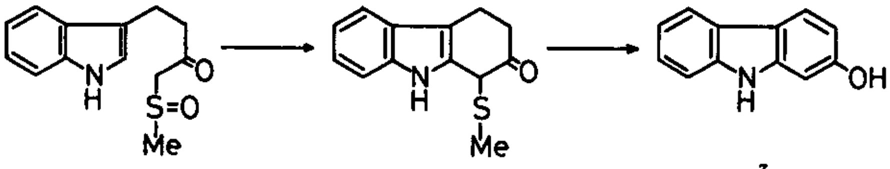
HETEROCYCLES, Vol 15, No 1, 1981

REACTIONS AND SYNTHETIC APPLICATIONS OF β-KETO SULFOXIDES IX. SYNTHESIS OF 5-METHYLTHIO AND 5-METHOXY ANALOGS OF ELLIPTICINE

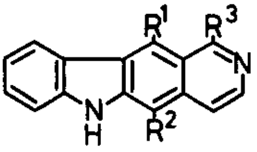
Yuji Oikawa, Masahide Tanaka, Hitoshi Hirasawa, and Osamu Yonemitsu*
Faculty of Pharmaceutical Sciences, Hokkaido University,
Sapporo 060, Japan

Abstract —— A β-keto sulfoxide (9) derived from ethyl indolebutyrate (8) and FAMSO was cyclized to a 2-keto-1,2,3,4-tetrahydrocarbazole derivative (10). After introduction of an acetic ester at the carbonyl group to give 11, its aromatization gave a 1-methylthiocarbazole (12), followed by construction of a pyridine ring to yield efficiently 5-methylthioellipticine (6). Compound 11 was quite easily hydrolyzed to a 1-keto derivative (18), which was aromatized and then converted to 5-methoxyellipticine (7).

Since the discovery of enhanced anti-cancer activity in 9-hydroxyellipticine compared to ellipticine itself,[1] many compounds functionalized at other positions have been synthesized. Among them, 1-substituted compounds have a still higher activity.[2] However, in spite of several attempts, a synthesis of 5- and/or 11-functionalized compounds has remained undeveloped.[3]



1 2 3



4: R^1=H,R^2=R^3=Me
5: R^1=R^2=Me,R^3=H
6: R^1=Me,R^2=SMe,R^3=H
7: R^1=Me,R^2=OMe,R^3=H

