THE PREPARATION AND REARRANGEMENT OF 1-PRENYLINDOLES AND 3-PRENYLINDOLENINES

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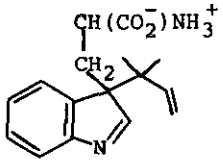
Abstract - The preparation of 3-alkyl-3-prenylindolenines was explored by rearrangement of 1-prenylindoles and by allylation of 2-(methylthio)indoles. Reaction of the 3-formylindole (6) with trifluoracetic acid gave first the addition product (7) and then the pyridinoindole (8); the esters (11) and (14) were formed similarly from the tryptophan derivative (10) and the 2-(methylthio)indolenine (13), respectively. Successive reaction of the indolenine (13) with lithium aluminium hydride and manganese dioxide gave 3-(3,3-dimethylallyl)-3-methylindolenine (18) in good yield.

The reversed prenyl group present in the 2-position of the indole ring of echinulin and other fungal diketopiperazines may be introduced in vivo by direct alkylation at C-2 of an indole precursor.[1] An alternative pathway involves the 3-alkyl-3-(1,1-dimethylallyl)indolenines (1) and/or (2). In connection with our biosynthetic studies[2] we sought a simple synthesis of these indolenines and of indoles substituted at the 2-position by a dimethylallyl group.



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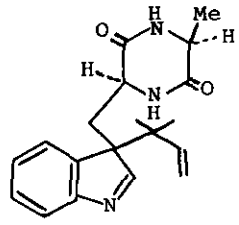

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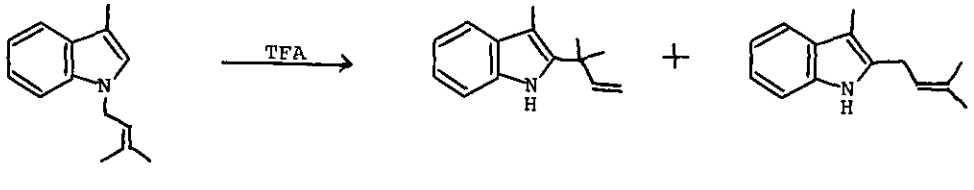
One approach to the synthetic problem stemmed from the work of Casnati and co-workers[3] who studied acid-catalysed reactions of 1-allylindoles. We have confirmed that the rearrangement products (96% yield) obtained from 1-(3,3-dimethylallyl)-3-methylindole (3) in trifluoracetic acid (TFA) consist of the (1,1-dimethylallyl)-indole (4) and the (3,3-dimethylallyl)-indole (5) in an approximate ratio of 1:1 (NMR); the compounds were separated by preparative t.l.c. on silica gel. In exploring the scope of this reaction, it was found that 1-(3,3-dimethylallyl)-3-formylindole (6) in TFA at 33°C gave the addition product (7) [IR (neat) $\nu_{max.}$ 1650 (CHO) and 1775 cm^{-1} (CO_2CF_3); NMR ($CDCl_3$) δ 9.95 (1H, s, CHO), 8.3 (1H, m, C-4H), 7.66 (1H, s, C-2H), ~ 7.3 (3H, m, arom.), 4.28 (2H) and 2.38 (2H), AA'BB' pattern, $-CH_2CH_2-$ and 1.67 (6H, s, CMe_2); MS m/e 327 (M^+, 56%), 213 ($M-CF_3CO_2H$, 20%), 158 ($M-CH_2C(OCOCF_3)Me_2$, 100%) and 130 ($M-CH_2C(OCOCF_3)Me_2$, -CHO, 11%)], but in refluxing TFA the product (8) of an intramolecular Friedel-Crafts reaction was formed in quantitative yield from an equilibrium mixture of the prenyl derivative (6) and the ester (7); the structure of the pyridinoindole (8) was indicated by IR absorption at 1650 cm^{-1} (CHO) by the mass spectrum [m/e 213 (M^+, 87%) and 198 (M-Me, 100%] and by the NMR spectrum in $CDCl_3$ [δ 9.89 (1H, s, CHO), 8.0 (1H, dd, J 3.5 and 10 Hz, C-4H), 7.56 (1H, s, C-2H), 7.30-7.07 (2H, m, C-5H and C-6H), 4.16 (2H) and 1.96 (2H), AA'BB' pattern, $-CH_2CH_2-$) and 1.35 (6H, s, CMe_2)]. Similar cyclisation reactions were reported recently by Sammes and co-workers.[4]



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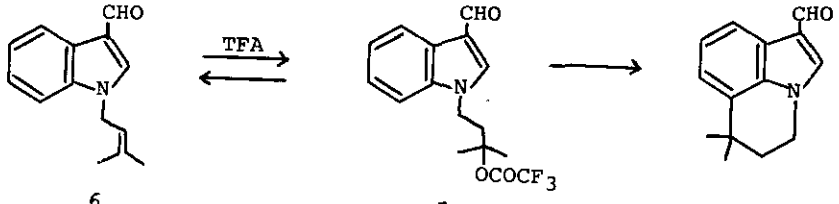

