product, which was extracted with ether and crystallized from methanol. The 6α-hydroperoxide gave 6α-hydroxy-Δ^4-cholesten-3-one, m.p. 161.5–162.5°, $[\alpha]_D$ +79.1°, λ^{EtOH} 241.5 mμ. The 6β-isomer gave 6β-hydroxy-Δ^4-cholesten-3-one, m.p. 188–189°, $[\alpha]_D$ +26.5°, λ^{EtOH} 237.5 mμ. The constants agree with those reported[8] and mixtures showed no melting point depression. Acetylation in pyridine gave 6α- and 6β-acetoxy-Δ^4-cholesten-3-one of the following properties: m.p. 105–106°, λ^{EtOH} 238 mμ; m.p. 102.5–104°, Δ^{EtOH} 237 mμ.

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The Azine and *p*-Toluenesulfonylhydrazone of 12-Oxocholane[*,1]

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12-Oxocholane,[2] when refluxed with tosylhydrazine in ethanol solution, yields the expected tosylhydrazone I, but in addition, gives rise to a second nitrogen-containing compound II. The crystalline product II, m.p. 158.0–159.4°, has been assigned the structure of 12-oxocholane azine on the basis of elemental analyses, molecular weight,[3] and infrared evidence[4] of a -C=N- band (medium strong at 6.18 μ) and no N-H stretching bands, and the fact that it is quantitatively hydrolyzed to the original ketone.[4a] Synthesis of II by treatment of 12-oxocholane with hydrazine confirms the assignment of structure.

The formation of ketazine II in the reaction involving tosylhydrazine is of interest (1) because an azine has not been reported previously in a preparation of any tosylhydrazone despite considerable current concern[5,6] with the latter group of compounds, and (2) because tosylhydrazine undergoes pyrolytic breakdown to give diimide, an unstable intermediate capable of hydrogenating double bonds.[7]

Hydrazone I is not an intermediate in the reaction[8]; I, when refluxed under the original conditions, is unchanged. Instead, II results from reaction of the ketone with hydrazine freed when tosylhydrazine is refluxed in ethanol. Girard's reagents T and P undergo an analogous cleavage to form azines with ketones.[9]

Hydrazine is not present as a significant impurity in the tosylhydrazine used, as shown by a Pesez and Petit test.[10] However, when tosylhydrazine is refluxed in ethanol solution, after 24 hr. the test for hydrazine is distinctly positive, and addition of 12-oxocholane to the prerefluxed tosylhydrazine–ethanol solution produced the first indications of formation of azine within a few minutes (t.l.c.). In contrast, under the original conditions, in which ketone was mixed with tosylhydrazine and ethanol, and the mixture was brought to reflux, t.l.c. showed no formation of azine for at least 8 hr.; tosylhydrazone I, although detected initially at 90 min., increases in concentration very gradually, and even after 24 hr., a substantial proportion of 12-oxocholane is still present. Evidently the rate of reaction of the hindered ketone with tosylhydrazine in refluxing ethanol solution without added catalyst is so slow, that hydrazine, evolved also slowly from tosylhydrazine, can compete successfully for the ketone to form azine. With added hydrochloric acid, the reaction is sufficiently fast[11] that no azine is formed.

The finding that azine derived from hydrazine is a product of the reaction, whereas no hydrogenation products of either ketone or azine were detected, does not preclude the possibility that diimide is also a product of the breakdown of tosylhydrazine in refluxing ethanol. Van Tamelen[12] has shown that multiple bonds between heteroatoms are not reduced readily by diimide. In this connection, 12-oxocholane azine did not undergo catalytic hydrogenation in ethanol solution in the presence of platinum oxide.[13]

While Bamford and Stevens[5a] reported instances of conversion of tosylhydrazones to corresponding azines by treatment with bases, compound I, when refluxed with base, yielded only olefinic material[14]; no nitrogenous product was detected.

