reductions run by inverse mixing at 55° and 2° gave, respectively, 69 and 75% yields of cholesterol. In another reduction carried out at 55° but with addition of ester to hydride ("normal mixing"), 58% cholesterol was obtained. As with lithium aluminum hydride the normal mixing seems to allow formation of Δ^4-isomers to a somewhat greater extent.

It is not unlikely that the initial step in this reaction is the solvolysis of the enol acetate to yield the free ketone, Δ^5-cholestenone, which is in the main then reduced before it can rearrange to the more stable Δ^4-cholestenone; reduction of this latter compound yields the Δ^4-stenols. The borohydride is not known to attack esters ordinarily,[3] and the ratio of Δ^5-stenols obtained is about what one would expect from direct reduction of the Δ^5-ketone.[4]

In addition to the simplified experimental technique and the increased yield, the borohydride method has the advantage that the conversion may be employed with steroids which contain other functional groups; *i.e.*, halogen atoms or carboxyl groups which would be removed or reduced in the presence of lithium aluminum hydride.[5] Further applications of this reduction are now being investigated in this Laboratory.

Acknowledgment.—The authors wish to express their appreciation to Professor Donald S. Noyce for his kind assistance with the course of this work.

Experimental[6]

Reduction of Enol Acetate; Inverse Mixing.—To a refluxing solution of 0.95 g. of cholestenone enol acetate (2.22 mmoles, m.p. 79–80°, prepared as in reference 2) in 40 ml. of methanol and 10 ml. of ether, there was added over a period of 30 minutes 0.4 g. of sodium borohydride[7] (10 mmoles) in 10 ml. of methanol. After further refluxing the solution for three hours there was added dropwise 6 ml. of concentrated hydrochloric acid and the heating continued for an additional hour. The salt which precipitated upon acidification caused some slight bumping during this final hour of reflux. The reaction mixture was diluted with 150 ml. of ether and washed with four 75-ml. portions of water. Evaporation of the dried (Na_2SO_4) ethereal solution yielded 851 mg. of residue which was chromatographed on 30 g. of alumina[8] using the solvent sequence hexane, 15% (by volume) ether in hexane, 25% ether in hexane. Table I summarizes the results.

TABLE I

Compound eluted	Wt. in mg.	Yield, %	M.p., °C. crude	M.p., °C. recrystd.
Cholestadiene	65	8	78–80	80–81[a]
Epicholesterol	141	13	134–137	140–141[b]
Cholesterol	592	69	144–146	147–148[c]

[a] Shows ultraviolet maxima at 229, 235 and 244 mμ. (H. E. Stavely and W. Bergmann, *J. Org. Chem.*, 1, 567 (1936)). [b] $[\alpha]^{25}D$ −47.4° (*c* 2.35, $CHCl_3$) (compare reference 2). [c] $[\alpha]^{25}D$ −39.3° (*c* 3.72, $CHCl_3$) (R. J. Anderson, *J. Biol. Chem.*, 71, 407 (1926–1927)).

Normal Mixing.—To a refluxing solution of 0.3 g. of sodium borohydride in 10 ml. of methanol there was added over a period of 30 minutes 0.40 g. of the enol acetate in 20 ml. of methanol in 10 ml. of ether. Additional 0.1-g. portions of the hydride were added when half of the ester solution had been added and again when all of the ester solution had been added. The solution was further refluxed for two hours and then processed as above. From the chromatograph there was obtained 82 mg. (23%) cholestadiene, 52 mg. (14%) epicholesterol and 209 mg. (58%) cholesterol.

Reduction at Lower Temperature.—To a stirred solution of 0.45 g. of enol acetate in 60 ml. of methanol and 20 ml. of ether, cooled in an ice-bath, there was added over a period of one hour a solution of 0.8 g. of sodium borohydride in 20 ml. of methanol. The solution was kept at ice-bath temperature for 30 hours and then warmed to reflux and processed as before. From this experiment there was obtained 30 mg. (7%) of cholestadiene, 55 mg. (13%) of epicholesterol and 318 mg. (75%) of cholesterol.[9]

(3) S. W. Chaikin and W. G. Brown, THIS JOURNAL, 71, 122 (1949).

