Stereochemical Studies with Derivatives of Octahydro-2*H*-pyrido[1,2-*a*]-pyrazine

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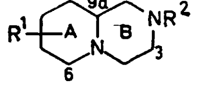
Some substituted octahydro-2-phenyl-2*H*-pyrido[1,2-*a*]pyrazin-4- and -3-ones have been synthesised and their configurations assigned on the basis of their i.r. and n.m.r. spectra. These lactams have been converted to the corresponding octahydro-2*H*-pyrido[1,2-*a*]pyrazines all of which preferentially adopt the *trans*-fused ring conformation. An examination of the i.r. spectra of the 3,3- and 4,4-dideuteriated derivatives of this latter system permits an evaluation of the relative contributions of the various C–H bonds α to nitrogen to Bohlmann band formation. The stereochemistry of the related octahydropyrido[2,1-*c*][1,4]oxazine system is discussed with reference to the 220 MHz n.m.r. spectra of some methyl substituted derivatives.

UNTIL the report [1,2] of hypotensive activity for some derivatives of octahydro-2*H*-pyrido[1,2-*a*]pyrazine (1), very little work had been reported [3-5] on this system. A variety of derivatives have now been described [6-10] and shown to possess a wide range of biological activity including muscle relaxing properties,[8] but the stereochemistry of the system has received only scant attention limited to the assignment of the predominance of the *trans*-fused ring conformation for (1; $R^1 = R^2 = H$) on the basis of the presence of Bohlmann bands in its i.r. spectrum [10] and in that of its 4-phenylthiourea derivative.[3] We therefore describe here the synthesis of some derivatives of (1) and the evaluation of the utility of the Bohlmann i.r. criterion and of the values of n.m.r. spectral parameters of protons adjacent to nitrogen in making configurational and conformational assignments in this system.

The biological activity possessed by certain 2-aryloctahydro-2*H*-pyrido[1,2-*a*]pyrazines [9] prompted the selection of systems (1; $R^1 = H$, $R^2 = Ph$)—(3; $R^1 = H$, $R^2 = Ph$) for this study, and a mixture of octahydro-2-phenyl-2*H*-pyrido[1,2-*a*]pyrazin-4- and -3-one was readily obtained by the reaction of 2-(*N*-phenylaminomethyl)piperidine [11] with ethyl chloroacetate. To test the influence, if any, of ring A substituents on the position of conformational equilibrium in these systems the two possible racemic diastereoisomeric 9-methyl derivatives of each of the systems (1)—(3) were also synthesised from the 3-methyl-2-(*N*-phenylaminomethyl)piperidines. These lactams were separated by column chromatography over alumina, and conversion to the substituted octahydro-2-phenyl-2*H*-pyrido[1,2-*a*]pyrazines was accomplished by reduction with lithium aluminium hydride. For comparison purposes, octahydro-2-t-butyl-2*H*-pyrido[1,2-*a*]pyrazin-3-one was prepared by the action of ethyl chloroacetate on 2-(*N*-t-butylaminomethyl)piperidine [12] followed by treatment of the resultant ethyl 2-(*N*-t-butylaminomethyl)piperidin-1-ylacetate with sodium in dry toluene. In order to assist the investigation into Bohlmann band absorption in the i.r. spectrum of (1), the 3,3- and 4,4-dideuterio-derivatives of (1) were prepared by reduction with lithium aluminium deuteride of the ketones (2) and (3) respectively, and in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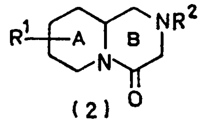
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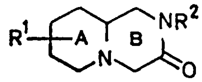
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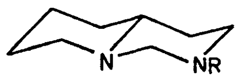
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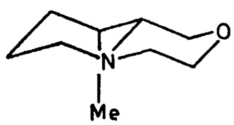
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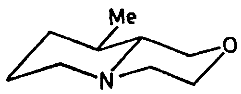
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this connection octahydropyrido[2,1-*c*][1,4]oxazine, its 9-methyl substituted derivatives and their 4,4-dideuteriated derivatives were also prepared.

RESULTS AND DISCUSSION

*Stereochemistry and Spectra of Octahydro-*2H*-pyrido-*[1,2-a]*pyrazin-*4*-ones* (2).—Examination of a Dreiding model of (2) incorporating a planar amido-group suggests as the preferred conformation of this lactam a

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4 K. Winterfield and G. Gierenz, *Chem. Ber.*, 1959, **92**, 240.
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7 A. R. Day and A. D. Lourie, U.S.P., 3,388,128/1968.
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11 T. A. Crabb and R. F. Newton, *J. Heterocyclic Chem.*, 1969, **6**, 301.
12 T. A. Crabb and R. F. Newton, *Tetrahedron*, 1968, **24**, 6327.

chair ring A and a half-chair ring B and the n.m.r. spectra of (2; R^1 = H or 9-Me, R^2 = Ph) are in accord with this. Thus in the n.m.r. spectrum of (2; R^1 = H, R^2 = Ph) 6*eq*-H absorbs as a ' doublet ' at δ 4·86 p.p.m. and the very low field absorption of this proton indicates that it lies in the plane of the amido-grouping.[13] The corresponding 6*ax*-H signals appear as a triplet of doublets at δ 2·13 p.p.m., showing the relatively large chemical shift difference between the C-6 methylene protons, characteristic of the octahydroquinolizin-4-one type of system.[14] The vicinal coupling constants involving the C-1 methylene protons ($J_{1ax,9a}$ 7·2, $J_{1eq,9a}$ 4·0 Hz) and the very negative value (−16·4 Hz) of the geminal coupling constant for the C-3 methylene protons are also evidence for the half-chair conformation for ring B in which the C-1 bonds deviate from axial and equatorial with a H–C-9a–C-1–H*ax*′ dihedral angle of <180°[15] and the lactam carbonyl group bisects the C-3 methylene group.[16]

