(CD_3)_2SO$ solutions [internal $(CH_3)_4Si$, δ 0] were recorded on a Varian A-60 or Perkin-Elmer T-60 spectrometer. High-resolution mass spectral data were recorded on an A.E.I. MS-30 instrument. Low-resolution mass spectral data were recorded on an Hitachi RMU6-E spectrometer. All aldehyde precursors employed in these syntheses were either commercially available or known. The preparation

of many of the unusually substituted aldehydes may be found in ref 11.

Method A. 5-(2-Methoxyphenyl)oxazolidine-2,4-dione (12). 2-Methoxybenzaldehyde (25 g, 0.18 mole) was dissolved in 150 mL of methylene chloride and cooled to 0–5 °C. Zinc iodide (500 mg) was added, followed by dropwise addition of trimethylsilyl cyanide (21.8 g, 0.22 mol). The reaction mixture was stirred for about 65 h at room temperature, then washed twice with saturated sodium bicarbonate, dried over anhydrous sodium sulfate, filtered, and evaporated to yield 2-(2-methoxyphenyl)-2-(trimethylsiloxy)ethanenitrile as an oil [41 g, 97%; IR (CH_2Cl_2) 1600, 1486, 1460, 1075; *m/e* 235]. Without further purification, 20 g was converted to the imidate by addition to a solution of ethanol (250 mL) saturated with hydrogen chloride at 0–5 °C. The reaction was held at 5 °C for 16 h. Evaporation of the reaction mixture and trituration of the residue with ether afforded ethyl 1-hydroxy-1-(2-methoxyphenyl)methanecarboximidate hydrochloride [18.6 g, 89%; mp 122–124 °C dec; *m/e* 209].

Ethyl 1-hydroxy-1-(2-methoxyphenyl)methanecarboximidate hydrochloride (18 g, 0.073 mol) was suspended in 500 mL of tetrahydrofuran, cooled to 0–5 °C, and triethylamine (23.6 g, 0.234 mol) was added. The stirred reaction mixture was perfused with phosgene for 30 min. Stirring at 0–5 °C was continued for 1 h. The reaction mixture was slowly poured over 1 L of crushed ice and product extracted into three portions of chloroform. The combined chloroform extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered, and evaporated to solids. The residue was recrystallized from toluene to yield 5-(2-methoxyphenyl)oxazolidine-2,4-dione (6.4 g, 42%; mp 175–177 °C; IR (KBr) 1802, 1724; *m/e* 207). A second crop (3.7 g, 24%, mp 175–177 °C) was obtained from the toluene mother liquor. Anal. ($C_{10}H_9O_4N$) C, H, N.

5-[2-(2-Methylureido)phenyl]oxazolidine-2,4-dione (19). Compound **22** (1.00 g, 4.4 mmol) was suspended in 50 mL of dichloroethane at 50 °C and treated with pyridine (0.35 g, 4.4 mmol) and methyl isocyanate (0.52 mL, 8.8 mmol) for 24 h. The cooled reaction mixture was partitioned between ethyl acetate and 1 N NaOH. The aqueous layer was washed with ethyl acetate, acidified with 1 N HCl, and extracted with three portions of ethyl acetate. These latter organic fractions were pooled, washed with brine, dried with $MgSO_4$, filtered, and concentrated in vacuo to an oil, which recrystallized from hot toluene/methanol and afforded **19** [400 mg, 37%; mp 186–188 °C dec; IR (KBr) 1812, 1854, 1675; anal. ($C_{11}H_{11}N_3O_4$) C, H, N].

5-[2-(Cyclohexylureido)phenyl]oxazolidine-2,4-dione (21). Compound **21** was prepared from cyclohexyl isocyanate isocyanate (1 equiv) and **22** by using the procedure for the preparation of compound **19** except that a 48-h reaction period was employed [0.655 g, 47%; mp 185–187 °C; IR (KBr) 1812, 1754, 1600; anal. ($C_{16}H_{19}N_3O_4$) C, H, N].

5-(2-Aminophenyl)oxazolidine-2,4-dione Hydrochloride (22). 5-(2-Nitrophenyl)oxazolidine-2,4-dione (5.0 g, 22.5 mmol) was taken up in a mixture of methanol (11.5 mL) and concentrated hydrochloric acid (12.3 mL). Powdered iron (3.77 g, 67.5 mmol) was added over 30 min, during which an exothermic reaction brought the temperature to reflux and the mixture became homogeneous. The mixture was cooled to room temperature and stirred for 3 h. Additional iron powder (1.2 g) was added and the mixture stirred for 0.5 h, poured into 100 mL of water, and extracted with three portions of ethyl acetate. The combined ethyl acetate extracts were back washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and evaporated in vacuo to a foam. The crude product was taken up in 55 mL of ethanol, cooled to 0 °C, perfused with hydrogen chloride for 10 min (crystallization began at this stage), diluted with ether, and filtered to recover purified 5-(2-aminophenyl)oxazolidine-2,4-dione hydrochloride [2.52 g, mp 205–209 °C dec; *m/e* 192; anal. ($C_9H_8O_3N_2$·HCl) C, H, N].

5-[2-[(Phenylsulfonyl)amino]phenyl]oxazolidine-2,4-dione (23). Compound **22** (1.00 g, 4.40 mmol), pyridine (0.71 mL, 8.80 mmol) and benzenesulfonyl chloride (0.561 mL, 4.40 mmol) were reacted in 100 mL of dichloromethane at room temperature for 16 h. The reaction mixture was filtered to afford crude **23** (1.23 g, 84%; mp 141–144 °C), which recrystallized from isopropyl alcohol [0.99 g, 68%; mp 144–146 °C; IR (KBr) 1818, 1754, 1351, 1330; anal. ($C_{15}H_{12}N_2O_5S$) C, H, N].

5-(2-Acetamidophenyl)oxazolidine-2,4-dione (24). 5-(2-Aminophenyl)oxazolidine-2,4-dione hydrochloride (1 g, 4.37 mmol) was taken into 15 mL of glacial acetic acid. Sodium acetate (358 mg, 4.37 mmol) was added and then, in a dropwise manner, acetic anhydride (449 mg, 0.41 mL, 4.37 mmol). The reaction mixture was stirred at room temperature for 16 h, poured into 50 mL of water, and extracted with three portions of ethyl acetate. The combined extracts were washed with two portions of water and then one of brine, dried over anhydrous magnesium sulfate, filtered, and evaporated in vacuo to give solids (0.72 g). Recrystallization from ethyl acetate gave purified 5-(2-acetamidophenyl)oxazolidine-2,4-dione in two crops [0.26 g, mp 197–198 °C; *m/e* 234; anal. ($C_{11}H_{10}O_4N_2$) C, H, N].

