Studies on the Fischer Indole Synthesis: Rearrangements of Five-, Six- and Seven-membered Cyclic Hydrazones of Pyrazoline, Tetrahydropyridazine and Tetrahydro-1,2-diazepine Series in Polyphosphoric Acid

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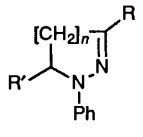
The rearrangements of a few cyclic phenylhydrazones structurally related to 1-phenyl-Δ^2-pyrazoline, 1-phenyl-1,4,5,6-tetrahydropyridazine, and 1-phenyl-4,5,6,7-tetrahydro-1,2-diazepine in hot polyphosphoric acid (PPA) are described. The five-membered-ring substrates (the pyrazolines) did not undergo the [3,3] sigmatropic rearrangement typical of the Fischer indolization, the main reaction course being homolytic N–N bond cleavage, leading to benzidine and its 4-(2-benzoylethyl)-4'-(3-phenyl-Δ^2-pyrazolin-1-yl) derivative. The six-membered heterocycles underwent two different reactions, both involving the tautomeric enehydrazine form: the first one is the [3,3] sigmatropic rearrangement, expected for open-chain hydrazones, affording 4-acyl-1,2,3,4-tetrahydroquinoline derivatives; the second one is a retro-Diels–Alder reaction producing methyleneaniline and α,β-unsaturated carbonyl compounds. The seven-membered-ring substrate gave a 5-acyltetrahydrobenz[*b*]azepine, resulting from the [3,3] rearrangement, together with both a pyrrolidine and a pyrazine by-product; their formation involves homolytic N–N bond cleavage of the ring, a δ hydrogen abstraction, followed by intramolecular or intermolecular ring closure. Chemical proofs are given for the new structures.

Within the framework of our research on rearrangements of arylhydrazones involving N–N bond cleavage,[1] we have studied the behaviour of some five-, six- and seven-membered-ring heterocyclic compounds **1** incorporating a hydrazonic function in the ring, under strongly acidic conditions (PPA). Here we report on the effect of the ring size on the reaction course which, in the absence of the cyclic linkage, would have been a simple Fischer indolization.



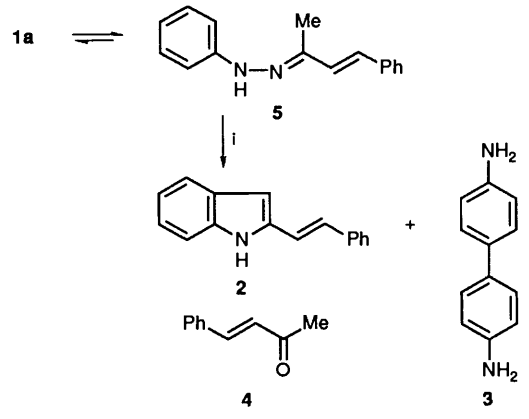
1

a; $n = 1$; R = Me, R' = Ph
b; $n = 1$; R = Ph, R' = H
c; $n = 2$; R = Ph, R' = H
d; $n = 2$; R = Me R' = H
e; $n = 2$; R = Ph R' = Ph
f; $n = 2$; R = CO_2Et, R' = H
g; $n = 3$; R = Ph R' = H

3-Methyl-1,5-diphenyl-Δ^2-pyrazoline **1a**[2] reacted in hot PPA to give a mixture of products from which the 2-[(*E*)-styryl]indole **2**, benzidine **3** and (*E*)-benzylideneacetone **4** were isolated. The structural assignment of the unknown indole derivative **2** was based on analytical and spectral data (see Experimental section).

The formation of these products can be explained through participation of the benzylideneacetone phenylhydrazone **5** which is in equilibrium with compound **1a** under the reaction conditions and is also its synthetic precursor.[3] The indolization of this intermediate would afford compound **2**, whereas a radical process, observed earlier by us,[1b,4] involves homolytic cleavage of the protonated N–N bond of intermediate **5**, and is responsible for the formation of products **3** and **4**.

The surprising product **6a** (65% yield) was observed from the reaction of the 1,3-diphenyl-Δ^2-pyrazoline **1b**[5] with PPA. The structure was established by a retro-Mannich hydrolytic



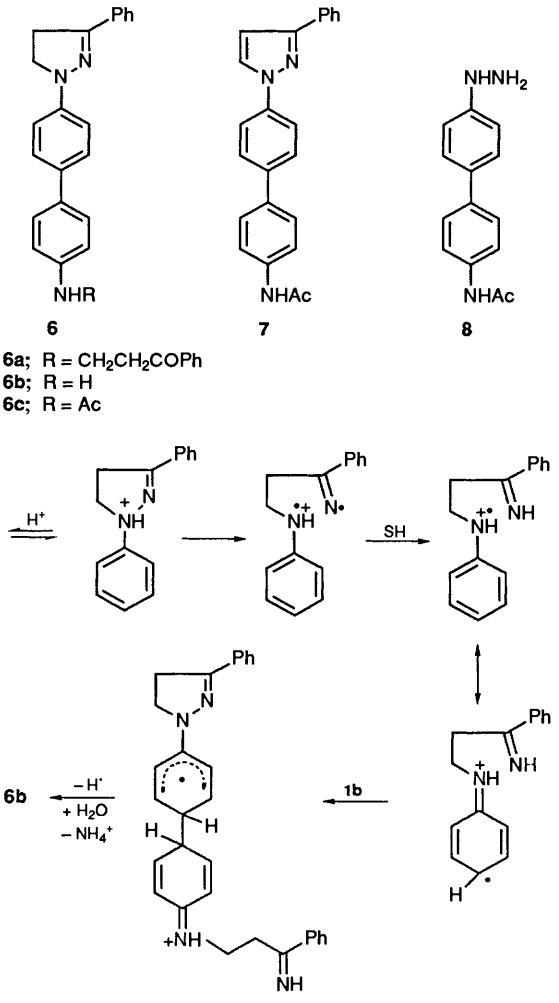
5 **2** **4** **3**

Reagents and conditions: i, PPA, 170 °C

reaction of compound **6a** to give compound **6b**, which was easily converted into its acetyl derivative **6c**; this was in turn aromatized to the pyrazole **7** with 10% palladized charcoal in refluxing mesitylene solution. A 2:1 mixture of compounds **6c** and **7** was produced by reaction of the 1-phenylprop-2-enone with the hydrazine **8**, unknown in the literature and prepared according to a conventional route (see Experimental section). Oxidation by air is probably responsible for the formation of compound **7** in this reaction.