Both 9-methyl compounds (2; R^1 = 9-Me, R^2 = Ph) show similar spectra to that of (2; R^1 = H, R^2 = Ph) indicating very similar conformations for all three compounds. The axial–equatorial nature of the methyl groups is shown by the ' shifts ' of the methyl group protons (centre of methyl group doublet at lower field for axial than for equatorial methyl group[17]) and the chemical shift of 9a-H which is sensitive to the orientation of a vicinal methyl group.[18]

It is well established that replacement of N–CH_2 by N–C(O) prevents participation of the nitrogen lone pair of electrons in Bohlmann band formation, but no work has been reported on the consequence of replacing N–CH_2 by N–Ph. In (2), the presence of the N–C-4(O) grouping will inhibit Bohlmann band formation from 6*ax*- and 9a-H, and any bands present in the 2800—2500 cm^{-1} region of the i.r. spectrum will arise from delocalisation involving the N-2 lone pair and 1*ax*′- and 3*ax*′-H. In fact, although the medium intensity band at 2810 cm^{-1} in the i.r. spectrum of (2) may possibly be a Bohlmann band, the absence of any bands in the 2800—2500 cm^{-1} region indicates that the nitrogen lone pair is not participating to any great extent in Bohlmann band formation, although the pseudoaxial nature of the C-1 and -3 protons in this conformation may be a contributory factor.

*Stereochemistry and Spectra of Octahydro-*2H*-pyrido-*[1,2-a]*pyrazin-*3*-ones* (3).—The i.r. and n.m.r. spectra of the octahydro-2*H*-pyrido[1,2-*a*]pyrazin-3-ones described in this paper provide evidence for their predominant existence in a *trans*-A : B ring fused conformation with a chair ring A and a half-chair ring B. Octahydro-2-phenyl-2*H*-pyrido[1,2-*a*]pyrazin-3-one and both 9-methyl compounds possess marked i.r. absorption bands in the 2800—2600 cm^{-1} region. Since the N–C(O) group prohibits participation of 1*ax*-H in the formation of Bohlmann bands, the observed bands must arise from the C-6–H*ax*, C-4–H*ax*′, and C-9a–H*ax* bonds and their presence confirms the *trans*-ring fusion. The Bohlmann bands in the i.r. spectrum of octahydro-2-t-butyl-2*H*-pyrido[1,2-*a*]pyrazin-3-one (3; R^1 = H,

N.m.r. spectra (CCl_4 solution) of [3,3-$^2H_2$]- and [4,4-$^2H_2$]-octahydro-2-phenyl-2*H*-pyrido[1,2-*a*]pyrazines and [4,4-$^2H_2$]octahydropyrido[2,1-*c*][1,4]oxazines

	Chemical shifts (δ/p.p.m.)							Coupling constants (*J*/Hz)					
Compound	1*eq*	1*ax*	3*eq*	3*ax*	6*eq*	Me [d]	Other	1*eq*,1*ax*	1*eq*,9a	1*ax*,9a	3*eq*,3*ax*	CH–Me [e]	1*eq*,3*eq*
[4,4-$^2H_2$]- (4) [a]	3·33	2·45	3·44	2·80	2·78			−11·1	2·4	10·0	−11·7		2·0
[4,4-$^2H_2$]- (1; R^2 = Ph, R^1 = 9*eq*-Me) [b]	3·62	2·35	3·36	2·76	2·74	0·90		−11·5	2·4	10·1	−11·5	6·0	1·8
[4,4-$^2H_2$]- (1; R^2 = Ph, R^1 = 9*ax*-Me) [b]	3·19	2·59	3·33	2·71	2·70	1·01	2·10 (9a) (d of t) [f]	−11·5	2·5	10·0	−11·5	7·0	2·5
(7) [c]	3·87	3·08	3·71	3·54	2·70	0·83	2·02 (6*ax*) (t of d) [g]	−11·0	2·5	10·0	−11·3	6·7	*ca.* 1·4
(6) [c]	3·49	3·31	3·70	3·53	2·74	0·97	2·07 (9a) 1·97 (6*ax*)	−11·0	3·5	10·5	−11·0	7·0	
	1*eq*	1*ax*	4*eq*	4*ax*	6*eq*	Me [d]	Other	1*eq*,1*ax*	1*eq*,9a	1*ax*,9a	4*eq*,4*ax*	CH–Me	1*eq*,3*eq*
[3,3-$^2H_2$]- (4) [a]	3·31	2·44	2·67	2·26	2·75			−11·1	2·5	10·1	−11·2		
[3,3-$^2H_2$]- (1; R^2 = Ph, R^1 = 9*eq*-Me) [b]	3·59	2·31	2·60	2·20	*ca.* 2·65	0·88		−11·6	3·0	10·1	−11·2	6·0	
[3,3-$^2H_2$]- (1; R^2 = Ph, R^1 = 9*ax*-Me) [b]	3·21	2·60	2·68	2·21	*ca.* 2·70	1·02	2·12 (9a) (d of t) [h]	−11·5	3·0	11·0	−11·1	6·8	

[a] 60 MHz. [b] 100 MHz. [c] 220 MHz. [d] Centre of Me doublet. [e] Apparent coupling constant. [f] First-order analysis of the 9a-H signal gave $J_{1ax,9a}$ 10·2, $J_{1eq,9a} = J_{9eq,9a}$ = 2·6 Hz. [g] $J_{6eq,6ax}$ −11·0, $J_{6ax,7ax}$ 11·0, $J_{6ax,7eq}$ 4·5 Hz. [h] First-order analysis of the 9a-H signal gave $J_{1ax,9a}$ 10·6, $J_{1eq,9a} = J_{9eq\,9a}$ = 3·0 Hz. s, d, and t Signify singlet, doublet, and triplet, respectively.

