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SYNTHETIC STUDY ON ECHINULIN AND RELATED COMPOUNDS. PART I.

ACID-CATALYZED AMINO CLAISEN REARRANGEMENT OF ALLYL- AND 3,3-DIMETHYLALLYL-ANILINE DERIVATIVES

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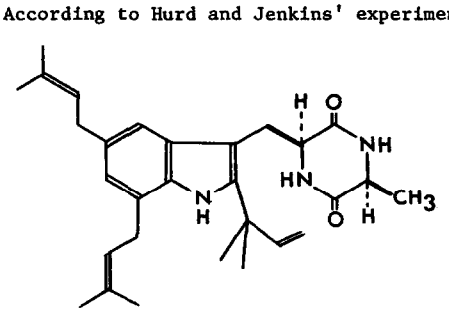
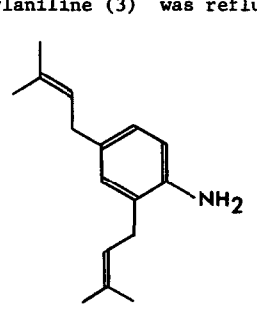
Since the structure of echinulin (1) was elucidated in 1959 by A. Quilico and his co-workers,[1] several attempts[2] to synthesize the alkaloid have been made. However, no successful total synthesis of echinulin (1) has been reported until now. One of the difficulties to accomplish the synthesis of the alkaloid is how to prepare 2,4-di(3,3-dimethylallyl)aniline (2), the indole moiety of echinulin (1). We considered the possibility that the difficulty could be overcome by an acid-catalyzed amino Claisen rearrangement of a N-(3,3-dimethylallyl)aniline derivative. However, unfortunately very few examples about the acid-catalyzed amino Claisen rearrangement are known; particularly only Hurd and Jenkins' report[3] is available in the case of N-allylaniline derivatives. Under these situations, we started to repeat the Hurd and Jenkins' experiment and then to extend the rearrangement to the synthesis of 2,4-di(3,3-dimethylallyl)-aniline (2).

According to Hurd and Jenkins' experiment, N-allylaniline (3)[3] was refluxed in the



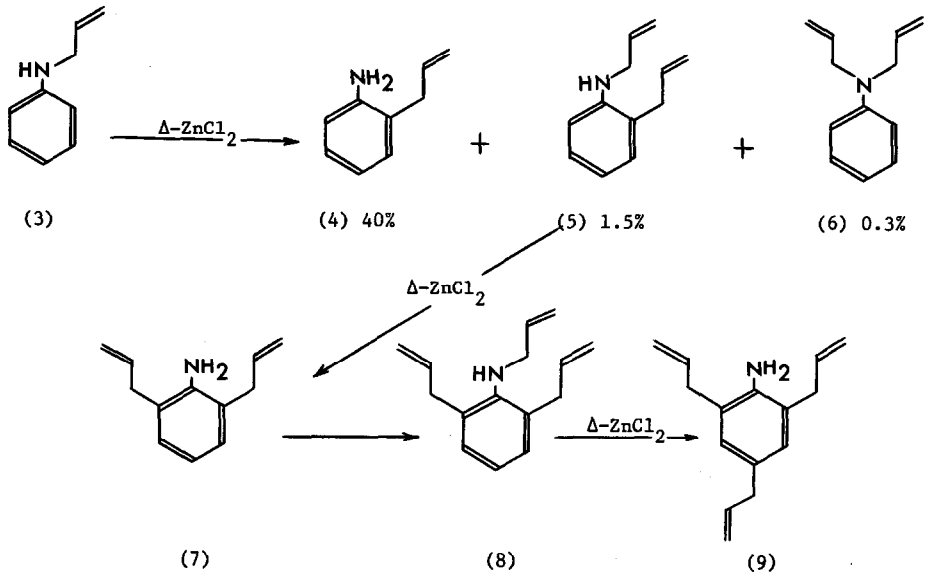
(1) ECHINULIN



(2)

presence of one equivalent of $ZnCl_2$ in xylene and the product was carefully isolated by silica

