

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 AZASTEROIDS<sup>1)</sup>

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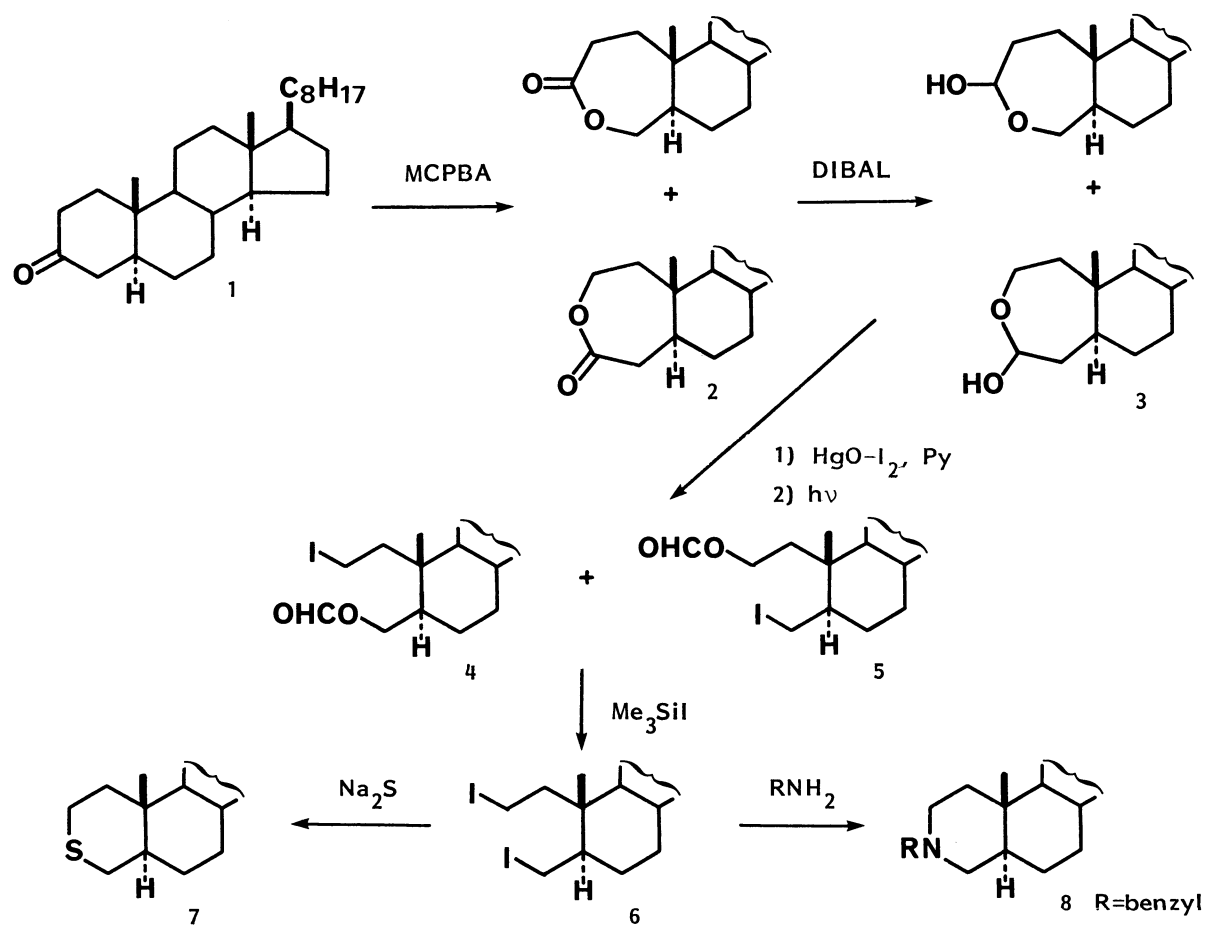
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We describe a new and versatile method for transforming cyclic ketones into cyclic sulfides or cyclic amines with the same ring size via five-step procedure. The transformation is stereospecific with regard to the chiral center adjacent to the carbonyl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