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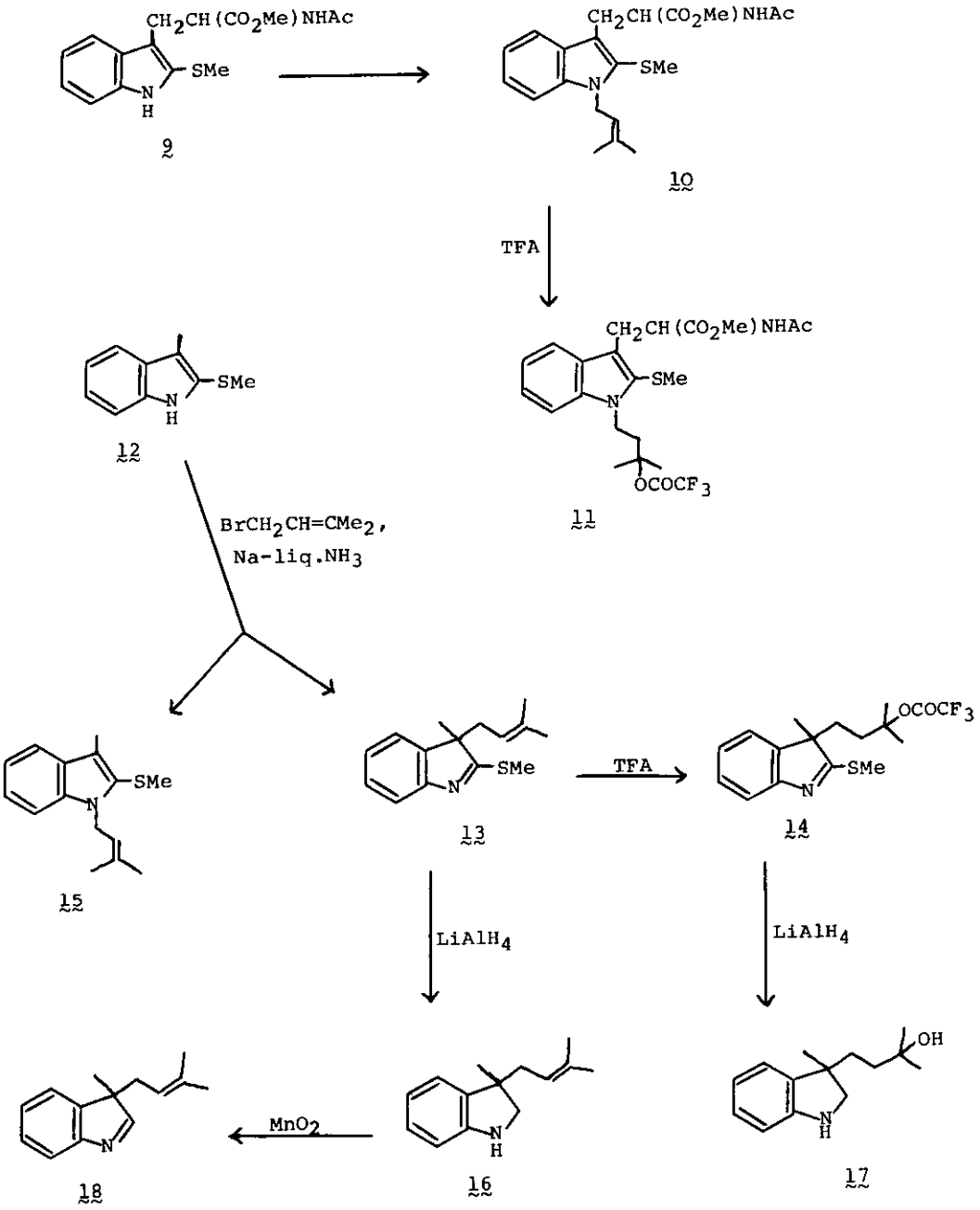
CH2CH(CO2Me)NHAc
SMe
N
H
9
10
TFA
11
12
BrCH2CH=CMe2,
Na-liq.NH3
13
14
15
OCOCF3
LiAlH4
16
17
18
MnO2
OH

Scheme

We have also studied the synthesis of 3-prenylindolenines lacking a 2-substituent. These compounds are apparently readily converted into 2-prenylindoles[5] and this acid-induced shift is presumably involved in the conversion of the 1-prenylindole (3) into 2-prenylindoles (4) and (5).[6] In the preparation of 1-(3,3-dimethylallyl)-3-methylindole (3) from 3-methylindole, 3,3-dimethylallyl bromide and NaH in DMF, the indolenine (18) was detected as a minor product in the crude reaction mixture [NMR ($CDCl_3$) δ 7.97 (1H, s, -CH=N-), 7.7-6.9 (4H, m, arom.), 4.93 (1H, t, J 7.5 Hz, -CH=C), 2.38 (2H, d, J 7.5 Hz, $-CH_2CH=C$), 1.60 and 1.53 (6H, 2 X s, $Me_2C=$) and 1.30 (3H, s, Me)]. Attempts to isolate this indolenine by chromatography on silica gel led to its quantitative isomerisation to the 2-(3,3-dimethylallyl) indole (5).

