Ring Homologation of Unsaturated Ketones and Lactones with Diazoethane: A New Route to Macrolides

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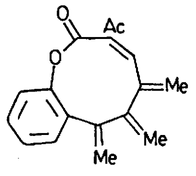
Summary The stepwise insertion of three ethylidene units into the rings of 2-acetylcycloalk-2-enones or the corresponding lactones can be readily effected by the addition of diazoethane and the elimination of nitrogen.

The stepwise ring expansion of 3-acetylcoumarin by diazoethane giving (I)[1] suggested a method of preparing lactones and cyclic ketones which might be particularly useful for medium-sized ring systems that are relatively difficult to obtain by ring-closure techniques.[2] Essentially the addition of a diazoalkane to a cyclic unsaturated diketone or ketonic lactone gives a pyrazoline which in losing nitrogen undergoes a ring homologation.

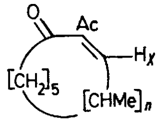
Although the requisite enediones (II) and (IX) were not accessible,[3] we found that 2-acetylcyclo-octanone and 2-acetylcyclododecanone could readily be dehydrogenated *via* their selenoxide derivatives[4] as reported by Reich *et al.*[5]

The (*Z*)-enedione (II) added diazoethane in ether at −20° during 45 min to give the pyrazoline (III), m.p. 32—33° (decomp.), ν_{max} (Nujol) 1700, 1695 and 1570 cm^{-1}, τ ($CDCl_3$) 5·75 (dq, *J* 7, H_z) and 8·63 (d, *J* 7, *Me*CH_z), which lost nitrogen in refluxing benzene to give the ring homologue (IV) as an oil, ν_{max} ($CHCl_3$) 1700, 1665 and 1630 cm^{-1}, τ 3·65 (d, *J* 10, H_x) and 8·89 (d, *J* 7, *Me*CH). Repetition *via* the pyrazoline (V) gave the next homologue (VI), and the succeeding pyrazoline (VII), m.p. 63—66°, provided the enedione (VIII), m.p. 110°, ν_{max} 1680, 1665 and 1618 cm^{-1}, τ 3·20 (d, 1H, *J* 10), 8·86 (d, 3H, *J* 7), and 9·15 (d, 6H, *J* 7).

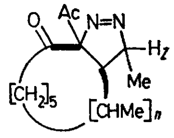
In a parallel series of reactions with the (*E*)-enedione (IX) and diazoethane the series of compounds (X)—(XIV) was produced, and finally the cyclopentadecenone derivative (XV), m.p. 36—38°. Like the oxonin derivative (I), enediones (VIII) and (XV) failed to react further with diazoethane; models suggest that these systems are becoming too congested to add the reagent easily.



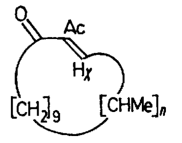
(I)



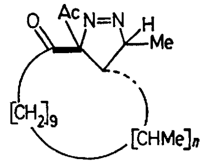
(II) *n* = 0
(IV) *n* = 1
(VI) *n* = 2
(VIII) *n* = 3



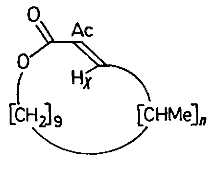
(III) *n* = 0
(V) *n* = 1
(VII) *n* = 2



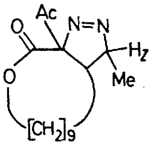
(IX) *n* = 0
(XI) *n* = 1
(XIII) *n* = 2
(XV) *n* = 3



(X) *n* = 0
(XII) *n* = 1
(XIV) *n* = 2



(XVI) *n* = 0
(XVIII) *n* = 1
(XIX) *n* = 2
(XX) *n* = 3



(XVII)

As an example of a macrolide synthesis, 2-acetyl-12-dodecanolide was prepared by treating the lithio enolate of 12-dodecanolide in tetrahydrofuran with acetic anhydride, and was then converted by the selenoxide technique into the (*E*)-ethylenic lactone (XVI), m.p. 42—43°, ν_{max} 1720, 1683 and 1620 cm^{-1}, τ 3·18 (d, *J* 8, H_x). This gave the pyrazoline (XVII) m.p. 59—61° (decomp.), which readily lost nitrogen in refluxing benzene (2h) to give the homologated lactone (XVIII) as an oil, ν_{max} 1720, 1690, 1670, 1630 and 1610 cm^{-1}, τ 3·50 (d, 1H, *J* 10) and 8·95 (d, 3H, *J* 7). The derived pyrazoline was converted at once into the homologous lactone (XIX), and the next pyrazoline was again converted at once into the desired 15-pentadecenolide

TABLE. Yields (%) of pyrazolines and homologation products

Pyrazoline	Enedione	Pyrazoline	Enedione	Pyrazoline	Ketolactone
(III) 58[a]	(IV) 59	(X) 74[b]	(XI) 95	(XVII)67[c]	(XVIII)82
(V) 78	(VI) 95	(XII) 74	(XIII) 95	[d]	(XIX) 67[e]
(VII) 90	(VIII) 95	(XIV) 43	(XV) 95	[d]	(XX) 84[f]

[a] From (II). [b] From (IX). [c] From (XVI). [d] Not isolated. [e] Overall, from (XVIII). [f] Overall, from (XIX).

derivative (XX), ν_{max} 1720, 1690, 1665, 1635 and 1620 cm^{-1}, τ 3·32 (d, 1H J 11), 8·87 (d, 3H, J 7), 9·09 (d, 3H, J 7) and 9·24 (d, 3H, J 7).

Spectroscopy indicated that in each case the pyrazoline was produced in one stereoisomeric form only, and that the ring insertions also supplied single stereoisomers. The implication that the stereochemistry of the products is similar to that proved for the oxonin derivative (I) awaits *X*-ray crystallographic confirmation.

Using a range of ring sizes from 6 to 16 members we have shown that the technique is not limited merely by ring size, though three adjacent methyl groups halt it. We find that in some cases diazomethane is useful for ring homologation without introducing methyl groups, and we are now examining the alternating use of the two reagents with the intention of obtaining the alternating methyl substitution pattern characteristic of many macrolides obtained from micro-organisms.[6]

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