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A Novel Bridgehead Azocine. The end of a controversy.

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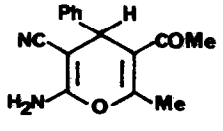
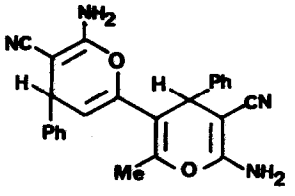
Abstract: *A novel bridgehead azocine* 4 *has been obtained from aminopyran* 1 *and benzylidinemalononitrile* 6. *The structure of* 4 *was confirmed by X-ray diffraction.*

The use of the 4H-pyran ring as starting material for the synthesis of fused polycyclic compounds is almost unknown, although the ring transformation into monoheterocyclic systems has been described.[1,2]

Acetyl substituted aminopyran 1 has, however, been reported to react with arylidenemalononitriles and the outcome of the reaction has proved controversial. Thus, either a bipyranyl (2)[3] or a pyrano[2,3-b]pyridine (3)[4] structure has been attributed to the resulting compound. We must now report that both of these are wrong.



1



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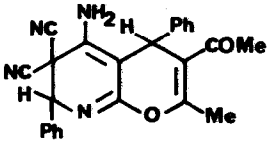
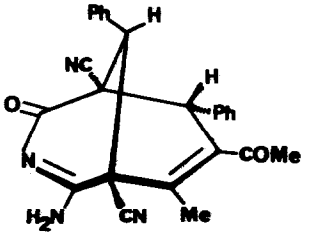


3

A reinvestigation of the reaction and the resulting product now allows us to conclude that the real structure of the compound is the novel bridgehead azocine 4 (7-acetyl-2-amino-3-aza-1,5-dicyano-8-methyl-4-oxo-6,9-diphenylbicyclo[3.3.1]non-2,7-diene, as revealed by X-ray diffraction.[5]



4

The compound contains four chiral centres and is formed as a mixture of diastereomers (high resolution ^{1}H-NMR) but only the racemic RRSR isomer (the one drawn in figure 1) and its enantiomer (the major stereoisomers in the crude product) were isolated.

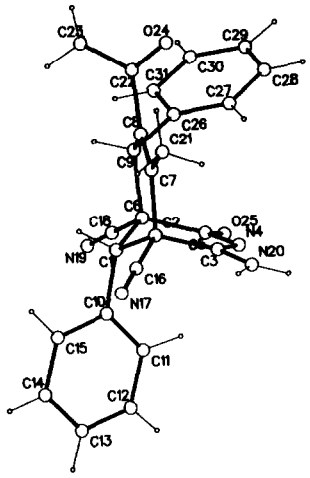
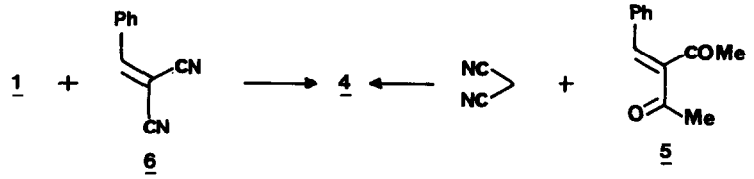


Figure 1. A view[17] of the molecular structure of compound **4**.

