Synthesis of Novel Analgesic Agents I: Pyrazolidines with an Oxygenated Phenyl Substituent

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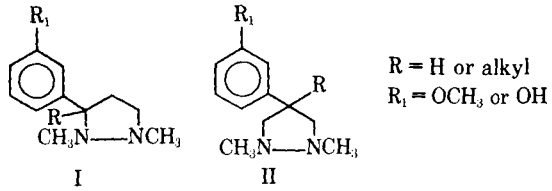
Abstract □ Several 3- and 4-(*m*-methoxyphenyl)pyrazolidines as well as 3-alkyl-3- and 4-alkyl-4-(*m*-methoxyphenyl)pyrazolidines were synthesized. Most of the compounds were demethylated and afforded the corresponding *m*-hydroxy products. These novel compounds were evaluated for analgesic activity; 1,2-dimethyl-3-*n*-propyl-3-(*m*-methoxyphenyl)pyrazolidine (VIc) was the most effective.

Keyphrases □ Pyrazolidines, hydroxy- and alkoxyphenyl substituted—synthesis, evaluation of analgesic activity □ 3- and 4-(*m*-Methoxyphenyl)pyrazolidines—synthesis, evaluation of analgesic activity □ 3-Alkyl-3- and 4-alkyl-4-(*m*-methoxyphenyl)pyrazolidines—synthesis, evaluation of analgesic activity □ Analgesic activity—evaluation of oxygenated phenyl pyrazolidines

In the past few years, a number of antinociceptive compounds having the pyrrolidine ring system were described in the literature (1–5). Among these compounds, 1-methyl-3-*n*-propyl-3-(*m*-hydroxyphenyl)pyrrolidine was found to be 2.5–4 times as active as codeine or meperidine in rats (6). Examples are known in the literature where replacement of a basic amine function in a pharmacological agent by a hydrazine moiety resulted in compounds having similar pharmacological effects.

In 1966, this laboratory (7) reported on the synthesis of hydrazine-derived ester-type local anesthetics which bear structural resemblances to procaine, piperocaine, and other synthetic local anesthetics. In these compounds, the customary amino alcohol was replaced by an alcohol incorporating a —N—N— linkage which is part of the pyrazolidine ring system. In the lidocaine-type local anesthetics, substitution of the basic amine function by a pyrazolidine ring resulted in compounds having varying degrees of local anesthetic activity (8). The pyrazolidine ring, as a *N*-methylpyrazolidino group, was also substituted for the customary dialkylamino group in a number of other clinically active agents (9). Recently, Kametani *et al.* (10) described the synthesis of azamorphinans with contiguous nitrogen atoms. The analgesic activity of the *N*-phenethyl compound obtained by these investigators was one-third that of morphine.

In the search for new analgesic agents, two series of compounds, represented by Structures I and II, were synthesized. Both of these structures incorporate the pyrazolidine ring system.



