[Contribution from the School of Chemistry and Physics of The Pennsylvania State College]

Reduction of Aliphatic Nitriles by the Stephen Reaction

By James A. Knight[1] and Harry D. Zook

Received February 18, 1952

An alternate course in the Stephen reduction of nitriles has been demonstrated under certain conditions. The products of this reaction are N,N′-alkylidenebisacylamides probably formed by way of a condensation of nitrile with the intermediate imine hydrochloride.

The reduction of nitriles by anhydrous stannous chloride gives complex aldimine salts, one of which has been assigned the formula $(RCH{=}NH{\cdot}HCl)_2{\cdot}SnCl_4$.[2,4] Stephen[2] reported the preparation of aliphatic aldehydes in quantitative yields by the hydrolysis of these salts, although other workers failed to confirm these results.[3] Recently, Lieber[4] reduced lauronitrile by variations of Stephen's procedure and reported high yields of lauraldehyde monomer, dimer, and trimer (m.p. 101°).

In an attempt to prepare quantities of palmitaldehyde we carried out numerous reductions of palmitonitrile by Lieber's procedures. No aldehyde could be isolated. The main product was a white solid containing nitrogen and melting at 103°. Quantitative hydrolysis of the compound by hydrochloric or hydroiodic acids gave palmitic acid and an equivalent amount of ammonia. When the hydrolysis was carried out in the presence of 2,4-dinitrophenylhydrazine, the 2,4-dinitrophenylhydrazone of palmitaldehyde was obtained. The compound showed strong absorption of light below 2500 Å. but did not exhibit a maximum above 2050 Å. It absorbed no hydrogen over platinum catalyst at 65° in glacial acetic acid solution.

Because the results differed greatly from those reported for the reduction of lauronitrile, we attempted to repeat a portion of the work on this compound. Three experiments by two of the described procedures were tried in which different batches of stannous chloride were used. Again, no aldehyde could be isolated. Instead, two solids containing nitrogen were obtained. These compounds were separated by crystallization from alcohol. The more soluble crystals (m.p. 101°) were identified as lauramide and the less soluble compound (m.p. 100°) was shown to be the N,N′-alkylidenebisacylamide, $C_{11}H_{23}CH(NHCOC_{11}H_{23})_2$, corresponding to lauraldehyde and lauramide. The results differ markedly from those reported by Lieber for the reduction of lauronitrile under the same conditions.[4]

Structure proof of the diamide was based on its analysis, quantitative hydrolysis to lauraldehyde, ammonia, and lauric acid, and comparison with a sample synthesized from lauramide and lauraldehyde by a method described for several lower molecular weight N,N′-alkylidenebisacylamides.[5]

It is unlikely that the amide is an intermediate in the formation of the diamide in the Stephen reaction. The reaction of an aldehyde with an amide requires vigorous conditions, whereas in this work the diamide was obtained in one case simply by shaking the reduction mixture with cold water. An N,N′-alkylidenebisacylamide has recently been prepared at 60° by the action of formaldehyde on acrylonitrile in the presence of phosphoric acid.[6] However, we were unable to obtain a reaction between lauraldehyde and lauronitrile under these conditions. Also, lauraldehyde was absent in the initial product obtained by hydrolysis of the reduction mixture. It appears likely, therefore, that condensation occurred between the imine hydrochloride and the nitrile in the Stephen reduction. One possibility involves the ions

$$[RCH{=}NH_2]^+Cl^- \xrightarrow{R'CN}$$

$$[R'\underset{+}{C}{=}NCH(NH_2)R]\,Cl^- \xrightarrow[HCl]{R'CN}$$

$$[R'\underset{+}{C}{=}NCHRN{=}\underset{+}{C}R']\,2\,Cl^- \xrightarrow{2\,H_2O}$$

$$(R'CONH)_2CHR + 2HCl$$

The composition of the complex tin salts obtained by storing the reduction mixture at 0° is still unsettled. These compounds are not always pure aldimine salts, $(RCH{=}NH{\cdot}HCl)_2{\cdot}SnCl_4$, since in this work their careful hydrolysis produced appreciable quantities of compounds still at the oxidation level of the nitrile.