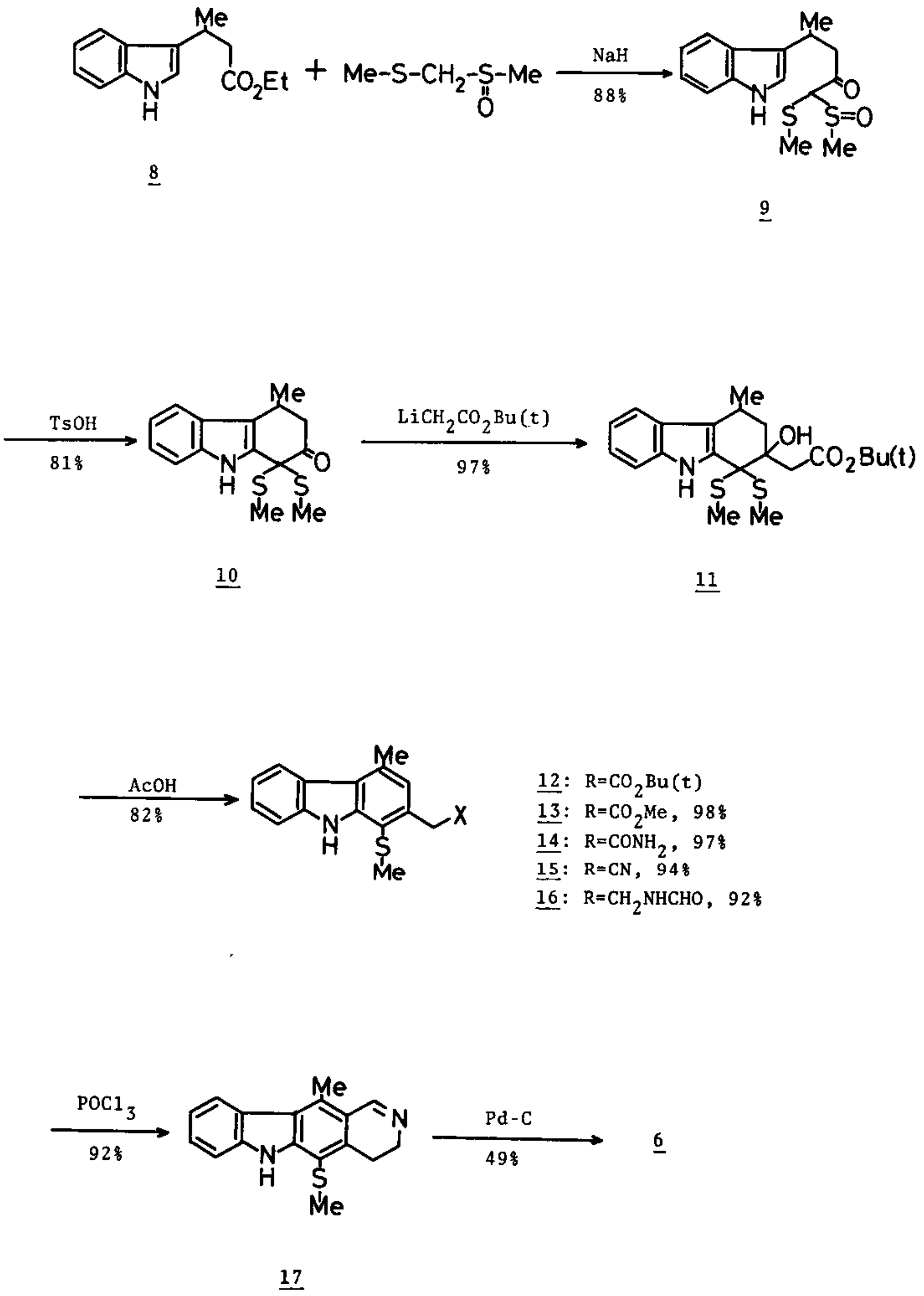
We recently reported that the acid-catalyzed cyclization of β-keto sulfoxides afforded a new synthesis of condensed aromatic[4] and heteroaromatic compounds, e.g., $1 \rightarrow 2 \rightarrow 3$,[5] and this method was applied to the synthesis of olivacine (4) and ellipticine (5) via keto sulfides (2).[6] In this method, keto thioacetal (10) may provide a potential intermediate for the synthesis of 5-functionalized ellipticine analogs.

The ester (8)[7] was readily condensed with FAMSO (formaldehyde dimethyldithioacetal S-oxide) in the presence of NaH to give 9.[8] This type of compounds are known to undergo quite easily an acid-catalyzed hydrolysis to carbonyl compounds,[9] but when 9 was heated at 60° with anhydrous p-toluenesulfonic acid (TsOH) in THF-benzene (4:1),[10] the acid-catalyzed cyclization occurred with the loss of water and afforded 10, mp 95-97°, in a good yield.[11]

