SOME NEW REACTIONS IN INDOLE CHEMISTRY AND THEIR APPLICATIONS

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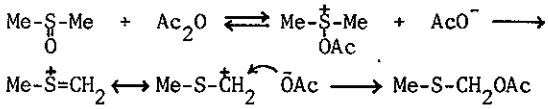
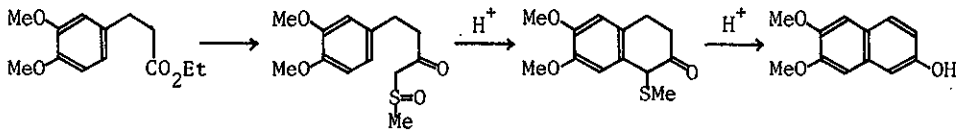
Two new basic and useful reactions in indole chemistry and their applications to syntheses of relatively simple natural products are presented here.

Acid-Catalyzed Cyclization of β-Ketosulfoxides to Condensed Heterocycles

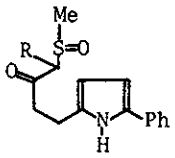
The Pummerer reaction, one of the most famous reactions in sulfur chemistry, has been used only for the formation of carbon-heteroatom bonds. The key step in its proposed mechanism is the intermolecular nucleophilic attack of an acetoxy group on a sulfur-stabilized carbocation.[1]



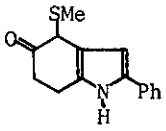
In the place of the acetoxy anion, a nucleophilic moiety attached to the suitable position in a sulfoxide molecule may attack the transient carbocation intramolecularly. This assumption was first realized by the synthesis of naphthalene and phenanthrene derivatives through an acid-catalyzed cyclization of β-ketosulfoxides,[2] which were readily accessible from the corresponding esters.[3] The electron-rich aromatic ring acted as an intramolecular nucleophile.



This reaction was extended to a new synthetic method for condensed heterocycles, indoles, carbazoles, and benzothiophenes,[4] by the use of electron-rich heterocycles such as pyrrole, indole, and thiophene instead of aromatics as intramolecular nucleophiles. Some examples are shown in the following scheme. Reductive desulfurization of 14 and 23 gave easily 28 and 29, respectively.



1, R=H
2, R=CONHPh



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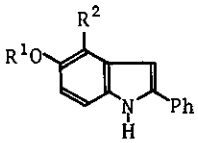
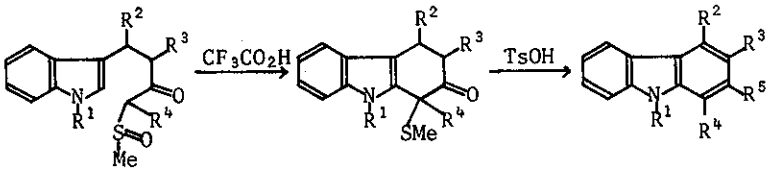
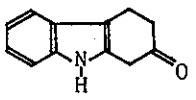


4, R^1=Me, R^2=H
5, R^1=Et, R^2=H
6, R^1=H, R^2=CONHPh



7, R^1=R^2=R^3=R^4=H
8, R^1=Me, R^2=R^3=R^4=H
9, R^1=CH_2Ph, R^2=R^3=R^4=H
10, R^1=Me, R^2=R^4=H, R^3=NHAc
11, R^1=R^2=R^3=H, R^4=Me
12, R^1=R^2=R^4=H, R^3=Me
13, R^1=CH_2Ph, R^2=Me, R^3=R^4=H,
14
15
16
17
18
19
20

21, R^1=R^2=R^3=R^4=H, R^5=OH
22, R^1=Me, R^2=R^3=R^4=H, R^5=OH
23, R^1=Me, R^2=R^3=R^4=H, R^5=SMe
24, R^1=Me, R^2=R^3=R^4=H, R^5=OMe
25, R^1=Me, R^2=R^3=R^4=H, R^5=OEt
26, R^1=R^2=R^4=H, R^3=Me, R^5=OH
27, R^1=CH_2Ph, R^2=Me, R^3=R^4=H, R^5=OMe