Experimental

Stannous Chloride.—One mole of Baker C.P. stannous chloride dihydrate was dehydrated by acetic anhydride according to Stephen's procedure.[7]

Aliphatic Nitriles.—Lauronitrile was prepared by passing ammonia into 250 g. of lauric acid, m.p. 42°, and 10 ml. of 85% phosphoric acid heated to 285°.[8] After six hours the crude nitrile was fractionated through a 15-plate column to give eleven fractions (89 g.) boiling at 120° at 5 mm., n^{23}_D 1.4332, m.p. 3–4°.

Palmitonitrile was obtained by careful fractionation of 1300 g. of commercial product (Armour & Co.). Nineteen fractions were collected, thirteen of which (784 g.) boiled constant at 146° at 1 mm. and melted at 29–30°.

Reduction of Palmitonitrile.—Dry hydrogen chloride was passed into a slowly stirred mixture of 42 g. (0.22 mole) of stannous chloride and 200 ml. of dry ether. The stannous chloride dissolved over a period of three hours with the formation of two liquid phases. Palmitonitrile (47.4 g., 0.20

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[1] A part of this work was taken from the Ph.D. thesis of James A. Knight, Procter and Gamble Fellow, The Pennsylvania State College, 1948–1949; present address, School of Chemistry, Georgia Institute of Technology, Atlanta, Georgia.

[2] H. Stephen, *J. Chem. Soc.*, 1874 (1925); 2786 (1930).

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[4] E. Lieber, This Journal, **71**, 2862 (1949).

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[6] C. C. Price and I. V. Krishnamurti, *ibid.*, **72**, 5334 (1950).

[7] H. Stephen, *J. Chem. Soc.*, 2786 (1930); J. W. Williams, *Org. Syntheses*, **23**, 64 (1943).

[8] A. W. Ralston, H. J. Harwood and W. O. Pool, This Journal, **59**, 986 (1937); R. W. Schiessler, A. W. Rytina and F. C. Whitmore, *ibid.*, **70**, 529 (1948).

mole) was then added over a period of 15 minutes. The mixture became homogeneous upon stirring for an additional hour. Copious precipitation of white solid occurred when the reaction mixture was stored for eight days at 0°. The precipitate was filtered and brought to constant weight (70 g.) in a vacuum desiccator. Hydrolysis was accomplished by stirring the solid for one hour on the steam-bath with 250 ml. of water. The resulting white solid and aqueous solution were shaken with 500- and 200-ml. portions of ether. Part of the white solid remained undissolved. This material was filtered from the ether layer and dried; wt. 18 g., m.p. 100–102°. Crystallization from hexane (cloudy solution) followed by extraction with hot 95% ethanol raised the melting point to 103°. The solid at this point gave a cloudy melt and a small residue upon burning. After treatment with Darco G-60 in boiling glacial acetic acid, a clear solution was obtained which deposited a white solid melting sharply at 103–103.5°. This material gave a clear melt and a negligible residue upon burning. An 80% recovery in the purification procedure was realized. Qualitative tests for halogen were negative.[9]

Anal. Calcd. for $C_{48}H_{96}N_2O_2$: N, 3.83. Found: N (Dumas), 3.94.

Removal of solvent from the ethereal layer gave 22 g. of curdy yellow solid. Most of this material distilled at 170–180° at 25 mm. The distillate, m.p. 17–27°, consisted mainly of palmitonitrile as was shown by alkaline hydrolysis to ammonia and potassium palmitate. A 3.651-g. sample was refluxed with a solution of potassium hydroxide in 20 ml. of water and 15 ml. of alcohol until ammonia was no longer evolved (12 hours). The ammonia was collected in standard acid solution. The alkaline residue was acidified with hydrochloric acid, extracted with ether, and the ether layer washed free of chloride ion. A 94% yield of palmitic acid (*p*-phenylphenacyl ester, m.p. 93–94°) and an 80% yield of ammonia were obtained based on the crude distillate.

