Table II—Desorption from Hydrocortisone–Sepiolite Suspensions by Washing with Water

pH	Hydrocortisone Adsorbed, mg/g	Hydrocortisone Desorbed, mg/g		
		First Wash	Second Wash	Third Wash
2.9	5.75	1.03	0.63	0.60
6.8	7.91	3.17	1.45	0.86
9.8	6.69	1.50	0.88	0.80

sample compared to the iron content of the attapulgite studied previously (2.6%). The oxidative degradation of hydrocortisone is affected minimally by sepiolite, although significant adsorption occurs. Adsorption of hydrocortisone by sepiolite can be explained by the high external surface area of sepiolite (400 m^2/g). However, attapulgite also has a significant external surface area (280 m^2/g), but no adsorption of hydrocortisone by attapulgite was observed by IR spectroscopy (1). It is hypothesized that the contact time needed for adsorption is greater than the contact time needed for the ferric iron-catalyzed oxidative degradation. Thus, in clays with a high ferric iron content, oxidative degradation is the predominant reaction. However, in clays such as sepiolite with a low ferric iron content and, therefore, a much smaller catalytic effect, the major reaction is adsorption.

The results of this study strongly suggest that sepiolite should be considered for use in pharmaceuticals. It has a very similar structure to attapulgite but a greater external surface area, which suggests that sepiolite will have excellent properties as a GI adsorbent. In addition, sepiolite is a desirable clay for use as a pharmaceutical excipient since its low ferric iron content means that it is compatible with drugs such as hydrocortisone that degrade by oxidative degradation. In addition, the reversible nature of the adsorption of hydrocortisone by sepiolite suggests that the bioavailability of neutral drugs will not be affected significantly by interaction with sepiolite. Finally, the rheological properties of sepiolite suspensions are very similar to attapulgite suspensions.

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Synthesis and Anticonvulsant Activity of Racemic 2-Amino-*N*-substituted Succinimide Derivatives

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Abstract □ Several derivatives of (*R,S*)-2-amino-*N*-substituted succinimides were synthesized and evaluated in mice against seizures produced by electroshock and pentylenetetrazol. The most active compound against both electroshock- and pentylenetetrazol-induced seizures was (*R,S*)-*N*-benzyl-2-(methanesulfamido)succinimide.

Keyphrases □ 2-Amino-*N*-substituted succinimide derivatives—synthesis and evaluation for anticonvulsant activity □ Anticonvulsant activity—2-amino-*N*-substituted succinimide derivatives, synthesis and evaluation for activity □ Structure–activity relationships—2-amino-*N*-substituted succinimide derivatives, synthesis and evaluation for anticonvulsant activity

Many epileptic seizures cannot be controlled by currently available anticonvulsants. Furthermore, those individuals whose seizures are controlled often tolerate harmful side effects (1). The development of carbamazepine and valproic acid has improved seizure protection for epileptics, of whom only 50% were completely protected by previously marketed antiepileptic drugs. Despite the beneficial effects of these drugs, new anticonvulsants with more selective action and less toxicity are needed (2).

BACKGROUND

In the development of new anticonvulsants, most attention has been centered on the ureide structure (I). Three succinimides, phensuximide, methsuximide, and ethosuximide, that contain this basic structure are used in the treatment of petit mal epilepsy (3).

Witiak *et al.* (4) reported the synthesis and anticonvulsant activity of

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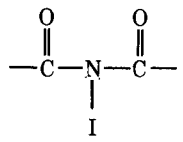


I

chiral 2-amino-*N*-benzyl-substituted succinimides. The most potent anticonvulsant activity against maximal electroshock was observed with the enantiomorphic imides II and III. However, no stereoselective differences in anticonvulsant activity were observed with the (*S*)-II and (*R*)-III enantiomorphs.

The purpose of this investigation was to evaluate the anticonvulsant activity of 2-amino-*N*-substituted succinimide derivatives in which the lipophilicity of the groups on the nitrogen and at the 2-position was varied. The relationship between log *p* of the compound and anticonvulsant activity was discussed previously (5, 6).

Sulfonamide or urea derivatives of (*R,S*)-2-amino-*N*-(*n*-propyl)-succinimide hydrochloride (VII) and (*R,S*)-2-amino-*N*-benzylsuccinimide hydrochloride (VIII) are described. These derivatives were chosen because both the size and the lipophilicity of the substituent could be varied easily. Additionally, previous investigators showed that nitrogen-containing substituents at the 2-position of the succinimide ring imparted good anticonvulsant activity (7). Based on the findings of Witiak *et al.* (4), no attempt was made to prepare the individual enantiomorphs of the compounds.

