# Development of the Novel Reactions Discovered in the Studies on the Anti-Leukemic Compounds

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a) Abnormal Fischer Indolization: In the course of studies on the synthetic approach to mitomycin, we[1] occasionally had a chance to examine Fischer indolization of ethyl pyruvate 2-[(o-methoxyphenyl)hydrazone] (1) and found that the expected ethyl 7-methoxyindole-2-carboxylate was not a main product but unexpected indolic compounds were yielded in this reaction. These results are summarized in Table 1. Formation of these abnormal products could be explained by supposing the pathway shown in Chart 1. This deduction[2] suggested that this reaction could be developed to provide a synthetic method for useful inole having an active methine group at $C_6$. We used enolizable dicarbonyl compounds as nucleophiles, expecting that they would serve as suitable acceptors of the electrophilic intermediate (2) even under the acidic conditions of Fischer indolization.

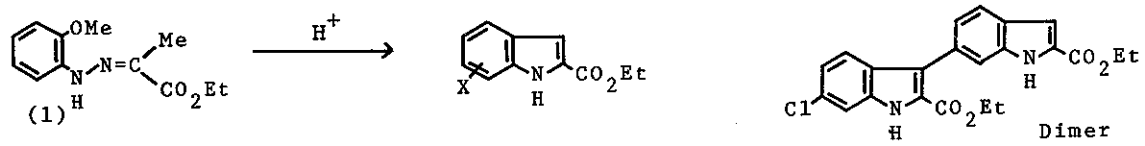
Treatment of 1 in benzene with p-TsOH in the presence of an exess amount of either acetylacetone or ethyl acetoacetate gave ethyl 6-(1-acetyl-2-oxopropyl)indole-2-carboxylate (3) and ethyl α-acetyl-2-ethoxycarbonylindole-6-acetate (4). The structures of 3 and 4 were established by chemical correlation with 4-methyl-3-nitropropiophenone (9) as shown in Chart 2.

We[3] aimed at synthesizing the naturally occurring 6-(3-methylbuta-1,3-dienyl)indole[4] (13) from 4 as an example for application of this reaction. The starting mono-acid (10) was obtained by treatment of 4 with KOH solution followed by esterification with diazoethane and partial hydrolysis with HCl-AcOH.

1) H. Ishii, Y. Murakami, K. Hosoya, H. Takeda, Y. Suzuki, and N. Ikeda, *Chem. Pharm. Bull. (Tokyo)*, 21, 1481(1973); H. Ishii, Y. Murakami, T. Furuse, K. Hosoya, and N. Ikeda, *ibid.*, 21, 1495(1973).

2) H. Ishii, Y. Murakami, T. Furuse, K. Hosoya, H. Takeda, and N. Ikeda, *Tetrahedron*, 29, 1991(1973).

Table 1 Products of Fischer Indolization of Ethyl Pyruvate 2-[(o-Methoxyphenyl)hydrazone](1)(%)

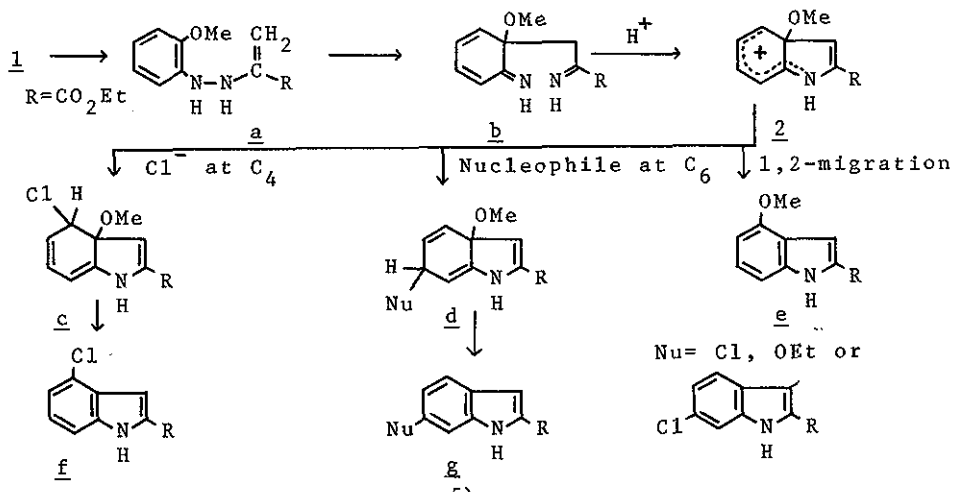



a) With Protic Acid.

