[CONTRIBUTION FROM THE NATIONAL INSTITUTES OF HEALTH]

N-DEMETHYLATION WITH POTASSIUM FERRICYANIDE

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In attempting to oxidize tropine to tropinone with alkaline potassium ferricyanide, following the directions of a German patent[1] (1), I obtained nortropine[1a] in place of the expected ketone. This surprising result was not further investigated, but at a later date, when a similar reaction was attempted with 3-dimethylaminocyclohexanol, the product isolated proved to be 3-monomethylaminocyclohexanol. This reaction of potassium ferricyanide seems not to have been previously reported[1b] and I was prompted to examine the scope of this means of N-demethylation.

Secondary bases were readily obtained from 2,2,4-trimethyl-4-dimethylaminopentane (dimethyl-*tert*-octylamine), N-methyldicyclohexylamine, dimethylcyclohexylamine,[2] 2-dimethylamino-1,2,3,4-tetrahydronaphthalene, and 1,2,6-trimethylpiperidine. On the other hand, no demethylation products (secondary amines) were isolated when the reaction was applied to N-methylmorpholine,[3] codeine, nicotine, and dimethylaniline. The ferricyanide, however, was reduced in each case, slowly by N-methylmorpholine and codeine, but rapidly by nicotine and dimethylaniline.

While this material represents only a cursory selection of examples, the results indicate that demethylation takes place only if the methylamino or dimethylamino group is attached to secondary or tertiary carbon atoms. If the group is attached to one or two primary carbon atoms the reaction fails. An exception to this hypothesis was found in the failure of 1,1-diphenyl-3-dimethylamino-1-butanol to demethylate. This compound appeared to be very little soluble in the reaction medium, and was recovered unchanged after a prolonged reaction period. The reduction of the ferricyanide was also extremely slow. It is probable that at least a certain minimum solubility in the reaction medium is a requirement for the success of the reaction.

I have made no attempt to elucidate the mechanism of this reaction. However, I plan to continue this investigation, especially with tropine and codeine.

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[1] In the patent (1), no information is given as to how tropinone was identified, or as to the yield.

[1a] Nortropine has been prepared by the action of alkaline $KMnO_4$ on tropine (12).

[1b] After the completion of this work, I found a thesis by R. N. de Haas (13) describing the oxidation of various amines, including trimethylamine, with potassium permanganate *and potassium ferricyanide.* While the indirect analytical methods employed were insufficient to prove the identity of the products, it seems very probable that trimethyl-, triethyl- and tripropyl- amines were converted to the corresponding secondary and primary amines by these oxidizing agents.

[2] Samples of this material were kindly supplied by E. I. du Pont de Nemours & Co., and by the Monsanto Chemical Co.

[3] A sample of this material was kindly supplied by the Carbide and Carbon Chemicals Corp.

EXPERIMENTAL[4]

PREPARATION OF TERTIARY AMINES[5] (2)

3-Dimethylaminocyclohexanol (I). 3-Aminocyclohexanol (10 g.), 130 g. of 90% formic acid and 94 g. of 37% formaldehyde were refluxed until the evolution of CO_2 had ceased. The resultant I was isolated and distilled; b.p. 66°/0.05 mm.; $n_D^{25.2}$ 1.4843; lit. (3) n_D^{22} 1.4846. The *hydrochloride* had m.p. 161–164°.

Anal. Calc'd for $C_8H_{17}NO \cdot HCl$: C, 53.5; H, 10.11.
Found: C, 53.4; H, 10.07.

I·picrate had m.p. 180–181° (crystallized from ethyl acetate).

1,2,6-Trimethylpiperidine (II). The methylation of 11.2 g. of 2,6-dimethylpiperidine (b.p. 128–134°) with 9 g. of 37% formaldehyde and 25 ml. of 85% formic acid, followed by purification through shaking with aqueous sodium hydroxide and benzoyl chloride, gave II, b.p. 25–30°/0.05 mm. The product was further purified through the picrate [m.p. 228°; lit. (4) 228°].

