Experimental Section[6]

Reaction of II with β-Propiolactone (Preparation of III).—2-Benzoyl-1,2-dihydroisoquinaldonitrile (II) (0.01 mole) and β-propiolactone (0.02 mole) were dissolved in 40 ml of dimethylformamide and 30% sodium hydride in oil (0.01 mole) was added to the stirred solution. After 1.5 hr stirring the mixture was poured onto 500 g of ice and filtered after standing. A solid (mp 104–109°) was obtained and recrystallized from hexane to give a 19% yield of III, mp 111–112° (λ_{KBr}^{max} 1730 and 1665 cm^{-1}).

Anal. Calcd for $C_{18}H_{15}NO$: C, 82.73; H, 5.79; N, 5.36. Found: C, 82.47; H, 6.03; N, 5.26.

A picrate (mp 202–204°) from ethanol, was prepared.

Anal. Calcd for $C_{24}H_{18}N_4O_8$: C, 58.78; H, 3.70; N, 11.43. Found: C, 58.83; H, 3.81; N, 11.32.

The 2,4-dinitrophenylhydrazone of III was prepared (mp 192–193°) from ethanol–dimethylformamide.

Anal. Calcd for $C_{24}H_{19}N_5O_4$: C, 65.30; H, 4.34; N, 15.87. Found: C, 65.42; H, 4.91; N, 15.98.

Preparation of III.—Reaction of 0.01 mole of II with 0.01 mole of β-bromopropiophenone and sodium hydride in dimethylformamide as above afforded a gum in 68% yield. Recrystallization from hexane–ethyl acetate gave a good recovery of solid (V or VI), mp 172–172.5° (λ_{KBr}^{max} 1740, 1700, 1630, 835 cm^{-1}).

Anal. Calcd for $C_{25}H_{19}NO_2$: C, 82.17; H, 5.24; N, 3.83. Found: C, 81.80; H, 5.43; N, 3.59.

A picrate (mp 163–164°) from ethanol, was prepared.

Anal. Calcd for $C_{31}H_{22}N_4O_9$: C, 62.73; H, 3.57; N, 9.44. Found: C, 62.52; H, 3.58; N, 9.27.

The crude intermediate (V or VI) obtained above (2.0 g) was refluxed for 1.5 hr in 50 ml of 50% ethanol containing 8 g of potassium hydroxide. Dilution with water and filtration gave a white solid (mp 108–109°) in 88% yield. Recrystallization from hexane gave mp 111–112°. This material was identical to compound III as demonstrated by mixture melting point and infrared spectra.

Reaction of II with β-Butyrolactone (Preparation of VII).—The reaction was carried out as described above for β-propiolactone on a 0.01 molar scale. A white solid was isolated and recrystallized from hexane–ethyl acetate to give a 50% yield, mp 85–86° (λ_{KBr}^{max} 1755 and 1665 cm^{-1}).

Anal. Calcd for $C_{18}H_{15}NO_2$: C, 77.96; H, 5.48; N, 5.05. Found: C, 78.13; H, 5.48; N, 5.08.

A picrate (mp 204–205°) from ethanol, was prepared.

Anal. Calcd for $C_{24}H_{18}N_4O_9$: C, 56.92; H, 3.58; N, 11.06. Found: C, 56.88; H, 3.64; N, 11.20.

1-(1-Isoquinolinyl)ethyl Benzoate (VII).—To a stirred solution of 0.02 mole of 2-benzenesulfonyl-1,2-dihydroisoquinaldonitrile[7] in 80 ml of dimethylformamide was added 0.02 mole of 30% sodium hydride in oil. After 1 hr the mixture was poured onto 500 g of ice and isoquinaldonitrile (VIII) (80%) (mp 86–88°) was collected. Without further purification VIII was treated with methyl magnesium iodide as reported[8] to give 1-acetylisoquinoline (IX) as a yellow oil in 72% yield (λ_{KBr}^{max} 1700 and 1625 cm^{-1}). Compound IX (0.0115 mole) was dissolved in 30 ml of methanol and 0.25 g of sodium borohydride was added with stirring. After 0.5 hr the mixture was poured onto ice and extracted with methylene chloride. 1-(1-Isoquinolinyl)ethanol (X) was isolated in 91% yield as an oil from the dried (Na_2SO_4) organic phase (λ_{KBr}^{max} 3400 and 1630 cm^{-1}). The oil (X) (0.0097 mole) was refluxed with 1.8 g (0.0129 mole) of benzoyl chloride in 50 ml of pyridine for 1 hr. After being poured onto ice, 2.61 g (97%) of white solid was collected. Recrystallization from hexane–ethyl acetate gave mp 87–88°. This material was identical with VII prepared from β-butyrolactone as demonstrated by mixture melting point and infrared spectra.

