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REPLACEMENT OF A CARBONYL GROUP OF CYCLIC KETONES BY A SULFUR OR A NITROGEN ATOM. A NEW METHOD FOR TRANSFORMATION OF STEROIDAL KETONES INTO THIA- OR AZASTEROIDS1)

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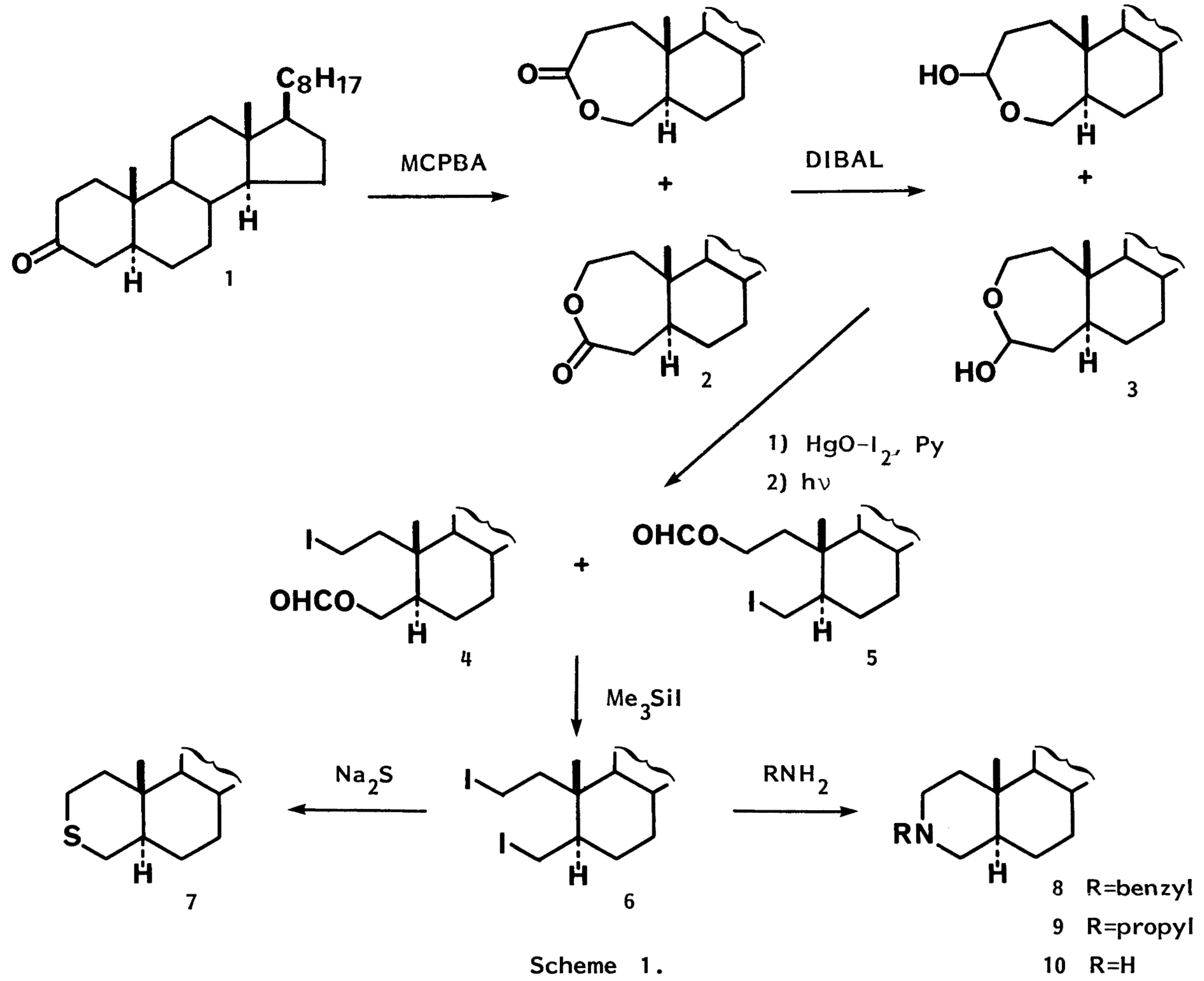
We describe a new and versatile method for transforming cyclic ketones into cyclic sulfides or cyclic amines with the same ring size *via* five-step procedure. The transformation is stereospecific with regard to the chiral center adjacent to the carbonyl group of the ketones.

