

Table II—Test of Additivity: F/V versus $1/V$

Series	Intercept	Slope	r	n	Group Constant Eq. 4	Ref. 1
Alkanes (H)	8.73	-194	0.997	7	33	80-100
Alcohols (OH)	8.95	218	0.998	7	452	—
Nitriles (CN)	8.60	167	0.965	5	457	410
Ketones (CO)	6.68	236	0.985	9	437	275
Esters (COO)	7.04	201	0.936	12	482	310
Acids (COOH)	9.12	201	0.978	3	452	—
Chlorides (Cl)	6.99	149	0.949	3	381	270
Iodides (I)	6.76	215	0.999	4	501	425
Sulfones (OSO)	7.61	527	0.999	3	—	—

of F does not appear to be related to a variability in F_c values since the described plots give excellent linear correlations with constant slopes. An attempt has been made to account for the variability in F_c values by considering the variation in chain length in a homologous series (10). The observed variations and inconsistencies, however, are most probably due to the poorly additive nature of F .

Deviations from strict additivity do not necessarily discredit the practical use of F . One must decide what sort of inaccuracies can be tolerated for an intended purpose. The calculation of F from group constants which are only approximately additive may be valuable on an operational basis. For example, in diols such as ethylene glycol, diethylene glycol, and propylene glycol, calculated values for a single OH group are 273, 273, and 278, respectively, while in hetero-functional analogs such as carbitol, the values for an OH group cluster around 325. Such dependencies on compound

type place even further limitations on the additivity of F . Nonetheless, there is a practical usefulness for an apparent additivity of F on a constitutive basis when used within the limits of recognized restrictions.

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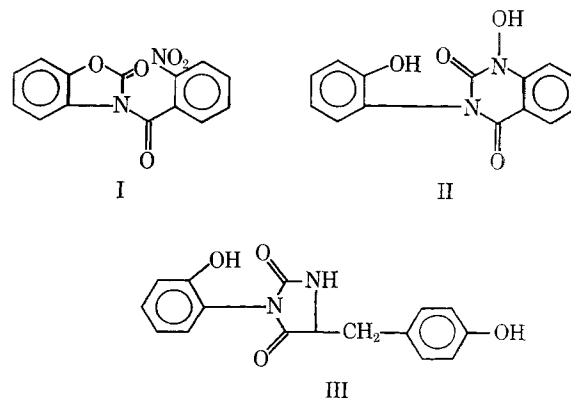
Preparation of Some Substituted Imidazolidine-2,4-diones

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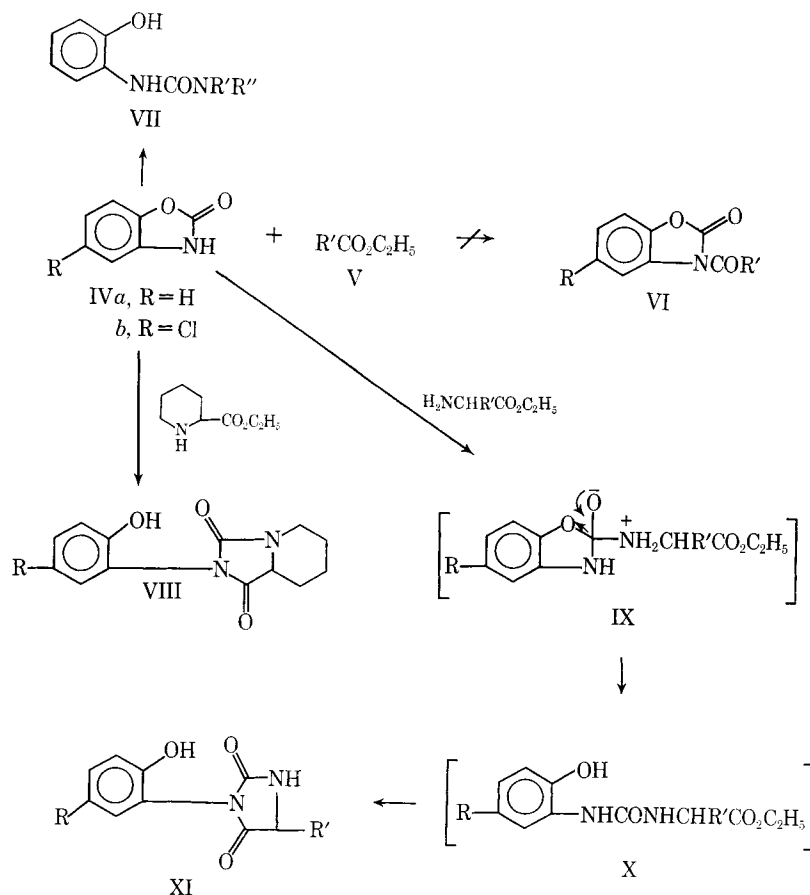
Abstract □ Heating 2-benzoxazolinone or 5-chloro-2-benzoxazolinone with aminoacid esters resulted in the formation of 3-(2-hydroxyphenyl) imidazolidine-2,4-dione derivatives. Results of preliminary pharmacological tests are reported.

