efficient condenser was required to condense the vapors; those vapors which were not trapped in an ice-cooled collection flask were caught in a Dry Ice trap at the end of the system.

The products of decomposition were washed with three 50-ml. portions of water and then steam distilled. The distillate was washed with three 50-ml. portions of water and the distillate dried with anhydrous potassium carbonate. The yield was 207 g. (56.6%). The mixture was subjected to fractional distillation at 690 mm.; results are noted below:

Fraction	Boiling range, °C.	Weight, g.	$n^{25}D$
1	57 -63	13.1	1.4328
2	63 -65.5	47.9	1.4342
3	65.5-68.5	25.2	1.4369
4	68.5-71.5	10.4	1.4415
5	71.5-75	17.0	1.4468
6	75 -77	81.4	1.4526

Redistillation of 35 g. of fraction six from barium oxide yielded 16.2 g. (46%) of material; b.p. 76.5-77°; $n^{24}D$ 1.4538; d^{25}_4 0.9316. Kishner[2] reported: b.p. 78.5-79°; $n^{18}D$ 1.457; d^{18}_4 0.9406.

NOYES CHEMICAL LABORATORY
URBANA, ILLINOIS, AND
FULMER LABORATORY
THE STATE COLLEGE OF WASHINGTON
PULLMAN, WASHINGTON

3,3-Dialkylpiperidines

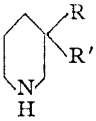
BY R. C. SCHREYER

RECEIVED DECEMBER 17, 1951

Several methods[1] for the synthesis of piperidines by ring closure at the nitrogen atom have been described. However, preparation by reductive amination of 4-cyanobutyraldehydes has not been previously reported. It has now been found in this Laboratory that 3,3-dialkylpiperidines can be synthesized from 2,2-dialkyl-4-cyanobutyraldehydes *via* the two-step process

$$\mathrm{RR'CHCHO + CH_2 = CHCN \longrightarrow RR'C(CHO)CH_2CH_2CN} \quad (1)$$

$$\mathrm{RR'C(CHO)CH_2CH_2CN + H_2 + NH_3 \longrightarrow}$$



(2)

Isobutyraldehyde, 2-methylbutyraldehyde and cyclohexanecarboxaldehyde were employed as the aldehydic components. Cyanoethylation of isobutyraldehyde[2,3,4] has been disclosed in the patent literature. The reaction of acrylonitrile with cyclohexanecarboxaldehyde was not exothermic in contrast to the other aldehydes used.

A novel spirane derivative, 2-azaspiro(5.5)hendecane, was obtained from 1-(2′-cyanoethyl)-cyclohexanecarboxaldehyde.

Experimental

2-Ethyl-2-methyl-4-cyanobutyraldehyde.—A charge of 86 g. of 2-methylbutyraldehyde and 159 g. of acrylonitrile was added slowly to 5 g. of a 50% sodium hydroxide solution over a one-hour period. The mixture was stirred throughout the addition and the temperature was maintained at 35-50° by external cooling. The solution was neutralized with 25% sulfuric acid and the oil layer distilled under vacuum to give 43 g., b.p. 66-70° (0.3-0.35 mm.), $n^{25}D$ 1.4441. *Anal.* Calcd. for $C_8H_{13}NO$: C, 69.06; H, 9.35; N, 10.07. Found: C, 68.78; H, 9.52; N, 9.99.

1-(2′-Cyanoethyl)-cyclohexanecarboxaldehyde.—A mixture of 106 g. of acrylonitrile, 102 g. of cyclohexanecarboxaldehyde and 2 g. of 50% sodium hydroxide solution was refluxed 30 minutes. The solution was cooled and 250 cc. of ether added. The ether solution was washed with 50 cc. of 10% hydrochloric acid, 50 cc. of 5% sodium bicarbonate solution and 50 cc. of water, and then distilled directly under vacuum to give 51 g., b.p. 103-105° (1 mm.), $n^{26}D$ 1.4750. *Anal.* Calcd. for $C_{10}H_{15}NO$: C, 72.72; H, 9.09; N, 8.48. Found: C, 72.56; H, 9.13; N, 8.54.

