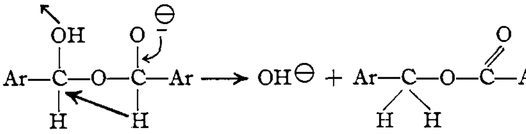
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

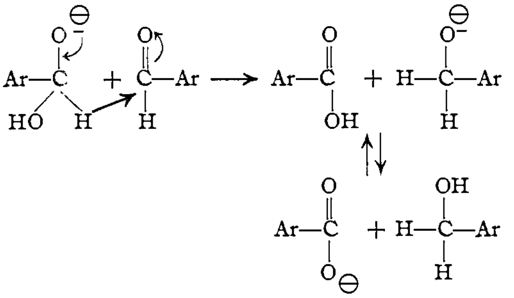
Studies on the Mechanism of the Cannizzaro Reaction. II. Hydroxy and Amino Aldehyde Derivatives

BY ELLIOT R. ALEXANDER

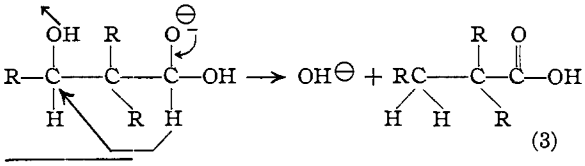
In an earlier communication[1] it was shown that the Cannizzaro reaction of benzaldehyde in a homogeneous system does not involve a chain reaction of the kind which is usually greatly influenced by the presence of peroxides or peroxide inhibitors. There are, then, two ionic mechanisms based upon the transfer of a hydrogen atom with its pair of electrons (*i. e.*, a hydride ion), which are in accord with much of the data. In one of the mechanisms which has been proposed by Geissman,[2,1] the essential feature of the reaction involves the *displacement* of a hydroxyl group from a saturated carbon atom (equation 1).


(1)

In the other mechanism, which is a slight modification of one originally proposed by Hammett[3,1] the *addition* of a hydride ion to a carbonyl group is postulated (equation 2).

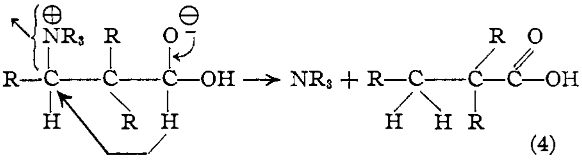

(2)

With respect to the first mechanism it appears that the direct chemical displacement of a hydroxyl group from a saturated carbon atom is unknown in alkaline solution.[4] If, however, such a displacement does occur over the carbon–oxygen–carbon system shown in equation 1, a similar displacement might be expected over the carbon–carbon–carbon system of a β-hydroxy aldehyde (equation 3).


(3)

Thus a saturated, non-hydroxylated acid should be a by-product in the transformation provided that the intramolecular reaction proceeded at a rate comparable to the normal Cannizzaro reaction or reverse aldolization. The normal reaction, of course, would be expected to give a molecule of a β-hydroxy acid and a molecule of a β-glycol.

A particularly favorable situation for such an intramolecular displacement is a quaternary aminoaldehyde. In this case the approach of the hydride ion to the carbon atom is favored by the positively charged nitrogen atom and subsequent bond-breaking would involve the separation of a neutral molecule.[5]


(4)

Accordingly it was the object of this work to isolate unsubstituted saturated acids from the Cannizzaro reaction of hydroxy and amino aldehyde derivatives.

Experimental[6]

Preparation of Starting Materials.—With the exception of the methiodide of α-dimethylaminoisobutyraldehyde which is described below, all of the starting materials were known and were prepared by the procedures given in the footnotes of Table I. The physical properties of these compounds agreed with those which were recorded in the literature.

α-Bromoisobutyraldehyde and α-Bromoisobutyraldehyde Diethylacetal.—In a one-liter, three-necked round-bottomed flask fitted with a stirrer, a dropping funnel, and a reflux condenser were placed isobutyraldehyde diethylacetal (146 g., 1.0 mole), calcium carbonate (150 g., 1.5 moles) and 300 ml. of carbon tetrachloride. The flask was immersed in an ice–salt mixture, stirring was commenced, and bromine (51 ml., 1.0 mole) was added dropwise over the course of an hour. The reaction mixture was then filtered, the filter cake was washed with two 50-ml. portions of carbon tetrachloride and the filtrate was fractionally distilled through an eight inch column packed with glass helices. The distillation gave 23 g. (15%) of α-bromoisobutyraldehyde, b. p. 110–113°, and 108 g. (48%) of α-bromoisobutyraldehyde diethylacetal, b. p. 99–100° (40 mm.).