Condensation of II with Acetaldehyde.—Acetaldehyde and II were reacted with phenyllithium in ether–dioxane at −20° as reported for other aldehydes.[4] A solid (mp 85–87°) from hexane–ethyl acetate, was isolated in 60% yield. This material was identical with VII as demonstrated by mixture melting point and infrared spectra.

Treatment of β-Butyrolactone with Sodium Hydride.—β-Butyrolactone (5 g) in 100 ml of dimethylformamide was treated with 5 g of 30% sodium hydride in oil while a stream of nitrogen was percolated through the mixture and into a reagent solution of 2,4-dinitrophenylhydrazine. In this manner low yields of acetaldehyde–2,4-dinitrophenylhydrazone (mp 144–146°) were obtained. The reaction was accompanied by the generation of considerable heat and polymer formation.

Registry No.—II, 844-25-7; III, 10293-89-7; picrate of III, 10293-90-0; 2,4-dinitrophenylhydrazone of III, 10293-91-1; V, 10293-92-2; picrate of V, 10293-93-3; VI, 10293-94-4; picrate of VI, 10293-95-5; VII, 10293-96-6; picrate of VII, 10293-97-7; VIII, 1198-30-7.

(6) All melting points are corrected. Analyses were by Spang Microanalytical Laboratory, Ann Arbor, Mich. We wish to thank the Tennessee Eastman Co. for a sample of β-butyrolactone.

(7) J. M. Wefer, A. Catala, and F. D. Popp, *J. Org. Chem.*, **30**, 3075 (1965).

(8) A. Kaufmann, P. Dandliker, and H. Burkhardt, *Ber.*, **46**, 2929 (9113).

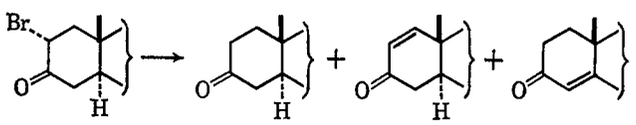
α-Halo Ketones. IV.[1] Reductive Dehalogenation by Substituted Pyridines

E. W. WARNHOFF AND D. R. MARSHALL[2]

Department of Chemistry, University of Western Ontario, London, Ontario, Canada

Received December 19, 1966

In part II of this series[3] the reaction of a typical cyclic α-halo ketone, 2α-bromocholestan-3-one (partial structure **1**), with a variety of alkyl-substituted pyridines was examined. It was found that, in addition to dehydrobromination (with and without rearrangement) and displacement, reductive debromination to cholestan-3-one (partial structure **2**) occurred. Accurate analysis for the reduction product was complicated both by the fact that the starting bromo ketone



1 **2** **3** **4**

was discovered to contain 12% of **2**, and by the analytical method. The difficulty in separating a small amount of **2** from a large amount of **3** made it most convenient to estimate cholestan-3-one as the remainder after Δ^1- and Δ^4-cholesten-3-one (partial structures **3** and **4**) had been determined from tlc spot intensities and ultraviolet measurements.

In a subsequent paper, Nace and Iacona[4] repeated the reaction of γ-collidine with pure **1** from which the contaminating cholestan-3-one had been removed by chromatography on silica gel. A shoulder corresponding to cholestan-3-one was observed in the glpc chromatogram and infrared spectrum of the reaction product, but it was claimed that the saturated ketone amounted to less than 2% of the total product. The authors concluded that "the reduction reaction is not significant in the reaction of bromo ketones with collidine."[4] Although the yields (20–46%) of cholestan-3-one reported in our earlier work[3] were admitted to be subject to cumulative error, it was certain that more than 2% of **2** was produced in the γ-collidine re-

(1) Part III: E. W. Warnhoff, *J. Org. Chem.*, **28**, 887 (1963).

(2) Province of Ontario Graduate Fellow, 1966–1967.