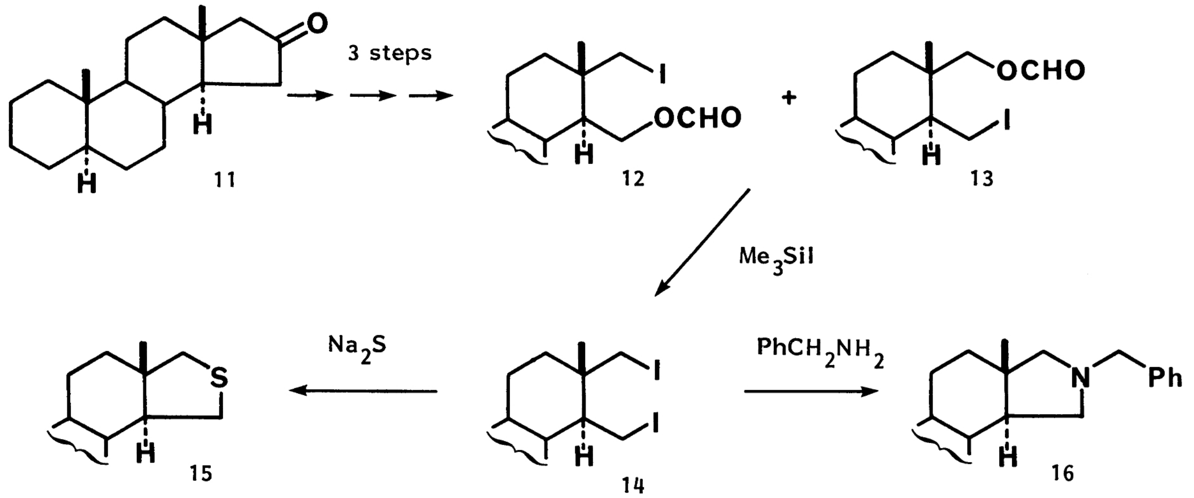
There are relatively few general methods available for effecting the synthesis of thia- and azasteroids.2) In this communication, we wish to report a new efficient general method of achieving the synthesis of thia- and azasteroids by replacing the carbonyl group of steroidal ketones by a sulfur or a nitrogen atom. The method may generally be applicable to transformations of cyclic ketones into cyclic sulfides and cyclic amines with the same ring size as the starting ketones. The transformation is stereospecific with regard to the chiral center adjacent to the carbonyl group of the ketones.

The transformation of 5α-cholestan-3-one (1) into 3-thia-(7) and 3-aza-5α-cholestanes (9) shown in Scheme 1 exemplifies our new method. Thus, a mixture of oily iodo formates (4 and 5) obtained by a three-step procedure3) from ketone (1) *via* mixtures of lactones (2) and lactols (3) was treated with trimethylsilyl iodide4) in carbon tetrachloride to give 2,3-diiodo-2,3-seco-*A*-nor-5α-cholestane (6)5) in an 87% yield. The treatment of diiodide (6) in ethanol with sodium sulfide under reflux gave 3-thia-5α-cholestane (7)6~7) in a 93% yield. The treatment of diiodide, on the other hand, in dioxane with either benzylamine or propylamine under reflux gave N-benzyl-(8)8) or N-propyl-3-aza-5α-cholestane (9)9) in 66% and 62% yields. Removal of the benzyl group of 8 by hydrogenolysis catalyzed with PtO_2 readily gave 3-aza-5α-cholestane (10)10) which was isolated as the crystalline hydrochloride11) in an 82% yield.

The transformation of steroidal 16-one into 16-aza- and 16-thiasteroids can similarly be achieved. Thus, a mixture of iodo formates (12 and 13) obtained *via* 3 steps3) from 5α-androstan-16-one (11) was subjected to the reaction with trimethylsilyl iodide in carbon tetrachloride at 60 °C for 48 h to yield a crystalline diiodide (14)12) in a 93% yield. The treatment of 14 either with sodium sulfide in ethanol or with benzylamine in dioxane afforded 16-thia-5α-androstane (15)13) or N-benzyl-16-aza-5α-androstane14) (16) in 85% and 69% yields, respectively.



