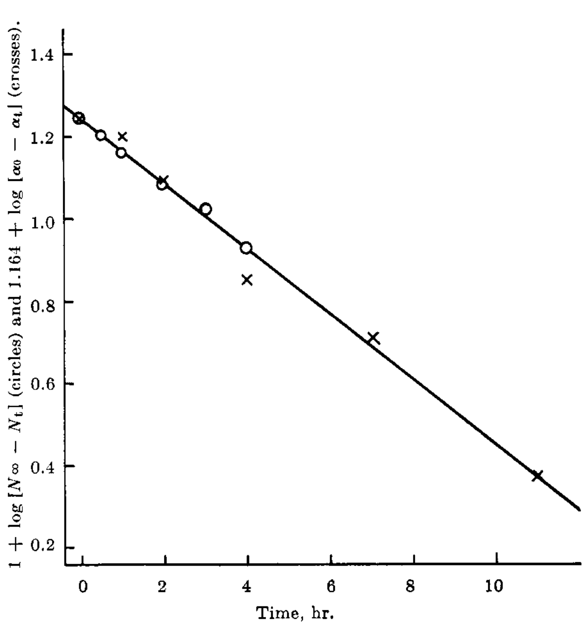


Fig. 1.—First-order kinetic plot of titrimetic and polarimetric data for acid-catalized hydrolysis of (−)-2-octyl ethyl methylphosphate. From the slope of the graph, $k_1 = 0.183$ hr.$^{-1}$.

fissions can occur, the latter reaction involving nucleophilic assistance from a water molecule (the $A_{AL}2$[6] or $A''2$[7] mechanism), which seems unlikely.

Experimental

Materials.—Dioxane was purified by refluxing with hydrochloric acid to hydrolyze any acetals, adding an excess of solid potassium hydroxide, decanting, drying over sodium, and finally distilling from over fresh sodium.

Optically active octanol-2 was prepared by fractional crystallization of the brucine salts of the phthalic acid monoester, followed by hydrolysis and distillation.[8]

(−)-2-Octyl methylphosphonochloridate was prepared in 79% yield by the reaction between (−)-octanol-2 and methylphosphonic dichloride in the presence of triethylamine in ether at 0°.[4] Specific gravity, 1.036; $[\alpha]^{18}\text{D}$ −12.65° (from octanol-2, $[\alpha]^{20}\text{D}$ −9.95°.)

Anal. Calcd. C, 47.7; H, 8.8; Cl, 15.7. Found: C, 48.1; H, 8.6; Cl, 15.7.

(−)-2-Octyl Ethyl Methylphosphonate.—A 22.6-g. sample (0.1 mole) of (−)-2-octyl methylphosphonochloridate was added slowly with agitation to 16.0 ml. (0.1 mole) of diethylaniline and 30.0 ml. (0.5 mole) of anhydrous ethanol. The reaction mixture was then heated on a boiling water bath for 0.5 hr. The semisolid pasty mass was allowed to cool and then shaken with 300 ml. of dry petroleum ether (b.p. 40–60°). The solid was removed by filtration and washed with more petroleum ether. The solvent was removed from the combined filtrate and washings and the residual oil distilled under reduced pressure; yield, 20.0 g. (85%), b.p. 73–74°/(0.2 mm.); specific gravity, 0.945; $[\alpha]^{18}\text{D}$ −11.87° (from alcohol $[\alpha]^{20}\text{D}$ −9.95°).

Anal. Calcd. C, 55.7; H, 10.5. Found: C, 54.8; H, 10.5.

An attempt to prepare the same compound by the reaction of octanol-2 with ethyl methylphosphonochloridate in the presence of a tertiary base was unsuccessful, probably due to the slow reaction with the octanol-2 which was recovered unchanged.