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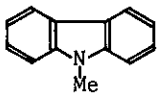

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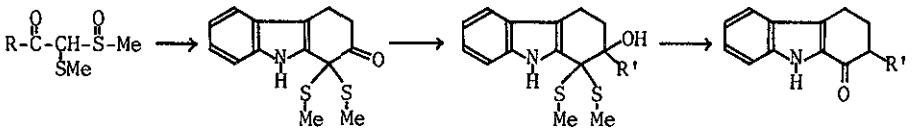
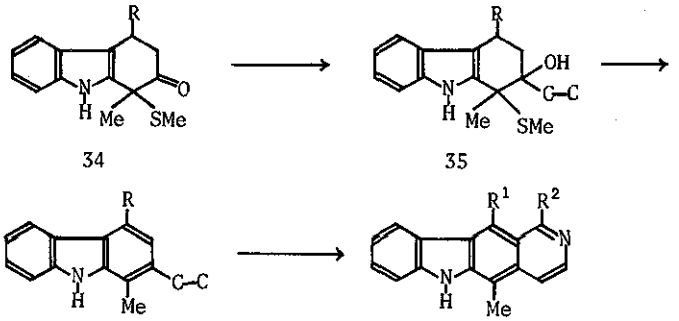
Although many useful synthetic methods for condensed heterocycles are available, the potential utility of the cyclization of β-ketosulfoxides can be emphasized because of the following advantages and characteristics. 1) This method is characterized by the construction of a benzene ring in contrast with the majority of usual syntheses. 2) The starting materials, β-ketosulfoxides, are easily prepared from the corresponding esters by the well-known procedure.[3] 3) The formation of aromatized products involves two consecutive acid-catalyzed reactions, cyclization of β-ketosulfoxide and aromatization with loss of methanethiol. Since the later usually requires a stronger acid and/or a higher temperature, either of the two types of product, (14-20; applied to pyrido[4,3-b]carbazole synthesis) and (21-27; applied to pyranocarbazole synthesis), can be selected by appropriate choice of acid and solvent. 4) 1-Substituted carbazoles are easily obtained by the prior introduction of substituents at the active methylene group of β-ketosulfoxides. 5) Compounds of type 30 prepared from formaldehyde dimethylmercaptal mono-S-methylsulfoxide (FAMSO) and esters



30 31 32 33

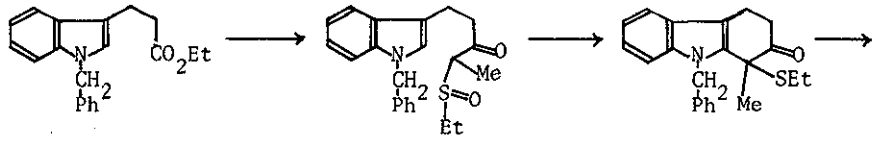
also cyclized easily to, for example, 31, which was converted to 1-oxo-1,2,3,-4-tetrahydrocarbazoles (33) via 32.

Synthesis of Pyrido[4,3-b]carbazole Alkaloids. As a first application, both olivacine (37) and ellipticine (38) were synthesized via unaromatized β-ketosulfoxides (34).[5] It was hoped that introduction of a side chain at the carbonyl group in 34 prior to aromatization (to 36) would give intermediates (35) appropriate for the synthesis of 37 and 38.