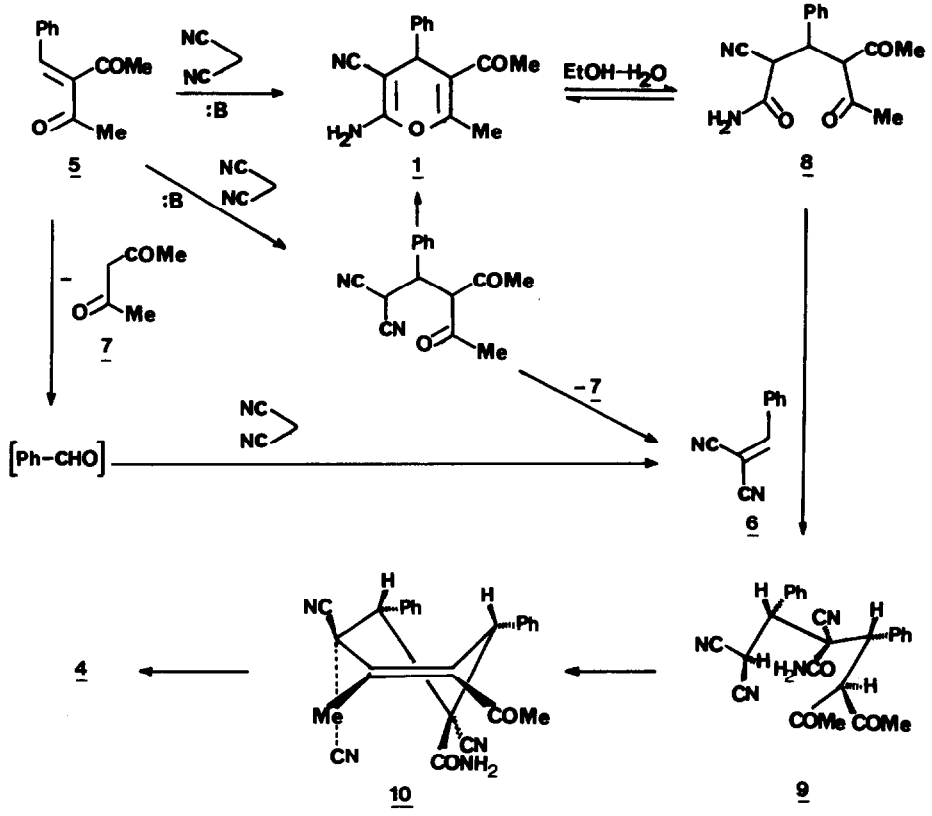
Both six-membered rings in the bicyclic system present an envelope conformation on C1, with a similar degree of puckering in both rings. Although the carbocyclic ring moiety contains a localized double bond, the nitrogen ring involves a delocalized π system involving C3-N4-C5, due to the amide-amidine resonance, with very similar bond lengths for C3-N4, N4-C5 and C3-N20.

Bridgehead azocine **4** exhibits an interesting NMR spectrum[6] in which the C-sp^3 proton at δ 4.94 is coupled with the methyl group on the double bond at δ 2.09 (J=2.0 Hz) (long range homoallylic coupling). Chemical shifts and multiplicities of the ^{13}C-NMR signals correspond to the different carbons in **4** and are confirmed by the J-modulated spin echo spectrum. The signals corresponding to the CH_3 and CH carbons appear inverted, whereas the other carbons remain in an upright position.

The route to compound **4** is not obvious. The compound can be arrived at either from pyran **1** or from the open chain precursors, malononitrile and benzylidenepentanedione **5**.



From a mechanistic standpoint, formation of azocine **4** by either route can be rationalized as depicted in Scheme 1. The first step, when starting from open chain precursors, involves the formation of pyran **1** which, although stable enough to be isolated,[7] acts as an intermediate. Ring cleavage of **1**, leading to oxoamide **8**, is followed by a conjugate addition to benzylidenemalononitrile **6**. This, in turn, is generated through a retro-Michael elimination of the initial adduct between malononitrile and the starting unsaturated dione **5**[8], a more likely step than the alternative generation of the free aldehyde. Finally, bis-adduct **9** undergoes two succesive cyclizations, giving rise to the carbocyclic ring (**10**) and then the nitrogen ring, although an inverse order of steps cannot be ruled out.[9]



Scheme 1

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References and notes

Discussions leading to this work were started while R. A. was on sabbatical leave at the Departamento de Química Orgánica, Universidad Autónoma de Barcelona, 08193-Bellaterra (Barcelona), Spain. R. A. is grateful to Prof. M. Moreno for his hospitality there.