(3) E. W. Warnhoff, *J. Org. Chem.*, **27**, 4587 (1962).

(4) H. R. Nace and R. N. Iacona, *ibid.*, **29**, 3498 (1964).

TABLE I

PRODUCTS FROM REACTION OF 2α-BROMOCHOLESTAN-3-ONE WITH PYRIDINES

Amine	Normal bp, °C	Pyridinium salt, %	Amine·HBr, %	Ether-soluble fraction, %	Cholestan-3-one (2), %	Δ¹-Ketone (3), %	Δ⁴-Ketone (4), %
Pyridine	115	.. (82)[a]	Not detmnd	.. (15)	.. (10)	.. (4.7)	.. (0)
γ-Picoline	145	.. (88)	.. (9.3)	.. (12.6)	.. (2)	.. (9)	.. (1.5)
β-Picoline	144	80 (82)	12 (13)	14 (14)	<1.8 (2)	9 (10)	3 (2)
α-Picoline[b]	129	10	92	87	<3.5 but real	26	35
2,4-Lutidine[b]	157	0 (0)	97 (95)	97 (100)	Trace? (20)	37 (55)	26 (25)
2,6-Lutidine[b]	144	0 (0)	89 (94)	89 (100)	8 (46)	36 (24)	40 (30)
γ-Collidine[b]	171	0 (0)	99 (103)	98 (99)	5.8–14.7[c] (37)	41 (38)	30 (25)
Pyrolysis of γ-picolinium salt				94 (89)	9 (29)	30 (15)	33 (44)

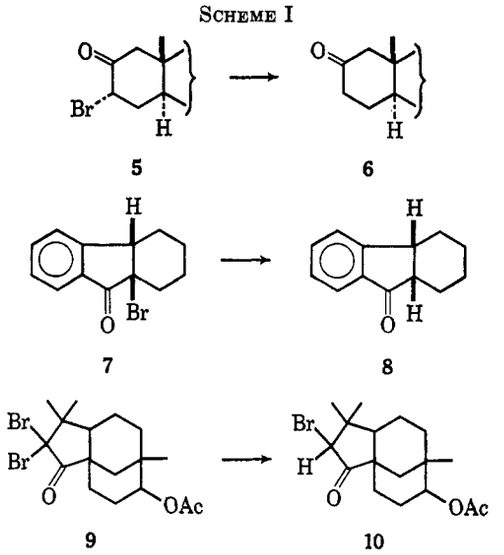
[a] All values given in parentheses are those taken from the earlier work described in the reference in footnote 3. [b] The difference between the sum of 2 + 3 + 4 and 100% is accounted for by pyridinium salts, other products formed in the reaction which were not examined, and incomplete recovery from thick layer chromatograms. [c] The higher figure is crude 2 containing some impurities from the ozonization reaction; the lower figure is the yield of pure 2. The true yield of 2 will lie somewhere in between and is estimated to be about 10%.

action.[5] Therefore, to resolve the discrepancy we have reexamined the reaction of 2α-bromocholestan-3-one free of 2 with pure substituted pyridines and determined the amount of reductive debromination by *isolation* of the cholestan-3-one formed.

Reagent grade chloroform was found to give a partial thick layer chromatographic separation of 2 from 3, and in this way it was possible to separate 5.8% of cholestan-3-one (2). However, this figure represented a minimum yield since some 2 remained in the 3. To circumvent the incomplete thick layer chromatographic separation, the unsaturated ketones 3 and 4 in one aliquot of the reaction product were destroyed by ozonization and the surviving cholestan-3-one was isolated by thick layer chromatography. Since thick layer chromatography of another aliquot of the reaction product gave almost complete separation of 4 from 2 + 3, Δ¹- and Δ⁴-cholesten-3-one were determined by calculation from the ultraviolet extinction coefficients of these fractions at 220 and 250 mμ. The results are summarized in Table I. The figures for the α-picoline reaction, not described previously, bear out the conclusion drawn earlier that the presence of only one α-methyl group suppresses quaternary salt formation, but not completely in this case. For the reactions with 2,6-lutidine and γ-collidine, the most important finding is that, although the yields (between 5.8 and 14.7%) of cholestan-3-one found by isolation are considerably lower than originally reported,[3] nevertheless, they are substantially greater than 2%. Moreover, these are probably minimum yields since 2 is slowly attacked by ozone despite the low temperature (−70°) used.

