Notes

N-Alkylation of Amides. A Novel Procedure

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In view of the known acid-catalyzed reaction of aldehydes[1] and acetals[2] with amides to give methylene diamides it seemed reasonable that the reaction could be adapted to a useful reductive amidation procedure. Thus, when acetamide, acetal, or 2,2-dimethoxypropane, and hydrogen were allowed to react at room temperature in acetic acid solution in the presence of a palladium catalyst and sulfuric acid the corresponding *N*-ethyl- and *N*-isopropylacetamides were produced in about 50% yield. Further investigation will undoubtedly increase the scope and usefulness of this reaction.

Experimental

N-Alkylation of Acetamide.—A mixture of 30 g. (0.51 mole) of acetamide, 62 g. (0.525 mole) of 1,1-diethoxyethane, 2 g. of 10% palladium-on-carbon, and 200 ml. of acetic acid containing 6 g. of concd. sulfuric acid was shaken in an atmosphere of hydrogen (40 p.s.i. initial pressure) for 6 hr., at which time absorption was complete. The catalyst was removed by a filtration and 10 g. of anhydrous sodium acetate added to neutralize the sulfuric acid. After removing the precipitated sulfate, the filtrate was fractionated to yield 20 g. (45%) of pure *N*-ethylacetamide, b.p. 97–98° (8 mm.), $n^{30}D$ 1.4313. The infrared spectrum was identical to that of an authentic sample.

N-Isopropylacetamide was similarly obtained from 2,2-dimethoxypropane in 46% yield, b.p. 87–88° (4.5 mm.), $n^{30}D$ 1.4303, and its identity confirmed by comparison of its infrared spectrum with the spectrum of known material. The use of acetone in place of the ketal or ethanol as a solvent produced none of the desired amide.

(1) For leading references see W. A. Noyes and D. B. Forman, *J. Am. Chem. Soc.*, **55**, 3493 (1933) and W. M. Kraft and R. M. Herbst, *J. Org. Chem.*, **10**, 483 (1945).

(2) C. Bischoff, *Ber.*, **7**, 628 (1874); H. E. Johnson and D. G. Crosby, *J. Org. Chem.*, **27**, 2077 (1962).

A New Route to 1-Oxygenated Steroids[1]

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In connection with work currently under way in our laboratory[4] on the relation of mass spectrometric fragmentation patterns and steroid structure, the need arose for a variety of C-1 oxygenated steroids with the 5α-orientation. Oxygenation at C-1 was the last nuclear location for which synthetic procedures were developed in the steroid field and a survey of the literature demonstrates that none of the methods are completely satisfactory.

The starting material for all of the chemical methods is Δ^1-cholesten-3-one (II).[5] Striebel and Tamm,[6] who were the first to develop a feasible route to cholestan-1-one (VIa), converted IIa into the 1α,2α-oxido 3-ketone (IIIa) and reduced it with lithium aluminum hydride. The resulting mixture of glycols (IVa) was partially acetylated at C-3, oxidized at C-1 and the 3-acetoxy group eliminated with alumina to furnish Δ^2-cholesten-1-one (Va), which could be hydrogenated to cholestan-1-one (VI). The Swiss investigators[6] reported an over-all yield of 47% from IIIa to VIa, but Shoppee and collaborators[7] were unable to duplicate the yields in the separation and partial acetylation of the diol mixture (IVa). Their modification involved oxidation of the diols IVa to the 1,3-diketone, preferential mercaptal formation at C-3, followed by desulfurization, the over-all yield of cholestan-1-one (VIa) from the oxido ketone IIa dropping to 14%. Striebell and Tamm[6] also reported that the diol mixture IVa could be completely acetylated and the 1α,3β-diacetoxy component partially saponified at C-3. The free 3β-hydroxy function was removed through the mesylate and iodide to provide cholestan-1α-ol (IXa) in 30% over-all yield.

An alternate scheme was developed by Henbest and Wilson,[8] who reduced Δ^1-cholesten-3-one (IIa) with lithium aluminum hydride, converted the resulting allylic alcohol to the chloride, removed the chlorine atom with lithium aluminum hydride, epoxidized the resulting Δ^1-cholestene and finally opened the oxide ring with lithium aluminum hydride to give cholestan-1α-ol (IXa), the over-all yield from IIa being less than 10%. A second and

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(2) Recipient of a Fulbright Travel Award from the U. S. Educational Commission in the United Kingdom.

