REACTIONS AND SYNTHETIC APPLICATIONS OF β-KETOSULFOXIDES VIII. SYNTHESIS OF 1,1-DIMETHYLTHIO-1,2,3,4-TETRAHYDROCARBAZOL-2-ONES AND THEIR 1,2-CARBONYL TRANSPOSITION

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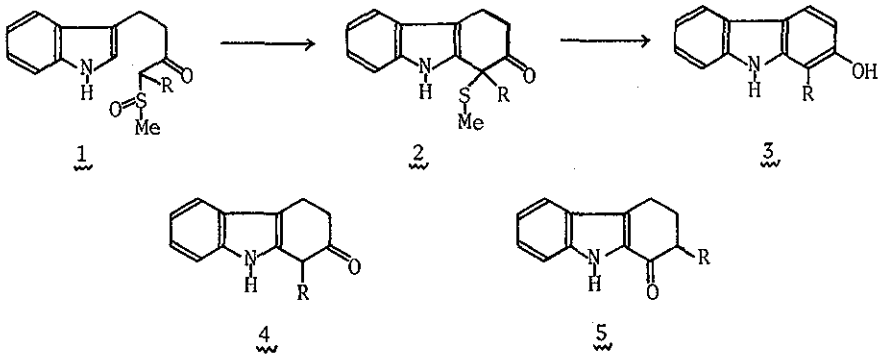
β-Ketosulfoxides (9, 10, 11), prepared from indolepropionic acid esters (6, 7, 8) with the K or Li salt of methyl methylthiomethyl sulfoxide, undergo the acid-catalyzed cyclization to yield 1,1-dimethylthio-1,2,3,4-tetrahydrocarbazol-2-ones (14, 15, 16), which were efficiently converted to 1,2,3,4-tetrahydrocarbazol-1-ones (22, 23, 25, 29) through the (alkylative) 1,2-carbonyl transposition. A pyrrolepropionic acid ester (12) similarly gave a 4,5,6,7-tetrahydroindol-4-one (31) via 4,4-dimethylthio-4,5,6,-7-tetrahydroindol-5-one (17).

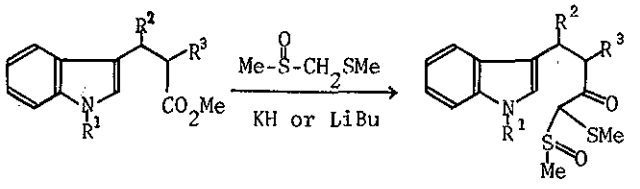
We have recently reported a new synthetic method of condensed heterocycles starting from heteroarylpropionic acid esters via β-ketosulfoxides[1] (e.g. 1→2→3) and its application to the synthesis of pyrido[4,3-b]carbazoles, olivacine and ellipticine,[2] and pyranocarbazoles, girinimbine and murrayacine.[3] The key step in this method is the acid-catalyzed dehydrative cyclization of 1 (e.g. R = H, Me, Me_2C=CH-CH_2) to 2.[4] Desulfurization of 2 easily gave 1,2,3,4-tetrahydrocarbazol-2-ones (4).[2] Our interest in the



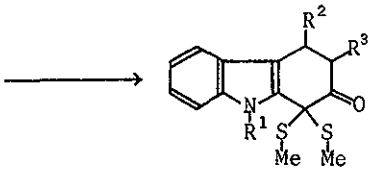
possible generality of this cyclization as well as in its synthetic utility prompted an investigation on the reaction of 1 having a heteroatom-containing group as R, because the expected products (2) are bifunctionalized compounds at both C-1 and C-2, effective intermediates to 1,2,3,4-tetrahydrocarbazol-1-ones as well as to ellipticine analogs.[5] We report here the acid-catalyzed cyclization of 1 (R = SMe) to 2 and its (alkylative) 1,2-carbonyl transposition to 5.

The starting β-ketosulfoxides (9, 10, 11) can be easily obtained by the treatment of the corresponding indolepropionic acid esters (6, 7, 8) with the K or Li salt of methyl methylthiomethyl sulfoxide (MMTS) in THF essentially according to the procedure by Schlessinger.[6] A pyrrolepropionic acid ester (12) was similarly converted to the β-ketosulfoxide (13).