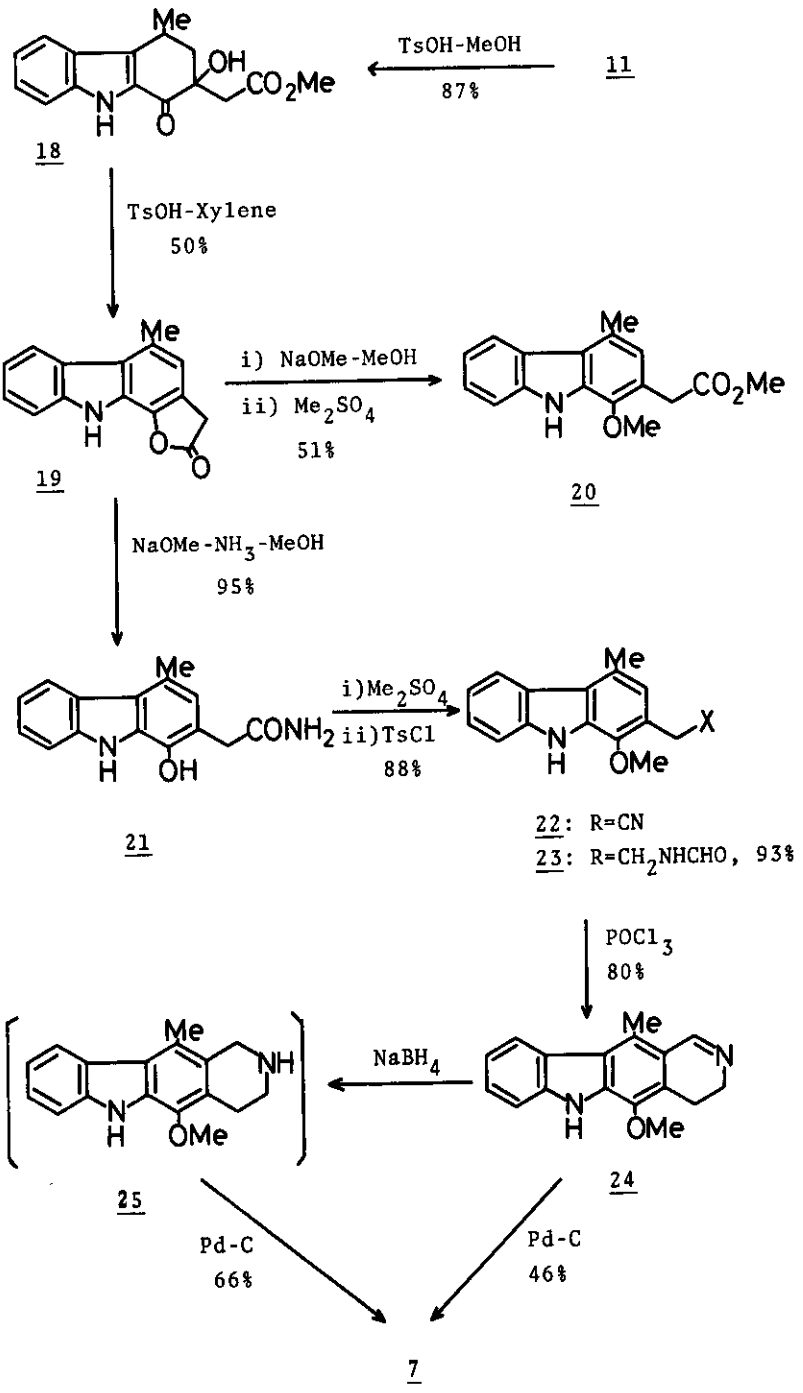
Compound 10 was then treated with t-butyl lithioacetate previously prepared from t-butyl acetate and lithium diisopropylamide in toluene to give 11 as an oily diastereomeric mixture (1:2) in 97% yield, which is a key intermediate to both 6 and 7. The acid-catalyzed aromatization of 11 was readily effected in refluxing xylene containing acetic acid to give an ester (12), mp 171.5-173.5°, in 82% yield.

The following sequence of reactions to a 5-methylthioellipticine analog (6) proceeded quite smoothly except the final dehydrogenation step. Transesterification of 12 with TsOH in MeOH gave a methyl ester (13), mp 140-140.5°, in 98% yield, which was treated with methanolic ammonia containing NaOMe to give an amide (14), mp 241-243°, in 97% yield, followed by dehydration with p-toluenesulfonyl chloride to a nitrile (15), mp 171-173°, in 94% yield. After reduction of 15 with $LiAlH_4$, the amine was heated with ethyl formate to give a formate (16), mp 167-169°, in 92% yield, followed by the dehydrative cyclization with $POCl_3$ in refluxing toluene to a dihydroellipticine analog (17), mp 269-271°, in 92% yield. Dehydrogenation of 17 with active MnO_2[2,12] in dioxane gave 5-methylthioellipticine (6), mp 252-253° (dec), though only in 46% yield. When 17 was treated with Pd-C in refluxing decalin, the yield was slightly improved to 49%. The overall yield of 6 from the starting ester (8) was 21%.

Next we set about a synthesis of the methoxy analog (7). When 11 was treated with a small amount of TsOH in MeOH at 50°, unusually easy cleavage of the dithioacetal group and transesterification occurred to give 18 in 87% yield. An acid-catalyzed dehydrative aromatization of 18 appears to easily occur, but 18 was



