from methanol to furnish 370 mg. of cholestan-1α-ol (IXa) as needles, m.p. 103–105°, $[\alpha]_D$ +33° (*c* 1.2); lit.,[6,8] m.p. 93–95° and 103–105°, $[\alpha]_D$ +35°.

Δ^1-Cholesten-1-one (Va).—A solution of 62.5 mg. of chromium trioxide in 0.09 cc. of 40% sulfuric acid was added dropwise at 22° to a solution of 107 mg. of Δ^2-cholesten-1α-ol (VIIIa) in 0.8 cc. of acetone. After shaking for 30 sec., the mixture was diluted with water and ether, the organic phase was separated and washed with water. Evaporation of the dried ether extract and crystallization of the colorless residue (103 mg., $\lambda_{\max}^{C_2H_5OH}$ 223 mμ, ϵ 7100) from methylene chloride–methanol gave 73 mg. of the unsaturated ketone Va as needles or prisms, m.p. 58–60°, $[\alpha]_D$ +128°, $\lambda_{\max}^{C_2H_5OH}$ 223 mμ, ϵ 7700, $\lambda_{\max}^{CHCl_3}$ 5.94 μ; lit.,[6] m.p. 58°, $[\alpha]_D$ +124°.

An attempt to oxidize the alcohol VIIIa in benzene solution with dichlorodicyanobenzoquinone[13] (15 hr., 25°) led to recovered starting material (80%), no trace of unsaturated ketone Va being detected by thin-layer chromatography.

Δ^2-Androstene-1α,17β-diol 17-Acetate (VIIIc).—A mixture of 15.0 g. of 1α,2α-oxidoandrostan-17β-ol-3-one (IIIb)[21] [m.p. 165–166°, $[\alpha]_D$ +106° (*c* 0.19)], 150 cc. of pyridine, and 70 cc. of acetic anhydride was left at room temperature for 16 hr. and then poured into ice water. Filtration of the precipitate and recrystallization from methylene chloride–heptane afforded 14 g. of the acetate IIIc, m.p. 164–165°, $[\alpha]_D$ +91° (*c* 0.23), $\lambda_{\max}^{KBr}$ 5.78, 5.83, and 8.0 μ; lit.,[21] m.p. 160–161°.

The above 1α,2α-oxidoandrostan-17β-ol-3-one acetate (IIIc) (19 g.) in 400 cc of isopropyl alcohol was mixed with 100 cc. of hydrazine hydrate and 5 cc. of acetic acid, heated on the steam bath for 30 min. (nitrogen evolution), and left at room temperature for 1 hr. Dilution with ice water and isolation with ethyl acetate gave a gummy product, which was chromatographed on 1 kg. of neutral alumina. Elution with benzene-chloroform (1:1) and recrystallization from methylene chloride–heptane provided 7.2 g. of the allylic alcohol VIIIc, m.p. 158–160°, $[\alpha]_D$ +118° (*c* 0.22), $\lambda_{\max}^{KBr}$ 2.95, 5.86, and 8.0 μ.

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70; O, 14.44. Found: C, 75.74; H, 9.72; O, 14.21.

Δ^2-Androsten-17β-ol-1-one 17-Acetate (Vc).—A solution of 1.0 g. of the allylic alcohol VIIIc in 15 cc. of pyridine was added with stirring to a suspension of 1.0 g. of chromium trioxide in 15 cc. of pyridine. After leaving at room temperature overnight, the crystalline product was isolated with ethyl acetate and filtered in benzene solution through 100 g. of neutral alumina. Recrystallization from isopropyl alcohol led to 0.95 g. of 4-Δ^2-androsten-17β-ol-1-one 17-acetate (Vc), m.p. 195–196°, $[\alpha]_D$ +116° (*c* 0.32), $\lambda_{\max}^{C_2H_5OH}$ 225 mμ, ϵ 7770, $\lambda_{\max}^{KBr}$ 5.78, 6.01, 6.12, and 8.01 μ.