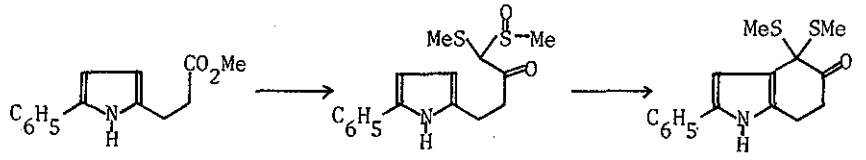
On treatment of 9 with trifluoroacetic anhydride in MeCN at 0° resulted in its ready conversion to the tetrahydrocarbazol-2-one (14) [mp 127-128°] nearly quantitatively. Under similar conditions, 11 gave 16, but 10 and 13 cyclized smoothly only with a stronger acid, p-toluenesulfonic acid at a higher temperature, 50-60°, in THF to give 15 [mp 95-97°] and 17 [mp 146-148°], respectively. It is well known that dimethylmercaptal S-oxides (i) readily undergo the acid-catalyzed hydrolysis to carbonyl compounds (iii)



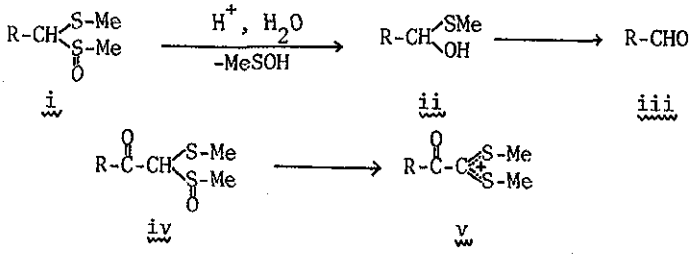
6: $R^1=CH_2C_6H_5, R^2=Me, R^3=H$: 9 (92%)
7: $R^1=R^3=H, R^2=Me$: 10 (84%)
8: $R^1=CH_2C_6H_5, R^2=H, R^3=Et$: 11 (78%)



14: $R^1=CH_2C_6H_5, R^2=Me, R^3=H$ (94.5%)
15: $R^1=R^3=H$, $R^2=Me$ (82.5%)
16: $R^1=CH_2C_6H_5, R^2=H, R^3=Et$ (80%)



12 13 (65%) 17 (67%)

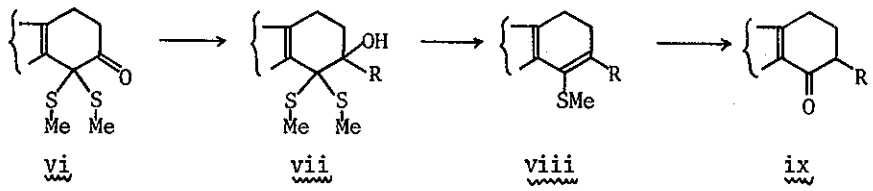


i ii iii iv v

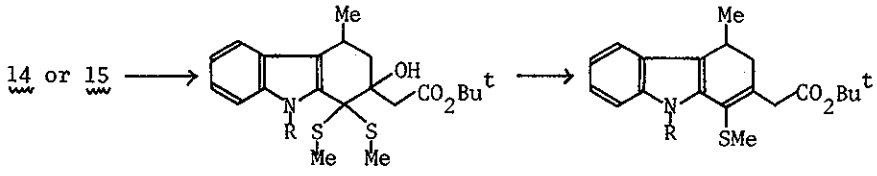
via hemimercaptal (ii).[7] The facile cyclizations of iv presented here, however, obviously proceed via the carbocations (v), which are formed by the loss of water instead of by the substitution of the methylsulfinyl group with water. This clearly discrepant reactivity of iv with that of i can be attributed to the enhanced acidity of the methine proton between the carbonyl and sulfoxide groups.

Since the cyclization products (14, 15, 16) are masked α-diketones, it is

expected that they can be converted to tetrahydrocarbazol-1-ones by the (alkylative) 1,2-carbonyl transposition as outlined in the next scheme (vi→ix) as well as to tetrahydrocarbazol-2-ones by desulfurization. On treatment with lithio t-butylacetate,[2] 14 gave 18 [89%; mp 128.5-129.5°], which was converted to 20 [86%; oil; m/e 433 (M^+); λ_{max} 249, 321, 340 nm] by the treatment with Zn in AcOH-EtOH-dimethoxyethane (3:2:4) at 45° for 9 hr. A few precedents for this type of reductive elimination have been reported,[8] but the procedure described here is so mild as to be applied to such delicate compounds as 18. Hydrolysis and transesterification of 20 with p-toluenesulfonic acid in boiling toluene containing MeOH readily gave the tetrahydrocarbazol-1-one (22) [92%; mp 118-120°; m/e 361 (M^+); ν 1730, 1650 cm^{-1}; λ_{max} 239, 308 nm].[9] Similarly, 15 was converted to 19 [97%; mp 162-164°], then

