Dehydrogenation of Tertiary Amines by Dibenzoyldi-imide

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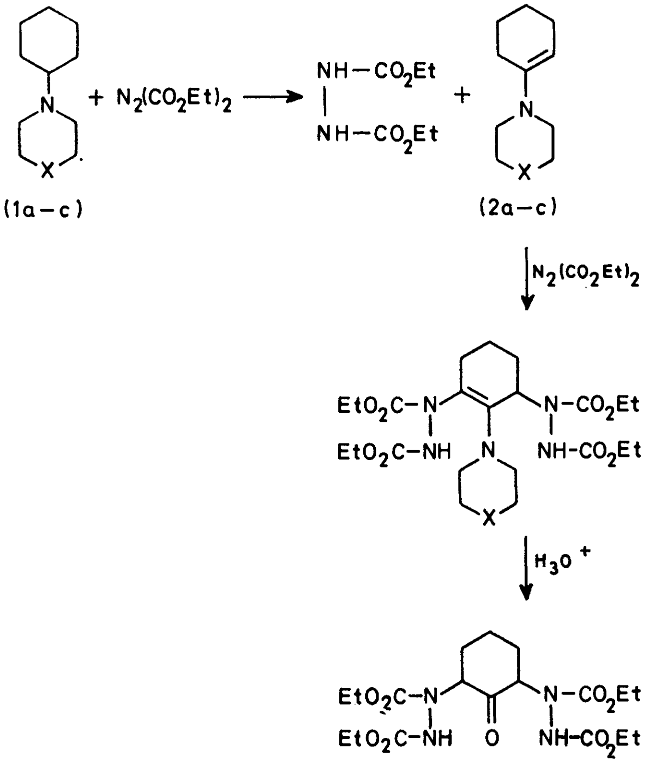
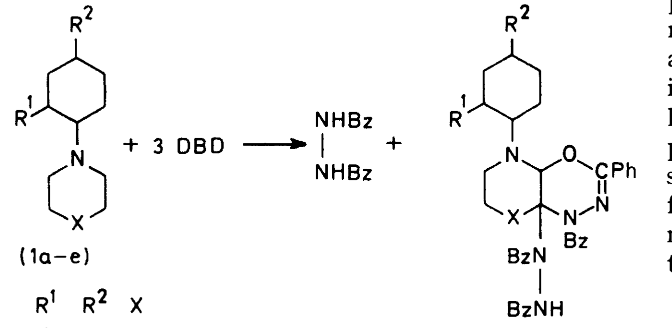
Dehydrogenation of *N*-cyclohexyl-pyrrolidines and -piperidines with dibenzoyldi-imides occurs on the heterocycle, in contrast with the analogous reaction of diethyl azodiformate. The enamines so obtained react with more dibenzoyldi-imide to give addition products, identified on the basis of ^{13}C n.m.r. spectra.

We have studied the dehydrogenation of several tertiary amines of the type $-\overset{|}{C}H-\overset{|}{C}H-NR_2$ by diethyl azodiformate and have shown that enamines are formed which react with more azodiformate to give bis-addition compounds.[1] In particular, *N*-cyclohexyl-pyrrolidine (1a), -piperidine (1b), and -morpholine (1c) gave the enamines (2a—c), respectively, as unique dehydrogenation products:



(1a−c) (2a−c)



(1a−e) (3a, b, d, e)

	R^1	R^2	X
a;	H	H	−
b;	H	H	CH$_2$
c;	H	H	O
d;	Me	H	−
e;	H	Bu^t	−

We are interested in the chemical behaviour of dibenzoyldi-imide (DBD),[2] and here report its dehydrogenating action on the tertiary amines (1a—e). The morpholine (1c) did not react, and the other amines gave the corresponding bis-addition compounds (3a, b, d, and e) in high yields. *NN'*-Dibenzoylhydrazine was isolated in almost 100% yield. The structure (3) was assigned by a ^{13}C n.m.r. study on compound (3a) and the corresponding starting material (1a) (Table 1). These spectra prove that DBD reacts with the pyrrolidine ring of (1a) and the cyclohexyl ring remains intact and unsubstituted.

TABLE 1

^{13}C N.m.r. spectra of compounds (1a) and (3a) (p.p.m. from Me$_4$Si)

		(1a)	(3a)
C-2		50.9	89.5
C-3		22.7	81.4
C-4		22.7	31.7
C-5		50.9	44.0
C-6		63.1	56.8
C-7		31.7	31.7
C-8		24.6	25.0
C-9		25.6	25.8
C-10		24.6	31.7
C-11		31.7	31.7
C=O			171.9 (3) [a] or (4)
C$_{Ar}$			135.2
			131.6
			130.9
			129.9
CH$_{Ar}$			128.2 (6)
			127.5 (10)
			126.4 (4)

[a] Numbers in parentheses indicate the number of carbon resonances in a degenerate peak.