More extreme examples are known in which reductive debromination is the major reaction leading to the only product isolated. The most closely related case is the reaction of pure 3α-bromocholestan-2-one (partial structure 5) with pure 2,6-lutidine in which 28% of cholestan-2-one (partial structure 6) was formed (see the Experimental Section). Other instances are the attempted dehydrobromination of the bromofluorenone 7 with refluxing γ-collidine which gave 31% of the debrominated ketone 8,[6] and the reaction of the caryophyllene derivative 9 with refluxing γ-collidine which afforded 22% of the monobromo ketone 10.[7] (See Scheme I.) Therefore, reductive debromination is definitely a significant path in the reaction of bromo ketones with the α-disubstituted pyridines 2,6-lutidine and γ-collidine.

SCHEME I



If these debrominations were taking place by nucleophilic attack of nitrogen on the bromine atom to provide an N-bromocollidinium ion and the enolate anion of 2, the reverse rebromination reaction would presumably be occurring also. An attempt to increase the amount of reduction of 1 to 2 by intercepting any N-bromocollidinium ion formed with β-naphthol gave, however, no noticeable increase in the amount of 2 produced.

It can be concluded that, in those α-halo ketones where displacement or dehydrohalogenation by an α-disubstituted pyridine is retarded or prevented for structural or stereochemical reasons, reductive debromination becomes a product-forming path.

Experimental Section

General.—Infrared spectra were determined on a Beckman IR-5 spectrophotometer. Ultraviolet analyses were carried out on a Cary Model 14 spectrophotometer. Nmr spectra were determined on deuteriochloroform solutions with a Varian A-60 instrument. Thick and thin layer chromatograms were run on

(5) Comparison of the carbonyl infrared absorption of the fraction containing 2 and 3 obtained by thick layer chromatography of the crude product from pure 1 (see the Experimental Section) with the carbonyl infrared absorption of known synthetic mixtures of 2 and 3 indicated that 5–10% of cholestan-3-one (2) was present in the crude reaction product.

(6) H. O. House, V. Paragamian, R. S. Ro, and D. J. Wluka, *J. Am. Chem. Soc.*, **82**, 1461 (1960).

(7) A. Aebi, D. H. R. Barton, and A. S. Lindsey, *J. Chem. Soc.*, 3128 (1953).

Camag DF-5 silica gel containing fluorescent indicator. Ultraviolet light, iodine vapor, and sulfuric acid charring were used for detection. Petroleum ether refers to the fraction of bp 60–80°.

Purity of the substituted pyridines was ascertained from their nmr spectra. 2,6-Lutidine (B.D.H.) and α- and β-picoline (Eastman) were of greater than 99% purity. γ-Collidine (Eastman) and 2,4-lutidine (Baker) were purified *via* their hydrobromide or hydrochloride salts.[3]

2α-Bromocholestan-3-one[8] was purified by column chromatography on silica gel and its degree of purity was assessed by tlc comparison in ether–benzene (2:98) with a set of synthetic mixtures (1 + 2) of known cholestan-3-one content run on one plate. Typical R_f values were 0.21 for **2**, 0.42 for **1**, and 0.52 for traces of 2β-bromocholestan-3-one. By this method 0.5% or more of **2** could easily be detected. In all experiments *less* than 0.5% of cholestan-3-one was present in the 2α-bromocholestan-3-one used. In each of the reactions described below the absence of any remaining **1** in the ether soluble part of the crude product was verified by tlc (ether–benzene, 3:97).