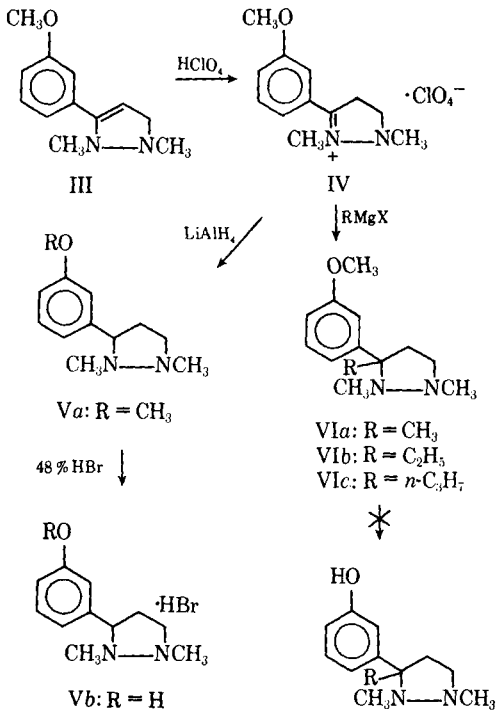
I II

SYNTHESIS

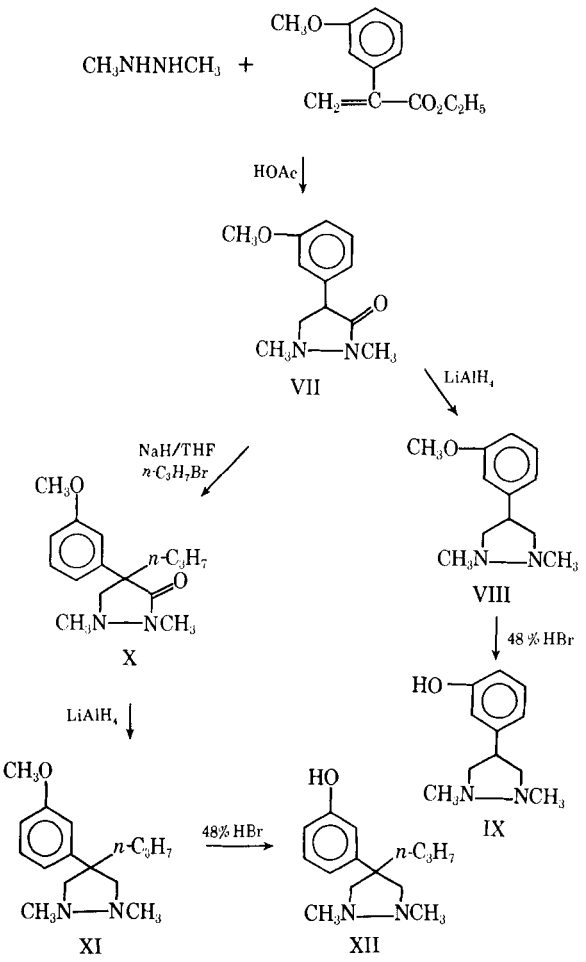
The synthesis of I was accomplished by a sequence of reactions starting with 1,2-dimethyl-3-(*m*-methoxyphenyl)-3-pyrazoline (III) (Scheme I). Similar pyrazolines are readily prepared by a number of routes (11–14). The most convenient synthetic route for III, however, is the method of Hinman *et al.* (14), which involves a one-step Mannich reaction. Following this method, III, a novel pyrazoline, was obtained from 1,2-dimethylhydrazine dihydrochloride, *m*-methoxyacetophenone, and paraformaldehyde. Treatment of III with perchloric acid gave 1,2-dimethyl-3-(*m*-methoxyphenyl)-2-pyrazolinium perchlorate (IV), which served as the key intermediate for the other members of this series.

Reduction of IV with lithium aluminum hydride afforded 1,2-dimethyl-3-(*m*-methoxyphenyl)pyrazolidine (V). This compound represents a potential analgesic having a central tertiary carbon atom. Previously, 1,2-dimethyl-3-phenylpyrazolidine was obtained directly from the corresponding pyrazoline by catalytic hydrogenation (14). A similar route from III was not utilized for the preparation of V, because other workers (15) found that catalytic reduction of pyrazolines can result in substantial —N—N— bond hydrogenolysis.

Treatment of IV with aliphatic Grignard reagents yielded 1,2-dimethyl-3-alkyl-3-(*m*-methoxyphenyl)pyrazolidines (VI) in yields varying from 34 to 85%. With methylmagnesium chloride, a single product uncontaminated by III was obtained. With higher alkyl Grignards, the addition products were contaminated by varying amounts of III as shown by IR and NMR spectral analysis. Purification of VIc was accomplished by fractional crystallization of the perchlorates. The starting material, IV, precipitated from an ethanolic solution, whereas the perchlorate of the product remained in



Scheme I



Scheme II

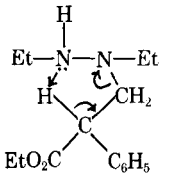
solution. After filtration of the crystalline precipitate, the filtrate was worked up to give pure VI*c* (see *Experimental*). Application of the same purification method to VI*b* was unsuccessful, since the small amount of IV would not crystallize in the presence of the perchlorate of VI*b* which was an oil. Purification was achieved by adding an amount of perchloric acid equivalent to the amount of III present (as determined by NMR analysis) in the mixture. The partially neutralized mixture was extracted with ether, and evaporation of the ether extracts afforded pure VI*b*.

This purification procedure was used in the belief that enehydrazines are more basic than hydrazines, in analogy with the fact that enamines are more basic than amines (16). The results obtained indicate that a preferential protonation does indeed occur.

Attempts to demethylate VI*a*, VI*b*, and VI*c* with 48% hydrobromic acid were unsuccessful and gave only intractable tars. Demethylation was only successful where the central carbon atom was tertiary. Thus, V*a* was easily demethylated with 48% aqueous hydrobromic acid to the corresponding *m*-hydroxy compound, V*b*, in 81% yield.

In earlier work (17), the authors found that 1,2-dialkylhydrazines underwent a 1,4-addition reaction with ethyl methacrylate. The adduct obtained was cyclized by means of sodium methoxide and gave 1,2-dialkyl-4-methyl-3-pyrazolidinones. It appeared plausible that a 1,2-dialkylhydrazine would react with an ethyl α-arylacrylate in a similar manner to give VII, which could serve as the precursor for compounds having Structure II (Scheme II).

At this period in the investigation, Kaiser *et al.* (18) reported on the addition of the lithium salts of several amines to ethyl α-phenylacrylate. Application of their method to the reaction of 1,2-diethylhydrazine with ethyl α-phenylacrylate led to addition followed by cyclization and afforded 1,2-diethyl-4-phenyl-3-pyrazolidinone (19) in 10–15% yields along with considerable amounts of a polymer believed to be derived from the starting acrylate. The low yields may be due to a facile intramolecular elimination reaction of the



adduct and subsequent polymerization of the acrylate in the basic reaction medium.