The shift assignments of (1a) follow directly from comparisons with the known shifts of cyclohexylamine[3] and pyrrolidine.[4] Thus, the doubly degenerate 24.6 p.p.m. resonance and the single carbon 25.6 p.p.m. resonance are allotted to C-8 and -10 and C-9 of (1a), respectively, in accord with the 24.4 and 25.0 p.p.m. signals of cyclohexylamine. The C-3 and -4 resonance of (1a) (22.7 p.p.m.) is 3 p.p.m. upfield of the equivalent pyrrolidine signal (25.7 p.p.m.), as a consequence of a mild γ-effect from the *N*-alkyl substituent. Single-frequency off-resonance decoupling determined the assignment of the lone methine signal, and the doubly degenerate

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[1] M. Colonna and L. Marchetti, *Gazzetta*, 1969, **99**, 14.

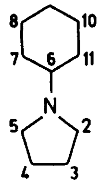
[2] (*a*) L. Marchetti, E. F. Serantoni, R. Mongiorgi, and L. Riva di Sanseverino, *Gazzetta*, 1973, **103**, 615; (*b*) L. Marchetti, *J.C.S Perkin II*, in the press.

[3] K. F. Koch, J. A. Rhoades, E. W. Hagaman, and E. Wenkert, *J. Amer. Chem. Soc.*, 1974, **96**, 3300.

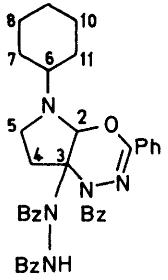
[4] G. C. Levy and G. L. Nelson, 'Carbon-13 Nuclear Magnetic Resonance for Organic Chemists,' Wiley–Interscience, New York, 1972.

C-2 and -5 and C-7 and -11 signals are distinguished by the *ca.* 20 p.p.m. deshielding influence of a directly bound nitrogen atom.[4]

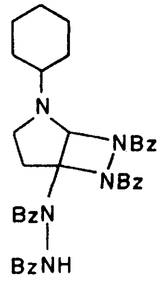
The molecular formula of the reaction product ($C_{38}H_{37}N_5O_4$), and its i.r. (3 366 cm^{-1}) and ^{1}H n.m.r. (δ 8.36) data reveal the presence of only one NH bond; as a consequence, structures (3a), (4), and (5) were considered. The ^{13}C n.m.r. spectrum reveals extensive degeneracy in the carbonyl and aromatic methine regions. A carbonyl resonance with high and low field shoulders probably accounts for at least three carbonyl resonances. A fourth signal (carbonyl or imino-ether equivalent) may be concealed by the broad 171.9 p.p.m. peak. No additional signal was observed in the spectrum when 10.0 intervals were allowed for re-establishment of thermal equilibrium between consecutive 45° pulses.



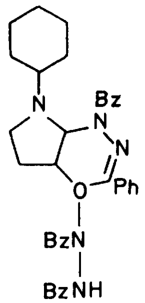
(1a)



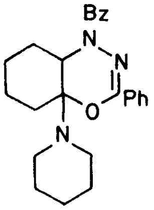
(3a)



(4)



(5)



(6)

Four unique, non-protonated aromatic carbon signals reminiscent of the *ipso*-carbon resonance of benzoic acid[4] (130.8 p.p.m.) accompany three degenerate aromatic methine signals which represent the *ortho*-, *meta*-, and *para*-phenyl carbon atoms. The area ratio of the latter three signals is not 8 : 8 : 4. While the intensity of the *para*-carbon resonance may be less than half those of the *ortho*- and *meta*-carbon resonances if a preferred rotation axis through the *ipso*- and *para*-carbon atoms exists, such a rotation mode should not alter the *ortho*- and *meta*-peak ratio, observed to be *ca.* 6 : 10 for the 128.2 and 127.5 p.p.m. signals. Thus, if we otherwise assume anisotropic molecular motion, one of the aromatic moieties may give rise to degenerate *ortho*- and *meta*-carbon resonances.

The tetrahedral carbon resonances show that the cyclohexyl ring is unsubstituted. Thus, C-7 and -11, C-8 and -10, and C-9 are assigned to the signals at 31.7, 25.0, and 25.8 p.p.m., respectively, almost coincident with the corresponding resonances of (1a). The 31.7 p.p.m. peak represents three carbon atoms, the third being a methylene carbon atom in the pyrrolidine ring. The aminomethine resonance appears at 56.8 p.p.m., 4.5 p.p.m. to higher field than the similar signal in (1a). This γ-effect requires that one of the pyrrolidine aminomethylene groups carries a substituent.

