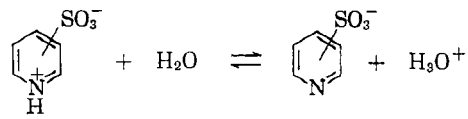

The equation now applicable is

$$pK_a = pH + \log \frac{A_2 - A_3}{A_1 - A_2} - \log \gamma_-$$

where each term has the same significance as before but γ_- represents the activity coefficient of the sulfonate anion. The zwitterion is assumed to have an activity coefficient of unity.

Experimental conditions were similar to those used for the parent bases; lower pH's were required and were generated with hydrochloric acid–potassium chloride solutions. It was found that Beer's law was obeyed by all the materials in both acidic and alkaline solutions in the concentration range of 5×10^{-5} to 15×10^{-5} M.

(2) **In Water.**—The sulfonic acids were studied in twice distilled water. The pK_a values were higher and consequently solutions of a different pH from those used under (1) were employed. Chloroacetic acid–sodium chloroacetate buffers were used for most of the solutions of low pH. A different Debye–Hückel expression was also employed, owing to the change in dielectric constant of the medium. It was

$$\log \gamma_- = \frac{-0.509\sqrt{\mu}}{1 + \sqrt{\mu}}$$

Infrared Spectra were obtained in Nujol mull using a Perkin-Elmer recording spectrometer.

Acknowledgment.—Our thanks are due to Mrs. C. S. Tang-Yeh and Mrs. S. L. Margerum for the analyses and Mrs. B. Polister for the infrared data.

Reaction of Isocyanates with Some Alkyl-Substituted Monohydroxamic Acids, Carbamoyl Derivatives of N-Acyl-O-alkylhydroxylamines. II[1,2]

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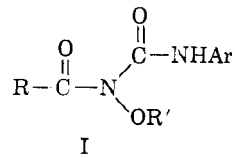
Received March 19, 1962

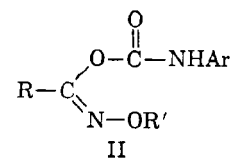
The reaction of phenyl isocyanate with hydroxamic acid esters results in the formation of an addition product which is obtained in a nearly quantitative yield when extreme care is used in the work-up. The phenyl carbamoyl group probably is attached to the nitrogen of the hydroxamic acid ester.

In 1905 Biddle[3] allowed phenyl isocyanate to react with methyl formohydroxamate and obtained a phenylcarbamoyl derivative. We have found the reaction of phenyl isocyanate and α-naphthyl isocyanate with hydroxamic acid esters to be a general reaction leading in most cases to solid derivatives in high yields.

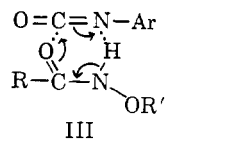
There are two possible structures for the carbamoyl derivatives. The carbamate group may be attached to nitrogen giving I or to oxygen giving II. Structure I would arise from a reaction of the isocyanate with an NH group, while structure II could occur from an enolization of the starting hydroxamic acid ester followed by the reaction of the isocyanate with the OH group of the enol form. Another mechanism for the formation of II would be by the "quasi" ring intermediate (III).



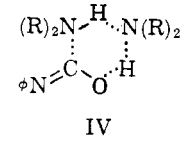
I



II



III



IV

A number of workers[4] have considered the mechanism of the reaction of isocyanates with amines and alcohols. It has been shown recently[4d] that the reaction of phenyl isocyanate with aniline can be interpreted as a termolecular reaction, intermediate IV, in which the nitrogen of one molecule of aniline acts as a nucleophile, and a hydrogen from a second molecule of aniline acts as an acid. With the hydroxamic acid esters the carbonyl oxygen could behave as a nucleophile and the hydrogen on nitrogen as a proton source as in III, to give II. On the other hand I could arise from intermediate IV, or by the enol of the hydroxamic acid ester reacting by intermediate III. More experiments will be necessary to determine which intermediate is correct.