(4) Unpublished results in this Laboratory; also compare C. W. Shoppee and G. H. R. Summers, *J. Chem. Soc.*, 687 (1950).

(5) R. F. Nystrom and W. G. Brown, THIS JOURNAL, 69, 1197, 3738 (1947).

(6) All melting points reported are corrected.

(7) Metal Hydrides Incorporated, Beverly, Massachusetts.

(8) Merck and Co., Inc., Reagent Grade Aluminum Oxide.

(9) A private communication from Dr. T. F. Gallagher indicates that somewhat higher yields of cholesterol can be obtained from this reduction by employing methanol–water as solvent at 0°.

DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING
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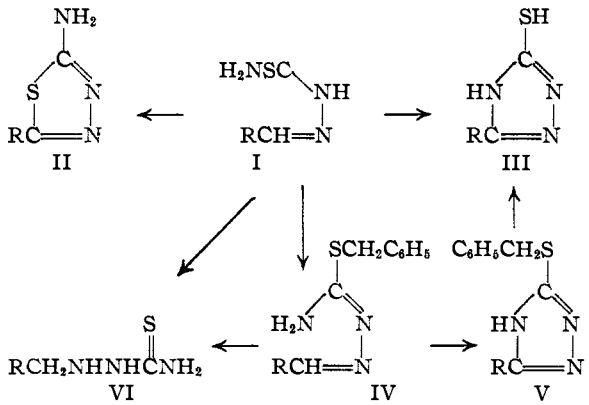
Oxidation and Reduction of 4-Acetamidobenzaldehyde Thiosemicarbazone

BY ROBERT DUSCHINSKY AND HAROLD GAINER

According to rather contradictory data found in the literature concerning the ferric chloride oxidation of thiosemicarbazones (I), the reaction may be expected to give either a 2-amino-1,3,4-thiadiazole (II)[1,2] or a 1,2,4-triazole-3-thiol (III)[3] or possibly a mixture of products containing both compounds. Quite recently Bernstein and co-workers[4] reported the preparation of II (R = 4-$CH_3CONHC_6H_4$) by ferric chloride oxidation of 4-acetamidobenzaldehyde thiosemicarbazone ("Tibione") (I), no mention being made of an alternative oxidation product III.



This prompts us to report a method yielding 5-(4-acetamidophenyl)-1,2,4-triazole-3-thiol (III) exclusively. The sulfur in I was protected by benzylation to give IV, which was identified as the S-benzyl derivative by alkaline cleavage yielding benzyl mercaptan. Ferric chloride oxidation of IV gave the triazole V which was debenzylated by sodium in liquid ammonia to yield III. The latter

(1) G. Young and W. Eyre, *J. Chem. Soc.*, 74, 54 (1901).

(2) S. C. De and S. K. Roy-Choudhury, *J. Indian Chem. Soc.*, 5, 269 (1928).

(3) E. Fromm, *Ann.*, 447, 275 (1926).

(4) J. Bernstein, H. L. Yale, K. Losee, M. Holsing, J. Martins and W. A. Lott, THIS JOURNAL, 73, 906 (1951).

could be deacetylated by alkaline hydrolysis. 3-Methylmercapto-5-(4-acetamidophenyl)-1,2,4-triazole was obtained in a similar oxidation from methylated I. The triazoles were found to be soluble in alkali whether or not they contained a free thiol group. The thiol group was identified by a characteristic color reaction with lead acetate, not given by the thio ethers, and by conversion of the thiol III into the disulfide.

Whereas the triazole nucleus, as shown above, was found to be stable toward reduction by sodium in liquid ammonia, the open chain compounds I and IV were reduced to 1-(4-acetamidobenzyl)-3-thiosemicarbazide (VI). The use of this reagent for the reduction of thiosemicarbazones might sometimes be preferable to the sodium amalgam method[4] because it is less likely to hydrolyze alkali-labile groups.

