compounds have in fact been shown by chemical methods to be identical.[5] Absorption curves obtained subsequently on synthetic 4-methyl-5-β-hydroxyethylthiazole and its methiodide show equally close correspondence to the curves of the basic cleavage product and its methiodide, respectively, but are omitted from Figs. 1 and 2 for

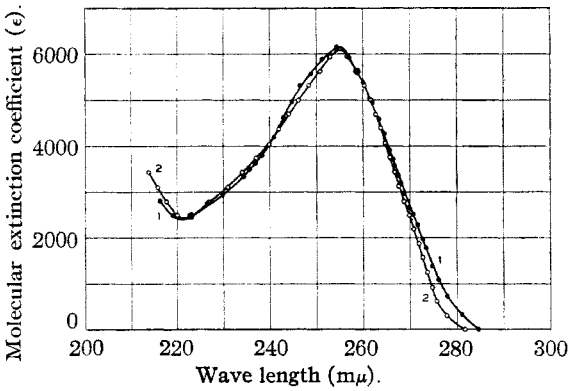

Fig. 3.—1, ●———● Oxidation product of basic cleavage product; 2, ○———○ 4-methylthiazole, 5-carboxylic acid.

purposes of clarity. A case in which substitution produced little change in absorption is shown in Fig. 4, where the curves of the basic cleavage product and its chloro derivative (V)[7] are compared. The replacement of the β-hydroxyl group by chlorine apparently does not involve the portion of the molecule associated with the observed absorption.

I wish to thank Dr. R. R. Williams for suggesting this problem to me and for helpful criticism and advice. I am indebted to Drs. H. T. Clarke, E. R. Buchman and S. Gurin for generously supplying me with the samples used, and especially to Dr. Clarke for the use of the spectrographic facilities in his laboratory. I am further indebted to the Carnegie Corporation of New York through the Carnegie Institution of Washington for financial support in the purchase of materials necessary in the work.

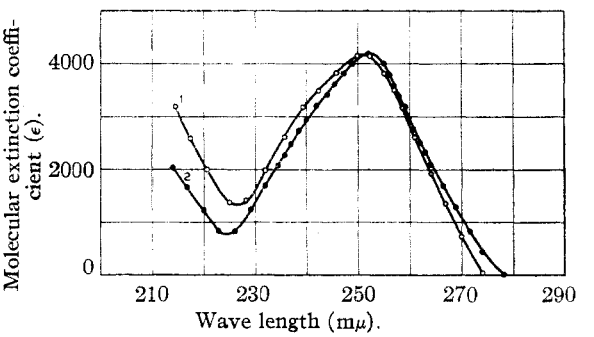

Fig. 4.—1, ○———○ Basic cleavage product hydrochloride; 2, ●———● chloro derivative of basic cleavage product hydrochloride.

Summary

The ultraviolet absorption of the basic cleavage product of vitamin B_1 is not only similar to that of the thiazoles but its derivatives exhibit absorption similar to that of corresponding thiazole derivatives.

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[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

Nitroso Compounds. IV. Reaction of Ethyl Nitrite with Certain Isopropyl and Cyclohexyl Ketones

BY JOHN G. ASTON AND M. GLENN MAYBERRY

In the present paper further[1] experiments with a variety of ketones and catalysts are described. It was found that when ethyl nitrite reacts with certain isopropyl or cyclohexyl ketones in the presence of concentrated aqueous hydrogen chloride as catalyst, substitution usually occurs both on the branched alpha carbon atom to yield the true nitroso compound and on the primary alkyl group to yield the α isonitroso compound.

(1) See Aston, Menard and Mayberry, THIS JOURNAL, **54**, 1530 (1932).

$$2(CH_3)_2CHCOCH_2R + 2HNO_2 \longrightarrow 2H_2O + (CH_3)_2C(NO)COCH_2R$$

$$(CH_3)_2CHCOCH_2R + HNO_2 \longrightarrow H_2O + (CH_3)_2CHCOC(NOH)R$$

However, better yields of both products are obtained if acetyl chloride or dry hydrogen chloride is used as catalyst.[2]

The numerical results appear in Tables I, II and III.