12: R=$CO_2Bu(t)$
13: R=CO_2Me, 98%
14: R=$CONH_2$, 97%
15: R=CN, 94%
16: R=CH_2NHCHO, 92%


Me
OH
CO_2Me
N
H
O
18
TsOH-MeOH
87%
11
TsOH-Xylene
50%
Me
N
H
O
O
19
i) NaOMe-MeOH
ii) Me_2SO_4
51%
Me
CO_2Me
N
H
OMe
20
$NaOMe-NH_3-MeOH$
95%
Me
$CONH_2$
N
H
OH
21
i) Me_2SO_4
ii) TsCl
88%
Me
X
N
H
OMe
22: R=CN
23: $R=CH_2NHCHO$, 93%
$POCl_3$
80%
Me
NH
N
H
OMe
25
$NaBH_4$
Me
N
N
H
OMe
24
Pd-C
66%
Pd-C
46%
7

completely recovered unchanged when heated in refluxing benzene containing TsOH or trifluoroacetic acid. Despite many trials of direct and indirect aromatization, no satisfactory method is so far available. At present the best result was obtained when 18 was heated in refluxing xylene containing TsOH, though the yield of 19, mp 269-270.5° (dec), was only 50%.

Cleavage of the lactone ring of 19 with methanolic NaOMe followed by methylation with Me_2SO_4 gave 20 in 51% yield, which can be converted to 22, but because the yield of 20 was unsatisfactory, alternative routes were examined. When 19 was treated with methanolic ammonia containing NaOMe at 60-65°, a facile cleavage of the lactone ring occurred to give almost qunatitatively an amide (21), mp 195-197°. After methylation of the phenolic group with Me_2SO_4 in the presence of K_2CO_3 in 50% aqueous acetone, the resulting methoxy compound, without purification, was dehydrated to a nitrile (22), mp 144-146°, in 88% yield. Reduction and formylation as described above gave a formate (23), mp 181-182°, in 93% yield, which was cyclized with $POCl_3$ to give 24, mp 255.5-257° (dec), in 80% yield. Dehydrogenation of 24 with Pd-C in refluxing decalin gave 5-methoxyellipticine (7), mp 226-228° (dec), in 46% yield. A more satisfactory result was obtained effecting dehydrogenation via a tetrahydro compound (25).[13] Thus, 24 was reduced with $NaBH_4$ in MeOH to 25, which, without purification, was dehydrogenated with Pd-C in decalin at 170° to give 7 in 66% yield.[14]

The synthesis of demethylated 5-mercapto and 5-hydroxy analogs, which are biologically more interesting, and the biological properties of all the analogs will be reported later.

ACKNOWLEDGEMENT

Financial support from the Ministry of Education, Science and Culture (Grant-in-Aid for Special Project Research) is gratefully acknowledged.

REFERENCES AND NOTES

1. J. B. LePecq, Nguyen-Dat-Xuong, C. Grosse, and C. Paoletti, Proc. Natl. Acad. Sci. USA, 71, 5078 (1974).
2. C. Ducrocq, E. Bisagni, C. Rivalle, and J. M. Lhoste, J. Chem. Soc. Perkin I, 142 (1979); E. Bisagni, C. Ducrocq, J. M. Lhoste, C. Rivalle, and A. Civier, J. Chem. Soc. Perkin I, 1706 (1979).

3. S. J. Martinez and J. A. Joule, *J. Chem. Soc. Chem. Comm.*, 818 (1976); M. Driver and M. Sainsbury, *Heterocycles*, **12**, 387 (1979); M. Driver and M. Sainsbury, *J. Chem. Soc. Perkin I*, 2502 (1979).
4. Y. Oikawa and O. Yonemitsu, *Tetrahedron*, **30**, 2653 (1974).
5. Y. Oikawa and O. Yonemitsu, *J. Org. Chem.*, **41**, 1118 (1976).
6. Y. Oikawa and O. Yonemitsu, *J. Chem. Soc. Perkin I*, 1479 (1976).
7. Y. Oikawa, H. Hirasawa, and O. Yonemitsu, *Tetrahedron Lett.*, 1759 (1978).
8. *Cf*. K. Ogura, S. Furukawa, and G. Tsuchihashi, *Tetrahedron Lett.*, 659 (1974).
9. K. Ogura and G. Tsuchihashi, *Tetrahedron Lett.*, 3151 (1971).
10. When **9** was heated with $TsOH \cdot H_2O$, the yield of **10** was 51%.
11. Y. Oikawa and O. Yonemitsu, *Heterocycles*, **8**, 307 (1977).
12. A. J. Fatiadi, *Synthesis*, 65 (1976).
13. *Cf*. F. Le Goffic, A. Gouyette, and A. Ahond, *Tetrahedron*, **29**, 3357 (1973).
14. Satisfactory spectral data and elemental analyses were obtained for all the new compounds described.

Received, 9th June, 1980