Additional quantities of α-bromoisobutyraldehyde were prepared by the hydrolysis of the acetal. The optimum conditions were found to be the following: α-bromoisobutyraldehyde diethylacetal (50.0 g., 0.22 mole), dioxane (100 ml.), water (50 ml.) and concentrated hydrochloric acid (10 ml.) were refluxed for about one minute at which time the cloudy solution abruptly became clear. The reaction mixture was then cooled rapidly in an ice-bath, poured into 300 ml. of cold water and extracted with

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[1] Alexander, THIS JOURNAL, **69**, 289 (1947).

[2] Geissman, "Organic Reactions," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 96.

[3] Hammett, "Physical Organic Chemistry," McGraw-Hill Book Company, Inc., New York, N. Y., 1940, p. 350.

[4] The Strecker and Bücherer reactions may involve such a displacement, however.

[5] The author is indebted to Dr. T. A. Geissman for this suggestion.

[6] All melting points and boiling points are uncorrected.

ether. The ether solution was dried over anhydrous magnesium sulfate and distilled. The fraction boiling at 108–113° amounted to 15.6 g. (47%).

α-Dimethylaminoisobutyraldehyde and α-Dimethylaminoisobutyraldehyde Methiodide.—α-Bromoisobutyraldehyde (40.0 g., 0.265 mole) was added dropwise to a cooled solution of aqueous 35% dimethylamine (300 g., 2.33 moles) at such a rate that the temperature did not rise above 10°. The resulting homogeneous solution was then allowed to come to room temperature and to stand overnight. After extracting the solution thoroughly with ether and drying over anhydrous magnesium sulfate, the ether extracts were distilled through a small six inch column packed with glass helices. The yield of α-dimethylaminoisobutyraldehyde was 9.9 g. (32%), b. p. 126–129°.

Since this material appeared to absorb carbon dioxide from the air, it was quickly rinsed into a 300-ml. round-bottomed flask with 100 ml. of dry benzene and refluxed on a hot water-bath with excess methyl iodide for two hours. The white amorphous solid which formed was filtered with suction, washed with benzene and dried in a vacuum desiccator. The yield of α-dimethylaminoisobutyraldehyde methiodide was 20.3 g. (92%); m. p. 119–121° (dec.).

No suitable solvent was found for the large scale recrystallization of this quaternary salt. It was almost insoluble in hot acetone, absolute alcohol, and methanol. In methanol-water or ethanol–water mixtures the recovery was very poor and the material appeared to decompose with the evolution of methyl iodide. It was sparingly soluble in nitroethane and nitromethane from which it crystallized in the form of clear compact crystals, m. p. 119–121° (dec.).

Anal. Calcd. for $C_7H_{16}ONI$: C, 32.75; H, 6.28. Found: C, 32.88; H, 6.37.

The Cannizzaro Reaction.—The reaction itself was carried out with the amounts of material indicated in Table I. The aldehyde was added portion-wise to 5 molar equivalents of potassium hydroxide solution,[7] (50% in a mixture of equal parts of water and methanol) at such a rate that the temperature did not rise above 20°. The reaction mixture (which was sometimes non-homogeneous) was then stirred overnight at room temperature and finally refluxed one hour to complete the reaction.

The reactions were worked up in the usual way.[8] With the more water soluble products a continuous ether extractor was used to separate them from the aqueous solution of inorganic salts. The properties of the products which were obtained agreed well with those recorded in the literature with the exception of *o*-ethoxymethyl benzoic acid. Repeated recrystallization of this material gave a melting point of 83–84° rather than the reported 85–86°.[9]

The runs with the quaternary salts were acidified with concentrated hydrogen iodide, extracted thoroughly with ether and evaporated to dryness *in vacuo* on a steam-bath. Evaporation of the ether extracts left no higher boiling material showing that no unsubstituted acid was formed. The residue was then broken up with a spatula and taken to dryness twice with a mixture of 50 ml. of benzene and 50 ml. of absolute alcohol. This residue was then extracted three times with 50 ml. portions of absolute alcohol and these extracts fractionally crystallized. A similar procedure was used for the isolation of the hydrochloride of dimethylaminopivalic acid.