How is the Mannich base **6a** formed? Our explanation envisages that the cyclic hydrazone **1b** undergoes a radical-chain mechanism which we have proposed for open-chain systems. It involves homolytic N–N bond cleavage of the protonated substrate to give, in general, a radical and a radical cation and, in the present case, a diradical cation. The latter then attacks the most electron-rich site of the substrate, namely the position *para* to the nitrogen-bonded phenyl group.[4]

The results demonstrate that, in the case of the five-membered hydrazones **1a** and **1b**, ring strain completely inhibits the Fischer rearrangement, instead directing the reactivity toward the radical process which is generally observed in the case of rather unreactive hydrazones. The different fate of substrates

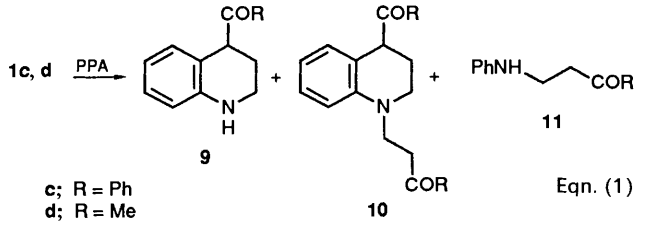


Scheme 1

1a and **1b** can be attributed to the tendency of compound **1a** to gain additional conjugation by ring opening.

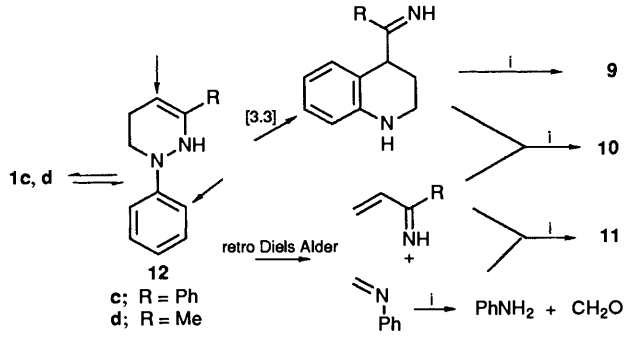
A totally different behaviour was observed for the six-membered cyclic hydrazones **1c–f** which were unknown in the literature; substrates **1c** and **1d** were prepared by condensation of phenylhydrazine with 4-chloro-1-phenylbutan-1-one and 5-chloropentan-2-one, respectively; substrate **1e** was obtained by catalytic hydrogenation of the known 1,4-dihydro-1,3,6-triphenylpyridazine;[6] substrate **1f** was synthesized by cyclization of the phenylhydrazone of the ethyl 5-chloro-2-oxopentanoate which, in turn, was obtained by the coupling of benzenediazonium chloride with ethyl 2-(3-chloropropyl)-acetoacetate (see Experimental section).

Substrates **1c** and **1d** underwent the same reaction pathway with PPA, according to equation (1).



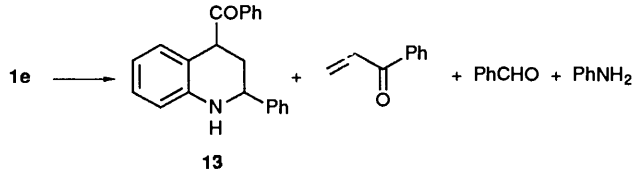
The structures were unequivocally demonstrated by the following reaction sequence: the 4-acyl-1,2,3,4-tetrahydroquinolines **9c** and **9d** were converted into the corresponding known 4-acylquinolines by treatment with palladium on charcoal in refluxing xylene solution, which were compared with authentic samples.[7] 3-Anilino-1-phenylpropan-1-one **11c** and 4-anilinobutan-2-one **11d** were identified by comparison with authentic samples.[8] The anilino ketones **10c** and **10d** were independently prepared by addition of compound **9c** to phenyl vinyl ketone and of compound **9d** to methyl vinyl ketone, respectively.

All the products could originate from the enehydrazinic tautomers **12c** and **12d** which could either undergo the [3,3] sigmatropic rearrangement typical of the Fischer indolization (arrows in Scheme 2 indicate the termini) or a retro-Diels–Alder reaction. Scheme 2 summarizes our mechanistic suggestions.



Scheme 2 *Reagent:* i, water

In order to establish an aldehydic product in the retro-Diels–Alder step, the reaction was performed with compound **1e**: benzaldehyde was indeed isolated from the reaction mixture together with phenyl vinyl ketone, aniline, and the two diastereoisomeric 4-benzoyl-2-phenyl-1,2,3,4-tetrahydroquinolines **13**. One of the latter was obtained pure by fractional crystallization; equilibration to the diastereoisomeric mixture took place under the strongly acidic reaction conditions.

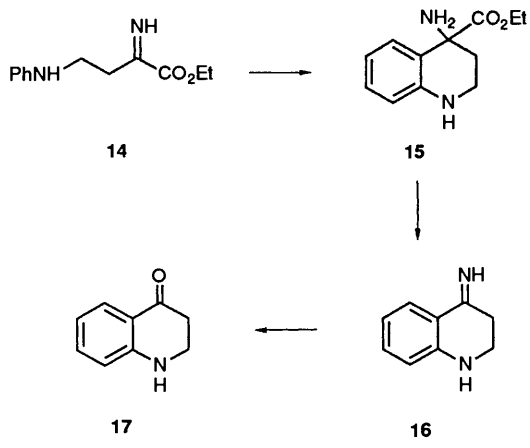


The structure of product **13** was demonstrated by aromatization to afford the hitherto unknown 4-benzoyl-2-phenylquinoline, unequivocally identified on the basis of its analytical and spectral data.