2,2,4-Trimethyl-4-dimethylaminopentane (III) (*dimethyl-tert-octylamine*). *tert*-Octylamine[6] (129 g.) was methylated[7] with 212 ml. of 90% formic acid and 180 ml. of 37% formaldehyde in the usual manner. The resultant III had b.p. 107°/110 mm. *III·HCl* had m.p. 182° (with sintering at 170°) (from ethyl acetate).

Anal. Calc'd for $C_{10}H_{23}N \cdot HCl$, M.W. 193.76: C, 61.98; H, 12.48.
Found: C, 62.00; H, 12.78.

N-Methyldicyclohexylamine (IV). The methylation of purified dicyclohexylamine with formaldehyde and formic acid gave IV; *IV·HCl* had m.p. 195–197°; lit. (5) 193–194°. This material crystallizes from water as the dihydrate.

Anal. Calc'd for $C_{13}H_{25}N \cdot HCl \cdot 2H_2O$, M.W. 276.84: C, 58.29; H, 11.29.
Found: C, 58.01; H, 11.25.

2-Dimethylamino-1,2,3,4-tetrahydronaphthalene (V). The formaldehyde-formic acid methylation of *ac*-β-aminotetralin gave a good yield of V; b.p. 126°/10 mm.; n_D^{22} 1.5382. *V·HCl* had m.p. 216.5°; lit. (6) 214–215°.

Anal. Calc'd for $C_{12}H_{17}N \cdot HCl$, M.W. 211.73: C, 68.07; H, 8.57.
Found: C, 68.23; H, 8.74.

V·Chloroplatinate (from 50% ethanol), crystallized as heavy orange prisms, m.p. 200–210°, depending on the rate of heating; lit. (6) 210°.

Anal. Calc'd for $C_{24}H_{34}N_2 \cdot H_2PtCl_6$, M.W. 760.52: C, 37.90; H, 4.77; Pt, 25.67.
Found: C, 37.91; H, 4.83; Pt, 25.85.

SECONDARY AMINES OBTAINED IN THE POTASSIUM FERRICYANIDE OXIDATION

Nortropine (VI). The crude base (4.7 g.) from the alkaline hydrolysis of 10.6 g. (0.037 mole) of atropine was dissolved in water and treated dropwise below 5° with 24.2 g. of $K_3Fe(CN)_6$ and 3.11 g. of NaOH in 110 ml. of H_2O during ½ hour. After allowing to warm to room temperature, the solution was concentrated *in vacuo*, and the residue was continuously extracted with ether. The ethereal solution was dried with solid NaOH and evaporated. The residue was sublimed *in vacuo* and gave 3.7 g. (87%) of a semicrystalline mass.

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[4] All melting points are uncorrected.

[5] The tertiary amines used in this work were either obtained commercially or prepared by the method of Clarke, *et al.* (2), except in the case of tropine, which was obtained by the hydrolysis of atropine.

[6] A generous sample of this material was kindly supplied by the Rohm & Haas Chemical Co.

[7] A slight modification of this procedure is described in literature supplied by the Rohm & Haas Chemical Co.

Upon recrystallization from ether an intermediate product was obtained which had m.p. 135–141°. For analysis, the material was resublimed.

Anal. Calc'd for $C_8H_{13}NO_2$: C, 61.91; H, 8.44; N, 9.03.
Found: C, 61.46, 61.78; H, 8.30, 8.15; N, 9.49, 9.19.

This compound may be formylnortropine. Warming briefly with dilute hydrochloric acid on the steam-bath and isolation of the resultant base gave VI,[8] m.p. 161–162°; lit. 161°. *VI·HCl* does not melt by 280°; *VI·aurichloride* (from water) has m.p. 218° (lit. 215–216°, 217°).

