Tetrahedron. Vol. 29, pp. 4049 to 4052. Pergamon Press 1973. Printed in Great Britain

CARBOCYCLIC PHENYLHYDRAZINES IN THE FISCHER INDOLE SYNTHESIS—II

REACTIONS WITH α,α-DISUBSTITUTED ALDEHYDES

M. K. EBERLE* and G. G. KAHLE

Department of Research, Division of Sandoz-Wander, Inc., Route 10, East Hanover, New Jersey 07936, U.S.A.

(*Received in the USA* 14 *May* 1973; *Received in the UK for publication* 4 *July* 1973)

Abstract—Reaction of 1-phenylpyrazolidine with α-disubstituted aldehydes yields 10,10-disubstituted-hexahydropyrimido[1,2-a]indoles. These products represent intermediates of the Fischer Indole Synthesis which are stable under acidic conditions due to their particular substitution pattern. The following aldehydes were used: isobutyraldehyde, cyclohexanecarboxaldehyde and 4-formylhexanoate. However, when 5-norbornene-2-carboxaldehyde is reacted with 1-phenylpyrazolidine the corresponding hexahydropyrimido[1,2-a]indole rearranges to a bridged indole in the presence of maleic acid.

In a preceeding paper[1] we have described the formation of 9-(3-aminopropyl)-1,2,3,4-tetrahydrocarbazole and some of its homologues in a one step synthesis from 1-phenylpyrazolidine **1** and cyclic ketones e.g. cyclohexanone. A hypothetical enehydrazine **2** was postulated to undergo a thermal [3,3] sigmatropic rearrangement via the intermediate **3** to the product **4** (Fig 1). In the examples presented the benzylic proton of the intermediate **3** was labile enough to allow the system to undergo further bond reorganisation to form the indole **4**. In order to gather more positive data to support **3** we undertook the preparation of compounds where alkyl substituents would replace the benzylic proton. Such compounds should be more stable and allow their isolation. It is the purpose of this paper to present examples[2] which fulfil this requirement.

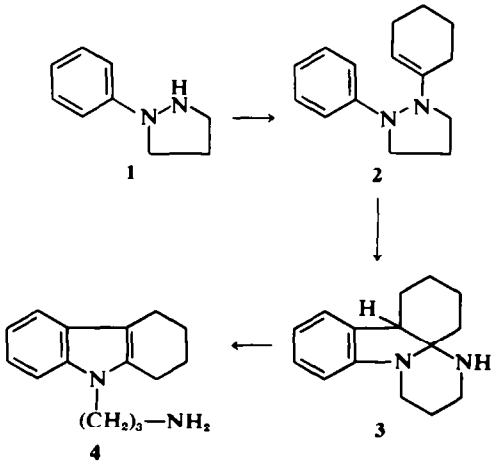


Fig 1.

When 1-phenylpyrazolidine **1** was reacted with isobutyraldehyde in refluxing toluene with azeotropic distillation of water during 2 hr 10,10-dimethyl-1,2,3,4,10,10a-hexahydropyrimido [1,2-a] indole **5** was isolated in 86% yield. The assigned structure is in agreement with the NMR spectrum of the free base of **5** which shows 2 singlets at δ 1·12 and 1·32 ppm corresponding to 2 nonequivalent Me groups, *one* proton exchangeable with D_2O with a signal at δ 1·4–1·9 ppm (secondary amino group) and a singlet at δ 3·66 ppm assigned to the proton at position 10a of **5** (N—CH—N). The latter signal is shifted to lower field in the presence of acid and appears at δ 4·39 ppm for the maleic acid salt of **5** and at δ 4·33 ppm for the hydrochloride of **5** in DMSO as solvent. More dramatic changes occur when the hydrochloride of **5** is dissolved in trifluoroacetic acid. The NMR spectrum now exhibits a singlet at δ 1·75 ppm for 2 equivalent Me groups, a triplet at δ 4·87 ppm and a broadened singlet at δ 9·37 ppm. Similar chemical shifts have been reported for physostigmine[3] which exists in the ring-opened 3H-indole form in moderately strong acid. Therefore it may be concluded that **5** also exists in the ring-opened form **5a** in trifluoroacetic acid.