A rather complex reaction mixture resulted from the rearrangement of compound **1f** in PPA: the only product isolated in a pure state by chromatography, in ~15% yield, was 4-oxo-1,2,3,4-tetrahydroquinoline **17**. Its structure was demonstrated by comparing the 4-hydroxyquinoline[9] and *N*-(*p*-tolylsulphonyl)-4-oxo-1,2,3,4-tetrahydroquinoline,[10] produced by aromatization or tosylation, respectively, of compound **17**, with authentic samples prepared according to the literature methods.

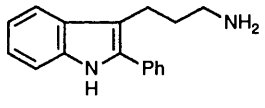
The mechanism we suggest for the formation of compound **17** involves the retro-Diels–Alder reaction already observed for the other six-membered substrates. The Mannich base **14** might cyclize to the tetrahydroquinoline **15**, which could then undergo an unusual conversion into the imine **16**, by a pathway recalling the transformation of benzilic acid into benzophenone.[11]

The results described above demonstrate that in the case of the six-membered-ring hydrazones the [3,3] sigmatropic rearrangement typical of the Fischer indolization can take place, even though in these cases the final cyclization to



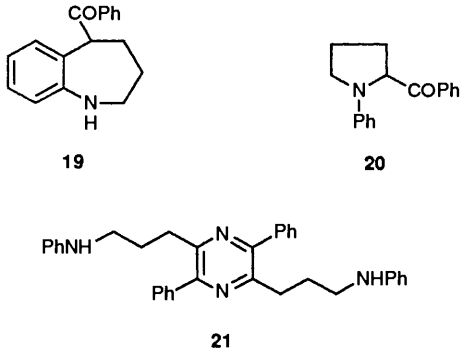
14 15 17 16

indoles is prevented. The cyclic enehydrazines, involved as intermediates in Robinson's general scheme[12] for the Fischer rearrangement, can undergo a noteworthy retro-Diels–Alder reaction instead. This retro-Diels–Alder reaction is not conceivable for the enehydrazine tautomer of the seven-membered-ring substrate **1g**; the latter, unknown in the literature, was prepared by reaction of 5-bromo-1-phenylpentan-1-one with phenylhydrazine. The yields of compound **1g** were modest, due to a concurrent reaction[13] leading to the indole **18**. Here, indolization of the phenylhydrazone preceded the intramolecular *N*-alkylation. Both compounds **1g** and **18** were isolated in a pure state by chromatography and were recognized on the basis of their analytical and spectral data.



18

The reaction of compound **1g** with PPA gave a mixture of 5-benzoyl-2,3,4,5-tetrahydro-1*H*-benz[*b*]azepine **19**, 2-benzoyl-1-phenylpyrrolidine **20** and 2,5-bis-(3-anilinopropyl)-3,6-diphenylpyrazine **21**.



19 20 21

The structures **19** and **21** were based on the interpretation of spectral data; compound **20** was independently synthesized by reaction of aniline with 2,5-dibromo-1-phenylbutan-1-one, unknown in the literature and prepared conventionally (see Experimental section).

The hydroazepine **19** was the expected product from the [3,3] sigmatropic rearrangement of the enehydrazine tautomer **22** of **1g**. In contrast, both **20** and **21** were new products, never previously observed in acid-catalysed rearrangements of arylhydrazones. This new pathway should be due to a few peculiar features of the substrate. Our mechanistic scheme (Scheme 3) involves again the homolytic cleavage of the N–N bond, this time of the protonated species **23**; this thermal initiation step furnishes the diradical cation **24**, which is converted into radical cation **25** by hydrogen abstraction from the medium. An easy internal hydrogen transfer[14] then gives rise to the radical cation **26** which, in turn, is oxidized to carbonium ion **27** by the protonated substrate **23** which here enters into the propagation cycle of the chain. The ketimino cation **27** could afford either (i) the pyrrolidino derivative **20** by intramolecular nucleophilic attack or (ii) the bisiminium salt **28** by dimerization. Aromatization of the latter to give compound **21** should occur easily.[15]

Conclusions.—The results reported above demonstrate that the [3,3] sigmatropic rearrangement of the enehydrazine tautomers, characteristic of open-chain arylhydrazones and generally leading to indoles, is still possible in six- and seven-membered cyclic hydrazones of the tetrahydropyridazine and tetrahydrodiazepine series. A rough representation of the geometry of the transition state based on molecular stereomodels suggests that a concerted process is allowed. This reaction course was not observed in the case of five-membered hydrazone rings on account of the unacceptable ring strain expected for the transition state.

For the five- and seven-membered-ring substrates good evidence was obtained for a radical process which seems to be rather general for the acidic rearrangements of arylhydrazones; it appears to occur when the enehydrazine formation and rearrangement are sluggish. This process involves an initial thermal N–N bond cleavage of the protonated hydrazone to give an anilinium radical cation which then either dimerizes or attacks the most electron-rich species present in solution, namely the substrate **1** itself, at the *para* position of the arylhydrazine moiety: benzidine derivatives are generally the products. A particular reaction course of the radical cation was observed for the seven-membered heterocycle; it is a Hoffmann–Loeffler rearrangement involving a δ hydrogen abstraction.