5-[2-[(Methylsulfonyl)amino]phenyl]oxazolidine-2,4-dione (25). Compound **22** (0.400 g, 1.70 mmol), pyridine (0.274 mL, 3.40 mmol), and methanesulfonyl chloride (0.132 mL, 1.70 mmol) were reacted in 40 mL of dichloroethane at room temperature for 16 h and then concentrated to a gummy solid. This was partitioned between 1 N NaOH and ethyl acetate. The aqueous phase was washed with ethyl acetate, acidified with 1 N HCl, and extracted with three portions of ethyl acetate. The latter organic fractions were pooled, washed with brine, dried with $MgSO_4$, filtered, and concentrated in vacuo to a gummy solid, which recrystallized from isopropyl ether [0.211 g, 46%; mp 205–208 °C). This was recrystallized from methanol to afford pure **25** [0.152 g, 33%; mp 207–209 °C; IR (KBr) 1808, 1724, 1389, 1361; anal. ($C_{10}H_{10}N_2O_5S \cdot {}^1/_4H_2O$) C, H, N].

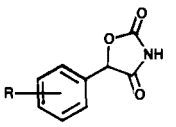
5-[4-[2-[(2-Methoxynicotinoyl)amino]ethyl]phenyl]oxazolidine-2,4-dione (31). 2-Methoxynicotinoyl chloride (15.7 g, 0.076 mmol; prepared from the acid and SO_2Cl_2 in refluxing CH_2Cl_2 after 2 h, followed by vacuum evaporation) was dissolved in 250 mL of $CHCl_3$ and added dropwise to a rapidly stirred solution of 2-(aminoethyl)benzene (9.20 g, 0.076 mol) in 150 mL of $CHCl_3$ while a solution of Na_2CO_3 monohydrate (28.3 g, 0.228 mol) in 250 mL of H_2O was simultaneously added. After the 0.25-h addition period and a further 1-h reaction period, the layers were separated, the aqueous layer was washed with 100 mL of $CHCl_3$, and the pooled organic layers were dried ($MgSO_4$), filtered, and evaporated in vacuo to a crude solid; quantitative, 62–65 °C. Spectral data were in accord with the desired amide structure, and the sample was used in the subsequent formylation step without further purification. Thus the amide (2.60 g, 0.01 mol) in 20 mL of dry CH_2Cl_2 was treated with $TiCl_4$ (15.18 g, 0.08 mol) at 0 °C for 2.5 h. The mixture was quenched with 250 mL of saturated $NaHCO_3$ and extracted with 3 × 100 mL of $CHCl_3$. The aqueous was filtered of insoluble material and reextracted with 3 × 100 mL of $CHCl_3$. The pooled organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo to a residue, which was chromatographed on silica gel, eluting with 4:1 $CHCl_3$–EtOAc. Fractions containing the desired 4-[2-[(2-methoxynicotinoyl)amino]ethyl]benzaldehyde were obtained as a pale colorless oil; 1.06 g, (37%). All analytical data were in accord with the assigned structure. The corresponding oxazolidinedione (**31**) was prepared from this aldehyde by method A without incident.

5-[2-(2-Chloroethoxy)phenyl]oxazolidine-2,4-dione. This compound, an intermediate in the preparation of compound **33**, was prepared by method A from 2-(2-chloroethoxy)benzaldehyde.[16] The yield of imidate was 81%, mp 126–128 °C dec. The oxazolidinedione was obtained in 72%, mp 169–171 °C; IR (KBr) 1812, 1725; anal. ($C_{11}H_{10}NO_4Cl$) C, H, N. NMR and mass spectral and analytical data were in accord with the proposed structure.

5-[2-(2-Imidazol-1-ylethoxy)phenyl]oxazolidine-2,4-dione (33). The preceding oxazolidinedione (1.02 g, 4.00 mmol) and imidazole (0.544 g, 8.00 mmol) were fused at 120 °C for 12 min while the reaction was monitored by thin-layer chromatography. The mixture was cooled, dissolved in 1 N NaOH, and washed with ethyl acetate. The aqueous layer was acidified with 1 N HCl to pH 6 and extracted with three portions of ethyl acetate. The later pooled organic layers were dried with $MgSO_4$, filtered, and concentrated in vacuo to a viscous oil that crystallized from hot toluene [0.219 g, 20%; mp 209–212 °C dec; IR (KBr) 1818, 1799,

(15) Hedding, L. G. *Diabetologia* **1972**, *8*, 260.
(16) Katz, L.; Karger, Schroeder, W.; Cohen, M. S. *J. Org. Chem.* **1953**, *18*, 1380.

