tended this work to include some *p*-alkylphenyl alkyl ketones, phenyl isopropyl ketone and *p*-xylyl isopropyl ketone. These latter compounds and the former four series have also been treated with methylmagnesium bromide in an active hydrogen apparatus.[5] The new rate values are recorded in Table I; the active hydrogen determinations in Table II.

TABLE I

RATE OF OXIME FORMATION OF ARYL ALKYL KETONES AT 30°

Rate constant in liters/moles/sec. × 10^3

Aryl	Methyl	Alkyl Ethyl	Isopropyl
Phenyl	24.6[a]	14.5[a]	2.22
p-Methylphenyl	16.2	9.90	1.79
p-Ethylphenyl	16.5	9.90	1.73
p-Isopropylphenyl	16.7	10.3	1.51
p-*t*-Butylphenyl	16.7	10.0	1.84
p-Xylyl	1.84[a]	0.863[a]	0.19

TABLE II

REACTION OF ARYL ALKYL KETONES WITH METHYLMAGNESIUM BROMIDE

E = % enolization; A = % addition

Aryl	Me E	Me A	Et E	Et A	Alkyl *n*-Prop-*n*-Hept[a] E	Alkyl *n*-Prop-*n*-Hept[a] A	Isoprop E	Isoprop A
Phenyl	9	88	4	96	3–4	92–99	2	100
p-Alkylphenyl[b]	7–9	87–90	3–4	91–95	...	...	2–3	93–98
p-Xylyl	15	87	7	96	7–8	90–94	5	93
Carvacryl	18	80	8	88	8–9	81–87	...	....
Thymyl	25	71	21	75	19–21	70–81	...	....

[a] The range of values given embraces all the *n*-alkyl groups from propyl through heptyl. [b] The range of values embraces the compounds in which the *p*-alkyl groups were methyl, ethyl, isopropyl and *t*-butyl.

There is qualitative agreement between rate of oximation and extent of enolization. For any given series of ketones containing the same acyl group the following approximation exists, oximation rate: phenyl = *p*-alkylphenyl > *p*-xylyl = carvacryl > thymyl. Enolization: phenyl = *p*-alkylphenyl < *p*-xylyl = carvacryl < thymyl.

The *p*-xylyl, carvacryl and thymyl methyl ketones give enolization values in close agreement with those reported by Kadesch[6] for the appropriate 4,7-dialkyl-α-indanones. These latter compounds have been termed "partially hindered ketones."[7]

Experimental

Ketones.—The *n*-alkyl ketones derived from benzene, *p*-xylene, 2-*p*-cymene and 3-*p*-cymene have been described.[4] The other ketones were all prepared by a suitable Friedel–Crafts reaction.[8] The *p*-alkylphenyl alkyl and phenyl isopropyl ketones will be described later. The *p*-xylyl isopropyl ketone had the following properties: b.p. 115° at 5 mm.; d_{30} 0.9747; $n^{30}D$ 1.5134; *Anal.* Calcd. for $C_{10}H_{16}O$: C, 81.8; H, 9.09. Found: C, 81.7; H, 9.17.

Rates of Oximation.—The medium and method were the same as that previously described.[4] The methyl and ethyl ketones were run in solution 0.05 *M* with respect to ketone and hydroxylamine hydrochloride. The isopropyl *p*-xylyl ketone was run, using 0.2 *M* solution of ketone and 0.1 *M* solution of amine. The other isopropyl ketones were run using 0.1 *M* each of ketone and hydroxylamine. The *k* values reported are averages of duplicate runs that agreed within 5%.

Active Hydrogen Determinations.—The measurements were made in duplicate, adding excess methylmagnesium bromide in dibutyl ether to 0.002 *M* amounts of each ketone. In an effort to obtain maximum reaction, the mixture was heated at 50° for 5 min. The values for enolization were reproducible to ±1%; those for addition to ±3%.

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(5) C. T. Lester and J. R. Proffitt, Jr., THIS JOURNAL, **71**, 1877 (1949).

(6) R. G. Kadesch, *ibid.*, **66**, 1207 (1944).

(7) A. E. Remick, "Electronic Interpretations of Organic Chemistry," 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1949, p. 321.

(8) C. T. Lester and E. C. Suratt, THIS JOURNAL, **71**, 2262 (1949).

The Reduction of Cholestenone Enol Acetate by Sodium Borohydride[1]

BY WILLIAM G. DAUBEN AND JEROME F. EASTHAM

In a continuation of the study of the conversion of cholestenone to cholesterol[2] it has been found that the enol acetate of cholestenone is reduced by sodium borohydride to yield approximately 75% cholesterol. Previously this reduction had been carried out with lithium aluminum hydride and cholesterol obtained in only 35% yield.[2] Use of the borohydride greatly simplifies the experimental technique required for the reduction. Whereas with the aluminum hydride anhydrous ether is employed as a solvent and the reaction is carried out in an atmosphere of nitrogen, the reduction can now be conducted in methanolic solution with no special precautions for anhydrous conditions. The work-up and isolation of products is essentially that previously described.[2]

In contrast to the results with lithium aluminum hydride, no cholestenone is obtained from the reaction when excess sodium borohydride is employed if the reaction is allowed to continue for a sufficient length of time. Similar to the earlier results, however, is the evidence that the four isomeric stenols, cholesterol, epicholesterol, and the two Δ^4-stenols (Δ^4-cholesten-3α-ol and Δ^4-cholesten-3β-ol), are formed in the reduction, with the cholesterol preponderating. A limited study of the effect of conditions for the reaction has been made. Low temperature and addition of hydride to ester ("inverse mixing") seem to favor the proportion of cholesterol. Thus, under otherwise similar conditions,

(1) This work was supported by a grant from the University of California Cancer Fund.

(2) W. G. Dauben and J. F. Eastham, THIS JOURNAL, **73**, 3260 (1951).

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°.

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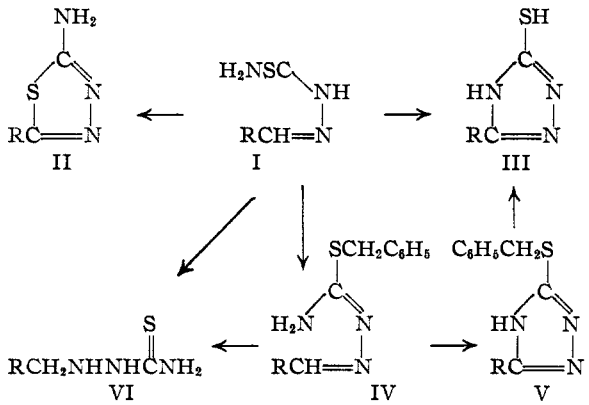
Oxidation and Reduction of 4-Acetamidobenzaldehyde Thiosemicarbazone

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).