BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, VOL. 49(3), 833—834 (1976)

The Acid-Catalyzed Rearrangement of 1-Allylindoles. A Hypothesis for the Biogenesis of Echinulin-Type Compounds

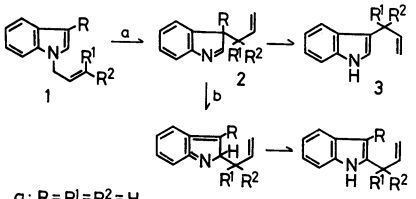
Seisaku INADA, Kunio NAGAI, Yasuo TAKAYANAGI, and Mitsuo OKAZAKI

Department of Chemical Engineering, Faculty of Engineering, Tokyo Institute of Technology, Ohokayama, Meguro-ku, Tokyo 152

(Received September 18, 1975)

Synopsis. The aluminum chloride-catalyzed rearrangement of 1-allyl- (**1a**) and 1-(*trans*-2-butenyl)indole (**1b**) produced 3-allyl-(**3a**) and 3-(1-methylallyl)indole (**3b**) in 58 and 43% yields, respectively. Based on this, a hypothesis for the biogenetic mechanism of echinulin is proposed.

Recently, Patterson *et al.* showed that the pyrolysis of a mixture of 1-(*trans*- and *cis*-2-butenyl)indole at 450—470 °C gave 3-(1-methylallyl)indole and indole as the major primary reaction products.[1] We wish to report here the exclusive charge-induced [3,3]-shift of 1-allylindoles in connection with our interest in the biogenesis of the mould metabolite echinulin.



a: R=R¹=R²=H
b: R=R¹=H, R²=Me
c: R=R¹=R²=Me

The experimental results for the rearrangement of 1-allylindole (**1a**) are summarized in Table 1. The $ZnCl_2$-catalyzed reaction of **1a** afforded an isolable amount of 3-allylindole (**3a**)[2] together with indole and 3-*n*-propyl-1-allylindole (**5**) only under the rather drastic conditions where the reaction was carried out in boiling tetralin. They were separated by preparative GLC and identified, based on analytical and/or spectral data, respectively. In the NMR spectrum of **5**, the presence of absorptions at 6.71 δ (s, 1H) due to 2-H in the indole nucleus and 4.48—4.62 δ (m, 2H) due to the α hydrogens of $N\text{-}CH_2CH{=}CH_2$ indicates the probable location of the propyl group at the 3-position, which may originate from the allyl group of **1a**.

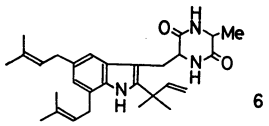
Although the reaction under $SbCl_5$ catalysis formed a fair amount of tarry matter, the $AlCl_3$- and $TiCl_4$-catalyzed reactions were found to give **3a** exclusively, with the exception of a slight formation of tarry matter. The former proceeds with higher reactivity and less formation of tarry products than the latter. Thus, when **1a** and $AlCl_3$ (equimolar amounts) were refluxed in benzene for 4 hr, **3a** was obtained in 58% yield. This was confirmed by GLC to contain no detectable amount of by-products.

Table 1. Acid-catalyzed reaction of **1a**

Acid	Solvent	Reaction time(hr)	Relative compositions (glc area %)
$ZnCl_2$	Benzene	24	**1a**, >99; **3a**, trace.
$ZnCl_2$	Tetralin	20	**1a**, 68; **3a**, 14; indole, 4; **5**, 9; unidentified, 5.
$SbCl_5$	Benzene	0.5	
$AlCl_3$	Benzene	1	**1a**, 15; **3a**, 85.
$TiCl_4$	Benzene	3	**1a**, 74; **3a**, 26.

The rearrangement of 1-(*trans*-2-butenyl)indole (**1b**) was similarly performed; heating of **1b** with $AlCl_3$ for 2 hr (**1b** seems more reactive than **1a**) gave 3-(1-methylallyl)indole (**3b**)[1] in 43% yield. This demonstrates that the isomerization is presumably a [3,3]-sigmatropic reaction followed by enamination.

The biogenesis of the mould metabolite echinulin (**6**) and the formally related alkaloids, which involve a



6

1,1-dimethylallyl group at the 2-position of the indole nucleus, has been of interest.[3] In particular, different biogenetic mechanisms for the process through which the reversed isoprene unit is inserted at the 2-position have been suggested.[4,5] Recently, Casnati *et al.* have found that 3-methyl-1-(3-methyl-2-butenyl)indole (**1c**) rearranged under acid catalysis to give 2-(1,1-dimethylallyl)3-methylindole (**4c**) and 3-methyl-2-(3-methyl-2-butenyl)indole with partial inversion of the migrating group, and stated that this represented a hitherto unobserved type of rearrangement, which might have a biogenetic implication for echinulin-type compounds.[6] However, in view of our experimental results, it seems possible to assume that the reaction affording **4c** (and consequently the process of the biogenesis for echinulin-type compounds also) involves a charge-induced [3,3]-shift to form an intermediate, 3-alkyl-3-allylindolenines (**2**),[7] followed by a [1,5]-shift and subsequent enamination to give 3-alkyl-2-allylindoles (**4**).

It is well-known that 3,3-dialkylindolenines isomerize readily to 2,3-dialkylindoles in an acidic medium, especially when one of the alkyl groups is an allylic group (route b).[5,8] On the other hand, the [3,3]-shift of 1-allylindoles (route a) has not been reported, except for the experiment which was carried out under the rather drastic conditions described above.[1] Our experimental results may be one of primary pieces of evidence supporting the proposed hypothesis.