(1) Taken in part from the Masters theses of James R. Throckmorton, June, 1960, and William D. Bills, June, 1960, both at the University of Idaho. We are indebted to the Research Corp. for financial support provided J. R. T. through the summer of 1959, and W. D. B. through the summer and fall terms of 1959. We wish to thank the National Science Foundation for grants, NSF G 8807 and NSF G 13289, which paid for many of the other costs of this work.

(2) Presented in part at the 136th National Meeting of the American Chemical Society, New York City, September 16, 1960. For paper I of this series see J. H. Cooley, W. D. Bills, and J. R. Throckmorton, *J. Org. Chem.*, **25**, 1734 (1960).

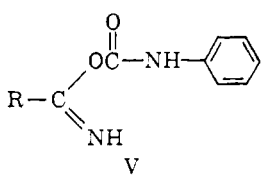
(3) H. C. Biddle, *Am. Chem. J.*, **33**, 60 (1905); H. L. Yale, *Chem. Rev.*, **33**, 209 (1944).

(4) (a) R. G. Arnold, J. A. Nelson, and J. J. Verbane, *ibid.*, **37**, 47 (1957); (b) J. W. Baker and D. N. Bailey, *J. Chem. Soc.*, 4647, 4652, 4663 (1957); (c) J. Burkus, *J. Org. Chem.*, **26**, 779 (1961); (d) K. Sauer and M. H. Kasparian, *ibid.*, **26**, 3498 (1961).

The reaction of isocyanates and hydroxamic acid esters was carried out by mixing equimolar amounts of the two without a solvent. In one experiment phenyl isocyanate and benzyl acetohydroxamate were allowed to react in dilute solution with dry benzene as the solvent. By carrying out the reaction in dilute solution a reaction intermediate such as III might be favored over IV. The same product was isolated in each case, however. To demonstrate that the reaction of isocyanates with hydroxamic acid esters gives just one product careful work-up of several preparations gave better than 90% yields of a single product. Crude products taken directly from the reaction gave essentially identical infrared spectra to analytical samples.

The infrared spectra of these carbamoyl derivatives in Nujol are consistent with structure II, urethan carbonyl at 1710–1725 (strong) and C=N at 1640–1670 cm.$^{-1}$ in Nujol (medium).[5] But, dicarbonyl compounds with structures similar to I have been found to give this type of absorption.[6,7]

Treatment of the phenylcarbamoyl hydroxamic acid esters with Raney nickel and hydrogen under two atmospheres pressure resulted in hydrogenolysis of the N—O bond. Phenylcarbamoyl derivatives of acetohydroxamic acid esters, benzohydroxamic acid esters, and anisohydroxamic acid esters gave N-acetyl-N′-phenylurea,[8] N-benzoyl-N′-phenylurea[9] and N-anisoyl-N′-phenylurea, respectively. Structure I is indicated by this degradation, for in order that structure II be correct, hydrogenolysis would give the imino compound (V) which would have to rearrange to the urea. Compounds with structures like V were not found in the literature, so it is impossible to say that a rearrangement of V to the urea would not occur.



V

For comparison N-acetyl-N′-phenylurea has been prepared in two ways which leaves no doubt as to its structure. The reaction of phenyl isocyanate and acetamide was used in this laboratory, and a sample was obtained from the Aldrich Chemical Co.[10] where the reaction of phenylurea with acetic anhydride was used. All three samples had identical infrared spectra and the mixed melting point did not depress.

Acid hydrolysis of phenylcarbamoyl benzyl acetohydroxamate gave a small yield of N-benzyloxy-N′-phenylurea,[11] identified by mixed melting point and comparison of infrared spectra. Again it is difficult to imagine a reaction path that would lead from II to N-benzyloxy-N′-phenylurea. The evidence from hydrogenolysis and hydrolysis strongly indicates structure I as the correct structure of the phenyl isocyanate hydroxamic acid ester adducts.