Anal. Calcd. for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15; O, 14.53. Found: C, 76.21; H, 8.75; O, 15.03.

Androstan-17β-ol-1-one 17-Acetate (VIc).—A solution of 6.0 g. of the unsaturated ketone Vc in 200 cc. of ethyl acetate was hydrogenated under 30 p.s.i. pressure with 5% palladized charcoal catalyst. After 1 hr., the catalyst was filtered, the solvent evaporated to dryness and the crystalline product (6.0 g., m.p. 140–142°) recrystallized from heptane; m.p. 141–142°, $[\alpha]_D$ +131° (*c* 0.29), $\lambda_{\max}^{KBr}$ 5.77, 5.89, and 8.10 μ. The rotatory dispersion curve closely resembled that[22] of cholestan-1-one (VIa): $[\alpha]_{589}$ +102°, $[\alpha]_{340}$ +313°, $[\alpha]_{317.5}$ +265°, $[\alpha]_{255}$ +1240° (*c* 0.05 in methanol).

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.71; H, 9.47.

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[21] W. M. Hoehn, *J. Org. Chem.*, **23**, 929 (1958).

[22] C. Djerassi, W. Closson, and A. E. Lippman, *J. Am. Chem. Soc.*, **78**, 3163 (1956).

Reduction of Disulfides with Copper. Preparation of Some Thioethers

J. Robert Campbell

Monsanto Chemical Company, Organic Chemicals Division, St. Louis Research Department, St. Louis 77, Mo.

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As noted by Adams *et al.*,[1,2] synthetic methods for aryl thioethers lack generality. A necessity for activated reactants and relatively severe experimental conditions are apparent from their summary of known preparative methods. A successful synthesis of both aryl and alkyl aryl thioethers by reaction of various organohalides and certain cuprous mercaptides was described.[1,2] Thus aromatic, heterocyclic, and aliphatic halogens were displaced by cuprous phenyl-, butyl-, ethyl-, and *t*-butylmercaptides and alkylenedimercaptides. While their procedure appeared straightforward, reaction conditions were severe (200–210°) and product isolation was involved. Moreover, isolation of the cuprous mercaptides was a necessary intermediate step. Insolubility of these salts in common organic solvents complicated utility further.

Prior to knowledge of this work a synthesis of thioethers, both aryl and alkyl aryl, which involved direct action of an alkyl or aryl disulfide, an organohalide, and copper powder, was developed in this laboratory. The reactions were conveniently carried out at 160–170° in dimethylacetamide. Most of the reaction intermediates and products were soluble in this medium. Good yields of sulfide were obtained when the solvent was removed by distillation and the residue worked up by appropriate conventional means.

The reaction apparently involves reduction of the disulfide linkage by copper metal forming intermediate cuprous mercaptide which then reacts with halide *via* a typical nucleophilic displacement. As far as can be determined this is the first report of reduction of a disulfide with copper. Disulfides have been reduced by other metals,[3] *e.g.* zinc, sodium, aluminum, and iron, but usually in the presence of acid which generates the corresponding thiols. Arsenic and antimony were used by McLeod[4] and silver by Schönberg *et al.*[5] to cleave certain alkyl and arylacyl disulfides into the corresponding metal mercaptides. None of the latter were employed in further synthesis.

[1] R. Adams, W. Reifschneider, and M. D. Nair, *Croatica Chem. Acta*, **29**, 277 (1957).

[2] R. Adams and A. Ferretti, *J. Am. Chem. Soc.*, **81**, 4927 (1959).

[3] For examples and references see Houben-Weyl, "Methoden der Organischen Chemie," Vol. IX, Georg Thieme Verlag, Stuttgart, pp. 23–25.

[4] G. D. McLeod, U. S. Patent 2,768,192 (1956).