Experimental[15]

Reaction of 12-Oxocholane (12-Cholanone) with *p*-Toluenesulfonylhydrazine.—12-Oxocholane, m.p. 117.0–119.5°, $[\alpha]_D$ +104.9° (lit.[2] m.p. 115–117°, $[\alpha]_D$ +89.4°), 0.70 g., was heated at reflux for 48 hr. with 1.0 g. of tosylhydrazine (Aldrich Co.) in 40 ml. of absolute ethanol. On cooling, a crop of dense crystals, 0.21 g. (30%), m.p. 153–157°, separated from the solution. Recrystallization from ethanol yielded prismatic crystals, m.p. 158.0–159.5°, $[\alpha]_D$ +125.5°, mol. wt.[3] 684, $\lambda_{max}^{CS_2}$ 6.18 μ

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[*] To Professor Louis F. Fieser.

[1] This investigation was supported in part by Grant CA-05011 from the National Cancer Institute, of the National Institutes of Health, U. S. Public Health Service.

[2] J. W. Huffman, D. M. Alabran, and T. W. Bethea, *J. Org. Chem.*, **27**, 3381 (1962).

[3] Molecular weight 684 by mass spectrometry. The author is indebted to Professor Kenneth L. Rinehart, Jr., for this determination obtained with a molecular beam inlet system.

[4] (a) L. E. Miramontes and M. A. Romero, *Chem. Ind.* (London), 1595 (1958); (b) J. Elks and G. H. Phillips, *J. Chem. Soc.*, 4326 (1956).

[5] (a) W. R. Bamford and T. S. Stevens, *ibid.*, 4735 (1952); (b) J. Elks, G. H. Phillips, D. A. H. Taylor, and L. G. Wyman, *ibid.*, 1739 (1954); (c) R. Hirschmann, C. Snoddy, Jr., C. F. Hiskey, and N. L. Wendler, *J. Am. Chem. Soc.*, **76**, 4013 (1954).

[6] J. W. Powell and M. C. Whiting, *Tetrahedron*, **7**, 305 (1959); L. Friedman and H. Shechter, *J. Am. Chem. Soc.*, **83**, 3159 (1961); L. Caglioti and M. Magi, *Tetrahedron*, **19**, 1127 (1963); H. Mitsuhashi and Y. Shimizu, *ibid.*, **19**, 1027 (1963); A. N. deBelder, and H. Weigel, *Chem. Ind.* (London), 1689 (1964); L. Caglioti and P. Grasselli, *ibid.*, 153 (1964); Y. Inouye and K. Nakanishi, *Steroids*, **3**, 487 (1964).

[7] R. S. Dewey and E. E. van Tamelen, *J. Am. Chem. Soc.*, **83**, 3729 (1961).

[8] Tosylhydrazones can be converted to azines by reflux in ethanol with hydrochloric acid [H. H. Szmant and C. McGinnes, *ibid.*, **72**, 2890 (1950)] or in ethanol with pyridine hydrochloride,[4a] and certain steroidal semicarbazones give azines on being heated in tetralin [H. Dannenberg, H. Scheurlen, and I. Simmer-Ruhle, *Ann.*, **600**, 69 (1964)].

[9] H. Cohen, R. W. Bates, and S. Lieberman, *J. Am. Chem. Soc.*, **74**, 3938 (1952).

[10] M. Pesez and A. Petit, *Bull. soc. chim. France*, 122 (1947).

[11] However, 12-oxocholane reacts with tosylhydrazine much more slowly than does the 12-oxo steroidal sapogenin, hecogenin acetate; the latter was converted to the corresponding tosylhydrazone under similar acidic conditions in 30 min.[5b,c] Hecogenin acetate tosylhydrazone has been prepared also in ethanol without catalyst, but no corresponding azine was reported.[5b]

[12] E. E. van Tamelen, R. S. Dewey, M. F. Lease, and W. H. Pirkle, *J. Am. Chem. Soc.*, **83**, 4302 (1961).

[13] This observation is in accord with earlier work on the hydrogenation of ketazines [H. T. Lochte, J. R. Bailey, and W. A. Noyes, *ibid.*, **43**, 2597 (1921); K. A. Taipale, *Zh. Fiz. Khim.*, **57**, 487 (1925); *Chem. Abstr.*, **19**, 3478 (1925)].

[14] Studies of this product will be reported in the future.

[15] Microanalyses by Weiler and Strauss, Oxford. Melting points were determined on an electrical hot stage, uncorrected. Optical rotations were determined in 2% chloroform solution; infrared spectra on a Perkin-Elmer Infracord.

