Self-condensation and Rearrangement of *N*-Alkylphenacylamines

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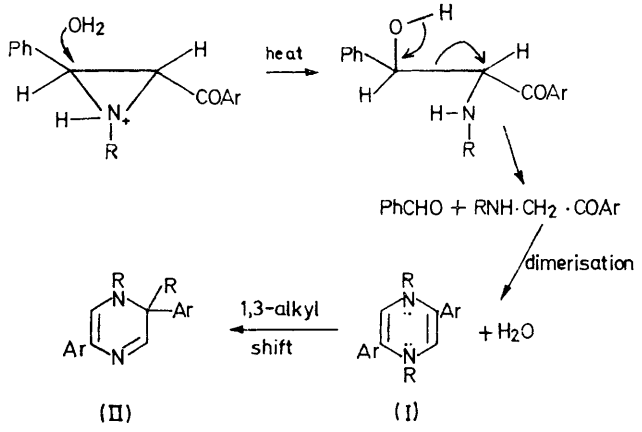
The reaction of phenacyl bromide with benzylamine affords 1,2-dibenzyl-1,2-dihydro-2,5-diphenylpyrazine (59%) and 1,2-dibenzyl-1,2-dihydro-3,6-diphenylpyrazine (21%), contrary to previous reports. In a series of reactions of *N*-alkylphenacylamines thermally induced self-condensation is followed by a regiospecific 1,3-alkyl shift to a substituted carbon atom, to give in good yield 1,2-dialkyl-1,2-dihydro-2,5-diphenylpyrazines at temperatures ranging from ambient to 140°. The reaction of phenacyl bromide with methylamine gives *N*-methyldiphenacylamine, then the reactive 1,4-dihydro-1,4-dimethyl-2,6-diphenylpyrazine. The latter readily forms an addition product with methanol and separately forms an odd-electron species characteristic of 1,4-dialkyl-1,4-dihydropyrazines.

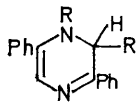
WHEREAS the spontaneous self-condensation of α-aminocarbonyl compounds to readily oxidisable dihydropyrazines is widely used as a general synthesis of substituted pyrazines,[1] the corresponding reaction of *N*-alkylphenacylamines has received little attention. We reported recently that 1,2-dihydropyrazines (shown to result from the self-condensation of *N*-alkylphenacylamines and subsequent rearrangement of the intermediate 1,4-dialkyl-1,4-dihydro-2,5-diphenylpyrazines) may be isolated from the products of controlled thermal decomposition of 3-aroylaziridines in acetonitrile solutions.[2] This observation, together with recent reports



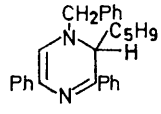
(II) (I)

on dihydropyrazine chemistry,[3,4] aroused our interest in the potentially antiaromatic[5] 8 π-electron 1,4-dialkyl-1,4-dihydropyrazines. We have reported the general synthesis of 1,4-dialkyl-1,4-dihydro-2,6-diphenylpyrazines.[6]

An apparent discrepancy existed between our results for the 1,4-dihydro-2,5-diphenylpyrazine rearrangement[2] and literature reports.[3a] Mason reported that the base-catalysed cyclodehydration of *N*-benzylphenacylamine hydrobromide gives the 1,4-dibenzyl-1,4-dihydropyrazine (I; R = $PhCH_2$, Ar = Ph).[7] Chen and Fowler later reported this assignment to be incorrect and showed that the product isolated in 20% yield was the rearranged 1,2-dihydropyrazine (III; R = $PhCH_2$) in which the benzyl group has migrated to an unsubstituted carbon atom, in contrast to our previous findings.



(III)



(IV)

We now report that compound (III) is a minor product of this reaction, the major product (59% yield) being the isomer in which the benzyl group has migrated to the phenyl-substituted carbon atom (II; R = $PhCH_2$, Ar = Ph). Moreover, this latter type of product was the only one isolated, in excellent yield, in a series of condensations and subsequent regiospecific rearrangements of other *N*-alkylphenacylamines, often conducted at moderate temperatures.