In the run with the methiodide of dimethylaminopivaldehyde only the methiodide of β-dimethylamino-α,α-dimethyl propyl alcohol was isolated. When the methiodide of α-dimethylaminoisobutyraldehyde was employed both the quaternary aminoalcohol and the hydrate of the quaternary aminoacid were isolated.

The methiodide of α-dimethylaminoisobutyl alcohol crystallized from absolute alcohol in which it was sparingly soluble in the form of clear compact crystals melting at 233–235° (dec.).

Anal. Calcd. for $C_7H_{18}ONI$: C, 32.50; H, 7.05. Found: C, 32.52; H, 7.15.

The hydrate of α-dimethylaminoisobutyric acid methiodide crystallized from hot absolute alcohol in which it was fairly soluble in the form of sponge-like microcrystalline clusters melting at 188–189° (dec.).

Anal. Calcd. for $C_7H_{18}O_3NI$: C, 28.90; H, 6.24. Found: C, 29.11; H, 6.50.

TABLE I

CANNIZZARO REACTION WITH HYDROXY AND AMINO ALDEHYDE DERIVATIVES

Aldehyde	Moles used	% Yield of the corresponding Acid[a]	Alcohol[a]
Aldol	1.00	..[b]	..[b]
Propionaldol[c]	0.30	..[b]	..[b]
Isobutyraldol[d]	.27	93[e] (isobutyric acid only)	75
Hydroxypivaldehyde[f]	.60	77[h]	84[h]
Dimethylaminopivaldehyde[i]	.70	59[j]	87[k]
Dimethylaminopivaldehyde methiodide[i]	.10	..[l]	37[k]
α-Hydroxy-α-ethyl-phenyl-acetaldehyde[m]	.15	60[n]	61[o]
o-Ethoxymethyl-benzaldehyde[p]	.13	18[q]	56[r]
o-Ethoxymethyl-benzaldehyde[s]	.24	27[q]	53[r]
α-Dimethylaminoisobutyraldehyde methiodide[t]	.05	32[t]	21[t]

[a] The physical properties of the compounds listed in this table agreed with the values given in the references unless it is indicated otherwise. [b] An aldehyde resin only was obtained. [c] Grignard and Abelmann, *Bull. soc.c him.*, [4] **7**, 639 (1910). [d] Saunders, *et al.*, THIS JOURNAL, **65**, 1715 (1943). [e] Calculated on the basis that from one mole of aldol 0.5 moles of acid would be expected. [f] Krestinski and Perssianzewa, *Ber.*, **63**, 182 (1930). [g] Stiller, Harris, Finkelstein, Keresztesy and Folkers, THIS JOURNAL, **62**, 1787 (1942). [h] Wesseley, *Monatsh.*, **22**, 66 (1901). This author also carried out the Cannizzaro reaction on hydroxypivaldehyde. He reported yields of 90 and 100% for the hydroxy acid and glycol, respectively. [i] Mannich, Lesser and Stilton, *Ber.*, **65**, 378 (1932). [j] Isolated as the hydrochloride. [k] Fourneau, Benoit and Firmenich, *Bull. soc. chim.*, [4] **47**, 880 (1930). [l] Any quaternary aminoacid which may have been present could not be separated from the potassium iodide formed by neutralizing the reaction mixture with hydrogen iodide. [m] Freon, *Ann. chim.*, 11, 501 (1939). [n] Grignard, *Compt. rend.*, **135**, 629 (1902). [o] Stoerner, *Ber.*, **39**, 2300 (1906). [p] Arditti, *Compt. rend.*, **223**, 635 (1946). [q] Noyes and Coss, THIS JOURNAL, **42**, 1283 (1920). Repeated recrystallization of this material gave a melting point of 83–84° rather than the reported 85–86°. [r] Braun and Zobel, *Ber.*, **56**, 2148 (1923). [s] This run was carried out with 1.2 moles of sodium ethoxide instead of potassium hydroxide. [t] See the experimental part.

Discussion

In Table I are summarized the results which were obtained by carrying out the Cannizzaro reaction on several α, β and γ-hydroxy and amino

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(7) In one run with *o*-ethoxymethyl benzaldehyde, sodium ethoxide in absolute ethanol was employed (see Table I).

(8) See ref. 2, p. 111–113.