RESULTS AND DISCUSSION

The succinimide derivatives (V–XI) were prepared as shown in Scheme I, and the physical properties of the (*R,S*)-2-ureido-*N*-substituted succinimides (IX*a*–IX*j*) are given in Table I.

The anticonvulsant activity of V–XI is shown in Table II. Only VI, VIII, IX*d*, and XI (ED_{50} = 288) exhibited activity in the maximal electroshock seizure (MES) test. Witiak *et al.* (4) reported the anticonvulsant activity of the individual enantiomorphs of VI. It is surprising that the polar compounds VIII and XI exhibited activity against MES. Only VIII was active against MES at 4 hr after administration. Several succinimide derivatives (V, VI, VIII, IX*c*, IX*h*–IX*j*, X, and XI) were active against subcutaneous pentylenetetrazol-induced seizures. Compound VIII showed activity at 300 mg/kg (four out of four mice protected) at 0.5 hr after administration. The ED_{50} of the sulfonamide XI was 120 mg/kg at the time of the peak effect (0.5 hr). Both VIII and XI (TD_{50} = 422) exhibited significant toxicity in the rotorod test. Among the ureas, IX*c* appeared to be the most active. To observe activity against subcutaneous pentylenetetrazol-induced seizures in the urea series, a propyl, butyl, or 2-chloroethyl group on one of the urea nitrogens is necessary.

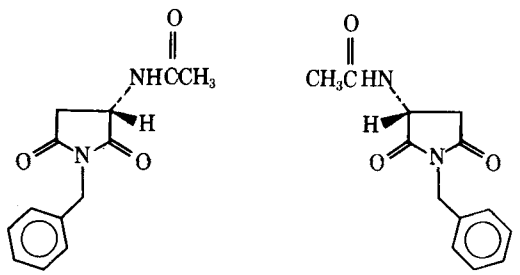
It appears that the 2-amino-*N*-benzylsuccinimide derivatives are more active than the corresponding 2-amino-*N*-(*n*-propyl)succinimides. The introduction of a urea substituent into the 2-position of the succinimide ring does not impart significant activity. The activity of (*R,S*)-2-amino-*N*-benzylsuccinimide hydrochloride (VIII) and (*R,S*)-*N*-benzyl-2-(methanesulfamido)succinimide (XI) against both maximal electroshock seizure and subcutaneous pentylenetetrazol-induced seizure is interesting since they are quite polar and are expected to penetrate the blood–brain barrier poorly. Further work is in progress to evaluate the anticonvulsant activity of VIII and XI as well as to prepare other hydrophilic derivatives related to these two compounds.

EXPERIMENTAL[1]

(*R,S*)-*N*-Acetylaspartic Acid (IV)—Compound IV was prepared by the method of Barker (8) in an 83% yield, mp 163–165° [lit. (8) mp 139–140°].

(*R,S*)-2-Acetamido-*N*-(*n*-propyl)succinimide (V)—A mixture of IV (23.0 g, 0.13 mole) and *n*-propylamine (15.5 g, 0.26 mole) was heated to 210°. Water was removed during heating *via* a Dean–Stark trap. The reaction mixture was cooled to yield a dark-brown oil. The oil was taken up into chloroform (100 ml) and chromatographed on a silica gel column

[1] Melting points were determined on a Fisher-Johns melting-point apparatus and are uncorrected. IR spectra were recorded as potassium bromide pellets with a Perkin-Elmer 137 spectrophotometer. NMR spectra were recorded on a Varian EM 360A spectrometer. Chemical shifts are reported in parts per million (δ) relative to tetramethylsilane (1%) as the internal standard. Analytical data were obtained from Micro-Analysis Inc., Wilmington, Del. TLC was performed on precoated silica gel plastic sheets (Macherey-Nagel). Column chromatography was carried out using MN-Kieselgel (70–325 mesh) as the adsorbent.