3,3-Dimethylpiperidine.[5]—A mixture of 55 g. of 2,2-dimethyl-4-cyanobutyraldehyde (b.p. 59-60° (0.6 mm.), $n^{23}D$ 1.4355) 119 g. of ammonia and 15 g. of Raney nickel was hydrogenated at 100-110° and 700 atmospheres pressure for one hour in a stainless steel shaker tube. The product was filtered to remove the catalyst and distilled under vacuum to give 12.5 g., b.p. 45-46° (33 mm.), $n^{25}D$ 1.4470. *Anal.* Calcd. for $C_7H_{15}N$: C, 74.34; H, 13.27; N, 12.39; neut. equiv., 113. Found: C, 74.58; H, 13.11; N, 11.91; neut. equiv., 115.

3-Ethyl-3-methylpiperidine.—A mixture of 50 g. of 2-ethyl-2-methyl-4-cyanobutyraldehyde, 102 g. of ammonia and 15 g. of Raney nickel was hydrogenated at 100-110° and 700 atmospheres for one hour in a silver shaker tube. The product was filtered to remove the catalyst and vacuum distilled to give 9 g., b.p. 67-69° (25 mm.), $n^{25}D$ 1.4565. *Anal.* Calcd. for $C_8H_{17}N$: neut. equiv., 127; N, 11.02. Found: neut. equiv., 126; N, 11.13.

2-Azaspiro(5.5)hendecane.—A charge of 50 g. of 1-(2′-cyanoethyl)-cyclohexanecarboxaldehyde, 119 g. of ammonia and 15 g. of Raney nickel was hydrogenated at 120-129° and 700 atmospheres pressure for one hour in a stainless steel shaker tube. The product was filtered to remove the catalyst and distilled under vacuum to give 17 g., b.p. 91-93° (10 mm.), $n^{25}D$ 1.4891. *Anal.* Calcd. for $C_{10}H_{19}N$: C, 78.43; H, 12.42; N, 9.15; neut. equiv., 153. Found: C, 78.15; H, 12.46; N, 9.21; neut. equiv., 149.

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(1) R. C. Elderfield, Editor, "Heterocyclic Compounds," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1950, pp. 642-655.

(2) H. A. Bruson and T. W. Reiner, U. S. Patent 2,353,687.

(3) J. F. Walker, U. S. Patent 2,409,086.

(4) I. G. Farbenindustrie A. G., French Patent 886,846.

(5) Dunlop, *J. Chem. Soc.*, **107**, 1112 (1915), has prepared 3,3-dimethylpiperidine by the reduction of 2,2-dimethylglutarimide with sodium and amyl alcohol.

E. I. DU PONT DE NEMOURS & CO.
POLYCHEMICALS DEPARTMENT
EXPERIMENTAL STATION
WILMINGTON, DELAWARE

Carbon Dioxide Production in the Browning Reaction[1]

BY F. H. STADTMAN, C. O. CHICHESTER AND G. MACKINNEY

RECEIVED NOVEMBER 26, 1952

Non-enzymatic browning reactions in certain natural systems and interactions of sugars and nitrogenous compounds have been thoroughly reviewed, the former by Stadtman in 1948,[2a] the latter by Danehy and Pigman[2b] in 1950. Many types of compounds can be involved. Haas and Stadtman[3] for example showed that brown pigments could be formed by combining and heating any two of the three fractions (anion, cation and neutral) that were obtained from apricot sirups by ion-exchange treatment. It is frequently assumed, however, in natural systems where both amino acids and carbohydrates are present, that

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(1) Presented at the XII International Chemical Congress, New York, 1951.

(2) (a) E. R. Stadtman, *Advances in Food Research*, **1**, 325 (1948), (b) J. P. Danehy and W. W. Pigman, *ibid.*, **3**, 241 (1951).

