

small flask gave hydroxylamine, converted to acethydroxamic acid (m. p. 87°) by addition of acetyl chloride.

**With Dilute Hydrochloric Acid (2:1).**—A mixture of 2 g. of acetyl 2-aci-nitropropane with 6 ml. of dilute hydrochloric acid was refluxed for ten minutes. Fractionation gave acetone and acetic acid, while a residue of 250 mg. of hydroxylamine hydrochloride remained.

**With 10% Sodium Hydroxide.**—Reaction of 2 g. of the acetyl compound with 6 ml. of 10% sodium hydroxide occurred rapidly at room temperature. Acetone and sodium acetate were formed, and a mixture of ammonia, nitrous oxide and nitrogen, all separately identified, was evolved. No hydroxylamine was noted.

**With Ethanol.**—No reaction occurred on refluxing acetyl 2-aci-nitropropane with either ethanol or 1-butanol alone.

A mixture of 2 g. of the acetyl compound with 4 g. of ethanol and one drop of 100% sulfuric acid was refluxed for one hour and fractionated. A trace of acetone was identified by conversion to the 2,4-dinitrophenylhydrazones, and an almost quantitative amount of ethyl acetate was separated and identified by odor, boiling point, and density. From the residue was obtained 300 mg. of acetoxime.

**With Aniline.**—A mixture of 4 g. of acetyl 2-aci-nitropropane and 8 g. of aniline was gently warmed on the water-bath for about ten minutes, during which ammonia was evolved. The resulting white crystalline product, representing quantitative formation of acetanilide, was identified as such after recrystallization from carbon tetrachloride. Distillation of the unreacted aniline gave a small amount of acetone, and a residue of 400 mg. of acetoxime. No free hydroxylamine was detected.

**Propionyl 2-Aci-nitropropane (from 2-Nitropropane).**—The procedure employed in preparing the acetyl derivative was used here. A mixture of 89 g. (1 mole) of 2-nitropropane, 180 g. (1 mole) of propionic anhydride and 10 g. of anhydrous potassium acetate in 200 g. of toluene was warmed to refluxing temperature. With the heat removed the reaction was continued by frequent additions of potassium acetate until no further reaction was noted. This required a total of 70 g. Removal of the insoluble salt, solvent and unreacted anhydride as before gave a pale yellow product. This was distilled through the packed column, giving 15.0 g. (10.3%) of substance boiling at 69° at 1 mm. In several runs an average yield of 9.5% was obtained.

**From Sodium 2-Nitropropane.**—To a mixture of 100 g. (0.90 mole) of sodium 2-nitropropane in 1000 g. of anhydrous ether, 140 g. (1.08 mole) of propionic anhydride was

added over a period of one hour, the temperature being maintained at 5° for three hours after the addition was complete. On warming to room temperature the usual evolution of carbon dioxide occurred. The precipitated salt, the ether and unreacted anhydride were removed as before, and the crude yellow product distilled through the packed column, giving 8.0 g. (6.1%) of propionyl 2-aci-nitropropane, boiling at 68° at one mm. In a series of experiments an average yield of 5.6% was obtained.

Samples for analysis were further purified by recrystallization from anhydrous ether in an ether-solid carbon dioxide-bath. The following characteristics were observed: b. p. 70° (1 mm.);  $n_D^{20}$  1.4340;  $d_4^{20}$  0.9850.

*Anal.* Calcd. for  $C_6H_{11}O_3N$ : N, 9.70; mol. wt., 141. Found: N, 10.03, 10.05; mol. wt., 140.

The reactions of propionyl 2-aci-nitropropane with water, ethanol and aniline were similar to those observed for the acetyl compound.

**Reaction of Sodium 2-Aci-nitropropane with Benzoyl Chloride.**—In several experiments benzoyl chloride was found to react slowly with an anhydrous ether suspension of sodium 2-aci-nitropropane at reflux temperature. Removal of the precipitated sodium chloride and distillation of the solvent left a residue of benzoic acid, although anhydrous conditions were maintained throughout. The reaction will be investigated further.