(3) Syntex, S. A., Mexico City, Mexico. The present paper represents Part CLXXXXII in the Syntex series on "Steroids."

(4) See H. Budzikiewicz and C. Djerassi, *J. Am. Chem. Soc.*, **84**, 1430 (1962), and subsequent papers.

(5) A. Butenandt, L. Mamoli, H. Dannenberg, L. W. Masch, and J. Paland, *Ber.*, **72**, 1617 (1939); C. Djerassi and C. R. Scholz, *J. Am. Chem. Soc.*, **69**, 2404 (1947).

(6) P. Striebel and C. Tamm, *Helv. Chim. Acta*, **37**, 1094 (1954).

(7) C. W. Shoppee, S. K. Roy, and B. S. Goodrich, *J. Chem. Soc.*, 1583 (1961).

(8) H. B. Henbest and R. A. L. Wilson, *J. Chem. Soc.*, 3289 (1956).

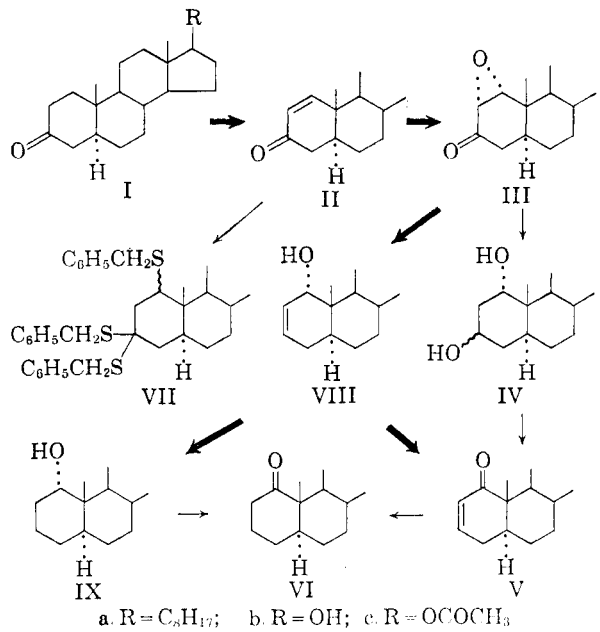
probably inferior approach is due to Plattner,[9a] who prepared a mixture of Δ^1 and Δ^2-cholestenes from IIa *via* the intermediate VIIa, the introduction of the C-1 oxygen function being effected by epoxidation and lithium aluminum hydride reduction. Albrecht and Tamm[9b] simplified this approach by obtaining the mixture of Δ^1- and Δ^2-cholestenes directly through lithium aluminum hydride–aluminum chloride reduction of II. The same authors[9b] also improved the earlier[6] synthesis by developing a seven-step conversion of II into cholestan-1-one (VI) in 30% over-all yield.

In summary, all of the literature procedures suffer either from poor overall yields or a large number of steps, coupled with tedious chromatographic separation of isomers. We should now like to report that application of the recently recorded[10] hydrazine reduction of epoxy ketones to $1\alpha,2\alpha$-oxido-3-keto steroids (III) constitutes the simplest access to a variety of 1-oxygenated steroids.

Cholestan-3-one (Ia) was converted to its 2α-bromo derivative[11] and then dehydrobrominated with calcium carbonate in dimethylacetamide solution.[12] Epoxidation of IIa with alkaline hydrogen peroxide[6] led to $1\alpha,2\alpha$-oxidocholestan-3-one (IIIa),[6] which was reduced in 57% yield with hydrazine hydrate[10] to Δ^2-cholesten-1α-ol (VIIIa). The structure of this allylic alcohol followed from its oxidation[13] with chromium trioxide in acetone solution[14] to the known[6] Δ^2-cholesten-1-one (Va) and from its catalytic hydrogenation in over 90% yield to cholestan-1α-ol (IXa).[6] The over-all yield in the two-step process from the oxido ketone IIIa to cholestan-1α-ol (IXa) is 52%, thus making it by far the most convenient synthetic route to 1-oxygenated 5α-steroids.