This unwanted breakdown of the adduct may be prevented if the reaction is conducted in a weak acid such as acetic acid. The acetic acid, in protonating the carbonyl oxygen, would also increase the electrophilic character of the β-carbon atom of the α-arylacrylate. In addition, it would be expected to activate the ester carbonyl of the adduct once it is formed and thus might lead in a single step to the cyclized product, VII. To determine if the hydrazine group still has enough nucleophilic character in acetic acid, the cyclization of ethyl 3-methyl-3-(1,2-diethylhydrazino)propanoate was attempted in this solvent. As expected, the cyclized product, 1,2-diethyl-4-methyl-3-pyrazolidinone (17), was formed in over 80% yield. More importantly, refluxing 1,2-dimethylhydrazine and ethyl α-(*m*-methoxyphenyl)acrylate in glacial acetic acid gave the key intermediate, VII, in 50% yield.

Lithium aluminum hydride reduction of VII afforded 1,2-dimethyl-4-(*m*-methoxyphenyl)pyrazolidine (VIII) in high yield. This compound represents the potential analgesics of type II, having a central tertiary carbon atom.

The 4-alkyl-4-arylpyrazolidine (XI) was obtained in two steps from VII. Alkylation of VII with *n*-propyl bromide and sodium hydride as the base in tetrahydrofuran gave 1,2-dimethyl-4-(*m*-methoxyphenyl)-4-*n*-propyl-3-pyrazolidinone (X) in a yield of 84%. Lithium aluminum hydride reduction of X yielded XI, which is representative of compounds of Structure II having a central quaternary carbon atom.

Demethylation of VIII and XI with 48% aqueous hydrobromic acid proceeded readily and resulted in the formation of the *m*-hydroxy analogs, IX and XII, respectively.

ANALGESIC ACTIVITY

The analgesic activity of the compounds was determined in mice by the hot-plate method (20). A subcutaneous route of administration was used for all compounds except VI*c*, which was given intraperitoneally. Compounds V*a*, V*b*, VI*b*, and VIII were found to be ineffective at doses up to 100 mg./kg. Compound VI*a* proved to be too toxic to permit evaluation. The ED_{50} values of IX, XI, and XII were 35.9, 47.7, and 71.7 mg./kg., respectively. By comparison, the value for codeine, the reference compound, was 7.5 mg./kg. The ED_{50} values for Compound VI*c* and codeine obtained by the intraperitoneal route were 47 and 29 mg./kg., respectively.

EXPERIMENTAL[1]

1,2-Dimethyl-3-(*m*-methoxyphenyl)-3-pyrazoline (III)—The method of Hinman *et al.* (14) was adapted for the preparation of this compound. To a solution of 33.25 g. (0.25 mole) of 1,2-dimethylhydrazine dihydrochloride in 500 ml. of absolute alcohol was added 15.0 g. of paraformaldehyde (0.50 mole of HCHO) and 75.0 g. (0.50 mole) of *m*-methoxyacetophenone with magnetic stirring under a nitrogen atmosphere. After refluxing for 21 hr., the mixture was worked up and afforded 14.12 g. (27.6%) of a pale-yellow oil, b.p. 153–156° (13 mm.) (98° at 0.70 mm.); $n_D^{23.7}$ 1.5604; IR(film), 6.13 μ (C=C—N); NMR ($CDCl_3$), δ 6.76–7.71 (m, 4, ArH), 5.26 (t, 1, vinyl H), 3.78 (s, 5, OCH_3 and aliphatic ring protons), 2.66 (s, 3, C=C—NCH_3), and 2.60 (s, 3, NCH_3).

[1] Melting points were obtained with a Fisher-Johns melting-point apparatus. A Mel-Temp apparatus was used for melting-point determinations in a sealed tube. All melting points are corrected, whereas boiling points are uncorrected. IR data were recorded on a Beckman IR-8 spectrophotometer. NMR spectra were determined with a Varian A-60A spectrometer using tetramethylsilane as the internal reference. Microanalyses were performed by Dr. Kurt Eder, Geneva, Switzerland. Magnesium sulfate was employed as the drying agent.

Anal.—Calc. for $C_{12}H_{16}N_2O$: C, 70.56; H, 7.90; N, 13.71. Found: C, 70.64; H, 7.96; N, 13.67.

1,2-Dimethyl-3-(*m*-methoxyphenyl)-2-pyrazolinium Perchlorate (IV)—This compound was obtained by dissolving III in ether and neutralizing with a solution of 70% $HClO_4$ in an equal volume of absolute alcohol (21) to Congo red indicator. Recrystallization from absolute alcohol afforded white needles, m.p. 118–120°.

Anal.—Calc. for $C_{12}H_{17}ClN_2O_5$: C, 47.29; H, 5.63; N, 9.19. Found: C, 47.34; H, 5.62; N, 9.10.