[13] T. H. Siddall and W. E. Stewart, *J. Mol. Spectroscopy*, 1967, **24**, 290.
[14] F. Bohlmann and D. Schumann, *Tetrahedron Letters*, 1965, 2435.
[15] M. Karplus, *J. Amer. Chem. Soc.*, 1963, **85**, 2870.
[16] M. Barfield and D. M. Grant, *J. Amer. Chem. Soc.*, 1963, **5**, 1899; R. C. Cookson, T. A. Crabb, J. J. Frankel, and J. Hudec, *Tetrahedron*, Supplement No. 7, 1966, 355.
[17] T. M. Moynehan, K. Schofield, R. A. Y. Jones, and A. R. Katritzky, *J. Chem. Soc.*, 1962, 2637.
[18] H. Booth, *Tetrahedron*, 1966, **22**, 615.

R^2 = Bu^t) are very similar to those of the corresponding 2-phenyl compound (3; R^1 = H, R^2 = Ph) and this observation confirms the existence of a similar geometry around the bridgehead nitrogen atom in both compounds.

In the 100 MHz (benzene solution) n.m.r. spectrum of (3; R^1 = H, R^2 = Ph) the C-4 methylene protons absorb as an AB quartet with J_{gem} −16·7 Hz, a value reconcilable only with a conformation possessing a near bisecting geometry between the plane of the lactam carbonyl group and the C-4 methylene protons.[16] The magnitudes (10·3 and 3·8 Hz) of the vicinal couplings between the C-1 methylene protons and 9a-H are consistent with *ax–ax* and *ax–eq* couplings arising from dihedral angles of *ca.* 180 and *ca.* 60° respectively as required by a half-chair perhydropyrazinone ring.

The configurations of the epimeric octahydro-9-methyl-2-phenyl-2*H*-pyrido[1,2-*a*]pyrazin-3-ones were assigned as described for the corresponding 4-oxo-compounds.

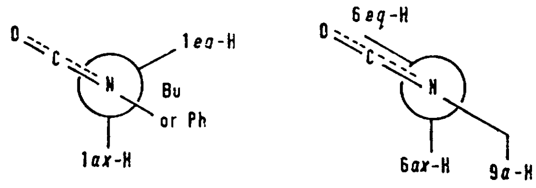
*Stereochemistry and Spectra of Octahydro-2-phenyl-*2H-*pyrido*[1,2-a]*pyrazines*.—The observation [10] of Bohlmann bands (2804, 2760, 2747, and 2660 cm^{-1}) in the i.r. spectrum (chloroform solution) of octahydro-2*H*-pyrido[1,2-*a*]pyrazine (1; R^1 = R^2 = H) indicates the predominance of the *trans*-fused conformation. This unsubstituted compound appears to be the only octahydro-2*H*-pyrido[1,2-*a*]pyrazine so far subjected to stereochemical studies.

Octahydro-2-phenyl-2*H*-pyrido[1,2-*a*]pyrazine (1; R^1 = H, R^2 = Ph) is expected to exist in the *trans*-fused ring conformation with an equatorial phenyl group (4), and in accord with this expectation is the appearance of marked Bohlmann bands (2815 and 2770 cm^{-1}) in the i.r. spectrum. In order to delineate more clearly the applicability of the Bohlmann criterion to such a system, it is necessary to evaluate the relative contributions to Bohlmann bands from the axial C–H bonds α to both the bridgehead nitrogen and the phenyl substituted nitrogen. Accordingly, the i.r. spectra of the [3,3-$^2H_2$]- and of the [4,4-$^2H_2$]-octahydro-2-phenyl-2*H*-pyrido[1,2-*a*]pyrazines were studied.

Replacement of the C-4 hydrogen atoms by deuterium in octahydro-2-phenyl-2*H*-pyrido[1,2-*a*]pyrazine causes the disappearance of the 2770 cm^{-1} band, and is accompanied by a drop in intensity of the 2815 cm^{-1} band and the appearance of a new band at 2785 cm^{-1}. Apart from the retention of some absorption at 2815 cm^{-1}, this behaviour is reminiscent of the changes in the i.r. spectrum of octahydro-4*H*-quinolizine caused by deuteriation at C-4,[19] which causes the two absorption bands at 2800 and 2761 cm^{-1} to be replaced by a single band at *ca.* 2780 cm^{-1}. In [4,4-$^2H_2$]octahydro-2-phenyl-2*H*-pyrido[1,2-*a*]pyrazine the medium intensity band at 2815 cm^{-1} probably arises from the C-1 and -3 methylene protons adjacent to N–Ph.

On going from (4) to the [3,3-$^2H_2$] compound, the positions of the main bands remain unaltered and only a small reduction in the intensities of the 2815, 2770, and 2680 cm^{-1} bands occurs. If the five axial C–H bonds α to nitrogen were contributing equally to Bohlmann band formation, then deuteriation at the 3-position should reduce the total intensity by one fifth. The small observed reduction in intensity indicates that 1-H*ax* and 3-H*ax* give rise to only weak Bohlmann bands. The methyl substituted derivatives of (4) show similar changes in their i.r. spectra on deuteriation.

