Tetrahedron Vol. 44, No. 12, pp. 3531 to 3538, 1988
Printed in Great Britain.

0040-4020/88 $3.00 + .00

THE SYNTHESIS AND CHEMISTRY OF AZOLENINES.[1] PART 12.[2] ISOLATION OF INTERMEDIATE 2-HYDROXY-3,4-DIHYDRO-2*H*-PYRROLES IN THE PAAL-KNORR 1*H*-PYRROLE SYNTHESIS.[3]

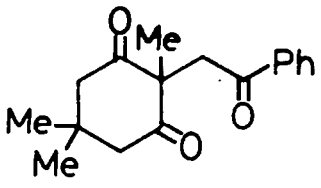
PAK-KAN CHIU AND MICHAEL P. SAMMES*

Department of Chemistry, University of Hong Kong,
Pokfulam Road, Hong Kong.

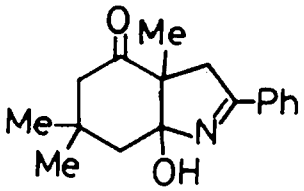
(*Received in Japan* 28 *January* 1988)

ABSTRACT — Treatment of 1,4-diketones with liquid ammonia gives high yields of isolable 2-hydroxy-3,4-dihydro-2*H*-pyrrole intermediates. These intermediates, which do not appear to have been observed previously in the Paal-Knorr synthesis with ammonia, have been fully characterized by i.r. and ^{1}H and ^{13}C n.m.r. spectroscopy; in most cases they decompose quantitatively into 1*H*-pyrroles on standing. The intermediate from hexane-2,4-dione may also be prepared using concentrated aqueous ammonia.

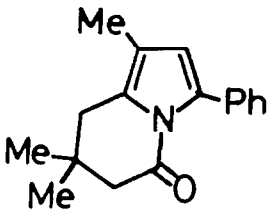
During an attempt to prepare the little-known 3*H*-pyrrole ring system *via* the Paal-Knorr reaction, the 1,4-diketone (1) was treated with liquid ammonia to give the stable intermediate 2-hydroxy-3,4-dihydro-2*H*-pyrrole (hydroxypyrroline) (2), which, on attempted dehydration, gave not a 3*H*-pyrrole but the isomeric 1*H*-pyrrole (3).[4]



(1)

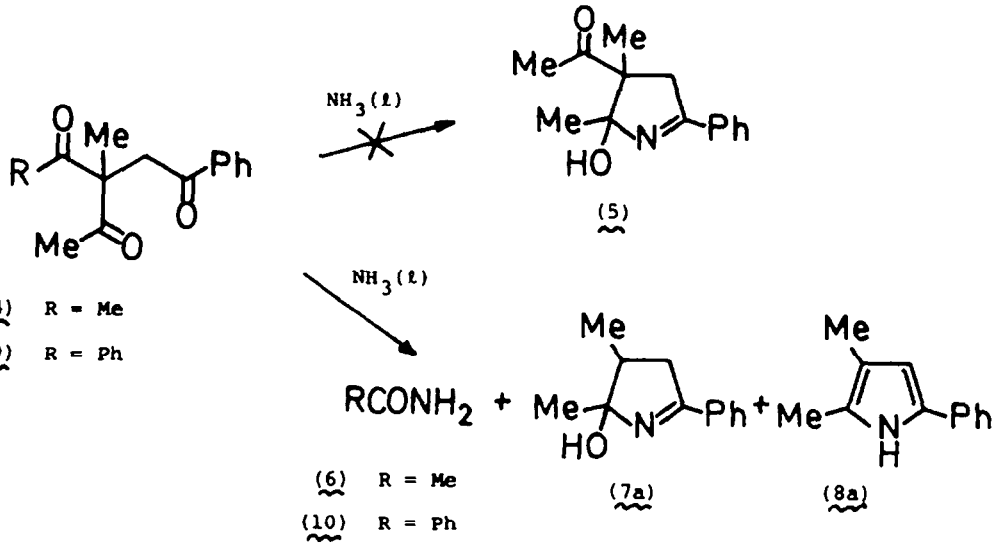


(2)



(3)