1,2-Dimethyl-3-(*m*-methoxyphenyl)pyrazolidine (V*a*)—To a stirred suspension of 5.29 g. (0.140 mole) of lithium aluminum hydride in 135 ml. of tetrahydrofuran was added, in small portions, 10.0 g. (0.0328 mole) of IV over a period of 5 min. After completion of the addition, the reaction mixture was refluxed for 18 hr. Decomposition of the complexes was effected by the addition of 40% aqueous KOH with ice bath cooling. The tetrahydrofuran was separated, and the inorganic sludge was extracted three times with 20-ml. portions of tetrahydrofuran. The combined tetrahydrofuran extracts were dried, filtered, and concentrated under reduced pressure. Distillation of the residue afforded 5.33 g. (78.8%) of a colorless oil, b.p. 83–85° (0.20 mm.); $n_D^{23.8}$ 1.5312; IR (film), no absorption at 6.13 μ (C=C—N); NMR ($CDCl_3$), δ 6.70–7.49 (m, 4, ArH), 3.83 (s, 3, OCH_3), and 1.42–3.74 (m, 11, including two NCH_3 singlets at 2.39 and 2.55).

Anal.—Calc. for $C_{12}H_{18}N_2O$: C, 69.87; H, 8.80; N, 13.58. Found: C, 69.65; H, 8.73; N, 13.65.

A hydrochloride derivative was prepared and recrystallized from absolute alcohol–ether, m.p. 213–216° (sealed tube).

Anal.—Calc. for $C_{12}H_{19}ClN_2O$: C, 59.36; H, 7.90; N, 11.54. Found: C, 59.36; H, 8.01; N, 11.77.

1,2-Dimethyl-3-(*m*-hydroxyphenyl)pyrazolidine Hydrobromide (V*b*)—A solution of 2.0 g. (0.0097 mole) of V*a* in 10.5 ml. of 48% aqueous HBr was refluxed for 1 hr., and the resulting clear light-brown solution was evaporated under reduced pressure. The solid residue remaining was azeotroped several times with absolute ethanol and recrystallized from isopropyl alcohol to afford 1.20 g. of a white granular powder, m.p. 229.5–231° dec. (sealed tube). From the mother liquor, an additional amount of product was obtained which, after recrystallization from isopropyl alcohol, amounted to 0.95 g., m.p. 229–230.5° dec. (sealed tube). The total yield was 81.1%. Twice-recrystallized material afforded the analytical sample, m.p. 230–231.5° dec. (sealed tube); IR (KBr), 3.13 μ (phenolic OH); NMR (D_2O), δ 6.83–7.60 (m, 4, ArH), and 2.09–4.32 (m, 11, including two NCH_3 singlets at 2.68 and 3.17).

Anal.—Calc. for $C_{11}H_{17}BrN_2O$: C, 48.36; H, 6.27; N, 10.25. Found: C, 48.40; H, 6.10; N, 10.46.

1,2,3-Trimethyl-3-(*m*-methoxyphenyl)pyrazolidine (VI*a*)—Twenty-three milliliters (0.0656 mole) of 2.85 *M* methylmagnesium chloride in tetrahydrofuran was diluted with 133 ml. of tetrahydrofuran. To this stirred Grignard reagent was added portionwise 10.0 g. (0.0328 mole) of IV over 4 min. The reaction mixture was refluxed for 23 hr., cooled, and decomposed with saturated aqueous NH_4Cl. After removal of the solvent under reduced pressure, the residue was suspended in ether and made strongly alkaline with 40% aqueous KOH. The ether layer was separated, the aqueous phase was repeatedly extracted with ether, and the combined ether solution was dried and filtered. After removal of the solvent, the residue was distilled and gave 6.11 g. (84.6%) of a colorless oil, b.p. 92–94° (0.30 mm.); $n_D^{23.5}$ 1.5348; IR (film), no absorption at 6.13 μ (C=C—N); NMR ($CDCl_3$), δ 6.53–7.34 (m, 4, ArH), 3.76 (s, 3, OCH_3), 1.69–3.41 (m, 10, including two NCH_3 singlets at 2.27 and 2.47), and 1.43 (s, 3, C—CH_3).

Anal.—Calc. for $C_{13}H_{20}N_2O$: C, 70.87; H, 9.15; N, 12.72. Found: C, 70.92; H, 9.02; N, 12.80.

A hydrochloride derivative was prepared which, upon recrystallization from absolute alcohol, yielded white needles, m.p. 230–232° (sealed tube).

Anal.—Calc. for $C_{13}H_{21}ClN_2O$: C, 60.80; H, 8.26; N, 10.91. Found: C, 60.95; H, 8.26; N, 11.08.