Surprisingly, the values of J_{gem} for the C-1 methylene protons in octahydro-2-t-butyl- (−11·2 Hz) and in the -2-phenyl-2*H*-pyrido[1,2-*a*]pyrazin-3-ones (−11·6 Hz) are closer to $J_{4eq,4ax}$ in octahydro-4*H*-quinolizine (−11·3 Hz) [20] than to $J_{6eq,6ax}$ in (2; R^2 = Ph) (−13·2 Hz), although the C-6 methylene protons in the latter system



(3) (2)

FIGURE Relative orientations of methylene protons to lactam group in compounds (3) and (2)

are adjacent to lactam nitrogen as are the C-1 methylene protons in (3; R^2 = Ph) and (3; R^1 = H, R^2 = Bu^t). However, whilst the nitrogen lone pair in the perhydropyrazin-3- and -4-ones is involved in the lactam grouping, this group considered as a whole is differently situated with respect to the methylene group protons in these two systems (Figure), and the magnitude of the inductive and hyperconjugative removal of electrons from the methylene group molecular orbitals will be different. In (3) the dihedral angle, ϕ, between the π bond of the lactam grouping and the methylene group is 30°, corresponding [16] to a maximum negative contribution to J_{gem} and in (2) ϕ is 90° corresponding to a nil contribution to J_{gem}. This prediction based upon the Barfield–Grant model and treating the N–C bond of the lactam group as a π bond leads therefore to an expected J_{gem} of of *ca.* −15 Hz for (3) and *ca.* −11 Hz for (2) which is directly at variance with the observed value.

In CH_2–C–X systems where X is an electron-withdrawing substituent, X will make a positive contribution to J_{gem} when it is gauche to both C–H bonds and a negative contribution when one of the C–H bonds is parallel to it.[21] If the system CH_2–N–CO is considered as an analogue of CH_2–C–X then C=O is an electronegative β substituent and the observed J_{gem} values in (3) and (2) may accordingly be rationalised.

In the n.m.r. spectrum of [4,4-$^2H_2$]octahydro-2-phenyl-2*H*-pyrido[1,2-*a*]pyrazine, a broad doublet at

[19] J. Skolik, P. J. Krueger, and M. Wiewiorowski, *Tetrahedron*, 1968, **24**, 5439.

[20] R. Cahill, T. A. Crabb, and R. F. Newton, *Org. Magnetic Resonance*, 1971, **3**, 263.

[21] J. A. Pople and A. A. Bothner-By, *J. Chem. Phys.*, 1965, **42**, 1339; A. A. Bothner-By, *Adv. Magnetic Resonance*, 1965, **1**, 195.

δ 2·78 p.p.m. was assigned to 6*eq*-H. This value is typical of an equatorial proton adjacent to nitrogen in a chair conformation (*cf.* δ 2·85 p.p.m. in octahydro-4*H*-quinolizine). 3*eq*- And 1*eq*-H absorb at lower field (*ca.* 0·5 p.p.m.) than 6*eq*-H since the former protons have lost the shielding effect of the C-4 methylene group, and in addition are subject to the influence of the aromatic ring (*cf.* δ 2·71 p.p.m. for the methyl group protons in dimethylaniline). Coupling constants of −11·7 and −11·1 Hz were observed for the C-3 and C-1 methylene protons respectively, and these values are close to that of $J_{4eq,4ax}$ (−11·3 Hz) [19] in octahydro-4*H*-quinolizine. Thus the effect on J_{gem} of the adjacent N–Ph group is small, and this implies that the phenyl group must be at right angles to the plane of the perhydropyrazine ring, preventing conjugation with the nitrogen lone pair of electrons. In contrast, J_{gem} for the C-1 methylene protons in octahydro-2*H*-pyrido[1,2-*c*]pyrimidine (5) [22] is −8·4 Hz when R = Me and becomes −2·1 Hz more negative (−10·5 Hz) when R = Ph, suggesting that in this 1,3-hetero-system, the phenyl group is orientated so as to allow overlap of the nitrogen lone pair with the aromatic ring orbitals.

The vicinal couplings between the C-1 methylene protons 9a-H (10·0 and 2·4 Hz) in [4,4-$^2H_2$]octahydro-2-phenyl-2*H*-pyrido[1,2-*a*]pyrazine are in accord with *ax–ax* and *ax–eq* couplings expected for a chair perhydropyrazine ring conformation, as is the observed long range coupling (2 Hz) between 1*eq*- and 3*eq*-H, since in the chair a planar **W** pathway connects these protons. As expected 1*eq*-H is not long range coupled when 3*eq*-H is replaced by deuterium in [3,3-$^2H_2$]-octahydro-2-phenyl-2*H*-pyrido[1,2-*a*]pyrazine. In the spectrum of the latter compound, the C-4 methylene protons absorb as an AB quartet at δ 2·67 and 2·27 p.p.m. with J_{gem} −11·2 Hz (*cf.* δ 2·85 and 2·03 p.p.m., J_{gem} −11·3 Hz for the C-4 methylene protons in octahydro-4*H*-quinolizine), and the 4*ax*-H signals are somewhat broadened consistent with vicinal *ax–ax* H–D coupling.