Treatment of *N*-benzylphenacylamine hydrobromide with aqueous 20% potassium carbonate or saturated sodium carbonate solution under reflux for 1 h followed by extraction with ether, evaporation, and trituration of the residual oil with ethanol gave compound (III; R = $PhCH_2$, Ar = Ph) in 21% yield. The n.m.r. spectrum of the product was consistent with the structure and in accordance with the literature report.[3a] Chromatographic separation of the residual oil gave compound (II; R = $PhCH_2$, Ar = Ph) as a yellow solid in 59% yield. The structure of (II) follows from analytical data, accurate mass measurement, and the n.m.r. spectrum [δ 3·84 and 4·86 (each 2H, s, $PhCH_2$) and 6·73 (sharp s, 6-H); no methine signal as seen for the isomer (III)]. Although the benzylic protons in structure (II; R = $PhCH_2$, Ar = Ph) might have been expected to be diastereotopic and therefore to exhibit AB quartets,[8] the benzylic protons in the related compound (IV) (obtained by thermal 1,3-alkyl shift of

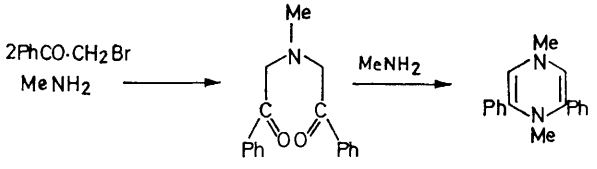
[1] Y. T. Pratt, in ' Heterocyclic Compounds,' ed. R. C. Elderfield, vol. 6, Wiley, New York, 1957, ch. 9.
[2] J. W. Lown and M. H. Akhtar, *Canad. J. Chem.*, 1972, **50**, 2236.
[3] S.-J. Chen and F. W. Fowler, *J. Org. Chem.*, (*a*), 1970, **35**, 3987; (*b*) 1971, **36**, 4025.
[4] R. A. Sulzbach and A. F. M. Iqbal, *Angew. Chem. Internat. Edn.*, 1971, **10**, 127.
[5] R. Breslow, J. Brown, and J. Gajewski, *J. Amer. Chem. Soc.*, 1967, **89**, 4383; R. Breslow, *Angew. Chem. Internat. Edn.*, 1968, **7**, 565.
[6] J. W. Lown and M. H. Akhtar, *Chem. Comm.*, 1972, 829.
[7] A. T. Mason and G. R. Winder, *J. Chem. Soc.*, 1893, **63**, 1355.
[8] L. M. Jackman and S. Sternhell, ' Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry,' 2nd edn., Pergamon, Oxford, 1969, p. 368.

4-benzyl-1-cyclopentyl-2,6-diphenyl-1,4-dihydropyrazine [6]) are also adventitiously equivalent and appear as a sharp singlet at δ 4·55. This latter experiment confirms the previously suggested intermediacy of 1,4-dialkyl-1,4-dihydro-2,6-diphenylpyrazines in this rearrangement.

In reactions related to the formation of compound (II; R = $PhCH_2$, Ar = Ph) the free bases *N*-t-butylphenacylamine and *N*-cyclohexylphenacylamine were isolated, characterised, and heated to give compounds (II; R = Bu^t, Ar = Ph) (89%) and (II; R = C_6H_{11}, Ar = Ph) (92%), respectively.

Data for a series of 1,2-dialkyl-1,2-dihydro-2,5-diphenylpyrazines prepared similarly are summarised in the Table. The yields are generally excellent, with the exception of the hindered chiral α-methylbenzyl compound. In all cases a regiospecific migration of the alkyl group to a substituted carbon atom is observed, with the exception of the benzyl derivative where a regioselective rearrangement results.