gel column chromatography. Three products were isolated in pure form; 2-allylaniline (4)[3](40%), N,2-diallylaniline (5)[4,5,6](1.5%), N,N-diallylaniline (6)[6,7](0.3%), and a tar.[8] The formation of the compounds (5) and (6) suggests that the acid-catalyzed amino Claisen rearrangement proceeds in an intermolecular mechanism as Hurd and Jenkins proposed.[3] To apply this rearrangement for the synthesis of the indole moiety of echinulin (1), it is required that the rearrangement must occur on the compound (5), too. Indeed, 2,6-diallylaniline (7)[9] was isolated in 37% yield when the compound (5) was treated with $ZnCl_2$ under the same condition as before. The structure of the product (7) was confirmed by the transformation of it into the known 2,6-diallylphenol[10] by the usual way. Similarly, 2,4,6-triallylaniline (9)[11] was produced in 22% yield on the rearrangement of the compound (8).[12] These results are summerized in the Scheme 1.

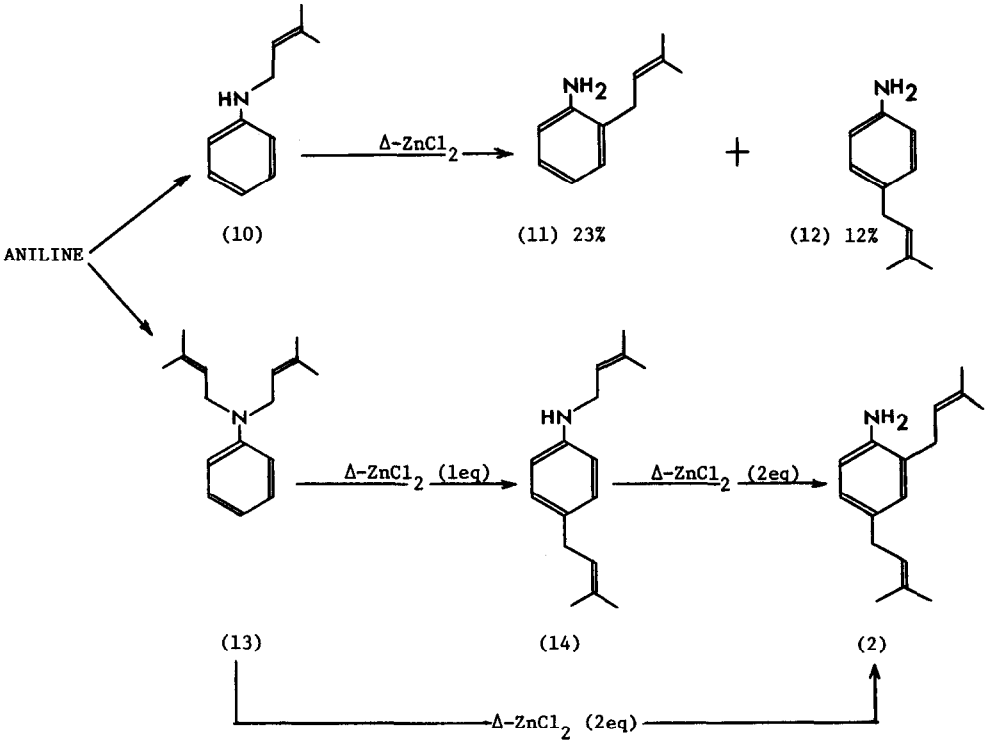


SCHEME 1. ACID-CATALYZED AMINO CLAISEN REARRANGEMENT OF N-ALLYLANILINE DERIVATIVES

To extend this rearrangement to the synthesis of 2,4-di(3,3-dimethylallyl)aniline (2), the rearrangement of N-(3,3-dimethylallyl)aniline (10) was examined next. Thus, when the compound (10)[13] was refluxed in the presence of one equivalent of $ZnCl_2$ in xylene and the product was isolated by silica gel column chromatography, 2-(3,3-dimethylallyl)aniline (11)[14](23%) and 4-(3,3-dimethylallyl)aniline (12)[15](12%) were obtained in pure form. It is important for the

synthesis of echinulin (1) that in this rearrangement the 3,3-dimethylallyl group migrated from the nitrogen atom to para- as well as ortho-position of the aniline nucleus without an isomerization or an inversion of the wandering radical.