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### Summary

The preparation of acetyl and propionyl 2-aci-nitropropane has been accomplished. They are reactive substances, being converted by action of water, alcohols, amines and hydrogen (catalytically) to acetone or acetoxime, the carboxylic acids, their esters and N-substituted amides, and nitrogeneous compounds whose formation can be traced to the decomposition of initially formed hyponitrous acid.

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## Hydrogenation of Esters to Alcohols over Raney Nickel. I

BY HOMER ADKINS AND A. A. PAVLIC<sup>1</sup>

Ovakimian, Kuna and Levene<sup>2</sup> reported the hydrogenation of the esters of certain amino acids to amino alcohols over Raney nickel in the temperature range of 35 to 100°. The conversion of a carbalkoxy to a carbinol group, under such mild conditions, was apparently due to the use of a high ratio of nickel to ester. Early attempts in this Laboratory to reproduce the results and develop a procedure of preparative value, gave rather erratic results. These successes and failures led to a modification of the procedure for the preparation of Raney nickel from the nickel alumi-

num alloy. The original process recommended by Raney,<sup>3</sup> as developed by Covert,<sup>4</sup> involved a prolonged digestion of the alloy at 115° or higher for about ten hours. According to a later and better process described by Mozingo<sup>5</sup> the digestion was for eight hours at 80°.

In attempting to obtain a very active catalyst, uniformly effective for the hydrogenation of  $\alpha$ -amino esters, a process for preparing the catalyst was developed,<sup>6</sup> in which the digestion was at 50°

(3) Murray Raney, U. S. Patent 1,628,190 (1927).

(4) Covert and Adkins, *THIS JOURNAL*, **54**, 416 (1932).

(5) Mozingo, "Organic Syntheses," **21**, 15 (1941).

(6) Pavlic and Adkins, *THIS JOURNAL*, **68**, 1471 (1946).

(1) Du Pont Fellow at the University of Wisconsin 1941-1942.

(2) Ovakimian, Kuna and Levene, *J. Biol. Chem.*, **135**, 91 (1940).

TABLE I  
 SUMMARY OF HYDROGENATION DATA

| G. | Ester<br>Ethyl  | Catalyst |              |    | Yield                                      |  |
|----|---|----------|--------------|----|--|--|
|    |   | G.       | Raney Nickel | %  | Alcohol                                    |  |
| 5  | Alaninate <sup>a</sup>  | 12       | W-3          | 10 | 2-Amino-1-propanol <sup>b</sup>            |  |
| 10 | Picolinate <sup>c</sup>                                       | 15       | W-2          | 92 | 2-Piperidylcarbinol <sup>d</sup>           |  |
| 10 | $\alpha$ -Piperidinoacetate <sup>e</sup>                      | 12       | W-2          | 90 | $\beta$ -Piperidylethanol <sup>f</sup>     |  |
| 10 | $\alpha$ -Piperidinoacetate                                   | 12       | W-3          | 90 | $\beta$ -Piperidinoethanol                 |  |
| 5  | $\alpha$ -Piperidinoacetate                                   | 10       | W-4          | 98 | $\beta$ -Piperidinoethanol                 |  |
| 5  | $\alpha$ -Piperidinopropionate <sup>g</sup>                   | 10       | W-4          | 42 | 2-Piperidino-1-propanol <sup>h</sup>       |  |
| 9  | $\beta$ -Piperindinopropionate <sup>i</sup>                   | 18       | W-4          | 30 | 3-Piperidino-1-propanol <sup>j</sup>       |  |
| 5  | $\alpha$ -Methyl- $\alpha$ -piperidinopropionate <sup>k</sup> | 10       | W-4          | 24 | 2-Methyl-3-piperidinopropanol <sup>l</sup> |  |
| 6  | Phenylglycinate <sup>m</sup>                                  | 12       | W-4          | 93 | 2-Amino-2-phenethyl alcohol <sup>n</sup>   |  |
| 7  | Phenylalaninate <sup>o</sup>                                  | 12       | W-4          | 52 | 2-Amino-3-phenyl-1-propanol <sup>p</sup>   |  |
| 10 | Leucinate <sup>q</sup>  | 18       | W-2          | 55 | 2-Amino-4-methyl-1-pentanol <sup>r</sup>   |  |
| 5  | $\alpha$ -Aminocaproate <sup>s</sup>                          | 12       | W-4          | 65 | 2-Amino-1-hexanol <sup>t</sup>             |  |
| 10 | $\alpha$ -Tetrahydrofuroate <sup>u</sup>                      | 12       | W-4          | 55 | Tetrahydrofuryl alcohol <sup>v</sup>       |  |