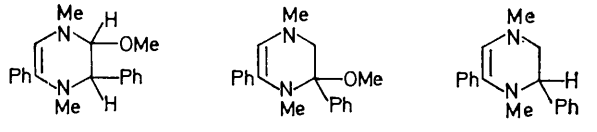
The reaction of phenacyl bromide with anhydrous methylamine gas in benzene, however gave the reactive 1,4-dihydro-1,4-dimethyl-2,6-diphenylpyrazine (VI). The structure was confirmed, and the alternative isomeric 2,5-diphenyl structure eliminated, by the isolation



(V) (VI)

and characterisation of the intermediate *N*-methyldiphenacylamine (V). Treatment of compound (V) with 1 equiv. of methylamine at 60° afforded compound (VI) (53%), identical with that obtained directly. Compound (VI) shows a simple n.m.r. spectrum consistent with its symmetry [δ 1·72 and 2·07 (each s, NMe), 5·32 (s, vinyl H), and aryl absorption]. Characteristically the spectrum is difficult to reproduce owing to the frequent onset of paramagnetic broadening due to the appearance of a stable odd-electron species,[6] which in turn gives a finely resolved and stable nine-line e.s.r. spectrum of width 62·67 mT in benzene.

Structure (VI) was confirmed by the isolation of a methanol addition product (VII). The n.m.r. spectrum eliminated the isomeric structure (VIII). Compound

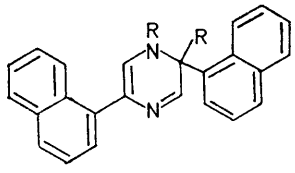


(VII) (VIII) (IX)

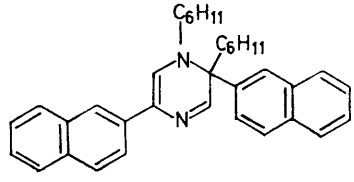
(VII) is not prone to form odd-electron species and therefore gives a normal, reproducible n.m.r. spectrum with sharp lines.

In addition, compound (VI) was hydrogenated over palladium to form the 1,2,3,4-tetrahydropyrazine (IX), identified by its n.m.r. spectrum. Addition of only 1 equiv. of hydrogen on atmospheric catalytic hydrogenation is characteristic of 1,4-dialkyl-1,4-dihydropyrazines.[3,6]

The reaction of 1-bromoacetylnaphthalene with t-butylamine gave the corresponding α-amino-ketone. Thermolysis of the latter in toluene at 110° gave the rearranged 1,2-dihydropyrazine (Xa). Similarly the reaction of the cyclohexyl analogue gave only compound (Xb), whereas with the 2-bromoacetylnaphthalene the isomer (XI) was isolated in good yield. In these cases,



(X) a; R = Bu^t
b; R = C_6H_{11}



(XI)

despite substantially increased steric crowding at the 1- and 2-positions of the product, migration of R is regiospecific to the substituted position as shown by the absence of a methine n.m.r. signal, which is clearly visible in the spectrum of (IV). The self-condensation and rearrangement of *N*-cyclohexylphenacylamine in cyclohexene or cumene gave no trace of bicyclohexenyl or cumene dimer, respectively. These observations, together with the great facility with which condensation and rearrangement of some *N*-alkylphenacylamines take place (*e.g.* ambient temperature for the isopropyl derivative and 52° for the 2-naphthyl), the high yields, and the absence of polymeric side products militate against a free-radical chain mechanism.

A more complete mechanistic study is possible of the rearrangement of the 1,4-dialkyl-2,6-diaryl-1,4-dihydropyrazines. The significance of the stereochemistry and regiospecificity and magnitude of the Arrhenius parameters with respect to the mechanism of the accompanying 1,3-alkyl shift, whether sigmatropic or radical-dissociation–recombination, will be discussed in a later paper.

EXPERIMENTAL

M.p.s were determined with a Fisher–Johns apparatus. I.r. spectra were recorded with a Perkin-Elmer model 421 spectrophotometer. N.m.r. spectra were recorded with Varian A60 and A100 spectrometers for *ca.* 5—10% (w/v) solutions; line positions are reported in p.p.m. from

tetramethylsilane. Mass spectra were determined with an A.E.I. MS12 double-focusing high-resolution instrument (ionisation energy usually 70 eV). Peak measurements were made by comparison with perfluorotributylamine at a resolving power of 15,000. Kieselgel DF-5 (Camag) and Eastman–Kodak precoated silica sheets were used for the t.l.c. Microanalyses were carried out by Mrs. D. Mahlow of this department. Alumina (B.D.H.) was used for column chromatography.