If the methyl substituted pair of compounds (1; R^1 = 9*ax*- or 9*eq*-Me, R^2 = Ph) are both *trans*-fused and in chair conformations, the *syn* axial arrangement of 9-Me and 1*ax*-H in the axially substituted compound will cause 1*ax*-H to absorb at lower field (up to 0·25 p.p.m.) [18] than in (1; $R^1 = R^2$ = H) and the equatorial 9-Me group in its epimer will cause 1*eq*-H to absorb at lower field (*ca.* 0·47 p.p.m.) than in (1; $R^1 = R^2$ = H). Examination of the n.m.r. spectra (Experimental section) in fact shows these chemical shift differences which confirms the *trans*-fused ring conformation for both compounds. In addition the centre of the methyl doublet is at lower field with a large apparent coupling constant in the case of the axially substituted compound.

Stereochemistry and Spectra of Octahydropyrido[2,1-*c*]-[1,4]*oxazines*.—220 MHz spectra were obtained for the 4,4-dideuterio-derivatives of the pair of compounds (6) and (7). Comparison of the chemical shifts of the C-1 protons in these compounds shows the deshielding of 1*ax*-H in (6) and of 1*eq*-H in (7) to be 0·23 and 0·38 p.p.m. respectively, relative to the unsubstituted compound proving the existence of both isomers in the two-chair *trans*-fused conformations (6) and (7). The 1*eq*-H proton in (6) is long range coupled (*ca.* 1·4 Hz), presumably to 3*eq*-H, although this is not obvious from the spectrum. The angular 9a-H in (6) is shielded by the adjacent equatorial methyl group, and the 9a-H signal, along with the signals of three other protons (probably 7*eq*-, 8*eq*-, and 9*ax*-H) formed a multiplet at *ca.* δ 1·65 p.p.m. (4H). However in (6) first-order analysis of the doublet of triplets at δ 2·07 p.p.m. arising from 9*ax*-H was possible, and gave vicinal couplings between 9a-H and 9*ax*-, 9*eq*, and 1*eq*-H of 11, 3, and 3 Hz, consistent with the two-chair *trans*-fused conformation.

Both compounds showed a ' doublet ' and a triplet of doublets at *ca.* δ 2·72 and 2·0 p.p.m. which were assigned to 6*eq*- and 6*ax*-H (J_{gem} −11·0 Hz) respectively (*cf.* δ 2·85 and 2·03 p.p.m. in octahydro-4*H*-quinolizine). The C-3 methylene proton signals in both compounds absorbed as AB quartets [J_{gem} −11·0 in (6) and −11·3 Hz in (7)], and the signals comprising the high-field half of the quartet in each case showed evidence of further splitting, consistent with *ax–ax* H–D vicinal couplings. Thus the high field signals must arise from 3*ax*-H. In (7), the methyl doublet was at higher field (δ 0·83 p.p.m.) and showed a smaller apparent coupling constant ('J'$_{CH-Me}$ 6·7 Hz) than in the axial epimer (δ 0·97 p.p.m.; 'J'$_{CH-Me}$ 7 Hz) confirming the assigned stereochemistry.

Replacement of 4-H by deuterium in (6) and (7) results in the replacement of the 2810 and 2760 cm^{-1} bands present in the i.r. spectra of (6) and (7) by a band at 2785—2790 cm^{-1}.

Conclusions.— Octahydro-2-phenyl-2*H*-pyrido[1,2-*a*]-pyrazin-4-one and the isomeric 9-substituted derivatives adopt a conformation with the piperidine ring in a chair conformation and the morpholinone ring in a half-chair conformation, such that the plane of the lactam carbonyl group bisects the C-3 methylene group and 6*eq*-H lies in the lactam plane. The substituted octahydro-2*H*-pyrido[1,2-*a*]pyrazin-3-ones exist in *trans*-fused ring conformations with the amido-containing ring in a half-chair conformation with the lactam plane bisecting the C-4 methylene group. In these two compounds the magnitude of J_{gem} for the methylene group protons adjacent to the lactam nitrogen is dependent upon the orientation of the lactam carbonyl group with respect to the methylene group.

The Bohlmann i.r. criterion is clearly applicable to all the systems studied, but in the case of the octahydro-2-phenyl-2*H*-pyrido[1,2-*a*]pyrazin-4-ones a band at *ca.* 2815 cm^{-1} must arise from the C-1 and -3 methylene protons adjacent to the nitrogen atom bearing the phenyl group. Thus unlike methylene protons adjacent to an N–C(O) group which do not give rise to Bohlmann bands, protons adjacent to N–Ph do give rise to weak

[22] T. A. Crabb and R. F. Newton, *Tetrahedron*, 1970, **26**, 701.

bands on the limit of the Bohlmann band region. Replacement of 4-H by deuterium in octahydropyrido-2*H*-pyrido[1,2-*a*]pyrazine and its methyl substituted derivatives, and in the analogous octahydropyrido-[2,1-*c*][1,4]oxazines, results in changes in the 2800—2500 cm^{-1} region of the i.r. spectra similar to those which occur in octahydro-4*H*-quinolizine, supporting the existence of similar *trans*-fused two-chair conformations for the 1,4-hetero-systems and the n.m.r. spectral data is also in accord with this stereochemistry.

EXPERIMENTAL

Elemental analyses were carried out by Drs. F. Pascher and E. Pascher, Microanalytical Laboratory, Bonn, Germany. M.p.s are uncorrected. I.r. spectra were recorded on a Perkin-Elmer 457 grating instrument, and measured as 0·2M solutions in carbon tetrachloride using 0·2 mm matched cells. The n.m.r. spectra were recorded on Perkin-Elmer R.10, JEOL 100, and Varian T.60, HA-100 and HR-220 spectrometers as 10% solutions in carbon tetrachloride or benzene solution using tetramethylsilane as internal reference.