Kinetic and Optical Activity Measurements.—The ester (2.36 g.) was dissolved in 100 ml. of N benzenesulfonic acid in 50% aqueous dioxane (v./v.) to give a 0.1 M solution of ester. Five-milliliter aliquots were removed with pipets and placed in glass ampoules and sealed. The ampoules were placed in an agitated oil bath maintained at 100.2°, and ampoules were removed for analysis at suitable time intervals. The formation of acid was determined by rapidly cooling the ampoule and titrating the contents against 0.25 N sodium hydroxide using methyl red indicator. The change in optical activity was determined by placing the cooled contents of ampoules in the 2-dm. polarimeter tube and measuring the rotation at the sodium "D" line.

The velocity constants for the acid production and optical activity change were determined using the equations,

$$k_1 = \frac{2.303}{t} \cdot \log\left\{\frac{N_\infty}{N_\infty - N_t}\right\} \quad \text{and} \quad k_1 = \frac{2.303}{t} \cdot \log\left\{\frac{\alpha_0}{\alpha_0 - \alpha_t}\right\}$$

where N_t is the volume of 0.25 N sodium hydroxide required to neutralize a 5-ml. reaction mixture at time t, and α_t is the optical rotation of the reaction mixture observed in a 2-dm. tube at time t, and also from the graph of log ($N\alpha - N_t$) or log ($\alpha_0 - \alpha_t$) *vs.* time, $k_1 = -2.303 \times$ slope of the graph.

The optical activity of the alcohol produced was also measured after isolation; 10 g. of ester was heated with 50 ml. of 1 N benzenesulfonic acid in 50% aqueous dioxane at 100° for 6 hr. in a large sealed ampoule. The ampoule was cooled; the contents made slightly alkaline with sodium hydroxide and immediately extracted twice with ether. The ether solution was dried over anhydrous magnesium sulfate and the solvent removed. The residue was distilled in a microfractionation unit to give 3.0 g. (55%) of octanol-2, b.p. 175–180° (lit. b.p. 178–179°), $[\alpha]^{20}\text{D}$ −0.84° (the octanol-2 used in the ester preparation had $[\alpha]^{20}\text{D}$ −9.95°).

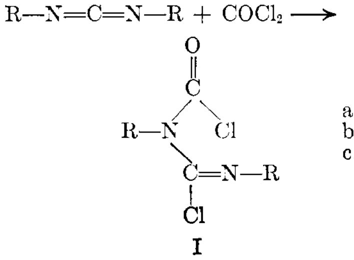
The Addition of Phosgene to Carbodiimides

Henri Ulrich and A. A. R. Sayigh[1]

The Carwin Company, Division of the Upjohn Company, North Haven, Connecticut

Received December 3, 1962

It is well known that carboxylic acids add to carbodiimides[2] and recently acetyl chloride was shown to do so,[3] although the products are unstable and tend to decompose to the starting compounds. We have found that phosgene, which has not previously been reported as taking part in addition reactions with cumulative double bonds,[4] also adds readily to aliphatic and aromatic carbodiimides to give N,N′-disubstituted chloroformamidine-N-carbonyl chlorides (I), which are remarkably stable as illustrated by their distillation in vacuum without decomposition.


$R{-}N{=}C{=}N{-}R + COCl_2 \longrightarrow$

I

a. R = *n*-butyl
b. R = cyclohexyl
c. R = *o*-tolyl

The structure of the 1:1 addition products was established by elementary analysis and infrared spectroscopy. The infrared spectra of I show C=O absorption at 5.73–5.75 μ and a C=N absorption at 5.98–6.0 μ.

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(6) C. A. Bunton, E. D. Hughes, C. K. Ingold, and D. F. Meigh, *Nature*, **166**, 680 (1950).

(7) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1956, p. 318.

(8) A. I. Vogel, "A Textbook of Practical Organic Chemistry," 2nd ed., Longmans Green and Co., London, 1951, p. 489.

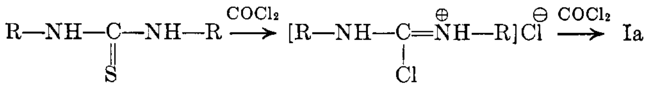
(1) To whom inquiries should be directed.

