Acknowledgment.—We are indebted to Mr. Wm. Washburn for the infrared spectra, Mr. E. F. Shelberg and Mr. O. Kolsto for the microanalyses, and to Mr. M. Freifelder for the catalytic hydrogenations.

The Bischler–Napieralski Cyclization of an Imide

GLENN C. MORRISON, WIACZESLAW CETENKO, AND JOHN SHAVEL, JR.

Warner-Lambert Research Institute, Morris Plains, New Jersey

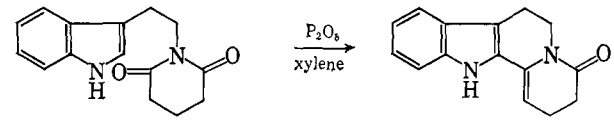
Received May 27, 1964

The cyclodehydration of amides derived from β-phenethylamines was first reported by Bischler and Napieralski[1] in 1893. Since that time many variations[2] of this reaction have been described.

In connection with one of our synthetic programs, we wished to be able to cyclize a substituted glutarimide of tryptamine. An examination of the literature pointed up the wide variety of results in examples of this type of cyclization. Wenkert, *et al.*,[3] were unable to cyclize N-(2-indol-3-ylethyl)succinimide. Haworth, *et al.*,[4] obtained a chloro intermediate from the treatment of 1,2,3,4-tetrahydro-2-piperonylmethyl-1,3-isoquinolinedione with phosphorus oxychloride. Křepelka and Štefec[5] were able to cyclize N,N′-(2,2′-biphenylylene)diphthalimide with aluminum chloride, but the product underwent cleavage to an amino acid. Kametani and Yanase[6] cyclized N-(3,4-dimethoxyphenethyl)-glutarimide with phosphorous oxychloride, but obtained a product which had suffered oxidation. Jost[7] claimed a 5–20% yield of a cyclization product from the treatment of *trans*-hexahydro-2-(2-indol-3-ylethyl)-1,3-(2H,4H)-isoquinolinedione with phosphorus oxychloride, but gave no direct experimental procedure or structure proof. Schlittler and Speitel[8] cyclized 1,2,-3,4-tetrahydro-2-(2-indol-3-ylethyl)-5-methyl-1,3-isoquinolinedione to ketoyobyrin with phosphorus oxychloride, but did not report the yield of the purified product.

In view of the lack of an example in which the experimental procedure, yield, and structure proof of the product were described, and the variation in the results of the different investigators, we decided to study a simple model for this reaction, namely, the cyclization of N-(2-indol-3-ylethyl)glutarimide (**1**). The synthesis of the required imide was accomplished by the condensation of tryptamine with diethyl glutarate to give an esteramide which was converted to the imide by refluxing in xylene with *p*-toluenesulfonic acid.

First, we attempted the cyclization of the imide **1** with phosphorus oxychloride which had been the catalyst used by most of the other workers. This gave only starting material and products which could not be characterized. However, when phosphorus pentoxide in xylene was utilized, the desired lactam **2** was obtained in 31% yield.



1 **2**

Melting point, ultraviolet absorption maxima, and infrared carbonyl absorption frequency of our material corresponds to the values previously reported for **2** by Vogt,[9] who obtained this compound by oxidation of 1,2,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizin-4-(3H)-one with N-bromosuccinimide. As a proof of structure, the lactam **2** was reduced with lithium aluminum hydride to the known 2,3,4,6,7,12-hexahydroindolo[2,3-*a*]quinolizine,[10] which was in turn reduced to 1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine and shown to be identical with an authentic sample prepared according to Reckhow and Tarbell.[11]

Experimental[12]

Ethyl N-(2-Indol-3-lyethyl)glutaramate.—A mixture of 20.0 g. of tryptamine and 26.0 g. of diethyl glutarate was heated at 175° for 18 hr. The reaction mixture was digested with 2.5 l. of chloroform, cooled to room temperature, and filtered. Removal of the solvent and crystallization of the residue from benzene gave a solid which on recrystallization from methylene chloride–petroleum ether (b.p. 30–60°) gave 32.8 g. (47%) of a crystalline solid, m.p. 101–102°.

Anal. Calcd. for $C_{17}H_{22}N_2O_3$: C, 67.52; H, 7.33; N, 9.27. Found: C, 67.67; H, 7.54; N, 9.47.

N-(2-Indol-3-ylethyl)glutarimide (1).—A mixture of 31.7 g. of ethyl N-(2-indol-3-ylethyl)glutaramate, 9.6 g. of *p*-toluenesulfonic acid and 1200 ml. of xylene was refluxed for 9 hr. while the water was continuously removed in a Dean–Stark tube. The reaction mixture was filtered and diluted with 1800 ml. of petroleum ether. On standing, there was deposited 15.0 g. (53%) of a crystalline solid, m.p. 170–172°. Recrystallization from methanol gave an analytical sample, m.p. 173–175°.

Anal. Calcd. for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.01; H, 6.29; N, 10.95.