According to information received from Dr. Schnitzer and Dr. Grunberg of the Chemotherapy Laboratory of Hoffmann–La Roche none of the compounds prepared exhibited anti-tubercular activity "*in vivo*."

Experimental[5]

4-Acetamidobenzaldehyde 3-Benzyl-3-thiopseudosemicarbazone Hydrochloride (IV).—A mixture of 17.7 g. (0.075 mole) of I and 17.2 ml. (0.15 mole) of benzyl chloride was refluxed for 1.5 hours, while gradual dissolution and then reprecipitation occurred. The product was filtered after cooling and washed with ethanol; yield 19.8 g. (73%), m.p. 215–216°. For the analysis it was recrystallized by dissolution in 20 volumes of hot methanol, followed by addition of 20 volumes of ether.

Anal. Calcd. for $C_{17}H_{18}ON_4S\cdot HCl$: C, 56.27; H, 5.28; N, 15.44. Found: C, 56.23; H, 5.43; N, 15.12.

For obtaining the base, 0.365 g. of the hydrochloride IV was dissolved in 50 ml. of boiling water and 1 ml. of *N* hydrochloric acid; the solution was cooled and neutralized with 2 ml. of *N* sodium hydroxide, whereupon 0.25 g. of product precipitated. After recrystallization from ethanol, it melted at 205–207°.

Anal. Calcd. for $C_{17}H_{18}ON_4S$: S, 9.82. Found: S, 9.61.

A solution of 0.365 g. (0.001 mole) of the hydrochloride IV in 13 ml. of ethanol and 11 ml. of 3 *N* sodium hydroxide was refluxed for 2 hours. After evaporating the alcohol *in vacuo*, the mixture was acidified with 33 ml. of *N* hydrochloric acid and extracted with ether. The ether extract left after evaporation a yellowish oil, which darkens when exposed to the air and exhibits the characteristic odor of benzyl mercaptan. It was dissolved in 5 ml. of ethanol; the filtered solution was mixed with 10 ml. of a 5% alcoholic solution of mercuric cyanide. Upon addition of 10 ml. of water, 140 mg. (63%) of mercuric salt crystallized in long needles. The product could be recrystallized from ethanol. It melted at 121° as reported[6] for $Hg(SCH_2C_6H_5)_2$; its mixed melting point with an authentic specimen showed no depression.

3-Benzylmercapto-5-(4-acetamidophenyl)-1,2,4-triazole (V).—To a boiling solution of 12.5 g. (0.034 mole) of crude hydrochloride IV in 800 ml. of water, was added, in 10 to 20 ml. portions, 186 ml. (0.069 mole) of a 10% ferric chloride hexahydrate solution. The crystals which separated upon cooling were filtered and washed with water; yield 9 g. (73%). After recrystallization from 400 ml. of methanol, 7 g. was obtained; m.p. 195–196° (dec.). The compound seems to contain initially one mole of water of crystallization which it loses upon drying *in vacuo* at 120°.

Anal. Calcd. for $C_{17}H_{16}ON_4S$: C, 62.94; H, 4.97. Found: C, 62.77; H, 5.11.

5-(4-Acetamidophenyl)-1,2,4-triazole-3-thiol (III).—To a solution of 20 g. (0.055 mole) of V in 500 ml. of liquid ammonia was added in small pieces 6.5 g. (0.28 mole) of sodium until the resultant blue color persisted. The solution was decolorized by the addition of *ca.* 0.1 g. of ammonium chloride and was then evaporated. The residue was dissolved in 300 ml. of water. The aqueous solution was extracted with a little ether and then clarified by filtration. Acidification with 160 ml. of 2 *N* hydrochloric acid precipitated 11.15 g. (86%) of product which decomposes at about 345°. Since the thiol is insoluble in organic solvents, it was purified with little loss of material by dissolving it in one mole of sodium hydroxide or ammonia and precipitating it with carbon dioxide, acetic acid or hydrochloric acid. The precipitate was then washed with water, followed by ethanol to remove a yellowish coloration, and finally ether. It was dried at 110° *in vacuo*.