| Products / Reagents | 7-OMe | 7-OEt | 6-Cl | 6-OEt | 4-OMe | 3,4,5-Cl mixture | H | Dimer |
|---|---|---|---|---|---|---|---|---|
| 3N HCl-EtOH | 15.5 | 1.1 | 9.9 | 4.8 | 0.7 | 11.6 | - | - |
| Sat.HCl-EtOH | 4.2 | 1.8 | 34.7 | 0.26 | - | 7.7 | - | 0.55 |
| HCl-AcOH | 17.2 | - | 20.5 | - | - | 6.1 | - | - |
| $H_2SO_4$-EtOH | 12.8 | - | \ | 2.0 | - | \ | 0.2 | - |

b) With Lewis Acid.

| Products / Reagents | 7-OMe | 5-OMe | 4-OMe | 5-Cl | H |
|---|---|---|---|---|---|
| $ZnCl_2$-AcOH | 17.7 | 0.67 | 0.26 | 1.32 | 0.91 |
| $BF_3$-AcOH | 13.5 | 0.85 | - | \ | 2.1 |
| $BF_3$-AcOEt | 15.0 | 4.7 | - | \ | 2.7 |
| $H_2SO_4$-AcOH | 5.0 | 0.32 | - | \ | 0.22 |




Oxidation of 10 with pyridine N-oxide[5] in $Ac_2O$ gave the corresponding aldehyde (11), which provided the acid (12) by aldol condensation with acetone followed by hydrolysis with base. Decarboxylation of 12 with Cu-chromite[6] followed by Wittig reaction with $\Phi_3P{=}CH_2$ gave the desired indole (13) as colourless leaflets, mp 126-130°(*lit.*[4] mp 124-127°).

Next, we[3] also planned to prepare another naturally occurring 6-(3-methyl-2-butenyl)indole[7] (17). Partial reduction of 10 was achieved with $B_2H_6$ at 0° to give the indole alcohol (14). Collin's reagent oxidised 14 to the desired indole acetaldehyde (15) with least amount of the indole aldehyde (11) as a by-product. Wittig reaction of 15 with $\Phi_3P{=}CHMe_2$ followed by hydrolysis with base and decarboxylation gave an oily product (17) which formed a complex with 1,3,5-trinitrobenzene, mp 111.5-113°. This complex was identical with the 1,3,5-trinitrobenzenate (*lit.*[7] mp 106°) derived from the natural product.