Keyphrases □ Imidazolidine-2,4-diones—synthesis □ Pharmacological screening—imidazolidine-2,4-diones □ IR spectrophotometry—structure □ NMR spectroscopy—structure

Heating of 2-benzoxazolinone with aniline (1) and hydrazine hydrate (2) was observed to yield a substituted urea and a semicarbazide derivative, respectively. A similar rearrangement was noted (3) when the hydrogenation of 3-(2-nitrobenzoyl)-2-benzoxazolinone (I) resulted in the formation of 1-hydroxy-3-(2-hydroxyphenyl) quinazoline-2,4-dione (II). More recently, 3-(2-hydroxyphenyl)-5-(4-hydroxybenzyl)imidazolidine-2,4-dione (III) was produced when 2-benzoxazolinone was heated with ethyl tyrosinate (4). The latter observation prompted a study to determine whether the initial reaction in the rearrangement was an acylation at Position 3 of the benzoxazolinone ring or an attack of the carbonyl group by the amino moiety of the aminoacid ester.



The acylation of 2-benzoxazolinone (IVa) or the potassium salt of IVa with ethyl benzoate or ethyl butyrate at different temperatures failed to occur. On the other hand, refluxing IVa with benzylamine, pyrrolidine, and 4-pipecoline in each case provided a urea derivative (VII) which was readily detected by the appearance of a 1650-1630 cm^{-1} carbonyl band in the IR spectrum. These observations, together with the fact that ureas containing an appropriate carbethoxy group spontaneously form cyclic derivatives (5, 6), indicate that the



Scheme I

reaction of 2-benzoxazolinones (IV) with amino acid esters occurs *via* Intermediate X (Scheme I).

Other substituted 2-(2-hydroxyphenyl)imidazolidine-2,4-diones (VIII, XI) (Table I) were prepared by heating 2-benzoxazolinone or its 5-chloro derivative with different amino acid esters. The identity of the compounds was substantiated by elemental analysis, as well as IR and NMR spectral data.

PHARMACOLOGICAL RESULTS

Nonfasted male mice were subjected to i.p. doses (250 and 500 mg./kg. in 5% acacia) of the compounds described herein and observed for general biological activity.

All compounds possess LD₅₀'s greater than 50 mg./kg. VIIa and XIc were inactive; VIIc, VIIa, VIIb, and XIb at doses of 500 mg./kg. produce slight CNS depression and decreased motor activity. Both XIa and XIb at 500 mg./kg. produce CNS depression.

Table I—3-(2-Hydroxyphenyl)Imidazolidine-2,4-diones

No.	R	R'	Yield, %	M.p. °C. (recryst. solvent) ^a	Molecular Formula	Anal., %	
						Calcd.	Found
VIIIa	H	—	64	223–225(M)	C ₁₃ H ₁₄ N ₂ O ₃	C, 63.4 H, 5.7 N, 11.4	C, 63.2 H, 5.7 N, 11.4
VIIIb	Cl	—	80	252–254(M)	C ₁₃ H ₁₃ ClN ₂ O ₃	Cl, — C, 55.6 H, 4.7 N, 10.0	Cl, — C, 55.8 H, 4.7 N, 10.0
XIa	H	CH(CH ₃) ₂	70	155–156(B)	C ₁₂ H ₁₄ N ₂ O ₃	Cl, 12.6 C, 61.5 H, 6.0 N, 12.0	Cl, 12.5 C, 61.7 H, 6.1 N, 11.9
XIb	Cl	CH(CH ₃) ₂	70	186–187(B)	C ₁₂ H ₁₃ ClN ₂ O ₃	Cl, — C, 53.6 H, 4.9 N, 10.4	Cl, — C, 53.7 H, 5.0 N, —
XIc	H	CH ₂ CH(CH ₃) ₂	40	145–147(B)	C ₁₃ H ₁₆ N ₂ O ₃	Cl, 13.2 C, 62.9 H, 6.5 N, 11.3	Cl, 13.1 C, 62.8 H, 6.4 N, 10.8
XId	Cl	CH ₂ C ₆ H ₄ OH	82	226–228(W)	C ₁₆ H ₁₃ ClN ₂ O ₄	Cl, — C, 57.8 H, 3.9 N, 8.4 Cl, 10.7	Cl, — C, 57.8 H, 4.0 N, 8.2 Cl, 10.5

^a M = methanol; B = benzene; W = water.