Table I. GTT Results of Substituted Phenyl Oxazolidinediones in Fasted Rats



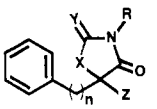
no.	substituent (R)	dose	act.[a]	mp, °C	formula	% yield	preparation[b] method	imidate yield	imidate mp, °C
2		10	13	105[c]	$C_9H_7NO_3$	67	A/B	89	119–21
6	4-Cl	50	12	151–3[d]	$C_9H_6ClNO_3$	50	B		
7	4-OCH_3	100	19	128–9.5[e]	$C_{10}H_9NO_4$	50	B		
8	4-OCH_2CH_3	100	18	123–5	$C_{11}H_{11}NO_4$	39	A		
9	4-CH_3	100	10	127–9[f]	$C_{10}H_9NO_3$	59	A		
10	4-NH_2	100	i	186–8[g]	$C_9H_8N_2O_3$	52	C		
11	4-F	100	21	154–5	$C_9H_6FNO_3$	53	A		
12	2-OCH_3	5	14	175–7	$C_{10}H_9NO_4$	66	A	89	122–4
13	2-OCH_2CH_3	5	15	165–7	$C_{11}H_{11}NO_4$	70	A	75	112–4
14	2-CF_3	10	11	91–3	$C_{10}H_6F_3NO_3$	54	A	25	oil
15	2-Cl	10	11	106–8	$C_9H_6ClNO_3$	68	A	85	127–9
16	2-$OCH_2C_6H_5$	100	11	191–3	$C_{16}H_{13}NO_3$	55	A	72	oil
17	2-CH_3	10	14	111–3	$C_{10}H_9NO_3$	77	A	92	123–5
18	2-F	5	10	129–31	$C_9H_6FNO_3$	60	A	89	123–31
19	2-$NHCONHCH_3$	100	i	186–8	$C_{11}H_{11}N_3O_4$	37	D		
20	2-NO_2	25	11	113–115	$C_9H_6N_2O_5$	76	A	92	135–6
21	2-NHCONH-c-$C_{16}H_{11}$	25	i	187 dec	$C_{16}H_{19}N_3O_4$	47	D		
22	2-NH_2	25	15	205–209	$C_9H_8N_2O_3$·HCl	49	D		
23	2-$NHSO_2C_6H_5$	25	i	144–146	$C_{15}H_{12}N_2O_5S$	68	D		
24	2-$NHCOCH_3$	5	14	197–198	$C_{11}H_{10}N_2O_4$	11	D		
25	2-$NHSO_2CH_3$	25	i	207–209	$C_{10}H_{10}N_2O_5S$	46	D		
26	3-Cl	100	26	142–4	$C_9H_6CNO_3$	56	A	87	117–20
27	3-CF_3	10	17	97–9	$C_{10}H_6F_3NO_2$	69	A	70	oil
28	3-OC_6H_5	100	12	104–6	$C_{15}H_{11}NO_4$	66	A	88	120–3
29	3-OCH_3	10	i	85–7	$C_{10}H_9NO_4$	53	A		
30	3-F	10	10	147–9	$C_9H_6FNO_3$	56	A	95	121–3
31	4-CH_2CH_2-N-(2-OMe-nicotinoyl)	100	26	215–7	$C_{18}H_{17}N_3O_5$	36	A		
32	4-O-$CH_2C_6H_5$	100	20	161–2	$C_{16}H_{13}NO_4$	9	A		
33	2-O-CH_2CH_2-imidazol-1-yl	25	i	209–212 dec	$C_{14}H_{13}N_3O_4$	20	D		
34	2-OCH_3, 5-Cl	1	12	178–80	$C_{10}H_8ClNO_4$	69	A	91	142–4
35	2-OCH_3, 5-CH_3	10	21	134–6[h]	$C_{11}H_{11}NO_3$	55	A	82	120–2
36	2-OCH_3, 5-F	2.5	15	186–8	$C_{10}H_8FNO_3$	60	A	77	135–7
37	2-OCH_3, 5-OCH_3	10	i	133–135	$C_{11}H_{11}NO_5$	57	A		
38	2-OCH_3, 5-Br	5	22	166–169	$C_{10}H_8BrNO_4$	76	A	88	*j*
39	2-OCH_3, 5-CH_3	2.5	10	165–167	$C_{11}H_{11}NO_4$	63	A	52	131–4
40	2-OCH_3, 5-NO_2	25	17	205–207	$C_{10}H_8N_2O_6$	60	A	89	158–61
41	2-OCH_3, 5-*i*-C_3H_7	10	i	138–139	$C_{13}H_{15}NO_4$	39	A		
42	2-OCH_3, 5-CN	25	19	207–209	$C_{11}H_8N_2O_4$[k]	51	D		
43	2-OCH_3, 5-$CONH_2$	25	i	266–268 dec	$C_{11}H_{10}N_2O_4$	62	D		
44	2-OCH_3, 5-CO_2H	25	i	287–289	$C_{11}H_9NO_6$	61	D		
45	2-OCH_3, 5-$SONH_2$	10	i	222–4	$C_{10}H_{10}N_2O_6S$	27	C		
46	2-OCH_3, 5-NH_2	25	i	206–208 dec	$C_{10}H_{10}N_2O_4$	56	D		
47	2-OC_2H_5, 5-F	5	9	188–190	$C_{11}H_{10}FNO_4$	82	A	81	*j*
48	2-OC_2H_5, 5-Cl	5	11	197–199	$C_{11}H_{10}ClNO_4$	40	A	quant	*j*
49	2-OCH_3, 6-Cl	0.63	11	200–203	$C_{10}H_8ClNO_4$	84	D	45	131
50	2-OCH_3, 6-F	1	11	139–141	$C_{10}H_8FNO_4$	14	D		
51	2-OC_2H_5, 6-F	5	9	127–128	$C_{11}H_{10}FNO_4$	30	A	51	*j*
52	2-OCH_3, 6-NO_2	25	10	181–183	$C_{10}H_8N_2O_6$	86	A	91	132–5
53	2-OCH_3, 6-OCH_3	10	12	212–213	$C_{11}H_{11}NO_5$	44	A		
54	2-OCH_3, 6-$NHCOCH_3$	25	i	232–234 dec	$C_{12}H_{12}N_2O_5$	56	D		
55	2-SCH_3, 6-Cl	25	21	136–138	$C_{10}H_8ClNO_3S$	23	D		
56	2-OCH_3, 6-NH_2	25	i	>300	$C_{10}H_{10}N_2O_4$·HCl	56	D		
57	2-F, 6-Cl	10	12	153–155	$C_9H_5ClFNO_3$	83	A	94	129–30
58	2-Cl, 6-NO_2	25	i	190–191	$C_9H_5ClN_2O_5$[l]	21	A		
59	2-Cl, 6-Cl	25	21	151–153	$C_9H_5Cl_2NO_3$	56	D		
60	2-F, 6-F	25	25	196–198	$C_9H_5F_2NO_3$	57	A	88	135–7
61	2-OBn, 6-Cl	25	i	179–180	$C_{16}H_{12}ClNO_4$[m]	9	D		
62	2-CH_3, 6-CH_3	10	13	136.5–137.5	$C_{11}H_{11}NO_3$	61	A		
63	2-OCH_3, 3-OCH_3	50	12	160–2[d]	$C_{11}H_{11}NO_5$	73	A		
64	2-OCH_3, 4-OCH_3	25	10	178–80[e]	$C_{11}H_{11}NO_5$	40	C		
65	3,4-O-CH_2-O	100	18	148–50	$C_{10}H_7NO_5$	65	A		
66	2-OCH_3, 5-$SO_2N(CH_3)_2$	10	i	182–4	$C_{12}H_{14}N_2O_6S$	57	D		
67	2-CH_3, 5-F	25	19	104–108	$C_{10}H_8FNO_3$	22	A		
68(–)	2-OCH_3, 5-Cl	2.5	26	164–6	$C_{10}H_8ClNO_4$	28	D		
69(+)	2-OCH_3, 5-Cl	2.5	12	171–4	$C_{10}H_8CNO_4$	47	D		
70	2-OCH_3, 5-CH_2CH_2-imidazol-1-yl	25	i	170 dec	$C_{15}H_{15}N_3O_4$[n]	26	D		
71	2-OCH_3, 5-C_6H_5	25	i	225–227	$C_{16}H_{13}NO_4$	57	A		
72	2-OCH_3, 5-$SO_2NHCONH$-c-C_6H_{11}	25	i	178	$C_{17}H_{21}N_3O_7S$	34	D		
73	2-O-*i*-C_3H_7, 6-F	25	15	198–9	$C_{12}H_{11}FNO_4$[o]	38	D		

Table I (Continued)