[5] A. Schönberg, E. Rupp, and W. Gumlich, *Chem. Ber.*, **66**, 1932 (1933).

TABLE I

MONOTHIOETHERS

Thioether	Starting Disulfide[a]	B.P. (mm.)	n^{25}_D	Yield, %	Formula	Sulfur Calcd.	Sulfur Found
n-$C_4H_9SC_6H_5$	$(n\text{-}C_4H_9S)_2$	123–129 (25)[b]	1.5312	50.8	...	...	...
$C_6H_5SC_6H_5$	$(C_6H_5S)_2$	139–141 (9)	1.631	86.5	...	...	...
m-$BrC_6H_4SC_6H_4CH_3$-p	...[c]	135–145 (0.4)	1.6406	..	$C_{18}H_{11}BrS$	11.48	11.50[d]

[a] Starting halide in every case was bromobenzene. [b] Palladium chloride derivative melts at 107–108°. V. N. Ipatieff, H. Pines, and B. S. Friedman, *J. Am. Chem. Soc.*, **60**, 2731 (1938) report m.p. 106–107° for this derivative, and b.p. 94–97° (4 mm.), n^{20}_D 1.5463, for the thioether. [c] By-product from synthesis of m-bis(p-tolylmercapto)benzene (Table II). [d] % Br. Calcd.: 28.62, Found: 28.50.

TABLE II

BISTHIOETHERS

$$RSSR + BrC_6H_4Br \longrightarrow RSC_6H_4SR$$

R	M.P. B.P. (mm.)	Yield, %	Formula	Sulfur Calcd.	Sulfur Found
meta					
C_6H_5	180–185 (0.35)[a]	80.2	$C_{18}H_{14}S_2$	21.78	21.99
p-$CH_3C_6H_4$	240–250 (0.3) 91–92[b]	84.0	$C_{20}H_{18}S_2$	19.87	19.60
o-$NO_2C_6H_4$	151–152[c]	40.0	$C_{18}H_{12}N_2O_4S_2$	16.68	16.70
$C_6H_5CH_2$	180–200 (10) 61–62[d]	46.5	...	...	...
para					
C_6H_5	82–83[e]	32.0[f]	...	...	...

[a] n^{25}_D 1.6760. [b] From isopropyl alcohol. [c] From carbon tetrachloride. [d] From ethanol. C. Finzi, *Gazz. chim. ital.*, **44** I, 602 (1914), reports m.p. 60°, prepared in low yield from dithioresorcinol and benzyl bromide. [e] This is the melting point given for this compound in ref. 1. [f] Low yield in this case resulted from utilization of ethylene glycol as solvent.

That reduction of the disulfide bond does occur with subsequent formation of intermediate cuprous mercaptide was proved by conducting one experiment in the absence of any halide. Cuprous phenylmercaptide was isolated in 87.5% yield and proved identical to that prepared by the method of Adams *et al.*[1] It was also shown that the reaction was not one of thermal disulfide cleavage with formation of thiyl radicals. One experiment with phenyl disulfide and dibromobenzene was carried out in the absence of copper powder. No reaction was apparent and no thioether was formed.

While the present synthetic method utilizes disulfides in contrast to the generally more available mercaptans as starting materials, it should be noted that many mercaptans react poorly with cuprous oxide. However, conversion of mercaptans to the corresponding disulfides is almost invariably facile. Moreover some cuprous mercaptides are unstable in the Adam's procedure. For example, Adams and Ferretti[2] found that cuprous benzylmercaptide decomposed into benzyl sulfide and stilbene before it could react with halide present. By our method benzyl disulfide, m-dibromobenzene, and copper gave a 46.5% yield of the expected product, bis(benzylmercapto)benzene.

An attempt was made to prepare hexaphenylmercaptobenzene from hexachlorobenzene, phenyl disulfide, and copper, but only unidentified black oil was obtained. Evidently, an Ullmann biaryl synthesis occurred between the copper and halide yielding a mixture of products.