(2) H. G. Khorana, *Chem. Rev.*, **53**, 145 (1953).

(3) K. Hartke and J. Bartulin, *Angew. Chem.*, **74**, 214 (1962).

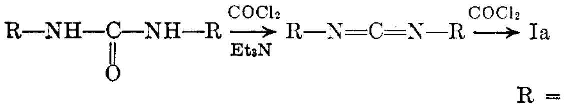
(4) While phosgene does not react with isocyanates, F. S. Fawcett, C. W. Tullock, R. D. Smith, and D. D. Coffman, Second International Symposium on Fluorine Chemistry, Estes Park, Colo., 1962, have observed that carbonyl fluoride adds to phenyl isocyanate.

The aliphatic members of the series were also obtained from N,N′-dialkylthioureas and excess phosgene. When this reaction is carried out with molar ratios of reactants, the products were reported to be N,N′-disubstituted chloroformamidine hydrochlorides (II),[5] which, therefore, can be invoked as intermediates in the reaction involving excess phosgene. This is supported by the fact that II (R = *n*-butyl) reacts with phosgene to give a high yield of Ia. Furthermore, Ia can also be obtained from N,N′-di-*n*-butylurea and phosgene in the presence of triethylamine,[6] the intermediate in this case being the carbodiimide.



$$\text{R—NH—}\underset{\underset{\text{S}}{\|}}{\text{C}}\text{—NH—R} \xrightarrow{\text{COCl}_2} [\text{R—NH—}\underset{\underset{\text{Cl}}{|}}{\text{C}}=\overset{\oplus}{\text{N}}\text{H—R}]\overset{\ominus}{\text{Cl}} \xrightarrow{\text{COCl}_2} \text{Ia}$$

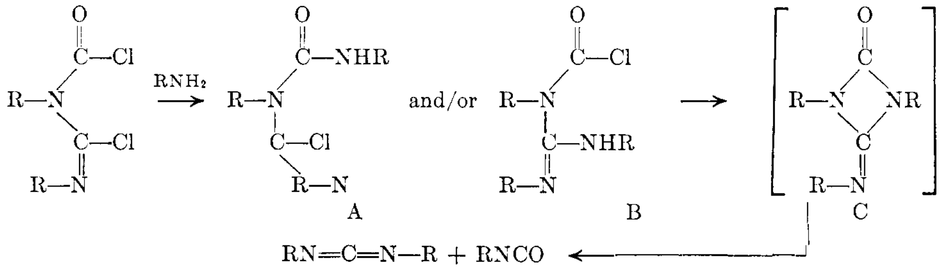
II



$$\text{R—NH—}\underset{\underset{\text{O}}{\|}}{\text{C}}\text{—NH—R} \xrightarrow[\text{Et}_3\text{N}]{\text{COCl}_2} \text{R—N=C=N—R} \xrightarrow{\text{COCl}_2} \text{Ia}$$

R = *n*-butyl

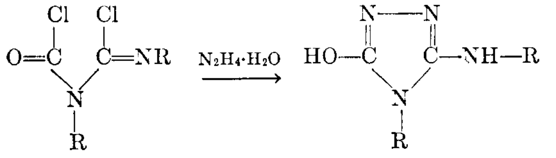
We investigated the reaction of amines and hydrazine with Ic. When it reacted with four equivalents of *o*-toluidine, the products were di-*o*-tolylcarbodiimide (84.7%) and some *o*-tolyl isocyananate; both could arise from the decomposition of a common four-membered ring intermediate.[7]



R = *o*-tolyl

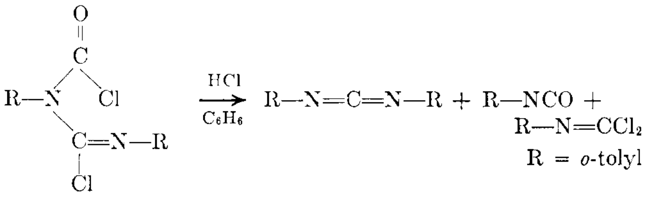
Similarly, di-*o*-tolylguanidine (III) was obtained from the reaction of Ic and alcoholic ammonia. Most likely, but not necessarily, III is formed by the addition of ammonia to di-*o*-tolylcarbodiimide.