In the belief that the rearrangement (2) → (3) was mediated by transannular interaction within a nine-membered ring,[4] the open-chain analogue (4) of (1) was prepared for conversion into the corresponding analogue (5) of the hydroxypyrroline (2), which was not expected to rearrange on dehydration. Treatment of the triketone (4) with liquid ammonia, however, yielded not the expected product (5), but rather a mixture (10:1:9 by ^{1}H NMR) of acetamide (6), the 1*H*-pyrrole (8a) and what appeared to be mixed diastereomers of the hydroxypyrroline (7a).[5] Similarly, the triketone (9) gave benzamide (10), and the same additional products, in a ratio of 10:2:8. In both cases, the mixed isomers (7a) were observed by ^{1}H NMR to decompose during a few days, with concomitant formation of the 1*H*-pyrrole (8a).



(4) R = Me
(9) R = Ph

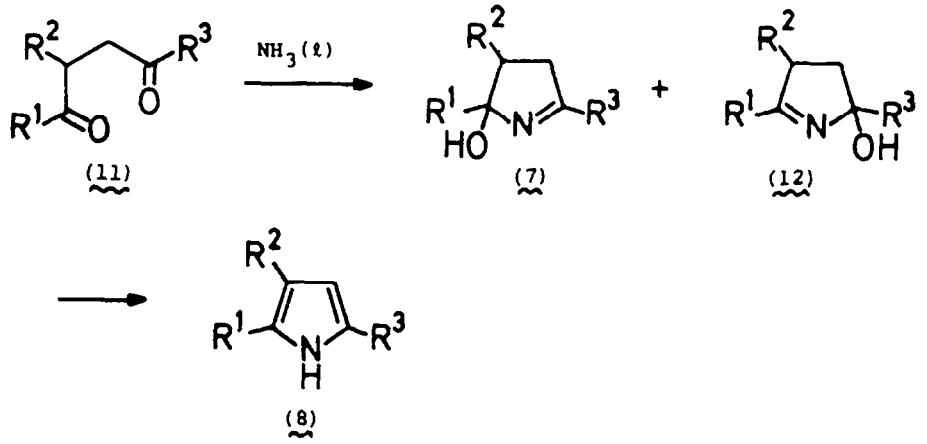
(5)

(6) R = Me
(10) R = Ph

(7a)

(8a)

The observation of the hydroxypyrrolines (7a), formed presumably *via* C-acyl cleavage of the triketones (4) and (9), suggested that compounds of this type might be isolable intermediates in the classical Paal-Knorr reaction between simple 1,4-diketones and ammonia. While analogous hydroxypyrrolines have been prepared by rearrangement of certain oximes and converted subsequently into 1*H*-pyrroles,[6,7] they do not appear to have been observed previously in Paal-Knorr reactions involving ammonia; however, they have been *implied* as intermediates, but without any supporting evidence.[8]



(11)

(7)

(12)

(8)

	R^1	R^2	R^3		R^1	R^2	R^3
a	Me	Me	Ph	e	$(CH_2)_4$		Me
b	Me	H	Me	f	$(CH_2)_4$		Ph
c	Me	H	Ph	g	Me	Ph	Ph
d	Ph	H	Ph				

Hexane-2,4-dione (11b) was thus dissolved in liquid ammonia, which was allowed to evaporate overnight. Examination of the oily residue by ^{1}H NMR ($CDCl_3$) showed that the diketone had been converted quantitatively into a mixture of the hydroxypyrroline (7b) (85%) and the 1*H*-pyrrole (8b) (15%); after 48 h in the NMR tube, all had been transformed into the 1*H*-pyrrole.
Several variously substituted 1,4-diketones were treated similarly with liquid ammonia, and the results are summarized in Table 1.