Table II—IR and NMR Spectral Data

No.	IR ^a cm. ⁻¹	NMR; Chemical Shift (δ) ^b
VIIa ^c	3500, 3300, 1630, 1520	3.4 ^d (1H, S), 4.1 (2H, S), 4.3 ^d (1H, S), 6.4 (3H, M), 7.3 (5H, S), 7.5 (1H, S), 8.2 ^d (1H, S)
VIIb ^c	3400, 3050, 1650, 1530	1.9 (4H, Qn), 3.4 (4H, T), 3.6–4.0 ^d (1H, S), 6.8 (3H, M), 7.5 (1H, M), 7.7 ^d (1H, S)
VIIc ^c	3400, 3000, 1630, 1520	0.9 (3H, D), 1.4 (4H, Qr), 2.8 (4, T), 3.3–4.0 ^d (1H, S), 4.2 (1H, M), 6.8 (3H, M), 7.4 (1H, M), 8.0 ^d (1H, S)
XIa ^e	3300, 1775, 1710	1.0 (3H, D), 1.1 (3H, D), 2.3 (1H, M), 2.7–3.2 ^d (1H, S), 4.1 (1H, D), 7.1 (4H, M), 8.3–8.6 ^d (1H, S)
XIb ^e	3250, 1775, 1700	1.0 (3H, D), 1.1 (3H, D), 2.3 (1H, M), 2.8–3.2 ^d (1H, S), 4.2 (1H, D), 7.2 (3H, M), 8.3–8.6 ^d (1H, S)
XIc ^e	3300, 1775, 1710	1.0 (6H, D), 1.6 (2H, T), 2.3 (1H, M), 2.9–3.3 ^d (1H, S), 4.2 (1H, T), 7.1 (4H, M), 8.2–8.5 ^d (1H, S)
XId ^e	3250, 3150, 1770, 1700	3.0 (2H, D), 3.2–3.8 ^d (2H, S), 4.5 (1H, T), 7.0 (7H, M), 8.3 ^d (1H, S)
VIIIa ^e	3150, 1775, 1700	1.7 (8H, M), 4.05 (1H, T), 3.4 ^d (1H, S), 7.1 (4H, M)
VIIIb ^e	3100, 1775, 1690	1.7 (8H, M), 4.05 (1H, T), 3.3–3.7 ^d (1H, S), 7.1 (3H, M)

^a The compounds exhibited characteristic aromatic absorption bands in regions of 1600–1490, and 1000–695. ^b S = singlet, D = doublet, T = triplet, Qr = quartet, Qn = quintet, M = multiplet. ^c NMR determined in deuterated dimethylsulfoxide. ^d Exchanged with D₂O. ^e NMR determined in deuterated acetone.

ataxia, and decreased motor activity with an indication of possible tranquilizer and vasodilator activity.

EXPERIMENTAL¹

Commercially available DL-valine, DL-leucine, and DL-tyrosine were esterified according to the Fischer method (7). 2-Carboxypiperidine was prepared according to the procedure described by Reckhow and Tarbell (8).

N-Benzyl-N'-(2-hydroxyphenyl)urea (VIIa)—A mixture of 1 g. (0.0075 mole) of 2-benzoxazolinone and 1 ml. of benzylamine was refluxed in an oil bath, preheated to 180° for 15 min. The product was triturated with ether, removed by filtration, and recrystallized from ethanol to give 1.4 g. (78%) of product, m.p. 167–169°.

Anal.—Calcd. for C₁₄H₁₄N₂O₂: C, 69.4; H, 5.8; N, 11.6. Found: C, 69.7; H, 6.0; N, 11.8.

2-Hydroxy-N-pyrrolidinocarbonylaniline (VIIb)—A mixture of 1 g. (0.0075 mole) of 2-benzoxazolinone and 2 ml. of pyrrolidine was refluxed in an oil bath preheated at 140° for 30 min. The excess pyrrolidine was then removed under reduced pressure and the residual solid recrystallized from ethanol to yield 0.7 g. (45%) of product, m.p. 159–160°.

Anal.—Calcd. for C₁₁H₁₄N₂O₂: C, 64.1; H, 6.8; N, 13.6. Found: C, 63.9; H, 6.9; N, 13.6.

2-Hydroxy-N-(4-pipecolino)carbonylaniline (VIIc)—The procedure utilized for the preparation of VIIb was applied to 2 g. (0.015 mole) of 2-benzoxazolinone and 4 ml. of 4-pipecoline. The product (1.4 g., 41%) was recrystallized from methanol; m.p. 122–124°.

Anal.—Calcd. for C₁₃H₁₈N₂O₂: C, 66.6; H, 7.7; N, 12.0. Found:

¹ All melting points were taken in open glass capillaries using a Thomas-Hoover melting point apparatus and are uncorrected. IR spectra were determined on a Perkin-Elmer model 137 infracord spectrophotometer using KBr pellets. NMR spectra were determined on a Varian A-60A spectrometer using tetramethylsilane as an internal standard.

C, 66.7; H, 7.8; N, 11.8.

Substituted 2-(2-Hydroxyphenyl)imidazolidine-2,4-diones (VIII XI) (Table I)—The procedure described for the preparation of VIIa was followed using 0.015 mole of 2-benzoxazolinone or 5-chloro-2-benzoxazolinone and 0.017 mole of the appropriate amino acid ester.

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