In conclusion the thioether synthesis reported here serves as a useful adjunct to that of Adams *et al.* It appears that the only limitation to the present one could be availability of disulfides. At any rate the two related methods provide a general synthesis of aryl and alkyl aryl thioethers.

Experimental[6]

General Procedure for Preparation of Thioethers.—A mixture of 0.1 mole of disulfide, 0.1 mole of dibromide (0.2 mole of monobromide), and 0.2 g.-atom of copper powder in 500–700 ml. of dimethylacetamide was stirred and heated to 135–140° where it was held for 1–2 hr. Reaction started at about 130° and was only mildly exothermic. The copper bronze color gave way to a very light green and cuprous benzenethiolate precipitated.[7] The reaction temperature was then raised to reflux (165–170°). Solids dissolved as the salt reacted and the mixture turned brown. Reflux temperatures were maintained for 10–15 hr. after which dimethylacetamide was distilled. Water and benzene were added to the residue. The insoluble cuprous bromide was collected on a filter and washed with benzene. The latter was combined with the benzene layer, washed with water, and evaporated to a residue, which was purified by distillation or recrystallization. Information regarding the thioethers, their physical properties, analytical data, etc., are presented in Tables I and II.

Little or no yield of thioether was obtained when other solvents–*e.g.*, ethylene glycol and diethylaniline—were tried. Their higher reflux temperatures allowed formation of by-products and they were less effective than dimethylacetamide in dissolving cuprous thiolates.

Refractory impurities were removed from the nitro derivative in Table II by passing a benzene solution through a

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(6) All melting and boiling points are uncorrected.

(7) In most cases there was a copious precipitation of solid cuprous thiolate making stirring difficult. Often additional solvent was added to give a stirrable slurry. As reaction progressed, this solid is used up and cuprous halide separates, but it creates no problem.

column of alumina. Some black cupric bromide was formed during the synthesis of the benzyl derivative in Table II indicating that a portion of the dihalide underwent a typical Ullmann biaryl coupling.

Cuprous Benzenethiolate.—Following the same method, but without added halide, a mixture of 15.2 g. (0.07 mole) of phenyl disulfide and 8.9 g. (0.14 g.-atom) of copper powder in 200 ml. of dimethylacetamide was heated to reflux for 3 hr. Water was added to precipitate all the cuprous salt as a light yellow solid, which was collected and washed with ethanol. There was obtained 21 g. (87.5% yield) of dry cuprous benzenethiolate, char point 255°, soluble in pyridine, insoluble in water.

Anal. Calcd. for C_6H_5CuS: S, 18.57. Found: S, 18.4. These results are identical to those produced by the same salt prepared by another method[1] from benzenethiol and cuprous oxide in ethanol.

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The Preparation of Cycloheptylamine

Morris Freifelder, William D. Smart, and
George R. Stone

Organic Research Department, Abbott Laboratories, North Chicago, Ill.

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The need in this laboratory for pure cycloheptylamine prompted an investigation of methods of synthesis in which readily available or easily prepared intermediates could be used. Since the Ritter reaction with cycloheptanol gives a mixture of products[1] and chemical reduction of cycloheptanone oxime results in poor yield,[2] they were not considered. A more logical approach appeared to be reductive amination of cycloheptanone (A) or catalytic hydrogenation of its oxime (B). While method A gave a good yield, the resultant product was found to be contaminated with cycloheptanol. High pressure reduction of the oxime in the presence of Raney nickel and ammonia gives a good yield.[3] However, except in small size runs, the exothermicity of the reaction even with a low catalyst ratio made us aware that the reduction could get out of hand. Rhodium-on-alumina on the other hand proved highly satisfactory even with undistilled oxime in low pressure hydrogenations in the absence of ammonia. Under these conditions, uptake of hydrogen was entirely too slow when Raney nickel was used.