When hydrazine hydrate and Ic reacted, 3-*o*-tolylamino-5-hydroxy-4-*o*-tolyl-1,2,4,4H-triazole (IV) was formed.



IV. R = *o*-tolyl

At 180° Ic, slowly generated phosgene but no carbodiimide could be detected. However, at 80° in the presence of hydrogen chloride, dissociation into carbodiimide (strong infrared absorption at 4.7 μ), isocyanate (weak infrared absorption at 4.4 μ), and isocyanide dichloride (weak infrared absorption at 11 μ) was observed.



R = *o*-tolyl

Experimental[8]

N,N-Dibutylchloroformamidine-N-carbonyl Chloride (Ia). A. From Di-*n*-butylcarbodiimide.—Phosgene was added to a solution of 3.08 g. (0.02 mole) of di-*n*-butylcarbodiimide in 50 ml. of toluene at room temperature. The temperature of the mixture rose to 45°. The unchanged phosgene was removed in a stream of nitrogen, and the solvent was evaporated to give 4.4 g. (98%) of Ia, b.p. 86° (0.5 mm.), $n^{23}\text{D}$ 1.4718, $\lambda_{\max}^{\text{CHCl}_3}$ (infrared): 3.43, 5.73, 5.98, 6.80, 7.35, and 8.05 μ.

Anal. Calcd. for $C_{10}H_{18}Cl_2N_2O$: C, 47.45; H, 7.16; N, 11.06. Found: C, 47.60; H, 7.40; N, 11.17.

B. From N,N′-Di-*n*-butylthiourea.—Phosgene was added to a solution of 30.2 g. (0.16 mole) of N,N′-di-*n*-butylthiourea in 600 ml. of benzene until the exothermic reaction stopped. The excess phosgene was removed in nitrogen and the solvent evaporated to give 39 g. (96.3%) of Ia. The infrared spectrum was superimposable on that of the Ia obtained, according to method A.

C. From N,N′-Di-*n*-butylchloroformamidine Hydrochloride.—Hydrogen chloride was bubbled into a solution of 7.7 g. (0.05 mole) of di-*n*-butylcarbodiimide in 77 ml. of benzene until the infrared spectrum of the mixture indicated the complete reaction of the carbodiimide. Then excess phosgene was added to the refluxing reaction mixture. After purging with nitrogen, 10.4 g. (91.6%) of Ia was obtained. The infrared spectrum was identical with that of the material prepared according to method A.

N,N′-Dicyclohexylchloroformamidine-N-carbonyl Chloride (Ib).—Phosgene was added to a solution of 4.12 g. (0.02 mole) of dicyclohexylcarbodiimide in 50 ml. of ethylene dichloride at 2°. When the excess phosgene was removed with nitrogen and the solvent evaporated, 6.1 g. (100%) of Ib was obtained, b.p. 140–142° (0.8 mm.), $n^{23}\text{D}$ 1.5132, $\lambda_{\max}^{\text{CHCl}_3}$ (infrared): 3.43, 5.73, 5.98, 6.88, 7.40, 7.83, 8.52, 9.45, 9.85, and 10.42 μ.

Anal. Calcd. for $C_{14}H_{22}Cl_2N_2O$: C, 55.05; H, 7.26; N, 9.17. Found: C, 54.99; H, 7.20; N, 9.40.