Mild heating of the phenylcarbamoyl hydroxamic acid esters especially under reduced pressure caused dissociation into phenyl isocyanate and hydroxamic acid ester. Some derivatives were dissociated at lower temperature than others, and the reaction goes cleanly without side reactions to completion. The thermal dissociation of these phenylcarbamates is analogous to the thermal dissociation of ureas,[12] urethanes,[13] and benzoyl isocyanate amide adducts,[14] but there are side reactions in these cases.

Phenylcarbamoyl *n*-propyl anisohydroxamate and phenylcarbamoyl *n*-propyl acetohydroxamate were found to be inactive as antibacterial and antifungal agents.[15] Oral administration of phenylcarbamoyl benzyl benzohydroxamate and phenylcarbamoyl allyl anisohydroxamate to rats failed to produce any overt activity.[16]

Experimental

Preparation of Phenylcarbamoyl Derivatives of Hydroxamic Acid Esters, General Method.—An equimolar mixture of phenyl isocyanate and the hydroxamic acid ester was heated either with a flame or on a steam bath. If a solid ester was employed, it would dissolve to give a homogeneous solution. The mixture was allowed to cool until the mass solidified. Recrystallization from an appropriate solvent, usually ether or alcohol, was then carried out.

Phenylcarbamoyl *n*-Propyl Anisohydroxamate.—To 1.54 g. (0.0074 mole) of *n*-propyl anisohydroxamate, m.p. 83.5–84°, in a test tube was added 0.88 g. (0.0074 mole) of phenyl isocyanate. This mixture was heated until the solution which formed began to boil spontaneously. The test tube was then fitted with a calcium chloride drying tube and set aside until the odor of phenyl isocyanate had disappeared, about 3-hr. The semisolid mixture was recrystallized twice from ethanol–water mixture to give 2.33 g. (0.0071 mole) 96% of phenylcarbamoyl *n*-propyl anisohydroxamate, m.p. 65–66°.

Anal. Calcd. for $C_{17}H_{20}N_2O_4$: C, 65.84; H, 6.14; N, 8.53: Found: C, 65.94; H, 5.96; N, 8.67.

α-Naphthylcarbamoyl Allyl Acetohydroxamate.—A mixture of 1.15 g. (0.01 mole) of allyl acetohydroxamate and

(5) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, 1954, p. 160.

(6) W Logemann, D. Artini, G. Tosolini, and F. Piccinini, *Ber.*, **91**, 951 (1958).

(7) R. A. Abramovitch, *J. Chem. Soc.*, 1413 (1957).

(8) (a) D. MacCreath, *Ber.*, **8**, 1181 (1875); (b) B. Kuhn, *ibid.*, **17**, 2882 (1884); (c) F. Kurzer, *J. Chem. Soc.*, 549 (1953).

(9) (a) P. Wiley, *J. Am. Chem. Soc.*, **71**, 1310 (1949); (b) D. G. Crosby and C. Niemann, *ibid.*, **76**, 4458 (1954).

(10) Prepared by Dr. Alfred Bader of the Aldrich Chemical Co., Milwaukee 10, Wisconsin.

(11) L. B. Voltmer, *Ber.*, **24**, 378 (1891).

(12) T. Mukaiyama and K. Uno, *J. Am. Chem. Soc.*, **73**, 4358 (1957).

(13) (a) T. Mukaiyama and M. Iwanami, *ibid.*, **79**, 73 (1957); (b) E. Dyer and G. C. Wright, *ibid.*, **81**, 4358 (1959).

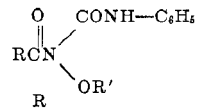
(14) W. Logmann and D. Artini, *Ber.*, **91**, 2574 (1958).

(15) We are indebted to Chas. Pfizer and Co., Inc., Groton, Conn. for screening these compounds.

(16) We wish to thank Smith Kline and French Laboratories, Philadelphia, Pennsylvania, for these tests.