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3. Elnagdi, M.H.; Abdel-Motaleb, R. M.; Mustafa, M; Zayed, M. F.; Kamel, E. M., *J. Heterocyclic Chem.*, **1987**, *24*, 1677.
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5. A prismatic colorless single crystal measuring 0.23x0.20x0.07 mm was chosen for the X-Ray measurements, $C_{25}H_{20}N_4O_2$; monoclinic, C2/c, Z=8, with a = 14.266(1) A, b = 11.9442(4) A, c = 25.257(2) A, β = 96.94(1) A, v = 4272.1(3) A. Data collection: Automatic four circle diffrac-

tometer Philips PW 1100 with graphite oriented monochromated Cu-Kα radiation. The intensity data were collected using the ω/2θ scan mode between $2 < \theta < 65°$; two standard reflections were measured every 90 minutes with no intensity variation. A total of 3611 reflections were measured and 2682 were considered as observed ($I > 3\sigma$ (I) criterium). The data were corrected for Lorenz and Polarization effects. The structure was solved by direct methods using SIR88[10] and sucesive Fourier synthesis. H Atoms were included in mixed refinement; they were located from difference Fourier synthesis. A convenient weighting scheme was applied to obtain flat dependence in $\langle W\Delta^2F \rangle$ vs.$\langle F_o \rangle$ and $\langle \sin\theta/\lambda \rangle$.[11] Final R (Rw) value was 4.9 (5.7). Atomic scattering factors were taken from International Tables for X-Ray Crystallography[12] and calculations were performed using XTAL[13], XRAY80[14] and PARST[15]. Suplementary data available: List of atomics coordinates, thermal components, hydrogen paramenters, geometrical features and structure factors.

6. Correct analytical ($C_{25}H_{20}N_4O_2$) and mass spectral data (M^+408). ^{1}H-NMR (d_6-DMSO, 300 MHz, 50° C): δ= 8.0 (b, 2H, NH_2, dissapears upon addition of TFA), 7.1-7.4 (10H, m, arom.), 4.94 (1H, q, J=2Hz, CH), 4.48 (1H, s, CH), 2.09 (3H, d, J=2.0 Hz, CH_3), 1.90 (3H, s, CH_3CO). ^{13}C-NMR (d_6-DMSO with a trace of TFA, 100.6 MHz) (SFORD multiplicities): δ= 17.2 (q, CH_3), 29.7 (q,$\underline{C}H_3CO$), 48.1 (s, $\underline{C}$-CN), 50.0 (d, $\underline{C}$H-Ph), 50.8 (d, $\underline{C}$H-Ph), 52.0 (s, $\underline{C}$-CN), 115.2 (s, CN), 117.7 (s, CN), 128.3 (2C, arom.), 128.4 (2C, arom.), 129.2 (4C, arom.), 129.3 (2C, arom.), 130.5, 134.5, 135.1, 139.4 (s, =$\underline{C}$-CH_3; =$\underline{C}$-$COCH_3$; 2C, ipso phenyl carbons), 163.4, 168.1 (s, =C-NH_2; s, CO-N), 201.5 (s, CO). It should be pointed out that these analytical and spectral data, are compatible with structure **3**. In fact, assignement of the wrong structure **3** for our compound was actually based on these data, together with the structure of its precursor, pyran **1**.
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   In fact, when benzylidenemalononitrile (**6**) and 2,4-pentanedione (**7**)[16] are used as starting materials, azocine **4** is obtained together with the monocyclic pyran (**1**):

   6 + **7** → **4** + **1**

8. The mechanism depicts the formation of the stereoisomer actually isolated (as a racemate) as shown by the x-ray diffractogram.
9. An analogous process can be observed by reaction of **1** with benzylidenecyanoacetate, leading to ethoxycarbonyl substituted azocines similar to **4**. If, however, benzylidenemalonate is used, the lack of a cyano group prevents a similar cyclization.
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