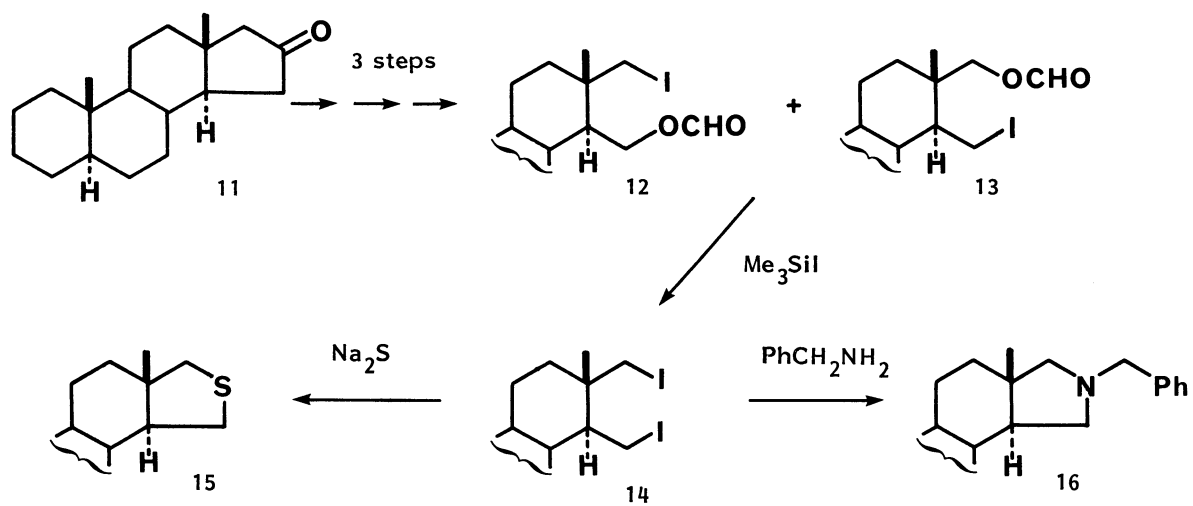
There are relatively few general methods available for effecting the synthesis of thia- and azasteroids.<sup>2)</sup> In this communication, we wish to report a new efficient general method of achieving the synthesis of thia- and azasteroids by replacing the carbonyl group of steroidal ketones by a sulfur 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 5 $\alpha$ -cholestan-3-one (1) into 3-thia-(7) and 3-aza-5 $\alpha$ -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 procedure<sup>3)</sup> from ketone (1) via mixtures of lactones (2) and lactols (3) was treated with trimethylsilyl iodide<sup>4)</sup> in carbon tetrachloride to give 2,3-diiodo-2,3-seco-A-nor-5 $\alpha$ -cholestane (6)<sup>5)</sup> in an 87% yield. The treatment of diiodide (6) in ethanol with sodium sulfide under reflux gave 3-thia-5 $\alpha$ -cholestane (7)<sup>6,7)</sup> 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)<sup>8)</sup> or N-propyl-3-aza-5 $\alpha$ -cholestane (9)<sup>9)</sup> in 66% and 62% yields. Removal of the benzyl group of 8 by hydrogenolysis catalyzed with PtO<sub>2</sub> readily gave 3-aza-5 $\alpha$ -cholestane (10)<sup>10)</sup> which was isolated as the crystalline hydrochloride<sup>11)</sup> 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 steps<sup>3)</sup> from 5 $\alpha$ -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)<sup>12)</sup> in a 93% yield. The treatment of 14 either with sodium sulfide in ethanol or with benzylamine in dioxane afforded 16-thia-5 $\alpha$ -androstan-16-one (15)<sup>13)</sup> or N-benzyl-16-aza-5 $\alpha$ -androstan-16-one<sup>14)</sup> (16) in 85% and 69% yields, respectively.



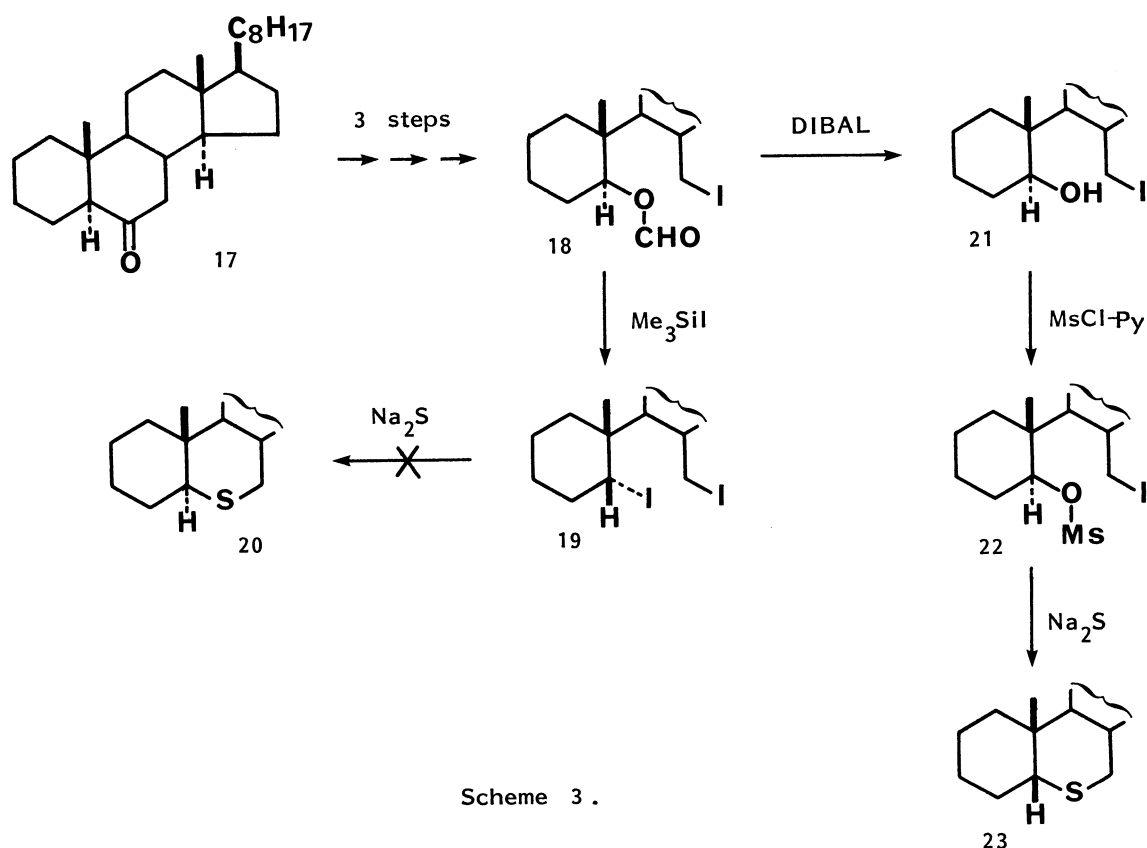
Scheme 1.