The 1-(*p*-chlorobenzoyl) derivative **5b** was devoid of any IR absorption in the region between 3000 and 3500 cm^{-1} thus further supporting the presence of a secondary amine in **5**.

Similar results were observed when we allowed to react cyclohexanecarboxaldehyde with 1-phenylpyrazolidine under conditions similar to those described above. The product 1′, 2′, 3′, 4′, 10′, 10a′-hexahydro-spiro {cyclohexane-1, 10′-pyrimido [1,2-a]indole} **6** was isolated in 82% yield as the hydrochloride. We found this compound distinctly

different from 5-(3-aminopropyl)-5, 6, 7, 8, 9, 10-hexahydrocyclohept[b]indole hydrochloride[1] thus precluding a rearrangement during the formation of the salt. Support for structure **6** stems from the NMR spectra of the compound: (1) for the base a singlet was recorded at δ 4·05 ppm in agreement with the partial structure N—CH—N; (2) for the maleate of **6** the same proton showed absorption at δ 4·90 ppm; (3) for the hydrochloride of the same compound the singlet was observed at δ 4·71 ppm in DMSO as solvent. When CF_3COOH was used as solvent of **6**.HCl a triplet appeared at δ 4·83 ppm (2H, J = 7·5 c/s) while the singlet shifted to δ 9·50 ppm. These observations indicate the presence of the ring opened 3H-indole form **6a** under these conditions.

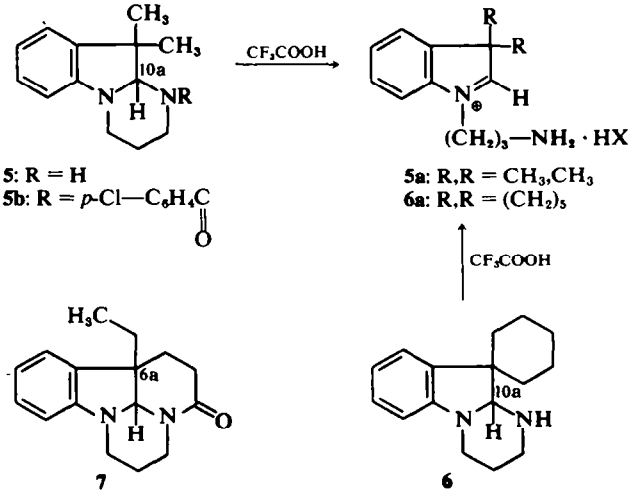
The reaction between 1-phenylpyrazolidine **1** and methyl 4-formyl-hexanoate[4] terminates in an 80% yield of the crystalline δ-lactam 2,3,6,6a-tetrahydro-6a-ethyl-1H-3a, 10b-diazafluoranthen-4(5H)-one **7**. The NMR spectrum of this compound is in agreement with the assigned structure. A singlet at δ 4·68 ppm corresponds to the partial structure N—CH—N—C=O. The observed absorption reflects the vicinity of an electron withdrawing group to one of the N atoms (previous examples). Further analytical data appears in the Experimental.

We reacted 5-norbornene-2-carboxaldehyde with 1-phenylpyrazolidine **1** in refluxing toluene followed by the addition of maleic acid. Inspection of the NMR spectrum of the compound thus isolated revealed the presence of a 5-(3-aminopropyl)-indole: a triplet at δ 4·20 ppm (J = 7 c/s) is assigned to the methylene group attached to the indole nitrogen.[1] A clearer spectrum was obtained from the free base of the same compound: a singlet at δ 1·42 ppm (2H, exchangeable with D_2O) corresponds to a primary amino group and the forementioned triplet appears at δ 4·08 ppm (J = 7 c/s). The product was therefore assigned the structure **9**: 5-(3-aminopropyl)-5, 6, 9, 10-tetrahydro-6, 9-methanocyclohept[b]indole maleate. Additional information in support of **9** was obtained by hydrogenation over Pt catalyst to give 5-(3-aminopropyl)-5, 6, 7, 8, 9, 10-hexahydro-6,9-methano-cyclohept[b]indole succinate **10**, the hydrochloride of the latter being identical in every respect with the product isolated from the reaction between 1-phenylpyrazolidine **1** hydrochloride and bicyclo[3.2.1]octan-2-one in hot glacial acetic acid.