II III

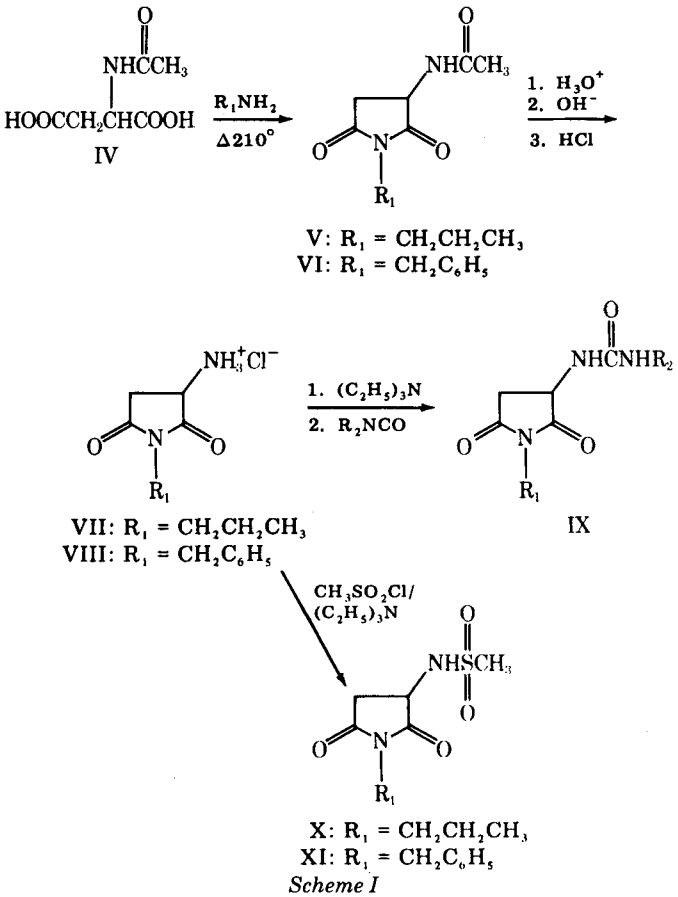
with chloroform–ethanol (8:2) as the solvent. Evaporation of the solvent gave 13.4 g (52%) of a light-tan solid. Recrystallization from chloroform–hexane gave an analytically pure product, mp 104–106°; IR (KBr): 3400 (NH), 1785 (C=O, imide), 1710 (C=O, imide), and 1670 (C=O, amide) cm^{-1}; NMR ($CDCl_3$): δ 0.90 (t, 3H, *J* = 7 Hz, $NCH_2CH_2CH_3$), 1.60 (m, 2H, $NCH_2CH_2CH_3$), 2.03 (s, 3H, $NCOCH_3$), 2.57–3.60 (m, 4H, ring CH_2 and NCH_2), 4.27 (m, 1H, ring CH), and 7.17 (d, 2H, NHCO).

Anal.—Calc. for $C_9H_{14}N_2O_3$: C, 54.52; H, 7.13; N, 14.13. Found: C, 54.27; H, 7.22; N, 13.96.

(*R,S*)-2-Acetamido-*N*-benzylsuccinimide (VI)—Compound VI was prepared from IV (20.0 g, 0.11 mole) and benzylamine (12.2 g, 0.11 mole) in the same manner as described for the synthesis of V. Recrystallization from ethanol–ethyl acetate gave analytically pure material, mp 172–174° [lit. (4) mp of the (*R*)- or (*S*)-enantiomer 171–175°]; IR (KBr): 3400 (NH), 1785 (C=O, imide), 1710 (C=O, imide), and 1667 (C=O, amide) cm^{-1}.

Anal.—Calc. for $C_{13}H_{14}N_2O_3$: C, 63.39; H, 5.74; N, 11.38. Found: C, 63.16; H, 5.60; N, 11.35.

(*R,S*)-2-Amino-*N*-(*n*-propyl)succinimide Hydrochloride (VII)—A suspension of V (3.00 g, 0.15 mole) in 27 ml of 6 *N* HCl was refluxed for 0.5 hr until a clear solution was obtained. The reaction mixture was cooled, made basic with 8 *N* NH_4OH, and extracted with two 75-ml portions of chloroform. The combined chloroform extracts were dried (sodium sulfate), filtered, and evaporated under reduced pressure to afford a light-yellow oil. The oil was taken up into absolute ethanol and converted to a crystalline hydrochloride derivative. Recrystallization from



Scheme I

Table I—Physical Properties of (*R,S*)-2-Ureido-*N*-substituted Succinimides (IX)