Reduction of Lauronitrile.—The normal type of Stephen reduction was carried out exactly as described by Lieber[4] for the preparation of the stannichloride complex. From 27.1 g. (0.15 mole) of nitrile, 30 g. of white dry powder was obtained after storage for ten days in the refrigerator. The solid complex was hydrolyzed by stirring for two hours on the steam-bath with 200 ml. of water. The solid disappeared almost immediately and an oily layer was formed. Partial solidification of the oil occurred upon cooling. The mixture was extracted with an equal volume of ether to give 7 g. of white ether-insoluble solid. Concentration of the ethereal solution gave an additional 2.1 g. of white solid. Five recrystallizations of the first fraction from 95% ethanol gave material melting at 98–99°. This material was later identified as N,N′-dodecylidenebislauramide. Extraction of the mother liquors by dilute base gave 0.62 g. of lauric acid, m.p. 44° (*p*-phenylphenacyl ester, m.p. 84–85°) and 3.1 g. of neutral oil. This latter fraction was hydrolyzed by refluxing with 30 ml. of concentrated hydrochloric acid in a nitrogen atmosphere. An additional 1.33 g. of lauric acid was obtained indicating that, even in this neutral residuum where most of the aldehyde would be expected, about half of the material appeared in its initial state of oxidation.

In an attempt to obtain more of the high-melting solid, Lieber's[4] procedure for the "trimer, high-melting form" was followed. From 27 g. (0.15 mole) of nitrile and 42.8 g. (0.23 mole) of stannous chloride, 5 g. of white solid and 34 g. of filtrate were obtained. After three crystallizations of the solid from 95% ethanol, the m.p. was 100° and was not altered by two additional recrystallizations. A qualitative test for nitrogen was strongly positive and for halogen was negative.[9] The melt was slightly cloudy and the solid gave a small amount (0.24%) of ash on burning. Treatment with Darco G-60 in boiling acetic acid gave a clear solution which deposited white solid melting at 99°. This product gave a clear melt and left no residue upon burning. Successive recrystallization from acetone and ethanol raised the m.p. to 100°. Admixture with lauramide gave a m.p. depression of 7° whereas admixture with N,N′-dodecylidenebislauramide gave no depression.

Anal. Calcd. for $C_{36}H_{72}N_2O_2$: C, 76.60; H, 12.77; N, 4.96. Found: C, 76.74; H, 12.77; N (Dumas), 5.15.

The original filtrate (34 g.) gave negative fuchsin-aldehyde test both before and after heating with water. (Lauraldehyde gives an immmediate positive test.) Much additional white solid was obtained by heating this filtrate with water for two hours on the steam-bath. By repeated crystallization from ethanol, this solid was separated into a small additional amount of the diamide and a much more soluble solid, m.p. 100–101°. Admixture with an authentic sample of lauramide gave no depression of the m.p.

Anal. Calcd. for $C_{12}H_{25}ON$: C, 72.36; H, 12.56; N, 7.03. Found: C, 72.27; H, 12.57; N (Dumas), 6.82.

Degradation of the Solid Products from the Stephen Reduction. Hydrolysis to Fatty Acids.—All equipment was flushed with nitrogen and all transfers made in a nitrogen atmosphere to prevent possible oxidation of aldehyde. A 0.5018-g. sample of the solid obtained by the reduction of palmitonitrile was refluxed for 24 hours with 20 ml. of concentrated hydrochloric acid. A light yellow oil soon formed and was present throughout the hydrolysis. When cooled, this oil solidified. The mixture was extracted with 130 ml. of ether and the ether layer washed free of chloride ion. Palmitic acid was determined in the ether layer by titration with standard sodium hydroxide solution. Alcohol (70 ml.) was added from time to time to keep the titration mixture homogeneous. The titration required 11.3 ml. of 0.122 *N* base corresponding to 100% of the theoretical acid based on the diamide. The titrated solution was diluted with 100 ml. of water, extracted with two 200-ml. portions of ether, and evaporated to dryness. A *p*-phenylphenacyl ester prepared on the resulting sodium salt gave m.p. 93–94°. Admixture with the *p*-phenylphenacyl ester of palmitic acid gave no depression. Ammonia was determined in the original hydrochloric acid layer by the usual Kjeldahl procedure.

In a similar manner, a 0.2815-g. sample of the solid product from the reduction of lauronitrile (m.p. 100°) was quantitatively hydrolyzed to lauric acid, *p*-phenylphenacyl ester, m.p. and mixed m.p. 83.5–84°.