no.	substituent (R)	dose	act.[a]	mp, °C	formula	% yield	preparation[b] method	imidate yield	imidate mp, °C
74	2-SCH_3, 6-F	25	18	134–5	$C_{10}H_8FNO_3S$	36	D		
75	2-SC_2H_5, 6-F	25	17	97–9	$C_{11}H_{10}FNO_3S$	10	D		
76	2-CF_3, 6-F	25	i	124–5	$C_{10}H_5F_4NO_3$	58	A		
77	2-CF_3, 4-F	10	i	134–5	$C_{10}H_5F_4NO_3$	96	A		
78	2-OCH_3, 5-C_2H_5	25	10	138–9	$C_{12}H_{13}NO_4$	64	A		
79	2-OCH_3, 6-CF_3	25	i	197–200	$C_{11}H_8F_3NO_4$[p]	40	D		
80	2-OCH_3, 6-CH_3	10	10	194–6	$C_{11}H_{11}NO_4$	54	D		
81	2-pyrrol-1-yl, 6-Cl	10	i	114–6	$C_{13}H_9ClN_2O_3$	13	D		
82	2-OCH=$CHCH_3$, 6-Cl	10	i	122–5	$C_{12}H_{10}ClNO_4$[q]	14	D		
83	2-OCH_2-c-C_3H_5, 6-Cl	10	i	188–9	$C_{13}H_{12}ClNO_4$	65	D		
84	2-$OCH_2CH{=}CH_2$, 6-Cl	2.5	17	114–6	$C_{12}H_{10}ClNO_4$[r]	4	D		
85	2-OCH_3, 3-CH_3, 5-Cl	10	17	184–6	$C_{11}H_{10}ClNO_4$	83	A	89	131–3
86	2-Cl, 4-CH_3, 5-OCH_3	10	i	204–6	$C_{11}H_{10}ClNO_4$	77	A		
87	2-OCH_3, 4-CH_3, 5-Cl	10	i	176–8	$C_{11}H_{10}ClNO_4$	49	A		
88	2-OCH_3, 5-Cl, 6-CH_3	10	12	193–5	$C_{11}H_{10}ClNO_4$	54	A	94	137–9
89	2-OCH_3, 3-Cl, 5-F	10	15	177–9	$C_{10}H_7ClFNO_4$	57	A	91	132–4
90	2-CH_3, 4-F, 5-OCH_3	10	i	144–5	$C_{11}H_{10}FNO_3$	79	A		
91	2-OCH_3, 3-F, 5-CH_3	10	17	138–9	$C_{11}H_{10}FNO_4$[s]	44	A	75	105–6

[a] Percent blood sugar lowering; [15]i = inactive. [b] Method A is shown in Figure 2; method B is that of Traube, W.; Ascher, R. *Chem. Ber.* **1913**, *46*, 2077; method C is that reported by Pellizzari, G. *Gass. Chim. Ital.* **1887**, *17*, 409; method D, see Experimental Section. [c] W. Traube (see footnote *b*). [d] Najer, H.; Guidicelli, R.; Joannic-Voisinet, E.; Joannic, M. *Bull. Soc. Chem. Fr.* **1961**, 1226. [e] King, F. E.; Clark-Lewis, J. W. *J. Chem. Soc.* **1951**, 3077. [f] Albert, A. *Fortsch. Chem. Org. Naturst.* **1954**, *11*, 356. [g] G. Pellizzari (see footnote *b*). [h] Aspelund, H. *Acta. Acad. Abo. Ser. B*, **1939**, *12*, 15. [j] Waxy solid. [k] Calcd: N, 12.07. Found: 11.42. [l] Calcd: C, 42.13. Found: 42.93. [m] Calcd: C, 60.48. Found: 59.89. [n] Calcd: C, 50.64. Found: 51.29. [o] Calcd: H, 4.38. Found: 4.82. [p] Calcd: H, 3.44. Found: 2.80. [q] Calcd: 53.85. Found: 53.32. [r] Calcd: C, 53.85. Found: 53.08. [s] Calcd: C, 55.23. Found: 54.77.

Table II. GTT Results of Phenyl Heterocycles in Fasted Rats



no.	R	X	Y	Z	*n*	dose	act.[a]	ref
2	H	O	O	H		100	35	*b*
						25	26	
92	H	O	O	C_2H_5		100	i	*c*
93	CH_3	O	O	H		100	i	*d*
2a	H	S	O	H		100	34	*e*
						25	i	
94	H	O	NH	H		100	i	*b*
95	H	NH	O	H		100	i	*f*
96	H	O	S	H		100	17	*g*
97	H	O	O	H	1	25	9	*h*

[a] See Table I, footnote *a*. [b] See Table I, footnote *b*. [c] Altwegg, J.; Ebin, D. U.S. Patent 1 375 949, 1921. [d] Iwaya, K.; Namikawa, Y.; Mitsuhashi, S.; Yoshida, K. *J. Pharm. Soc. Jpn.* **1940**, *69*, 248. [e] Eberly, F. A.; Dains, F. B. *J. Am. Chem. Soc.* **1936**, *58*, 2546. [f] Bergs, H. German Patent 466,094, 1929, *Chem. Abstr.* **1933**, *27*, 1001. [g] Ushenko, N. K.; Gorizdra, T. E. *Ukrain. Khim. Zh.* **1950**, *16*, 545; *Chem. Abstr.* **1954**, *48*, 11391e. [h] Aspelund, H. *Acta Acad. Abolnsis Math Phys.* **1936**, *10(1)*, 12 (see footnote 11).

1739, 1605; anal. ($C_{14}H_{13}N_3O_4 \cdot {}^1/_2CH_3CO_2H$) C, H, N]. The NMR spectrum indicated the presence of $^1/_2$ equiv of acetic acid likely arising during the workup and isolation.

5-(5-Cyano-2-methoxyphenyl)oxazolidine-2,4-dione (42). 5-(5-Bromo-2-methoxy)oxazolidine-2,4-dione (**38**; 8 g, 0.028 mol) was dissolved in 50 mL of dimethylformamide. Cuprous cyanide [$(CuCN)_2$, 78.52 g, 0.042 mol] was added and the reaction mixture heated to reflux for 22 h. To force the reaction to completion, an additional one-tenth portion (752 mg) of cuprous cyanide was added and reflux continued for a further 7 h. The reaction mixture was cooled to room temperature and most of the dimethylformamide removed by vacuum distillation. The residue was partitioned between ethyl acetate (250 mL) and 1 N hydrochloric acid (250 mL). The organic layer was separated, washed in sequence with two portions of fresh 1 N hydrochloric acid, twice with 100-mL portions of 10% ferric chloride in 3 N hydrochloric acid and once with brine, dried with $MgSO_4$, filtered, and concentrated to a solid. Recrystallization form toluene/methanol gave purified 5-(5-cyano-2-methoxy)oxazolidine-2,4-dione in two crops [3.32 and 0.45 g, 58%, mp 207–209 °C, *m/e* 232; anal. ($C_{11}H_8N_2O_4$) C, H, N].

5-[5-(Aminocarbonyl)-2-methoxyphenyl]oxazolidine-2,4-dione (43). A solution of compound **42** (2.00 g, 8.60 mmol), 25 mL of formic acid, and 25 mL of concentrated HCl was heated at 70 °c for 19 h. The mixture was concentrated in vacuo to a solid, which was triturated with H_2O, filtered, and dried (2.02 g, 94%). Recrystallization from methanol afforded pure **43** [1.33 g, 62%; mp 266–268 °C dec; IR (KBr) 1812, 1792, 1724, 1652; anal. ($C_{11}H_{10}N_2O_5 \cdot {}^1/_4H_2O$) C, H, N].

5-(5-Carboxy-2-methoxyphenyl)oxazolidine-2,4-dione (44). Extended reaction times of the above hydrolysis procedure afforded the acid. Thus a solution of **43** (0.500 g, 2.00 mmol), 5 mL of formic acid, and 5 mL of concentrated HCl were refluxed for 24 h, cooled, and filtered. The solid was washed with water and dried to afford pure **44** [0.305 g, 61%; mp 27–289 °C; IR (KBr) 1802, 1748; anal. ($C_{11}H_9NO_6$) C, H, N].