Removal of the isolated double bond in **8** via hydrogenation over Pd on charcoal yielded 1′, 2′, 3′, 4′-tetrahydro-spiro {norbornane-2, 10′ (10a′H)-pyrimido [1,2-a] indole} **11** characterized as the maleic acid salt. Spectral data seems to indicate that compound **11** consists of a near equal mixture of diastereoisomers at positions 10′ (*exo*/*endo*) and/or 10a′ since we observed 2 proton signals at δ 4·7 and 5·0 ppm of approximately equal intensity. The NMR spectrum of **8** seems to exhibit the corresponding singlets at δ 4·0 and 4·16 ppm although a very complex spectrum makes the assignment less definitive.

DISCUSSION

Our experiments with 5-norbornene-2-carboxaldehyde seem to indicate that the formation of the intermediary enehydrazine is *not* a stereospecific process. The same might be expected for the formation of the enehydrazine of methyl 4-formyl-hexanoate. On the other hand the NMR spectrum of **7** indicates the presence of only *one* isomer considering the signals for both the Me group (triplet) and the singlet for the partial structure N—CH—N. Equilibration could then take place prior to the formation of the lactam via a ring-opened 3H-indole similar to **5a**. The stereochemical



5: R = H
5b: R = *p*-Cl—C_6H_4C(=O)
5a: R,R = CH_3,CH_3
6a: R,R = $(CH_2)_5$
7
6

Fig 2.

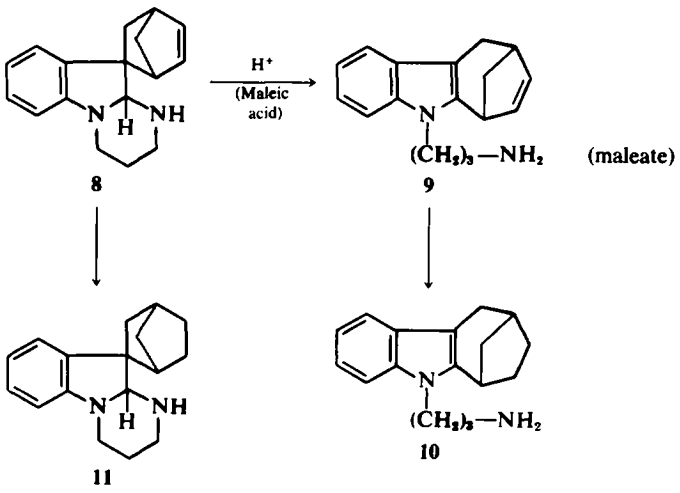


Fig 3.

aspect of this reaction is currently under investigation.

It is worthwhile noticing that hydrochloric acid does not affect compounds **5**, **6** and **11**. This is in contrast to 3,3-disubstituted-3H-indoles which are reported to rearrange to 2,3-disubstituted indoles.[5] On the other hand maleic acid was found to be acidic enough to form the indole **9** from the spiro compound **8**. The specificity of this rearrangement can be explained on the basis of an activated σ bond flanked by a ¶ electron system migrating from position 10′ to 10a′.

EXPERIMENTAL

M.ps are determined on a Thomas Hoover capillary m.p. apparatus and are not corrected. NMR spectra were measured on either a Varian A-60 and/or T-60 spectrometer and are recorded in δ ppm values from TMS as internal standard. UV absorption spectra were measured in ethanol on a Cary spectrometer Model 14. IR spectra were taken on a Perkin-Elmer Model 257 or 457. Gas–liquid chromatography was carried out on a Hewlett-Packard 5750 Chromatograph. Mass spectra were taken on a LKB 9000 Mass spectrometer.