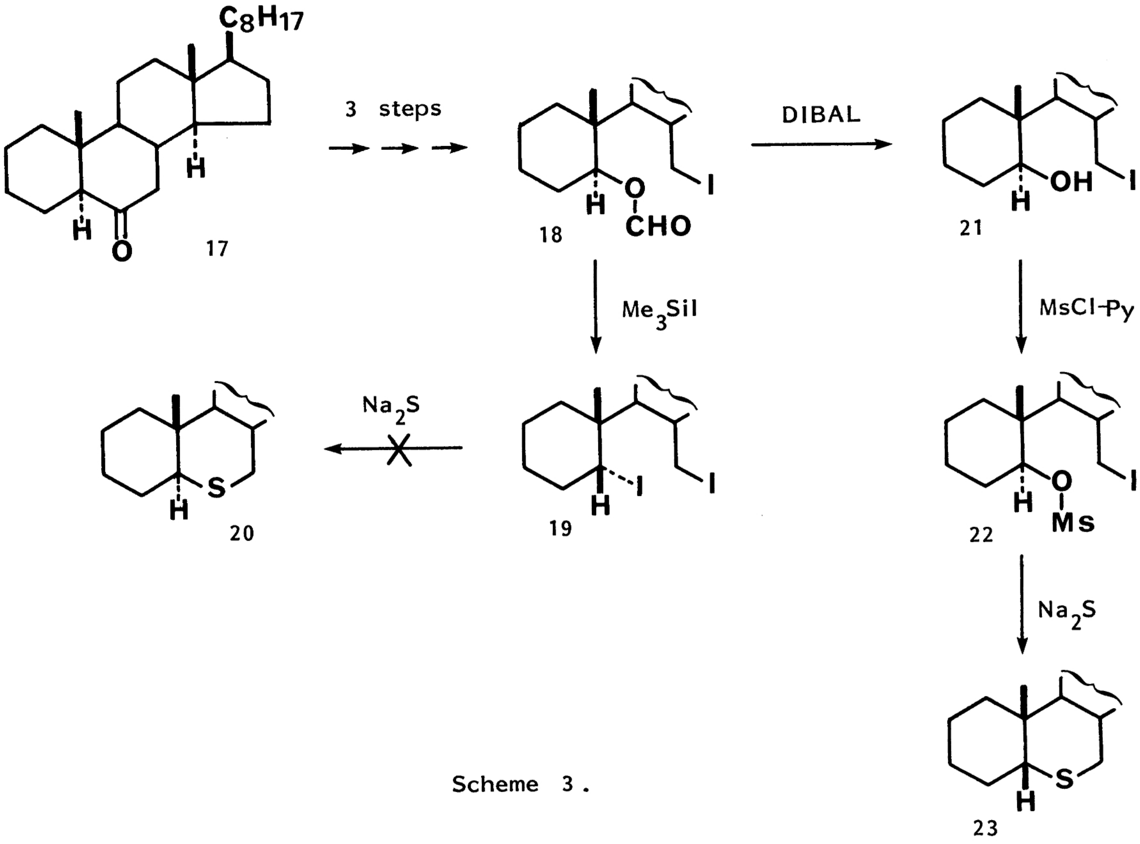
Scheme 1.



Scheme 2.

An attempt to transform 5α-cholestan-6-one (17) into 6-thia-5α-cholestane by this 5 step procedure was, however, unsuccessful; a formate 18 obtained via 3 steps from 5α-cholestan-6-one (17)[3] was treated with trimethylsilyl iodide in carbon tetrachloride at 60 °C for 6 h to give 5,6-diiodo-5,6-seco-B-norcholestane (19). Treatment of this diiodide with sodium sulfide led only to the elimination of HI to give a 5,6-seco-B-norcholest-4-ene and failed to give 6-thiasteroid. 6-Thia-5β-cholestane (23),[15] however, was obtained via 3 steps from formate (18) by means of an alternative procedure. Thus, treatment of 18 with DIBAL in hexane at -78 °C gave 6-iodo-5,6-seco-B-norcholestan-5β-ol (21) in a 90% yield. Its mesylation with mesyl chloride-pyridine to give the corresponding mesyl ester (22) followed by the treatment of the latter with sodium sulfide in ethanol gave hitherto unknown 6-thia-5β-cholestane (23)[15] in a 40% yield.

A survey of the literature indicates that only a few thiasteroids have previously been synthesized in rather poor overall yields.[2,7] Thia- and azasteroids can be obtained in a far simpler manner by the present method. Application of this method to the synthesis of a variety of thia- and azasteroids and the related heterocyclic compounds is under investigation and will be reported in due course.



Scheme 3.