N,N′-Di-*o*-tolylchloroformamidine-N-carbonyl Chloride (Ic).—Phosgene (15 g., 0.15 mole) was added to a solution of 22.2 g. (0.1 mole) of di-*o*-tolylcarbodiimide in 200 ml. of ethylene dichloride at 2°. The excess phosgene and the solvent were removed to give 31.7 g. (98.8%) of Ic, $n^{21}\text{D}$ 1.5851, $\lambda_{\max}^{\text{CHCl}_3}$ (infrared): 5.73, 6.00, 6.72, 6.85, 8.50, and 9.00 μ.

Anal. Calcd. for $C_{16}H_{14}Cl_2N_2O$: N, 8.72. Found: N, 8.98.

Reaction of Ic with *o*-Toluidine.—A 21.4-g. sample (0.2 mole) of *o*-toluidine in 21 ml. of dry benzene was added dropwise over a period of 30 min. to a stirred solution of 16.05 g. (0.05 mole) of Ic in 110 ml. of benzene. The mixture was stirred for an additional 45 min. at room temperature and the precipitated solid was filtered off. The infrared spectrum of the benzene solution had a strong absorption band at 4.7 μ and a weak band at 4.4 μ. The benzene was evaporated and the residue distilled to give 9.4 g. (84.7%) of di-*o*-tolylcarbodiimide, b.p. 134–141° (0.4 mm.). The filtered solid was separated into *o*-toluidine hydrochloride,

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(5) H. Eilingsfeld, M. Seefelder, and H. Weidinger, *Angew. Chem.*, **72**, 836 (1960).

(6) H. Ulrich, J. N. Tilley, and A. A. R. Sayigh, in print.

(7) One of the referees prefer not to involve the four-membered ring intermediate (C) but to decompose intermediates A and/or B concertedly to the products. However, we prefer to involve C in view of the tendency of similar derivatives (A, B) to form four-membered rings.

(8) Microanalyses by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. Infrared absorption spectra were determined using a Perkin-Elmer Model 21 spectrophotometer.

and the water-insoluble di-*o*-tolylurea, m.p. 270° dec. The infrared spectrum of the isolated urea was identical with that of an authentic sample.

Reaction of Ic with Ammonia.—A 3.2-g. sample (0.01 mole) of Ic was added to methanolic ammonia. When the solvent was evaporated, the hydrochloride of N,N′-di-*o*-tolylguanidine was obtained. From this, on treatment with aqueous sodium hydroxide, was isolated di-*o*-tolylguanidine (III), m.p. 183–185° (lit., m.p. 179°). A solution of 1 g. of di-*o*-tolylcarbodiimide in 10 ml. of benzene was saturated with ammonia in the presence of 10 mg. of cupric chloride to give 74.5% of III, m.p. 186–187°. No depression of the melting point was caused when samples of III prepared by the above methods were mixed. The infrared spectrum was identical with that of an authentic sample.

Reaction of Ic with Hydrazine Hydrate.—A 2.2-g. sample (0.007 mole) of Ic was added to 1.44 g. (0.03 mole) hydrazine hydrate in a mixture of 20 ml. of tetrahydrofuran and 20 ml. of water. An immediate reaction took place. After the mixture had been stirred, with ice-cooling, 1.4 g. (73%) of 3-*o*-tolylamino-5-hydroxy-4-*o*-tolyl-1,2,4,4H-triazole (IV) had separated. It crystallized from benzene in white crystals, m.p. 198–199°; $\lambda_{\max}^{\mathrm{CHCl_3}}$ (infrared): 2.96, 3.20, 3.30–3.40, 5.84, 6.17, 6.28, 6.48, 6.84, 7.27, 7.62, and 11.61 μ.

Anal. Calcd. for $C_{16}H_{16}N_4O$: C, 68.55; H, 5.75, N, 19.99. Found: C, 68.72; H, 5.96; N, 19.92.

In a similar experiment, using benzene as the solvent, IV was obtained in 83% yield. IV is soluble in dilute sodium hydroxide and it could be reprecipitated by acid.

Acknowledgment.—The authors wish to thank Mr. B. Tucker for his valuable help with the experiments and Mr. F. Geremia for the determination of numerous infrared spectra.