TABLE I

PHENYLCARBAMOYL DERIVATIVES OF HYDROXAMIC ACID ESTERS



R	R′	M.p.,[a] °C.	Yield, %	Calcd. (Found) C	H	N
Phenyl	Benzyl	115.5–116.5	53	72.81 (73.08)	5.24 (5.38)	8.09 (8.35)
Phenyl	Methyl	65–66	57	66.65 (66.62)	5.22 (5.12)	10.37 (10.37)
p-Tolu	Benzyl	101.5–102.5	92	73.32 (73.20)	5.59 (5.76)	7.77 (7.67)
p-Tolu	*n*-Propyl	71.5–72.5	50	69.21 (69.52)	6.45 (6.67)	8.97 (8.99)
p-Tolu	*n*-Butyl	72.5–73.5	79	69.91 (70.08)	6.79 (6.69)	8.58 (8.64)
p-Tolu	Propargyl	75.5–76.5	50	70.12 (69.93)	5.23 (5.29)	9.09 (9.03)
p-Tolu	Allyl	61.5–62.5	40	69.66 (70.15)	5.85 (5.92)	9.03 (9.31)
p-Anisyl	Allyl	63–64	44	66.24 (66.05)	5.56 (5.59)	8.59 (8.54)
Ethyl	*n*-Propyl	60–61	90	62.38 (62.24)	7.20 (7.15)	11.20 (11.38)
p-Anisyl	Propargyl	70–71	51	66.66 (66.83)	4.97 (5.13)	8.64 (8.85)
p-Anisyl	*n*-Butyl	53–54	73	66.65 (66.79)	6.46 (6.49)	8.18 (8.35)
p-Anisyl	Benzyl	104.5–105.5	84	70.20 (70.50)	5.36 (5.46)	7.44 (7.50)
Methyl	*p*-Nitrobenzyl	128.5–129.5	75	58.35 (58.18)	4.59 (4.45)	12.76 (12.80)
Methyl	Benzyl	84.5–85	61	67.59 (67.66)	5.67 (5.86)	9.86 (9.52)

[a] All melting points are corrected and represent analytical samples. [b] Yields are based on equal number of moles of phenyl isocyanate and hydroxamic acid ester.

1.69 g. (0.01 mole) of α-naphthyl isocyanate was warmed briefly on a steam bath. The mixture soon solidified, and the solid was recrystallized from petroleum ether (b.p. 30–60°). A yield of 2.2 g. (77%, m.p. 78.5–79.5°) was obtained as white needles.

Anal. Calcd. for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67; N, 9.89. Found: C, 67.93; H, 5.59; N, 9.97.

α-Naphthylcarbamoyl allyl propionhydroxamate[17] was prepared in the same way in 50% yield, m.p. 78.5–79°.

Anal. Calcd. for $C_{17}H_{18}O_3N_2$: C, 68.44; H, 6.08; N, 9.39. Found: C, 68.30; H, 5.91; N, 9.41.

Infrared Spectra.[18]—The infrared spectra of the carbamoyl derivatives show NH stretching at 3200 and C=O stretching at 1710–1725 strong and 1640–1670 medium cm.$^{-1}$ in Nujol mull. In chloroform the NH stretching band is at 3300 and C=O at 1730–1740 strong and 1650–1685 cm.$^{-1}$. Table I lists other phenylcarbamoyl derivatives prepared by this method.

Hydrogenolysis of Phenylcarbamoyl Derivatives.—To 3.0 g. (0.0083 mole) of phenylcarbamoyl benzyl anisohydroxamate in a hydrogenation pressure bottle were added a teaspoonful of Raney nickel and 200 ml. of absolute ethyl alcohol. This mixture was shaken with 2.5 atm. of hydrogen in a Parr apparatus for 6.5 hr. at 26°. Approximately 1.4 p.s.i. (0.016 mole) of hydrogen was taken up. The catalyst was separated and the white solid was recrystallized from ethyl acetate giving 2.0 g. (0.0074 mole) 90% of N-anisoyl-N′-phenylurea, m.p. 223–226°.