Degradation to Aldehydes.—Ten ml. of a saturated boiling ethanolic solution of the solid product (m.p. 100°) from the reduction of lauronitrile was refluxed with 8 ml. of saturated 2,4-dinitrophenylhydrazine reagent in 95% ethanol containing 3 ml. of concentrated sulfuric acid. A light yellow solid crystallized upon cooling. After two crystallizations from ethanol the m.p. was 105–106°. The m.p. was not depressed by admixture with an authentic sample of the 2,4-dinitrophenylhydrazone of lauraldehyde. Similarly, the solid (m.p. 103) obtained by the reduction of palmitonitrile formed a 2,4-dinitrophenylhydrazone which after three crystallizations from ethanol gave m.p. 104–105°, mixed m.p. with an authentic derivative prepared from palmitaldehyde, 105–106°.

Preparation of N,N′-Dodecylidenebislauramide.—Lauric acid, 200 g., m.p. 42°, was converted to lauroyl chloride by heating for five hours on the steam-bath with 130 g. of thionyl chloride. The acyl chloride was cooled to 0° and 1200 ml. of 28% ammonium hydroxide added with stirring over a period of ten hours. The crude amide was filtered and separated from ammonium laurate by treatment with 1500 ml. of ether and 500 ml. of 12% potassium hydroxide. From the ethereal layer there was obtained 61 g. of lauramide, m.p. 99–101°, after crystallization from acetone.

Lauraldehyde was obtained by passing the vapors of lauryl alcohol at 360° over 5 g. of copper–chromium oxide catalyst suspended on copper screens in a 40 × 1.5 cm. tube. The aldehyde was purified through the sodium bisulfite addition compound. The regenerated aldehyde had a b.p. of 134° at 20 mm., $n^{21}D$ 1.4350, 2,4-dinitrophenylhydrazone, m.p. 106°.[10]

The N,N′-alkylidenebisacylamide was prepared by heating 4.0 g. of lauramide and 1.84 g. of lauraldehyde at 140° for three days in a nitrogen atmosphere according to a reaction described by Noyes and Forman.[5] The acetic acid catalyst was omitted to ensure no contamination of the product by N,N′-dodecylidenebisacetamide. The product solidified on cooling and was triturated with 20 ml. of ether, filtered, and washed with three 20-ml. portions of ether. Seven crystallizations from ethanol raised the m.p. from 96 to 99°. Admixture with lauramide gave a m.p. depression of 7°.

Hydrolysis of 0.0588-g. sample as described above gave the theoretical amount of lauric acid and 96% of the theoretical quantity of ammonia based on the diamide. The

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[9] R. L. Shriner and R. C. Fuson, "Identification of Organic Compounds," 3rd ed., John Wiley and Sons, Inc., New York, N. Y., 1948, pp. 52–57.

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2,4-dinitrophenylhydrazone of lauraldehyde, m.p. 105.5°, was obtained when the hydrolysis was carried out in the presence of 2,4-dinitrophenylhydrazine reagent.

Anal. Calcd. for $C_{36}H_{72}N_2O_2$: N, 4.96. Found: N (Kjeldahl), 4.76.

Acknowledgment.—The authors are indebted to the Procter and Gamble Company for a fellowship in support of this investigation.

STATE COLLEGE, PENNSYLVANIA

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY COLLEGE, CORK NATIONAL UNIVERSITY OF IRELAND]

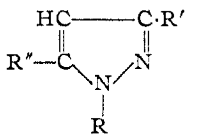
Studies in the Pyrazole Series. I. Halogenation of the 1-Guanylpyrazoles[1]