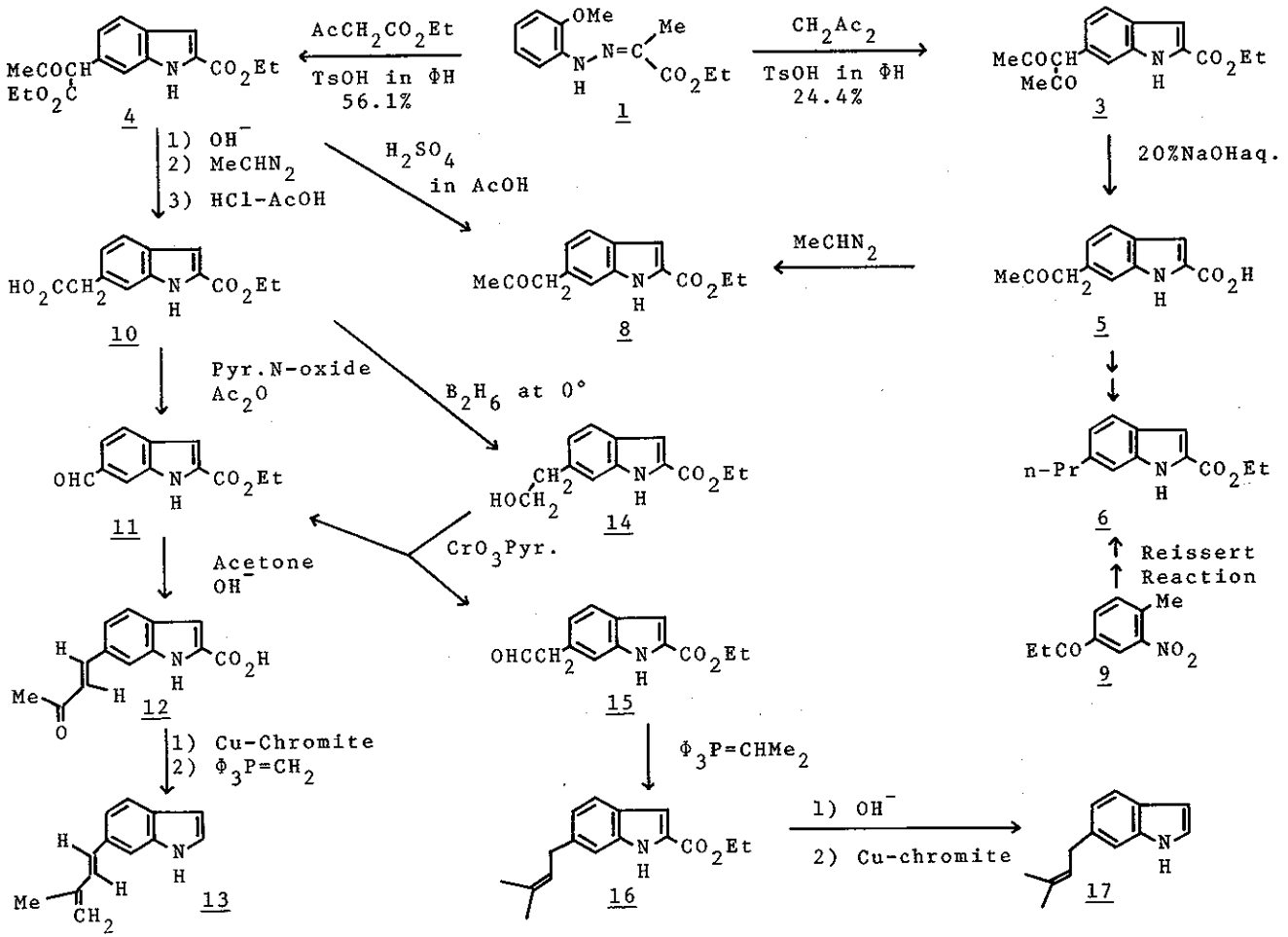

3) H. Ishii and Y. Murakami, Tetrahedron, 31, 933(1975).

4) M. N. Nwaji, S. O. Onyiriuka, and D. A. H. Taylor, J. Chem. Soc.Chem.Comm., 1972, 327.

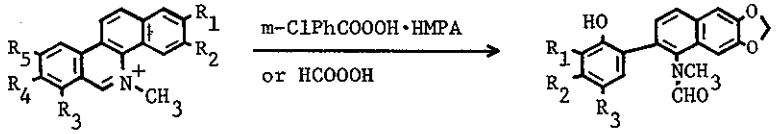
5) C. Rüchardt, S. Eichler, and O. Krätz, Tetrahedron Letters, 233(1965); T. Cohen, I. W. Song and J. H. Fager, *ibid.*, 237(1965).

6) W. A. Lazier and H. R. Arnold, Org. Synth. Coll. Vol., 2, 142(1943).

7) V. Benesová, Z. Samek, V. Hérout, and F. Sorm, Coll. Czech. Chem. Comm., 34, 1807 (1969).

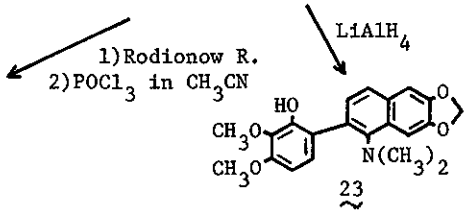

AcCH2CO2Et
TsOH in ΦH
56.1%
CH2Ac2
TsOH in ΦH
24.4%
4
1
3
1) OH⁻
2) MeCHN2
3) HCl-AcOH
H2SO4
in AcOH
20%NaOHaq.
MeCHN2
10
8
5
Pyr.N-oxide
Ac2O
B2H6 at 0°
11
14
6
Reissert
Reaction
CrO3Pyr.
Acetone
OH⁻
9
12
15
1) Cu-Chromite
2) Φ3P=CH2
Φ3P=CHMe2
1) OH⁻
2) Cu-chromite
13
16
17