References

1) Photoinduced Transformations. Part 74. Part 73. H. Suginome and S. Yamada, J. Org. Chem., in the press.
2) H. O. Huisman and W. N. Speckamp, "Steroid, International Review of Science, Organic Chem.," ed by W. F. Johns, Butterworths, London (1977), Series Two, vol. 8, Chap. 8, pp. 207-236.
3) H. Suginome and S. Yamada, Tetrahedron Lett., 1984, 3995.
4) T. L. Jung and M. A. Lyster, J. Am. Chem. Soc., 99, 968 (1977).
5) Mp 75-77 °C; IR (Nujol) 1202 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 0.64 (3H, s, 18-H), 0.73 (3H, s, 19-H), 2.81 (1H, dd J=10.25 and 10.25, 4-H), 3.08 (2H, t J=9.02, 2-H), 3.48 (1H, dd J=10.25 and 2.20, 3-H); MS m/e (%) 612 (M$^+$, 1), 485 (M$^+$-I, 25), 57 (100); HR-MS. Calcd for $C_{26}H_{46}I_2$: 612.1690. Found: 612.1716.
6) Mp 98-99 °C. Lit.7) 98.5-99.5 °C.
7) D. Gust, J. Jacobus, and K. Mislow, J. Org. Chem., 33, 2996 (1968).
8) Mp 68-70 °C; IR, (Nujol) 1159, 1070, 1028 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 0.63 (3H, s, 18-H), 0.79 (3H, s, 19-H), 1.91-2.87 (4H, m, 2-H and 4-H), 3.70 (2H, s, CH$_2$ph); MS m/e (%) 463 (M$^+$, 100), 91 ($C_7H_7^+$, 63); Found: C, 85.36; H. 11.49; M, 2.84%. Calcd for $C_{33}H_{53}N$: C, 85.46; H, 11.52; N, 3.02%.
9) Mp 91-92 °C; IR (Nujol) 1162, 1129, 1113, 1071, 994, 860 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 0.65 (3H, s, 18-H), 0.79 (3H, s, 19-H), 2.05-2.82 (4H, m, 2-H and 4-H); MS m/e (%) 415 (M$^+$, 2), 386 (100); Found: C, 83.77; H, 12.75; N, 3.54%. Calcd for $C_{29}H_{53}N$: C, 83.78; H, 12.85; N, 3.37%.
10) C. W. Shoppee, R. W. Killick, and G. Krüger, J. Chem. Soc., 1962, 2275.
11) Mp 260-265 °C. Lit.10) 280-285 °C.
12) Mp 95-104 °C; IR (Nujol) 1304, 1239, 1182, 960, 850 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 0.78 (3H, s, 19-H), 1.08 (3H, s, 18-H), 3.15 (2H, dd J=11.23 and 2.93, 15-H), 3.27 (2H, s, 16-H); MS m/e (%) 500 (M$^+$, 2), 373 (M$^+$-I, 73), 109 (100); HR-MS. Calcd for $C_{18}H_{30}I_2$: 500.0438. Found: 500.0473.
13) Mp 96-97 °C; IR (Nujol) 1226, 1163, 968, 950 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 0.78 (3H, s, 19-H), 0.90 (3H, s, 18-H), 2.25-3.00 (4H, m, 15-H and 17-H); MS m/e (%) 278 (M$^+$, 100); Found: C, 77.51; H, 10.87; S, 11.03%. Calcd for $C_{18}H_{30}S$: C, 77.63; H, 10.86; S, 11.51%.
14) Mp 91-93 °C; IR (Nujol) 1228, 1139, 1072 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 0.79 (3H, s, 19-H), 0.92 (3H, s, 18-H), 2.35-2.68 (4H, m, 15-H and 17-H), 3.80 (2H, s, CH$_2$ph); MS m/e (%) 351 (M$^+$, 67), 133 (100), 91 ($C_7H_7^+$, 67); HR-MS. Calcd for $C_{25}H_{37}N$: 351.2937. Found: 351.2930.
15) Mp 94-95 °C; ^{1}H NMR (CDCl$_3$) δ 0.67 (3H, s, 18-H), 1.19 (3H, s, 19-H), 2.20 (1H, brs, 5β-H), 2.27 (1H, dd J=13.4 and 3.4, 7α-H), 2.49 (1H, dd J=13.4 and 11.5, 7β-H); MS m/e (%) 390 (M$^+$, 9), 321 (100); Found: C, 79.99; H, 11.96; S, 7.98%. Calcd for $C_{26}H_{46}S$: C, 79.92; H. 11.87; S. 8.21%.

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