<sup>a</sup> B. p. 56° (16 mm.). <sup>b</sup> B. p. 77° (17 mm.),  $n_D^{25}$  1.4481. Picrate, m. p. 114–115.5°. *Anal.* Calcd. for  $C_6H_9O_2N_3$ : C, 35.53; H, 3.98. Found: C, 35.44; H, 4.02. <sup>c</sup> Prepared by esterification of picolinic acid hydrochloride. B. p. 99° (4 mm.),  $n_D^{25}$  1.5080, hydrochloride, m. p. 146–147°. <sup>d</sup> B. p. 88° (5 mm.), m. p. 69–70° (from petroleum ether, 65–85°) m. p. of picrate, 134–135.5° (reported, <sup>7</sup> m. p. 128°). <sup>e</sup> B. p. 93–94° (11 mm.),  $n_D^{25}$  1.4518. Picrate, m. p. 118–119°. Hydrochloride m. p. 130–131°. <sup>f</sup> B. p. 86° (15 mm.),  $n_D^{25}$  1.4470 (reported<sup>8</sup> 1.4749),  $d_4^{25}$  0.9704, picrate, m. p. 99–100°. <sup>g</sup> B. p. 102–103° (13 mm.),  $n_D^{25}$  1.4538. <sup>h</sup> The alcohol was removed by extraction of the saponified mixture and converted to the picrate, m. p. 114–115.5°. *Anal.* Calcd. for  $C_{14}H_{20}O_8N_4$ : C, 45.16; H, 5.42. Found: C, 45.39; H, 5.37. Hydrochloride, m. p. 152–153.5°. <sup>i</sup> Prepared by method of Thomas and McElvain.<sup>9</sup> B. p. 102–103° (11 mm.),  $n_D^{25}$  1.4517. Picrate, m. p., 121–122.5°. <sup>j</sup> Product removed from saponified mixture and converted to the picrate, m. p. 62–64° (Braun, *et al.*, reported<sup>9</sup> m. p. 63–64°). <sup>k</sup> See Drake and McElvain.<sup>10</sup> B. p. 110° (19 mm.),  $n_D^{25}$  1.4520. <sup>l</sup> Yield determined by neutral equivalent of mixture. <sup>m</sup> B. p. 114–115° (5 mm.),  $n_D^{25}$  1.5147. <sup>n</sup> B. p. 101–104° (2 mm.), m. p. (from alcohol–water) 108–111°. Picrate, m. p. 207–208° (reported<sup>2</sup> 208–210°). <sup>o</sup> B. p. 105–107° (2 mm.);  $n_D^{25}$  1.5081. Hydrochloride, m. p. 127.5°. <sup>p</sup> Isolated as hydrochloride m. p. 156°. *Anal.* Calcd. for  $C_9H_{14}NOCl$ : Cl, 18.90. Found: Cl, 19.04. <sup>q</sup> B. p. 87–88° (17 mm.),  $n_D^{25}$  1.4260. <sup>r</sup> B. p. 93–98° (11 mm.), m. p. (from 60–68° petroleum ether) 44°. Hydrochloride, m. p. 162–163° (reported<sup>11</sup> 161–162°). <sup>s</sup> B. p. 94° (18 mm.),  $n_D^{25}$  1.4281. <sup>t</sup> B. p. 103–104° (13 mm.). Picrate, m. p. 113.5–114.5°. Hydrochloride, m. p. 92–94° (reported<sup>12</sup> 93–94.5°). <sup>u</sup> B. p. 75° (12 mm.),  $n_D^{25}$  1.4339. <sup>v</sup> The yield reported is based upon the saponification of the ester–alcohol mixture and the isolation of the phenylurethan, m. p. 61° (reported<sup>13</sup> 61°).

for only fifty minutes after the alloy was added. A method was devised which minimized the loss of hydrogen from the nickel and its exposure to air during the process of washing the catalyst.