(3) V. A. Haas and E. R. Stadtman, *Ind. Eng. Chem.*, **41**, 983 (1949).

browning is limited to interactions between these two classes of compounds. The reaction between amino acids and reducing sugars was first studied by Maillard.[4] His work has been responsible for the direction of much of the subsequent thinking. Maillard observed that when an amino acid and a reducing sugar such as glucose were heated together, considerable quantities of carbon dioxide were evolved, and at the same time brown-colored substances were formed.

He deduced that the carbon dioxide was produced by decarboxylation of the amino acid. When he compared the weight of the dried reaction mixture with the original dry weight of the reactants, he found a weight loss not accounted for as carbon dioxide. He concluded that this loss was due to water formed as a result of condensations. A weight balance on this basis indicated that twelve mols of water were formed for each mol of amino acid decarboxylated. Thus a maximum of twelve mols of sugar might be involved for each mol of carbon dioxide. These conclusions neglect the possibilities of losses due to escape of other volatile fragments and of carbon dioxide from sources other than the amino acid carboxyl.

Recent browning studies[5] here have utilized C^{14}-labeled sugars. Glucose and fructose were incorporated into apricot sirups as radioactive tracers. These sirups were then browned at 55°. Carbon dioxide formed during the reaction was trapped as barium carbonate and its specific activity determined. It was found that appreciable quantities of carbon from sugar sources were present in the carbon dioxide evolved (Fig. 1). Consequently, the possibility of carbon dioxide formed from sugar sources in the Maillard reaction cannot be disregarded. A simple glucose–glycine system was therefore studied by use of radioactive tracer techniques to determine whether some carbon dioxide also comes from the sugar. This should ultimately permit evaluation of Maillard reaction CO_2 in natural systems.

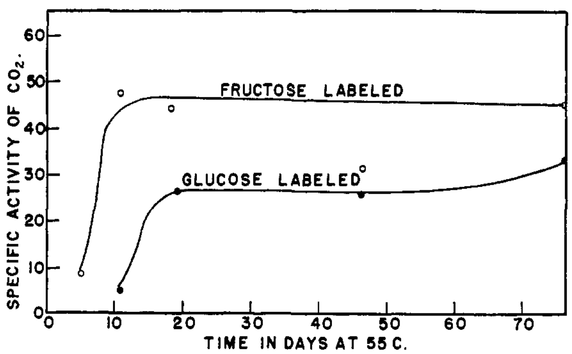

Fig. 1.—Specific activities of carbon dioxide from fructose- and glucose-labeled apricot sirups, as a function of time.

Experimental

Glucose–glycine browning reactions were carried out with the same concentrations of reactants as those used in Maillard's original experiment. The reaction was studied at two temperatures; at 100° to approximate the reflux temperatures used by Maillard, and at 56.5°, the temperature of a boiling acetone-bath, to duplicate reaction temperatures used by us in apricot browning studies. To check possible participation of both glucose and glycine as sources of carbon dioxide production, two experiments were run at each temperature. In one, uniformly labeled glucose-C^{14} reacted with unlabeled glycine, and in the other, carboxyl-labeled glycine reacted with unlabeled glucose. The pigment concentration as measured at 440 mμ in an Evelyn colorimeter, the quantity and specific activity of carbon dioxide produced, and the *p*H of the reaction mixtures were determined as a function of time. Reactions at 100° were followed for two hours, approximately the time used in Maillard's experiments, while the reactions at 56.5° were continued for over 450 hours, for comparison with long-time reactions in browning of apricot sirups.

For the tracer experiments, the reaction chamber (3 ml. in volume) was immersed in a bath of water or acetone according to the temperature desired, under independent reflux. A weighed amount of reactant mixture (*ca.* 2 ml. in volume) was inserted in the reaction chamber and maintained under its own reflux to prevent loss of water. The CO_2 produced was allowed to diffuse from the solution into a stream of nitrogen (CO_2-free, humidified) and swept into a sodium hydroxide trap. All-glass connections were used, and the apparatus was tested for leaks.

For measurement of total CO_2 and pigment, a similar train was used with a larger reaction chamber (25 ml.) and an exact weight (*ca.* 20 ml. in volume) of reactants introduced.

