A NOVEL METHOD FOR ACETALIZATION OF FORMYL GROUP AT THE C_3-POSITION OF 2,3-DIHYDRO-1H-PYRROLO[1,2-a]INDOLE SKELETON

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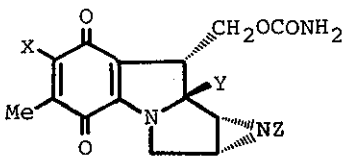
Reaction of 2,3-dihydro-7-methoxy-6-methyl-1H-pyrrolo[1,2-a]indole-9-carboxaldehydes 2, 3, 4, 5, and 6 with thiolacetic acid in the presence of 6N sulfuric acid at room temperature gave 2,3-dihydro-7-methoxy-6-methyl-9-dithiolacetylmethyl-1H-pyrrolo[1,2-a]indoles 12, 13, 14, 15, and 16, respectively. The same reaction of the compound 2 at 0° afforded 1-acetoxy-2,3-dihydro-7-methoxy-6-methyl-8-nitro-9-dithiolacetyl-methyl-1H-pyrrolo[1,2-a] indole (11). Successive treatment of the compound 11 with anhydrous methanol in the presence of sodium methoxide gave 2,3-dihydro-1-hydroxy-7-methoxy-9-dimethoxymethyl-6-methyl-8-nitro-1H-pyrrolo[1,2-a]indole (17).

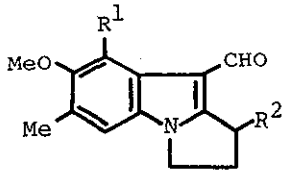
In the course of the synthetic studies[1~4] directing toward

In memory of Dr. Hans Schmid, Professor of Organic Chemistry at the University of Zürich, Switzerland, who passed away on Sunday December 19, 1976.

mitomycins (1), we felt it necessary to develop a general method for the protection of a formyl group at the C_3-position of indole skeleton, especially the formyl group of 1-acetoxy-2,3-dihydro-7-methoxy-6-methyl-8-nitro-1H-pyrrolo[1,2-a]indole-9-carboxaldehyde (2) which seems to have proper substituents for the synthesis of mitomycins (1).

Scheme 1





(1)

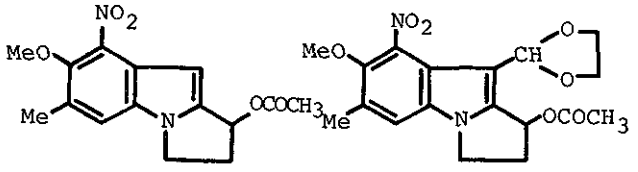
	X	Y	Z
Mitomycin A	MeO	MeO	H
Mitomycin B	MeO	HO	Me
Mitomycin C	NH_2	MeO	H
Porfiromycin	NH_2	MeO	Me

	R^1	R^2
(2)	NO_2	$OCOCH_3$
(3)	NO_2	H
(4)	H	O=
(5)	H	$OCOCH_3$
(6)	H	H

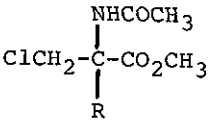
The difficulty was encountered in the preliminary experiment for the acetalization of the compound 2 by using a usual method, namely heating a solution of 2, ethylene glycol, and p-toluenesulfonic acid in benzene. The sole compound isolated was not the acetalized one 8, but rather the compound 7 resulting from a decarbonylation, which showed a carbonyl absorption at 1735 cm^{-1} in its ir spectrum and the nmr spectrum revealed the following

resonances; δ 1.91 (3H, s, $ArC\underline{H}_3$), 2.25 (3H, s, $C\underline{H}_3CO_2$-), 3.73 (3H, s, $C\underline{H}_3O$-), 5.87 (1H, dd, J = 6.8 and 2.8 Hz, C_1-H), 6.30 (1H, s, C_9-H), 6.97 (1H, s, C_5-H).