10,10-*Dimethyl*-1, 2, 3, 4, 10, 10*a*-*hexahydropyrimido*[1,2a]*indole* **5**

A. *Synthesis in ethanol.* A soln of 7·5 g (0·050 mol) of **1** and 7·5 g (0·104 mol) isobutyraldehyde in 25 ml abs EtOH was refluxed for 6 hr under N_2. The solvent was evaporated under reduced pressure and there was obtained 9·1 g (89%) of **5** after distillation; b.p. 100–105°/0·03 mm; *m/e* 202 [M⁺]; NMR ($CDCl_3$) δ 1·12 (s, 3, CH_3) 1·32 (s, 3, CH_3) 1·4–1·9 (m, 3, 1 D_2O exchangeable, NH) 2·5–4·0 (m, 4) 3·66 (s, 1, N—CH—N) 6·3–7·3 (m, 4, C_6H_4); IR (film) 3300 (NH) 1600; UV 252 nm (ϵ 10,170) 294 (3,284).

From 9·0 g (0·045 mol) of **5** and 5·5 g (0·048 mol) maleic acid in MeOH there was obtained 12·2 g (76%) of **5** maleate; m.p. 166–167°; *m/e* 202 [M⁺]; NMR ($CDCl_3$·DMSO) δ 1·35 (s, 3, CH_3) 1·42 (s, 3, CH_3) 1·6–2·5 (m, 2) 2·8–4·1 (m, 4) 4·39 (s, 1, N—CH—N) 6·16 (s, 2, maleic acid) 5·4–7·4 (m, 4, C_6H_4) 10·3–12·6 (m, 3); UV 243 nm (ϵ 11,200) 293 (2,650). (Found: C, 64·3; H, 7·0; N, 8·7. Calcd for $C_{13}H_{18}N_2.C_4H_4O_4$ (318·4): C, 64·1; H, 7·0; N, 8·8%).

B. *Synthesis in toluene.* A soln of 7·4 g (0·05 mol) of **1** and 7·4 g (0·103 mol) isobutyraldehyde in 80 ml toluene was refluxed under N_2 for 2 hr with azeotropic distillation of water. To the cold soln dry HCl was added. The product precipitated and was filtered off to give 10·2 g (85%) of **5**.HCl, m.p. 236–238°; *m/e* 202 [M⁺]; NMR (DMSO) δ 1·31 and 1·35 (2s, 6, $2CH_3$) 1·5–2·1 (m, 2) 2·6–4·1 (m, 5) 4·33 (s, 1) 6·5–7·4 (m, 4, C_6H_4) 8·3–10·0 (broad, 1); NMR (CF_3—COOH) δ 1·75 (s, 6, $2CH_3$) 2·5–3·2 (broad, 2) 3·2–4·0 (broad, 2) 4·87 (t, 2, J = 7·5 c/s) 6·7–8·0 (broad, 3) 7·81 (s, 4) 9·37 (s, 1); IR (Nujol) 2400–3150 (NH) 1610; UV 243 nm (ϵ 10,630) 292 (5,980). (Found: C, 65·5; H, 8·3; N, 11·7; Cl, 14·8. Calcd for $C_{13}H_{18}N_2$.HCl (238·8): C, 65·4; H, 8·0; N, 11·7; Cl, 14·8%). The free base **5** was recovered unchanged from **5**.HCl following conventional procedures (GLC, NMR).

1-(p-*Chlorobenzoyl*)-10, 10-*dimethyl*-1, 2, 3, 4, 10, 10a-*hexahydropyrimido*[1,2a]*indole* **5b**