5-[5-(Aminosulfonyl)-2-methoxyphenyl]oxazolidine-2,4-dione (45). A mixture of compound **12** and chlorosulfur acid (5 mL) was reacted at room temperature for 30 min and then poured onto ice/H_2O. The aqueous was extracted with 3 × 100 mL of methylene chloride. The pooled organic layers were dried with $MgSO_4$, filtered, and concentrated in vacuo to 100 mL. This solution was perfused with NH_3 for 30 min to afford a heterogeneous reaction mixture. The residue obtained after concentration in vacuo was dissolved in 1 N NaOH and washed with three portions of ether. The aqueous was poured into 1 N HCl with stirring and scratching to expedite crystallization. The solid obtained after filtration was washed with water, air-dried, and recrystallized from isopropyl alcohol [0.270 g, 27%, mp 222–224 °C; IR (KBr) 1845, 1754, 1605, 1374, 1337; anal. ($C_{10}H_{10}N_2O_6S$) C, H, N].

5-(5-Amino-2-methoxyphenyl)oxazolidine-2,4-dione (46).

A solution of compound **40** (2.38 g, 9.40 mmol), 5 mL of methanol, and 5 mL of concentrated HCl was stirred while iron (1.56 g, 28.0 mmol) was added in three portions. An exothermic reaction ensued and subsided. After 3 h at room temperature some starting material remained by thin-layer chromatography analysis, and an additional 0.456 g of iron and 1 mL of concentrated HCl were added. After 18 h at room temperature the reaction mixture was poured into 50 mL of H_2O and extracted with three portions of ethyl acetate. The pooled organic layers were washed with brine, dried with $MgSO_4$, filtered, and concentrated in vacuo to a solid, which recrystallized from methanol [1.33 g, 56%; mp 206–208 °C dec; IR (KBr) 1805, 1754; anal. ($C_{16}H_{19}N_2O_4$) C, H, N].

5-(2-Chloro-6-methoxyphenyl)oxazolidine-2,4-dione (49). 5-(2-Chloro-6-fluorophenyl)oxazolidine-2,4-dione (**57**; 22 g, 0.096 mol) was taken into a mixture of dimethyl sulfoxide (100 mL) and methanol (31.5 mL). Sodium methoxide (10.8 g, 0.2 mol) was added over about 4 min, during which time the temperature of the reaction mixture rose to 57 °C. As a matter of convenience the reaction mixture was allowed to stand for 16 h at room temperature before heating at 106 °C for 5 h. After cooling to 65 °C, the reaction mixture was quenched by pouring into 450 mL of ice and water, treated with activated carbon, filtered, and made strongly acidic with concentrated HCl. The precipitated product was recovered by filtration and the wet cake slurried in 100 mL of toluene. Water was removed by azeotropic distillation in vacuo. The residual slurry was taken into solution by the addition of 100 mL of acetone and warming. After clarification, the acetone was removed by evaporation in vacuo (final volume 70 mL). Filtration gave 5-(2-chloro-6-methoxyphenyl)oxazolidine-2,4-dione (20.3 g, mp 199–202 °C). Recrystallization from toluene gave purified 5-(2-chloro-6-methoxyphenyl)oxazolidine-2,4-dione [mp 202–203 °C, anal. ($C_{10}H_8O_4NCl$) C, H, N].

5-(2-Fluoro-6-methoxyphenyl)oxazolidine-2,4-dione (50). 5-(2,6-Difluorophenyl)oxazolidine-2,4-dione (**60**; 2.0 g, 9.4 mmol) was dissolved in 50 mL of dimethyl sulfoxide. Methanol (5 mL) and then potassium *tert*-butoxide (2.11 g, 18.8 mmol) were added, and the reaction mixture was heated in an oil bath maintained at 155 °C for 4 h. The reaction mixture was cooled to room temperature, poured into 200 mL of 1 N hydrochloric acid, and extracted with three portions of ethyl acetate. The combined organic extracts were washed with water and then brine, dried with $MgSO_4$, filtered, and concentrated to a solid. The solid was taken up in 1 N sodium hydroxide, and the solution was washed with three portions of ethyl acetate and then acidified with 1 N hydrochloric acid to precipitate purified 5-(2-fluoro-6-methoxyphenyl)oxazolidine-2,4-dione [1.32 g, 62%; mp 138–142 °C]. For analysis, the product was recrystallized from toluene [930 mg recovered; mp 139–141 °C; anal. calcd for $C_{10}H_8O_4NF$: C, H, N].

5-(6-Acetamido-2-methoxyphenyl)oxazolidine-2,4-dione (54). Compound **54** was prepared from compound **56** by the procedure used to prepare compound **24** [0.640 g, 56%; mp 232–234 °C dec; IR (KBr) 1802, 1748, 1667; anal. ($C_{10}H_9NO_4$) C, H, N].

5-[2-Chloro-6-(methylthio)phenyl]oxazolidine-2,4-dione (55). Potassium *tert*-butoxide (234 mg, 2.1 mmol) was taken into 2.0 mL of dimethyl sulfoxide. Methyl mercaptan (0.16 mL, 146 mg, 3.0 mmol) was condensed and added to the reaction mixture. Finally, 5-(2-chloro-6-fluorophenyl)oxazolidine-2,4-dione (**57**; 229 mg, 1.0 mmol) was added and the reaction mixture heated at 100 °C for 16 h, cooled to room temperature, poured into 10 mL of 1 N hydrochloric acid, and extracted with three portions of ethyl acetate. The combined organic extracts were washed with two portions of water and one of brine, dried with $MgSO_4$, filtered, and evaporated to an oil (223 mg). Crystallization from 2-propanol/hexane gave purified 5-[2-chloro-6-(methylthio)-phenyl]oxazolidine-2,4-dione (58 mg, mp 136–138 °C).

5-(6-Amino-2-methoxyphenyl)oxazolidine-2,4-dione (56). Compound **56** was prepared from **52** by using the procedure of **46**. The oily solid product was converted to its HCl salt by dissolution in ethanol and perfusion with gaseous HCl. Concentration in vacuo of this solution afforded a solid, which was recrystallized from ethanol/ether [4.47 g, 56%; mp >300 °C (scinter 230 °C black at 280 °C); IR (KBr) 1811, 1736, anal. ($C_{10}H_{11}N_2O_4Cl \cdot {}^1/_4H_2O$) C, H, N].