*Octahydro-2-t-butyl-*2H-*pyrido*[1,2-*a*]*pyrazin-3-one*.— 2-(*N*-t-Butylaminomethyl)piperidine [12] (12·8 g) was heated at 120—125° with ethyl chloroacetate (11 g) for 2 h. The cooled solution was basified with saturated aqueous sodium carbonate solution and was extracted with chloroform three times. The extracts were dried (Na_2SO_4), concentrated and the residue was distilled *in vacuo* to give ethyl 2-(*N*-t-butylaminomethyl)piperidin-1-ylacetate (5·5 g) as an oil, b.p. 94° at 0·2 mmHg. This ester (5 g) was dissolved in dry toluene (50 ml), and sodium (0·15 g) was added. The solution was refluxed until the sodium had dissolved, and toluene was then slowly distilled with continuous addition of further dry toluene until 350 ml had distilled. The remaining toluene was removed under reduced pressure, and the residue was distilled *in vacuo* to give the ketone as an oil, b.p. 144° at 4 mmHg, which solidified on standing at room temperature, $\nu_{max.}$ (CCl_4) 2795 (ε 79), 2755 (59), 2700 (18) and 1650 cm^{-1} (C=O). δ (100 MHz; CCl_4) 3·19 and 2·89 (1*eq*- and 1*ax*-H, $J_{1eq,1ax}$ −11·5, $J_{1ax,9a}$ 10·3, and $J_{1eq,9a}$ 3·8 Hz), 3·16 and 2·56 (4*eq*- and 4*ax*-H, $J_{4eq,4ax}$ −16·2 Hz), and 2·77 p.p.m. (6*eq*-H). The solid rapidly darkened on exposure to air, but was stable under nitrogen at −40°. It formed a *picrate*, m.p. 189—190° (Found: C, 49·2; H, 5·8; N, 15·6. $C_{18}H_{25}N_5O_8$ requires C, 49·2; H, 5·75; N, 15·95%).

*Synthesis of Substituted Octahydro-2-phenyl-*2H-*pyrido*-[1,2-a]*pyrazin-4- and -3-ones.—General procedure*. The appropriate 2-(*N*-phenylaminomethyl)piperidine [11] (0·05M) and ethyl chloroacetate (7·5 g, 0·06M) were heated under reflux for 10 h. The cooled solution was basified with saturated aqueous sodium carbonate solution, and was extracted with chloroform three times. The extracts were dried (Na_2SO_4) and concentrated. The residue (either crude or after distillation) containing a mixture of the required lactams was chromatographed over alumina (Woelm neutral, activity II), using benzene as eluant. The bridgehead lactam (perhydropyrazin-4-one) was the first compound to come off the column, and the perhydropyrazin-3-one was obtained on further elution with benzene followed by ether. The following compounds were obtained: *octahydro-2-phenyl-*2H-*pyrido*[1,2-a]*pyrazin-4-one*, m.p. 105—106° (Found: C, 72·8; H, 7·85; N, 12·3. $C_{14}H_{18}N_2O$ requires C, 73·0; H, 7·9; N, 12·15%), $\nu_{max.}$ 2810 (ε 43) and 1655 cm^{-1} (C=O), δ (100 MHz; C_6H_6) 3·17 and 2·58 (1*eq*- and 1*ax*-H, $J_{1eq,1ax}$ −11·9, $J_{1ax,9a}$ 7·2, and $J_{1eq,9a}$ 4·0 Hz), 3·88 and 3·62 (3*eq*- and 3*ax*-H, $J_{3eq,3ax}$ −16·4 Hz), and 4·86 and 2·13 p.p.m. (6*eq*- and 6*ax*-H, $J_{6eq,6ax}$ −13·2, $J_{6ax,7ax}$ 8·8, and $J_{6ax,7eq}$ 3·6 Hz); *octahydro-2-phenyl-*2H-*pyrido*[1,2-a]*pyrazin-3-one*, m.p. 77° (Found: C, 73·2; H, 7·9; N, 12·0%), $\nu_{max.}$ 2795 (ε 74), 2750 (51), 2660 (18), and 1670 cm^{-1} (C=O), δ (100 MHz; C_6H_6) 2·90 and 3·24 (1*eq*- and 1*ax*-H, $J_{1eq,1ax}$ −11·2, $J_{1ax,9a}$ 10·2, and $J_{1eq,9a}$ 3·5 Hz), 3·55 and 2·81 (4*eq*- and 4*ax*-H, $J_{4eq,4ax}$ −16·7 Hz), and 2·55 p.p.m. (6*eq*-H); cis(9-H,9a-H)-*octahydro-9-methyl-2-phenyl-*2H-*pyrido*[1,2-a]*pyrazin-4-one*, b.p. 170—174° at 0·05 mmHg (Found: C, 73·6; H, 8·15; N, 11·55. $C_{15}H_{20}N_2O$ requires C, 73·75; H, 8·25; N, 11·45%), $\nu_{max.}$ 2810 (ε 42) and 1675 cm^{-1} (C=O), δ (60 MHz; C_6H_6) *ca.* 3·0 (1*eq*- and 1*ax*-H), 3·73 (s, 3*eq*- and 3*ax*-H), and 4·82 and 2·20 p.p.m. (6*eq*- and 6*ax*-H, $J_{6eq,6ax}$ −12·7 and $J_{6ax,7ax}$ 8·8 Hz); cis(9-H,9a-H)-*octahydro-9-methyl-2-phenyl-*2H-*pyrido*[1,2-a]*pyrazin-3-one*, b.p. 145—147° at 0·01 mmHg (Found: C, 74·0; H, 8·4; N, 11·45%), $\nu_{max.}$ 2795 (ε 67), 2750 (50), 2710 (16), 2660 (13), and 1675 cm^{-1} (C=O). δ (60 MHz; C_6H_6) 2·87 and 3·56 (1*eq*- and 1*ax*-H, $J_{1eq,1ax}$ −11·6, $J_{1ax,9a}$ 10·9, and $J_{1eq,9a}$ 4·0 Hz), 3·57 and 3·0 (4*eq*- and 4*ax*-H, $J_{4eq,4ax}$ −17·0 Hz), and 2·60 p.p.m. (6*eq*-H); trans(9-H,9a-H)-*octahydro-9-methyl-2-phenyl-*2H-*pyrido*[1,2-a]*pyrazin-4-one*, m.p. 91—92° (Found: C, 73·8; H, 8·3; N, 11·5%), $\nu_{max.}$ 2810 (ε 40) and 1655 cm^{-1} (C=O), δ (100 MHz; C_6H_6) 3·23 and 2·76 (1*eq*- and 1*ax*-H, $J_{1eq,1ax}$ −12·8, $J_{1ax,9a}$ 7·0, and $J_{1eq,9a}$ 4·3 Hz), 3·80 and 3·60 (3*eq*- and 3*ax*-H, $J_{3eq,3ax}$ −16·4 Hz), and 4·86 and 2·06 p.p.m. (6*eq*- and 6*ax*-H, $J_{6eq,6ax}$ −13·0 Hz); and trans(9-H,9a-H)-*octahydro-9-methyl-2-phenyl-*2H-*pyrido*[1,2-a]*pyrazin-3-one*, b.p. 150° at 0·05 mmHg (Found: C, 73·95; H, 8·5; N, 11·5%), $\nu_{max.}$ 2795 (ε 70), 2750 (54), 2705 (15), 2660 (14), and 1670 cm^{-1} (C=O), δ (100 MHz; C_6H_6) 3·28 (1*eq*- and 1*ax*-H), 3·57 and 2·83 (4*eq*- and 4*ax*-H, $J_{4eq,4ax}$ −16·9 Hz), and 2·50 p.p.m. (6*eq*-H).