(2) In nitrosating menthone to the bisnitroso compound acetyl chloride gave better yields than aqueous hydrochloric acid. (a) Baeyer and Manasse, *Ber.*, **27**, 1912 (1894); (b) Baeyer, *ibid.*, **28**, 1586 (1895).

TABLE I

KETONES WITH ETHYL NITRITE IN THE PRESENCE OF AQ. HCl

Ketone	% EtONO absorbed	% NO	M. p.,°C.	% NOH	M. p., °C.	M. p. of dioxime, °C.	% Ketone recovered
i-Pr *i*-bu	..	4.3	85.9–86.7	7.3	liquid	162–163	10
Me cyclohexyl	..	12.9	114.5–115	0.0	.....	.....	39.6
Et cyclohexyl	83.3	3.8	119.5–120	14.7	78–78.2	.....	49.4

TABLE II

KETONES WITH ETHYL NITRITE IN THE PRESENCE OF ACETYL CHLORIDE

Ketone	% EtONO absorbed	% NO	M. p., °C.	% NOH	M. p., °C.	M. p. of dioxime, °C.	% Ketone recovered
Me *i*-Pr	70	43.2	99–99.5	0.0	.....	.....	35.7
Et *i*-Pr	53.3	49	122–123	34.2	92–93	.....	27.1
Pr *i*-Pr	77.5	0.0	.....	35.4	liquid	148.5–149	69
n-Bu *i*-Pr	43.7	.0	.....	45.8	liquid	140–140.3	50
i-Bu *i*-Pr	71.4	50.1	89.2–90.	8.4	liquid	162–163	40.8
Me cyclohexyl	48.0	17.0	114.5–115	0.0	.....	.....	50
Et cyclohexyl	39.0	3.0	119.5–120	25.6	78–78.2	.....	52.2

TABLE III

KETONES WITH ETHYL NITRITE IN THE PRESENCE OF HYDROGEN CHLORIDE GAS

Ketone	% EtONO absorbed	% NO	M. p., °C.	% NOH	M. p., °C.	M. p. of dioxime, °C.	% Ketone recovered
Me *i*-Pr	61.8	38.8	99–99.5	0.0	.....	.....	29.7
Et *i*-Pr	62.4	30.3	122–123	53.2	92–93	.....	23.3
Pr *i*-Pr	69.7	0.0	.....	46.5	liquid	148–149	60.3
n-Bu *i*-Pr	73.7	.0	.....	28.7	liquid	140–140.3	36
i-Bu *i*-Pr	51.3	51.7	89.2–90	19.0	liquid	162–163	45.1
Me cyclohexyl	60.9	43.5	114.5–115	0.0	.....	.....	56.2
Et cyclohexyl	63.6	3.7	119.5–120	38.5	78–78.2	.....	31

The results using dry hydrogen chloride and acetyl chloride should be considered together as in the absence of any information concerning the mechanism[3] there is, *a priori*, nothing to distinguish between them. The somewhat surprising fact already discussed[1] is that with ethyl isopropyl ketone substitution occurs to an approximately equal extent on either alkyl group.

Another significant fact is that in the case of propyl isopropyl and *n*-butyl isopropyl ketones, no substitution occurred on the isopropyl group. However, only about 40% of the ketone yielded the isonitroso compound with the fate of the rest still in doubt. As it does not seem likely that there would be any difficulty in isolating the true nitroso compound, if formed, either due to increased solubility or rapid decomposition, we are tempted to believe that in these cases substitution only involved the primary alkyl group. The fact that the isonitroso compound was liquid necessitated conversion into its oxime with consequent loss, so that our inability to account for the rest of the ketone may be due to this cause.