(-C═N). The compound gave a strong qualitative test for nitrogen, and was characterized as **12-oxocholane azine (II)**.

Anal. Calcd. for $C_{48}H_{80}N_2$ (685.14): C, 84.14; H, 11.77; N, 4.09. Found: C, 84.28; H, 11.82; N, 3.96.

On concentration of the mother liquor and cooling, a second crop of crystals (0.31 g., 30%) was obtained, which was recrystallized from ethanol as large prisms: m.p. 178.0–180.5°; $[\alpha]_D$ +60.3°; λ_{max}^{KBr} 3.1, 6.15, 6.28, 7.51, 8.62 (s), and 12.28 μ (tosylhydrazone[16]). The compound was characterized as **12-oxocholane *p*-toluenesulfonylhydrazone (I)**.

Anal. Calcd. for $C_{31}H_{50}N_2O_2S$ (514.80): C, 72.32; H, 9.79. Found: C, 72.53; H, 9.61.

Acid-Catalyzed Preparation of 12-Oxocholane Tosylhydrazone (I). A. With Hydrochloric Acid.—12-Oxocholane (30 mg.) was heated at reflux with 30 mg. of tosylhydrazine in 3 ml. of absolute ethanol containing 0.05 ml. of concentrated hydrochloric acid. The reaction was followed by t.l.c. In 10 min., a faint spot of hydrazone I appeared; in 3 hr., ketone was still present; in 5 hr., ketone had disappeared. No 12-oxocholane azine II was detected. On concentration of the solution, dense crystals (29 mg., 65%), identical with 12-oxocholane tosylhydrazone (I) according to mixture melting point, t.l.c., and infrared, separated.

B. With Acetic Acid.—An experiment identical with A, but with acetic substituted for hydrochloric acid, was carried out and monitored by t.l.c. The reaction is considerably slower than in A. Tosylhydrazone was first observed at 0.5 hr.; at 6.5 hr., ketone was still present, and azine was seen. On concentration and cooling, crystals separated which consisted of a 4:1 mixture of tosylhydrazone and azine, as estimated by t.l.c.

Hydrazine from Tosylhydrazine.—The tosylhydrazine (20 mg.) used in the previous experiment when tested with the Pesez and Petit reagent[10] showed no free hydrazine, but, when another portion in 2 ml. of absolute ethanol was refluxed for 24 hr., a strong test was obtained. When 10 mg. of 12-oxocholane was added to such a prerefluxed solution and heated at reflux, and the reaction was followed by t.l.c., a spot corresponding to the azine appeared in less than 5 min. After 90 min., the reaction was stopped; on cooling, dense microcrystals separated from the solution. These melted at 155.0–158.5° and were identical with azine II, according to R_f and infrared.

An experiment was set up identically, but with the starting reagents refluxed together. By t.l.c. no evidence of azine formation was seen even after 8 hr.

12-Oxocholane Azine from Hydrazine.—12-Oxocholane (60 mg.), refluxed in a solution containing 0.25 ml. of hydrazine hydrate (95%), 4.5 ml. of ethanol, and 0.5 ml. of acetic acid, and monitored by thin layer chromatography, showed formation of the azine within a few minutes. Reaction was complete in 35 min. On cooling, the solutions deposited dense crystals, 45 mg. (76%), identical with the azine product II, according to t.l.c., infrared, and mixture melting point.

Attempts to Convert Tosylhydrazone I to Azine II.—12-Oxocholane tosylhydrazone (30 mg.) was recovered largely unchanged either after overnight refluxing with 3 ml. of ethanol, or after 24 hr. refluxing with 30 mg. of tosylhydrazine and 3 ml. of ethanol. No azine was detected (t.l.c.) in either experiment.

Treatment of 12-Oxocholane Tosylhydrazone with Base.—Tosylhydrazone I, 100 mg., suspended in a mixture containing 230 mg. of sodium methylate and 3 ml. of ethylene glycol, was heated, and the temperature maintained at 180° for 1.5 hr. At 140°, gas evolution was observed. T.l.c. showed disappearance of the hydrazone and appearance of a major fast-running material, with R_f corresponding to that of a cholene. When processed, an oil was obtained, which appears to be a mixture of olefins.[14]

Hydrolysis of Azine by HCl.—Ketazine II (17 mg.) was suspended in 2 ml. of ethanol and 5 ml. of 10% hydrochloric acid, and refluxed for 8 hr. On cooling the solution, flaky crystals separated, which were identical with 12-oxocholane, according to melting point, t.l.c., and infrared; the yield was quantitative.