Compound	R_1	R_2	Melting Point	Yield, %	Recrystallization Solvent[a]	Formula	Analysis, %	Calc.	Found
IX*a*	$CH_2CH_2CH_3$	CH_3	117–118°	43	A	$C_9H_{15}N_3O_3$	C	50.68	50.70
							H	7.10	7.20
							N	19.71	19.60
IX*b*	$CH_2CH_2CH_3$	CH_2CH_3	84–87°	57	A	$C_{10}H_{17}N_3O_3$	C	52.84	52.81
							H	7.55	7.58
							N	18.49	18.50
IX*c*	$CH_2CH_2CH_3$	$CH_2CH_2CH_3$	102–104°	52	A	$C_{11}N_{19}N_3O_3$	C	54.74	54.55
							H	7.95	8.04
							N	17.42	17.31
IX*d*	$CH_2CH_2CH_3$	$CH_2CH_2CH_2CH_3$	101–102°	68	A	$C_{12}H_{21}N_3O_3$	C	56.43	56.29
							H	8.31	8.39
							N	16.46	16.33
IX*e*	$CH_2CH_2CH_3$	CH_2CH_2Cl	133–135°	62	A	$C_{10}H_{16}ClN_3O_3$	C	45.88	46.13
							H	6.17	6.15
							N	16.06	16.24
IX*f*	$CH_2C_6H_5$	CH_3	163–165°	69	B	$C_{13}H_{15}N_3O_3$	C	59.75	59.70
							H	5.80	5.83
							N	16.08	16.32
IX*g*	$CH_2C_6H_5$	CH_2CH_3	139–141°	49	B	$C_{14}H_{17}N_3O_3$	C	61.07	61.37
							H	6.24	6.24
							N	15.26	15.39
IX*h*	$CH_2C_6H_5$	$CH_2CH_2CH_3$	147–149°	70	A	$C_{15}H_{19}N_3O_3$	C	62.26	62.42
							H	6.63	6.59
							N	14.52	14.50
IX*i*	$CH_2C_6H_5$	$CH_2CH_2CH_2CH_3$	145–147°	62	A	$C_{16}H_{21}N_3O_3$	C	63.34	63.56
							H	6.99	6.98
							N	13.85	14.06
IX*j*	$CH_2C_6H_5$	CH_2CH_2Cl	191–194°	71	B	$C_{14}H_{16}ClN_3O_3$	C	54.27	54.37
							H	5.23	5.50
							N	13.57	13.50

[a] A = acetone–ether, and B = acetone.

Table II—Anticonvulsant Activity of Succinimide Derivatives

Compound	MES Activity[a] 0.5 hr	MES Activity[a] 4 hr	sc Met Activity[a,b] 0.5 hr	sc Met Activity[a,b] 4 hr	Toxicity[c]
V	–	–	+ (1/4)	–	0/4
VI	+	–	++ (2/4)	–	0/4
VII	–	–	–	–	0/4
VIII	++ (4/4)	+ (1/4)	++ (4/4)	–	4/4 at 600 mg/kg
IX*a*	–	–	–	–	0/4
IX*b*	–	–	–	–	0/4
IX*c*	–	–	++ (3/4)	–	0/4
IX*d*	+	–	+ (2/4)	–	3/4 at 600 mg/kg
IX*e*	–	–	–	–	0/4
IX*f*	–	–	–	–	0/4
IX*g*	–	–	–	–	0/4
IX*h*	–	–	+++ (1/4)	–	0/4
IX*i*	–	–	++ (1/4)	–	0/4
IX*j*	–	–	+++ (1/4)	–	0/4
X	–	–	++ (4/4)		0/4
XI	288[d] (217–310)[e,f]	–	120[d] (90–166)[e,f]	–	422[g] (390–457)[e,f]
Phensuximide	112[d] (104–131)[e,f]		50 (21–65)[e,f]		232[g] (187–267)[e,f]

[a] +++, ++, and + signify activity at 100, 300, and 600 mg/kg, respectively; – denotes no activity observed at 600 mg/kg. [b] Numbers in parentheses indicate the number of animals protected against sc Met-induced seizures or maximal electroshock-induced seizures. [c] Number of animals exhibiting neurotoxicity as determined by the rotorod test. [d] ED_{50}. [e] The 95% confidence limits. [f] Determined at time of the peak effect (0.5 hr). [g] TD_{50}.

absolute ethanol–ether gave 1.68 g (58%) of a white solid, mp 207–208°; IR (KBr): 2750 (NH_3^+), 1785 (C=O, imide), and 1710 (C=O, imide) cm^{-1}; NMR (D_2O): δ 0.80 (t, 3H, J = 7 Hz, $NCH_2CH_2CH_3$), 1.57 (m, 2H, $NCH_2CH_2CH_3$), 2.60–3.63 (m, 4H, ring CH_2 and NCH_2), and 4.47 (m, 1H, ring CH).

