TABLE I

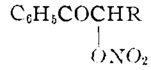
CONVERSION OF KETONES TO α-DIKETONES

Ketone	Yield,[a] % of nitratoketone	Yield,[a] % of diketone
Acetophenone	68	35
Propiophenone	80	71
Butyrophenone	93	79
n-Valerophenone	82	67
Isovalerophenone	84	65

[a] Based on α-bromoketone.

TABLE II

PROPERTIES OF α-NITRATOKETONES,



$$C_6H_5\underset{ONO_2}{\underset{|}{C}}HR$$

R	B.p., °C.	B.p., Mm.	$n^{25}D$	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
H[a]	M.p. 4–5°								
CH_3	101–103	0.4	M.p. 27–29°	55.38	55.59	4.65	4.54	7.18	7.21
C_2H_5	105–106	.2	1.5260	57.41	57.39	5.30	4.80	6.70	6.60
n-C_3H_7	108–110	.4	1.5206	59.18	59 36	5.87	5.04	6.28	6.09
i-C_3H_7	105–106	.25	1.5214	59.18	59.82	5.87	5.39	6.28	6.14

[a] This compound evolved nitrogen oxides on standing and could not be distilled or recrystallized.

There is one previous report of the conversion of α-bromoketones to α-diketones by means of silver nitrate but this reaction certainly involved a different course. When *m*-nitrophenacyl bromide was treated with aqueous silver nitrate, *m*-nitrophenylglyoxal was obtained.[5] It was postulated that hydrolysis to the keto alcohol followed by oxidation of the alcohol with silver oxide had occurred.

Efforts to extend this method to the synthesis of cyclic diketones failed in the attempted preparation of the nitratoketone. 2-Chloro- and 2-bromocyclohexanone and 2-chlorocyclopentanone reacted very sluggishly with silver nitrate and poorly characterized products were obtained. 3-Bromocamphor was completely inert to silver nitrate in acetonitrile. Attempts also were made to synthesize pyruvic esters by the action of bases on α-nitratoesters. While the nitratoesters could be prepared quite easily and appeared to react readily with a variety of bases (as evidenced by the production of nitrite ion), none of the desired α-ketoesters could be isolated. Usually only gummy materials which were resistant to distillation were obtained. Apparently the alkaline conditions employed in their synthesis caused these sensitive compounds to undergo complex self-condensations.

Experimental[6]

α-Bromoketones.—Phenacyl bromide, α-bromopropiophenone and α-bromobutyrophenone were purchased from Sapon Laboratories and used without further purification.

α-Bromovalerophenone.—This bromoketone was prepared by the addition of 35.0 g. (0.21 mole) of bromine to 32.4 g. (0.2 mole) of *n*-valerophenone dissolved in 100 ml. of glacial acetic acid. The product was isolated in the conventional manner. It was obtained as a colorless liquid, b.p. 94–96° (0.25 mm.), yield 43.3 g. (90%).

Anal. Calcd. for $C_{11}H_{13}BrO$: C, 54.79; H, 5.43. Found: C, 54.28; H, 5.51.

α-Bromoisovalerophenone.—This bromoketone was prepared in 87% yield by the method described above. It was obtained as a solid, m.p. 35–39° (lit. m.p. 46°[7]), and was not purified further.

α-Nitratoketones.—These compounds were all prepared by the action of silver nitrate on the corresponding α-bromoketone in acetonitrile solvent according to the procedure recently described.[4] Their physical constants and analyses are summarized in Table II.

Phenyl Ethyl Diketone.—A solution of 10.4 g. (0.05 mole) of α-nitratobutyrophenone in 50 ml. of ether was cooled to 0–10° and 4.3 g. (0.05 mole) of piperidine was added from a dropping funnel with stirring at such a rate that the temperature did not rise above 20°. During the addition a solid separated from solution. After the addition was complete the mixture was stirred at room temperature for 30 minutes and then poured into water. The layers were separated and the water layer was extracted with ether. The combined organic extracts were washed with 10% hydrochloric acid and water and dried over magnesium sulfate. Upon evaporation of the ether and distillation of the residue there was obtained 7.0 g. (86%) of phenyl ethyl diketone, b.p. 74–76° (0.5 mm.), $n^{19}D$ 1.5239. It formed a dioxime, m.p. 201–203° (lit. m.p. 205°[8]).

Phenyl Methyl Diketone.—Following the general method 15.2 g. (0.078 mole) of α-nitratopropiophenone was converted to 9.3 g. (88%) of the diketone, b.p. 55–56° (0.3 mm.). It formed a dioxime, m.p. 237–240° (lit. m.p. 239–240°[8]).