With isobutyl isopropyl ketone the results are practically the same as with ethyl isopropyl ketone if one considers that the lower yield of isonitroso ketone is due to the fact that the isonitroso compound was isolated by converting it into its oxime. It is difficult to reconcile this fact with the immediately previous one. Speculating one might attribute the non-activity of the alpha hydrogen on the isopropyl group of *n*-propyl and *n*-butyl isopropyl ketones to (a) steric hindrance by the far end of the other alkyl group through incipient ring formation, or (b) to a higher relative activity (rate) of the alpha carbon on the *n*-propyl and *n*-butyl groups, inasmuch as Ponzio found that branching reduced the tendency for (rate of) substitution on the alpha carbon atom of a ketone by nitrous acid.[4]

Experimental

The Results with Aqueous Hydrogen Chloride.—These have been given in Table I. The procedure followed was in general the same as already given[1] with the following exceptions. The isopropyl α-isonitrosoisobutyl ketone is a liquid[5] and was isolated as the dioxime. The unreacted ketone and low boiling material was distilled off under reduced pressure, and the remaining liquid converted into diisopropyl glyoxime as described later. The isonitroso-ethyl cyclohexyl ketone, which did not crystallize by simple evaporation of the reaction mixture, was isolated by

(3) Rate studies are precluded because of practical restrictions obvious from the experimental details of this paper.

(4) Ponzio, *J. prakt. Chem.*, [2] **58**, 394 (1898).

(5) Locquin, *Bull. soc. chim.*, [3] **31**, 1166 (1904).

the method described below for isolating isonitrosoethyl isopropyl ketone from the reaction using acetyl chloride as catalyst.

The Results Using Acetyl Chloride.—The procedure followed is given below for ethyl isopropyl ketone. The yields, given in Table II, are based on the amount of ethyl nitrite absorbed except in cases where the amount of ketone reacted (unrecovered) was less than the amount of ethyl nitrite absorbed. Then the yield is based on the unrecovered ketone. The isonitroso compounds of propyl isopropyl and butyl isopropyl ketones, being liquids, were converted into the corresponding dioximes which were then isolated and identified as described under "Diisopropyl Glyoxime."

Products from Ethyl Isopropyl Ketone Using Acetyl Chloride as Catalyst.—To 45 g. (0.45 mole) of ethyl isopropyl ketone was added 5 g. of acetyl chloride. The theoretical amount of dry gaseous ethyl nitrite was passed in over a period of two and one-half hours, keeping the temperature between 45–55°. During the process, the reaction mixture turned green; 18 g. (0.24 mole) of ethyl nitrite was absorbed during the reaction. The reaction mixture deposited 15.2 g. (0.117 mole) of almost pure bimolecular ethyl α-nitrosoisopropyl ketone on standing overnight in the icebox.

The α-isonitrosoethyl isopropyl ketone was isolated from the mother liquor; 31.7 g. of the liquid was cooled in ice, shaken with 40 cc. of 10% solution of sodium hydroxide and 9 g. of a non-aqueous upper layer removed. The aqueous layer, after extraction with ether, was cooled in ice and acidified with dilute sulfuric acid. Precipitation of the isonitroso ketone was complete when the solution was neutral; 5.7 g. (0.0044 mole) was thus obtained nearly pure after washing with water.

The ether extract of the basic solution was then evaporated. The liquid remaining was combined with the liquid insoluble in sodium hydroxide solution and distilled; 7.3 g. (0.073 mole) of ketone, identified by refractive index and by isolation of its semicarbazone, was recovered.

The Results, Using Dry Hydrogen Chloride.—The yields in Table III were calculated on the same basis as in Table II. The isonitroso compounds were isolated as described above.