Anal.—Calc. for $C_7H_{13}ClN_2O_2$: C, 43.63; H, 6.81; N, 14.54. Found: C, 46.61; H, 6.73; N, 14.53.

(*R,S*)-2-Amino-*N*-benzylsuccinimide Hydrochloride (VIII)—Compound VIII was prepared, as described for VII, from VI (3.12 g, 0.13 mole) and 27 ml of 6 *N* HCl. Workup in the normal manner gave 1.84 g (71%) of the free base, mp 67–68°. The hydrochloride was prepared and recrystallized from absolute ethanol to give analytically pure material, mp 217.5–219°; IR (KBr): 2750 (NH_3^+), 1785 (C=O, imide), and 1710 (C=O, imide) cm^{-1}; NMR (dimethyl sulfoxide-d_6): δ 2.90–3.17 (m, 3H, ring CH_2 and CH), 4.57 (s, 2H, NCH_2), 7.40 (s, 5H, C_6H_5), and 9.20 (s, 3H, NH_3^+).

Anal.—Calc. for $C_{11}H_{13}ClN_2O_2$: C, 54.88; H, 5.45; N, 11.64. Found: C, 55.15; H, 5.38; N, 11.65.

(*R,S*)-2-Ureido-*N*-substituted Succinimides (IX*a*–IX*j*)—The synthesis of (*R,S*)-2-[3-(2-chloroethyl)ureido]-*N*-(*n*-propyl)succinimide (IX*e*) is representative of the general method. The amine hydrochloride (VII) (2.00 g, 0.010 mole) and triethylamine (1.05 g, 0.010 mole) in 50 ml of tetrahydrofuran were stirred for a few minutes and treated with 2-chloroethyl isocyanate[2] (1.10 g, 0.010 mole). The reaction mixture was stirred overnight and filtered to remove the precipitated triethylamine hydrochloride. The filtrate was removed under reduced pressure to yield a white solid. Recrystallization of the solid from acetone–ether gave 1.45 g (62%) of analytically pure product, mp 133–135°; IR (KBr): 3320 (NH), 1785 (C=O, imide), 1710 (C=O, imide), and 1670 (C=O, urea) cm^{-1}; NMR ($CDCl_3$): δ 0.87 (t, 3H, J = 6 Hz, $NCH_2CH_2CH_3$), 1.47 (m, 2H, $NCH_2CH_2CH_3$), 2.30–3.72 (m, 8H, $NCH_2CH_2CH_3$, ring CH_2, and CH_2CH_2Cl), 4.40 (m, 1H, ring CH), and 6.37–6.87 (m, 2H, NHCONH).

Anal.—Calc. for $C_{10}H_{16}ClN_3O_3$: C, 45.88; H, 6.17; N, 16.06. Found: C, 46.13; H, 6.15; N, 16.24.

(*R,S*)-2-Methanesulfamido-*N*-(*n*-propyl)succinimide (X)—A

[2] Eastman Kodak.

solution of VII as the free base (1.96 g, 0.013 mole) in 50 ml of tetrahydrofuran was treated with triethylamine (1.27 g, 0.013 mole), followed by the dropwise addition of methanesulfonyl chloride (1.43 g, 0.013 mole). The reaction mixture was stirred at room temperature for 4 hr and filtered to remove the precipitated triethylamine hydrochloride. The filtrate was evaporated under reduced pressure to yield a light-yellow oil. Column chromatography of the oil using silica gel as the adsorbent and chloroform–methanol (9:1) as the solvent gave, after evaporation of the solvents, 0.77 g (26%) of a white crystalline solid. An analytical sample was obtained by recrystallization from chloroform–hexane to give white crystals, mp 82–83°; IR (KBr): 3300 (NH), 1785 (C=O, imide), 1710 (C=O, imide), and 1150 (SO_2) cm^{-1}; NMR: δ 0.90 (t, 3H, J = 6 Hz, $NCH_2CH_2CH_3$), 1.60 (m, 2H, $NCH_2CH_2CH_3$), 2.40–3.67 (m, including s at 3.13, 7H, SO_2CH_3), 4.47 (m, 1H, ring CH), and 5.77 (s, 1H, NH).

