clear yellow solution was cooled and poured into 200 ml. of cold water. The white precipitate was filtered, washed with 50 ml. of water and dried to give 0.60 g. (98.4%) of 1,4-dihydro-3-methylindeno(1,2-c)pyrazole, m.p. 183–184°, no depression in melting point with authentic sample.

Wolff–Kishner Reduction of 2-Diphenylacetyl-1,3-indandione 1-Hydrazone.—One gram (0.0024 mole) of 2-diphenylacetyl-1,3-indandione 1-hydrazone was reduced using the same procedure as in the previous experiment. Diethylene glycol (30 ml.) was the solvent and 1.5 ml. of hydrazine hydrate and 1 g. of potassium hydroxide was used. The white crystalline product was washed with water and dried to give 0.65 g. (70.7%) of 1,4-dihydro-3-diphenylmethylindeno(1,2-c)pyrazole, m.p. 172–174°, mixed m.p. with an authentic sample was also 172–174°.

3-*t*-Butylindeno(1,2-c)pyrazol-4(1H)-one.—To 6.90 g. (0.03 mole) of 2-pivalyl-1,3-indandione in 150 ml. of ethanol was added 1.5 g. (0.03 mole) of hydrazine hydrate. The clear yellow solution was heated at reflux for 48 hours. After cooling, the solution was diluted with one liter of cold water. The white solid was filtered, dried and recrystallized from aqueous methanol (using decolorizing charcoal); m.p. 198–199°, 87.2% yield as white plates.

Anal. Calcd. for $C_{14}H_{14}N_2O$: C, 74.31; H, 6.24; N, 12.38; mol. wt., 246. Found: C, 75.02; H, 6.27; N, 12.19; mol. wt. (Rast), 252.

The Wolff–Kishner reduction of 3-*t*-butylindeno(1,2-c)-pyrazol-4(1H)-one gave 1,4-dihydro-3-*t*-butylindeno(1,2-c)-pyrazole in 87.2% yield.

3-Isobutylindeno(1,2-c)pyrazol-4(1H)-one Hydrazone.—To a mixture of 2.09 g. (0.015 mole) of 2-isobutyl-1,3-indandione in 100 ml. of anhydrous ethanol was added 1.02 g. (0.032 mole) of anhydrous hydrazine. The resulting clear yellow solution was heated at reflux for 45 hours. Upon cooling, 2.08 g. (61.2%) of a white crystalline solid was obtained, m.p. 227–228° (placed in apparatus at 220°). After three recrystallizations from ethanol the m.p. was not changed; however, upon slow heating the compound did not melt up to 360°.

Anal. Calcd. for $C_{13}H_{14}N_4$: C, 69.00; H, 6.24; N, 24.77. Found: C, 68.95; H, 6.13; N, 24.10.

Using the same procedure the following are prepared: **3-methylindeno(1,2-c)pyrazol-4(1H)-one hydrazone**, 88.1%, m.p. 250–255°. *Anal.* Calcd. for $C_{11}H_{10}N_4$: C, 66.65; H, 5.09; N, 28.27. Found: C, 66.33; H, 5.03; N, 28.45. **3-Ethylindeno(1,2-c)pyrazol-4(1H)-one hydrazone**, 53.4%, m.p. 263–264°. *Anal.* Calcd. for $C_{12}H_{12}N_4$: C, 67.32; H, 5.69; N, 26.34. Found: C, 67.22; H, 5.79; N, 26.34 and **3-Benzylindeno(1,2-c)pyrazol-4(1H)-one hydrazone**, 86.8%, m.p. 263–264°. *Anal.* Calcd. for $C_{17}H_{14}N_4$: C, 74.45; H, 5.15; N, 20.43. Found: C, 74.50; H, 5.33; N, 20.12. All of these compounds are converted to the corresponding 1,4-dihydro-3-substituted-indeno(1,2-c)pyrazoles in 80 to 98% yield simply by heating to 200° for one hour with excess potassium hydroxide in diethylene glycol.