A mixture of 5·0 g (0·016 mol) of **5**, 50 ml 2N NaOH and 50 ml ether was treated with 4·0 g (0·023 mol) *p*-chlorobenzoylchloride. The organic phase was separated and the aqueous layer extracted with ether. After washing with water the ether was dried over K_2CO_3 and evaporated under reduced pressure to yield the title compound, m.p. 117–118°; it was recrystallized from MeOH/water, m.p. 122–124°; NMR ($CDCl_3$) δ 1·37 (s, 6, $2CH_3$) 1·5–2·3 (m, 2) 2·5–4·2 (m, 4) 5·81 (1) 6·6–7·3 (m, 4, C_6H_4) 7·40 (s, 4, C_6H_4); IR (CH_2Cl_2) no NH 1630 (C=O) 1605; UV 246 nm (ϵ 18,400) 296 (3,180). (Found: C, 70·2; H, 6·2; N, 8·1. Calcd for $C_{20}H_{21}ClN_2O$ (340·9): C, 70·5, H, 6·2; N, 8·2%).

1′, 2′, 3′, 4′, 10′, 10a′-*Hexahydrospiro*{*cyclohexane*-1,10′-*pyrimido*[1,2-a]*indole*} **6**

A mixture of 7·5 g (0·050 mol) of **1** and 6·0 g (0·054 mol) cyclohexanecarboxaldehyde was refluxed in 50 ml toluene for 2 hr with azeotropic distillation of water. Dry HCl gas was passed through the soln to give 10·0 g (82%) of **6**.HCl, m.p. 201–202°, which was recrystallized from MeOH/ether, m.p. 217–218°; *m/e* 242 [M⁺]; NMR (DMSO) δ 1·0–2·2 (m, 12) 2·8–4·2 (m, 4) 4·71 (s, 1, (N—CH—N) 6·4–7·4 (m, 4, C_6H_4) 8·0–9·7 (broad, 2) NMR

(CF_3—COOH) δ 1·5–2·4 (10) 2·4–3·2 (broad, 2) 3·2–3·8 (broad, 2) 4·83 (t, 2, J = 7·5 c/s; indole N—CH_2) 6·5–8·0 (broad, 3) 7·75 (s, 4, C_6H_4) 9·5 (s, 1, vinyl). (Found: C, 68·8; H, 8·4; N, 9·9; Cl, 13·1. Calcd for $C_{16}H_{22}N_2$.HCl (278·9): C, 68·9; H, 8·3; N, 10·0; Cl, 12·7%).

The free base was prepared from **6**.HCl following conventional procedures to give **6**, b.p. 160–180°/0·03 mm; NMR ($CDCl_3$) δ 1·2–2·0 (m, 13, 1 exchangeable in D_2O; NH) 2·6–3·5 (m, 3) 3·5–4·0 (m, 1) 4·05 (s, 1, N—CH—N) 6·4–7·4 (m, 4, C_6H_4); IR (CH_2Cl_2) 3300 (NH) 1605; UV 254 nm (ε 10,700) 301 (2,860).

The maleic acid salt was prepared from the free base to give **6**.maleate, m.p. 174–175° (from MeOH/ether); NMR ($CDCl_3$ + DMSO) δ 1·0–2·0 (m, 12) 3·0–4·1 (m, 4) 4·90 (s, 1, N—CH—N) 6·06 (s, 2, maleic acid) 6·5–7·4 (m, 4, C_6H_4) below 8·0 (broad, 3); IR (Nujol) 2400–3100 (NH) 1680, 1606; UV 244 nm (ε 10,150) 293 (2,520). (Found: 66·9; H, 7·4; N, 7·9. Calcd for $C_{16}H_{22}N_2.C_4H_4O_4$ (358·5): C, 67·0; H, 7·3; N, 7·8%).

2, 3, 6, 6a-*Tetrahydro*-6a-*ethyl*-1H-3a, 10*b*-*diazafluoranthen*-4(5H)-*one* **7**