Phenyl Propyl Diketone.—Following the general procedure from 8.9 g. (0.04 mole) of α-nitratovalerophenone there was obtained 6.3 g. (81%) of the diketone, b.p. 82–84° (3 mm.), $n^{18.5}D$ 1.5215 (lit. $n^{18.5}D$ 1.5215[9]).

Phenyl Isopropyl Diketone.—Similarly, 12.3 g. (0.055 mole) of α-nitratoisovalerophenone was converted to 7.8 g. (77%) of phenyl isopropyl diketone, b.p. 58–60° (0.1 mm.), $n^{20}D$ 1.5158.

Anal. Calcd. for $C_{11}H_{12}O_2$: C, 74.97; H, 6.04. Found: C, 74.94; H, 6.20.

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(5) W. L. Evans and E. J. Witzeman, THIS JOURNAL, **33**, 1772 (1911).

(6) We are indebted to Miss Annie Smelley for the micro-combustion data.

(7) F. Kunckell and K. Stahel, *Ber.*, **37**, 1088 (1904).

(8) A. Collet, *Bull. soc. chim. France*, **17**, 77 (1897).

(9) J. Wieman and G. Laude, *Compt. rend.*, **226**, 345 (1948).

The Oxidation of Sodium Diphenylcyanomethide with Nitrate Esters[1]

BY WILLIAM D. EMMONS AND JEREMIAH P. FREEMAN

RECEIVED MARCH 21, 1955

The reaction of active methylene compounds with acetone cyanohydrin nitrate to produce the corresponding nitro compounds recently has been described.[2] In connection with this work the reaction between acetone cyanohydrin nitrate and sodium diphenylcyanomethide (I) was investigated. Since this reaction took a completely different course from that described for the other active methylene compounds, it is being reported separately.

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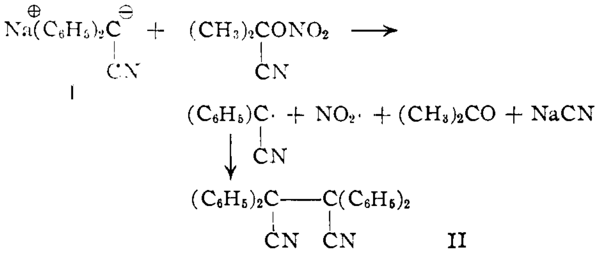
(1) This research was carried out under Army Ordnance Contract W-01-021-ORD-334.

(2) W. D. Emmons and J. P. Freeman, THIS JOURNAL, **77**, 4387 (1955).

The product in this case was tetraphenylsuccinonitrile (II). None of the desired nitro derivative was obtained. An examination of the water-soluble products from this reaction revealed the presence of both cyanide and nitrite ions in nearly equal amounts. It is believed that this reaction involves a one-electron transfer between acetone cyanohydrin nitrate and the diphenylacetonitrile anion followed by dimerization of the diphenylcyanomethyl radical. The nitrite ion presumably



$$\overset{\oplus}{Na}(C_6H_5)_2\overset{\ominus}{\underset{CN}{C}} + (CH_3)_2\underset{CN}{C}ONO_2 \longrightarrow$$

I

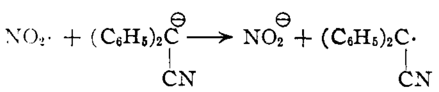
$$(C_6H_5)\underset{CN}{C}\cdot + NO_2\cdot + (CH_3)_2CO + NaCN$$

$$\downarrow$$

$$(C_6H_5)_2\underset{CN}{C}-\underset{CN}{C}(C_6H_5)_2$$

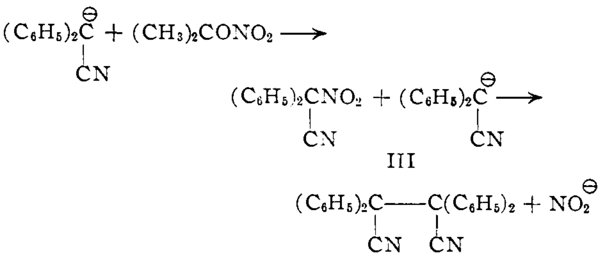
II

arises through another one-electron transfer reaction, the interaction of nitrogen dioxide with the diphenylacetonitrile anion. This proposed mechanism predicts the formation of equivalent amounts of nitrite and cyanide ion as observed. Although



$$NO_2\cdot + (C_6H_5)_2\overset{\ominus}{\underset{CN}{C}} \longrightarrow \overset{\ominus}{NO_2} + (C_6H_5)_2\underset{CN}{C}\cdot$$

little is known about the transition state of oxidation-reduction reactions, it is interesting to speculate that the driving force for this process may be similar to that of the ionic reactions[2] of acetone cyanohydrin nitrate, *i.e.*, the concerted formation of the carbon-oxygen double bond as the electron transfer to the nitro group occurs. A second possible reaction path involves the intermediate formation of diphenylnitroacetonitrile (III) by the usual nitration followed by displacement of nitrite ion by a second diphenylacetonitrile anion. To test



$$(C_6H_5)_2\overset{\ominus}{\underset{CN}{C}} + (CH_3)_2CONO_2 \longrightarrow$$