NEWARK, DEL.

[CONTRIBUTION FROM THE ORGANIC CHEMICAL RESEARCH SECTION, RESEARCH DIVISION, AMERICAN CYANAMID CO.]

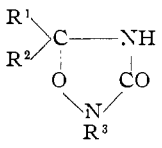
The Synthesis of Some 1,2,4-Oxadiazolidinones

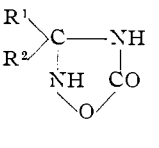
BY S. R. SAFIR AND R. J. LOPRESTI

RECEIVED APRIL 5, 1958

The reaction of ethyl (1,1-diphenylmethylene)-carbamate with hydroxylamine in the presence of alkoxide ion gives rise to 3,3-diphenyl-1,2,4-oxadiazolidin-5-one. The reaction of (1,1-diphenylmethylene)-carbamoyl chloride with hydroxylamine gives an isomeric product, 5,5-diphenyl-1,2,4-oxadiazolidin-3-one.

The widespread use of barbituric acid and hydantoin derivatives in medicine during the past twenty-five years has stimulated great interest in the search for related heterocyclic systems which would provide useful drugs, particularly those with action on the central nervous system. While several dozen systems have been studied, only a few, of which the 2,4-oxazolidinediones,[1] the succinimides[2] and the 2,4-piperidinediones[3] are examples, have yielded clinically useful products. The 1,2,4-oxadiazolidin-3-one nucleus (Ia), a previously unknown system combining some of the structural features of the



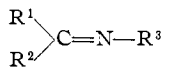


Ia, $R^1 = R^2 = R^3 = H$
Ib, $R^1 = R^2 = C_6H_5$, $R^3 = H$
Ic, $R^1 = R^2 = C_6H_5$, $R^3 = CH_3$

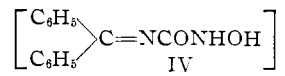
IIa, $R^1 = R^2 = H$
IIb, $R^1 = R^2 = C_6H_5$

barbiturates, the hydantoins and the oxazolidinediones, appeared to be an appropriate nucleus for investigation. The synthesis of several diphenyl derivatives of Ia and the isomeric system, 1,2,4-oxadiazolidin-5-one (IIa), is the subject of this paper.

The starting point for this work is based on the observation by Banfield, *et al.*,[4] that N-acyldiarylketimines (IIIa) form addition products with alcohols and amines. Ethyl (1,1-diphenylmethylene)-carbamate (IIIb) was prepared by the method of Banfield, *et al.*,[4] but attempts to form adducts with either methanol or acetoxime were unsuccessful. Because of this lack of reactivity it was thought that the carbamate could be made to react with hydroxylamine in the presence of alkoxide ion to give a presumably unstable hydroxamic acid IV which would then cyclize spontaneously to Ib.



IIIa, $R^1 = R^2$ = aryl, R^3 = acyl
IIIb, $R^1 = R^2 = C_6H_5$, $R^3 = COOC_2H_5$
IIIc, R^1 = aryl, R^2 = alkyl, R^3 = acyl



IV

When this reaction was carried out, a small amount

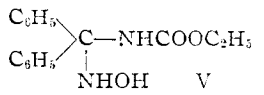
(1) (a) M. A. Spielman, THIS JOURNAL, **66**, 1244 (1944); (b) G. M. Everett and R. K. Richards, *J. Pharmacol. Exptl. Therap.*, **81**, 402 (1944).

(2) (a) C. A. Miller and L. M. Long, THIS JOURNAL, **73**, 4895 (1951); (b) G. Chen, R. Portman, C. R. Ensor and A. C. Bratton, Jr., *J. Pharmacol. Exptl. Therap.*, **103**, 54 (1951).

(3) (a) O. Schnider, H. Frick and A. H. Lutz, *Experientia*, **10**, 135 (1954); (b) Von B. Pellmont, A. Studer and R. Jürgens, *Schweiz. med. Wochschr.*, **85**, 350 (1954).