The 31.7 p.p.m. methylene group mentioned above and the 44.0 p.p.m. aminomethylene group must be assigned to the pyrrolidine ring. The former signal is 9.0 p.p.m. downfield and the latter 6.9 p.p.m. upfield of the equivalent signals of (1a). These shifts require that the aminoethylene is influenced by γ-substituents and the methylene site by β-substituents. The structures (3a), (4), and (5) meet these requirements. A choice is possible on the basis of the remaining two tetrahedral carbon resonances, whose positions indicate that each is bonded to two heteroatoms. Structures (4) and (5) require a methine bound to two nitrogen atoms, while (3a) contains a methine bound to one oxygen and one nitrogen atom. The *ca.* 90 p.p.m. methine resonance is characteristic of the latter system.[5] Similarly the *ca.* 80 p.p.m. non-protonated carbon resonance is acceptable for a site bound to two nitrogen atoms. Moreover, the ^{1}H n.m.r. spectrum of the reaction product shows a sharp singlet at δ 6.18, attributable to N·CH·O.[6] On the basis of these criteria structure (3a) was assigned. Other spectroscopic (Table 2) and chemical data are in agreement with this structure. In particular, the reaction product underwent simple protonation (with formation of the corresponding hydrochloride) and no hydrolysis, on treatment with acid; also it did not undergo catalytic hydrogenation at room temperature and normal pressure, whereas diazetidines [structure (4)] are known to undergo ring opening on hydrogenation.[7] Finally, the ability of DBD to give by cycloaddition an oxadiazine ring rather than a diazetidine one [*i.e.* (3a) rather than (4)], with the oxygen atom bonded to the α-carbon of the starting enamine, was shown by the results of *X*-ray analysis [2a] of the cycloaddition product (6) obtained from 1-piperidinocyclohexene (1b) and DBD.

Structures of the other products (3b, d, and e) were assigned in the light of the similarity of their analytical, spectroscopic, and chemical properties with those of (3a).

The first stage of the reaction is the formation of an enamine, together with *NN'*-dibenzoylhydrazine; this was demonstrated, as in ref. 1, by carrying out the

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[5] Y. Rolland, N. Kunesh, J. Poisson, E. W. Hagaman, F. M. Schell, and E. Wenkert, *J. Org. Chem.*, 1976, **41**, 3270.

[6] I. Fleming and M. H. Karger, *J. Chem. Soc.* (*C*), 1967, 226, give δ 5.96 for an analogous hydrogen atom in the cycloadduct of methyl vinyl ketone with an enamine. Also ^{13}C n.m.r. data therein reported agree with our data for analogous carbon atoms.

[7] E. Korner von Gustdorf, D. V. White, B. Kin, D. Hess, and J. Leitich, *J. Org. Chem.*, 1970, **35**, 1155.

TABLE 2

Physical, analytical, and spectroscopic data of compounds (3a, b, d, and e)