The reagents were anhydrous C.P. glucose, C.P. glycine and CO_2-free water. The weight ratios for the three were 4:1:6, representing a 2.4 to 1 mol ratio for glucose to glycine.

Results.—During the course of the reaction, the *p*H of the reaction mixture decreased from *p*H 4.83 to 4.15. This acid condition of the reaction mixture is not unlike that existing in browning fruit products and some comparisons should be possible. However, one should be cautious when comparing these results with those obtained at much lower or higher *p*H levels.

The amount of pigment produced as a function of time is shown in Fig. 2. The shape of the curve is the same for the reaction at 100 and at 56.5°. The data for both curves may be represented by third degree polynomials. Browning proceeds at a much slower rate at the lower temperature, 250 hours being required to produce the same degree of browning as is reached at the higher temperature in two hours.

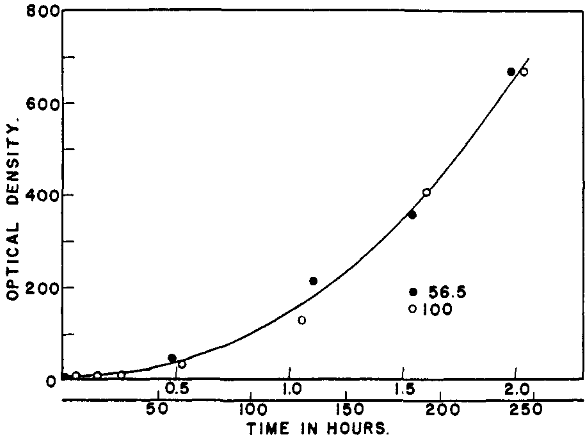

Fig. 2.—Pigment production as a function of time: optical density (calculated per gram solids) as a measure of pigment concentration *vs.* upper scale, time at 100°, lower scale, time at 56.5°.

The curve for CO_2 production is of a similar form, but when the amount of CO_2 produced per gram of

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(4) L. C. Maillard, *Compt. rend.*, **154**, 66 (1912); **155**, 1554 (1912).

(5) Unpublished data.

solids is plotted against the optical density at 440 mμ (Fig. 3) it is clear that far more carbon dioxide is produced per unit optical density at 100° than at 56.5°. The carbon dioxide-producing reaction therefore may not follow the same course at the two different temperatures, though the color-producing parts of the two reactions appear to be similar. This suggests the carbon dioxide liberation in amino acid–sugar reactions may not be essential for color production, which is substantiated by the fact that brown pigments retained after dialysis[6] contain less carboxyl carbon when browning occurs at 100° than when it takes place at 56.5°. It is significant that considerable amounts of carboxyl carbon from glycine become associated with the brown pigment produced.[5] CO_2 liberation may therefore take place subsequent to pigment formation.

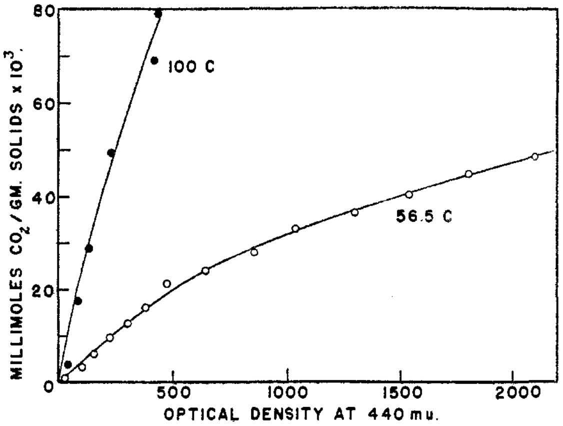

Fig. 3.—Carbon dioxide production in relation to pigment production at the two temperatures.

