Synthesis of Bridged 1,5-Benzodiazepines by Condensation of o-Phenylenediamines with 4,6-Dimethylbicyclo[3.3.1]nona-3,6-diene-2,8-dione

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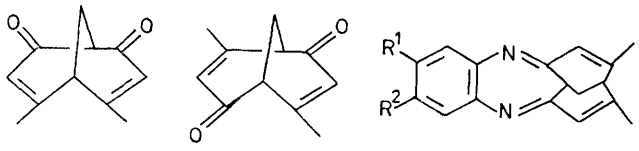
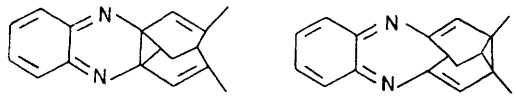
Summary *o*-Phenylenediamines react with 4,6-dimethylbicyclo[3.3.1]nona-3,6-diene-2,8-dione to give 1,5-benzodiazepines; physical and chemical properties of the bridged imines are described.

Few bridged heterocyclic annulenes have been reported. Vogel and his co-workers have described routes to carbocyclic annulenes which require either construction of a central bridge using an established peripheral carbon

skeleton, *e.g.* synthesis of bridged [14]annulenes[1] from anthracene, or construction of the peripheral skeleton from a bridged compound, *e.g.* elaboration[2] of bicyclo[5.4.1]-dodeca-2,5,7,9,11-pentaenes. The latter route is limited by the difficulty of preparation of the bicyclic unit. We have been investigating the use of the readily available bicyclo[3.3.1]nonadienediones[3] (**1**) and (**2**) in the construction of novel bridged systems. Here we report the preparation of bridged 1,5-benzodiazepines by reaction at the carbonyl centres in (**1**).



(1) (2) (3)



(4) (5)

a; $R^1 = R^2 = H$
b; $R^1 = R^2 = Me$
c; $R^1 = H$; $R^2 = Cl$
d; $R^1 = H$; $R^2 = NO_2$

Reaction of (**1**) with *o*-phenylenediamine in acetic acid gives a bridged 1,5-benzodiazepine (**3a**), m.p. 168—169 °C (ethyl acetate); λ_{max} (EtOH) 247, 253, and 350 nm (ϵ 35500, 38000, and 4400); ν_{max} ($CHCl_3$) 2960, 1620, 1575, and 1455 cm^{-1}, and showed M^+ at *m/e* 248.

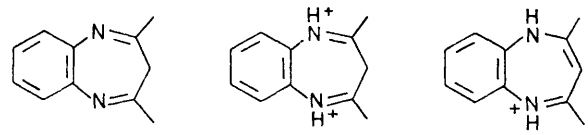
Distinguishing features of the ^1H n.m.r. spectrum ($CDCl_3$) were 1H triplets at δ 1·37 and 3·07 attributable to the bridgehead protons in either (**3a**) or the alternative structures (**4**) or (**5**) incorporating a barbaralane skeleton. Structure (**3a**) is established by the ^{13}C n.m.r. spectrum, which shows a total of 10 resonances, and significantly, in addition to signals associated with a methyl and a methylene group, only two other signals at δ 38·15 and 42·14 p.p.m. associated with sp^3 carbons. In the ^1H n.m.r. spectrum[4] of 2,4-dimethyl-1,5-benzodiazepine (**6**) the methylene protons are split at −60 °C in CD_3OD to give signals at δ 2·04 and 3·74. In (**3a**) similarly one proton (at the bridgehead) is directed towards the aromatic ring and is observed at high field (δ 1·37).

TABLE. Synthesis of bridged heterocyclic systems from (**1**).

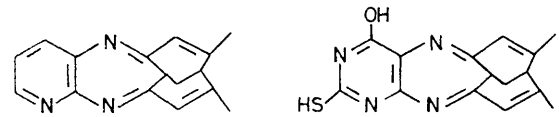
Starting diamine	Temp./°C	Product (% yield[a])
o-Phenylenediamine	75	(**3a**) (81)
4,5-Dimethyl-*o*-phenylenediamine	70	(**3b**) (52)
4-Chloro-*o*-phenylenediamine	75	(**3c**) (60)
4-Nitro-*o*-phenylenediamine	80	(**3d**) (48)
2,3-Diaminopyridine	Reflux	(**9**) (32)
4,5-Diaminothiouracil[b]	Reflux	(**10**) (11)

[a] After crystallisation. [b] Used as 4,5-diaminothiouracil sulphate.

Results in the Table establish the generality of condensation of (**1**) both with a series of *o*-phenylenediamines and with heteroaromatic diamines.



(6) (7) (8)



(9) (10)

Simple 1,5-benzodiazepines are characterized by ready proton loss from C-3. Indeed alkylation[5] with methyl iodide leads to *C*-alkylation, not *N*-alkylation. Further on protonation[6] of (**6**), whilst the diprotonated species has structure (**7**), the monoprotonated species is the highly coloured (**8**). In contrast the constraints imposed by Bredt's rule prevent similar behaviour in (**3a**). In acid (**3a**) remains pale yellow and on alkylation with Me_3OBF_4 *N*-alkylation and then *NN'*-dialkylation proceed smoothly to give pale coloured salts in high yield.

These studies confirm the utility of (**1**) in the construction of bridged heterocyclic compounds. The properties of the products, related in structure to systems of known physiological activity are being studied.

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