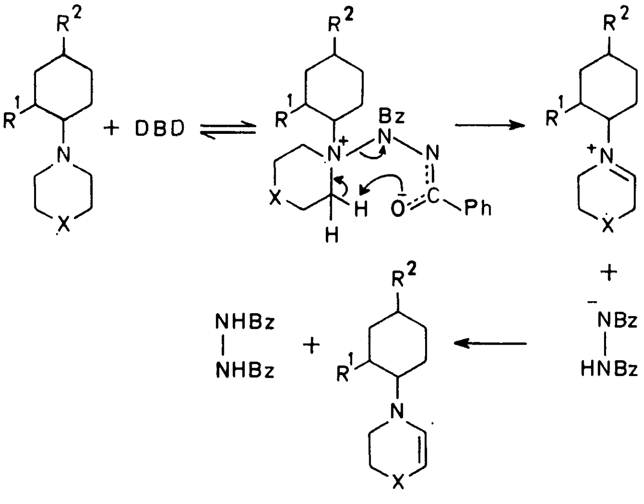
Compound	M.p. (°C)	Yield (%)	Formula	Found *(%) C	Found *(%) H	Found *(%) N	$\nu_{\max.}$/cm^{-1} (Nujol)	δ
(3a)	203 †	90	$C_{38}H_{37}N_5O_4$ ‡	73.05 (72.7)	5.85 (5.95)	11.65 (11.95)	3 352 (NH), 1 693—1 685 (CO), 1 048—1 640; 3 366 (NH; CCl_4)	8.35br (1 H, NH), 7.65—7.4 (8 H, m, arom.), 7.35—7.1 (12 H, m, arom.), 6.18 (1 H, s, N·CH·O), 3.25—2.7 (5 H, m, aliph.), 2.3—1.15 (10 H, complex m, aliph.)
(3b)	171 †	65	$C_{39}H_{39}N_5O_4$	73.45 (73.0)	6.1 (6.15)	10.6 (10.9)	3 395 (NH), 1 700—1 678 (CO), 1 645—1 628; 3 365 (NH; CCl_4)	7.7br (1 H, NH), 7.5—7.1 (20 H, complex m, arom.), 6.60 (1 H, s, N·CH·O), 2.4—1.1 (17 H, complex m, aliph.)
(3d)	151 §	75	$C_{39}H_{39}N_5O_4$	73.1 (73.0)	6.0 (6.15)	10.9 (10.9)	3 335 (NH), 1 700—1 681 (CO), 1 652—1 632	7.9br (1 H, NH), 7.7—7.1 (20 H, complex m, arom.), 6.15 (1 H, s, N·CH·O), 3.3—3.1 (4 H, m, CH_2·O·CH_2), 1.8—1.4 (10 H, complex m, aliph.), 1.2 (3 H, d, CH_3, *J* 7 Hz)
(3e)	206 †	60	$C_{42}H_{45}N_5O_4$	73.95 (73.75)	6.85 (6.65)	10.05 (10.25)	3 370 (NH), 1 760—1 685 (CO), 1 650—1 631; 3 365 (NH; CCl_4)	8.1br (1 H, NH), 7.8—7.55 (8 H, m, arom.), 7.5—7.25 (12 H, m, arom.), 6.28 (1 H, s, N·CH·O), 3.35—2.65 (5 H, m, aliph)., 2.5—1.0 (9 H, complex m, aliph.), 0.92 (9 H, s, Bu^t)

* Calc., in parentheses. † From benzene–light petroleum. ‡ Molecular weight determination: found: 638; calc.: 627.7. § From light petroleum.

reaction in the presence of 2,5-dichloro-3,6-dimethoxy-1,4-benzoquinone which cannot dehydrogenate the amines (1a—e) but which reacts very rapidly with enamines to give blue dialkylaminovinylquinones.[8] The complex nature of the reaction of the intermediate enamine with DBD prompted us to study more carefully the behaviour of DBD with enamines.[2b]

The initial dehydrogenation of the heterocycle is in contrast with the dehydrogenation of the carbocycle in the analogous reactions of (1a—c) with azodiformate.[1] Moreover, the failure of DBD to dehydrogenate *N*-cyclohexylmorpholine, which on the contrary is dehydrogenated by azodiformate, is surprising; *N*-(α-methylbenzyl)morpholine exhibits the same behaviour as (1c) towards DBD and azodiformate. It is difficult to give a satisfactory explanation of these differences; probably the reaction mechanism is different. DBD is a more powerful electron-acceptor than azodiformate, as indicated by polarographic reduction of DBD: a one-electron reduction was observed with a half-wave potential of —0.44 V, less negative than the value for azodiformate (—0.71 V).* A set of Hückel MO calculations on the π-system of DBD, made by using the same parameters as employed by Zweig and Hoffmann [9] for calculations on the azodiformate π-system, with the aim of obtaining the energy of the LUMO, gave a value of —0.142 0 β, lower than the value of —0.119 0 β calculated for azodiformate.

Dehydrogenation of tertiary amines by azodiformate was shown to occur by a free radical mechanism, whereas an ionic one can be postulated (Scheme) for dehydrogenation with DBD. The latter mechanism seems capable of explaining the detachment of the secondary instead of the tertiary hydrogen atom, which is in a sterically more hindered position, far from the Bz–N–$\bar{N}$–Bz group. Detachment of a secondary hydrogen atom, on the contrary, may be facilitated by the neighbouring Bz–N–N$\cdots\bar{C}$Ph$\cdots$O group. Moreover, in an ionic pathway, the (*ca.* 10^3 times) lower basicity of morpholines in comparison with pyrrolidines and piperidines can explain the failure of DBD to dehydrogenate (1c).



SCHEME

EXPERIMENTAL

I.r. spectra were recorded with a Beckman IR 12 spectrometer for Nujol mulls or solutions in carbon tetrachloride. N.m.r. spectra were recorded with a JEOL JNM-C60-HL

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* Values were determined in anhydrous dimethylformamide containing tetraethylammonium perchlorate with a platinum rotating electrode (A. Trazza, personal communication).