Products from Isopropyl Isobutyl Ketone Using Dry Hydrogen Chloride as Catalyst.—The theoretical quantity of dry gaseous ethyl nitrite was passed through a solution of 0.6 g. of dry hydrogen chloride in 32.5 g. of ketone over a period of one hour, starting at a temperature of 18°. After about ten minutes the liquid which had turned blue was heated to 45° and thus maintained for the remainder of the reaction; 9.6 g. (0.128 mole) of ethyl nitrite was absorbed. The reaction mixture after standing for two days in the icebox deposited 8.7 g. (0.055 mole) of white crystals of bimolecular α-nitrosoisopropyl isobutyl ketone which was almost pure after washing with ether.

Diisopropyl Glyoxime.—After filtering off the above solid, 15.7 g. of mother liquor was cooled in ice and shaken with 40 cc. of a 10% aqueous solution of sodium hydroxide; 9.5 g. of liquid did not dissolve. The aqueous layer, after separation and extraction with ether, was cooled in ice and made slightly acid with dilute sulfuric acid. The acid solution was extracted with ether, and the ether solution evaporated; 3.5 g. of liquid remained.

This liquid, containing the isonitrosoisobutyl isopropyl ketone was cooled in ice and shaken with a solution containing 4.7 g. of sodium hydroxide in 27.8 cc. of water. To this solution, with continued cooling, was added 2.7 g. of hydroxylamine hydrochloride dissolved in 11.7 cc. of water. The solution was then warmed to 40–50° for ten minutes and kept at room temperature for two days. After cooling in ice 1.8 g. (0.01 mole) of dioxime was precipitated by acidification with sulfuric acid. After recrystallization from chloroform it melted at 162–163°.[6]

The ether extract of the basic solution was evaporated and the remaining liquid combined with the material insoluble in the sodium hydroxide solution. When this was distilled, 6.7 g. of ketone identified by refractive index and by isolation of its semicarbazone was obtained.

Analyses and Molecular Weights.—The results of the necessary analyses on new compounds are given in Table IV and those of the molecular weight determinations in Table V.

TABLE IV

ANALYSES

Compound	Source	Calcd. C, %	Calcd. H, %	Found C, %	Found H, %
Methyl nitrosocyclohexyl ketone	A	61.89	8.44	61.67	8.43
Ethyl nitrosocyclohexyl ketone	A	63.9	8.87	63.75	8.9
α-Isonitrosoethyl cyclohexyl ketone	A	63.9	8.87	63.75	8.88
α - Nitrosoisopropyl isobutyl ketone	A	61.1	9.62	61.22	9.72
Ethyl isopropyl glyoxime	B	53.12	8.92	53.41	9.11
Propyl isopropyl glyoxime	C	55.77	9.37	55.76	9.37

TABLE V

MOLECULAR WEIGHT DETERMINATIONS

Compound	Source	Calcd.	Found
(a) Cryoscopic in Benzene			
Bimolecular methyl nitrosocyclohexyl ketone	A	310	291
Bimolecular α-nitrosoisopropyl isobutyl ketone	B	314	316
(b) Rast Camphor Method			
Isonitrosoethyl cyclohexyl ketone	B	169.1	167.2
Ethyl isopropyl glyoxime	B	158.1	159.2
Propyl isopropyl glyoxime	C	172.1	175.7

In Tables IV and V the materials marked "A" were obtained by the action of ethyl nitrite on the ketones in the presence of aqueous hydrogen chloride, "B," of acetyl chloride and "C," of dry hydrogen chloride.

Known compounds were identified by melting point and with the exception of diisopropyl glyoxime by mixed melting point.

Structure of Nitroso Derivatives.—That a compound was a true nitroso derivative was shown by a double molecular weight and that the colorless crystals yielded a

(6) (a) Bouveault and Locquin, *Bull. soc. chim.*, [3] **35**, 653 (1906); (b) Ponzio, *J. prakt. Chem.*, [2] **63**, 368 (1901)

blue liquid on melting or when dissolved in solvents. The identity of an isonitroso compound was shown beyond reasonable doubt by a "normal" molecular weight together with lack of color and by solubility in alkali.