Reaction of 2α-Bromocholestan-3-one with γ-Collidine. A. Without Ozonization.—The bromo ketone **1** (1.000 g, 2.15 mmoles) was refluxed (oil bath 195–200°) with 4 ml of γ-collidine for 12 hr. Dilution with ether and filtration gave 430 mg (99%) of γ-collidine hyrobromide. Extraction of the filtrate with dilute hydrochloric acid removed the γ-collidine. Evaporation of the dried ethereal solution left 810 mg (98%) of amber, partly crystalline product. Thick layer chromatography of 358 mg of crude product in ethyl acetate–petroleum ether (15:85) yielded 223 mg (62% of total product) of a mixture of **2** + **3** (R_f 0.31) and 118 mg (33% of total product) of **4** (R_f 0.22). Visual comparison of the carbonyl infrared absorption of the **2** + **3** mixture with prepared mixtures of **2** + **3** containing 5% and 10% of **2** (concentration, 10 mg/0.10 ml of carbon disulfide in a 0.10-mm cell) indicated that about 5–10% of **2** was present in the crude ether-soluble product. Part of the **2** + **3** zone (213 mg) was put back on thick plates and developed in reagent grade chloroform (contained 0.75% of ethanol). Although the cholestan-3-one did not quench the fluorescence of the ultraviolet indicator in the silica gel, the area just ahead of the blue Δ^1-ketone band under ultraviolet light was separated and extracted to yield 20.1 mg (5.8% of total product) of crystalline cholestan-3-one, mp 126–129°, undepressed by authentic **2** (mp 129–130°), whose tlc spot showed only the faintest trace of **3**. The blue zone yielded 193 mg of Δ^1-cholesten-3-one which still contained cholestan-3-one.

B. With Ozonization.—A solution of bromo ketone **1** (3.209 g, 6.90 mmoles) in 10 ml of γ-collidine was refluxed (oil bath 180°) for 18 hr. Dilution with ether and filtration removed 1.434 g (98%) of γ-collidine hydrobromide. The ethereal filtrate was washed with dilute sulfuric acid to remove collidine, dried, and evaporated to give 2.588 g (98%) of crude product which was dissolved in carbon tetrachloride and made up to 10 ml in a volumetric flask.

Thick layer chromatography of 1.00 ml of the stock solution in ether–benzene (4:96) and separation of zones yielded 160 mg of mainly **2** + **3** and 68 mg of mainly **4**. Calculation from the ultraviolet absorption of these fractions at 220 ($\epsilon_3 - \epsilon_4$ 2000) and 250 mμ ($\epsilon_4 - \epsilon_3$ 10,300) and that of authentic specimens [Δ^1-cholesten-3-one, $\lambda_{max}^{95\%\ EtOH}$ 230 mμ (ϵ 11,050), and Δ^4-cholesten-3-one, $\lambda_{max}^{95\%\ EtOH}$ 241 mμ (ϵ 16,500)] at these same wavelengths showed that 64% of **3** and 11.3% of **4** were present in the **2** + **3** band while 76% of **4** and 9% of **3** were present in the **4** band.

A solution of 1.00 ml of the stock solution in 20 ml of redistilled ethyl acetate was cooled to −70° and ozonized for 8 min.[9] The reaction was quenched by the addition of 10 ml of 25% potassium iodide solution, and the mixture was shaken until it reached room temperature. The organic solution was washed with aqueous sodium thiosulfate solution and water and dried over magnesium sulfate. Filtration and evaporation left 306 mg of amber gum which was separated on thick layer plates developed in ether–benzene (4:96). The position of cholestan-3-one was ascertained by charring monitor plates run under identical conditions. White, crystalline, impure cholestan-3-one (38 mg, 14.7%, mp 100–112°) was recovered. Two recrystallizations from 95% ethanol gave 11 mg (4%) of pure **2**, mp 126–128°, undepressed on admixture with authentic cholestan-3-one, mp 129–130°. The recrystallized product gave a single tlc spot with the same R_f value as that of authentic **2**.

Ozonization of another sample of 868 mg of combined crude products in ethyl acetate at −70° gave a crude product which was separated by thick layer chromatography. The **2** band revealed by iodine vapor was extracted to give 96 mg (11%) of crude cholestan-3-one which was recrystallized twice from acetone to give 18 mg (2.0%) of small, colorless prisms, mp 125–127°, R_f 0.24 in benzene–ether (94:6).

C. In the Presence of β-Naphthol.—2α-Bromocholestan-3-one (247 mg, 0.53 mmole) and 171 mg (1.19 mmoles) of β-naphthol were refluxed in 5 ml of γ-collidine for 18 hr. Dilution with ether and filtration gave 93 mg (87%) of collidine hydrobromide. The β-naphthol and collidine were removed from the filtrate by extraction with 10% sodium hydroxide solution and dilute hydrochloric acid. Evaporation of the dried ethereal solution left 198 mg (97%) of product. Ozonization and isolation of the cholestan-3-one fraction as described in B gave 22 mg (11%) of crude **2** which tlc showed to contain impurities.