TABLE 1

Product ratio (from ^{1}H NMR)

Ketone	(7)	(12)	(8)	Comment
(4)	9	0	1	$MeCONH_2$ (10 pts.) also formed
(9)	8	0	2	$PhCONH_2$ (10 pts.) also formed
(11b)	17		3	
(11c)	19	0	2	
(11d)	0		0	Ketone recovered unchanged
(11e)	6	19	trace	
(11f)	1	20	trace	NH_4Cl added as catalyst
(11g)	9	0	1	

With the exception of (11d), which is known to undergo the Paal-Knorr reaction only with difficulty,[9] all diketones were converted in high yields into hydroxypyrrolines, together with small amounts of the corresponding 1*H*-pyrroles (8). For the diketone (11f), however, reaction occurred only after the addition of ammonium chloride as an acid catalyst. Where $R^2 \neq H$ or $R^1 \neq R^3$, two regioisomeric products (7) and (12) may be formed, and for $R^2 \neq H$ mixed diastereomers are possible. In practice, two regioisomers were observed only from (11e) and (11f), but mixed diastereomers were found among all products except (7e) and (7f), where presumably only that with *cis*-fused rings was formed to a measurable extent. Due to the instability of the hydroxypyrrolines, it was generally not possible to separate the mixed isomers, or to free them from the small amounts of 1*H*-pyrroles. However, (7c) was obtained pure, as was the mixture of diastereomers (12f), by recrystallisation, while washing with benzene freed the mixed diastereomers (7g) from the 1*H*-pyrrole.

The hydroxypyrrolines were characterised by IR (Table 2), ^{1}H NMR (Table 3), and ^{13}C NMR (Table 4); bands due to 1*H*-pyrrole contaminants were readily identifiable from the spectra of pure samples.

TABLE 2

IR Data (cm^{-1}) for hydroxypyrrolines (7) and (12)

Compound	Medium	ν_{OH}	$\nu_{C=N}$	ν_{C-O}
(7a)	Nujol	3190	1615	1115
(7b)	Film	3270	1645	1110
(7c)	Nujol	3190	1610	1120
(7e) & (12e)	Film	3290	1650	1140 1105
(12f)	Nujol	3110	1645	1040 1025
(7g)	Nujol	3160	1620	1155 1095

The presence of conjugation between the imine group and a phenyl substituent was readily detected by the shift of $\nu_{C=N}$ in the IR to lower frequency. Lack of such conjugation in (12f) was further confirmed by ν_{C-O} which showed a characteristic benzylic shift.

TABLE 3

^{1}H NMR Data (δ; $CDCl_3$) for hydroxypyrrolines (7) and (12)

Compound	H-3	H-4	OH	2-Subst.	3-Subst.	4-Subst.	5-Subst.
(7a)	2.2-3.3(m)		3.10	1.36(s) 1.58(s)	1.15(d)		7.3-7.5(3H,m) 7.7-7.9(2H,m)
(7b)	1.6-2.0(m)	2.4-2.7(m)	2.22	1.30(s)			1.96(s)
(7c)	1.9-2.3(m)	2.9-3.1(m)	2.21	1.44(s)			7.3-7.5(3H,m) 7.7-7.9(2H,m)
(7e) & (12e)	1.2-2.6(m)		2.3	1.26(s) 1.46(s)	1.2-2.6(m)		1.98(s)
(12f)	1.2-2.6(m)			7.1-7.5(m)		1.2-2.6(m)	
(7g)	3.1-3.8(m)		2.80	1.12(s) 1.67(s)	7.2-7.4(m)		7.4-7.6(3H,m) 7.8-8.0(2H,m)

In the ^{1}H NMR spectra the presence of mixed diastereomers was readily confirmed by the presence of two separate singlets for the 2-Me groups. For the mixed regioisomers (7e) and (12e), the ring proton signals for the heterocycle and the cyclohexane moieties were poorly resolved, but (7e) was identified from the Me singlet at δ 1.98.