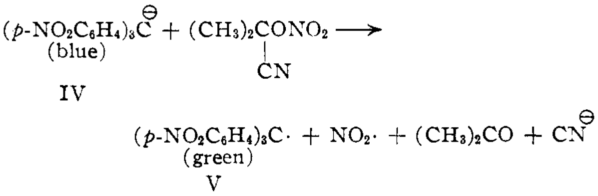
$$(C_6H_5)_2\underset{CN}{C}NO_2 + (C_6H_5)_2\overset{\ominus}{\underset{CN}{C}} \longrightarrow$$

III

$$(C_6H_5)_2\underset{CN}{C}-\underset{CN}{C}(C_6H_5)_2 + \overset{\ominus}{NO_2}$$

this possibility, the reaction between diphenylacetonitrile anion and diphenylnitroacetonitrile[3] was examined; tetraphenylsuccinonitrile was obtained in 95% yield. This result, however, may be ambiguous since it is possible for a one-electron process to occur between these reactants also.

There is, however, additional independent evidence which supports the free radical mechanism. It is known that the diphenylacetonitrile anion is oxidized by iodine to the free radical[4]; high yields of the dimer can be obtained from this reaction. Also a similar coupling reaction, the conversion of the nitrofluorene anion to 1,2-dinitrobidiphenyleneethane by means of iodine,[5] has been shown to occur by intermediate formation of radicals, and the dimer is not obtained by the displacement of iodine from preformed 9-iodo-9-nitrofluorene. That acetone cyanohydrin nitrate can undergo a one-electron transfer has been established by treating it with sodium tri-(*p*-nitrophenyl)-methide (IV) and observing the production of the tri-(*p*-nitrophenyl)-methyl radical (V). This visual observation may be made readily as the anion possesses a deep blue color while the radical is green and partially separates from solution. The facile oxidation of this anion to the radical recently has been reported.[6]



$$\underset{\text{(blue)}}{(p\text{-}NO_2C_6H_4)_3\overset{\ominus}{C}} + (CH_3)_2\underset{CN}{C}ONO_2 \longrightarrow$$

IV

$$\underset{\text{(green)}}{(p\text{-}NO_2C_6H_4)_3C\cdot} + NO_2\cdot + (CH_3)_2CO + \overset{\ominus}{CN}$$

V

The oxidation of sodium diphenylcyanomethide also may be accomplished by the use of ethyl nitrate. In this case the reaction is much slower, but a comparable yield of the dimer results. Apparently nitrite esters are also effective agents for this oxidation as it has been reported that diphenylacetonitrile is converted to tetraphenylsuccinonitrile when treated with isopropyl nitrite and sodium ethoxide.[7]

Experimental

Reaction of Diphenylacetonitrile with Acetone Cyanohydrin Nitrate.—The sodio derivative of diphenylacetonitrile was prepared from 19.3 g. (0.1 mole) of the nitrile and 2.5 g. (0.11 mole) of sodium hydride in 150 ml. of tetrahydrofuran.[8] (The entire operation was carried out under a current of nitrogen to prevent any possible air oxidation of the radicals. It has been found, however, that air has no effect on the reaction course.) A solution of 19.5 g. (0.15 mole) of acetone cyanohydrin nitrate[9] in 75 ml. of tetrahydrofuran was added and the mixture was stirred at room temperature for four hours. It then was poured into cold distilled water and the white solid that separated was collected on a filter; m.p. 193-197°, yield 11.7 g. (61%). Upon recrystallization from acetic acid, a sample melted at 205-207°. Tetraphenylsuccinonitrile is reported to melt at 205°.[10] A mixed melting point with an authentic sample[3] was not depressed.

The filtrate was washed with ether. Concentration of these washings yielded more of the succinonitrile derivative, but it was contaminated with acetone cyanohydrin nitrate and was discarded. The aqueous solution was titrated for cyanide and nitrite ions[11] and there was found to be 0.048 mole of cyanide ion and 0.060 mole of nitrite ion.