Anal.—Calc. for $C_8H_{14}N_2O_4S$: C, 41.01; H, 6.03; N, 11.96. Found: C, 41.19; H, 5.90; N, 12.22.

(*R,S*)-*N*-Benzyl-2-(methanesulfamido)succinimide (XI)—Compound XI was synthesized from VIII as the free base (1.00 g, 0.005 mole), triethylamine (0.496 g, 0.005 mole), and methanesulfonyl chloride (0.561 g, 0.005 mole) in 50 ml of tetrahydrofuran in the same manner as described for X. Recrystallization of the solid product from chloroform–hexane gave 0.729 g (57%) of analytically pure product, mp 118–121°; IR (KBr): 3300 (NH), 1785 (C=O, imide), 1710 (C=O, imide), and 1150 (SO_2) cm^{-1}; NMR ($CDCl_3$): δ 2.50 (m, including s at 3.10, 5H, SO_2CH_3), 4.10–4.77 (m, including s at 4.63, 3H, $NCH_2C_6H_5$), 5.77 (d, 1H, NH), and 7.33 (s, 5H, C_6H_5).

Anal.—Calc. for $C_{12}H_{14}N_2O_4S$: C, 51.04; H, 5.01; N, 9.92. Found: C, 50.97; H, 4.91; N, 10.08.

Pharmacological Testing[3]—Three tests were performed: the maximal electroshock seizure test (MES), the subcutaneous pentylenetetrazol seizure threshold test (sc Met), and the rotorod test to evaluate neurotoxicity[4].

All tests were performed on male Carworth Farms No. 1 mice. All compounds were tested at 30, 100, 300, and 600 mg/kg at 30 min and 4 hr after intraperitoneal administration. Four animals were injected with each dose. After 30 min, each animal was examined for toxicity in the rotorod test. Immediately thereafter, anticonvulsant activity was evaluated by subjecting one mouse to the MES test and another to the sc Met test. The same tests were repeated 4 hr later on the two remaining mice.

All compounds were solubilized in either 0.9% NaCl or 30% polyethylene glycol 400 and administered intraperitoneally in a volume of 0.01 ml/g. The ED_{50} and TD_{50} values and their confidence limits were determined by the method of Litchfield and Wilcoxon (11). The MES activity is defined as abolition of the hindlimb tonic extensor component of the maximal electroshock seizure elicited in mice with a 60-Hz alternating current of 50 mamp delivered for 0.1 sec *via* corneal electrodes. The sc Met activity is defined as failure to observe even a threshold seizure (a single episode of clonic spasms of at least 5 sec).

[3] All compounds were tested for anticonvulsant activity by the Antiepileptic Drug Development Program administered by the Section on Epilepsy, National Institutes of Health, Bethesda, MD 20014. The compounds were evaluated using the Anticonvulsant Screening Project test systems (9, 10).

[4] Neurological toxicity is defined as failure of an animal to remain for 1 min on a rod rotating at 6 rpm.

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First-Pass Effect: Nonlinear Concept Comprising an Explicit Solution of Integrated Michaelis–Menten Equation

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Abstract □ The first-pass effect results from metabolism during the first liver passage of a drug given by mouth. The metabolism is described by the Michaelis–Menten equation, but the integrated form of the Michaelis–Menten equation has no explicit solution for concentration and its handling requires a computer. However, the presented nonlinear equation of the first-pass effect is an explicit integration of the Michaelis–Menten equation and involves only general mathematics. However, the problem of evaluating the Michaelis–Menten constants V_m and K_m is not resolved. Therefore, linear equations are also derived, which correspond to previous clearance models.

Keyphrases □ Pharmacokinetics—first-pass effect, nonlinear approach to solution of Michaelis–Menten equation □ First-pass effect—nonlinear approach to solution of integrated Michaelis–Menten equation □ Michaelis–Menten kinetics—first-pass effect, nonlinear approach □ Clearance—first-pass effect, nonlinear approach to solution of integrated Michaelis–Menten equation

First-pass effect is defined as the reduced systemic bioavailability resulting from metabolism during the first liver passage of an orally administered drug (Fig. 1) (1). The mathematical description of this effect usually is based on first-order compartment or clearance models (1–3). However, metabolism follows nonlinear kinetics

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