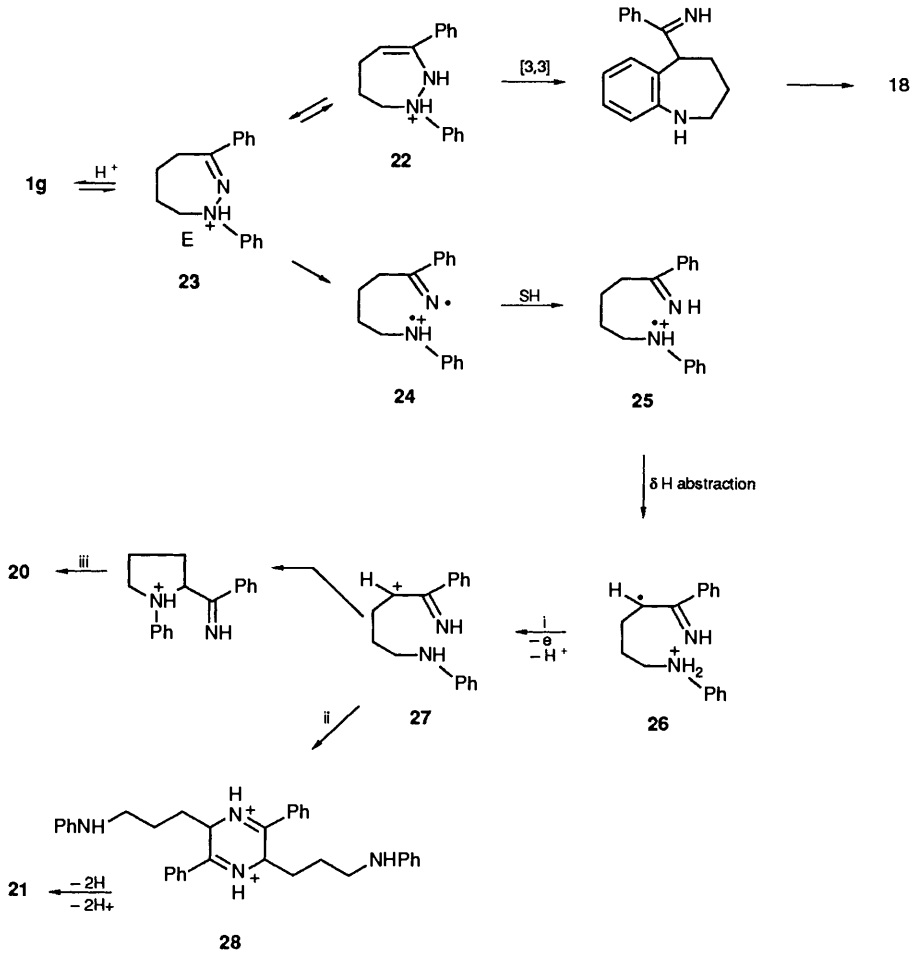
Noteworthy is the retro-Diels–Alder reaction observed for the six-membered cyclic hydrazones, adding a new aspect to the acidic rearrangements of arylhydrazones.

Experimental

M.p.s were measured on a Büchi and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on Varian EM-390 and Varian XL300 spectrometers with deuteriochloroform as solvent unless otherwise stated and with tetramethylsilane as internal standard. Chemical shifts are given in δ-units and refer to the centre of the signal: qt, quintet; *J*-values are given in Hz.

1,3-*Diphenyl*-1,4,5,6-*tetrahydropyridazine* **1c**.—A solution of phenylhydrazine (5.9 g) and sodium acetate trihydrate (7.4 g) in methanol (100 cm^3)–acetic acid (3.1 cm^3) was added at room temperature to a solution of 4-chloro-1-phenylbutan-1-one[16] (10 g) in methanol (20 cm^3). The solution was refluxed for 3 h; the solid that precipitated out upon cooling was washed with methanol to afford the *title compound*: m.p. 136 °C (9.6 g, 75%) [Found: C, 81.2; H, 6.7; N, 11.7%; M (mass spectrum), 236. $C_{16}H_{16}N_2$ requires C, 81.32; H, 6.82; N, 11.86%; M, 236]; δ_H 7.78 (2 H, m, phenyl 2- and 6-H in position 1), 7.32 (6 H, m, ArH), 6.88 (2 H, m, ArH), 3.65 (2 H, t, *J* 6, tetrahydropyridazine 6-H_2), 2.62 (2 H, t, *J* 5, tetrahydropyridazine 4-H_2) and 2.16 (2 H, m, tetrahydropyridazine 5-H_2).

3-*Methyl*-1-*phenyl*-1,4,5,6-*tetrahydropyridazine* **1d**.—Phenylhydrazine (13.4 g) was added to a solution of 5-chloropentan-2-one (15 g) in 50% acetic acid (150 cm^3); the reaction mixture



Scheme 3 *Reagents:* i, **23**; ii, dimerization; iii, water

was left at room temperature overnight, then diluted with water, and exhaustively extracted with diethyl ether. The combined extracts were washed with 5% aq. sodium hydrogen carbonate, dried (Na_2SO_4), and evaporated to dryness to give a residue, which was distilled *in vacuo* (b.p. 120 °C at 0.2 mmHg) to afford the *title compound* (3.2 g, 15%) (Found: C, 75.4; H, 8.2; N, 15.75. $C_{11}H_{14}N_2$ requires C, 75.43; H, 8.57; N, 16.00%); δ_H 7.73 (4 H, m, ArH), 7.3 (1 H, m, aryl 4-H), 3.6 (2 H, t, *J* 5, CH_2N) and 2.13 (7 H, m, CH_2CH_2 and Me).

1,3,6-*Triphenyl*-1,4,5,6-*tetrahydropyridazine* **1e**.—A solution of 1,3,6-triphenyl-1,4-dihydropyridazine[6] (7.8 g) in ethyl acetate (100 cm^3) was hydrogenated in the presence of 10% Pd on charcoal (0.35 g) at 20 atm of hydrogen pressure at room temperature. The catalyst was filtered off and the solvent was removed under reduced pressure. The residue was chromatographed on a silica gel column with benzene–ethyl acetate (9:1) to give *pure compound* **1e**, m.p. 130 °C (4.15 g, 53%) [Found: C, 85.0; H, 6.0; N, 9.0%; M (mass spectrum), 312. $C_{22}H_{20}N_2$ requires C, 84.58; H, 6.45; N, 8.97%; M, 312]; δ_H 7.85 (2 H, m, 2- and 6-H of 3-Ph), 7.3 (12 H, m, ArH), 6.8 (1 H, m, 4-H of 1-Ph), 5.27 (1 H, m, CH) and 2.3 (4 H, m, 2 × CH_2).

