Benzo[4,5]cyclohepta[1,2-c]pyrrole Derivatives *via* Intramolecular Cycloaddition and Solvolytic Ring Expansion

By MICHAEL T. COX†

(*Imperial Chemical Industries Ltd., Pharmaceuticals Division, Mereside, Alderley Park, Macclesfield, Cheshire* SK10 4TG)

Summary The intramolecular Diels–Alder reaction of compounds (**4**) and (**12**) leads to (**5**) and (**13**), which, after appropriate modification, are converted into the ring-expanded products (**9**) and (**15**).

THE synthetic utility of the intramolecular Diels–Alder reaction has recently been demonstrated.[1] Various non-activated dienophiles have been shown to participate in these reactions,[2] and Oppolzer[3] and Kametani[4] have used this route, *via* substituted benzocyclobutenes, in their syntheses of various alkaloids. Gschwend and his co-workers[5] have demonstrated the use of fumaric ester-amides in intramolecular cycloaddition reactions, for the construction of the isoindoline framework. Apart from the syntheses of some lignin lactones by Klemm and his co-workers,[6] there are few examples of intramolecular Diels–Alder reactions in which a benzenoid double bond participates as part of the diene component. The use of such a reaction for the synthesis of certain benz[*f*]isoindoles and the solvolytic ring expansion of derived products to benzo[4,5]-cyclohepta[1,2-*c*]pyrroles is now described.

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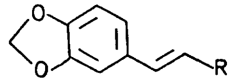
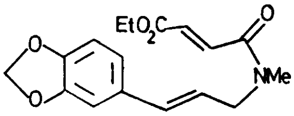
† *Present address*: Imperial Chemical Industries United States Inc., Wilmington, Delaware 19897, U.S.A.

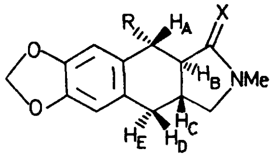
The cinnamaldehyde (**1**)[7] was treated with methylamine in the presence of sodium sulphate in toluene and the resultant Schiff base was reduced with sodium borohydride to (**2**), b.p. 134° at 0·6 mmHg. Reaction with the acid chloride of ethyl hydrogen fumarate in pyridine and methylene chloride afforded the amide (**4**), which was not isolated but was cyclised to (**5**) (56% overall), m.p. 156—158°, in refluxing toluene under N_2 for 8 h. The reaction is regiospecific, leading only to the *trans*-fused product (**5**), J_{AB} 12, J_{BC} 12·5, J_{CD} 7, and $J_{CE} = J_{DE} = 9$ Hz in [$^2H_5$]pyridine. Thus, (**5**) arises from the transition state (as in **4**) having the ester function *endo*.‡ Careful chromatography of the mother liquors failed to reveal any of the *cis*-fused isomer; only a small amount of dimeric material was detected. In the absence of N_2, the intermediate (**8**) underwent an 'ene' reaction with atmospheric oxygen to afford, after workup, the hydroxy-compound (**6**), m.p. 210—212°.



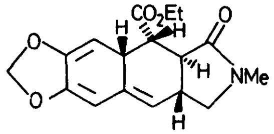
(1) R = CHO
(2) R = CH_2NHMe
(3) R = $[CH_2]_2NHMe$



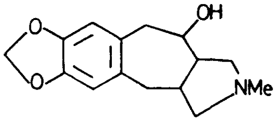
(4)



(5) R = CO_2Et, X = O
(6) R = CO_2Et, X = O, OH replaces H_D
(7) R = CH_2OH, X = H_2



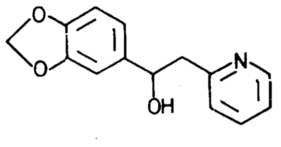
(8)



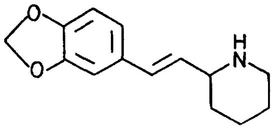
(9)

The lactam–ester (**5**) was reduced with $LiAlH_4$ in tetrahydrofuran (THF) to give the amino alcohol (**7**) (67%), m.p. 255—257°. The tosylate, m.p. 169—171°, of (**7**) was solvolysed[8] in formic acid at 90° for 10 h and, after alkaline hydrolysis of the formate ester, the ring-expanded amino-alcohol (**10**), m.p. 199—202°, was obtained.

As a further example, the anion from 2-picoline (BuLi) was treated with piperonal to afford the alcohol (**10**), m.p 111—113°. The hydrochloride of (**10**) was reduced (H_2–PtO_2–MeOH) and dehydrated *in vacuo* at 100° to the olefin (**11**), m.p. 62—64°. Acylation with the acid chloride of ethyl hydrogen fumarate (K_2CO_3–MeCN) gave the amide (**12**) which was unstable at 0°, being partly converted into (**13**). Complete conversion into (**13**) (37%), m.p. 188—189°, occurred on reflux in MeCN for 15 min under N_2. Reduction with $LiAlH_4$ in THF gave the amino alcohol (**14**), m.p. 168—169°, which was ring expanded *via* the tosylate, m.p. 152—154°, to the isomeric amino alcohol (**15**) (63%), m.p. 203—205°.



(10)



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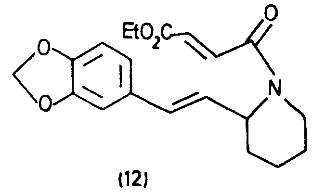

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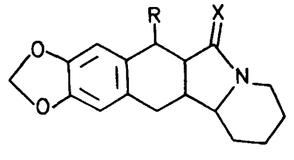
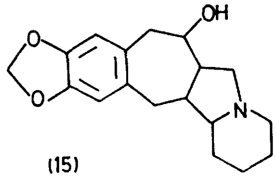
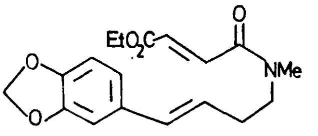


(13) R = CO_2Et, X = O
(14) R = CH_2OH, X = H_2



(15)



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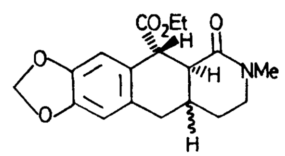

(17) *cis*-ring junction
(18) *trans*-ring junction

The influence of substituents in the benzene ring on the intramolecular cycloaddition has not been studied. A homologue of (**2**) has been found to undergo a similar reaction in lower yield. Thus (**3**), prepared from piperonal and 3-methylaminopropyl(triphenyl)phosphonium bromide hydrobromide[9] using Schlosser's conditions,[10] formed a stable amide (**16**), which cyclised in *o*-dichlorobenzene at reflux. The 6-membered lactams (**17**) (18%), m.p. 184—186°, and (**18**) (27%), m.p. 104—105°, were isolated after chromatography on silica. Their formation presumably reflects a less strained transition state in this case.

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‡ Dreiding models indicate that this transition state is less strained than that with the amide function *endo*.

All new compounds gave correct analytical data and the structures shown were supported by ^{1}H n.m.r. and i.r. spectra.

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