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

Series	Intercept	Slope	*r*	*n*	Group Constant Eq. 4	Group Constant *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_i 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.

REFERENCES

(1) P. A. Small, *J. Appl. Chem.*, **3,** 71(1953).

(2) J. Brandrup and E. H. Immergut, "Polymer Handbook," Interscience Publishers, New York, N. Y., 1966, p. IV-341.

(3) J. A. Ostrenga, *J. Med. Chem.*, **12,** 349(1969).

(4) O. Exner, *Collection Czechoslov. Chem. Commun.*, **31,** 3222(1966).

(5) *Ibid.*, **32,** 1(1967).

(6) *Ibid.*, **32,** 24(1967).

(7) *Ibid.*, **32,** 4327(1967).

(8) J. L. Gardon, *J. Paint Technol.*, **38,** 43(1966).

(9) "Handbook of Chemistry and Physics," 44th ed., C. D. Hodgman, Ed., The Chemical Rubber Publishing Co., Cleveland, Ohio, 1961.

(10) A. E. Rheineck and K. F. Lin, *J. Paint Technol.*, **40,** 611 (1968).

ACKNOWLEDGMENTS AND ADDRESSES

Received June 5, 1969 from *Syntex Research, Institute of Pharmaceutical Sciences Stanford Industrial Park, Palo Alto, CA 94304*

Accepted for publication July 23, 1969.

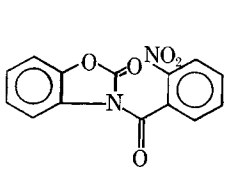
Preparation of Some Substituted Imidazolidine-2,4-diones

J. SAM, E. B. MCLAURIN*, and R. M. SHAFIK†

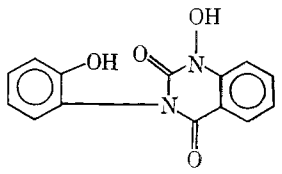
Abstract □ Heating 2-benzoxazolinone or 5-chloro-2-benzoxazolinone with aminoacid esters resulted in the formation of 3-(2-hydroxyphenyl) imidazolidine-2,4-dione derivatives. Results of preliminary pharmacological tests are reported.

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

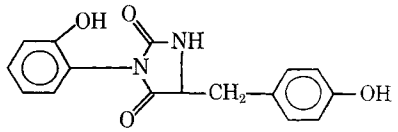
Heating of 2-benzoxazolinone with aniline (1) and hydrazine hydrate (2) was observed to yield a substituted urea and a semicarbazide derivative, respectively. A similar rearrangement was noted (3) when the hydrogenation of 3-(2-nitrobenzoyl)-2-benzoxazolinone (I) resulted in the formation of 1-hydroxy-3-(2-hydroxyphenyl) 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.