Ethyl 1-*Phenyl*-1,4,5,6-*tetrahydropyridazine*-3-*carboxylate* **1f**.—Potassium carbonate (4.5 g) was added to a solution of the phenylhydrazone of ethyl 5-chloro-2-oxopentanoate[17] (12.1 g) in ethanol (250 cm^3); the reaction mixture was refluxed for 24 h, then the solvent was removed under reduced pressure and the residue was treated with water and diethyl ether. The organic layer was washed successively with 5% hydrochloric acid and with water. Evaporation of the solvent left a solid, which was crystallized from cyclohexane to afford *ester* **1f**, m.p. 70 °C (4.3 g, 41%) (Found: C, 67.5; H, 7.1; N, 12.1. $C_{13}H_{16}N_2O_2$ requires C, 67.22; H, 6.92; N, 12.06%); δ_H 7.2 (4 H, m, ArH), 6.88 (1 H, m, 4-H of Ph), 4.25 (2 H, q, *J* 6, CH_2O), 3.55 (2 H, t, *J* 6, tetrahydropyridazine 6-H_2), 2.5 (2 H, m, tetrahydropyridazine 4-H_2), 1.98 (2 H, m, tetrahydropyridazine 5-H_2) and 1.32 (3 H, t, *J* 6, Me).

1,3-*Diphenyl*-4,5,6,7-*tetrahydro*-1H-1,2-*diazepine* **1g**.—A solution of 5-bromo-1-phenylpentan-1-one[18] (8 g), phenylhydrazine (3.6 g), and acetic acid (1.9 cm^3) in ethanol (40 cm^3) was refluxed for 12 h. Removal of the solvent left a residue, which was dissolved in chloroform and the undissolved hydrochloride of the 3-(3-aminopropyl)-2-phenylindole **18** was filtered off. The organic layer was washed successively with 5% hydrochloric acid and with 5% aq. sodium hydrogen carbonate. The organic extracts were dried (Na_2SO_4) and evaporated to dryness to give a residue, which was chromatographed on a silica gel column with chloroform. The first fractions eluted gave the *title compound* **1g** as an oil, which was distilled *in vacuo*, b.p. 160 °C (0.2 mmHg) (2.3 g, 28%) [Found: C, 81.35; H, 7.2; N, 11.3%; M (mass spectrum), 250. $C_{17}H_{18}N_2$ requires C, 81.56; H, 7.25; N, 11.19%; M, 250]; δ_H 7.8 (2 H, m, 2- and 6-H of 3-Ph), 7.3 (7 H, m, ArH), 6.85 (1 H, m, 4-H of 3-Ph), 3.65 (2 H, m, tetrahydrodiazepine 7-H_2), 2.9 (2 H, m, tetrahydrodiazepine 4-H_2) and 1.8 (4 H, m, tetrahydradiazepine 5- and 6-H_2). The hydrochloride of the indole **18** previously isolated was treated with 5% ammonium hydroxide and exhaustively extracted with diethyl ether; the combined extracts

were dried (Na_2SO_4) and evaporated to dryness to give a residue, which was crystallized from ethanol to give pure *compound* **18** [Found: C, 81.4; H, 7.05; N, 11.0%; M (mass spectrum), 250. $C_{17}H_{18}N_2$ requires C, 81.56; H, 7.25; N, 11.19%; M, 250]; δ_H 8.43 (1 H exchanging with D_2O, s, NH), 7.3 (9 H, m, ArH), 2.91 (2 H, t, *J* 6, CH_2N), 2.72 (2 H, t, *J* 6, CH_2), 1.88 (2 H, qt, *J* 6, $CH_2CH_2CH_2$) and 1.07 (2 H, exchanging with D_2O, s, NH_2).

Reaction of Compound **1a** *with PPA.*—A mixture of compound **1a** (11.0 g) and PPA (110 g) was heated at 170 °C for 40 min, then poured into ice–water; a brown, sandy solid precipitated out, which was recovered by filtration. The filtrate was treated with 26% aq. ammonium hydroxide to adjust the pH to 5 (universal indicator paper) and was then extracted with diethyl ether; some unsoluble material was recognized as benzidine **3** with m.p. 121 °C (from benzene) (0.35 g). The organic extracts were dried (Na_2SO_4) and evaporated to dryness to give a brown viscous residue (2.3 g), which was chromatographed on a silica gel column with chloroform and purified by distillation *in vacuo*, and was recognized as benzylideneacetone **4**. The solid precipitate obtained by quenching of the reaction with water was dissolved in chloroform and the solution was washed with 5% aq. ammonium hydroxide and dried (Na_2SO_4). Evaporation of the solvent left a brown residue (7.0 g), which was treated with diethyl ether. Some insoluble material was filtered off and the solution was washed with 5% hydrochloric acid: some benzidine hydrochloride precipitated out and was removed by filtration. The ethereal solution was washed successively with water and 5% aq. ammonium hydroxide, and dried (Na_2SO_4). Removal of the solvent left a residue (3.0 g, 30%), which was triturated with hexane to give 2-*styrylindole* **2**, m.p. 201 °C [Found: C, 87.2; H, 6.1; N, 6.3%; M (mass spectrum), 219. $C_{16}H_{13}N$ requires C, 87.64; H, 5.98; N, 6.39%; M, 219]; δ_H 8.20 (1 H, br s, NH), 7.35 (10 H, m, ArH), 6.86 (1 H, d, *J* 7, vinylic H bonded to indole) and 6.60 (1 H, d, *J* 2, indole 3-H).

Reaction of Compound **1b** *with PPA.*—A mixture of compound **1b** (6 g) and PPA (50 g) was heated at 110 °C for 2 h, then poured into ice–water, neutralized with 26% aq. ammonium hydroxide and exhaustively extracted with diethyl ether. The combined extracts were dried (K_2CO_3) and evaporated to dryness to give 1-*phenyl*-3-[4′-(3-*phenyl*-4,5-*dihydropyrazol*-1-*yl*)*biphenyl*-4-*yl*]*aminopropan*-1-*one* **6a** as a residue, which was first triturated with warm diethyl ether then crystallized from 1,4-dioxane: m.p. 208 °C (3.5 g, 58%) [Found: C, 80.4; H, 6.1; N, 9.5%; M (mass spectrum), 445. $C_{30}H_{27}N_3O$ requires C, 80.87; H, 6.11; N, 9.43%; M, 445]; $\delta_H(C_6D_5N)$ 7.55 (14 H, m, ArH), 8.05 (2 H, m, 2- and 6-H of 1-Ph), 6.90 (2 H, d, *J* 7, biphenyl 3- and 5-H), 5.35 (1 H, br s exchanging with D_2O, NH), 3.8 (4 H, resulting from the superimposition of 2 t, CH_2NH and pyrazoline 5-H_2), 3.38 (2 H, t, *J* 5, CH_2CO) and 3.08 (2 H, t, *J* 9, pyrazoline 4-H_2).