1,2-Dimethyl-3-ethyl-3-(*m*-methoxyphenyl)pyrazolidine (VI*b*)—To ethylmagnesium bromide prepared in the usual way from 7.00 g. (0.064 mole) of ethyl bromide, 1.54 g. (0.064 g.-atom) of magnesium in 150 ml. of tetrahydrofuran was added portionwise 10.0 g. (0.032 mole) of IV over 5 min. The reaction mixture was refluxed for 23.5 hr. and worked up in a manner similar to that used for VI*a*. Distillation afforded 5.21 g. (70%) of a colorless oil (75% pure by NMR analysis), b.p. 108–110° (0.30 mm.). The product was dissolved in ether, and a solution of 0.98 g. of 70% $HClO_4$ in 1 ml. of absolute alcohol was added. The ether was separated from the precipitated solid which was then repeatedly extracted with ether. Recrystallization of the solid from absolute alcohol led to a recovery of 267 mg. of IV, m.p. 117–120.5°. The combined ether solutions were dried, filtered, and evaporated under reduced pressure. Distillation of the residue yielded 2.46 g. (31.5%) of a pure colorless oil, b.p. 108.5–109° (0.30 mm.); $n_D^{24.5}$ 1.5315; IR (film), no absorption at 6.13 μ (C=C—N); NMR ($CDCl_3$), δ 6.70–7.64 (m, 4, ArH), 3.86 (s, 3, OCH_3), 1.61–3.15 (m, 12, including two NCH_3 singlets at 2.34 and 2.49), and 0.71 (t, 3, C—CH_3).

Anal.—Calc. for $C_{14}H_{22}N_2O$: C, 71.76; H, 9.46; N, 11.95. Found: C, 71.81; H, 9.43; N, 11.92.

A hydrochloride derivative was prepared and recrystallized from absolute alcohol–ether to yield white needles, m.p. 167–168°.

Anal.—Calc. for $C_{14}H_{23}ClN_2O$: C, 62.10; H, 8.56; N, 10.34. Found: C, 61.95; H, 8.65; N, 10.20.

1,2-Dimethyl-3-*n*-propyl-3-(*m*-methoxyphenyl)pyrazolidine (VI*c*)—To *n*-propylmagnesium bromide, prepared in the usual way from 10.16 g. (0.0826 mole) of *n*-propyl bromide and 2.00 g. (0.0826 g.-atom) of magnesium in 200 ml. of tetrahydrofuran, was added portionwise 12.60 g. (0.0413 mole) of IV over 5 min. The reaction mixture was refluxed for 24 hr., worked up (see VI*a*), and yielded 6.73 g. (66%) of a colorless oil (68% pure by VPC), b.p. 109–112° (0.35 mm.). This oil was dissolved in ether and neutralized to Congo red indicator with a solution of equal volumes of 70% $HClO_4$ and absolute alcohol. The precipitated perchlorate, IV, was filtered and recrystallized from absolute alcohol. A total of 1.60 g. of IV was recovered, m.p. 117.5–119°. The filtrate was made strongly alkaline with 40% aqueous KOH, the ether phase was separated, and the aqueous phase was repeatedly extracted with ether. The combined ether solution was dried, filtered, and evaporated under reduced pressure. Distillation of the residue afforded 3.43 g. (33.7%) of a colorless oil (100% pure by VPC), b.p. 99–100° (0.20 mm.); $n_D^{23.8}$ 1.5298; IR (film), no absorption at 6.13 μ (C=C—N); NMR ($CDCl_3$), δ 6.54–7.33 (m, 4, ArH), 3.75 (s, 3, OCH_3), and 0.59–3.38 (m, 17, including two NCH_3 singlets at 2.29 and 2.42).

Anal.—Calc. for $C_{15}H_{24}N_2O$: C, 72.54; H, 9.74; N, 11.28. Found: C, 72.61; H, 9.76; N, 11.39.

A hydrochloride derivative was prepared and recrystallized from isopropyl alcohol–ether to afford white needles, m.p. 166–166.5°.

Anal.—Calc. for $C_{15}H_{25}ClN_2O$: C, 63.24; H, 8.86; N, 9.84. Found: C, 63.42; H, 8.98; N, 9.89.

Ethyl *m*-Methoxyphenylacetate—The procedure used for the preparation of this ester was similar to that described by Mićović (22). From 25.0 g. (0.150 mole) of *m*-methoxyphenylacetic acid, 46 ml. of absolute alcohol, 1 ml. of concentrated H_2SO_4, and 27 ml. of dry toluene, there was obtained 26.63 g. (91.5%) of a colorless oil, b.p. 96–98° (0.35 mm.) [lit. (23) b.p. 118–122° (4 mm.)]; IR (film), 5.78 μ (ester C=O); NMR ($CDCl_3$), δ 6.64–7.50 (m, 4, ArH), 4.14 (q, 2, OCH_2), 3.78 (s, 3, OCH_3), 3.56 (s, 2, $ArCH_2$), and 1.23 (t, 3, C—CH_3).

Ethyl 3-*m*-Methoxyphenyl-2-oxosuccinate—This compound was prepared by a procedure adapted from the method of Levene and Meyer (24). The crude viscous oil obtained from 53.5 g. (0.275 mole) of ethyl *m*-methoxyphenylacetate, 37.7 g. (0.258 mole) of diethyl oxalate, and 5.93 g. (0.258 g.-atom) of sodium in 120 ml. of absolute alcohol was used directly in the following experiment.