3-Monomethylaminocyclohexanol (VII). To 47 g. of $K_3Fe(CN)_6$ and 9.5 g. 86% KOH in 130 ml. of H_2O was added 10 g. of 3-dimethylaminocyclohexanol in 100 ml. of H_2O. The temperature was held below 5° for ¾ hour. After stirring and allowing to warm to room temperature, the mixture was let stand overnight. After evaporation to dryness, the solids were extracted with hot 95% ethanol, the ethanol replaced with ether, the ether dried and evaporated. The residue weighed 9.2 g. (93%) and had b.p. 68°/0.05 mm. and n_D^{25} 1.4861. An analytical sample was redistilled but there was no change in the above constants.

Anal. Calc'd for $C_7H_{15}NO$: C, 65.1; H, 11.70.
Found: C, 64.98, 65.39; H, 11.87, 11.80.

Methylaminocyclohexane (VIII). Dimethylaminocyclohexane [m.p. of hydrochloride 226–227°; lit. (7) 224°], (4.65 g.) was added to 3.11 g. of NaOH and 24.2 g. of $K_3Fe(CN)_6$ in 110 ml. of H_2O. When most of the ferricyanide had been reduced, the reaction mixture was extracted with ether. The resultant VIII gave a *picrate*, m.p. 169–170°; lit. (7) 170°. The *N-benzoyl* derivative of VIII melted at 84–85° (from ether); lit. (8) 85–86°.

2,6-Dimethylpiperidine (IX). The oxidation of 3.5 g. of 1,2,6-trimethylpiperidine was conducted below 5° with 37.2 g. of $K_3Fe(CN)_6$ and 7.5 g. of KOH in 100 ml. of H_2O. After standing overnight at room temperature, the solution was distilled, the distillate being caught in a receiver containing excess dilute sulfuric acid. The base liberated from this distillate gave *IX·picrate*, m.p. 161–163° (from ethanol); lit. (9) 162–164°. The *N-benzoyl* derivative of IX had m.p. 108–109°; lit. (10) 111°.

2,2,4-Trimethyl-4-methylaminopentane (X) (*methyl-tert-octylamine*). Dimethyl-*tert*-octylamine (14.5 g.) was oxidized with 132 g. of $K_3Fe(CN)_6$, 27 g. of KOH, and 600 ml. of H_2O. After stirring 4 hours at room temperature, the reaction mixture was allowed to stand overnight. The resultant X was extracted with ether; yield 12.6 g. The crude *p-nitrobenzamide* of X had m.p. 79–82° (83–84° after sublimation). Treatment of X with dilute acetic acid and aqueous $NaNO_2$ gave the *N-nitroso* derivative of X, flat plates from petroleum ether, m.p. 60°.

X was also prepared from *tert*-octylamine by catalytic hydrogenation of the azomethine formed from *tert*-octylamine and formaldehyde;[9] b.p. 85–95°. *X·HCl* had m.p. 196–202° (from alcohol-ether).

Anal. Calc'd for $C_9H_{21}N\cdot HCl$, M.W. 179.73: C, 60.14; H, 12.34.
Found: C, 60.05; H, 12.09.

X·p-nitrobenzamide had m.p. 83–84° (after sublimation), alone or in admixture with material prepared by ferricyanide oxidation of III.

Anal. Calc'd for $C_{16}H_{24}N_2O_3$, M.W. 292.37: C, 65.72; H, 8.27.
Found: C, 65.94; H, 8.14.

The *N-nitroso* derivative, from a hydrochloric acid solution of X (obtained by hydrogenation of the azomethine) and $NaNO_2$, melted at 60° and showed no depression when mixed with that from the ferricyanide oxidation product.

Anal. Calc'd for $C_9H_{20}N_2O$, M.W. 172.27: C, 62.74; H, 11.70.
Found: C, 62.69; H, 11.64.

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[8] Tropinone melts at 41°, its hydrochloride at 188–189°, and its aurichloride at 163°.