Reaction of 2α-Bromocholestan-3-one with Other Pyridines. A. β-Picoline.—The bromo ketone **1** (2.782 g, 6.00 mmoles) and 10 ml of β-picoline were refluxed for 3 hr. Dilution with ether and filtration gave 2.969 g of crystals which were triturated with water and filtered. There remained 2.680 g (80%) of water-insoluble β-picolinium salt of **1**. β-Picoline hydrobromide (123 mg, 12%) was recovered from the aqueous filtrate. The ether-soluble product (326 mg, 14%) was isolated and analyzed as described for the γ-collidine reaction in B.

B. α-Picoline.—2α-Bromocholestan-3-one (1.592 g, 3.43 mmoles) and 10 ml of α-picoline were refluxed for 19 hr. Dilution with ether–water and filtration gave 194 mg (10%) of water-insoluble α-picolinium salt of **1**, mp 332–334° dec when placed on the hot stage at 185°. The salt was shown to be different from the pyridinium, β-picolinium, and γ-picolinium salts of **1**.[3] Evaporation of the aqueous layer left oily α-picoline hydrobromide whose yield was estimated as 92% by precipitation and weighing of silver bromide. The ether-soluble product (1.148 g, 87%) was isolated and analyzed as described for the γ-collidine reaction in B.

C. 2,4-Lutidine.—The bromo ketone **1** (545 mg, 1.17 mmoles) in 5 ml of 2,4-lutidine was refluxed for 5.5 hr. Dilution with ether and filtration gave 213 mg (97%) of 2,4-lutidine hydrobromide. Evaporation of the filtrate after acid extraction of excess 2,4-lutidine left 437 mg (97%) of dark greenish brown gum which was analyzed as described for the γ-collidine reaction in B.

D. 2,6-Lutidine.—2α-Bromocholestan-3-one (614 mg, 1.32 mmoles) in 10 ml of 2,6-lutidine was refluxed for 22 hr. Dilution with ether and filtration gave 219 mg (89%) of 2,6-lutidine hydrobromide. Evaporation of the ether from the filtrate after removal of excess 2,6-lutidine by acid extraction left 451 mg (89%) of pale yellow solid which was analyzed as described for the γ-collidine reaction in B.

Pyrolysis of γ-Picolinium Salt of 2α-Bromocholestan-3-one.—The pyrolysis of 259 mg of pure salt was carried out at 300–320° (0.02 mm). Complete decomposition occurred within 4 hr. The sublimate consisted of 24.9 mg of sublimed γ-picolinium salt of **1** and 151.9 mg of ether-soluble product which was analyzed as described in B for the γ-collidine reaction.

Reaction of 3α-Bromocholestan-2-one (5) with 2,6-Lutidine (with P. NaNonggai-Suwanrath).—3α-Bromochlolestan-2-one [mp 152–155°, $[\alpha]^{20}D$ +198° (*c* 2.22, chloroform) (lit.[10] mp 151–153°, $[\alpha]D$ +184°] was prepared by chromic acid oxidation of 3α-bromocholestan-2β-ol by the procedure of Alt and Barton.[10] A solution of 233 mg (0.50 mmole) of the pure bromo ketone **5**,[11] in 2 ml of 2,6-lutidine, purified *via* the crystalline picrate,[3] was refluxed under a nitrogen atmosphere for 48 hr. Dilution with ether and filtration gave 43 mg (45%) of 2,6-lutidine hydrobromide. The filtrate was extracted with dilute sulfuric acid and water and dried. Chromatography of the residue (210 mg) left after evaporation of the ether on 7 g of activity II Merck alumina gave 86 mg (44%) of crude cholestan-2-one (**6**) eluted with benzene–ether mixtures. The product had no ultraviolet absorption peaks in the 200–260-mμ range. Two recrystallizations from methanol afforded 55 mg (28%) of short needles, mp

(8) L. F. Fieser and X. A. Dominguez, *J. Am. Chem. Soc.*, **75**, 1704 (1953).

(9) Control ozonizations on pure **2**, **3**, and **4** showed that **3** and **4** were converted completely to much more polar (tlc) substances within this time, but that **2** was detectably changed only during longer reaction periods.

(10) G. H. Alt and D. H. R. Barton, *J. Chem. Soc.*, 4284 (1954).