A mixture of 9·0 g (0·060 mol) of **1** and 9·7 g (0·060 mol) methyl 4-formylhexanoate[4] was refluxed for 1·5 hr in 100 ml toluene with azeotropic distillation of water under N_2. The solvent was evaporated under reduced pressure leaving a liquid which was distilled. The fraction boiling at 130°/0·03 mm was collected and brought to crystallization from MeOH/water to give 12·4 g (80%) of **7**, m.p. 73–75°; *m/e* 256 [M⁺]; NMR ($CDCl_3$) δ 0·86 (t, 3, J = 7·5 c/s, CH_3) 1·2–3·0 (m, 9) 3·0–4·0 (m, 2) 4·68 (s, 1, N—CH—N) 4·5–5·0 (m, 1) 6·4–7·4 (m, 4, C_6H_4); IR (CH_2Cl_2) 1640 (C=O) 1600; UV 251 nm (ε 8,500) 299 (2,760). (Found: C, 75·1; H, 7·9; N, 10·6. Calcd for $C_{16}H_{20}N_2O$ (256·4): C, 75·0; H, 7·9; N, 10·9%).

5-(3-*Aminopropyl*)-5, 6, 9, 10-*tetrahydro*-6, 9-*methanocyclohept*[b]*indole* **9**

A mixture of 22·2 g (0·15 mol) of **1** and 18·3 g (0·15 mol) 5-norbornene-2-carboxaldehyde (commercial compound) in 200 ml toluene was refluxed for 3 hr with azeotropic distillation of water under N_2. The cold soln was treated with 18·0 g (0·155 mol) maleic acid in 25 ml MeOH and the product was precipitated by adding ether. There was obtained 49·0 g (89%) of **9**, m.p. 150–152°, that upon recrystallization from MeOH/ether gave m.p. 165–166°; *m/e* 252 [M⁺]; NMR ($CDCl_3$ + DMSO) δ 1·6–3·7 (m, 10) 4·20 (t, 2, J = 7 c/s; indole N—CH_2) 5·6–6·0 (m, 1, vinyl) 6·1–6·5 (m, 1, vinyl) 6·20 (s, 2, maleic acid) 6·8–7·6 (m, 4, C_6H_4) below 7·8 (broad, 3); IR (Nujol) 3420 (NH) 1575; UV 231 nm (ε 28,500) 288 (6,190) 294 (6,190). (Found: C, 68·1; H, 6·7; N, 7·6. Calcd for $C_{17}H_{20}N_2.C_4H_4O_4$ (368·4): C, 68·5; H, 6·6; N, 7·6%).

The free base of **9** was obtained from the maleate as a liquid: NMR ($CDCl_3$) δ 1·42 (s, 2, exchangeable with D_2O, NH_2) 1·5–3·4 (m, 9) 3·4–3·6 (m, 1) 4·08 (t, 2, J = 7 c/s, indole N—CH_2) 5·6–6·1 (m, 1, vinyl) 6·2–6·4 (m, 1, vinyl) 6·8–7·8 (m, 4, C_6H_4).

5-(3-*Aminopropyl*)-5, 6, 7, 8, 9, 10-*hexahydro*-6,9-*methano*-*cyclohept*[b]*indole* **10**

A. *From hydrogenation of* **9**. A soln of 5·0 g (0·014 mol) of **9**.maleate in 150 ml EtOH was hydrogenated in a Parr apparatus in the presence of 0·5 g PtO_2. When the uptake of H_2 had ceased the catalyst was filtered off and the solvent was evaporated under reduced pressure. Upon addition of ether the product solidified to yield 3·1 g of **10**.succinate (61%), m.p. 147–151° which was recrystallized from MeOH/ether to give a m.p. 156–158°; *m/e* 254 [M⁺]; NMR ($CDCl_3$ + DMSO) δ 1·0–3·4 (m, 18) 4·11 (t, 2, J = 7 c/s, indole N—CH_2) 6·8–7·5 (m, 4, C_6H_4) 9·1 (4); IR (Nujol) 2300–3300 (NH) 1700, 1640 (both weak); UV 231 nm (ε 32,900) 286 (6,810) 294 (6,610). (Found: C, 67·9; H, 7·5; N, 7·8. Calcd for $C_{17}H_{22}N_2.C_4H_6O_4$ (372·5): C, 67·7; H, 7·6; N, 7·5%).