The work of Bycroft and Landon[7] on the reaction of 3-methyl-2-(methylthio)-indole with 3,3-dimethylallyl bromide seemed to offer the attractive possibility of employing a methylthio substituent as a blocking group to stabilise 3-prenylindolenines.

We decided, therefore, to prepare the (2-methylthio)indoles (9) and (12) and investigate their reactions (Scheme).

Treatment of L- N-acetyl tryptophan methyl ester with methane sulphenyl chloride in acetic acid gave the 2-methylthio derivative (9) in 58% yield, which was converted with 3,3-dimethylallyl bromide in Na-liquid ammonia into the 1-(3,3-dimethylallyl)indole (10) (32% yield), m.p. 124°C. Under the same conditions, 3-methyl-2-(methylthio)indole (12) afforded two products, the 1-(3,3-dimethylallyl)indole (15) (19% yield) [NMR ($CDCl_3$) δ 7.6-7.0 (4H, m, arom.), 5.20 (1H) and 4.85 (2H), AB_2 pattern (J_{AB} ~ 7Hz), $CH_2CH=CMe_2$, 2.40 (3H) and 2.15 (3H), 2 X s, SCH_3 and indolyl CH_3 (or v.v.), 1.85 (3H) and 1.65 (3H), 2 X s, $C=C(CH_3)_2$], and the 3-(3,3-dimethylallyl)indolenine[7] (13) (62% yield) [NMR ($CDCl_3$) δ 7.5-7.0 (4H, m, arom.), 4.68 (1H, t, J 7.5Hz, CH_2CH), 2.57 (3H, s, SMe), 2.4 (2H, m, CH_2CH), 1.47 (3H) and 1.41 (3H), broad singlets, $C=CMe_2$, 1.28 (3H, s, indolyl Me)]. The tryptophan derivatives (10) with trifluoroacetic acid at 50°C gave in low yield the addition product (11) as an oil [NMR ($CDCl_3$) δ 7.37-7.0 (4H, m, arom.), 6.13 (1H, d, NHCOMe), 4.99-4.77 (1H, m, $CH_2CH<$), 4.25-4.13 (2H, m, $>NCH_2CH_2$), 3.70 (3H, s, CO_2Me), 3.41 (2H, d, $CH_2CH<$), 2.27 (3H, s, SMe), 2.10-1.92 (5H, m, $NHCOCH_3$ and $>NCH_2CH_2$ and 1.39 (6H, s, CMe_2)]. In TFA at 30°C the 3-(3,3-dimethylallyl) indolenine (13) also gave an addition product (14) [NMR

($CDCl_3$) δ 7.4-7.1 (4H, m, arom.), 2.60 (3H, s, SMe), 2.1-1.6 (2H, m) and 1.3-0.8 (2H, m) (2 X CH_2) and 1.39 (3H), 1.35 (3H), 1.32 (3H), 3 X s, 3 X Me; MS m/e 359 (M^+, 98%), 245 (M-CF_3CO_2H, 33%) and 177 (M-$C_7H_9O_2F_3$, 100%)], which was converted by lithium aluminium hydride into the indoline (17).

The 2-(methylthio)indolenine (13) was reduced quantitatively with lithium aluminium hydride in boiling ether to the indoline (16) [NMR ($CDCl_3$) δ 7.10-6.45 (4H, m, arom.), 5.15 (1H, t, J 7.5Hz, -CH=), 3.13 and 3.31 (2H, m, J 9Hz, $-CH_2NH-$) 2.25 (2H, d, J 7.5Hz, $-CH_2CH=$), 1.69, 1.53 (6H, 2 X s, $Me_2C=$) and 1.25 (3H, s, Me); MS m/e 201 (M^+, 12.5%), 132 (M-C_5H_9, 100%), 131 (10%) and 130 (15%)]. Reoxidation with MnO_2 in boiling benzene or toluene then furnished 3-(3,3-dimethylallyl)-3-methylindolenine (18) (60-80% yield). This sequence which avoids acidic conditions may prove to be useful in the preparation of highly functionalised and labile 3,3-dialkyl-indolenines since MnO_2 oxidation may be performed as the terminal step in the synthesis.

ACKNOWLEDGEMENTS

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