TABLE 4

^{13}C NMR Data (δ; $CDCl_3$) for hydroxypyrrolines (7) and (12)

Compound	C-2	C-3	C-4	C-5	2-Subst.	5-Subst.
(7b)	84.8	35.2	36.8	170.7	26.3	17.9
(7c)	86.9	34.6	36.7	169.3	28.1	134.6*i* 127.6*o** 128.4*m** 130.5*p*
(7e)	83.5	43.2	34.2*	171.7	42.6*	19.5
(12e)	83.7 84.1	43.5 42.3*	46.6 47.3	174.9 176.2	27.0 29.8	33.6 34.8*
(12f)	101.9 101.2	45.7 46.0	47.4 47.9	182.8 180.7	147.7, 125.0 *i* 146.8, 124.8 *o* 127.6*m* 126.5*p*	34.1
(7g)	103.2 101.3	54.0 53.3	39.6 42.2	171.3	24.4 28.3	

The proposed structures were further confirmed from the ^{13}C NMR spectra (^{1}H and off-resonance decoupled), which clearly showed the presence of quaternary sp^3 and imine carbon atoms. Where doubling of signals was observed due to mixed diastereomers, data for the most abundant isomer are given first. For compound (7c), and the mixture (7e) and (12e), assignments of signals with similar chemical shifts marked with an asterisk are uncertain. For (7g), the aryl region was too complex to permit assignments.

Solutions of hydroxypyrrolines on standing in NMR tubes showed clean and essentially quantitative conversion into the corresponding 1*H*-pyrroles (8), over a range of times varying from two days [for (7b)] to six days [for (7c)]. The exception was (12f) which gave equal amounts of (8f) and the diketone (11f). IR and ^{1}H NMR data for the product 1*H*-pyrroles are given in Table 5.

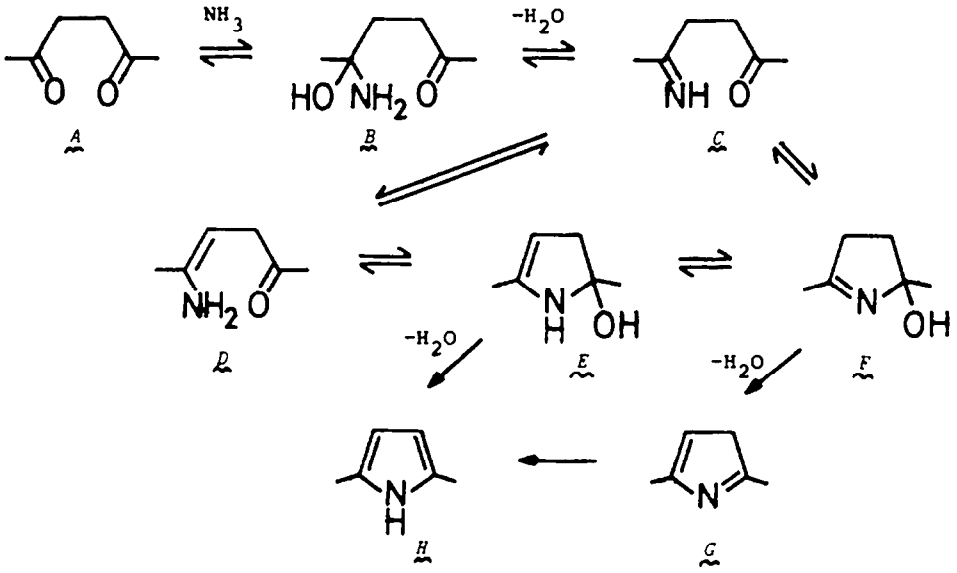
TABLE 5

IR (cm^{-1}) and ^1H NMR (δ; $CDCl_3$) Data for the 1*H*-pyrroles (8)

Compound	ν_{NH}	δ_H
(8a)	3400	2.03(3H, s), 2.20(3H, s), 6.27(1H, d), 7.0-7.4(5H, m), and 7.91(1H, s, br)
(8b)	3360	2.17(6H, s), 5.70(2H, d), and 7.50(1H, s, br)
(8c)	3410	2.27(3H, s), 5.94(1H, m), 6.38(1H, m), 7.15-7.45(5H, m), and 8.03(1H, s, br)
(8e)	3360	1.6-1.9(4H, m), 2.20(3H, s), 2.4-2.6(4H, m), 5.63(1H, d), and 7.35(1H, s, br)
(8f)	3405	1.6-1.9(4H, m), 2.3-2.7(4H, m), 6.21(1H, d), 7.0-7.4(5H, m), and 7.75(1H, s, br)
(8g)	3420	2.40(3H, s), 6.50(1H, d), 7.0-7.5(10H, m), and 8.00(1H, s, br)

Although the mechanism of the Paal-Knorr reaction with primary amines has been investigated recently,[10] and discussed earlier,[11] that with ammonia appears not to have been studied. Possible pathways for the reaction between hexane-2,4-dione and ammonia are shown in the Scheme.