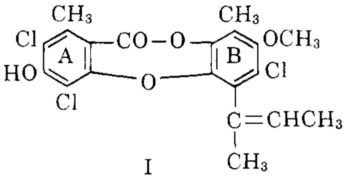
The Structure of Nidulin

B. W. Bycroft and John C. Roberts

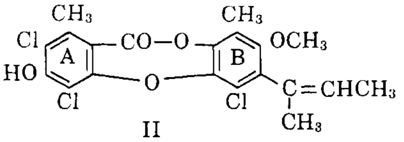
Department of Chemistry, The University, Nottingham, England

Received November 27, 1962

Nidulin,[1] the chief chlorine-containing metabolite of a non-ascosporic strain of *Aspergillus nidulans*, has been allocated[2,3] structure I. Shortly after the publication of our last paper,[3] Beach and Richards claimed[4] that nidulin should be represented by structure II. Although we still maintain that the evidence which we have already presented[2,3] is sufficient to establish the correctness of our structure, we present the following additional arguments in favor of structure I.



I



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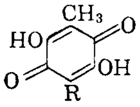
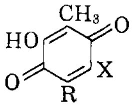
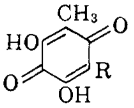


III



IV



V

a. R = —C(CH$_3$)=CHCH$_3$
b. R = —CH(CH$_3$)$_2$

Degradation of nidulin under strictly defined conditions[3] yielded nucleus B as a dihydroxybenzoquinone which we have formulated,[3] on the basis of analysis, color reactions, and ultraviolet absorption spectrum,[5] as IIIa. If nidulin had possessed structure II, then the degradation product would have had structure Va. We have now compared (see Table I) the ultraviolet and infrared absorption spectra of the degradation product IIIa with the corresponding spectra of dihydroxythymoquinone[6] (IIIb) and of 3,5-dihydroxy-2,6-dimethylbenzoquinone[7] (V; R = CH$_3$). We also record (see Table I) the spectra of monohydroxythymoquinone[6] (IVb; X = H) and of the chloroquinone (IVa; X = Cl) which is obtainable[3] as a degradation product of nidulin. The three last-mentioned quinones, as expected,[8] show two carbonyl bands in their infrared spectra. (The two bands are not clearly resolved in the solution spectra of the chloroquinone and of 3,5-dihydroxy-2,6-dimethylbenzoquinone.)

Information from the ultraviolet absorption spectra does not differentiate clearly between the two possibilities for the nidulin degradation product (IIIa or Va). However, the evidence from the infrared absorption spectra establishes unequivocally that the degradation product has structure IIIa. Hence the chloroquinone has structure IVa (X = Cl). We maintain, therefore, that nidulin is correctly represented by structure I.

Table I

Compound	Ultraviolet absorption spectrum[a] (EtOH), $\lambda_{\max}$ in mμ (log ϵ)	Infrared absorption spectrum[b] (O—H and C=O stretching vibrations), $\nu_{\max}$ in cm.$^{-1}$ Disk (KBr)	Solution (CHCl$_3$)
IIIa	287 (4.24), 436 (2.40)	3310, 1617	3365, 1642
IIIb	293 (4.31), 435 (2.36)	3319, 1616	3327, 1640[c]
IVb (X = H)	267 (4.16), 404 (3.01)	3252, 1668, and 1643	3431, 1662, and 1645
IVa (X = Cl)	278 (4.15), 334 (3.24) 405 (2.77)[d]	3411, 1665, and 1655	3431, 1662, and 1654[d]
V (R = CH$_3$)	297 (4.26), 426 (2.26)	3417, 1660, and 1641	3476, 1653, and 1645[d]

[a] Taken on a Unicam S. P. 500. [b] Taken on a Unicam S. P. 100. [c] Compound IIIb is only sparingly soluble in chloroform. It is more soluble in bromoform and a solution in this solvent showed a single carbonyl peak at 1637 cm.$^{-1}$. [d] Shoulder.

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