1,2-Dibenzyl-1,2-dihydro-2,5-diphenylpyrazine and 1,2-Dibenzyl-1,2-dihydro-3,6-diphenylpyrazine.—To *N*-benzylphenacylamine hydrobromide (4·6 g, 15 mmol) was added aqueous 20% potassium carbonate (30 ml) and the mixture was heated under reflux with stirring for 1 h. The red oil obtained on cooling was extracted with ether, and the extract dried (Na_2SO_4) and evaporated. Trituration of the residual oil with ethanol deposited yellow 1,2-dibenzyl-1,2-dihydro-3,6-diphenylpyrazine (III; R = $PhCH_2$, Ar = Ph) (0·627 g, 21%), m.p. 156—157·5° (lit.,[3] 153—157°). The spectral data, in particular the n.m.r. spectrum, were in accord with literature reports.[3] The residual oil from the filtrate was chromatographed on alumina (50 g). Elution with benzene–hexane (1 : 1) gave as the main fraction a yellow oil which on trituration with ethanol and cooling gave yellow *1,2-dibenzyl-1,2-dihydro-2,5-diphenylpyrazine* (1·77 g, 59%) (II; R = $PhCH_2$, Ar = Ph), m.p. 101—102·5° (see Table), δ ($CDCl_3$) 3·84 (2H, s, CH_2Ph), 4·86 (2H, s, CH_2Ph), 6·73 (1H, s, 6-H), and 6·93—8·34 (21H, m, ArH and 3-H).

Virtually identical yields and product ratio were obtained when saturated sodium carbonate solution was used as the base catalyst.

N-Cyclohexylphenacylamine.—A mixture of α-bromoacetophenone (10 g, 5 mmol) and cyclohexylamine (10 g, 10 mmol) in dry ether (150 ml) was stirred at room temperature for 6 h. The precipitated cyclohexylamine hydrobromide was collected and the filtrate washed with cold water (2 × 25 ml) and dried (Na_2SO_4). Removal of the solvent *in vacuo* gave yellow *N-cyclohexylphenacylamine* (8·64 g, 80%), m.p. 113—115·5° (from methanol) (Found: C, 77·1; H, 8·9; N, 6·5. $C_{14}H_{19}NO$ requires C, 77·3; H, 8·8; N, 6·4%), $\nu_{max.}$ ($CHCl_3$) 3310 (NH) and 1670 cm^{-1} (CO).

N-t-Butylphenacylamine.—A similar reaction between α-bromoacetophenone and t-butylamine in dry ether gave *N-t-butylphenacylamine* (75%), m.p. 125—126° (Found: C, 75·1; H, 8·7; N, 7·2. $C_{12}H_{17}NO$ requires C, 75·3; H, 8·9; N, 7·3%).

Self-condensation and Rearrangement of Free N-Alkylphenacylamines.—A solution of *N*-t-butylphenacylamine (4·75 g, 25 mmol) in *o*-xylene (100 ml) was heated under reflux for 7 h. Removal of the solvent *in vacuo* gave a red oil which slowly solidified. Trituration with methanol afforded *1,2-dihydro-2,5-diphenyl-1,2-di-t-butylpyrazine* (II; R = Bu^t, Ar = Ph) (3·73 g, 89%), m.p. 145—147, δ ($CDCl_3$) 0·66 (9H, s, 2-Bu^t), 1·38 (9H, s, 1-Bu^t), 6·86 (1H, s, 6-H), and 7·16—7·82 (11H, m, ArH and 3-H).

The analogous reaction of *N*-cyclohexylphenacylamine afforded *1,2-dicyclohexyl-1,2-dihydro-2,5-diphenylpyrazine* (II; R = C_6H_{11}, Ar = Ph), m.p. 97—98·5°, in 92% yield.

Similar reaction conditions were employed to prepare the 1,2-dialkyl-1,2-dihydro-2,5-diphenylpyrazines listed in the Table. In the case of the t-butyl derivative a 2·5-fold excess of t-butylamine was added and the temperature of refluxing *o*-xylene used.