(4) J. E. Banfield, G. M. Brown, F. H. Davey, W. Davies and T. H. Ramsay, *Austr. J. Sci. Research*, **A1**, 330 (1948).

of a colorless solid, $C_{14}H_{12}N_2O_2$, was isolated. From its sparing solubility in dilute alkali, the failure to give a color with ferric chloride and the absence of absorption above 225 mμ in the ultraviolet,[5] IV and Ib were excluded.[6] It appeared likely that the hydroxylamine had, in fact, added to IIIb to give V in a manner analogous to the addition of ammonia to α,β-unsaturated carbonyl systems; V then eliminated ethoxide to give IIb. This se-

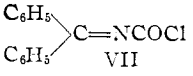


V

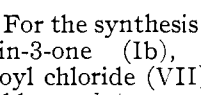
quence was demonstrated to be correct in the following manner. Hydroxylamine was warmed briefly with a methanolic solution of IIIb. On cooling, there was isolated in 76% yield a colorless solid, $C_{16}H_{18}N_2O_3$, which on treatment with methanolic sodium methoxide gave IIb in 67% yield and was therefore V. In the infrared the formation of V was characterized by the disappearance of the >C=N—band displayed at 6.21 μ by the starting carbethoxyketimine and the appearance of a >NH and/or OH band in the 3 μ region.

When the adduct V was refluxed in methanol for ninety minutes in the absence of alkoxide ion two products were formed: benzophenone oxime and ethyl carbamate. This elimination reaction thus establishes the presence of the >C–N–O–linkage in the adduct. Hence cyclization of V would be expected to occur in the manner indicated to give IIb.

Attempts to extend the addition of hydroxylamine to N-acylarylalkylketimines (IIIc) were unsuccessful probably because these compounds exist as enamines[7] (VIa).



VIa, R^1 = alkyl, R^2 = aryl, R^3 = acyl
VIb, R^1 = CH_3, R^2 = phenyl, R^3 = $COOC_2H_5$



VII

For the synthesis of 5,5-diphenyl-1,2,4-oxadiazolidin-3-one (Ib), (1,1-diphenylmethylene)-carbamoyl chloride (VII), made by the method of Banfield, *et al.*,[4] was condensed with hydroxylamine. Despite many attempts to improve the procedure the best yield of Ib was about 10%. There was isolated, in addition, about 2% of the isomeric 5-one (IIb) and 63% of benzophenone oxime. The presumed intermediate IV was not isolated. The structure of the 3-one Ib was assigned on the basis of analysis, ready solubility in dilute alkali, and absence of absorption above 225 mμ in the ultraviolet.

Treatment of Ib with diazomethane gave a monomethyl derivative which was assigned structure Ic on the basis of analysis (including N-methyl and O-methyl determinations) and insolubility in alkali.[8]

Evaluation of the two substances as anticonvulsants in the mouse corneal electroshock procedure of Swinyard, *et al.*,[9] showed that 5,5-diphenyl-1,2,4-oxadiazolidin-3-one was about one-third, and 3,3-diphenyl-1,2,4-oxadiazolidin-5-one was one-sixth as active as 5,5-diphenylhydantoin.

Experimental[10]