SCHEME



In reactions with primary amines, intermediates of type *C* have been isolated,[10,11] and very recently, those of type *E*;[12] however, with ammonia *C* apparently cyclises rapidly to the hydroxypyrroline *F*. It is uncertain whether this occurs directly, as implied without supporting evidence in some recent publications,[6,7,13] or *via* the enamine *D*, as appears to be the case with primary amines.[10,11] Likewise, it is not clear whether dehydration occurs directly from *E*, present to an undetectably small extent in equilibrium with *F*, or through the 3*H*-pyrrole *G*. The route *via* *G* seems the more likely under basic conditions, and this would make *F* a true intermediate in the reaction sequence *A* → *H*.

A 2,5-dihydroxypyrrolidine intermediate has been proposed[14] in reactions with primary amines. We were unable to detect such an intermediate, even after adding increasing amounts of water to the liquid ammonia, although to our surprise

the hydroxypyrroline F(7b) was still isolable from the reaction between aqueous (0.880) ammonia and hexane-2,4-dione at 5-10°C.

We thank the Croucher Foundation for a Studentship (for P.K.C.).

EXPERIMENTAL

General: IR Spectra were recorded on a Perkin-Elmer 157G instrument using polystyrene in calibration. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a JEOL FX-90Q spectrometer, with TMS as internal standard.

Preparation of the Ketones (4), (9), and (11). — Hexane-1,4-dione (11b) and 1-phenylpentane-1,4-dione (11c) were purchased.

3-Acetyl-3-methyl-1-phenylpentane-1,4-dione (4). To a mixture of pentane-2,4-dione (10g, 0.1 mol) and anhydrous potassium carbonate (41.4g) in refluxing acetone (100 ml) was added dropwise a solution of phenacyl bromide (19.9g, 0.1 mol) in acetone (50 ml). Refluxing was continued for 24 h, the solvent was evaporated (water pump) and the residue stirred with ether (150 ml). The ether extract was washed with water, dried ($MgSO_4$), evaporated, and the residue distilled to give 3-acetyl-1-phenylpentane-1,4-dione, 13.8g (60%), b.p. 110°C/0.05 mmHg; $\nu_{max.}$ (film) 1700, 1685, 1595, and 1580 cm^{-1}; δ_H 2.34(6H, s), 3.60(2H, d, *J* 6.7 Hz), 4.30(1H, t, *J* 6.7 Hz), 7.4-7.6(3H, m), and 7.9-8.1(2H, m). The product (10g, 0.045 mol) was dissolved in dry dimethyl sulphoxide (DMSO) (50 ml), and added to a slurry of sodium hydride (1.98g, 0.05 mol) in dry DMSO (50 ml) under N_2. After stirring for 1 h at 25°C, methyl iodide (8.4g, 0.054 mol) was added, and stirring continued overnight. The mixture was diluted with water (100 ml), extracted with ether (3x 60 ml), the ether extracts were washed with water (3x100 ml) and dried ($MgSO_4$). Evaporation of the solvent gave the product (4), 5.1g (40%), m.p. 60-61°C (95% EtOH); $\nu_{max.}$ (Nujol) 1700, and 1685 cm^{-1}; δ_H 1.57(3H, s), 2.20(6H, s), 3.70(2H, s), 7.4-7.6(3H, m), and 7.9-8.1(2H, m). (Found: C, 72.35; H, 7.1. $C_{14}H_{16}O_3$ requires C, 72.4; H, 6.95%).