The physical constants of our Δ^2-cholestan-1α-ol (VIIIa) proved to be completely different from those recorded by Tamm and Albrecht[15] for the product of the alumina-catalyzed epimerization of 1β-acyloxy-Δ^2-cholestene and to which structure VIIIa had been assigned. Direct comparison with Tamm's specimen[15] showed that the two products were indeed different and that the earlier substance[15] represented a mixture of 3α and 3β-hydroxy-Δ^1-cholestene.[16]

By a similar sequence of reactions, the known[17] Δ^1-androsten-17β-ol-3-one (IIb), was transformed into the oxido ketone IIIb, acetylated at C-17 to give IIIc, and reduced with hydrazine to Δ^2-androstene-$1\alpha,17\beta$-diol 17-acetate (VIIIc). Oxidation with chromium trioxide in pyridine[18] led to Δ^2-androsten-17β-ol-1-one 17-acetate (Vc), an isomer[19] of the male sex hormone testosterone (acetate), which on catalytic hydrogenation provided androstan-17β-ol-1-one 17-acetate(VIc).



Experimental[20]

Δ^2-Cholesten-1α-ol (VIIIa).—$1\alpha,2\alpha$-Oxidocholestan-3-one (IIIa)[6] (2.0 g.) and 12.0 cc. of 100% hydrazine hydrate were heated under reflux for 5 min. while nitrogen was evolved, followed by heating of the two-phase mixture for an additional 15-min. period. Cooling, dilution with water, and extraction with ether provided 1.96 g. of a pale yellow oil, which was passed in benzene solution through a 15-g. column of silica gel (E. Merck AG., Darmstadt, Germany). The benzene-eluted material (1.3 g.) was crystallized from acetone to afford (after drying at 56°/0.1 mm.) 1.1 g. of Δ^2-cholesten-1α-ol (VIIIa) as colorless needles, double m.p. 90–92° and 103–104°, $[\alpha]D$ +124° (*c* 1.4), which possessed no carbonyl absorption in the infrared.

Anal. Calcd. for $C_{27}H_{46}O$: C, 83.87; H, 11.99. Found: C, 83.65; H, 12.11.

Cholestan-1α-ol (IXa).—The above unsaturated alcohol VIIIa (400 mg.) was hydrogenated at room temperature and atmospheric pressure over a period of 4 hr. in 30 cc. of cyclohexane with 100 mg. of 30% palladized charcoal catalyst. Filtration of the catalyst and evaporation to dryness left a crystalline residue, which was recrystallized

(9) (a) P. A. Plattner, A. Fürst, and H. Els, *Helv. Chim. Acta*, **37**, 1399 (1954). (b) R. Albrecht and C. Tamm, *Helv. Chim. Acta*, **40**, 2216 (1957).

(10) P. S. Wharton and D. H. Bohlen, *J. Org. Chem.*, **26**, 3615 (1961); P. S. Wharton, *J. Org. Chem.*, **26**, 4781 (1961).

(11) A. Butenandt and A. Wolff, *Ber.*, **68**, 2091 (1935).

(12) G. F. H. Green and A. G. Long, *J. Chem. Soc.*, 2532 (1961).

(13) Oxidation with dicyanodichlorobenzoquinone [D. Burn, V. Petrow, and G. O. Weston, *Tetrahedron Letters*, No. **9**, 14 (1960)] failed, only starting material being recovered.

(14) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946); C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).

(15) C. Tamm and R. Albrecht, *Helv. Chim. Acta*, **42**, 2177 (1959).

(16) We are indebted to Prof. Tamm (University of Basel) for this information, which will be published elsewhere.

(17) A. Butenandt and H. Dannenberg, *Ber.*, **73**, 206 (1940).

(18) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarrett, *J. Am. Chem. Soc.*, **75**, 422 (1953).

(19) W. Schütt and C. Tamm, *Helv. Chim. Acta*, **41**, 1730 (1958), have prepared a similar isomer of progesterone.

(20) All melting points are corrected and were determined in capillaries. Rotations were measured in chloroform and ultraviolet absorption spectra in 95% ethanol. The microanalyses are due in part to Mr. E. Meier (Stanford University, Microanalytical Laboratory) and in part to Dr. A. Bernhardt (Mülheim, Germany).

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°.

Δ¹-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 Δ²-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.

Δ²-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), λ_{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), λ_{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.

Δ²-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-Δ²-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, λ_{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), λ_{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.

(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

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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).