[9] Directions for this preparation are given in literature supplied by the Rohm & Haas Chemical Co.

Hydrogenation of *X*·*p*-nitrobenzamide with a palladium-charcoal catalyst in 95% ethanol solution at room temperature and atmospheric pressure gave 2,2,4-trimethyl-4-methylamino-N-*p*-aminobenzoylpentane (XI). *XI·HCl* had m.p. 155–156°. $XI \cdot H_2SO_4 \cdot H_2O$[10] melted at 139°, resolidified about 180–185°, and remelted at 208–212° (rapid heating); these salts are unstable in boiling water.

Anal. Calc'd for $C_{32}H_{52}N_4O_2 \cdot H_2SO_4 \cdot H_2O$, M.W. 622.86: C, 60.00; H, 8.81; N, 8.76.
Found: C, 59.68; H, 8.50; N, 9.10.

Compound XI, from 40% ethanol, had m.p. 54.5–57.0°.

Anal. Calc'd for $C_{16}H_{26}N_2O$, M.W. 262.39: C, 73.23; H, 9.99.
Found: C, 73.06; H, 9.71.

Dicyclohexylamine (XII). Methyldicyclohexylamine hydrochloride dihydrate (5.9 g.) was converted to the base and oxidized with 40 g. of $K_3Fe(CN)_6$ and 7 g. of KOH in 200 ml. of water. The mixture was shaken overnight at room temperature and the XII isolated by ether extraction. The yield was 3.4 g. (87%). An assay of this material with nitrous acid gave 95% of the *N-nitroso* derivative of m.p. 106°; lit. (11) 104–105°. A mixture m.p. determination with authentic material showed no depression.

XII·HCl, very sparingly soluble in water, sublimes but does not melt up to 300°. This is identical with the behavior of authentic dicyclohexylamine hydrochloride.

2-Methylamino-1,2,3,4-tetrahydronaphthalene (XIII). When 17.5 g. of *ac*-*β*-dimethylaminotetralin was shaken with 150 g. of $K_3Fe(CN)_6$, 50 g. of KOH, and 1000 ml. of H_2O for 24 hours, and the base extracted with ether, a colorless oil was obtained. Precipitation with gaseous HCl and crystallization from alcohol-ether gave 6.1 g. of crude *XIII·HCl*, m.p. 173–176°. This was recrystallized from butanol, washed with ether, and sublimed at 100°/1μ; m.p. 185–186°.

Anal. Calc'd for $C_{11}H_{15}N \cdot HCl$, M.W. 197.71: C, 66.82; H, 8.16.
Found: C, 66.72; H, 8.02.

One gram of the hydrochloride was dissolved in water and converted to the *N-nitroso* derivative by warming with $NaNO_2$ and dilute acetic acid. The product precipitated as an oil; crude yield 0.7 g. This crystallized readily, and was recrystallized several times from ether and sublimed *in vacuo*; m.p. 49°. Analysis indicated that the material was not entirely pure.

Anal. Calc'd for $C_{11}H_{14}N_2O$, M.W. 190.24: C, 69.44; H, 7.42.
Found: C, 69.87, 69.96, 70.00, 70.02; H, 7.35, 7.61, 7.24, 7.21.

XIII·chloroplatinate was crystallized from 50% ethanol in thin, light yellow prisms; m.p. about 200°; lit. (6) 228°.

Anal. Calc'd for $C_{22}H_{30}N_2 \cdot H_2PtCl_6$, M.W. 732.47: C, 36.07; H, 4.40; Pt, 26.65.
Found: C, 36.35; H, 4.58; Pt, 26.78.

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SUMMARY

It has been found that certain tertiary amines are demethylated by alkaline ferricyanide to the corresponding secondary amines. Some limitations of the reaction are discussed.

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[10] This compound was submitted to Dr. N. B. Eddy of this Institute for analgesic tests. Results will be published elsewhere.

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