3-Benzoyl-3-methyl-1-phenylpentane-1,4-dione (9). 3-Benzoyl-1-phenyl-pentane-1,4-dione was prepared similarly (58%) from 1-phenylbutane-1,4-dione and phenacyl bromide, m.p. 80-81°C (95% EtOH), $\nu_{max.}$ (Nujol) 1720, 1695, and 1670 cm^{-1}; δ_H 2.20(3H, s), 3.60(1H, dd, *J* 6.7, 17.9 Hz), 3.78(1H, dd, *J* 4.4, 17.9 Hz), 5.30 (1H, t, *J* 6.7 Hz), 7.4-7.6(3H, m), and 7.9-8.1(2H, m) (Found: C, 76.95; H, 5.8. $C_{18}H_{16}O_3$ requires C, 77.1; H, 5.75%). It was methylated, as above to give the triketone (9), 40%, m.p. 83-84°C (95% EtOH); $\nu_{max.}$ (Nujol) 1700, 1680, 1595, 1580 and 1420 cm^{-1}; δ_H 1.63(3H, s), 2.23(3H, s), 3.79(1H, d, *J* 18.4 Hz), 3.95(1H, d, *J* 18.4 Hz), 7.3-7.5(3H, m), and 7.7-7.9(2H, m); (Found: C, 77.3; H, 6.25. $C_{19}H_{18}O_3$ requires C, 77.5; H, 6.15%).

1,4-Diphenylbutane-1,4-dione (11d). Prepared from 1-phenyl-1-pyrrolidino-ethene[15] and phenacyl bromide according to Stork's procedure.[16] Yield 58%, m.p. 144°C (95% EtOH) (Lit.[17] 145°C), δ_H 3.46(4H, s), 7.3-7.7(6H, m), and 7.9-8.2 (4H, m).

2-(3-Oxopropyl)cyclohexanone (11e). Prepared similarly from 1-pyrrolidino-cyclohexene and bromoacetone. Yield 43%, b.p. 68.5-72°C/3.5 mmHg (Lit.[18] 124-5°C/ 16 mmHg) $\nu_{max.}$ (film) 1715, 1420, and 1350 cm^{-1}; δ_H 1.0-2.6(9H, m), 2.17(3H, s), and 2.7-3.2(2H, m).

2-Phenacylcyclohexanone (11f). Prepared similarly from 1-pyrrolidinocyclo-hexene and phenacyl bromide. Yield 62%, m.p. 44-6°C (95% EtOH) (Lit.[18] 47-8°C), $\nu_{max.}$ (Nujol) 3050, 1715, and 1682 cm^{-1}; δ_H 1.1-2.6(8H, m), 2.7-3.8(3H, m), 7.3-7.6(3H, m), and 7.9-8.1(2H, m).

1,3-Diphenylpentane-1,4-dione (11g). 4-Nitro-1,3-diphenyl-1-pentanone was prepared from nitroethane and 1,3-diphenylpropenone using the method of Smith,[19] and its properties matched reported data.[20] The nitroketone (6.8g, 0.024 mol) was stirred overnight with a solution of sodium hydroxide (1.25g) in aqueous ethanol (1:9; 100 ml). The mixture was acidified (dilute HCl), extracted with ether (3x 50 ml), the ether extract was dried ($MgSO_4$) and the solvent evaporated to give the product (11g), 4.8g, 79%, as a viscous oil;[21] $\nu_{max.}$ 3050, 1720, 1690 and 1345 cm^{-1}. δ_H 2.17(3H, s), 3.10(1H, dd, *J* 3.5, 18 Hz), 4.03(1H, dd, *J* 10, 18 Hz), 4.47(1H, dd, *J* 3.5, 10 Hz), 7.1-7.6(8H, m) and 7.9-8.1(2H, m).

Preparation of the Hydroxypyrrolines (7) and (12). — The appropriate 1,4-diketone (1g) was dissolved in liquid ammonia (ca. 60 ml) in an insulated container, and the ammonia was allowed to evaporate overnight. The last traces were removed *in vacuo*, and the product was examined by IR and NMR spectroscopy immediately, without further purification.

For the diketone (11f), ammonium chloride (50mg) was added to the liquid ammonia, the residue after evaporation was taken up in benzene, the solution was filtered, and the solvent was removed under reduced pressure to give the mixture of products.