Summary

1. The action of ethyl nitrite on certain ketones using aqueous hydrogen chloride, acetyl chloride and dry hydrogen chloride as catalysts has been studied. The results are expressed in tabular form.

2. Certain new compounds prepared are listed in Table IV.

STATE COLLEGE, PENNSYLVANIA RECEIVED JULY 12, 1935

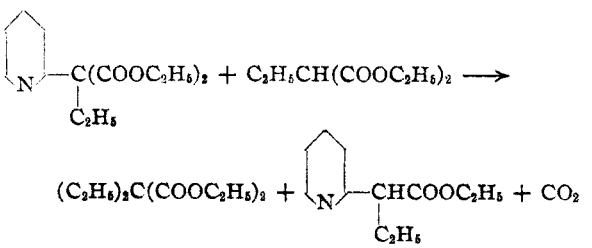
[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

Ethyl-2-pyridylmalonic Ester

BY L. A. WALTER AND S. M. MCELVAIN

The observation that the presence of a pyridine nucleus in certain types of therapeutic agents definitely lowers the intravenous toxicities of these substances[1] suggested the preparation and pharmacological evaluation of some pyridyl substituted barbituric acids. The first work along this line was directed toward the preparation of 5-ethyl-5-(2-pyridyl)-barbituric acid. Although it has not been possible to obtain this barbituric acid by the condensation of urea with the corresponding malonic ester, the preparation and properties of the ethyl-2-pyridylmalonic ester seem to be of sufficient interest to report.

This ester was prepared by the reaction of 2-bromopyridine with sodio-ethylmalonic ester in the absence of alcohol. When the reaction was carried out in alcoholic solution practically all of the bromopyridine which reacted was converted into 2-ethoxypyridine. Even in the absence of alcohol the yield of the pyridyl substituted malonic ester was not high (19%). Considerable amounts of ethyl α-(2-pyridyl)-butyrate and diethylmalonic ester were obtained as by-products of the reaction. These products apparently were the result of the alkylation of ethylmalonic ester by the ethyl-2-pyridylmalonic ester, thus



All attempts to condense ethyl-2-pyridylmalonic ester with urea either by means of dry or alcoholic sodium ethoxide were unsuccessful. The reaction product was in each case α-(2-pyridyl)-butyramide. Thus the behavior of this pyridyl substituted malonic ester parallels that which has been observed[2] for diphenylmalonic ester. It appears, therefore, that the 2-pyridyl group when substituted in a malonic ester approaches the effectiveness of two phenyl groups in promoting the cleavage of the ester. When compared to a single phenyl group the 2-pyridyl group is certainly very much more effective in increasing the sensitivity of the malonic ester to cleavage. For example, it was found that after refluxing for one hour with alcoholic sodium ethoxide, ethyl phenylmalonic ester suffered alcoholysis to ethyl carbonate and the corresponding acetic ester to the extent of 31% while under the same conditions ethyl-2-pyridylmalonic ester underwent alcoholysis to the extent of 93%.

The unusual labilizing effect of the 2-pyridyl group on the carbethoxy group of this pyridylmalonic ester is probably associated with the 2-linkage. It is well known that certain pyridine substituents, such as methyl, halogen, etc., are most reactive when they are in the 2-position. In the 4-position they are somewhat less reactive, while in the 3-position they are least reactive and resemble more closely the corresponding benzene derivatives in their behavior. It would be reasonable to expect, therefore, that a 3-pyridylmalonic ester, when it is made, will be found to have a resistance to alcoholysis comparable to that of a monophenyl substituted malonic ester and consequently be the most promising intermediate for the preparation of a 5-pyridylbarbituric acid.

(1) Strong and McElvain, THIS JOURNAL, **55**, 816 (1933); Snell and McElvain, *ibid.*, **56**, 1612 (1934).

(2) Dox and Thomas, *ibid.*, **45**, 1811 (1923); Cope and McElvain, *ibid.*, **54**, 4319 (1932).