Experimental

Gas chromatographic analyses were made on a Shimadzu GC 3AH gas chromatograph using a 3 mm×2 m column packed with 25% Apiezon L on Chromosorb W at 220 °C.

For preparative GLC, a Schimadzu GC 1B gas chromatograph having a 6 mm × 1.5 m column packed similarly was employed. 1-Allylindole (**1a**)[9] and 3-allylindole (**2a**)[2] were prepared according to the methods reported in the literature.

*1-(*trans*-2-Butenyl)indole (**1b**).* According to the method of Cardillo *et al.* for preparing **1a**,[9] **1b** (34.5 g, bp 116 °C/2 mmHg) also was prepared from indole (30.0 g, 0.256 mol), sodium hydride (50% dispersion, 12.6 g, 0.262 mol), and *trans*-1-chloro-2-butene (23.2 g, 0.256 mol) in DMF. This was contaminated with a by-product which could not be excluded by distillation. This was treated with picric acid (46.6 g) in methanol (300 ml) and the picrate obtained (51 g) was repeatedly recrystallized from methanol to give red needles (20.4 g) which melted at 73.5—74.5 °C. IR (KBr, cm^{-1}) 3125, 1635, 970. Found: N, 13.76%. Calcd for $C_{18}H_{16}N_4O_7$: N, 13.99%.

The purified picrate was added to 5% aqueous NaOH and extracted with ethyl acetate. The organic solution was washed with water and dried over $MgSO_4$. After removal of the solvent the residue was distilled *in vacuo* and a fraction of bp 91 °C/1.5 mmHg was collected. Yield, 5.0 g (11.4%). The GLC analysis denoted that this fraction consisted of a single product. IR (neat film, cm^{-1}) 3050, 1455, 1320, 970. NMR ($CDCl_3$, δ) 1.59 (br. d, 3H), 4.42 (br. d, 2H), 5.20—5.64 (m, 2H), 6.30 (d, 1H), 6.80 (d, 1H), 6.88—7.14 (m, 3H), 7.36—7.52 (m, 1H). Found: N, 8.10%. Calcd for $C_{12}H_{13}N$: N, 8.18%.

*Acid-catalyzed Reaction of **1a**.* A mixture of **1a** (0.5 g) and a Lewis acid (equimolar amounts) in a solvent (4 ml) was refluxed for an appropriate time. The reaction mixture was poured into 10% aqueous NaOH and extracted with ethyl acetate. The organic layer was washed with water and provided for GLC analysis. The results are shown in Table 1.

*1-Allyl-3-*n*-propylindole (**5**).* Pale yellow oil. IR (neat film, cm^{-1}) 3050, 1465, 990, 920. NMR ($CDCl_3$, δ) 1.00 (t, 3H), 1.44—1.90 (m, 2H), 2.70 (t, 2H), 4.48—4.62 (m, 2H), 4.78—5.08 (m, 2H), 5.60—6.20 (m, 1H), 6.71 (s, 1H), 6.80—7.15 (m, 3H), 7.35 —7.55 (m, 1H). Found: N, 7.00%. Calcd for $C_{14}H_{17}N$: N, 7.03%.

$AlCl_3$-catalyzed Rearrangement. *Synthesis of **2a***: A solution of **1a** (5.0 g, 32 mmol) and $AlCl_3$ (4.3 g, 32 mmol) in benzene (80 ml) was refluxed for 4 hr. To the cooled solution 2% HCl (100 ml) was added and the organic solution was separated, washed with water, and dried over $MgSO_4$. After removal of the solvent, the residue (4.6 g) was distilled *in vacuo*; a fraction of bp 105 °C/2 mmHg was collected. Yield, 2.9 g (58%). The IR and NMR spectra were completely in accord with those of an authentic sample prepared according to the method of Brown *et al.*[2]

*Synthesis of **2b***: A mixture of **1b** (3.0 g, 18 mmol) and $AlCl_3$ (2.3 g, 18 mmol) was refluxed in benzene (60 ml) for 2 hr. The reaction mixture was treated similarly and a fraction of bp 111—112 °C/1.5 mmHg was collected. Yield, 1.3 g (43%). The IR and NMR spectra corresponded to those described by Patterson *et al.*[1] This sample was 98% pure (GLC area %), but sensitive to the air; it darkened after standing for a few days.

References

1) J. M. Patterson, A. Wu, C. Kook, and W. T. Smith, Jr., *J. Org. Chem.*, **39**, 486 (1974).

2) J. B. Brown, H. B. Henbest, and E. R. H. Jones, *J. Chem. Soc.*, **1952**, 3172.

3) A. J. Birch, G. E. Blance, S. Davis, and H. Smith, *ibid.*, **1961**, 3128.

4) B. W. Bycroft and W. Landon, *Chem. Commun.*, **1970**, 967; A. H. Jackson and A. E. Smith, *Tetrahedron*, **21**, 989 (1965); A. J. Birch and K. R. Farrar, *J. Chem. Soc.*, **1963**, 4277.

5) G. Casnati, M. Francioni, A. Guareschi, and A. Pochini, *Tetrahedron Lett.*, **1969**, 2485.

6) G. Casnati, R. Marchelli, and A. Pochini, *J. Chem. Soc., Perkin I*, **1974**, 754. See also G. Casnati and A. Pochini, *Chem. Commun.*, **1970**, 1328.

7) Schmid *et al.* also pointed out a similar intermediacy for this migration. M. Schmid, H. -J. Hansen, and H. Schmid, *Helv. Chim. Acta*, **56**, 105 (1973).

8) A. H. Jackson and P. Smith, *Tetrahedron*, **24**, 2227 (1968).

9) B. Cardillo, G. Casnati, A. Pochini, and A. Ricca, *Tetrahedron*, **23**, 3771 (1967).