2,3,4,6,7,12-Hexahydroindolo[2,3-*a*]quinolizin-4-one (2).—To a solution of 3.0 g. of N-(2-indol-3-ylethyl)glutarimide in 410 ml. of refluxing xylene was added three 15-g. portions of phosphorus pentoxide with stirring over a 45-min. interval. Then the mixture was refluxed for 5 hr. The reaction mixture was filtered and the solid was added to 1 l. of ice–water, made basic with 40% potassium hydroxide solution, and extracted with chloroform. The chloroform layer was washed with water and dried over sodium sulfate, and the solvent was removed. One recrystallization from ethanol gave 0.94 g. (31%) of a crystalline solid, m.p. 234–235°. Further recrystallization gave an analytical sample, m.p. 237–238° (lit.[9] m.p. 232–233°); $\nu_{max}^{CHCl_3}$, cm.$^{-1}$, 3460 (NH), 1645 (C=O), 1665 (C=O) [lit.[9] 3450 (NH), 1640 (C=O), 1600 (C=O)]; λ_{max}^{EtOH}, mμ (ε), 220 sh (27,000), 232 (30,000), 308 (22,200) 319 (20,500) [lit.[9] λ_{max}^{MeOH}, mμ (ε), 222 (27,100), 308 (18,700), 318 (16,000)]; $\lambda_{max}^{0.1\ N\ HCl}$, mμ (ε), 245 (8400), 395 (33,900).

Anal. Calcd. for $C_{15}H_{14}N_2O$: C, 75.60; H, 5.92; N, 11.76. Found: C, 75.71; H, 5.90; N, 11.50.

1,2,3,4,6,7-Hexahydro-12H-indolo[2,3-*a*]quinolizinium Perchlorate.—To a suspension of 4.8 g. of lithium aluminum hydride in 750 ml. of ether was added, over a 1-hr. interval, a solution of 1.5 g. of 2,3,4,6,7,12-hexahydroindolo[2,3-*a*]quinolizin-4-one in

(1) A. Bischler and B. Napieralski, *Ber.*, **26**, 1903 (1893).
(2) W. Whaley and T. Govindachari, *Org. Reactions*, **6**, 74 (1951).
(3) E. Wenkert, S. Garratt, and K. Dave, *Can. J. Chem.*, **42**, 489 (1964).
(4) R. Haworth, W. Perkin, and H. Pink, *J. Chem. Soc.*, **127**, 1709 (1925).
(5) V. Křepelka and R. Štefec, *Collection Czech. Chem. Commun.*, **9**, 29 (1937); *Chem. Abstr.*, **31**, 3909 (1937).
(6) T. Kametani and R. Yanase, *J. Pharm. Soc. Japan*, **83**, 1039 (1963).
(7) J. Jost, *Helv. Chim. Acta*, **32**, 1297 (1949).
(8) E. Schlittler and R. Speitel, *ibid.*, **31**, 1199 (1948).
(9) W. Vogt, Ph.D. Thesis, "Versuche zur Darstellung pentacyclischer Indolalkaloide," T. H. Braunschweig, Germany, 1960.
(10) E. Wenkert and B. Wickberg, *J. Am. Chem. Soc.*, **84**, 4914 (1962).
(11) W. A. Reckhow and D. S. Tarbell, *ibid.*, **74**, 4960 (1952).
(12) Melting points are corrected. The authors are indebted to Mr. R. Puchalski for the spectral data and Mrs. U. Zeek for analytical determinations.

2800 ml. of ether. Stirring was continued for 4 hr. after the addition had been completed. The excess hydride was destroyed by the dropwise addition of water. The ether solution was acidified with hydrogen chloride and the solvent was removed *in vacuo*. The residue was dissolved in 175 ml. of 2% hydrochloric acid, filtered, neutralized with ammonium hydroxide solution to pH 8.5, and filtered. The solution on acidification with perchloric acid gave, after recrystallization from methanol, 0.7 g. (33%) of a crystalline solid, m.p. 214–216°. Further recrystallization gave a sample, m.p. 219.5–220.5 (lit.[10] m.p. 223–227°).

1,2,3,4,6,7,12,12b-Octahydroindolo[2,3-*a*]quinolizine.—To a solution of 366 mg. of 1,2,3,4,6,7-hexahydro-12H-indolo[2,3-*a*]-quinolizinium perchlorate in 120 ml. of ethanol was added 137 mg. of platinum oxide and the mixture was hydrogenated unti uptake ceased. The catalyst was removed by filtration and the alcohol was removed *in vacuo*. The residue was treated with a mixture of 10% sodium hydroxide solution and ether. The ether layer was washed with water and dried over sodium sulfate. Removal of the solvent gave 198 mg. of a crystalline solid, m.p. 149.5–151°. Recrystallization from petroleum ether gave a sample, m.p. 151–152°.

This sample was shown to be identical with an authentic sample[11] by the methods of mixture melting point and infrared analysis.