I

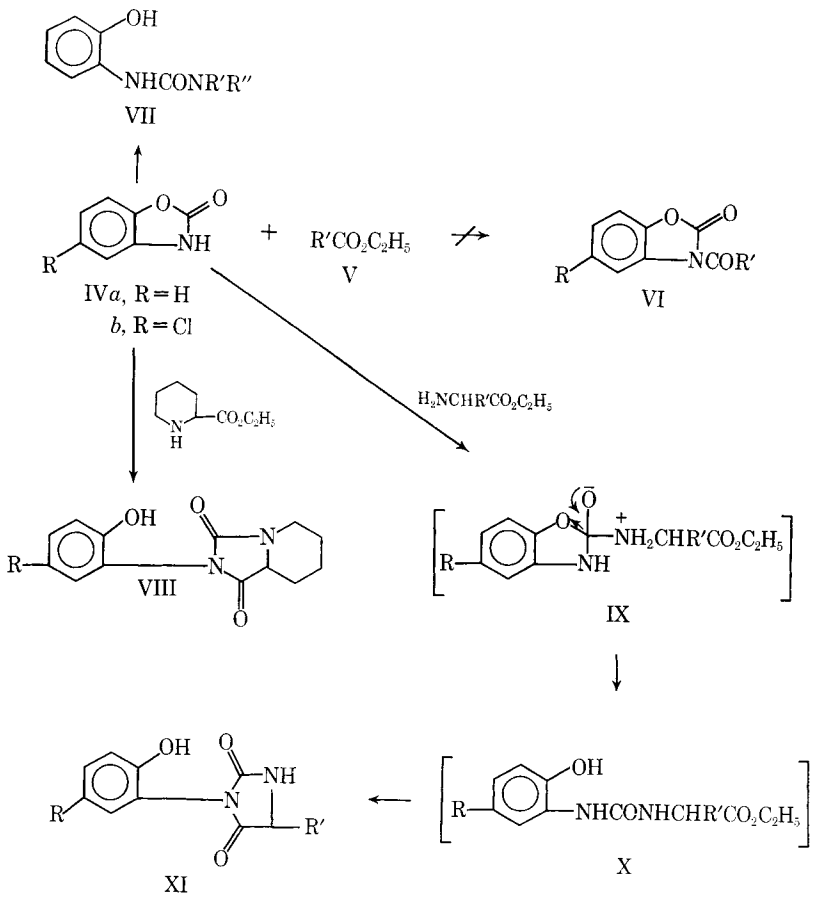


II



III

The acylation of 2-benzoxazolinone (IV*a*) or the potassium salt of IV*a* with ethyl benzoate or ethyl butyrate at different temperatures failed to occur. On the other hand, refluxing IV*a* 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 aminoacid 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 aminoacid 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 LD_{50}'s greater than 50 mg./kg. VII*a* and XI*c* were inactive; VII*c*, VIII*a*, VIII*b*, and XI*d* at doses of 500 mg./kg. produce slight CNS depression and decreased motor activity. Both XI*a* and XI*b* 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.	Anal., % Found
VIII*a*	H	—	64	223–225(M)	$C_{13}H_{14}N_2O_3$	C, 63.4 H, 5.7 N, 11.4 Cl, —	C, 63.2 H, 5.7 N, 11.4 Cl, —
VIII*b*	Cl	—	80	252–254(M)	$C_{13}H_{13}ClN_2O_3$	C, 55.6 H, 4.7 N, 10.0 Cl, 12.6	C, 55.8 H, 4.7 N, 10.0 Cl, 12.5
XI*a*	H	$CH(CH_3)_2$	70	155–156(B)	$C_{12}H_{14}N_2O_3$	C, 61.5 H, 6.0 N, 12.0 Cl, —	C, 61.7 H, 6.1 N, 11.9 Cl, —
XI*b*	Cl	$CH(CH_3)_2$	70	186–187(B)	$C_{12}H_{13}ClN_2O_3$	C, 53.6 H, 4.9 N, 10.4 Cl, 13.2	C, 53.7 H, 5.0 N, — Cl, 13.1
XI*c*	H	$CH_2CH(CH_3)_2$	40	145–147(B)	$C_{13}H_{16}N_2O_3$	C, 62.9 H, 6.5 N, 11.3 Cl, —	C, 62.8 H, 6.4 N, 10.8 Cl, —
XI*d*	Cl	$CH_2C_6H_4OH$	82	226–228(W)	$C_{16}H_{13}ClN_2O_4$	C, 57.8 H, 3.9 N, 8.4 Cl, 10.7	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]
VII*a*[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)
VII*b*[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)
VII*c*[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)
XI*a*[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)
XI*b*[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)
XI*c*[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)
XI*d*[c]	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)
VIII*a*[c]	3150, 1775, 1700	1.7 (8H, M), 4.05 (1H, T), 3.4[d] (1H, S), 7.1 (4H, M)
VIII*b*[c]	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 D_2O. [e] NMR determined in deuterated acetone.

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

EXPERIMENTAL[1]

Commercially available DL-valine, DL-leucine, and DL-tyrosine were esterified according to the Fischer method (7). 2-Carbethoxypiperidine 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 $C_{14}H_{14}N_2O_2$: 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 $C_{11}H_{14}N_2O_2$: 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 VII*b* 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 $C_{13}H_{18}N_2O_2$: C, 66.6; H. 7.7; N, 12.0. Found: 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 VII*a* was followed using 0.015 mole of 2-benzoxazolinone or 5-chloro-2-benzoxazolinone and 0.017 mole of the appropriate aminoacid ester.

[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.

REFERENCES

(1) G. Young and A. E. Dunstan, *J. Chem. Soc.*, **1908,** 1052.

(2) J. D. Bower and F. F. Stephens, *ibid.*, **1951,** 326.

(3) J. Sam and C. W. Richmond, *J. Heterocyclic Chem.*, **1,** 245(1964).

(4) J. Sam and S. B. Advani, *J. Pharm. Sci.*, **57,** 1693(1968).

(5) N. A. Lange and F. E. Sheibley, "Organic Synthesis," *Coll.* vol. II, Wiley, New York, N. Y., 1955, p. 79.

(6) J. Sam and C. W. Richmond, *J. Heterocyclic Chem.*, **1,** 134 (1964).

(7) E. Fischer, *Ber.*, **34,** 438(1901).

(8) W. A. Reckhow and D. S. Tarbell, *J. Am. Chem. Soc.*, **74,** 4960(1952).

ACKNOWLEDGMENTS AND ADDRESSES

Received April 23, 1969 from the *Department of Pharmaceutical Chemistry, The University of Mississippi, University, MS 38677*

Accepted for publication June 24, 1969.

This investigation was supported in part during a tenure of a fellowship (R. M. S.) of the Mississippi Heart Association.

The authors are grateful to Dr. John Brown, University of Mississippi, for the biological data.

* National Science Foundation Undergraduate Research Participant.

† Present address: Department of Pharmaceutical Chemistry, College of Pharmacy, University of Alexandria, Alexandria, Egypt (U.A.R.).