Treatment of 1·4 g (0·004 mol) of **10**.succinate with dry HCl in EtOH gave 1·0 g (93%) of crude **10**.HCl, m.p. 293–297°, which was recrystallized from MeOH/ether, m.p. 304–306°; *m/e* 254 [M⁺]; NMR ($CDCl_3$ + DMSO) δ 1·0–2·5 (m, 7) 2·6–3·2 (m, 4) 3·2–3·8 (m, 3) 4·23 (t, 2, 33,300) 286 (7,169) 294 (6,810). (Found: C, 69·9; H, 8·0; N, 9·3. Calcd for $C_{17}H_{22}N_2$.HCl (290·8): C, 70·2; H, 8·0; N, 9·6%).

The maleic acid salt of **10** was prepared from the corresponding succinate following the usual procedures, m.p. 162–164°. (Found: O, 17·5. Calcd for $C_{17}H_{22}N_2.C_4H_4O_4$ (370·5): O, 17·3%).

B. *From bicyclo*[3.2.1]*octan*-2-*one*. A mixture of 4·5 g (0·024 mol) of **1**.HCl and 3·0 g (0·024 mol) bicyclo-[3.2.1]octan-2-one (commercial compound) in 50 ml gla- (0·024 mol) of **1**.HCl and 3·0 g (0·024 mol) bicyclo-[3,2,1]octan-2-one (commercial compound) in 50 ml glacial AcOH was refluxed for 1 hr under N_2. The product precipitated from the hot soln. A second crop was collected after addition of ether to the cold soln to give a total yield of 4·3 g (62%) of **10**.HCl, m.p. 305–307° (MeOH/ether). This compound was found to be identical with **10** from **9** in the following respects: NMR, IR, UV, TLC ($CHCl_3$/MeOH 90:10), mass spectra, mixture m.p. 304–306°.

1′, 2′, 3′, 4′-*Tetrahydro*-*spiro*{*norbornane*-2,10′(10a′H)-*pyrimido*[1,2-a]*indole*} **11**

A mixture of 7·4 g (0·050 mol) of **1** and 6·1 g (0·050 mol) 5-norbornene-2-carboxaldehyde in 80 ml toluene was refluxed for 3 hr as described. The solvent was evaporated under reduced pressure and the liquid distilled to yield 8·0 g (64%) of **8** b.p. 160–180°/0·03 mm; NMR ($CDCl_3$) δ 4·0 (s) and 4·16 (s) both singlets could be due to the partial structure N—CH—N. This compound was hydrogenated in 100 ml EtOH in the presence of 0·5 g Pd/C and the resulting product treated with maleic acid to give 8·9 g (48% overall) of **11**.maleate, m.p. 156–162°. The product was recrystallized from MeOH/ether, m.p. 173–174° (yield 8·0 g; 43%); *m/e* 254 [M⁺]; NMR ($CDCl_3$ + DMSO) δ 1·0–2·5 (m, 12) 3·2–4·2 (m, 4) 4·70 (s) 5·0 (s, total 1, N—CH—N) 6·16 (s, 2, maleic acid) 6·5–7·5 (m, 4, C_6H_4) below 8·0 (4); IR (Nujol) 2300–3100 (NH) 1600; UV 244 nm (ε 10,110) 294 (2,800). (Found: C, 67·8; H, 7·2; N, 7·4. Calcd for $C_{17}H_{22}N_2.C_4H_4O_4$ (370·5): C, 68·1; H, 7·1; N, 7·6%).

Acknowledgments—We thank Dr. W. J. Houlihan for his interest and encouragement. We also thank Dr. S. Barcza for helpful discussions and Mr. U. Stöckli for furnishing the mass spectral data.

REFERENCES

[1]M. K. Eberle, G. G. Kahle, S. M. Talati, *Tetrahedron.* **29**, 4045 (1973)
[2]M. K. Eberle, U.S. Patents 3,634,426 and 3,696,118
[3]A. H. Jackson, A. E. Smith, *J. Chem. Soc.* 5510 (1964)
[4]G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, R. Terrell, *J. Am. Chem. Soc.* **85**, 207 (1963)
[5]A. H. Jackson, P. Smith, *Tetrahedron* **24**, 2227 (1968)