Attempted Hydrogenation of Azine II.—The ketazine II (60 mg.) in 30 ml. of ethanol was shaken with 18 mg. of platinum oxide in a Parr apparatus with hydrogen at 2 atm. pressure for 6 hr. The ketazine was recovered unchanged.

Thin Layer Chromatography.—Reactions were followed by t.l.c. using silica gel G (Merck, Darmstadt) plates. The R_f values of compounds were [development solvent, 10% ethyl acetate in ligroin (b.p. 63–70°)]: 12-oxocholane azine, 0.95; 12-oxocholane, 0.82; 12-oxocholane tosylhydrazone, 0.38; tosylhydrazine, 0.00. The spray used was ethanol–sulfuric acid–vanillin.[17]

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[17] J. S. Matthews, *Biochim. Biophys. Acta*, **69**, 163 (1963).

Reactions of Potassium *t*-Butoxide in Dimethyl Sulfoxide. IV.[1] With Primary Tosylates and Halides*

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When treated with potassium *t*-butoxide in dimethyl sulfoxide (KtBD)[2] at room temperature, 24-cholanyl tosylate yielded predominantly the *t*-butyl ether, as might be expected from previous work.[3] 24-Chlorocholane, however, surprisingly reacted with KtBD to give mainly the elimination product, 23-cholene. The strikingly unexpected difference between tosylate and corresponding chloride led us to investigate further reactions on 24-iodocholane and on selected aliphatic derivatives.

Experimental results of these studies, summarized in Table I, indicate that the difference between primary tosylates and primary halides in reaction with KtBD is a general one: tosylates give predominantly substitution products; halides, chiefly products of elimination. The one exception encountered was perforce a methyl halide.

TABLE I

PRODUCTS OF REACTION OF POTASSIUM *t*-BUTOXIDE IN DIMETHYL SULFOXIDE WITH PRIMARY TOSYLATES AND HALIDES AT ROOM TEMPERATURE

	Reaction time,	Yield of products	
Compd.	min.	Ene (%)	Ether (%)
24-Cholanyl tosylate	30	*a* (21)	*b* (78)
chloride	15	*a* (79)	*b* (21)
iodide	<1	*a* (73)	*b* (17)
n-Octadecyl tosylate	<5	*c* (25)	*d* (71)
n-Octadecyl chloride	5	*c* (86)	*d* (14)
iodide	<1	*c* (90)	*d* (10)
n-Octyl tosylate[e]	. . .	*e* (16[f])	*g* (49[f])
iodide	*h*	*e* (90)	*g* (10)
methyl iodide	*h*	. . .	*i* (78)

[a] 23-Cholene. [b] 24-Cholanyl *t*-butyl ether. [c] 1-Octadecene. [d] *n*-Octadecyl *t*-butyl ether. [e] 1-Octene. [f] From ref. 3b. [g] *n*-Octyl *t*-butyl ether. [h] Reaction could not be monitored by t.l.c. [i] Methyl *t*-butyl ether.

During the final stages of this work prior to preparation of this paper, Veeravagu, Arnold, and Eigenmann[4] reported very much slower reactions in which primary

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* To Professor Louis F. Fieser.

[1] Part III: *Tetrahedron Letters*, 2969 (1964).

[2] KtBD has been proposed as an abbreviation for this reagent by F. C. Chang and N. F. Wood [*Steroids*, **4**, 55 (1964)].

[3] (a) R. T. Blickenstaff and F. C. Chang, *J. Am. Chem. Soc.*, **80**, 2726 (1958); (b) C. H. Snyder and A. R. Soto, *J. Org. Chem.*, **29**, 742 (1964).

[4] P. Veeravagu, R. T. Arnold, and E. W. Eigenmann, *J. Am. Chem. Soc.*, **86**, 3072 (1964).