(11) That there was no cholestan-2-one in the **5** follows from the method of preparation and tlc examination. With reagent grade chloroform as developing solvent, the sample of **5** gave a single spot, R_f 0.60, on the same plate on which **6** had R_f 0.43.

127–128.5°, $[\alpha]^{20}D$ +51° (*c* 2.00, chloroform). The mixture melting point with authentic cholestan-2-one (mp 130–131°, $[\alpha]^{23}D$ +51°) was undepressed. Tlc alongside authentic **6** gave a single spot with the same R_f 0.35 when developed in reagent grade chloroform.

Registry No.—**1**, 1452-34-2; pyridine, 110-86-1; γ-picoline, 108-89-4; β-picoline, 108-99-6; α-picoline, 109-06-8; 2,4-lutidine, 108-47-4; 2,6-lutidine, 108-48-5; γ-collidine, 108-75-8; γ-picolinium salt of **1**, 10294-04-9; **5**, 2042-01-5.

Chromic Acid Oxidation of *endo*-5,6-Trimethylenenorbornyl Alcohols

IRVIN ROTHBERG AND ROBERT V. RUSSO

Department of Chemistry, Rutgers The State University, Newark, New Jersey 07102

Received December 8, 1966

Solvolysis studies of the tosylate esters of the *endo*-5,6-trimethylenenorbornane[1] system have recently been the subject of much interest.[2] In connection with this work, comparisons of nonbonded interactions being relieved by movement of the oxygen atom would be of value. Some of these ground-state interactions which could be relieved in the transition state assuming a decrease in steric strain have been estimated,[2a] but not experimentally evaluated. If the chromic acid oxidation of these alcohols behaves normally, that is, if the rate is increased by greater steric strain in the ground state, then this should permit an evaluation of free-energy differences.[3,4] The rates of oxidation are given in Table I.

The results indicate that the oxidation rates are normal. *endo*-5,6-Trimethylene-*endo*-2-norbornanol (**2**) is oxidized 151 times faster than its epimer (**1**), representing a ΔF difference of 3.0 kcal/mole. *endo*-Trimethylene-*endo*-2-norbornanol (**2**) is oxidized 48 times faster than *endo*-2-norbornanol. We believe that this difference is due almost entirely to steric effects corresponding to a free-energy difference of 2.3 kcal/mole. Comparison of **3** with *exo*-2-norbornanol shows that the inductive effect of the *exo*-trimethylene bridge is negligible and comparison of **4** with *endo*-2-norbornanol shows only a very slight rate increase, part of which may be due to greater rigidity of the *endo*-5,6-hydrogens because of the attached trimethylene ring. There are reactions where *exo* and *endo* substituents have different effects,[5] but the considerably lower value of the ρ expected here[6] and the relatively poor electron-donating ability of the uncharged methylene groups should lead to very small differences. *endo*-5,6-Trimethylene-*endo*-8-norbornanol (**6**) is oxidized 25 times faster than its less strained epimer (**5**), which corresponds to a free-energy difference of 1.9 kcal/mole. Comparison of the epimers **7** and **8** shows that there is essentially no difference in their ground-state nonbonded interactions.

TABLE I

CHROMIC ACID OXIDATION RATES (25.0° in 75% ACETIC ACID AND 0.1 *M* PERCHLORIC ACID)

Alcohol	$k_2 \times 10^2$, l. mole^{-1} sec^{-1}	Relative rate
exo-2-Norbornanol	4.08	1.00
endo-2-Norbornanol	26.4	6.47
endo-5,6-Trimethylene-*exo*-2-norbornanol (**1**)	8.43	2.07
endo-5,6-Trimethylene-*endo*-2-norbornanol (**2**)	1270	311
exo-5,6-Trimethylene-*exo*-2-norbornanol (**3**)	4.43	1.09
exo-5,6-Trimethylene-*endo*-2-norbornanol (**4**)	35.8	8.77
Cyclopentanol	4.03	1.00
endo-5,6-Trimethylene-*exo*-8-norbornanol (**5**)	4.93	1.22
endo-5,6-Trimethylene-*endo*-8-norbornanol (**6**)	124	30.8
endo-5,6-Trimethylene-*exo*-9-norbornanol (**7**)	9.33	2.31
endo-5,6-Trimethylene-*endo*-9-norbornanol (**8**)	7.22	1.79