Experimental

Method A.—A solution of 101.5 g. (0.905 mole) of cycloheptanone,[4] 100 cc. of ethyl alcohol and 100 cc. of liquid ammonia was placed in a 1-l. rocker bomb. Raney nickel (20.0 g.) was added and the mixture hydrogenated at 70° and 100 atm. Uptake of hydrogen was complete in less than 1 hr. The reaction mixture was filtered from the catalyst and the solution and washings concentrated. The residue was treated with 20% hydrochloric acid and the mixture extracted with ether to remove cycloheptanol (about 20 g. of crude alcohol was obtained). The acidic solution was kept at room temperature while adding solid potassium hydroxide until the mixture was strongly basic. The mixture was then extracted thoroughly with ether (some water may be added to dissolve potassium chloride). The extract was dried over potassium hydroxide. The solution was filtered and the ether distilled. The residue on fractionation yielded 61% of cycloheptylamine boiling at 172–175° (750 mm.).[5]

Low pressure reductions with a higher catalyst ratio (30%) required a longer time but gave about the same yield.

Method B. Cycloheptanone Oxime.[6]—A solution of 4000 g. (35.72 moles) of cycloheptanone in 3500 cc. of methyl alcohol was treated with 3000 g. (43.16 moles) of hydroxylamine hydrochloride. It was then stirred for 1 hr. while heating to 80°. While this temperature was maintained, a solution of 1560 g. of sodium hydroxide in 3500 cc. of water was added over a 4-hr. period. The reaction mixture was then refluxed for 1–2 hr. and allowed to cool to room temperature. An oily layer separated, which was removed and dried over anhydrous magnesium sulfate. The oil,[7] after filtration from the drying agent, was dissolved in 9000 cc. of methyl alcohol and placed in a 10-gal. glass-lined reactor, to which 450 g. of 5% rhodium-on-alumina[8] was added. The mixture was hydrogenated under 0.75 to 1.0 atm. The temperature rose gradually to 60° and was maintained there until reduction was complete. The solution was filtered from the catalyst and concentrated. The residue was fractionated. An over-all yield of 80% of cycloheptylamine based on cycloheptanone was obtained.

Hydrogenation of distilled oxime carried out in a Parr shaker under 3 atm. pressure gave about the same over-all yield.

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[1] R. Jacquier and H. Christol, *Bull. Soc. Chim.*, 560 (1954).

[2] W. Markownikoff, *J. Russ. Phys. Chem. Soc.*, **25**, 365 (1893), and V. Prelog, M. F. El-Neweihy, and O. Häflinger, *Helv. Chim. Acta*, **33**, 365 (1950).

[3] A. C. Cope, R. A. Pike, and C. F. Spencer, *J. Am. Chem. Soc.*, **75**, 3212 (1953).

[4] Aldrich Chemical Co., Milwaukee, Wis.

[5] R. Willstatter, *Ann.*, **317**, 204 (1901), reports 169°.

[6] The method is essentially as described for benzophenoneoxime by A. Lachman, *Org. Syntheses*, Coll. Vol. I, 10 (1930).

[7] Cycloheptanoneoxime from a 675-g. run was distilled successfully. An 86% yield of product boiling at 125–130° (22 mm.) was obtained. When distillation of a larger run was attempted, decomposition took place, resulting in the thermometer being blown from the stillhead.

[8] Baker and Co., Division of Engelhard Industries, 113 Astor Street, Newark, N. J.

A Correlation in the Infrared Spectra of Some C-Benzoylated Nitrogen Heterocycles

D. G. Farnum[1] and Peter Yates[2]

Department of Chemistry, Harvard University, Cambridge 38, Massachusetts

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In the course of studies related to heterocyclic chemistry[3] we have had occasion to examine the

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[1] National Institutes of Health Pre-doctoral Fellow, 1957–1959.

[2] Present address: Department of Chemistry, University of Toronto.