N-1,1-Trichlorocyanoacetimidoyl Chloride

WAYNE R. CARPENTER AND PATRICIA ARMSTRONG

Chemistry Division, Research Department, U. S. Naval Ordnance Test Station, China Lake, California

Received January 6, 1964

Ott and Löpmann[1] isolated a by-product, $C_3N_2Cl_4$ (II), in the preparation of dichloromalononitrile (I) by the aqueous chlorination of malononitrile. The name tetrachloromalononitrile was given to II but a structure was not proposed. A third compound, dichlorocyanoacetamide (III), was also isolated.[2]

$$CH_2(CN)_2 \xrightarrow[H_2O]{Cl_2} \underset{\text{I}}{CCl_2(CN)_2} + \underset{\text{II}}{C_3N_2Cl_4} + \underset{\text{III}}{NCCl_2CONH_2}$$

The procedure of Ott and Löpmann[1] called for the addition of 2 moles of chlorine to 1 of malononitrile in an ice-cold aqueous solution; no yields were reported. By using a 3:1 mole ratio of chlorine to malononitrile under similar conditions we isolated 74% of I, 8.5% of II, and none of III. Ammonium chloride (13%) was also isolated but no dichloroacetamide, as noted by Rosenblatt and Broome in chlorination of malononitrile with aqueous sodium hypochlorite.[3] No attempt was made to optimize the yield of III, but in one variation of the reaction which failed to produce any of I or II (see Experimental) the yield of III was 8.5%.

On the basis of the following evidence, it is proposed that tetrachloromalononitrile (II) is N-1,1-trichlorocyanoacetimidoyl chloride (IIa). Infrared spectra of I and II both show cyano group absorption at about 4.45 μ; whereas the spectrum of I has no peak in the C=N bond region, the spectrum of II has a strong band at 6.3 μ (see Table I). Reaction of both I and II with excess sodium iodide in acetone caused the formation of free iodine and sodium chloride in the molar amounts listed in Table II.

TABLE I

SIGNIFICANT INFRARED ABSORPTION MAXIMA[a]

Compd.	Wave length, μ
I	4.45 (m), 9.22 (s), 10.00 (m), 10.50 (s), 10.76 (m), 12.65 (s) broad,
II	4.48 (w), 5.79 (w), 6.32 (s), 6.49 (w), 8.72 (s), 9.02 (w), 9.91 (s), 10.25 (w), 10.40 (w), 11.62 (s), 12.60 (s) broad, 14.35 (s)

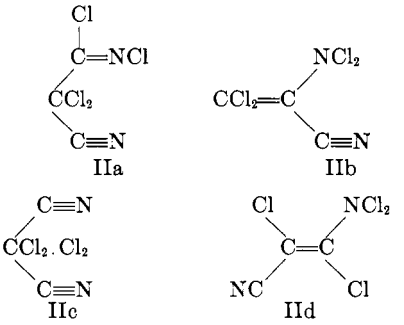
[a] Intensity: s, strong: m, medium; w, weak.

TABLE II

PRODUCT STOICHIOMETRY OF SODIUM IODIDE REACTION

Compound	Moles of I_2/mole of compound	Moles of NaCl/mole of compound
I	1.10	2.16
II	2.15	4.03

The presence of a nitrile group and two positive chlorines reduces the number of possible structures for a monomeric form to four, where IIb and IId represent rearrangements and IIc represents a molecular complex.



Structure IIb can be eliminated because I and II are interconvertible. Chlorine reacted with I to form II, which was converted back to I by treatment with zinc. It is very unlikely that the rearrangements required in going from I to IIb would be so readily reversible. Structure IIc is also improbable in view of the good

$$I \underset{Zn}{\overset{Cl_2}{\rightleftharpoons}} II$$

thermal stability of II. Furthermore, IIc would not be expected to absorb at 6.3 μ, whereas the C=N bond of IIa would. IId is improbable because the rearrangement involved in its formation from I would require the removal of a chlorine atom from a carbon atom in exchange for placing a chlorine atom on a nitrogen atom. Thermodynamically, this exchange would be unfavorable because the N–Cl bond has a much lower bond energy than that of C–Cl. Molecular weight determinations eliminated the possibility that II could be anything but monomeric.

The addition of halogen to the triple bond of a nitrile group is unusual, but not without precedent. One of the products of the action of mercuric fluoride on acetonitrile is N-fluoroacetimidoyl fluoride.[4]

(1) E. Ott and B. Löpmann, *Ber.*, **55B**, 1255 (1922).

(2) It is interesting that the infrared spectrum of III does not show a nitrile group absorption. However, this result is consistent with the fact that chlorodicyanoacetamide also does not have a nitrile group absorption [S. Trofimenko, E. L. Little, Jr., and H. F. Mower, *J. Org. Chem.*, **27**, 433 (1962)]. The infrared spectrum of III also has a doublet at 2.93 and 3.15 and a strong band at 5.85 μ. These figures are consistent with expected values for NH and C=O stretching frequencies in an electronegatively substituted primary amide.

(3) D. H. Rosenblatt and G. H. Broome, *ibid.*, **26**, 2116 (1961).

(4) F. Nerdel, *Naturwissenschafen*, **39**, 209 (1952).