Anal. Calcd. for $C_{10}H_{10}ON_4S$: C, 51.27; H, 4.30; S, 13.61. Found: C, 51.51; H, 4.41; S, 13.31.

A drop of alkaline thiol solution mixed on a filter paper with lead acetate solution produced a yellow color.

3,3′-Dithiobis-[5-(4-acetamidophenyl)-1,2,4-triazole].—A solution of 0.34 g. (0.00145 mole) of III in 15.5 ml. of 0.1 *N* sodium hydroxide was oxidized at room temperature by the addition of 14.5 ml. of 0.1 *N* iodine solution, followed by short heating on a steam-bath. After cooling, the jelly-like precipitate which formed was filtered and washed with water, methanol, and ether. The product (0.32 g.) was soluble in alkali and strong ammonia and could be reprecipitated with acid. A negative lead acetate test showed the absence of a free thiol group.

The product, which undergoes decomposition at about 322°, retained water tenaciously; for the analysis it had to be dried at 140° *in vacuo*.

Anal. Calcd. for $C_{20}H_{18}O_2N_8S_2$: C, 51.49; H, 3.89; S, 13.74. Found: C, 50.94; H, 4.28; S, 13.32.

5-(4-Aminophenyl)-1,2,4-triazole-3-thiol.—A solution of 8.3 g. (0.035 mole) of III in 80 ml. of 1.93 *N* sodium hydroxide was refluxed for 1 hour. After the addition of charcoal, filtration, and neutralization with 30.9 ml. of 5 *N* hydrochloric acid, the solution was cooled and the product was filtered and washed with water; yield 5.95 g. (87%); m.p. 283–285° (dec.). Upon recrystallization from 600 ml. of water, 5.4 g. was obtained. The compound gives a yellow color with lead acetate. It is soluble in dilute hydrochloric acid and alkali. A crystalline hydrochloride could not be obtained.

Anal. Calcd. for $C_8H_8N_4S$: C, 49.98; H, 4.19; N, 29.15. Found: C, 49.42; H, 4.02; N, 28.80.

4-Acetamidobenzaldehyde 3-Methyl-3-thiopseudosemicarbazone Hydroiodide and Hydrochloride.—A suspension of 50 g. (0.212 mole) of I in one liter of ethanol and 120 ml. of methyl iodide was shaken overnight. The hydroiodide was filtered and washed with ethanol and ether; yield 78 g. (97%); m.p. 227–228° (dec.). After recrystallization from 100 volumes of water, the m.p. was 235° (dec.). Upon heating with alkali, the characteristic odor of methyl mercaptan was noticed.

Anal. Calcd. for $C_{11}H_{14}ON_4S\cdot HI$: C, 34.93; H, 4.00. Found: C, 35.22; H, 4.12.

For the preparation of the hydrochloride, 35 g. (0.0926 mole) of the hydroiodide were suspended in 1 liter of methanol and 100 ml. of water, and refluxed for 2 hours with moist silver chloride prepared from 20 g. of silver nitrate and hydrochloric acid. The hot solution was filtered, cooled, and mixed with 2 liters of ether and 20 ml. of concentrated hydrochloric acid; yield 18 g. of hydrochloride; m.p. *ca.* 177° (dec.). For the analysis, 3.3 g. was dissolved in a boiling mixture of 35 ml. of methanol and 5 ml. of water. Five ml. of concentrated hydrochloric acid was then added to the cooled solution to crystallize the product; yield 2.77 g.; m.p. 179–180° (dec.). The product contained 2 moles of water.

Anal. Calcd. for $C_{11}H_{14}ON_4S\cdot HCl\cdot 2H_2O$: C, 40.92; H, 5.62; N, 17.36. Found: C, 41.37; H, 5.61; N, 17.09.