Many "special" or "modified" Raney nickel catalysts are referred to in the literature, without a precise definition of the procedure followed in preparing them from the nickel–aluminum alloy. We intend hereafter to indicate by a letter and number the exact procedure followed in preparing a given Raney nickel catalyst. The symbols W-1 and W-2 will be used for the catalysts prepared by the Covert and Mozingo procedures, respectively. W-3 and W-4 are the catalysts prepared at 50° with a digestion period of fifty minutes. W-3 differs from W-4 in that in the former all of the alloy was added to the alkali at –20° while in W-4 the alloy was slowly added at 50° precisely as described.<sup>6</sup> Insofar as we know, there is no difference in the activity of W-3 and W-4.

It seems unnecessary to report in detail the long

(7) Renshaw, Ziff, Kornblum and Brodie, *THIS JOURNAL*, **61**, 638 (1939).

(8) (a) Barnes and Adams, *ibid.*, **49**, 1312 (1927); (b) Braun, Braunsdorf and Rath, *Ber.*, **55**, 1674 (1922).

(9) Thomas and McElvain, *THIS JOURNAL*, **56**, 1808 (1934).

(10) Drake and McElvain, *ibid.*, **56**, 697 (1934).

(11) Ovakimian, Kuna and Levene, *J. Biol. Chem.*, **134**, 151 (1940).

(12) Leiffer and Adams, *THIS JOURNAL*, **59**, 2252 (1937).

(13) Kaufman and Adams, *ibid.*, **45**, 3040 (1923).

series of experiments involved in the development of the preferred procedure. Ethyl piperidinoacetate was the ester used for evaluation of the relative activity of catalysts in alcohol at 50°, under a pressure of 150 to 200 atmospheres. The catalyst W-4, containing 12 to 13% aluminum, gave a 98% yield of piperidinoethanol, while digestion of the catalyst for six hours reduced the yield of alcohol to 55%. A longer period of digestion (twenty-four hours) or the elimination of the digestion period gave poor catalysts which showed amino alcohol yields of 14 and 4%, respectively. The aluminum content of the catalyst and its catalytic activity do not appear to be closely related.

Several observations suggested that the reduction in the process under discussion is a reaction of nickel hydride with the ester and not a catalytic hydrogenation. Among these observations may be noted the high ratio of nickel to ester required, the loss of hydrogen and deterioration of the catalyst on storage for two or three weeks, and the fact that the amount of amino alcohol found was not infrequently 10 to 30% in excess of that calculated from the drop in pressure of hydrogen during the reduction. However, attempts to reduce ethyl piperidinoacetate in a sealed glass tube at 60° with freshly prepared Raney nickel W-4 gave only a 5% yield of the amino alcohol.

The results of the hydrogenations of various

esters, which now seem the more significant and useful, are summarized in the table. All of the hydrogenations were carried out at 50° for seven hours, except for the first two entries which were stopped after four and five hours, respectively. The hydrogen was under 150 to 200 atmospheres pressure. The reaction medium was 20 to 35 ml. of dry alcohol contained in a steel reaction vessel of 96-ml. capacity. The names and amounts of ester, type and amount of catalyst and the yield of the major product are given in the table.

In general the esters were prepared and isolated by procedures previously described.<sup>14</sup> The products of hydrogenation were isolated by fractional distillation except as noted under Table I. The amino alcohols were characterized, and in some instances estimated by neutral equivalents, as well as in most instances by solid derivatives.