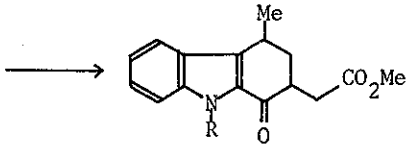


vi vii viii ix

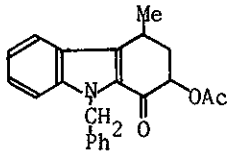


18: R=$CH_2C_6H_5$
19: R=H

20: R=$CH_2C_6H_5$
21: R=H



22: R=$CH_2C_6H_5$
23: R=H



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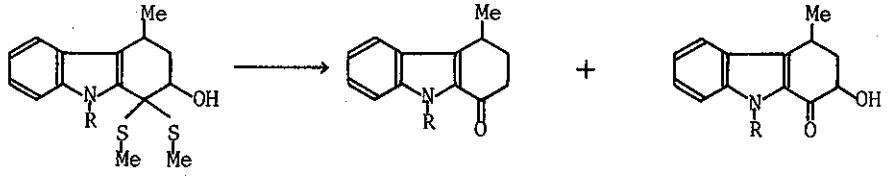
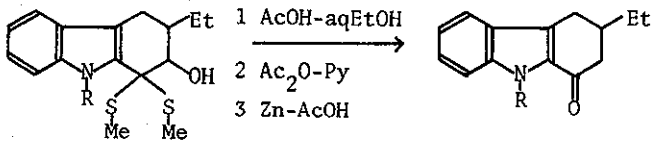
to 21 [85%; mp 120-122°; m/e 343 (M^+); λ_{max} 246, 318, 334 nm], and finally to 23 [91%; mp 142-146°; m/e 271 (M^+); ν 1735, 1650 cm^{-1}; λ_{max} 230, 307 nm].

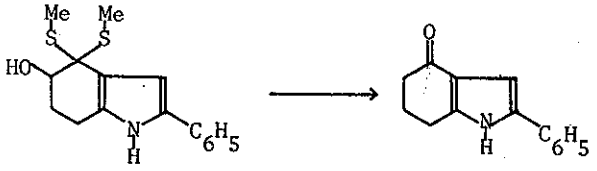
Compound 24, prepared quantitatively by the $NaBH_4$ reduction of 14, was unreactive to Zn under the conditions described above, but reacted at a higher temperature (85°, Zn in AcOH-MeOH) to give a mixture of 25 [33%; oil; m/e 289 (M^+); ν 1660 cm^{-1}; λ_{max} 238, 308 nm] and 26 [31%; mp 130-133°; m/e 305 (M^+); ν 3450, 1650 cm^{-1}; λ_{max} 233, 307 nm]. An alternative way for the effective synthesis of 25 was next sought. Hydrolysis of 24 in AcOH-EtOH-H_2O gave 26 (93%), which was acetylated with Ac_2O-pyridine to give 27 (85%), and then the Zn-dust reduction[10] of 27 in AcOH at 80° gave 25 (82%). Similarly, 28 was converted into 29 [mp 71-72°; m/e 303 (M^+); ν 1665 cm^{-1}; λ_{max} 232, 307 nm] through the above three-step processes in 64% overall yield.



24: R=$CH_2C_6H_5$ 25 26



28: R=$CH_2C_6H_5$ 29



30 31

The (alkylative) 1,2-carbonyl transposition presented here may provide an efficient and useful method for the preparation of alkylated tetrahydrocarbazol-1-ones.[11]

Finally, the 4,5,6,7-tetrahydroindol-4-one (31) [mp 219-222°; m/e 211 (M^+); ν 3225, 1640 cm^{-1}][13] was obtained in the same way from 30 prepared by the $NaBH_4$ reduction of 17 in 40% overall yield.

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8) T. Mukaiyama, S. Shiono, and T. Sato, Chemistry Lett., 1974, 37; I. Kuwajima, S. Sato, and Y. Kurata, Tetrahedron Lett., 1972, 737.
9) This compound is an effective intermediate to ellipticine analogs.[5]
10) R. S. Rosenfeld, J. Am. Chem. Soc., 1957, 79, 5540.
11) Although 1,2,3,4-tetrahydrocarbazol-1-one is easily prepared from indolebutyric acid with PPA,[12] tetrahydrocarbazol-1-ones with various substituents are difficult to synthesize, because no effective method for the preparation of indolebutyric acids having substituents at their side chains is so far available. Moreover, Y. O. has recently found a very efficient one-pot synthesis of various indolepropionic acid esters, which will be reported soon.
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