3-Methylmercapto-5-(4-acetamidophenyl)-1,2,4-triazole Hydrochloride.—To a solution of 5.7 g. of crude 4-acetamidobenzaldehyde 3-methyl-3-thiopseudosemicarbazone hydrochloride in 150 ml. of boiling water was added 108 ml. of 10% ferric chloride hexahydrate solution in *ca.* 10-ml.

(5) All melting points are corrected; we are indebted to Dr. Al Steyermark and his staff for the microanalyses and to Mr. Harry Parkhurst for his technical assistance.

(6) A. Gutmann, *Ber.*, **49**, 954 (1916).

portions. After cooling, filtering, and washing under carbon dioxide with water, ethanol and ether, 2.69 g. of clustered needles was obtained. The product was recrystallized by the addition of 2 ml. of concentrated hydrochloric acid to its solution in a hot mixture of 115 ml. of methanol and 10 ml. of water. It was found to be a hydrochloride with a melting point at about 270°. It is soluble in *N* sodium hydroxide.

Anal. Calcd. for $C_{11}H_{12}ON_4S \cdot HCl$: C, 46.39; H, 4.60; N, 19.68. Found: C, 46.46; H, 4.71; N, 19.51.

1-(4-Acetamidobenzyl)-3-thiosemicarbazide (VI).—To a suspension of 23.6 g. (0.1 mole) of I in 400 ml. of liquid ammonia was added in small pieces 7.3 g. of sodium. A clear solution resulted, after the addition of the first few pieces. By adding 0.6 g. of ammonium chloride, the persistent blue color was discharged. The residue obtained after evaporation was taken up with 200 g. of ice-water and the insoluble material was filtered and washed with water, ethanol and ether; yield 11.18 g. (47%), m.p. 209° (dec.). After recrystallization from 800 ml. of 50% methanol, the product melted at 217–218°. It is insoluble in *N* hydrochloric acid and alkali.

Anal. Calcd. for $C_{10}H_{14}ON_4S$: C, 50.40; H, 5.92; N, 23.51. Found: C, 50.68; H, 5.92; N, 23.24.

RESEARCH LABORATORIES
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Condensation of Nitroparaffins with α,β-Unsaturated Ketones Using Calcium Hydride[1]

BY NORTON FISHMAN[2] AND SAVERIO ZUFFANTI

Introduction.—Kloetzel,[3] in 1947, used diethylamine as a condensing agent for the reaction between nitroparaffins and α,β-unsaturated ketones. At room temperature he obtained yields of 58–97.5% in 6–35 days.

The basic character of calcium hydride[4] led us to investigate its efficacy as a condensing agent in this reaction. 2-Nitropropane, benzalacetophenone and calcium hydride produced no reaction even on prolonged standing over a period of several weeks.

In the presence of methanol, however, an immediate reaction results and within 15 hours a 92% yield of 4-methyl-4-nitro-1,3-diphenyl-1-pentanone is obtained. Nitromethane, 1-nitropropane and 2-nitropropane were condensed with benzalacetone and benzalacetophenone using calcium hydride and methanol. At room temperature the reactions were complete in from 1–21 days and the yields ranged from 65–92%.

Experimental

Purification of Materials.—The methanol and nitroparaffins were purified by allowing them to stand over calcium hydride for several weeks and then filtering and fractionating.

It was noted that although the hydride will not react with the pure alcohol or nitroparaffins individually, an instantaneous evolution of hydrogen is observed if the hydride is added to a mixture of the alcohol and the nitroparaffin. From the reaction mixture can be recovered the entire quantity of alcohol and the calcium salt of the nitroparaffin. The benzalacetone and benzalacetophenone were purified by repeated recrystallizations.