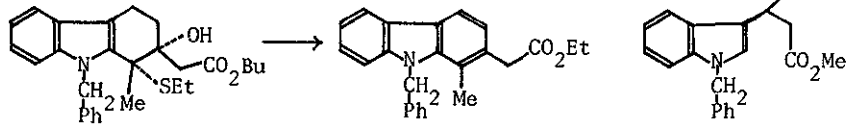


34 35

36 37, R^1=H,R^2=Me
38, R^1=Me,R^2=H



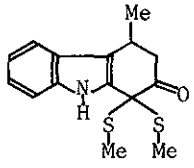
39 40 41



42 43 44

Actually, 39 was treated with diethyl sulfoxide in the presence of a base to give 40 (95%), which was cyclized with CF_3CO_2H to 41 (51%). t-Butyl

lithioacetate[6] reacted with 41 at room temperature to give the expected product (42) in quantitative yield, and then heating of 42 in xylene-EtOH gave the aromatized ester (43) quantitatively. Several step conversion of 43 to olivacine (37) proceeded efficiently in the usual procedures. The overall yield from 39 was 28%. Similarly, ellipticine (38) was synthesized from 44 in 23% overall yield. A compound 45 (of type 31) without N-benzylation also converted to a nonnatural ellipticine analog (46).



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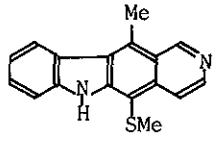

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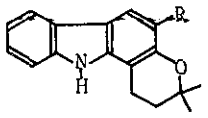
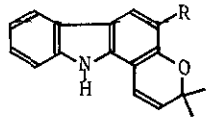
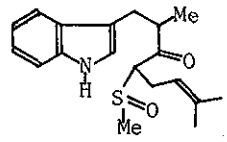
Synthesis of Pyranocarbazole Alkaloids. As a second application, pyranocarbazoles (47-50) were synthesized.[7] Thus, when 51 prepared from 12 by prenylation was heated with TsOH in MeCN, three consecutive acid-catalyzed reactions, cyclization, aromatization, and another cyclization occurred to give directly dihydrogirinimbine (47), which, after phenylsulfonylation, was dehydrogenated with NBS in the presence of azobisisobutyronitrile to girinimbine (49). Both 47 and 49 were oxidized with DDQ in MeOH at room temperature to cycloheptaphylline (48) and murrayacine (50),[8] respectively.



47, R=Me
48, R=CHO



49, R=Me
50, R=CHO

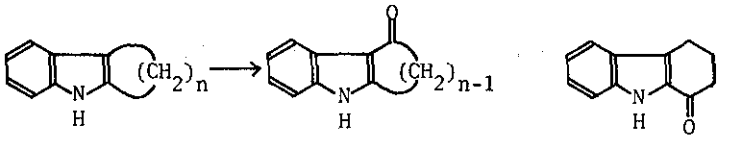


51

Selective Oxidation of C-3 Side Chains of Indoles

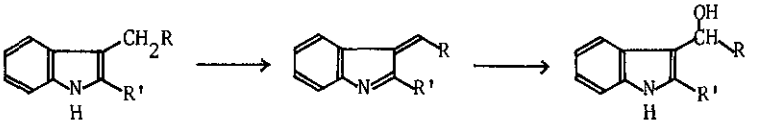
Oxidation of 3-substituted and 2,3-disubstituted indoles usually occurs on the pyrrole ring and at the 2-substituent, not at the 3-substituent, because most oxidants act as electrophiles and first attack C-3 of the indole ring. Therefore, no general method for the selective oxidation of C-3 side chains has been established.

When tetrahydrocarbazole (53) was treated with 2 equiv of DDQ in aq THF, the oxidation proceeded quite rapidly to yield 59, and no detectable formation of 57 was observed. Because DDQ is a strong electron acceptor, the initial

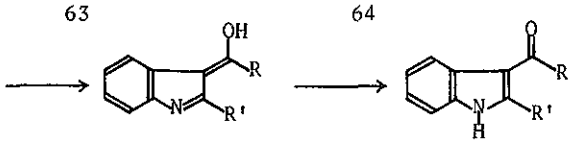


52, n=3 58 (53%)
53, n=4 59 (83%)
54, n=5 60 (90%)[9]
55, n=6 61 (60%)
56, n=10 62 (96%)