Comparison of **1** with *exo*-2-norbornanol and **5** with cyclopentanol shows that, as steric strain becomes greater on the methine hydrogen, the rate becomes more rapid with the ease of approach of solvent apparently playing no major role in determining the rate of oxidation.[7] The rate of **7** is 1.89 times faster than **5**. This was unexpected because both steric and inductive effects would have predicted the opposite result. Possibly this is due to conformational differences. In summary, the results with one exception of minor magnitude appear to be self-consistent and to provide experimental evaluation of the ground-state differences due to nonbonded interactions. In the compounds where comparisons can be made, the experimental values are in reasonable agreement with the values previously estimated.[2a]

Experimental Section

The alcohols are known compounds and the properties agreed with those reported in the literature.[2a,e,f,8]

Rate studies were carried out using essentially the procedure of Stewart and Lee[9] in 75% acetic acid and 0.10 *M* in perchloric acid. Treatment of the slope of a plot of Cr(VI) concentration *vs.* time by the procedure of Benson[10] for second-order reactions with stoichiometric concentration yielded the rate constants. The rate plots all gave straight lines up to 70% of reaction. All

(1) The nomenclature used is described by P. v. R. Schleyer and M. M. Donaldson [*J. Am. Chem. Soc.*, **82**, 4645 (1960)] and in ref 2a.

(2) (a) H. C. Brown, I. Rothberg, P. v. R. Schleyer, M. M. Donaldson, and J. J. Harper, *Proc. Natl. Acad. Sci. U. S.*, **56**, 1653 (1966); (b) H. C. Brown, "Chemistry in Britain," Vol. 2, 1966, p 199; (c) J. A. Berson, in "Molecular Rearrangements," Part 1, P. DeMayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, Chapter 3; (d) G. D. Sargent, *Quart. Rev.* (London), **20**, 301 (1966); (e) P. D. Bartlett and R. S. Barnes, Abstracts of the 12th National Organic Symposium of the American Chemical Society, June 1951, p 1; (f) K. Takeuchi, T. Oshika, and Y. Koga, *Bull. Chem. Soc. Japan*, **38**, 1318 (1965); (g) M. M. Donaldson, Ph.D. Thesis, Princeton University, Princeton, N. J., 1958; *Dissertation Abstr.*, **22**, 738 (1961); (h) P. v. R. Schleyer, Ph.D. Thesis, Harvard University, Boston, Mass., 1956.

(3) For discussion of the use of chromic acid oxidations as a measure of free-energy differences, see (a) E. L. Eliel, S. H. Schroeter, T. J. Brett, F. J. Biros, and J. C. Richer, *J. Am. Chem. Soc.*, **88**, 3327 (1966); (b) J. C. Richer and C. Gilardeau, *Can. J. Chem.*, **43**, 538 (1965); (c) C. F. Wilcox, M. Sexton, and M. F. Wilcox, *J. Org. Chem.*, **28**, 1079 (1963); (d) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Publishers, Inc., New York, N. Y., 1965, pp 81–85.

(4) For an example of abnormal behavior, see ref 3d, p 271.

(5) H. Kwart and L. J. Miller, *J. Am. Chem. Soc.*, **83**, 4552 (1961).

(6) A ρ value of −1.06 was found by J. Rocek [*Collection Czech. Chem. Commun.*, **25**, 1052 (1962)] for an aliphatic system where the distance separating reaction site from substituents was shorter than in our compounds.

(7) For discussion on the mechanism of chromic acid oxidation, see (a) K. B. Wiberg in "Oxidation in Organic Chemistry," Part A, K. B. Wiberg, Ed., Academic Press Inc., New York, N. Y., 1965, Chapter 2; (b) R. Stewart, "Oxidation Mechanisms," W. A. Benjamin Inc., New York, N. Y., 1964, Chapter 4.

(8) H. A. Bruson and T. W. Riener, *J. Am. Chem. Soc.*, **67**, 723 (1945); S. J. Cristol, W. K. Seifert, and S. B. Soloway, *ibid.*, **82**, 2351 (1960).

(9) R. S. Stewart and D. G. Lee, *Can. J. Chem.*, **42**, 439 (1964).

(10) S. W. Benson, "The Foundations of Chemical Kinetics," McGraw-Hill Book Co., Inc., New York, N. Y., 1960, p 20.