4-Methyl-4-nitro-1,3-diphenyl-1-pentanone.—Into a 250 ml. flask are placed 10 g. (0.048 mole) of benzalacetophenone, 44 g. (0.49 mole) of 2-nitropropane and 40 ml. of dry methanol. These are mixed thoroughly till the ketone is dissolved and 2 g. (0.048 mole) of calcium hydride is added. Thereafter continuous evolution of hydrogen is observed while the reaction progresses.[5] The mixture is allowed to stand stoppered with a calcium chloride tube for 24 hours, and then the solidified contents are extracted with anhydrous chloroform. The extract is concentrated and the crystals are filtered off, washed with alcohol, and dried. The product, 4-methyl-4-nitro-1,3-diphenyl-1-pentanone, melts at 133–135°. Yields of 85–92% are obtained. The purified crystals melt at 146°.

(1) Presented before the Chicago Meeting of the American Chemical Society, September 8, 1950. This note is part of the thesis presented by Norton Fishman to Northeastern University, in partial fulfillment of the requirements of the A.M. degree.

(2) Harvard University, Cambridge, Mass.

(3) M. C. Kloetzel, THIS JOURNAL, **69**, 2271 (1947).

(4) S. Zuffanti and J. Sardella, *ibid.*, **72**, 4322 (1950).

(5) Note the order of addition, for when calcium hydride is added before the ketone, little or no reaction product is obtained.

DEPARTMENT OF CHEMISTRY
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RECEIVED MAY 2, 1951

5-Methyl-2-nitraminopyridine

BY LUTHER A. R. HALL AND CALVIN A. VANDERWERF

In the course of work aimed toward the synthesis of certain pyridotriazoles, it was of interest to prepare a number of new compounds derived from 2-aminopyridine. All of these except 5-methyl-2-nitraminopyridine have since been reported by Lappin and Slezak.[1]

5-Methyl-2-nitraminopyridine.—The nitration of 5 methyl-2-aminopyridine was carried out by a modification of the general method of Seide.[2] To a cold (0–5°) solution of 15.0 g. (0.139 mole)[3] of 5-methyl-2-aminopyridine[4] in 33 ml. of concentrated sulfuric acid, 9 g. of fuming nitric acid (sp. gr. 1.50) was added carefully with efficient stirring. The nitration mixture was allowed to stand for 2 hours in an ice-bath during which time its color changed from light yellow to dark orange-brown. It was then poured onto about 75 g. of ice. The product, which came down as a yellow precipitate, weighed 14.9 g. (70.0%). After three recrystallizations from water, the pure product melted at 183.0–183.5° (dec.).

Anal. Calcd. for $C_6H_7N_3O_2$: C, 47.1; H, 4.6. Found: C, 47.1; H, 4.6.

(1) G. R. Lappin and F. B. Slezak, THIS JOURNAL, **72**, 2806 (1950).

(2) O. Seide, *Ber.*, **57**, 791 (1924); *ibid.*, **57**, 1802 (1924).

(3) Small scale runs were preferred in order that adequate cooling might be maintained. The reaction is extremely exothermic, with the product decomposing at temperatures above 50°.

(4) Obtained from the Reilly Tar and Chemical Corp.

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The Preparation of Some Substituted 2-Thiouracils and 2,4-Dimercaptopyrimidines

BY ELVIRA A. FALCO, PETER B. RUSSELL AND GEORGE H. HITCHINGS

The discovery of the chemotherapeutic activity of certain 5-phenoxy-2-thiouracils (I)[1] against vaccinia virus prompted the preparation of a series of 5-phenoxy, and other 2-thiouracils carrying weighty substituents at the 5- or 6-position.

The preparations of these compounds were carried out by conventional methods.[2,3] The compounds are listed in Table I.

(1) R. L. Thompson, S. A. Minton, Jr., E. A. Falco and G. H. Hitchings, *Federation Proc.*, **10**, 421 (1951); *J. Immunol.*, in press (1951).

(2) T. B. Johnson and H. H. Guest, *Am. Chem. J.*, **42**, 271 (1909).

(3) T. B. Johnson and J. C. Ambelang, THIS JOURNAL, **60**, 2941 (1938).