Scheme 2.

An attempt to transform 5 $\alpha$ -cholestan-6-one (17) into 6-thia-5 $\alpha$ -cholestane by this 5 step procedure was, however, unsuccessful; a formate 18 obtained via 3 steps from 5 $\alpha$ -cholestan-6-one (17)<sup>3)</sup> 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-5 $\beta$ -cholestane (23)<sup>15)</sup> 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-5 $\beta$ -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-5 $\beta$ -cholestane (23)<sup>15)</sup> in a 40% yield.

A survey of the literature indicates that only a few thiasteroids have previously been synthesized in rather poor overall yields.<sup>2,7)</sup> 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. Sugimoto 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. Sugimoto 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  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  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 ( $\text{M}^+$ , 1), 485 ( $\text{M}^+-\text{I}$ , 25), 57 (100); HR-MS. Calcd for  $\text{C}_{26}\text{H}_{46}\text{I}_2$ : 612.1690. Found: 612.1716.
- 6) Mp 98-99 °C. Lit.<sup>7)</sup> 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  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  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,  $\text{CH}_2\text{ph}$ ); MS  $m/e$  (%) 463 ( $\text{M}^+$ , 100), 91 ( $\text{C}_7\text{H}_7^+$ , 63); Found: C, 85.36; H, 11.49; N, 2.84%. Calcd for  $\text{C}_{33}\text{H}_{53}\text{N}$ : C, 85.46; H, 11.52; N, 3.02%.
- 9) Mp 91-92 °C; IR (Nujol) 1162, 1129, 1113, 1071, 994, 860  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  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 ( $\text{M}^+$ , 2), 386 (100); Found: C, 83.77; H, 12.75; N, 3.54%. Calcd for  $\text{C}_{29}\text{H}_{53}\text{N}$ : 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.<sup>10)</sup> 280-285 °C.
- 12) Mp 95-104 °C; IR (Nujol) 1304, 1239, 1182, 960, 850  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  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 ( $\text{M}^+$ , 2), 373 ( $\text{M}^+-\text{I}$ , 73), 109 (100); HR-MS. Calcd for  $\text{C}_{18}\text{H}_{30}\text{I}_2$ : 500.0438. Found: 500.0473.
- 13) Mp 96-97 °C; IR (Nujol) 1226, 1163, 968, 950  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  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 ( $\text{M}^+$ , 100); Found: C, 77.51; H, 10.87; S, 11.03%. Calcd for  $\text{C}_{18}\text{H}_{30}\text{S}$ : C, 77.63; H, 10.86; S, 11.51%.
- 14) Mp 91-93 °C; IR (Nujol) 1228, 1139, 1072  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  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,  $\text{CH}_2\text{ph}$ ); MS  $m/e$  (%) 351 ( $\text{M}^+$ , 67), 133 (100), 91 ( $\text{C}_7\text{H}_7^+$ , 67); HR-MS. Calcd for  $\text{C}_{25}\text{H}_{37}\text{N}$ : 351.2937. Found: 351.2930.
- 15) Mp 94-95 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  0.67 (3H, s, 18-H), 1.19 (3H, s, 19-H), 2.20 (1H, brs, 5 $\beta$ -H), 2.27 (1H, dd  $J=13.4$  and  $3.4$ , 7 $\alpha$ -H), 2.49 (1H, dd  $J=13.4$  and  $11.5$ , 7 $\beta$ -H); MS  $m/e$  (%) 390 ( $\text{M}^+$ , 9), 321 (100); Found: C, 79.99; H, 11.96; S, 7.98%. Calcd for  $\text{C}_{26}\text{H}_{46}\text{S}$ : C, 79.92; H, 11.87; S, 8.21%.

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