Ethyl α-(*m*-Methoxyphenyl)acrylate—This compound was obtained by modifying the Kaiser *et al.* method (18) for the preparation of ethyl α-phenylacrylate. The crude ethyl 3-*m*-methoxyphenyl-2-oxosuccinate obtained above was treated with 34.6 ml. of 40% aqueous formaldehyde and 115 ml. of water. To this milky solution was added dropwise a solution of 28 g. of K_2CO_3 in 52 ml. of water over 3 hr. with rapid stirring at 12–18°. After the mixture was stirred for an additional 3 hr. at 15°, the organic phase was extracted with two 75-ml. portions of ether. The combined ether solution was dried, filtered, and evaporated under reduced pressure. Fractional distillation through a column (17.5 cm. long) packed with glass helixes afforded 25.18 g. (53.7%) of a pale-yellow oil, b.p. 88–90° (0.20 mm.); $n_D^{24.1}$ 1.5270; IR (film), 5.18 μ (ester C=O); NMR ($CDCl_3$), δ 6.76–7.48 (m, 4, ArH), 6.33 (d, 1, C=CH_2), 5.90 (d, 1, C=CH_2), 4.30 (q, 2, OCH_2), 3.81 (s, 3, OCH_3), and 1.12 (t, 3, C—CH_3). The compound was stored by refrigeration under a nitrogen atmosphere in the presence of hydroquinone methyl ether.

Anal.—Calc. for $C_{12}H_{14}O_3$: C, 69.89; H, 6.84. Found: C, 69.63; H, 7.23.

A *p*-toluidide derivative was made *via* the Bodroux reaction (8). A solution of 4.83 ml. of 2.85 *M* methylmagnesium chloride in tetrahydrofuran (0.014 mole) was diluted with 6 ml. of tetrahydrofuran. To this Grignard solution was added dropwise a solution of 1.50 g. (0.014 mole) of *p*-toluidine in 3 ml. of tetrahydrofuran with stirring under nitrogen atmosphere. After the vigorous reaction subsided, a solution of 1.52 g. (0.007 mole) of ethyl α-(*m*-methoxyphenyl)acrylate in 3 ml. of tetrahydrofran was added dropwise. The mixture was refluxed for 2 hr. and worked up. Distillation of the product afforded 0.76 g. of a viscous red oil, boiling at about 232° (0.30 mm.), which solidified upon standing. Recrystallization from hexane with charcoal treatment yielded white needles, m.p. 108–109.5°; IR (KBr), 6.02 μ (amide C=O).

Anal.—Calc. for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.28; H, 6.63; N, 5.16.

1,2-Dimethyl-4-(*m*-methoxyphenyl)-3-pyrazolidinone (VII)—A solution of 23.16 g. (0.112 mole) of ethyl α-(*m*-methoxyphenyl)-acrylate in 20 ml. of glacial acetic acid was added dropwise to a stirred solution of 6.72 g. (0.112 mole) of 1,2-dimethylhydrazine in 79 ml. of glacial acetic acid with ice-cooling under a nitrogen atmosphere. After the solution was refluxed for 21 hr., the acetic acid was removed under reduced pressure. The residue was dissolved in 30 ml. of water, and the resulting solution was made alkaline by the addition of solid K_2CO_3. Solid NaCl was added to obtain a salt-saturated solution, and the mixture was extracted three times with 30-ml. portions of ether. The combined ether solutions were dried, filtered, and concentrated under reduced pressure, and the liquid remaining was distilled and gave 12.38 g. (50.3%) of a colorless oil, b.p. 138–141° (0.20 mm.); $n_D^{24.5}$ 1.5542; IR (film), 5.94 μ (amide C=O); NMR ($CDCl_3$), δ 6.70–7.49 (m, 4, ArH), 3.17–4.20 (m, 6, including one OCH_3 singlet at 3.80), 3.06 (s, 3, $CONCH_3$), and 2.65 (s, 3, NCH_3).

Anal.—Calc. for $C_{12}H_{16}N_2O_2$: C, 65.43; H, 7.32; N, 12.72. Found: C, 65.43; H, 7.32; N, 12.57.

1,2-Dimethyl-4-(*m*-methoxyphenyl)pyrazolidine (VIII)—A solution of 9.61 g. (0.0437 mole) of VII in 10 ml. of anhydrous ether was added dropwise to a stirred suspension of 1.66 g. (0.0437 mole) of lithium aluminum hydride in 55 ml. of anhydrous ether. After completion of the addition, the mixture was refluxed for 18.5 hr. Decomposition of the complexes was effected by the addition of 40% aqueous KOH, and the mixture was worked up as described for V*a*. Distillation afforded 7.23 g. (80.3%) of a colorless oil, b.p. 99.5–101° (0.15 mm.); $n_D^{24.5}$ 1.5358; IR (film), no absorption at 5.94 μ (amide C=O); NMR ($CDCl_3$), δ 6.66–7.45 (m, 4, ArH), 3.81 (s, 3, OCH_3), and 3.71–2.43 (m, 11, including one NCH_3 singlet at 2.54).

Anal.—Calc. for $C_{12}H_{18}N_2O$: C, 69.87; H, 8.80; N, 13.58. Found: C, 69.76; H, 8.99; N, 13.51.

A hydrochloride derivative was prepared and recrystallized from absolute alcohol–ether to afford white crystals, m.p. 154.5–156.5°.