4′-(3-*Phenyl*-4,5-*dihydropyrazol*-1-*yl*)*biphenyl*-4-*amine* **6b**.—A solution of compound **6a** (0.4 g) in 37% hydrochloric acid (1 cm^3)–acetic acid (5 cm^3) was refluxed for a few min to give the *hydrochloride of the title amine* **6b** which crystallized out on cooling; m.p. >210 °C (0.1 g, 36%) [Found: C, 71.7; H, 5.6; N, 11.7%; M (mass spectrum), 313. $C_{21}H_{20}ClN_3$ requires C, 72.09; H, 5.76; N, 12.01%; M, 313]; $\delta_H[(CD_3)_2SO]$ 7.40 (7 H, m, ArH), 7.75 (2 H, m, 2- and 6-H of the pyrazoline 3-Ph), 7.1 (2 H, d, biphenyl 3- and 5-H), 6.60 (2 H, dd, biphenyl 3′- and 5′-H), 5.1 (2 H, br s exchanging with D_2O, NH_2), 3.91 (2 H, t, *J* 9, pyrazoline 5-H_2) and 3.35 (2 H, t, *J* 9, pyrazoline 4-H_2).

N-[4′-(3-*Phenyl*-4,5-*dihydropyrazol*-1-*yl*)*biphenyl*-4-*yl*] *acetamide* **6c**.—The hydrochloride of compound **6b** (0.1 g) was dissolved in water (5 cm^3) and the solution was neutralized with 26% aq. ammonium hydroxide and then exhaustively extracted with ethyl acetate. The combined extracts were dried (K_2CO_3) and evaporated to dryness to give a residue, which was dissolved in hot acetic acid (1 cm^3)—acetic anhydride (0.1 cm^3) and the solution was refluxed for 5 min, diluted with water, neutralized with 26% aq. ammonium hydroxide, and extracted with ethyl acetate. The extract was dried (K_2CO_3) and evaporated to dryness to give *pure compound* **6c** [Found: C, 77.6; H, 5.6; N, 11.5%; M (mass spectrum), 355. $C_{23}H_{21}N_3O$ requires C, 77.72; H, 5.95; N, 11.82%; M, 355]; $\delta_H(C_5D_5N)$ 7.75 (13 H, m, ArH), 3.77 (2 H, t, *J* 8, pyrazoline 5-H_2), 3.10 (2 H, t, *J* 8, pyrazoline 4-H_2) and 2.22 (3 H, s, Me).

N-(4′-*Hydrazinobiphenyl*-4-*yl*)*acetamide* **8**.—Aq. $NaNO_2$ (0.92 g in 5 cm^3) was slowly added to a suspension of *N*-acetylbenzidine[19] (3 g) in 10% hydrochloric acid (20 cm^3) while the temperature was kept below 0 °C. Some undissolved material was filtered off and a solution of tin(II) chloride dihydrate (6 g) in conc. hydrochloric acid (25 cm^3) was added to the filtrate, with the temperature kept below 5 °C. The resulting suspension was stirred for 24 h. The solid was collected by filtration and treated with sodium hydroxide (excess) under cooling. The crude hydrazine was extracted with ethyl acetate. The organic layer was dried (K_2CO_3) and evaporated to dryness to give compound **8** (0.8 g, 81%) as a pale yellow solid, which was used for the next reaction with no further purification.

N-[4′-(3-*Phenyl*-4,5-*dihydropyrazol*-1-*yl*)*biphenyl*-4-*yl*]*acetamide* **6c** *and* N-[4′-(3-*Phenylpyrazol*-1-*yl*)*biphenyl*-4-*yl*]*acetamide* **7**.—A solution of 1-phenylprop-2-enone (0.38 g) and the hydrazine **8** (0.66 g) in ethanol (100 cm^3) containing acetic acid (0.5 cm^3) was stirred overnight. The solid precipitate was identical with a sample of compound **6c** prepared by acetylation of free amine **6b**, prepared in turn by acidic hydrolysis of compound **6a**. Short refluxing of compound **6c** in acetic acid solution, followed by neutralization with 26% aq. ammonium hydroxide and exhaustive extraction with ethyl acetate, gave a residue, which was chromatographed on a silica gel column with benzene–ethyl acetate (1:1). The *pyrazole* **7** was obtained in a pure state, m.p. >210 °C [Found: C, 77.9; H, 5.6; N, 11.8%; M (mass spectrum), 353. $C_{23}H_{19}N_3O$ requires C, 78.16; H, 5.42; N, 11.89%; M, 353]; $\delta_H[(CD_3)_2SO]$ 10.05 (1 H, s exchanging with D_2O, NH), 8.64 (1 H, d, *J* 2, pyrazole 5-H), 7.7 (13 H, m, ArH), 7.02 (1 H, d, *J* 2, pyrazole 4-H) and 2.15 (3 H, s, Me).

Aromatization of compound **6c** to compound **7** could also be achieved in refluxing xylene solution in the presence of 10% palladized charcoal.

Reaction of Compound **1c** *with PPA.*—A mixture of compound **1c** (5 g) was heated at 110 °C for 20 min, then poured into ice–water, neutralized with 26% aq. ammonium hydroxide and exhaustively extracted with chloroform. The combined extracts were dried (Na_2SO_4) and evaporated to dryness. The crude residue was dissolved in a little chloroform and the solution was added to stirred diethyl ether. Some insoluble material was filtered off and the clear filtrate was treated with dry hydrogen chloride until precipitation was complete. The solid was filtered off and suspended in water, then treated with 26% aq. ammonium hydroxide. The free bases were extracted with chloroform; the extract was washed with water, dried (K_2CO_3), and evaporated to dryness to give a residue, which was chromatographed on a silica gel column with chloroform. The first product to be eluted was 3-anilino-1-phenylpropan-1-one **11c**[8] (0.2 g, 4%), m.p. 113 °C [Found: C, 79.8; H, 6.65; N, 5.8%; M (mass spectrum), 225.