*Synthesis of Methyl-substituted Octahydro-2-phenyl-*2H-*pyrido*[1,2-a]*pyrazines, their* 3,3- *and* 4,4-*Dideuterio-derivatives, and Octahydropyrido*[2,1-c]*oxazines and their* 4,4-*Dideuterio-derivatives.—General procedure*. The appropriate lactam (0·0025M) in dry ether (10 ml) was added dropwise to a stirred solution of lithium aluminium hydride or deuteride (0·005M) in dry ether (50 ml). The solution was refluxed gently for 2 h, and cooled. Water was carefully added, followed by aqueous sodium hydroxide. The ether layer was decanted, and the aqueous layer was extracted three times with ether. The combined ethereal solutions were dried (Na_2SO_4), concentrated, and the residue was distilled *in vacuo* to give the required product in almost quantitative yield: *octahydro-2-phenyl-*2H-*pyrido*[1,2-a]*pyrazine*, b.p. 116° at 0·1 mmHg (Found: C, 77·6; H, 9·25; N, 12·8. $C_{14}H_{20}N_2$ requires C, 77·75; H, 9·3; N, 12·95%), $\nu_{max.}$ 2815 cm^{-1} (ε 105), 2770 (70), and 2680 cm^{-1} (20), [4,4-$^2H_2$]*octahydro-2-phenyl-*2H-*pyrido*-[1,2-a]*pyrazine*, b.p. 120° at 0·2 mmHg (Found: C, 76·7; H, 9·75; N, 12·7. $C_{14}H_{18}D_2N_2$ requires C, 77·0; H, 10·15; N, 12·85%), $\nu_{max.}$ 2815 (ε 73), 2785 (72), and 2735 cm^{-1} (28); [3,3-$^2H_2$]*octahydro-2-phenyl-*2H-*pyrido*[1,2-a]*pyrazine*, b.p. 130° at 0·5 mmHg (Found: C, 76·5; H, 10·0: N, 12·65%), $\nu_{max.}$ 2815 (ε 80), 2770 (55), and 2680 cm^{-1} (18); cis(9-H,9a-H)-*octahydro-9-methyl-2-phenyl-*2H-*pyrido*[1,2-a]-*pyrazine*, b.p. 138° at 0·75 mmHg (Found: C, 78·0;