[8] D. Buckley, S. Dunstan, and H. Henbest, *J. Chem. Soc.*, 1957, 4480, 4901.

[9] A. Zweig and A. K. Hoffmann, *J. Amer. Chem. Soc.*, 1963, **85**, 2736.

spectrometer for solutions in $CDCl_3$, with Me_4Si as internal standard. Molecular weight determinations were carried out with a Hewlett-Packard 301 A vapour pressure osmometer. ^{13}C N.m.r. spectra were recorded with a Varian DP-60 spectrometer operating at 15.1 MHz in the pulse Fourier transform mode. Substrates were examined as *ca.* 0.5M-solutions in chloroform and chemical shifts are expressed on the Me_4Si scale: $\delta_{Me_4Si} = \delta_{CHCl_3} + 77.2$ p.p.m. Tertiary amines were prepared by platinum-catalysed hydrogenation of the corresponding enamines, obtained in the usual way from ketones and secondary amines. DBD was prepared according to the method of Leffler and Bond,[10] slightly modified, the mercury salt of *NN'*-dibenzoylhydrazine being oxidized in ethereal solution with bromine.

1-*Benzoyl*-5-*cyclohexyl*-7a-(1,2-*dibenzoylhydrazino*)-1,4a,-5,6,7,7a-*hexahydro*-3-*phenylpyrrolo*[3,2-e][1,3,4]*oxadiazine* (3a).—*N*-Cyclohexylpyrroline (1a) (1 g, 6.7 mmol) dissolved in anhydrous benzene (15 ml) was added with stirring under nitrogen * to a solution in anhydrous benzene (100 ml) of DBD (4.76 g, 20 mmol) cooled at 6 °C (ice-bath). The addition rate was such that the temperature never rose above 8 °C. The mixture was stirred at room temperature under nitrogen for 2—3 h; then the precipitate was filtered off and identified as *NN'*-dibenzoylhydrazine (1.4 g, 89%) by comparison with an authentic sample. To the filtrate, light petroleum was added to precipitate the *product* (3a), which was filtered off (3 g, 73%); m.p. 203 °C (from benzene–light petroleum). The filtrate was evaporated to dryness and the residue chromatographed on silica gel (benzene–acetone, 8 : 2). More product (3a) was obtained (0.7 g, total 90%), together with traces of dibenzoylhydrazine. Analytical and spectroscopic data are in Table 2.

When the reaction was carried out with an amine–DBD ratio of 1 : 1 or 1 : 2, the same results were obtained but the yields were proportionately lower. No other products were ever observed.

When the product (3a) was stirred with 10% sulphuric acid at room temperature for 3 days, no reaction was observed and the starting material was recovered. If 10% hydrochloric acid was used, either at room temperature or at reflux, a white precipitate was obtained, m.p. 240—241 °C (from chloroform–light petroleum), of the *hydrochloride* of (3a) [and from which (3a) could be recovered by treatment with sodium carbonate] (Found: C, 69.1; H, 5.7; Cl, 5.05; N, 10.8. $C_{38}H_{38}ClN_5O_4$ requires C, 68.7; H, 5.75; Cl, 5.35; N, 10.55%). All attempts to hydrogenate (3a) over 10% platinum–charcoal at room temperature in a Parr apparatus failed; starting material was recovered.

The addition products (3b, d, and e) were similarly prepared from DBD and (1b, d, and e) respectively. Yields and physical data, *etc.*, are in Table 2. From (3b) by treatment with aqueous hydrochloric acid the hydrochloride was obtained, m.p. 225 °C, from which (3b) could be recovered by treatment with sodium carbonate. No product was obtained from DBD with (1c) or *N*-(α-methylbenzyl)morpholine; starting materials were recovered.

Enamine Formation.—The reaction of Buckley, Dunstan, and Henbest [1,8] was used to demonstrate the intermediate formation of an enamine. Two experiments were carried out in anhydrous benzene with (*a*) compound (1a) and 2,5-dichloro-3,6-dimethoxybenzoquinone (1 : 1 molar ratio), and (*b*) (1a), 2,5-dichloro-3,6-dimethoxybenzoquinone, and DBD (1 : 1 : 1 molar ratio). In the experiment (*a*) no reaction was observed; in (*b*) a deep blue colour was obtained immediately, characteristic of dialkylaminovinylquinones.[8]

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[6/2335 *Received, 29th December,* 1976]

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* The reaction is best carried out in a dry box.

[10] J. E. Leffler and W. B. Bond, *J. Amer. Chem. Soc.*, 1956, **78**, 335.