Calc. for $C_{15}H_{15}NO$: C, 79.97; H, 7.61; N, 6.22%; **M**, 225]; δ_H 7.98 (2 H, m, 2- and 6-H of COPh), 7.49 (3 H, m, 3-, 4- and 5-H of COPh), 7.19 (2 H, m, aniline 3- and 5-H), 6.70 (3 H, m, aniline 2-, 4- and 6-H), 4.10 (1 H, br s exchanging with D_2O, NH), 3.75 (2 H, t, *J* 5, CH_2CH_2NH) and 3.30 (2 H, t, *J* 5, $COCH_2CH_2$).

The second product to be eluted was 4-*benzoyl*-1,2,3,4-*tetrahydroquinoline* **9c** (0.2 g, 4%), m.p. 126 °C [Found: C, 80.7; H, 6.4; N, 5.7%; M (mass spectrum), 237. $C_{16}H_{15}NO$ requires C, 80.98; H, 6.37; N, 5.90%; M, 237]; δ_H 8.05 (2 H, m, 2-, 6-H of Ph), 7.50 (3 H, m, 3-, 4- and 5-H of Ph), 6.8 (4 H, m, quinoline ArH), 4.80 (1 H, t, *J* 5, $CHCH_2$), 3.79 (1 H, br s exchanging with D_2O, NH), 3.32 (2 H, m, $NHCH_2CH_2$) and 2.22 (2 H, m, $CHCH_2CH_2$).

The acidic ethereal filtrate from which the hydrochlorides of compounds **9c** and **11c** had been separated was washed successively with water and 5% aq. sodium hydrogen carbonate. The organic layer was then dried (Na_2SO_4), and removal of the solvent left a residue (0.5 g), which was chromatographed on a silica gel column with chloroform to give 3-(4-benzoyl-1,2,3,4-tetrahydroquinolin-1-yl)-1-phenylpropan-1-one **10c** (0.25 g, 6%); δ_H 8.0 (4 H, m, 2- and 6-H of two Phs), 7.40 (6 H, m, 3-, 4- and 5-H of two Phs), 6.9 (4 H, m, quinoline ArH), 4.75 (1 H, t, *J* 5, CH), 3.85 (2 H, m, tetrahydroquinoline 2-H_2), 3.35 (4 H, m, NCH_2CH_2CO) and 2.22 (2 H, q, *J* 5, tetrahydroquinoline 3-H_2).

Reaction of Compound **1d** *with PPA*.—A mixture of compound **1d** (2.5 g) and PPA (50 g) was heated at 110 °C for 45 min, then poured into ice–water, neutralized with 26% aq. ammonium hydroxide, and exhaustively extracted with diethyl ether. The combined extracts were dried (Na_2SO_4) and evaporated to dryness to give a residue (2.1 g), which was chromatographed on a silica gel column with benzene–ethyl acetate (9:1). A roughly equimolar mixture (0.75 g) of 4-acetyl-1,2,3,4-tetrahydroquinoline **9d** and 4-anilinobutan-2-one **11d**[8] was eluted first: the components were identified on the basis of spectral data in comparison with those obtained from pure samples. 4-Acetyl-1,2,3,4-tetrahydroquinoline **9d** could be obtained in a pure state by reflux of the mixture with 10% aq. hydrochloric acid for 30 min. Chromatography of the resulting bases on a silica gel column with chloroform, followed by distillation *in vacuo*, gave *compound* **9d**, b.p. 110 °C (0.2 mmHg) [Found: C, 75.4; H, 7.1; N, 7.8%; M (mass spectrum), 175. $C_{11}H_{13}NO$ requires C, 75.40; H, 7.48; N, 7.99%; M, 175]; δ_H 7.00 (2 H, m, ArH), 6.58 (2 H, m, quinoline 6- and 8-H), 3.76 (1 H, t, *J* 5, CH), 3.31 (3 H, one exchanging with D_2O, NH and tetrahydroquinoline 2-H_2) and 2.04 (5 H, m, Ac and tetrahydroquinoline 3-H_2).

The final fractions from the first chromatography gave 4-(4-*acetyl*-1,2,3,4-*tetrahydroquinolin*-1-*yl*)*butan*-2-*one* **10d**, which was purifed by distillation *in vacuo*, b.p. 170 °C (0.2 mmHg) (recovery 0.2 g, 11%) [Found: C, 73.3; H, 7.8; N, 5.7%; M (mass spectrum), 245. $C_{15}H_{19}NO_2$ requires C, 73.44; H, 7.81; N, 5.71%; M, 245]; δ_H 7.03 (2 H, m, ArH), 6.58 (2 H, m, quinoline 6- and 8-H), 3.63 (3 H, m, CH_2N and CH), 3.27 (2 H, m, tetrahydroquinoline 2-H_2), 2.75 (2 H, t, *J* 6, CH_2CO) and 2.2 (8 H, m, 2 × Ac and tetrahydroquinoline 3-H_2).