5,5-Diphenyl-1,2,4-oxadiazolidin-3-one (Ib).—To a solution of 5.4 g. (0.05 mole) of phosgene in 20 cc. of dry toluene, there was added slowly at −20° a solution of 17.2 g. (0.095 mole) of 1,1-diphenylmethyleneimine[11] in 200 cc. of toluene. After standing for 1 hour at −20° the 1,1-diphenylmethyleneimine hydrochloride was filtered. The filtrate, which contained the (1,1-diphenylmethylene)-carbamoyl chloride (VII),[4] was added, with stirring, to a solution of hydroxylamine prepared from 21.2 g. (0.30 mole) of hydroxylamine hydrochloride, 24.5 g. (0.30 mole) of sodium acetate and 60 cc. of water. The mixture was stirred at 25° for 18 hours and the layers were separated. The toluene layer was extracted with 300 cc. of 0.5 *N* sodium hydroxide; the alkaline extract was washed with ether and acidified to *p*H 5–7 (the combined toluene and ether solution gave, on work-up, 6 g. (63%) of benzophenone oxime). The resulting solution was extracted with ether. Drying and evaporation gave 1.46 g. of a colorless solid, m.p. 134–147° dec. This material, a mixture of the 3-one and the 5-one, was purified by suspending it in water, adding 1 *N* alkali to *p*H 11.5 and filtering the insoluble 5-one (2%). Acidification of the filtrate gave 1.1 g. (9.6%) of the 3-one, m.p. 140–156° dec. Two recrystallizations from benzene raised the m.p. to 170–172° dec.

Anal. Calcd. for $C_{14}H_{12}N_2O_2$: C, 70.0; H, 5.0; N, 11.7. Found: C, 69.8; H, 5.3; N, 12.1.

5,5-Diphenyl-1,2,4-oxadiazolidin-3-one shows major bands in the infrared at 3.15 and 5.88 μ. The compound is readily soluble in dilute sodium hydroxide solution and gives a wine-red color with ferric chloride–pyridine.

5,5-Diphenyl-2-methyl-1,2,4-oxadiazolidin-3-one (Ic).—To a solution of 0.240 g. (0.001 mole) of 5,5-diphenyl-1,2,4-oxadiazolidin-3-one in 50 cc. of methanol, there was added an ethereal solution of diazomethane[12] prepared from 2 g. of N-methyl-N-nitroso-*p*-toluenesulfonamide. After storing overnight the solution was evaporated to dryness *in vacuo*. The resulting yellow solid was washed with 3 cc. of methanol to give 0.10 g. (39%) of a colorless solid, m.p. 204–207°. One recrystallization from methanol raised the melting point to 207–208°.

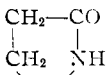
Anal. Calcd. for $C_{15}H_{14}N_2O_2$: C, 70.9; H, 5.5; N, 11.0; 1 N–CH_3, 5.9. Found: C, 70.9; H, 5.5; N, 11.1; N–CH_3, 4.7; O–CH_3, 0.0.

5,5-Diphenyl-2-methyl-1,2,4-oxadiazolidin-3-one is insoluble in dilute alkali and fails to give a color with ferric chloride–pyridine.

Ethyl [(Hydroxyamino)-diphenylmethyl]-carbamate (V).—A solution of 4.9 g. (0.15 mole) of hydroxylamine[13] and 14.8 g. (0.059 mole) of ethyl (1,1-diphenylmethylene)-carbamate (IIIb)[4] in 100 cc. of methanol was heated for 5

(5) In contrast, IIIb shows λ_{max} 253 mμ, ϵ16,700.

(6) Compound Ib would be expected to be readily soluble in aqueous alkali because of analogy with 3-isoxazolidinone (i) which is reported to have pK_a 6.70 [P. H. Hidy, E. B. Hodge, V. V. Young, R. L. Harned, G. A. Brewer, W. F. Phillips, W. F. Runge, H. E. Stavely, A. Pohland, H. Boaz and H. R. Sullivan, THIS JOURNAL, **77**, 2345 (1955)]. Moreover, esters of hydroxamic acids alkyl-CONHO-alkyl (ii) in general, of which i may be regarded as a cyclic representative, are known to be soluble in alkali [F. Mathis, *Bull. soc. chim. France*, D9 (1953)].



i

(7) Banfield, *et al.* (ref. 4), proposed structure VIa to explain the unreactivity of their N-acylarylalkylketimines toward nucleophilic reagents. By way of confirmation we have observed the presence of a strong NH band at 3.13 μ for ethyl (1-phenylpropenyl)-carbamate (VIb).