(9) Footnote *q*, Table I.

aldehyde derivatives. Aldol and propionaldol formed aldehyde resins and isobutyraldol apparently underwent a simultaneous dealdolization and Cannizzaro reaction since the glycol was isolated but only isobutyric acid could be found in the acid fraction. In the other examples the normal Cannizzaro reaction occurred.

Obviously it cannot be concluded from this work that a displacement reaction such as the one shown in equation 1 does not occur, but it is quite clear that even in what appears to be the most favorable case (the quaternary amino aldehydes) the displacement shown in equations 3 and 4 does not proceed at a rate comparable to the Cannizzaro reaction.

Summary

A study of the products obtained by carrying out a Cannizzaro reaction on a number of hydroxy and amino aldehyde derivatives revealed that aldol and propionaldol formed aldehyde resins. Isobutyraldol gave the corresponding glycol and isobutyric acid, but in the other cases which were investigated the Cannizzaro reaction proceeded normally. These reactions are of interest since the occurrence of an intramolecular hydride ion displacement similar to one postulated for the Cannizzaro reaction would be expected to result in the formation of unsubstituted acids of the same carbon skeleton.

URBANA, ILLINOIS RECEIVED MARCH 29, 1948

NOTES

Catalytic Oxidation of Alcohols at Low Temperatures

BY ROBERT H. BAKER AND DAVID STANONIS

By making use of the ease of oxidation of anthrahydroquinone by air, it has been possible to modify the usual Oppenauer reaction[1] and to demonstrate a catalytic oxidation of the alcohols. Thus, instead of anthraquinone being used as the oxidant in the reversible reaction,[2] $RCH(OH)R + \text{quinone} \rightleftarrows RCOR + \text{hydroquinone}$, it is used only in catalytic amounts, and the progress of the reaction is followed manometrically. The conventional catalyst, aluminum *t*-butoxide, must be used in sufficient quantity to react with the water produced in the reaction, but this amount is no larger than that which is generally used.[1] The catalytic oxidation fails with aluminum *t*-butoxide made from certain batches of metal, but this is remedied by the addition of anhydrous cupric sulfate, or better cupric oleate, to the reaction mixtures.

Cholesterol was found to take up more than two atoms of oxygen while 4-cholesten-3-one with the same catalyst took up none. This is in agreement with the observations of Bergstrom and Wintersteiner[3] on the emulsion oxidation of steroid derivatives, in which those containing the 5,6 double bond are oxidized more extensively than those with 4,5 unsaturation.

Experimental

Apparatus.—The reactions were carried out in flasks shaken by a motor-driven eccentric and connected to a 100-ml. buret by means of a spiral of copper tubing bearing standard taper brass connections. Rubber connections were found to be unsatisfactory because of the rapid uptake of oxygen.

Oxidations.—The conditions of typical runs are shown in Table I. The amount of solvent used was 5 ml. per millimole of alcohol. Unpurified aluminum *t*-butoxide was used and the cupric salt was added only when necessary. The oxygen pressure was maintained at one atmosphere by means of a leveling bulb containing mercury.

TABLE I

Run	Compound	Millimoles	$Al(O\text{-}t\text{-}Bu)_3$, millimoles	Cupric oleate, mg.	Quinone, millimoles	Solvent	T, °C.	O_2, atoms/mole compound	Time, hr.
1	Benzohydrol	50	30	..	5	*m*-Xylene	60	..	56
2	Same	3	4	50	0.3	Toluene	35	0.3	71
3	Fluorenol	3	4	50	0.3	Benzene	30	0.5	65
4	Same	3	4	..	0.3	Benzene	25	0.78	114
5	Cholesterol	15	20	..	15	Benzene	30	2.0	407
6	Cholestenone	3	4	..	15	Benzene	30	0.04	144

In numerous experiments fluorenol was found to take up oxygen more rapidly than benzohydrol, but duplicate rates on either compound could not be obtained. The yield of benzophenone from Run 1 was 56% (determined polarographically[2]). Fluorenone was isolated by steam

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[1] Oppenauer, *Rec. trav. chim.*, **56**, 137 (1937); *Org. Syn.*, **21**, 18 (1941).

[2] Baker and Adkins, THIS JOURNAL, **62**, 3305 (1940).

[3] Bergstrom and Wintersteiner, *J. Biol. Chem.*, **145**, 327 (1942).