The results obtained with C^{14}-labeled glucose show that some CO_2 is derived from the sugar as well as the amino acid, Fig. 4. The major portion,

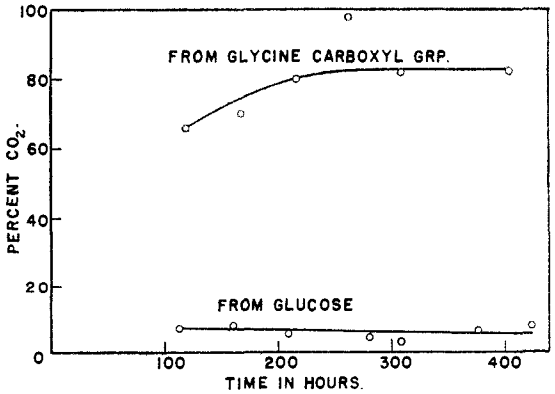

Fig. 4.—The percentages of carbon dioxide derived from glucose and glycine as a function of time.

well over 80%, is derived from the carboxyl group of the amino acid, as Maillard suggested, and somewhat less than 10% comes from the sugar. The rather unlikely possibility that the methyl carbon of the glycine contributes to the CO_2 will be checked, and the fate of the amino acid residue will be determined, through the use of methyl-labeled glycine.

DIVISION OF FOOD TECHNOLOGY
UNIVERSITY OF CALIFORNIA
BERKELEY, CALIFORNIA

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(6) C. O. Chichester, F. H. Stadtman and G. Mackinney, THIS JOURNAL, **74**, in press (1952).

N-Methyl-6,7,8-trimethoxy-1,2,3,4-tetrahydroisoquinoline

BY E. P. TAYLOR

RECEIVED MARCH 11, 1952

In an attempt to synthesize trichocereine, *i.e.*, N-dimethylmescaline, by methylation of mescaline with formic acid–formaldehyde, Reti and Castrillón[1] found that the product was a tetrahydroisoquinoline base. This has now been identified by Castrillón[2] as N-methyl-6,7,8-trimethoxy-1,2,3,-4-tetrahydroisoquinoline. Oxidation of the hydrochloride to the known N-methyl-3,4,5-trimethoxyphthalimide confirms the structure of the base, which is claimed as a new compound. May I point out that this substance has already been prepared and described[3]: its constitution has been established by a Bischler–Napieralski reaction upon N-formylmescaline, followed by reduction of the methiodide of the resultant 6,7,8-trimethoxy-3,4-dihydroisoquinoline. In addition, reduction of the ethiodide of this base yielded the corresponding N-ethyl-1,2,3,4-tetrahydroisoquinoline.

(1) L. Reti and J. A. Castrillón, THIS JOURNAL, **73**, 1767 (1951).
(2) J. A. Castrillón, *ibid.*, **74**, 558 (1952).
(3) E. P. Taylor, *J. Chem. Soc.*, 1153 (1951).

RESEARCH DIVISION
ALLEN AND HANDBURYS, LTD.
WARE, HERTS, ENGLAND

The Reaction of Silyl Bromide with Magnesium

BY E. R. VAN ARTSDALEN[1] AND JEROME GAVIS

RECEIVED FEBRUARY 5, 1952

The preparation of compounds of the type SiH_3MgX, analogous to organic Grignard reagents, should offer many interesting new possibilities for syntheses of compounds containing the silyl group. Emeleus, Maddock and Reid[2] in conjunction with their studies on the synthesis and properties of silyl iodide, SiH_3I, describe a reaction between SiH_3I and magnesium in diisoamyl ether. The reaction yielded hydrogen, silane and silicon but no stable addition compound. Complete reaction took place. These results were attributed to the formation of an unstable Grignard-type compound.

This note describes an attempt to prepare a Grignard compound using silyl bromide. It was hoped that use of the bromide would impart greater stability to the desired product, which was then to be used in synthesis of other silyl compounds.

We were unable to obtain any stable Grignard compound, nor did any easy reaction of the type found by Emeleus, Maddock and Reid take place. Indeed, no reaction occurred between Mg and

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(1) Chemistry Division, Oak Ridge National Laboratory, Oak Ridge, Tennessee.

(2) H. J. Emeleus, A. G. Maddock and C. Reid, *Nature*, **144**, 328 (1939); *J. Chem. Soc.*, 353 (1941).