The catalyst W-2 prepared by the Mazingo procedure gave in some instances a good yield of an amino alcohol. However, with the  $\alpha$ - and  $\beta$ -piperidino propionates, and the  $\alpha$ -piperidinoisobutyrate and phenylalaninate, the hydrogenation proceeded to the extent of from 0 to 6% while over the preferred catalyst W-4 yields of 30 to 52% were obtained with these esters. Data are not available for a precise comparison of the activity

(14) F. W. Forman, *J. Biochem.*, **13**, 378 (1919); Uchida and Sanye, *J. Soc. Chem. Ind. Japan*, **36**, 221 (1933); *C. A.*, **27**, 3489 (1934).

of the catalysts used, but it seems certain that the catalysts W-3 and W-4, prepared by a short digestion at 50°, are in every case equal to and in several cases very superior to the catalysts prepared under more drastic conditions.

The average yield given in the table, of amino alcohols obtained from eight different alpha aminoesters, is about 75% of the theoretical. Thus the process as described has good preparational value. Less favorable yields of amino alcohol were obtained from the two beta-aminoesters tested. The process is apparently also applicable to  $\alpha$ -oxysubstituted esters since  $\alpha$ -tetrahydrofuroate was converted in 55% yield to tetrahydrofurfuryl alcohol. The successful application of the process to a considerable number of alpha amino and hydroxy esters at 25 to 100° will be described in a subsequent paper.

### Summary

A procedure has been described whereby esters of alpha amino acids may be hydrogenated in rather good yields to the corresponding amino alcohols. A properly prepared Raney nickel catalyst is effective at 50° with a rather high ratio of nickel to amino ester. The low temperature required is advantageous in that the alkylation of the amino group and the racemization of the amino alcohol may be avoided.

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[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF CALIFORNIA AT LOS ANGELES]

## Dissociation Constants of Some Substituted Phenyltrimethylammonium Perchlorates in Ethylene Chloride; Effect of Ion Asymmetry

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It is well known that all salts which are typically strong electrolytes in aqueous solution and in which the binding force between the positive and negative constituents is solely electrostatic, or coulombic, are only partially dissociated into free ions in dilute solution in solvents of sufficiently low dielectric constant. That the molecular structures of the constituent ions of a salt are important factors in determining its dissociation constant has been amply shown by Kraus<sup>2</sup> and co-workers from the results of electrolytic conductance measurements. The effective volume, or size, of the ions and the charge distribution within the ions are among the structural features which have been found to influence the extent of association of the ions of a salt into short-range ion-pairs.

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(2) (a) Gleysteen and Kraus, *THIS JOURNAL*, **69**, 451 (1947); (b) Tucker and Kraus, *ibid.*, **69**, 454 (1947); (c) Mead, Ramsey, Rothrock and Kraus, *ibid.*, **69**, 528 (1947); (d) Kline and Kraus, *ibid.*, **69**, 814 (1947). For summaries of previous results see C. A. Kraus, *Trans. Electrochem. Soc.*, **66**, 179 (1934); *J. Franklin Inst.*, **225**, 687 (1938); *Science*, **90**, 281 (1939).

In order to determine the effect of varying any particular structural feature of an ion on the dissociation constant, a series of salts is desired in which this structural feature alone is appreciably changed from one salt to another. The influence of variation in the ion-size alone has been adequately demonstrated by the increase in the dissociation constant found to accompany the increase in size of the alkyl radical in the homologous series of symmetrically substituted tetraalkylammonium picrates and nitrates in ethylene chloride at 25°. <sup>2b,3</sup>

It has been the purpose of this investigation to determine the dissociation constants of a series of salts in ethylene chloride as solvent in which the electrical asymmetry of one of the ions is consistently varied in such a way that the effective ion-size remains substantially unchanged and thereby to obtain some indication of the specific influence of such a variation on the dissociation constant. Nine monosubstituted phenyltrimethylammonium perchlorates were used, namely, the ortho,

(3) Mead, Fuoss and Kraus, *Trans. Faraday Soc.*, **32**, 594 (1936).