5-(2,6-Dichlorophenyl)oxazolidine-2,4-dione (59). The method of Stoughton[10] was employed (Figure 3). Sodium bisulfite (10.7 g, 0.103 mol) was dissolved in 150 mL of water and warmed to 50 °C. 2,6-Dichlorobenzaldehyde (15 g, 0.086 mol) was added and warming at 50 °C continued for 1.5 h. The mixture was cooled to 0 °C, overlaid with 150 mL of ether and a mixture of sodium cyanide (4.66 g, 0.095 mol) and 100 mL of ether added dropwise over 10 min. The two-phase system was stirred at 0 °C for 1 h. The organic layer was separated and the aqueous layer extracted with two additional portions of ether. The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated to dryness, yielding the cyanohydrin of 2,6-dichlorobenzaldehyde [15.9 g, 91%; mp 79–82 °C; IR (KBr) 3333, 1563, 1435, 1042]. Ten grams (0.049 mol) of this solid was dissolved in 30 mL of formic acid. Concentrated hydrochloric acid (30 mL) was added over 3 min and the mixture stirred at room temperature for 2.5 h. The reaction mixture was then poured over 300 mL of crushed ice and extracted with three portions of ethyl acetate. The organic extracts were combined, washed in sequence with water, three portions of 1 N sodium hydroxide, and brine, dried with $MgSO_4$, filtered, and concentrated to yield 2-(2,6-dichlorophenyl)-2-hydroxyacetamide [556 g, 52%; mp 155–158 °C; IR (KBr) 3390, 3106, 1667, 1425, 1047]. This was used without further purification.

Potassium *tert*-butoxide (5.16 g, 0.046 mol) was dissolved in 60 mL of *tert*-butyl alcohol. Dimethyl carbonate (4.14 g, 0.046 mol) and then 2-(2,6-dichlorophenyl)-2-hydroxyacetamide (5 g, 0.023 mol) were added. The suspension was heated at reflux for 2 h and cooled to room temperature. Then 46 mL of 1 N HCl was added followed by 100 mL of water, and the mixture was extracted with three portions of methylene chloride. The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated to dryness. Recrystallization of the residue from toluene gave purified 5-(2,6-dichlorophenyl)oxazolidine-2,4-dione [3.15 g, 50%; mp 151–153 °C; IR (KBr) 1818, 1739, 1724, 1434, 1377; anal. ($C_9H_5O_3NCl_2$) C, H, N].

5-[2-(Benzyloxy)-6-chlorophenyl]oxazolidine-2,4-dione (61). Benzyl alcohol (0.864 g, 8.00 mmol), NaOMe (Fisher, 0.113 g, 2.09 mmol), and compound **57** (0.229 g, 1.00 mmol) were reacted in 1.5 mL of Me_2SO at 100 °C for 3 h according to the procedure used to prepare compound **55**, thus yielding compound **61** [0.030 g, 9%; mp 179–180 °C; anal. ($C_{16}H_{12}NO_4$) C, H, N].

5-[5-[(Dimethylamino)sulfonyl]-2-methoxyphenyl]oxazolidine-2,4-dione (66). The procedure for making **45** was used to prepare compound **66** except that dimethylamine gas was used instead of ammonia [0.470 g, 57%; mp 102–107 °C]. The crude solid was recrystallized from toluene to afford pure **66** (0.420 g, 51%; mp 182–184 °C; IR (KBr) 1835, 1748, 1715, 1376, 1348; anal. ($C_{12}H_{14}N_2O_6S$) C, H, N].

Optical Resolution of 5-(5-Chloro-2-methoxyphenyl)oxazolidine-2,4-dione (68 and 69). 5-(5-Chloro-2-methoxyphenyl)oxazolidine-2,4-dione (**34**; 1.520 g, 5 mmol) and L-cinchonidine (1.47 g, 5 mmol, $[\alpha]_D$ −109.2°) were dissolved at reflux in 10 mL of ethanol. On cooling slowly to room temperature, the salt crystallized (1.23 g, mp 142–144 °C $[\alpha]_D$ (ethanol) −58.6°). The solids were reserved. The mother liquor was partitioned between ethyl acetate and 1 N hydrochloric acid. The organic layer was dried over anhydrous magnesium sulfate, filtered and evaporated to dryness (520 mg). This residue was taken up in 20 mL of methanol and recrystallized by the addition of 30 mL of water. After 20 min, a first crop of racemate was recovered (157.4 mg, mp 177.5–179 °C $[\alpha]_D$ (ethanol) −6.6°). A second crop of crystals then precipitated from the mother liquor and was found to be (−)-5-(5-chloro-2-methoxyphenyl)oxazolidine-2,4-dione (**68**) of 73% optical purity. Recrystallization of 50 mg of this product from 1 mL of methanol and 1.5 mL of water gave **68** of 85% optical purity (25.4 mg, mp 164–166, $[\alpha]_D$ (ethanol) −22.14°).

The earlier reserved solid salt was decomposed by partitioning between chloroform and 1 N hydrochloric acid, yielding an evaporation of the dried chloroform layer, 0.488 g of solids. The latter solids were taken up in 20 mL of methanol and recrystallization of (+)-5-(5-chloro-2-methoxyphenyl)oxazolidine was induced by addition of 30 mL of water. Product **69** was obtained in two crops: 182.4 mg, mp 173–174.5 °C, $[\alpha]_D$ (ethanol) +26.66°; 103 mg, mp 171–174 °C, $[\alpha]_D$ (ethanol) +27.06. Recrystallization of 59 mg of the first crop from 1 mL of methanol and 1.5 mL of water gave a slight increase in rotation (40 mg, mp 171.5–173 °C,

$[\alpha]_D$ (ethanol) +26.96°). Optical shift reagent ^1H NMR studies using tris[3-[(heptafluoropropyl)hydroxymethylene]-3-camphorato]europium(III) demonstrated that the material rotating at +27.06° was essentially 100% optically pure.

5-[5-(2-Chloroethyl)-2-methoxyphenyl]oxazolidine-2,4-dione. This compound, an intermediate in the preparation of compound **70**, was prepared by method A from 5-(2-chloroethyl)-2-methoxybenzaldehyde. The yield of the imidate was 83% (amorphous). The oxazolidinedione was obtained in 84% [8.36 g, mp 162–164 °C, IR (KBr) 1834, 1754, 1515]. Other spectral data were in accord with the structure. The compound was used directly in the preparation of **70**.

5-[5-(2-Imidazol-1-ylethyl)-2-methoxyphenyl]oxazolidine-2,4-dione (70). Imidazole (0.681 g, 10.0 mmol) and the preceding oxazolidinedione (1.35 g, 5.00 mmol) were fused at 135 °C for 15 min. The cooled reaction mixture was dissolved in 1 N NaOH, washed with three portions of ethyl acetate, acidified to pH 6 with 1 N HCl, and concentrated until a precipitate formed. Solid **70** was filtered and dried in vacuo [0.390 g, 26%; mp 170 °C dec; IR (KBr) 1795, 1724; anal. ($C_{15}H_{16}N_3O_4Cl \cdot {}^1/_2H_2O$) C, H, N].

5-[5-[(3-Cyclohexylureido)sulfonyl]-2-methoxyphenyl]-oxazolidine-2,4-dione (72). Compound **23** (0.286 g, 1.00 mmol) was dissolved in 5 mL of DMF and treated with NaH (50% oil dispersion 0.096 g, 2.00 mmol) at 45 °C for 30 min. The mixture was cooled and cyclohexyl isocyanate (0.125 g, 1.00 mmol) was added. The mixture was brought to 50 °C and held there for 3 h and then cooled and poured into 100 mL of H_2O. The aqueous layer was washed with ethyl acetate, acidified with 1 N HCl, and extracted with three portions of ethyl acetate. The latter organic phases were combined, washed with brine, dried with $MgSO_4$, filtered, and concentrated in vacuo to yield **72** as a foam, which recrystallized from isopropyl alcohol–H_2O [0.140 g, 34%; mp 173–178 °C dec; IR (KBr) 1825, 1724, 1527; anal. ($C_{17}H_{21}N_3O_7S$) C, H, N].