Scheme 2



(7) (8)

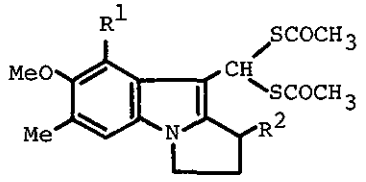


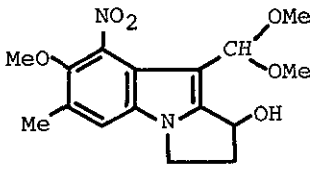
(9) R : $SCOCH_3$

(10) R : OCH_3

Thus, our attention was turned to explore an effective pathway for the acetalization. Thiolacetic acid has been known as a strong nucleophile to result a 1,4-addition to α,β-unsaturated carbonyl compounds[5~8] and a displacement of halogen.[9~11] On the other hand, N-acetyl-2-acetylthio-3-chloroalanine methyl ester (9) has been transformed into 2-methoxyalanine 10 by the reaction with sodium methoxide in anhydrous methanol.[12] In our case, once the dithiolacetylmethyl compound 11 is obtained, successive transformation of 11 to the dimethylacetal 17 would be anticipated to proceed readily under the same conditions for the compound 9 because of its vinylogous character of 9.

Scheme 3





(17)

	R^1	R^2
(11)	NO_2	$OCOCH_3$
(12)	NO_2	$SCOCH_3$
(13)	NO_2	H
(14)	H	O=
(15)	H	$SCOCH_3$
(16)	H	H

At first, the carboxaldehydes 2, 3, 4, 5, and 6 were treated with thiolacetic acid in the presence of 6N sulfuric acid under the conditions shown in Table for each compounds to obtain the dithiol-acetylated compounds 11, 12, 13, 14, 15, and 16 in high yield, respectively.

The typical procedure is as follow: to a solution of the aldehyde 2 (332 mg) in thiolacetic acid (5 ml) was added 6N sulfuric acid (2.5 ml) at 0° and the resulting mixture was stirred for 28 h at 0° in a current of nitrogen. After an usual work-up, the dithiol-acetylated compound 11 was obtained as pale yellow needles (430 mg, 92 %), mp 218.5 - 220°, ν_{max} ($CHCl_3$): 1735 (CO), 1695 (CO), 1520 and 1368 cm^{-1} (NO_2); δ ($CDCl_3$): 2.13 (3H, s, $C\underline{H}_3CO_2$-), 2.27 (6H, s, 2 x $C\underline{H}_3COS$-), 2.42 (3H, s, $ArC\underline{H}_3$), 3.4 - 2.5 (2H, m, C_2-$\underline{H}_2$), 3.88

(3H, s, $C\underline{H}_3O$-), 4.15 (2H, distorted t, C_3-$\underline{H}_2$), 6.52 (1H, dd, J 6.4 and 3.2 Hz, C_1-$\underline{H}$), 6.67 (1H, s, $C\underline{H}(SAc)_2$), 7.18 (1H, s, Ar$\underline{H}$); m/e: 466 (M^+).

Acetoxy group at the C_1-position of the compounds 2 and 5 was substituted by thiolacetyl group to give the compounds 12 and 15 when the reaction was run at room temperature. Thus we could demonstrate that the dithiolacetylation of 1H-pyrrolo[1,2-a]-indole-9-carboxaldehydes proceeds smoothly and in a very high yield and next, successive conversion of the dithiolacetylated compound into the acetal was studied.

Table

Compound 11 was treated with anhydrous methanol in the presence of sodium methoxide at room temperature and it was found that the reaction occurred very readily to give the dimethyl acetal 17 in a quantitative yield, which lacked carbonyl absorption in its ir spectrum and showed the signals due to two methoxyl groups of dimethyl acetal as singlet at 3.20 and 3.42 and signal due to methine of dimethyl acetal as singlet at 5.65 p.p.m.

Thus, a novel method for the dithiolacetylation of formyl group at the C_3-position of indole skeleton was developed and successive transformation of the dithiolacetylated compound 11 into 17 was found to proceed very readily. The scope and limitation of this new method is now under investigation.

Table

Dithiolacetylation of 1H-pyrrolo[1,2-a]indole-9-carboxaldehyde derivatives[a)]

Aldehydes	Reaction time (h)	Reaction temperature (°C)	Products[b)]	mp (°C)	Yield(%)
1[13)]	28	0	11	218.5-220	92
2	9	room temp.	12	200-201	84
3[2)]	1	room temp.	13	175-176	89
4[4)]	6	room temp.	14	219-220	92
5[4)]	2	room temp.	15	134-135	87
6[4)]	0.5	room temp.	16	141-142	89

a) All the reactions were performed in the presence of 6N sulfuric acid in a current of nitrogen.

b) Elemental Analyses and spectral data of the products are satisfied.

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