(8) Methylation in the 4-position, although not rigorously excluded, is unlikely; see ref. 6.

(9) E. A. Swinyard, W. C. Brown and L. S. Goodman, *J. Pharmacol. Exptl. Therap.*, **106**, 319 (1952).

(10) All melting points are uncorrected. Infrared spectra were taken using KBr disks.

(11) C. Moureu and G. Mignonac, *Compt. rend.*, **156**, 1801 (1913).

(12) Th. J. DeBoer and H. J. Backer, "Organic Syntheses," John Wiley and Sons, Inc., New York, N. Y., 1956, Vol. 36, p. 16.

(13) C. D. Hurd, "Inorganic Syntheses," McGraw-Hill Book Co., Inc., New York, N. Y., 1939, vol. I, p. 87.

minutes at 50°. The mixture was quickly cooled in ice and filtered to give 7.9 g. of the adduct as a colorless solid, m.p. 81–83°. An additional 4.9 g. (total yield 76%) of product was obtained by concentration of the filtrate *in vacuo*. For analysis, a sample was recrystallized from methanol by cautious heating; m.p. 81–83°.

Anal. Calcd. for $C_{16}H_{18}N_2O_3$: C, 67.1; H, 6.3; N, 9.8. Found: C, 67.0; H, 6.7; N, 9.9.

3,3-Diphenyl-1,2,4-oxadiazolidin-5-one (IIb).—A solution of 5 g. (0.017 mole) of V in 250 cc. of dry methanol was treated with a solution of 1 g. (0.017 mole) of sodium methoxide in 100 cc. of methanol. After having been stored at 25° for 4.5 hours the solution was evaporated to dryness *in vacuo;* the residual solid was dissolved in water and the resulting solution was acidified. The colorless solid was filtered, dried and recrystallized from benzene–ethanol to give 2.8 g. (67%) of the 5-one, m.p. 150–153° dec. An analytical sample, m.p. 156–159° dec., was prepared from another run by recrystallization from ethanol.

Anal. Calcd. for $C_{14}H_{12}N_2O_2$: C, 70.0; H, 5.0; N, 11.7. Found: C, 70.2; H, 5.0; N, 11.4.

3,3-Diphenyl-1,2,4-oxadiazolidin-5-one is sparingly soluble in dilute sodium hydroxide and gives no color change with ferric chloride–pyridine. It shows major bands at 3.14 and 5.73 μ. Admixture of the 5-one and the 3-one produced a marked depression in melting point.

Decomposition of Ethyl [(Hydroxyamino)-diphenylmethyl]-carbamate (V).—A solution of 0.50 g. (0.0017 mole) of V in 50 cc. of methanol was refluxed for 1.5 hours and then evaporated to dryness *in vacuo*. The resulting solid was washed with 1.7 cc. of methanol and filtered. The insoluble portion, 0.2 g. (66%), m.p. 141–142.5°, did not depress the melting point of an authentic sample of benzophenone oxime. Evaporation of the filtrate gave a solid, which, on evaporative distillation *in vacuo*, gave colorless crystals, 0.040 g. (26%), m.p. 47.5–48.5°. This material did not depress the melting point of an authentic sample of ethyl carbamate.

Ethyl (1-phenylpropenyl)-carbamate (VIb) was prepared according to the procedure described by Banfield, *et al.*,[4] for the synthesis of some analogous N-acylketimines. To a solution of the Grignard reagent prepared from 26.4 g. (1.1 g.-atoms) of magnesium, 108 g. (1 mole) of ethyl bromide and 425 cc. of ether there was added, with cooling, 113 g. (1.1 moles) of benzonitrile in 500 cc. of ether. The mixture was refluxed for 1 hour and the supernatant liquid was decanted. A fresh 500-cc. portion of ether was added, the liquid was again decanted and replaced by 500 cc. of fresh ether. A solution of 120 g. (1.1 moles) of ethyl chloroformate in 150 cc. of ether was added with stirring and cooling. The mixture was decomposed carefully with ice and water. The ether layer was separated, washed with dilute sodium bicarbonate solution, then with water and dried. Evaporation to dryness *in vacuo* gave an oily solid which was recrystallized from petroleum ether to give 50 g. (24%) of the product as colorless crystals, m.p. 55–58°. The analytical sample melted at 57.5–58.5°.