5-(2-Fluoro-6-isopropoxyphenyl)oxazolidine-2,4-dione (73). A solution of compound **60** (3.00 g, 14.1 mmol), potassium *tert*-butoxide (Aldrich, 3.16 g, 28.2 mmol), isopropyl alcohol (10 mL), and anhydrous Me_2SO (75 mL) was heated at 150 °C for 6 h and then cooled and poured into 200 mL of 1 N HCl. A precipitate formed and was washed with water, air-dried, and recrystallized from toluene [1.34 g, 38%; mp 198–199 °C; IR (KBr) 1831, 1742; anal. ($C_{12}H_{11}NO_4F$) C, H, N].

5-[2-Fluoro-6-(methylthio)phenyl]oxazolidine-2,4-dione (74). A solution of compound **60** (3.00 g, 14.1 mmol), potassium *tert*-butoxide (3.16 g, 28.2 mmol), Me_2SO 75 mL), and methyl mercaptan (2.0 mL, 36.0 mmol) was heated at 100 °C for 16 h and then cooled and poured into 200 mL of 1 N HCl. The aqueous was extracted with three portions of ethyl acetate, and the pooled organic phases were washed with H_2O and brine, dried with $MgSO_4$, filtered, and concentrated to an oil, which crystallized from toluene–hexane (2.10 g). Pure **74** was obtained after recrystallization from toluene [1.22 g; 36%; mp 134–135 °C; IR (KBr) 1808, 1748; anal. ($C_{10}H_8NO_3FS$) C, H, N].

5-[2-Fluoro-6-(ethylthio)phenyl]oxazolidine-2,4-dione (75). This compound was prepared in the same way as compound **74** except that ethyl mercaptan was employed. Pure **75** was obtained after recrystallization from toluene and finally from methanol–H_2O [0.24 g, 10%; mp 97–99 °C; IR (KBr) 1824, 1734; anal. ($C_{11}H_{10}NO_3FS$) C, H, N].

5-[2-Methoxy-6-(trifluoromethyl)phenyl]oxazolidine-2,4-dione (79). A solution of compound **76** (0.375 g, 1.42 mmol), potassium *tert*-butoxide (0.352 g, 3.13 mmol), methanol (0.127 mL, 3.13 mmol), and 10 mL of Me_2SO was heated at 100 °C for 2 h and then cooled and poured into 50 mL of 1 N HCl. The aqueous was extracted with three portions of ethyl acetate, and the pooled organic layers were washed with water and brine, dried with $MgSO_4$, filtered, and concentrated in vacuo to a solid (0.32 g). Pure **79** was obtained after recrystallization from toluene [0.155 g, 40%; mp 197–200 °C; IR (KBr) 1816, 1747; anal. ($C_{11}H_8NO_4F \cdot H_2O$) C, H, N].

5-(2-Methoxy-6-methylphenyl)oxazolidine-2,4-dione (80). A solution of 2-hydroxy-(2-methoxy-6-methylphenyl)acetamide (see below; 0.755 g, 3.87 mmol), diethyl carbonate (MC/B, 0.945 mL, 7.80 mmol), potassium *tert*-butoxide (0.875 g, 7.80 mmol), and 15 mL of *tert*-butyl alcohol was refluxed for 5 h, cooled, acidified with 7.8 mL of 1 N HCl, and concentrated in vacuo to a tan solid. This was partitioned between 1 N NaOH and ether. The aqueous was washed with ether and acidified with 1 N HCl, yielding a solid, which was collected, dried, and recrystallized from toluene [0.465 g, 54%; mp 194–196°C; IR (KBr) 1814, 1740; anal. ($C_{11}H_{11}NO_4$) C, H, N].

2-Hydroxy-2-(2-methoxy-6-methylphenyl)acetamide. A Diels–Alder reaction between 2,3-dihydroanisole (Aldrich, 6.9 g, 62.4 mmol) and ethyl 2-butynoate (ICN, 7.02 g, 62.4 mmol) was carried out at 110 °C for 4 days, and the reaction mixture was distilled under reduced pressure. The fraction boiling at 130–135 °C (15 torr) was ethyl 2-methoxy-6-methylbenzoate (3.85 g; 32%). Spectral data were in accord with the proposed structure, and the product was used directly in the next step. Thus, commercial 48% oil dispersion NaH (1.90 g, 39.6 mmol) was washed three times with hexane and reacted with 23 mL of Me_2SO at 75 °C for 2 h. To the cooled mixture was added dropwise a THF (5 mL) solution of the above ester (3.85 g, 19.8 mmol) over a 5-min period and the reaction mixture was stirred for 1.5 h at room temperature. The mixture was poured into 200 mL of H_2O, acidified with 1 N HCl to pH 4, and extracted with three portions of methylene chloride. The pooled organic layers were washed with H_2O and brine, dried with $MgSO_4$, filtered, and concentrated in vacuo to a brown oily β-keto sulfoxide, which crystallized from hexane [1.69 g, 38%; mp 68–70 °C; NMR and IR consistent with structure]. A Pummerer reaction as described by Corey[17] was carried out on this β-keto sulfoxide (1.69 g, 7.47 mmol), using sodium acetate (1.70 g, 20.7 mmol) and acetic anhydride (21 mL) in 30 mL of toluene at 100 °C for 24 h. The volatile materials were removed at reduced pressure, and the residue was taken up in ethyl acetate, washed with two portions of 2 N NaOH and brine, dried with $MgSO_4$, filtered, and concentrated in vacuo to an oil. NMR was consistent with the assigned structure, 2-acetoxy-(2-methoxy-6-methylphenyl)thioacetic acid methyl ester, and the oil was dissolved in ethanol (30 mL) and concentrated NH_4OH (30 mL). After 55 h the thin-layer chromatography indicated that the reaction was complete, and the volatiles were distilled off in vacuo to yield an oil, which crystallized from ethyl acetate, yielding 2-hydroxy-(2-methoxy-6-methylphenyl)acetamide [0.755 g, 20% overall from ethyl 2-methoxy-6-methylbenzoate; mp 121–125 °C; IR (KBr) 1688; NMR ($Me_2SO/CDCl_3$) 1.8 (s, 1 H), 2.3 (s, 3 H), 3.7 (s, 3 H), 5.3 (br s, 1 H), 6.9 (br m, 3 H)].