57

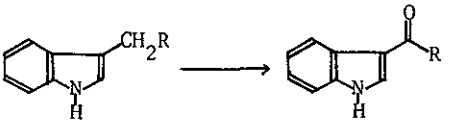


63 64 65



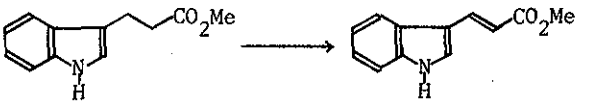
66 67

step of this oxidation must be the formation of charge transfer complexes between electron-rich indoles and DDQ, not the attack of DDQ at C-3 of indoles. The complexes readily change to 64 (dehydrogenation of 63), then three reactions, addition of water, another dehydrogenation, and isomerization occur successively to yield 67. Various 3-monosubstituted indoles (68-72) were similarly oxidized to the corresponding carbonyl compounds (73-77).[10]

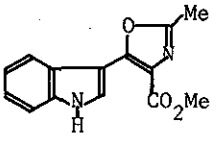


68, R=H 73 (55%)
69, R=CO_2Et 74 (46%)
70, R=CH_2CO_2Et 75 (38%)
71, R=2-pyridyl 76 (48%)
72, R=CH(NHAc)CO_2Me 77 (84%)

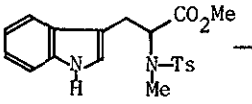
Dehydrogenation under Anhydrous Conditions. When 78 was treated with DDQ (1.3 equiv) in anhydrous THF at room temperature, the dehydrogenation proceeded smoothly to afford 79. Compound 70 gave similarly 80, but a N-acetyltryptophan derivative (72) gave 81. This process may afford a short cut way for the synthesis of oxazolylindole alkaloids. A N-tosyl derivative (82) again gave a dehydrogenated product (83). Finally, as a model experiment for the



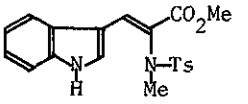
78, R=CH_2Ph 79 (80%)
70, R=H 80 (77%)



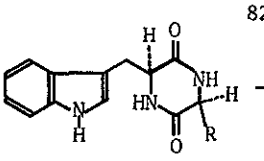
81



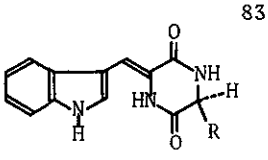
82



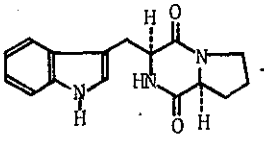
83 (97%)



84, R=H
85, R=Me



87 (21%)
88 (62%)



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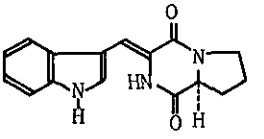

89 (14%)

synthesis of neoechinulin alkaloids, some optically active diketopiperazines (84-86) were converted to the corresponding products (87-89).

REFERENCES

1) C.R.Johnson, J.C.Sharp, and W.G.Phillips, Tetrahedron Lett., 5299 (1967); C.R.Johnson and W.G.Phillips, J. Am. Chem. Soc., 91, 682 (1969).
2) Y.Oikawa and O.Yonemitsu, Tetrahedron, 30, 2653 (1974).
3) E.J.Corey and M.Chaykovsky, J. Am. Chem. Soc., 87, 1345 (1965).
4) Y.Oikawa, O.Setoyama, and O.Yonemitsu, Heterocycles, 2, 21 (1974); Y. Oikawa and O.Yonemitsu, J. Org. Chem., 41, 1118 (1976).
5) Y.Oikawa and O.Yonemitsu, J. C. S. Perkin I, 1479 (1976).
6) M.W.Rathke and D.F.Sullivan, J. Am. Chem. Soc., 95, 3050 (1973).
7) Y.Oikawa and O.Yonemitsu, Heterocycles, 5, 233 (1976).
8) F.Anwer, A.S.Masaldan, R.S.Kamil, and S.P.Popli, Indian J. Chem., 11, 1314 (1973).
9) K.Yamane and K.Fujimori, Bull. Chem. Soc. Jpn., 49, 1101 (1976).
10) Y.Oikawa and O.Yonemitsu, J. Org. Chem., 42, 1213 (1977).