BY FRANCIS L. SCOTT AND JOSEPH REILLY

RECEIVED OCTOBER 29, 1951

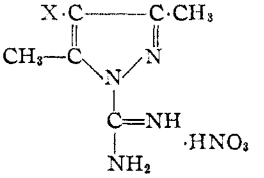
The halogenation of the 1-guanylpyrazoles and their N-substituted derivatives has been studied. With 3,5-dimethyl-1-guanylpyrazole salts and its acyl derivatives chlorine and bromine combine rapidly and reaction ceases normally at the substitution stage. Iodine is slower to react, and, under the more drastic conditions required, the process goes a step further, with a simultaneous rupture of the 1-substituent. This is lost by hydrolytic fission of the 1-imino group. With the N-naphthylcarbamyl- and N-phenylthiocarbamylguanylpyrazoles chlorine and bromine substitute initially and this is invariably accompanied by either hydrolysis or oxidation of the carbamylguanyl systems. The slower reaction of iodine has revealed the initial stages of the more complex halogenations. With the substituted naphthylcarbamylguanylpyrazole, for example, urethans result and with the thiocarbamyl, a disulfide—the heterocyclic moiety cleaving as dialkyl-4-iodopyrazole. Unambiguous synthesis of the 4-halo-1-naphthylcarbamyl- and -1-phenylthiocarbamylguanylpyrazoles confirmed that these compounds were formed initially in the halogenation of the respective carbamylguanylpyrazoles.

Variation in lability of the 1-substituent may be used as a criterion for the division of N-substituted pyrazoles into two classes, *e.g.*, while 1-alkyl (or aryl) substituted pyrazoles (I, type A) normally react[2-4] without loss of the N-substituent, pyrazoles of the 1-carbamyl[5] or 1-phenylcarbamyl[6] type (I, type B) are less stable and readily revert to the free imino compounds.



R = alkyl/aryl, type A;
(= $-CONH_2$/$-CONHC_6H_5$, type B)

I



II

This lability depends upon the reagents used and on the reaction conditions. In this present investigation we have taken a typical reaction—halogenation—as a basis for comparison and have applied it to the 1-guanylpyrazole type.

3,5-Dimethyl-1-guanylpyrazole nitrate (A, II, X = H) taken as typical of its class, has shown the 1-guanylpyrazoles to be intermediary between the 1-carbamyl and the 1-aryl types.

With chlorine and bromine (A) gives the 4-chloro- and 4-bromo-substituted derivatives (II, X = Cl, Br); with iodine and sodium acetate, deguanylation as well as substitution occurs; with stronger iodinating agents, substitution only.

Deguanylation also occurred when (A) was refluxed with sodium acetate alone in aqueous ethanolic solution—with 20–30% conversion to 3,5-dimethylpyrazole. This was a prototype of the general basic catalyzed decomposition of this type of pyrazole, taking place by one of the following schemes (next page).

Reaction by mode A results in the formation of 3,5-dimethylpyrazole (III) and urea; mode B, however, involves the intermediary formation of 3,5-dimethyl-1-carbamylpyrazole (IV), followed by its subsequent hydrolytic rupture to (III) with simultaneous evolution of carbon dioxide and ammonia.

From analogy with the hydrolytic decomposition of guanidine,[7] mode B would be the expected reaction mechanism. It was found, however, that this decomposition of the guanylpyrazole (A) occurred by the mode A formulation. This was shown by (i) the detection of urea (characterized as its dixanthyl derivative), (ii) by the absence of ammonia and carbon dioxide, in the acetate hydrolysis, and (iii) by the detection of these latter gases in the hydrolysis of the carbamylpyrazole (IV) under identical conditions.

This formulation is comparable to the mechanism of the ammonolytic and hydrazinolytic decomposition of the 1-nitroguanyl- and guanylpyrazoles, reported from this Laboratory.[8]

Deguanylation of (A) by iodine alone was also observed. A 15% conversion to 3,5-dimethyl-4-iodopyrazole took place when equimolar quantities of (A) and iodine were refluxed for eight hours in ethanolic solution. This effect is probably an acid-catalyzed hydrolysis of the guanyl group—the hydriodic acid necessary resulting from an initial iodination. This susceptibility of the guanylpyrazoles to acid hydrolysis was confirmed independently.

To define the extent of the deguanylating effect, and in order to determine its mechanism, the halogenation of substituted guanylpyrazoles of the general type (V) was undertaken.

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(1) Presented in part at the XII International Conclave of Chemistry, New York, 1951, Section 12.

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(3) L. Knorr and A. Blank, *Ber.*, **18**, 311 (1885).

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