5-[2-Chloro-6-(1-pyrrolyl)phenyl]oxazolidine-2,4-dione (81). A solution of compound **57** (2.08 g, 9.06 mmol), potassium *tert*-butoxide (1.02 g, 9.06 mmol), and 15 mL of Me_2SO was stirred while potassium pyrrole (1.91 g, 18.0 mmol) was added. After heating at 120 °C for 48 h, the mixture was poured into 100 mL of H_2O and extracted with three portions of ethyl acetate. The aqueous was acidified to pH 2 with 1 N HCl and extracted with two portions of ethyl acetate. The latter organic layers were pooled, washed with 1 N HCl and brine, dried with $MgSO_4$, filtered, and evaporated in vacuo to an oil, which crystallized from toluene to yield pure **81** [0.334 g, 13%; mp 214–216 °C; IR (KBr) 1829, 1759; anal. ($C_{13}H_9N_2O_3Cl$) C, H, N]. Potassium pyrrole was freshly prepared from pyrrole and potassium in xylene at 125 °C during 1 h and isolated as a powder after cooling, filtration, and washing with hexane.

5-[2-Chloro-6-(1-propenyloxy)phenyl]oxazolidine-2,4-dione (82) and 5-[2-Chloro-6-(allyloxy)phenyl]oxazolidine-2,4-dione (84). These two products were formed as a mixture and separated by chromatography. Thus, a solution of compound **57** (5.00 g, 21.8 mmol), allyl alcohol (20 mL), potassium *tert*-butoxide (4.89 g, 43.6 mmol), and 75 mL of Me_2SO was heated at reflux for 18 h, cooled, and poured into 200 mL of 1 N HCl. The aqueous was extracted with three portions of ethyl acetate, and the pooled organic layers were washed with water and brine, dried with $MgSO_4$, filtered, and concentrated in vacuo to a brown oil, which solidified upon sitting. Thin-layer chromatography on silica gel eluted with 1:1 ether–hexane indicated two components of R_f 0.32 and 0.35. Flash column chromatography on silica gel eluted with the same solvent mixture yielded two pure oxazolidinediones, **82** (R_f 0.35) and **84** (R_f 0.32). Compound **82** was the cis isomer [0.837 g, 14%; mp 122–125 °C; IR (KBr) 1809, 1740; NMR ($CDCl_3$) δ

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1.7 (d, J = 7.5, 3 H), 5.0 (dd, J = 7.5, 1.75, 1 H), 6.2 (d, J = 1.75, 1 H), 6.4 (s, 1H), 7.2 (m, 4 H); anal. ($C_{12}H_{10}NO_4Cl$) C, H, N]. Compound **84** [0.218 g, 4%; mp 114-116 °C; IR (KBr) 1817, 1723; NMR ($CDCl_3$) 4.5 (d, J = 5, 2 H), 5.3 (m, 2 H), 6.0 (m, 1 H), 6.4 (s, 1 H), 7.1 (m, 4 H); anal. ($C_{12}H_{10}NO_4Cl$) C, H, N].

5-[2-Chloro-6-[(cyclopropylmethyl)oxy]phenyl]oxazolidine-2,4-dione (83). A solution of compound **57** (2.00 g, 8.71 mmol), potassium *tert*-butoxide (1.95 g, 17.42 mmol), cyclopropylmethyl alcohol (10 mL), and 10 mL of Me_2SO was heated at reflux for 3 h, cooled, and poured into 200 mL of 1 N HCl. The aqueous was extracted with three portions of ethyl acetate, and the pooled organic layers were washed with water and brine, dried with $MgSO_4$, filtered, and concentrated in vacuo to a brown oily solid, which recrystallized from ethyl acetate/hexane [1.37 g, 65%; mp 188-189 °C; IR (KBr) 1827, 1744; anal. ($C_{13}H_{12}NO_4Cl$) C, H, N].

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Crystal Structures of α- and β-Funaltrexamine: Conformational Requirement of the Fumaramate Moiety in the Irreversible Blockage of μ Opioid Receptors

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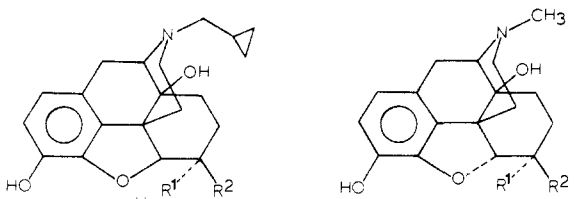
α- and β-funaltrexamine (α- and β-FNA, **1a** and **1b**) are naltrexone derivatives differing only in chirality at C(6). Both epimers bind to μ opioid receptors in GPI and MVD preparations, but only the β-epimer irreversibly blocks these receptors in both preparations. In an effort to investigate the reasons for this difference, we have determined the molecular structures of **1a** and **1b** by X-ray diffraction techniques. The two epimers have almost identical conformations in the fused ring system except for ring C, which is observed in a twist-boat conformation in α-FNA and a chair in β-FNA. As a result the electrophilic fumaramate moieties are equatorial in both structures and orthogonal to one another when the fused rings are superimposed. In the crystal structure of β-FNA there is a close intermolecular contact between a phenolic oxygen and the fumaramate double bond that can serve as a model for nucleophilic attack on the fumaramate group. When **1a** and **1b** are superimposed, the fumaramate double bond of **1a** is more than 2 Å away from that in its epimer **1b** and in the wrong orientation for nucleophilic attack from the proposed direction to take place. The results of this study are consistent with a model that postulates the involvement of two consecutive recognition steps leading to the irreversible blockage by β-FNA (Sayre, L. M.; Larson, D. L.; Fries, D. S.; Takemori, A. E.; Portoghese, P. S. *J. Med. Chem.* **1983**, *26*, 1229) and underscores the importance of the second recognition step in conferring selectivity in the Michael addition of a nucleophile to the fumaramate group.

β-Funaltrexamine (β-FNA, **1b**) is a naltrexone-derived nonequilibrium narcotic antagonist that is highly selective for the μ-type opioid receptor system.[1-5] The available evidence suggests that the nonequilibrium nature of β-FNA arises as a consequence of the reaction of the fumaramate moiety with a putative nucleophile near the recognition locus of the receptor.[6-9]



1a R^1=NHCOC(H)=C(H)-CO_2CH_3, R^2=H
1b R^1=H, R^2=NHCOC(H)=C(H)-CO_2CH_3
2a R^1=NH_2, R^2=H
2b R^1=H, R^2=NH_2

The high selectivity of β-FNA for the μ opioid receptor, despite its interaction with other opioid receptor types, has been attributed to the involvement of two consecutive recognition steps.[6-9] The first is reflected by affinity of the ligand for the recognition site; the second involves the proper alignment between the electrophilic center of the ligand with a chemically compatible receptor-based nucleophile. Because two recognition steps rather than one lead to covalent binding, enhanced receptor selectivity (recognition amplification) is obtained. Due to the high selectivity of β-FNA as a nonequilibrium antagonist at μ opioid receptors, it has been employed widely as a tool in the investigation of opioid receptor mechanisms.[10]

In contrast to β-FNA, its epimer α-FNA (**1a**) does not irreversibly block the effects of μ receptor agonists but does protect against β-FNA-induced irreversible antagonism.[9] This suggests that both α- and β-FNA interact with the same site, but the second recognition step is achieved only with β-FNA. Since there is no substantial difference between the reactivity of **1a** and **1b** in solution,[9] an obvious explanation for the observed difference in irreversible antagonism between these epimers may be related to

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