Anal. Calcd. for $C_{12}H_{15}NO_2$: C, 70.2; H, 7.3; N, 6.8. Found: C, 70.5; H, 7.6; N, 6.5.

Ethyl (1-phenylpropenyl)-carbamate displays major bands in the infrared at 3.13 and 5.93 μ (shoulder at 5.86 μ).

Acknowledgment.—The authors express their appreciation to Dr. A. C. Osterberg and Mr. C. E. Rauh for the pharmacological data, to Mr. W. Fulmor and associates for spectral determinations, and to Mr. L. Brancone and associates for the microanalyses.

PEARL RIVER, N. Y.

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF FLORIDA STATE UNIVERSITY]

A Precise Potentiometric Method for Measuring Reaction Rates. Application to the γ-Chymotrypsin-catalyzed Hydrolysis of Methyl Hippurate[1]

BY JOSEPH H. LANG,[2] EARL FRIEDEN AND ERNEST GRUNWALD

RECEIVED JANUARY 3, 1958

A method is described for following *p*H change with time in a buffered medium in which a reaction is producing acid and for translating that change into reaction rate. The method is used to study the kinetics of the γ-chymotrypsin-catalyzed hydrolysis of methyl hippurate. The dependence of the rate on the substrate concentration conforms to the Michaelis–Menten scheme of enzyme action but the reaction deviates from first order in total enzyme concentration. An explanation for the deviation in terms of the dimerization of the enzyme is offered. The buffer, sodium and potassium chloride and calcium chloride were found to influence the rate in qualitatively different ways. The effect of *p*H was studied over a limited range, and the inactivation of the enzyme also was investigated.

Reactions catalyzed by enzymes are often so complex that their kinetic analysis can be carried out conveniently only in terms of instantaneous reaction rates, dx/dt. At the same time, the direct measurement of dx/dt in open systems[3] may not be feasible because substantial amounts of enzyme might be required. In closed systems, where one measures x as a function of time, accurate derivation is possible only if the experimental points are so dense and so precise that the shape of the rate curve is defined within narrow limits.

The recent commercial availability of highly sensitive *p*H-meters has prompted us to investigate the potentiometric method of rate measurement. For the sample system we chose the γ-chymotrypsin-catalyzed hydrolysis of methyl hippurate.[4] Ester hydrolysis catalyzed by chymotrypsin has proved to be a fruitful model system in the study of enzyme action and a precise knowledge of the kinetics is of considerable current interest.[5] In the present work, a number of kinetic features could be established or confirmed.

Potentiometric Rate Measurement.—A reaction producing acid or base and taking place in a lightly buffered solution may be followed by measuring

(1) Work supported in part by the Office of Naval Research. Reproduction in whole or in part is permitted for any purpose of the United States Government.

(2) Department of Biochemistry and Nutrition, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, Pennsylvania.

(3) See, for example, H. H. Young and L. P. Hammett, THIS JOURNAL, **72**, 280 (1950); J. Saldick and L. P. Hammett, *ibid.*, **72**, 283 (1950); M. J. Rand and L. P. Hammett, *ibid.*, **72**, 287 (1950).

(4) The α-chymotrypsin-catalyzed hydrolysis of methyl hippurate was investigated by H. T. Huang and C. Niemann, *ibid.*, **74**, 4634 (1952).

(5) N. M. Green and H. Neurath in "The Proteins," Vol. II, Part B, H. Neurath and K. Bailey, eds., Academic Press, Inc., New York, N. Y.