Results, and spectroscopic data are given in Tables 1-4. Products from the ketones (4) and (9) were separated from amide byproducts by dissolving in anhydrous ether, filtering, and evaporating the solvent. The hydroxypyrroline (7c) was freed from 1*H*-pyrrole (8c) by dissolving in ether and reprecipitating with light petroleum (b.p. 40-60°C), while the mixed diastereomers (12f) were freed from the isomer (7f) and the 1*H*-pyrrole (8f) by recrystallising from benzene/hexane. Contaminant 1*H*-pyrrole (8g) was removed from (7g) by washing the solid product with benzene.

Reaction of Hexane-2,4-dione (11b) *with Aqueous Ammonia*. — The diketone (1g) was stirred with concentrated (0.880) aqueous ammonia (10 ml) at 5-10°C for 10 h. The mixture was diluted with water (20 ml), extracted with dichloromethane (3x20 ml), the solution was dried ($MgSO_4$), and evaporated to give a mixture (from ^1H NMR) containing the hydroxypyrroline (7b) (80%), together with diketone (11b) and the 1*H*-pyrrole (8b).

REFERENCES AND NOTES

1. The term 'azolenines' refers to the non-aromatic isomers of the azoles.
2. Part 11. M.W.L. Chung, T.F. Lai, and M.P. Sammes, *J. Chem. Res.*, (S) 366, (M) 3042 (1987).
3. For a preliminary communication, see: P.K. Chiu, K.H. Lui, P.N. Maini, and M.P. Sammes, *J. Chem. Soc., Chem. Commun.*, 109 (1987).
4. P.N. Maini, M.P. Sammes, and A.R. Katritzky, *J. Chem. Soc., Perkin Trans. 1*, in the press (Paper 6/2079).
5. δ_H ($CDCl_3$) *inter alia* 1.17(d, J 6 Hz, 3-Me), 1.35(s, 2-Me), 1.58(s, 2-Me), and 2.2-3.7(m).
6. H. Saki and T. Mukai, *Chem. Lett.*, 1561 (1981).
7. B.A. Trofimov, S.E. Korostova, A.I. Mikhaleva, L.N. Sobenina, V.V. Shcherbakov, and M.V. Sigalov, *Khim. Geterotsikl. Soedin.*, 276 (1983).
8. R.J. Sundberg in "Comprehensive Heterocyclic Chemistry," ed. A.R. Katritzky and C.W. Rees, Pergamon Press, Oxford, 1984, vol 4, p 329-330.
9. C.F.H. Allen, D.M. Young, and A.R. Gilbert, *J. Org. Chem.*, 2, 235 (1937); A. Kreutzberger and P.A. Kalter, *ibid.*, 25, 554 (1960).

10. A.R. Katritzky, T.I. Yousaf, B.C. Chen, and G.Z. Zeng, *Tetrahedron*, 42, 623 (1986).
11. H.S. Broadbent, W.S. Burnham, R.K. Olsen, and R.M. Sheeley, *J. Heterocycl. Chem.*, 5, 757 (1968).
12. O.A. Attanasi, M. Grossi, F. Serra-Zanetti, and E. Foresti, *Tetrahedron*, 43, 4249 (1987).
13. D.H.R. Barton, W.B. Motherwell, E.S. Simon, and S.Z. Zard, *J. Chem. Soc., Perkin Trans. 1*, 2243 (1986).
14. Quoted as ref. 8 in ref. 10 above.
15. K. Taguchi and F.H. Westheimer, *J. Org. Chem.*, 36, 1570 (1971).
16. G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Am. Chem. Soc.*, 85, 216 (1963).
17. Y. Kobayashi, T. Taguchi, and E. Tokuno, *Tetrahedron Lett.*, 3741 (1977).
18. M.A. Volodina, V.G. Mishina, A.P. Terent'ev, and G.V. Kiryushkina, *Zh. Obshch. Khim.*, 32, 1922 (1962).
19. L.I. Smith and W.L. Kohlhase, *J. Org. Chem.*, 21, 816 (1956).
20. C.W. Davey and D.J. Tivey, *J. Chem. Soc.*, 2276 (1958).
21. For an earlier preparation, see J.H. Clark and D.G. Cork, *J. Chem. Soc., Perkin Trans. 1*, 2253 (1983).