Anal.—Calc. for $C_{12}H_{19}ClN_2O$: C, 59.36; H, 7.90; N, 11.54. Found: C, 59.68; H, 8.07; N, 11.61.

1,2-Dimethyl-4-*n*-propyl-4-(*m*-methoxyphenyl)-3-pyrazolidinone (X)—Sodium hydride (50% mineral oil dispersion, 3.17 g., 0.066 mole) was rapidly weighed, washed three times with hexane and once with tetrahydrofuran, suspended in 90 ml. of tetrahydrofuran, and charged into a reaction flask. To this suspension was added dropwise at 40° a solution of 12.15 g. (0.055 mole) of VII in 20 ml. of tetrahydrofuran, whereupon hydrogen evolution was observed. The reaction mixture was refluxed for 90 min. and then cooled to room temperature; a solution of 13.53 g. (0.110 mole) of *n*-propyl bromide in 15 ml. of tetrahydrofuran was added dropwise. The mixture was then refluxed for 20 hr., cooled in an ice bath, and decomposed with saturated aqueous NH_4Cl solution. The tetrahydrofuran was decanted, and the inorganic sludge was extracted three times with 25-ml. portions of tetrahydrofuran. The combined tetrahydrofuran solution was evaporated under reduced pressure, and the residue was dissolved in 50 ml. of ether. The ether solution was dried, filtered, and concentrated under reduced pressure. Distillation of the remaining liquid afforded 12.06 g. (83.7%) of a colorless oil, b.p. 145° (0.20 mm.); $n_D^{23.2}$ 1.5365; IR (film), 5.97 μ (amide C=O); NMR ($CDCl_3$), δ 6.67–7.49 (m, 4, ArH), 3.82 (s, 3, OCH_3), 3.56 (d, 1, aliphatic ring proton), 3.32 (d, 1, aliphatic ring proton), 3.01 (s, 3, $CONCH_3$), 2.53 (s, 3, NCH_3), and 0.64–2.17 (m, 7, *n*-propyl protons).

Anal.—Calc. for $C_{15}H_{22}N_2O_2$: C, 68.67; H, 8.65; N, 10.68. Found: C, 68.51; H, 8.60; N, 10.84.

1,2-Dimethyl-4-*n*-propyl-4-(*m*-methoxyphenyl)pyrazolidine (XI)—To a stirred suspension of 1.63 g. (0.043 mole) of lithium aluminum hydride in 50 ml. of anhydrous ether was added dropwise a solution of 11.32 g. (0.043 mole) of X in 15 ml. of anhydrous ether. The reaction mixture was refluxed for 19 hr. The mixture was worked up as described for V*a*. Distillation of the product yielded 8.58 g. (80.5%) of a colorless oil, b.p. 115–116° (0.20 mm.); $n_D^{24.0}$ 1.5245; IR (film), no absorption at 5.97 μ (amide C=O); NMR ($CDCl_3$), δ 6.62–7.46 (m, 4, ArH), 3.81 (s, 3, OCH_3), 3.26 (d, 2, aliphatic ring protons), 2.97 (d, 2, aliphatic ring protons), 2.49 (s, 6, NCH_3), and 0.64–2.03 (m, 7, *n*-propyl protons).

Anal.—Calc. for $C_{15}H_{24}N_2O$: C, 72.54; H, 9.74; N, 11.28. Found: C, 72.48; H, 9.83; N, 11.44.

A picrate derivative was prepared and recrystallized from absolute alcohol to give yellow needles, m.p. 99.5–100.5°.

Anal.—Calc. for $C_{21}H_{27}N_5O_8$: C, 52.83; H, 5.70; N, 14.67. Found: C, 53.00; H, 5.65; N, 14.82.

1,2-Dimethyl-4-(*m*-hydroxyphenyl)pyrazolidine (IX)—A solution of 4.00 g. (0.0194 mole) of VIII in 21 ml. of 48% aqueous HBr was refluxed for 1 hr. After cooling, the solvent was removed under reduced pressure and the residue was azeotroped several times with absolute ethanol. A brown hygroscopic powder was obtained which, after recrystallization from absolute ethanol–ether, afforded white hygroscopic crystals. The crystals were dissolved in 10 ml. of water, and the solution was made alkaline by the addition of solid K_2CO_3 to pH 8. After saturation with NaCl, the mixture was extracted three times with 10-ml. portions of chloroform. The combined chloroform solution was dried, filtered, and evaporated under reduced pressure. The remaining residue was distilled and afforded 2.21 g. (59.4%) of a yellow viscous oil, b.p. 156–158° (0.28 mm.), which solidified in the receiver. Recrystallization of the solid from benzene–hexane afforded pale-yellow crystals, m.p. 118–120°; IR (KBr), 2.95 μ (phenolic OH); NMR ($CDCl_3$), δ 7.92 (s, 1, ArOH), 6.67–7.51 (m, 4, ArH), and 2.50–3.89 (m, 11, including one NCH_3 singlet at 2.64).