The similar rearrangement of more readily available N,N-di(3,3-dimethylallyl)aniline (13) was examined. When the compound (13)[16] was refluxed with one equivalent of $ZnCl_2$ in xylene, N,4-di(3,3-dimethylallyl)aniline (14)[17] was produced in 11% yield, which was converted to the desired 2,4-di(3,3-dimethylallyl)aniline (2)[18] in 14% yield on the further treatment with one equivalent of $ZnCl_2$ in xylene. On the other hand, when the compound (13) was refluxed in the presence of two equivalents of $ZnCl_2$ in xylene, the desired compound (2) was directly produced in 23% yield. The sructure of the product (2) was carefully confirmed from analytical and spectroscopic data. These results are summerized in the Scheme 2.



SCHEME 2. ACID-CATALYZED AMINO CLAISEN REARRANGEMENT OF N-(3,3-DIMETHYLALLYL)ANILINE DERIVATIVES

The successful synthesis of optically active echinulin (1) from 2,4-di(3,3-dimethylallyl)aniline (2) thus obtained is described in the following paper.

REFERENCES AND FOOTNOTES

1. A. Quilico, Res. Prog. Org. Biol. Med. Chem., 1, 225 (1964), and references therein.
2. E. Houghton and J. E. Saxton, J. Chem. Soc., 595 and 1003 (1969), and references therein.
3. C. D. Hurd and W. W. Jenkins, J. Org. Chem., 22, 1418 (1957)
4. Satisfactory analytical and spectroscopic data were obtained for all the new compounds.
5. The compound (5) was alternatively prepared by allylation of the compound (4) (1 eq.) with allyl bromide (0.5 eq.) (yield based on allyl bromide: 70%) (bp at 8mm: 102-4°; picrate mp 124-5°).
6. The purity of 2-allylaniline (4) used is higher than 99% from a vpc analysis. Therefore, the origin of the product (5) can not be an impurity of the starting material, but in the case of the product (6) the situation is not so clear.
7. The compound (6) was alternatively prepared by allylation of the compound (3) with allyl bromide-$NaNH_2$ in liq. ammonia.
8. Acid-catalyzed amino Claisen rearrangement of N-allyl- or N-(3,3-dimethylallyl)aniline derivatives always accompanied a tar, which caused the yield of the desired product rather low.
9. acetyl derivative: mp 92-93°
10. L. Claisen, Liebigs Ann., 418, 69 (1918)
11. acetyl derivative: mp 86-87°
12. The compound (8) was prepared by allylation of the compound (7) with allyl bromide-$NaNH_2$ in liq. ammonia (yield: 32%).
13. The compound (10) was prepared by allylation of aniline (1 eq.) with 3,3-dimethylallyl bromide (0.5 eq.) in liq. ammonia (yield based on the bromide: 49%; bp at 3mm: 95-8°).
14. $\delta_{ppm}^{DMSO-d_6}$ 1.69($2CH_3$), 3.12(2H, d, J=7), 5.28(1H, broad t, J=7), 6.6-7.0(4H, m)
15. $\delta_{ppm}^{DMSO-d_6}$ 1.67($2CH_3$), 3.14(2H, d, J=7), 5.23(1H, broad t, J=7), 6.48(2H, AB, J=8.5), 6.97(2H, AB, J=8.5)
16. The compound (13) was prepared by allylation of aniline by 3,3-dimethylallyl bromide-$NaNH_2$ in liq. ammonia (yield based on the bromide: 80%; bp at 3.5mm: 142-3°; picrate mp: 124.5-6.0°).
17. $\delta_{ppm}^{DMSO-d_6}$ 1.68($4CH_3$), 3.13(2H, d, J=7), 3.57(2H, d, J=7), 5.23(2H, broad t, J=7), 6.47(2H, AB, J=8), 6.87(2H, AB, J=8)
18. $\delta_{ppm}^{DMSO-d_6}$ 1.68($4CH_3$), 3.10(4H, d, J=7), 5.25(2H, broad t, J=7), 6.7(3H); ms 229(M^+), 214, 175, 160, 146; acetyl derivative mp: 77-8°