b) Baeyer-Villiger like Oxidation of an Immonium Base: Recently, several benzo[c]phenathridine alkaloids, nitidine[8] (18) and fagaronine[9] (19), which were isolated from only *Rutaceous* plants (*Xanthoxylum*) attract an attention of the organic chemist and the pharmacologist because of their anti-leukemic activity. In the course of studies on the chemical constituents of *Rutaceous* plants, we found the natural occurrence of three new amide alkaloids, arnottianamide[10,11] (20), isoarnottianamide[10b, 11] (21), and iwamide[10a,12] (22), which, in the NMR spectra, show a characteristic 1H formyl proton as a singlet. Formation of the N,N-dimethyl derivative[11] (23) by reduction of 20 with $LiAlH_4$ indicated the presence of a $CH_3NCHO$ group in its molecule. This observation allowed us to imagine that these new amides would be formed by Baeyer-Villiger like oxidation of the quaternary benzo[c]phenathridine alkaloid in a plant




18: $R_1+R_2=OCH_2O$, $R_3=H$, $R_4=R_5=OCH_3$
19: $R_1=OH$, $R_2=R_4=R_5=OCH_3$, $R_3=H$
24: $R_1+R_2=OCH_2O$, $R_3=R_4=OCH_3$, $R_5=H$
25: $R_1+R_2=OCH_2O$, $R_3=OCH_3$, $R_4=OH$, $R_5=H$
27: $R_1+R_2=OCH_2O$, $R_3=OCH_3$, $R_4=OCH_2Ph$, $R_5=H$
28: $R_1+R_2=R_4+R_5=OCH_2O$, $R_3=H$

20: $R_1=R_2=OCH_3$, $R_3=H$
21: $R_1=H$, $R_2=R_3=OCH_3$
22: $R_1=OCH_3$, $R_2=OH$, $R_3=H$
29: $R_1=OCH_3$, $R_2=OCH_2Ph$, $R_3=H$
30: $R_1=H$, $R_2+R_3=OCH_2O$

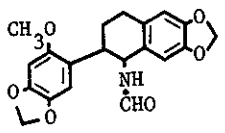



31: $R_1+R_2=OCH_2O$
32: $R_1=R_2=OCH_3$

23

8) M. E. Wall, M. C. Wani, and H. L. Taylor; Abstracts of the Third International Congress of Heterocyclic Chemistry: B, Sendai, Japan, 1971, p. 29.
9) W. M. Messer, M. Tin-Wa, H. H. S. Fong, C. Bevelle, N. R. Farnsworth, D. J. Abraham, and J. Trojanek, *J. Pharm. Sci.*, 61, 1858(1972).
10) a) H. Ishii, T. Ishikawa, and J. Haginiwa, *Yakugaku Zasshi*, in press; b) H. Ishii, T. Ishikawa, S.-T. Lu, and I.-S. Chen, *ibid.*, 96, 1458(1976).
11) H. Ishii, T. Ishikawa, S.-T. Lu, and I.-S. Chen, *Tetrahedron Letters*, 1976, 1203.
12) T. Ishikawa and H. Ishii, *Heterocycles*, 5, 275(1976).

body. Examination of the NMR signals of 20, 21, and 22 in the aromatic region suggested that chelerythrine (24), 18, and the quaternary base (25) formed by N-methylation of decarine (26) should be attributable to the parent bases of them, respectively. According to this assumption, 24, 18, the quaternary base (27) obtained from 26, and the naturally occurring avicine (28) were treated with a peracid to give 20, 21, benzyl iwamide (29), and the amide (30), respectively. This is the first case of Baeyer-Villiger like oxidation of an immonium group.




33

It should be noted here that 30 and 21 were easily subjective to Bischler-Napieralski reaction[13] to give the natural $O_5$-benzo[c]phenanthridine alkaloids, chelirubine (31) and chelilutine (32). These facts indicate the correctness of the structural proposal for 31 and 32, and provide a versatile route for synthesis of other $O_5$-bases,[14] although all trials[15] to cyclize the partially hydrogenated formamide (33) were failed in past.

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13) H. Ishii, T. Ishikawa, Y.-I. Ichikawa, and M. Sakamoto, *Tetrahedron Letters,* Submitted.

14) H. Ishii, K.-I. Harada, T. Ishida, E. Ueda, K. Nakajima, I. Ninomiya, T. Naito, and T. Kiguchi, *ibid.*, 1975, 319.

15) H. Ishii, T. Deushi, T. Ishida, M. Sakamoto, K.-I. Harada, and K. Takizawa, *Chem. Pharm. Bull. (Tokyo)*, in preparation.