Anal.—Calc. for $C_{11}H_{16}N_2O$: C, 68.72; H, 8.39; N, 14.57. Found: C, 68.92; H, 8.13; N, 14.55.

1,2-Dimethyl-4-*n*-propyl-4-(*m*-hydroxyphenyl)pyrazolidine (XII)—A solution of 2.00 g. (0.0081 mole) of XI in 8.7 ml. of 48% aqueous HBr was refluxed for 1 hr. After cooling, the solvent was removed under reduced pressure. The residue was dissolved in 10 ml. of water, and the resulting solution was neutralized by the addition of solid K_2CO_3. The mixture was saturated with NaCl and extracted three times with 10-ml. portions of chloroform. The chloroform solution was dried, filtered, and evaporated under reduced pressure. Distillation of the residue afforded 1.38 g. (72.5%) of a semisolid oil, b.p. 156–158° (0.15 mm.); NMR ($CDCl_3$), δ 6.63–7.60 (m, 5, ArH and OH), 3.41 (d, 2, aliphatic ring protons), 3.08 (d, 2, aliphatic ring protons), 2.62 (s, 6, NCH_3), and 0.55–2.07 (m, 7, *n*-propyl protons).

Anal.—Calc. for $C_{14}H_{22}N_2O$: C, 71.76; H, 9.46; N, 11.95. Found: C, 71.93; H, 9.43; N, 11.96.

The picrate derivative was recrystallized from absolute alcohol, m.p. 161.5–162.5°.

Anal.—Calc. for $C_{20}H_{25}N_5O_8$: C, 51.83; H, 5.44; N, 15.11. Found: C, 51.79; H, 5.37; N, 15.15.

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ACKNOWLEDGMENTS AND ADDRESSES

Received May 5, 1971, from the *Department of Pharmaceutical Chemistry, College of Pharmacy, University of Kentucky, Lexington, KY 40506*

Accepted for publication September 27, 1971.

Presented to the Medicinal Chemistry Section, APhA Academy of Pharmaceutical Sciences, San Francisco meeting, March 1971.

Abstracted in part from a dissertation submitted by H. S. I. Tan to the Graduate School, University of Kentucky, in partial fulfillment of the Doctor of Philosophy degree requirements.

The authors are grateful to Dr. J. Adams, Astra Research Laboratories, for the ED_{50} of VIc, and to Dr. L. J. Sargent, National Institutes of Health, for the analgesic data of the remaining compounds.

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Theoretical Model Studies of Drug Absorption and Transport in the GI Tract III

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Abstract □ The diffusional transport of drugs across a membrane under the influence of hydrostatic (or osmotic) flow is described. The physical model consists of a bulk aqueous phase with a diffusion layer followed by a heterogeneous (lipid/aqueous) compartment and a perfect sink. The steady-state rate of change of the total drug concentration in the bulk aqueous phase is in the general form of a first-order equation useful for the evaluation of experiments. Computations are made for different cases in simulation of the *in situ* absorption of drugs in animals when the tonicity of the drug solution is varied. Several limiting models are mathematically deduced from the more general approach.

Keyphrases □ Drug transport—effect of hydrostatic (or osmotic) flow and surface pH in the GI tract, theoretical □ Membrane diffusion—effect of hydrostatic (or osmotic) flow and surface pH on GI drug absorption, theoretical □ Absorption, GI, theoretical—effect of hydrostatic (or osmotic) flow and surface pH on drug transport

Previous theoretical studies of drug absorption and transport in the GI tract have been involved with diffusion models (1, 2). The correlation of the intestinal, gastric, and rectal absorption of sulfonamides and barbituric acid derivatives with the models were found to be generally satisfactory and encouraging. More recently, the application of one of the models for the quantitative interpretation of the *in vivo* buccal absorption of a homologous series of *n*-alkanoic acids was highly successful (3).

This paper is an extension of the previous theoretical studies. It is also a description of a physical model for the transport of neutral, acidic, basic, and amphoteric drugs applicable to situations in which the diffusional flux of the drug is influenced by bulk fluid flow. The surface pH is also considered in a manner not previously treated. The general nature of the drugs, the ionic equilibria, and the distribution of drug species in a compartment were already described. Thus, Eqs. 1–9 of *Reference 2* are also appropriate here. To be consistent, the notations and definitions used in the previous papers will be generally followed[1].

The aqueous channel (or pore) is an important pathway of drug transport across biological membranes. In this connection, the permeation of solute as well as solvent should be simultaneously considered. The concepts of the aqueous pore route of mass transport in *in vitro* and biological membrane systems and the results of some experimental studies with biological membranes such as the gastric mucosa of animals, cell and capillary membranes, and tissues are found in the reviews of Pappenheimer (4), Solomon (5), and others (6–9). The well-known work of Renkin (10) provided the present physicochemical basis for the effective restriction on the diffusion of small solute molecules through pores. This was rigorously tested by Beck and Schultz (11). The meaning of pores in biological membranes was reviewed

[1] In this paper, K (instead of P) is used for the intrinsic partition coefficient and K_e (instead of P_e) is used for the effective partition coefficient.