Reaction of Compound **1e** *with PPA*.—A mixture of compound **1e** (3.1 g) and PPA (50 g) was heated at 110 °C for 30 min, then poured into ice–water. The mixture was steam distilled and the distillate was exhaustively extracted with diethyl ether. Removal of the solvent from the extract left an oily residue (0.45 g, 45%) consisting of a 1:1 mixture (GLC) of benzaldehyde and phenyl vinyl ketone. The aq. residue was made alkaline with 26% aq. ammonium hydroxide and exhaustively extracted with chloroform. The extract was washed with water, dried (K_2CO_3), and evaporated to dryness to give a residue, which was chromatographed on a silica gel column with chloroform. The first fractions eluted gave some unchanged material **1e** (0.2 g recovery). The following fractions gave a mixture of the two diastereoisomers expected for 4-*benzoyl*-2-*phenyl*-1,2,3,4-*tetrahydroquinoline* **13** (0.9 g, 27%); one of them (0.08 g) was obtained in a pure state by fractional crystallization from benzene; m.p. 183 °C [Found: C, 84.0; H, 6.1; N, 4.6%; M (mass spectrum), 313. $C_{22}H_{19}NO$ requires C, 84.31; H, 6.11; N, 4.47%; M, 313]; δ_H 7.90 (2 H, m, benzoyl 2- and 6-H), 7.35 (8 H, m, ArH), 6.97 (1 H, t, *J* 6, tetrahydroquinoline 8-H), 6.77 (1 H, t, *J* 5, tetrahydroquinoline 5-H), 6.54 (2 H, m, tetrahydroquinoline 6- and 7-H), 4.79 (1 H, t, *J* 4, CHCO), 4.54 (1 H, t, *J* 5, CHN), 4.15 (1 H, s exchanging with D_2O, NH) and 2.26 (2 H, m, CH_2).

4-*Benzoyl*-2-*phenylquinoline*.—A solution of compound **13** (0.04 g) in xylene (10 cm^3) was refluxed for 7 h in the presence of 10% Pd on charcoal. The catalyst was filtered off and the solvent was removed under reduced pressure. The residue was purified by distillation *in vacuo*, b.p. 193 °C (0.2 mmHg). The distillate (*title compound*) crystallized on storage; m.p. 107 °C [Found: C, 85.2; H, 4.8; N, 4.5%; M (mass spectrum), 309. Calc. for $C_{22}H_{15}NO$: C, 85.44; H, 4.85; N, 4.53%; M, 309].

Reaction of Compound **1f** *with PPA*.—A mixture of compound **1f** (4.3 g) and PPA (50 g) was heated at 110 °C for 15 min, then poured into ice–water, neutralized with 26% aq. ammonium hydroxide, and exhaustively extracted with diethyl ether. The combined extracts were dried (Na_2SO_4) and evaporated to dryness to give a residue (1.6 g), which was chromatographed on a silica gel column with chloroform. The only product isolated in a pure state after distillation *in vacuo*, b.p. 100 °C (0.2 mmHg), was 4-oxo-1,2,3,4-tetrahydroquinoline **17** (0.5 g, 19%) [Found: C, 73.7; H, 5.8; N, 9.8%; M (mass spectrum), 147. Calc. for C_9H_9NO: C, 73.47; H, 6.12; N, 9.52%; M, 147]; δ_H 7.85 (1 H, dd, *J* 2, 5-H), 7.28 (1 H, m, 7-H), 6.72 (2 H, m, 6- and 8-H), 4.52 (1 H, br s exchanging with D_2O, NH), 3.6 (2 H, t, *J* 6, CH_2NH) and 2.72 (2 H, t, *J* 6, $COCH_2$).

Reaction of Compound **1g** *with PPA*.—A mixture of compound **1g** (2 g) and PPA (20 g) was heated at 110 °C for a few minutes, then poured into ice–water, neutralized with 26% aq. ammonium hydroxide, and exhaustively extracted with diethyl ether. The combined extracts were dried (Na_2SO_4) and evaporated to dryness to give a residue, which was chromatographed on a silica gel column with chloroform. The first product to be eluted (0.2 g, 10%) was 2-*benzoyl*-1-*phenylpyrrolidine* **20**, which was purified by treatment with diisopropyl ether, m.p. 97 °C [Found: C, 81.6; H, 7.0; N, 5.5%; M (mass spectrum), 251. $C_{17}H_{17}NO$ requires C, 81.24; H, 6.82; N, 5.57%; M, 251]; δ_H 8.10 (2 H, dd, *J* 6.2, benzoyl 2- and 6-H), 7.57 (3 H, m, ArH), 7.18 (2 H, t, *J* 6, 3- and 5-H of NPh), 6.63 (1 H, t, *J* 6, 4-H of NPh), 6.43 (2 H, d, *J* 8, 2- and 6-H of NPh), 5.20 (1 H, dd, *J* 7.2 CH), 3.6 (2 H, m, pyrrolidine 5-H_2) and 2.15 (4 H, m, pyrrolidine 3- and 4-H_2). The second product eluted was triturated with diisopropyl ether to give 5-*benzoyl*-2,3,4,5-*tetrahydro*-1H-*benz*[b]*azepine* **19** (0.35 g, 17.5%), m.p. 75 °C [Found: C, 81.0; H, 6.8; N, 5.55%; M (mass spectrum), 251. $C_{17}H_{17}NO$ requires C, 81.24; H, 6.82; N, 5.57%; M, 251]; δ_H 7.87 (2 H, m, benzoyl 2- and 6-H), 7.10 (7 H, m, ArH), 4.83 (1 H, m, CH), 3.25 (3 H, one exchangeable with D_2O, m, tetrahydroazepine 2-H_2 and NH) and 2.10 (4 H, m, tetrahydroazepine 3- and 4-H_2). The last fractions, eluted with chloroform–methanol (9.9:0.1), gave a solid, which was purified by crystallization from a diisopropyl ether to give 2,5-*bis*(3-*anilinopropyl*)-3,6-*diphenylpyrazine* **21** (0.4 g, 10%), m.p. 101 °C [Found: C, 81.5; H, 7.0; N, 11.0%; M (mass spectrum), 498. $C_{34}H_{34}N_4$ requires C, 81.89; H, 6.87; N, 11.24%; M, 498]; δ_H

7.50 (10 H, m, 2 × COPh), 7.10 (4 H, t, *J* 6, 3- and 5-H of NPhs), 6.64 (2 H, t, *J* 6, 4-H of NPhs), 6.45 (4 H, d, *J* 7, 2- and 6-H of NPhs), 3.67 (2 H, s exchangeable with D_2O, 2 × NH), 3.05 (8 H, m, 2 × $CH_2CH_2CH_2$) and 2.07 (4 H, m, 2 × $CH_2CH_2CH_2$).

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