Reaction of Sodium Diphenylcyanomethide with Diphenylnitroacetonitrile.—The sodium diphenylcyanomethide was prepared from 1.9 g. (0.01 mole) of diphenylacetonitrile and 0.25 g. (0.011 mole) of sodium hydride in 20 ml. of tetrahydrofuran. To this solution was added 2.3 g. (0.01 mole) of diphenylnitroacetonitrile[3,12] in 10 ml. of tetra-

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(3) A sample of this material was generously furnished by Mr. Henry A. Rolewicz.

(4) K. Auwers and V. Meyer, *Ber.*, **22**, 1227 (1889).

(5) C. D. Nenitzescu and D. A. Isacescu, *ibid.*, **63**, 2484 (1930).

(6) M. F. Hawthorne and G. S. Hammond, THIS JOURNAL, **77**, 2549 (1955).

(7) K. Neure, *Ann.*, **250**, 140 (1889).

(8) The tetrahydrofuran employed was obtained from Matheson, Coleman and Bell, Inc. Before use it was treated with solid potassium hydroxide to remove the stabilizer. The absence of peroxides was indicated by its negative test with starch iodide paper.

(9) W. D. Emmons and J. P. Freeman, THIS JOURNAL, **77**, 4387 (1955).

(10) I. A. Smith, *Ber.*, **71B**, 634 (1938).

(11) We are indebted to Mr. Karl Bosserman for these titrations.

(12) G. Wittig and U. Pockels, *Ber.*, **69B**, 790 (1936).

hydrofuran. The mixture was stirred for an hour and poured into water. The tetraphenylsuccinonitrile that separated was collected; yield 3.6 g. (95%).

Reaction of Sodium Diphenylcyanomethide with Ethyl Nitrate.—The same method described above for acetone cyanohydrin nitrate was followed. From 19.3 g. (0.1 mole) of diphenylacetonitrile, 2.5 g. (0.11 mole) of sodium hydride and 13.7 g. (0.15 mole) of ethyl nitrate there was obtained 15.4 g. (80%) of crude tetraphenylsuccinonitrile.

Reaction of Sodium Tri-(*p*-nitrophenyl)-methide with Acetone Cyanohydrin Nitrate.—Sodium tri-(*p*-nitrophenyl)-methide was prepared under nitrogen by dissolving 3.8 g. (0.01 mole) of tri-(*p*-nitrophenyl)-methane[6] in 25 ml. of absolute alcohol containing 0.23 g. (0.01 g. atom) of sodium. A deep blue solution resulted. Acetone cyanohydrin nitrate (1.3 g., 0.01 mole) was added. After stirring for several hours at room temperature a small amount of dark green material began to separate from solution. Stirring was continued for 12 hours. At the end of this period the whole solution had taken on a dark green color. Upon admission of air, the green color gradually disappeared.

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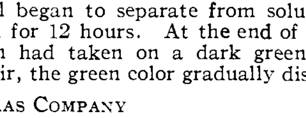
Vitamin B_{12}. XXV. 3,3-Dimethyl-2,5-dioxopyrrolidine-4-propionamide: A New Degradation Product

BY FREDERICK A. KUEHL, JR., CLIFFORD H. SHUNK, MARJORIE MOORE AND KARL FOLKERS

RECEIVED MAY 12, 1955

Vitamin B_{12} was degraded by stepwise acid hydrolysis and chromate oxidation to 3,3-dimethyl-2,5-dioxopyrrolidine-4-propionic acid (I).[1] Since this acid was not obtained as an oxidation product of unhydrolyzed vitamin B_{12}, it was suggested[1] that the free carboxyl group of the acid I is present as an amide in the vitamin B_{12} molecule. We now have evidence that the amide interpretation is correct since 3,3-dimethyl-2,5-dioxopyrrolidine-4-propionamide (II) has been obtained as an oxidation product of unhydrolyzed vitamin B_{12}.



I, R = OH; II, R = NH_2

Vitamin B_{12} was subjected to oxidation by sodium chromate in acetic acid. The crude product was divided into neutral and acidic chloroform-soluble fractions. The neutral material was subjected to countercurrent distribution between water and ether. The fraction more soluble in the aqueous phase yielded an optically active neutral compound, m.p. 150–151°. Infrared analysis showed absorption at 2.92, 3.12, 3.70, 6.0 and 6.2 μ, compatible with an imide-amide structure. This substance, when hydrolyzed with acid, was converted to 2-methylpentane-2,3,5-tricarboxylic acid.[1,2]

A sample of synthetic DL-3,3-dimethyl-2,5-dioxopyrrolidine-4-propionic acid was converted to the acid chloride by treatment with thionyl chloride. The crude acid chloride was treated with aqueous ammonia to yield DL-3,3-dimethyl-2,5-dioxopyrrolidine-4-propionamide, m.p. 151–152°. The melting point of a mixture of this synthetic DL-amide and the optically active degradation product was not depressed. This melting point behavior indicates that the synthetic amide is a racemic solid solution. The infrared absorption spectrum of the synthetic amide is the same as that of the amide obtained by degradation, a result of greater significance than the melting point behavior.