Reaction of α-Bromoacetophenone with Methylamine.—Into a solution of α-bromoacetophenone (10 g, 50 mmol)

1,2-Dialkyl-1,2-dihydro-2,5-diphenylpyrazines

			Required (%)				Found (%)					
R	M.p. (°C)	Yield (%)	C	H	N	*M*	C	H	N	M^+	$\lambda_{max.}$/nm	log ε
C_6H_{11}	97—98·5	92 [a] 80 [b]	84·3	8·6	7·0	398·2722	84·0	8·65	6·9	398·2724	269	4·29
Bu^t	145—147	89 [a] 73 [b]	83·2	8·7	8·1	346·2409	83·35	8·7	8·15	346·2417	262	4·29
cyclo-C_5H_9	85—87	79	84·3	8·2	7·6	370·2409	84·0	8·1	7·4	370·2419	270	4·33
cyclo-C_8H_{15}	73—74·5	70	84·5	9·3	6·2	454·3348	84·5	9·5	6·1	454·3338	259	4·30
cyclo-$C_{12}H_{23}$	111—112·5	59	84·7	10·3	4·9	566·4600	84·3	10·2	5·2	566·4606	267	4·33
2-Naphthyl [c]	193—194·5	89	86·7	7·7	5·6	498·3035	86·8	7·6	5·3	498·3046	259	4·49
											268	4·56
											311	4·35
cyclo-C_7H_{13}	63—64·5	78	84·4	9·0	6·6	426·3035	84·2	8·7	6·8	426·3030	267	4·18
CH_2Ph	101—102·5	59	87·0	6·3	6·8	414·2096	86·9	6·1	6·4	414·2085	251	4·14
											392	2·45

[a] Yield when pure *N*-alkylphenacylamine is dimerised. [b] Yield without isolation of the *N*-alkylphenacylamine. [c] A reaction between 2-bromoacetylnaphthalene and cyclohexylamine in benzene at 52 ± 1° for 14 h gave the rearranged product in 88% yield.

in benzene (200 ml) was passed a slow stream of anhydrous methylamine gas for 10 min. The mixture was set aside for 2 h and then heated at 60 ± 1° for 1 h, cooled, and filtered. The filtrate was washed with cold water and dried (Na_2SO_4). Removal of the solvent *in vacuo* left a viscous red oil which solidified upon trituration with ethanol (95%) to give the red *1,4-dihydro-1,4-dimethyl-2,6-diphenylpyrazine* (V) (1·04 g, 16%), m.p. 97—99·5° [Found: N, 10·8%; *M* (mass spec.), 262·1468. $C_{18}H_{18}N_2$ requires N, 10·7%; *M*, 262·1470], δ (C_6D_6) 1·72 (3H, s, N·CH_3), 2·07 (3H, s, N·CH_3), 5·32 (2H, s), and 6·45—7·37 (10H, m, aromatic). The filtrate was concentrated and treated with methanol and when chilled deposited reddish yellow *1,2,3,4-tetrahydro-2-methoxy-1,4-dimethyl-3,5-diphenylpyrazine* (VI) (0·437 g, 6%), m.p. 83—85° [Found: N, 9·6%; *M* (mass spec.) 294·1738. $C_{19}H_{22}N_2O$ requires N, 9·5%; *M*, 294·1732], δ ($CDCl_3$) 2·52 (3H, s, CH_3), 2·86 (3H, s, CH_3), 3·42 (3H, s, O·CH_3), 4·52 (1H, d, $J_{2,3}$ 2·0 Hz, 3-H), 4·76, (1H, q, $J_{2,6}$ 1·0 Hz, 2-H), 5·72 (1H, d, $J_{2,6}$ 1·0 Hz, 6-H) and 7·05—7·67 (10H, m, ArH).

Attempted recrystallisation of compound (V) from warm methanol afforded compound (VI).

Removal of the solvent from the filtrate of the original reaction gave a dark red oil which resisted crystallisation and was chromatographed on alumina to give, as a dark

red oil, *N*-methyldiphenacylamine (3·38 g, 50%) [Found: *M* (mass spec.), 267·1256. Calc. for $C_{17}H_{17}NO_2$: *M*, 267·1259], δ ($CDCl_3$) 2·58 (3H, s, CH_3), 4·20 (4H, s, CH_2), and 7·35—8·18 (10H, m, ArH); $\nu_{max.}$ ($CHCl_3$) 1655 cm^{-1} (CO). The structure was confirmed by an independent preparation followed by conversion into (V) with methylamine as follows.