Using these same conditions, phenylcarbamoyl allyl anisohydroxamate gave N-anisoyl-N′-phenylurea, and phenylcarbamoyl benzyl acetohydroxamate gave N-acetyl-N′-phenylurea in 95% yields,[8] and phenylcarbamoyl benzyl benzohydroxamate gave N-benzoyl-N′-phenylurea in a 25% yield.[9] These were all shown to be identical by infrared spectra and mixed melting point with the corresponding ureas which had been synthesized in an alternate manner.

N-Phenyl-N′-anisoylurea.—Reaction of anisoamide with phenyl isocyanate[19] gave an 89% yield of the urea which was recrystallized from *p*-dioxane, m.p. 225–226°.

Anal. Calcd. for $C_{15}H_{14}N_2O_3$: C, 66.65; H, 5.28; N, 10.37. Found: C, 66.45; H, 5.30; N, 10.26.

Infrared Spectra.—Infrared spectra of acyl phenyl ureas show NH stretching bands at 3200 and 3100, C=O at 1680–1700 and 1640–1660 cm.$^{-1}$ in Nujol. The pair carbonyl bands appear at higher wave numbers with the acetyl compounds than with the aroyl compounds. In the chloroform spectrum of N-acetyl-N′-phenylurea NH stretching is at 3450 and 3280 cm.$^{-1}$, while the two distinct carbonyl bands observed in the Nujol spectrum became nearly superimposed appearing as a poorly resolved doublet at about 1700 cm.$^{-1}$. In a very dilute solution of N-acetyl-N′-phenylurea in carbon tetrachloride a single carbonyl peak appears at 1705 cm.$^{-1}$.

Hydrolysis of Phenylcarbamoyl Benzyl Acetohydroxamate.—Phenylcarbamoyl benzyl acetohydroxamate, 2.20 g. (0.0077 mole), was heated with 75 ml. of 6 *N* hydrochloric acid for several hours. A white solid, 0.41 g., separated from the acid solution. The infrared spectrum suggested that this solid was a mixture of benzyloxamine hydrochloride and a small amount of N-benzyloxy-N′-phenylurea.[11] The solid was partitioned between ether and water and the ether extract was dried and diluted with petroleum ether (b.p. 30–60°). Upon cooling a small amount of solid m.p. 103–105° was obtained. The infrared spectrum of this solid

(17) Prepared by R. Gabbe in undergraduate organic laboratory.

(18) All infrared spectra were run on a Perkin-Elmer Infracord.

(19) This method originated with Kuhn, ref. 8b.

was identical with that of N-benzyloxy-N′-phenylurea, and a mixed melting point of the two samples did not depress.

Pyrolysis of Phenylcarbamoyl Benzyl Acetohydroxamate.—Phenylcarbamoyl benzyl acetohydroxamate, 0.73 g., was refluxed at 1 mm., for 1 hr. The effluent gas was trapped in a Dry Ice–cooled trap containing cyclohexanol. The material in the trap was recrystallized from ethanol–water mixture and was obtained in a 0.1-g. yield, m.p. 81–83°. A mixed melting point with cyclohexyl phenylurethan did not depress. The material remaining in the boiling flask had an infrared spectrum identical to that of benzyl acetohydroxamate.

Pyrolysis of Phenylcarbamoyl Benzyl Benzohydroxamate.—When 0.1 g. of phenylcarbamoyl benzyl benzohydroxamate was heated at 87° at atmospheric pressure as long as the odor of phenylisocyanate could be detected, an oil remained which gradually solidified. The solid was recrystallized from an ether–petroleum ether (b.p. 30–60°) mixture, m.p. 103–105°. Infrared spectrum in Nujol was identical to that of benzyl benzohydroxamate.

Substituted Indole-3-acetic Acids by the Reformatsky Reaction

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Received March 19, 1962

4-Chloro-2-methyl-, 5-chloro-2-methyl-, and 6-chloro-2-methylindole-3-acetic acids have been synthesized *via* the Reformatsky reaction applied to the appropriate chloro-substituted derivatives of 1-acetyl-2-methylindoxyl. The Fischer indole synthesis applied to ethyl levulinate *m*-chlorophenylhydrazone gave, after hydrolysis, a eutectic mixture of 4-chloro-2-methyl- and 6-chloro-2-methylindole-3-acetic acids.