H, 9·55; N, 12·05. $C_{15}H_{22}N_2$ requires C, 78·2; H, 9·65; N, 12·15%), $\nu_{max.}$ 2815 (ε 81), 2765 (66), and 2680 cm^{-1} (45); cis(9-H,9a-H)-[4,4-$^2H_2$]*octahydro*-9-*methyl*-2-*phenyl*-2H-*pyrido*[1,2-a]*pyrazine*, b.p. 178° at 6 mmHg (Found: C, 77·3; H, 10·1; N, 11·9. $C_{15}H_{20}D_2N_2$ requires C, 77·55; H, 10·4; N, 12·05%), $\nu_{max.}$ 2790 (ε 98), 2740 (35), and 2710 cm^{-1} (34), cis(9-H,9a-H)-[3,3-$^2H_2$]*octahydro*-9-*methyl*-2-*phenyl*-2H-*pyrido*[1,2-a]*pyrazine*, b.p. 118° at 0·4 mmHg (Found: C, 77·4; H, 10·05; N, 11·9%), $\nu_{max.}$ 2810 (ε 75), 2760 (73), and 2670 cm^{-1} (45); trans(9-H,9a-H)-*octahydro*-9-*methyl*-2-*phenyl*-2H-*pyrido*[1,2-a]*pyrazine*, b.p. 115° at 0·06 mmHg (Found: C, 78·05; H, 9·45; N, 12·1. $C_{15}H_{22}N_2$ requires C, 78·2; H, 9·65; N, 12·15%), $\nu_{max.}$ 2815 (ε 127), 2770 (80), and 2680 cm^{-1} (25); trans(9-H,9a-H)-[4,4-$^2H_2$]*octahydro*-9-*methyl*-2-*phenyl*-2H-*pyrido*[1,2-a]*pyrazine*, b.p. 166—168° at 5 mmHg (Found: C, 77·25; H, 10·0; N, 12·0%), $\nu_{max.}$ 2790 (ε 80), 2740 (30), and 2710 cm^{-1} (35); trans(9-H,9aH)-[3,3-$^2H_2$]*octahydro*-9-*methyl*-2-*phenyl*-2H-*pyrido*[1,2-a]*pyrazine*, b.p. 116—120° at 0·2 mmHg (Found: C, 77·4; H, 10·2; N, 12·1%), $\nu_{max.}$ 2810 (ε 105), 2760 (80), and 2670 cm^{-1} (43); cis(9-H,9a-H)-*octahydro*-9-*methylpyrido*[2,1-c][1,4]*oxazine*, b.p. 56° at 1·5 mmHg, $\nu_{max.}$ 2810 (ε 80), 2760 (80), and 2680 cm^{-1} (28). *Picrate*, m.p. 193—194° (Found: C, 46·65; H, 5·05; N, 14·2. $C_{15}H_{20}N_4O_8$ requires C, 46·85; H, 5·25; N, 14·6%); cis(9-H,9a-H)-[4,4-$^2H_2$]*octahydro*-9-*methylpyrido*[2,1-c]-[1,4]*oxazine*, b.p. 50° at 1 mmHg, $\nu_{max.}$ 2785 (ε 80), 2735 (35), and 2700 cm^{-1} (30). *Picrate*, m.p. 193—194° (Found: C, 46·65; H, 5·25; N, 14·35. $C_{15}H_{18}D_2N_4O_8$ requires C, 46·65; H, 5·75; N, 14·5%); trans(9-H,9a-H)-*octahydro*-9-*methylpyrido*[2,1-c][1,4]*oxazine*, b.p. 60° at 2·5 mmHg, $\nu_{max.}$ 2810 (ε 80), 2760 (61), and 2675 cm^{-1} (48). *Picrate* m.p. 189—191° (decomp.) (Found: C, 46·8; H, 5·35; N, 14·3%); trans(9-H,9a-H)-[4,4-$^2H_2$]*octahydro*-9-*methylpyrido*[2,1-c][1,4]*oxazine*, b.p. 62° at 4 mmHg, $\nu_{max.}$ 2790 (ε 63) and 2715 cm^{-1} (28). *Picrate*, m.p. 188—190° (decomp.) (Found: C, 46·9; H, 5·4; N, 14·45%); [1,4,4-$^2H_3$]*octahydropyrido*[2,1-c][1,4]*oxazine*, b.p. 72° at 15 mmHg, $\nu_{max.}$ 2790 (ε 73), 2720 (29), and 2695 cm^{-1} (21). *Picrate*, m.p. 205—206° (Found: C, 44·9; H, 5·6; N, 13·85. $C_{14}H_{15}D_3N_4O_8$ requires C, 45·05; H, 5·65; N, 14·0%); cis(6-H,9a-H)-[1,4,4-$^2H_3$]*octahydro*-9-*methylpyrido*[2,1-c][1,4]*oxazine*, b.p. 83° at 12 mmHg, $\nu_{max.}$ 2790 (ε 60), 2715 (25), and 2700 cm^{-1} (20). *Picrate*, m.p. 204—206° (decomp.) (Found: C, 46·85; H, 5·45; N, 14·35. $C_{15}H_{17}D_3N_4O_8$ requires C, 46·5; H, 6·0; N, 14·45%); *octahydro*-1H-*pyrido*[1,2-d][1,4]*oxazepine*, b.p. 90° at 12 mmHg, $\nu_{max.}$ 2815 (ε 56), 2770 (70), 2710 (48), and 2690 cm^{-1} (45). *Picrate*, m.p. 160—161° (Found: C, 46·9; H, 5·6; N, 14·8. $C_{15}H_{20}N_4O_8$ requires C, 46·85; H, 5·25; N, 14·6%); [5,5-$^2H_2$]*octahydro*-1H-*pyrido*[1,2-d]-[1,4]*oxazepine*, b.p. 84° at 10 mmHg, $\nu_{max.}$ 2785 (ε 70), 2740 (35), 2710 (33), and 2690 cm^{-1} (18). *Picrate*, m.p. 160—161° (Found: C, 46·45; H, 5·65; N, 14·75. $C_{15}H_{18}D_2N_4O_8$ requires C, 46·65; H, 5·75; N, 14·5%).

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