Anhydrous methylamine was passed into a hot (60 ± 1°) solution of *N*-methyldiphenacylamine (2·65 g, 10 mmol) in benzene (100 ml) for 20 min. The mixture was kept at 60° for 1 h. Removal of the solvent *in vacuo* gave a red oil, trituration of which with cold methanol gave red 1,4-dihydro-1,4-dimethyl-2,6-diphenylpyrazine (1·37 g, 53%), m.p. and mixed m.p. 98—100·5°.

Catalytic Hydrogenation of 1,4-*Dihydro*-1,4-*dimethyl*-2,6-*diphenylpyrazine*.—The pyrazine (0·60 g) hydrogenated over palladium–charcoal (100 mg) in ethyl acetate (75 ml) at atmospheric pressure during 48 h. The residual oil obtained by filtration through Celite and removal of the solvent *in vacuo* was chromatographed on alumina (50 g) with benzene–hexane (1 : 3) as eluant to give 1,2,3,4-*tetrahydro*-1,4-*dimethyl*-2,6-*diphenylpyrazine* as an oil (0·292 g, 47%) [Found: N, 10·2%; *M* (mass spec.), 264·1627. $C_{18}H_{20}N_2$ requires N, 10·6%; *M*, 264·1627], δ ($CDCl_3$) 2·43 (3H, s, N·CH_3), 3·18 (2H, 2d, J_{AB} 2·0, J_{AB}, 4·0 Hz, 3-H_2), 4·18br (1H, t, 2-H_2), 5·78 (1H, s, 5-H), and 7·08—7·55 (10H, m, ArH).

4-*Benzyl*-1-*cyclopentyl*-1,4-*dihydro*-2,6-*diphenylpyrazine*.—A mixture of *N*-benzyldiphenacylamine hydrobromide (4·24 g, 10 mmol.) and cyclopentylamine (Aldrich) (1·78 g, 20 mmol) was heated at 110 ± 1° under dry nitrogen for 1·5 h. The resulting red-orange oil was diluted with ether and the precipitated cyclopentylamine hydrobromide was collected. Removal of the ether *in vacuo* left a red-orange oil, trituration of which with ethanol resulted in the deposition of red 4-*benzyl*-1-*cyclopentyl*-1,4-*dihydro*-2,6-*diphenylpyrazine* (1·19 g, 30·4%), m.p. 107—108·5° [Found: C, 85·5; H, 7·3; N, 7·2%; *M* (mass spec.), 392·2245. $C_{28}H_{28}N_2$ requires C, 85·7; H, 7·2; N, 7·2%; *M*, 392·2253], δ ($CDCl_3$) 0·92—2·02 (8H, m, cyclopentyl), 3·20—3·60 (1H, m, methine), 3·70 (2H, s, PhCH_2), 6·23 (2H, s, vinyl H), and 6·96—7·79 (15H, m, ArH).

Thermal Rearrangement of 4-*Benzyl*-1-*cyclopentyl*-1,4-*dihydro*-2,6-*diphenylpyrazine*.—A solution of the 1,4-dihydropyrazine (1·09 g) in *o*-xylene (25 ml) was heated under reflux for 7 h. Removal of the solvent *in vacuo* gave a red-orange oil which was chromatographed on alumina (60 g). Elution with benzene–hexane (1 : 4) gave an oil (0·474 g, 47·4%) which on trituration with ethanol deposited yellow 1-*benzyl*-2-*cyclopentyl*-1,2-*dihydro*-3,5-*diphenylpyrazine*, m.p. 101—102·5° [Found: C, 85·4; H, 7·4; N, 7·2%; *M* (mass spec.), 392·2257. $C_{28}H_{28}N_2$ requires C, 85·7; H, 7·2; N, 7·1%; *M*, 392·2253], δ ($CDCl_3$) 0·83—1·75 (8H, m, cyclopentyl), 1·88—2·55 (1H, m, methine), 4·38 (1H, dd, *J* 9·5, $J_{2,6}$ 1·3 Hz, 2-H), 4·53 (2H, s, PhCH_2), 6·52 (1H, d, $J_{2,6}$ 1·3 Hz, 6-H), and 7·02—7·87 (15H, m, ArH).

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