The auxinlike activity of substituted derivatives of the natural plant growth hormone indole-3-acetic acid (*heteroauxin*) varies with the nature and positions of substituent groups.[2] 4-Chloro-2-methyl- and 6-chloro-2-methylindole-3-acetic acids would be of interest for phytological studies in this connection. Apparently a eutectic mixture of these acids was obtained following application of the Fischer indole synthesis to ethyl levulinate *m*-chlorophenylhydrazone. Analogous results were obtained by Fox and Bullock[3] with succinaldehydic acid *m*-chlorophenylhydrazone. An unambiguous method of synthesis was required to obtain the separate isomers and to show that the product of the Fischer synthesis was indeed a mixture of the two.

A synthesis based on the work of Pretka and Lindwall[4] appeared more promising than alternative possible routes such as those involving reduction of 2,β-dinitrostyrenes[5] or reduction of *o*-nitrobenzyl carbonyl compounds[6]; syntheses of the Madelung type apparently fail when substituents other than alkyl groups are desired in the benzene moiety.[7] The key step in the method of Pretka and Lindwall is a Reformatsky reaction applied to a 1-acetylindoxyl. We extended this approach to the synthesis of 4-chloro-2-methyl-, 5-chloro-2-methyl-, and 6-chloro-2-methylindole-3-acetic acids.

Two of the chloroanthranilic acids required for preparing the appropriately substituted indoxyls were prepared from the corresponding chloro-substituted *o*-toluidines. The *N*-acetyl derivatives of 5-chloro-2-methylaniline and 3-chloro-2-methylaniline were oxidized by hot aqueous potassium permanganate solution buffered by magnesium sulfate. Subsequent acid hydrolysis of the resulting *N*-acetyl derivatives of the chloroanthranilic acids gave 4-chloro- and 6-chloroanthranilic acids. 5-Chloroanthranilic acid was obtained from a commercial source.

1-Acetyl-4-chloro-2-methylindoxyl and the 5-chloro and 6-chloro isomers were prepared by methods similar to those employed by Pretka and Lindwall in their preparation of 1-acetyl-2-methylindoxyl. Condensation of the chloroanthranilic acids with α-chloropropionic acid in aqueous sodium carbonate solution afforded *N*-(1-carboxyethyl)-4-chloroanthranilic acid and the 5-chloro- and 6-chloro isomers (group I). Heating solutions of the chloro-substituted *N*-(1-carboxyethyl)anthranilic acids with sodium acetate in acetic anhydride provided 1-acetyl-4-chloro-2-methylindoxyl acetate and the 5-chloro and 6-chloro isomers (group II). Selective hydrolysis of the *O*-acetyl function of the indoxyl acetates with sodium sulfite in aqueous dioxane gave 1-acetyl-4-chloro-2-methyl-

(1) Present address: Southern Research Institute, Birmingham, Alabama.

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(3) S. W. Fox and M. W. Bullock, *J. Am. Chem. Soc.*, **73**, 2756 (1951).

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(6) A. Baeyer and O. R. Jackson, *Ber.*, **13**, 187 (1880); **14**, 879 (1881); A. B. Sen and P. M. Bhargava, *J. Indian Chem. Soc.*, **25**, 282, 403 (1948); R. Giuliano and M. L. Stein, *Ann. Chim.* (Rome), **48**, 1284 (1958); W. Borsche, *Ber.*, **42**, 601 (1909); A. Reissert and H. Heller, *ibid.*, **37**, 4364 (1904).

(7) L. Marion and W. R. Ashford, *Can. J. Research*, **23B**, 26 (1945); E. Hardegger and H. Corrodi, *Helv. Chim. Acta*, **39**, 514 (1956); J. A. Barltrop and D. A. H. Taylor, *J. Chem. Soc.*, 3399 (1954); H. Burton, J. A. Duffield, and P. F. G. Praill, *ibid.*, 1062 (1950).