As indicated previously, the oxidation of acid hydrolyzed vitamin B_{12} yields DL-3,3-dimethyl-2,5-dioxopyrrolidine-4-propionic acid.[1] However, none of this acid was isolated when unhydrolyzed vitamin B_{12} was similarly oxidized, only the corresponding amide was obtained. From these data, it is concluded that the amide group of II exists in the vitamin B_{12} molecule. The carboxyl group of I corresponds to the amide group of II with the potential formation of ammonia in all vitamin B_{12} degradation products containing the skeletal moiety of amide II. Furthermore, the carboxyl group of I is not formed during the oxidative degradation.

Experimental

Isolation of 3,3-Dimethyl-2,5-dioxopyrrolidine-4-propionamide.—A solution of 5 g. of vitamin B_{12} and 17.4 g. of sodium chromate in 300 ml. of glacial acetic acid, after standing for three hours at room temperature, was heated on the steam-bath overnight. The acetic acid was then removed *in vacuo* and an aqueous solution of the residue. acidified to pH 2 with hydrochloric acid, was extracted continuously with chloroform for sixteen hours. The residue obtained, after removal of the chloroform, was redissolved in water, adjusted to *p*H 7, and again extracted continuously with chloroform. The solvent soluble material, freed of acidic impurities, was separated from traces of 5,6-dimethylbenzimidazole by redissolving it in water and continuously extracting this aqueous solution with chloroform at *p*H 2.

The chloroform soluble fraction, 165 mg., consisting of neutral and weakly acidic products, was subjected to a 39 transfer countercurrent distribution. The system ether-water was used in the proportion of 10 ml. of water and 15 ml. of ether in each tube. The combined residues from tubes 16 to 23, when recrystallized from a mixture of chloroform, ether and petroleum-ether yielded 12 mg. of 3,3-dimethyl-2,5-dioxo-4-hydroxypyrrolidine-4-propionic acid lactone.[1] The residue of tubes 0 and 1 yielded, when dissolved in acetone–ether, 25.6 mg. of crystalline 3,3-dimethyl-2,5-dioxopyrrolidine-4-propionamide. After sublimation *in vacuo* and recrystallization from acetone to constant melting point, the amide melted at 150.5–151°, $[\alpha]^{25}\text{D}$ −10° (*c*, 2.8 in water).

Anal. Calcd. for $C_9H_{14}N_2O_3$: C, 54.54; H, 7.12; N, 14.14. Found: C, 54.16; H, 6.50; N, 13.62.

A second preparation of 3,3-dimethyl-2,5-dioxopyrrolidine-4-propionamide in which particular care was taken to prevent racemization by avoiding elevated temperatures, the product was recrystallized to constant rotation, $[\alpha]^{25}\text{D}$ −42° (*c*, 0.85 in water). This material, m.p. 150.5–151°, as in the case of the first preparation, did not depress the melting point of the synthetic amide. Furthermore the compounds were shown to be identical by a comparison of their infrared absorption spectra in the solid state.

Hydrolysis of 3,3-Dimethyl-2,5-dioxopyrrolidine-4-propionamide.—A solution of 3.5 mg. of the amide, in 20 ml. of 6 *N* hydrochloric acid, was refluxed for 20 hours. The acid was removed *in vacuo* to yield a dry residue which was separated from the ammonium chloride by trituration with acetone. The acetone-soluble material, when recrystallized from ether, yielded 2.2 mg. of an acid, m.p. 151–152°. This acid, upon admixture with 2-methylpentane-2,3,5-tricarboxylic acid,[2] m.p. 152–153°, melted at 151–152°.

Synthesis of 3,3-Dimethyl-2,5-dioxopyrrolidine-4-propionamide.—3,3-Dimethyl-2,5-dioxopyrrolidine-4-propionic acid[1] (30 mg.) was suspended in thionyl chloride (1 ml.) and the mixture was heated on a steam-bath for 5 minutes. The resulting solution was evaporated to dryness under reduced

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(1) F. A. Kuehl, Jr., C. H. Shunk and K. Folkers, THIS JOURNAL, **77**, 251 (1955).

(2) Perkin and Thorpe, *J. Chem. Soc.*, **85**, 128 (1904).