

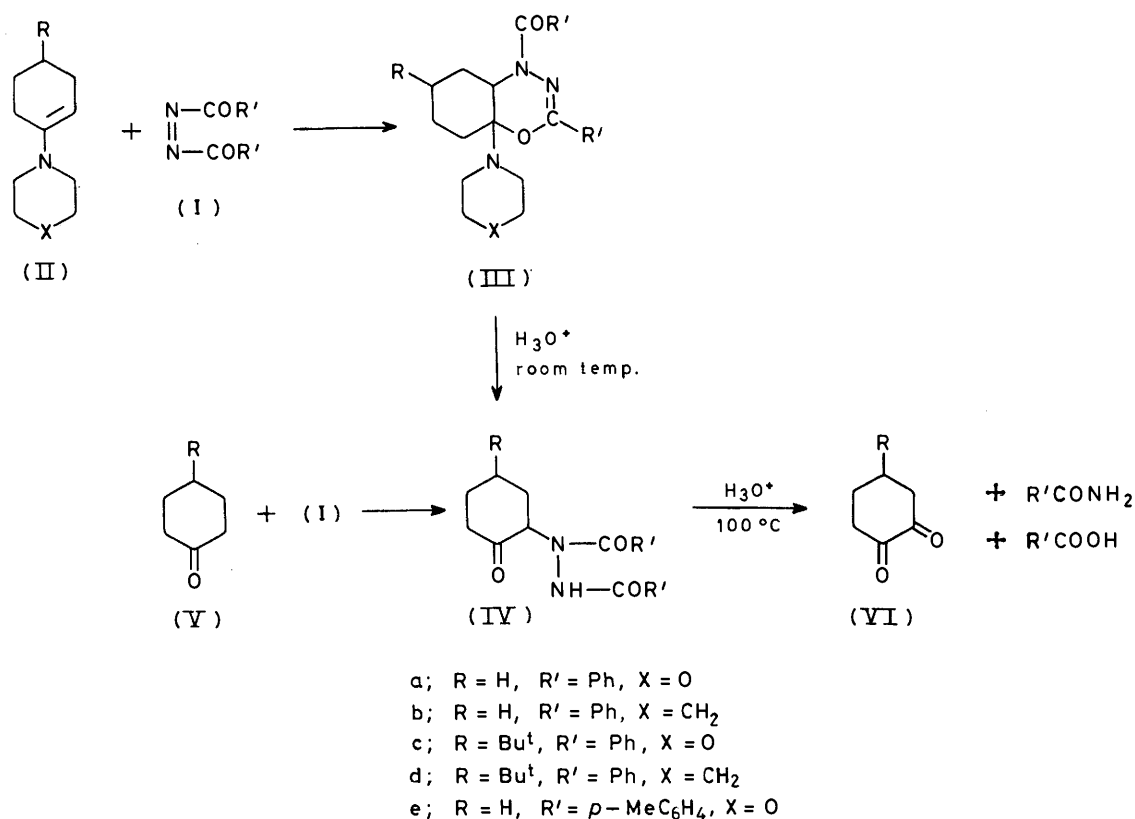
Reaction of Cyclohexanone Enamines with Diacyldi-imides

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Cyclohexanone morpholine and piperidine-enamines react with diacyldi-imides to give only monocycloaddition products, while pyrrolidine enamines also give bisaddition products in the 2,2- and 2,6-positions. The results of hydrolysis in D_2O form the basis of a reaction scheme which takes the experimental findings into account. Di-benzoyldi-imide reacts with 2-methylcyclohexanone enamines giving two stereoisomeric cycloadducts, which are different in the orientation of the methyl group, while bisaddition products could not be isolated. The stereochemistry of the reaction is discussed.

DEHYDROGENATION of tertiary amines of the type $R_2N-CH-CH$ with dibenzoyldi-imide¹ leads to the formation of enamines, $R_2N-C=C$, which further react with dibenzoyldi-imide present in the solution. This second reaction is rather complex and prompted us to investigate the behaviour of enamines towards the diacyldi-imides. In this paper, the results obtained for

dino-derivative (IIIb), respectively (Scheme 1). Structure (III) with the *cis*-fused rings was assigned by means of X-ray analysis of compound (IIIb).³ The enamines of a rigid system such as 4-*t*-butylcyclohexanone (IIc and d) afford the compounds (IIIc and d), while 1-morpholinocyclohexene reacts with di-*p*-toluoyldi-imide (DTD) (Ie) to give (IIIe). All these compounds have similar



SCHEME 1

cyclohexanone and 2-methylcyclohexanone enamines are reported.

The reaction of these enamines with ethyl azodicarboxylate has been shown² to lead to mono- and bisaddition on the carbon atom β to nitrogen.

1-Morpholino (IIa) and 1-piperidinocyclohexene (IIb) react with dibenzoyldi-imide (DBD) (Ia) in cold benzene solution to afford high yields of the 1,4-cycloaddition products 4-benzoyl-4a,5,6,7,8,8a-hexahydro-8a-morpholino-2-phenyl-4*H*-1,3,4-benzoxadiazine (IIIa) and piperi-

spectroscopic properties to those of (IIIb) and have therefore been assigned the same structure as the 1,4-cycloaddition products (Scheme 1).

When these reactions are performed with an excess of DBD or of DTD no further addition occurs; compounds (III) were again isolated together with benzaldehydes and other decomposition products of the imides.⁴

Mild acid hydrolysis of the cycloadducts (III) gave 2-

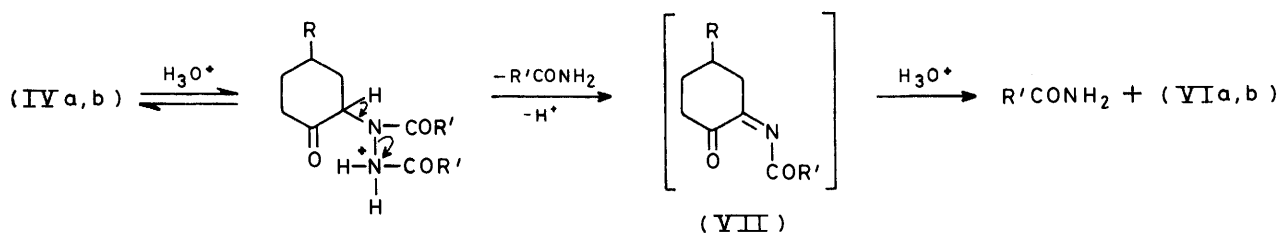
³ L. Marchetti, E. Foresti Serantoni, R. Mongiorgi, and L. Riva, *Gazzetta*, 1973, **103**, 615.

⁴ For the decomposition of dibenzoyldi-imides see J. E. Leffler and W. Bredford Bond, *J. Amer. Chem. Soc.*, 1958, **78**, 335.

¹ L. Marchetti, *J.C.S. Perkin II*, 1977, 1977.

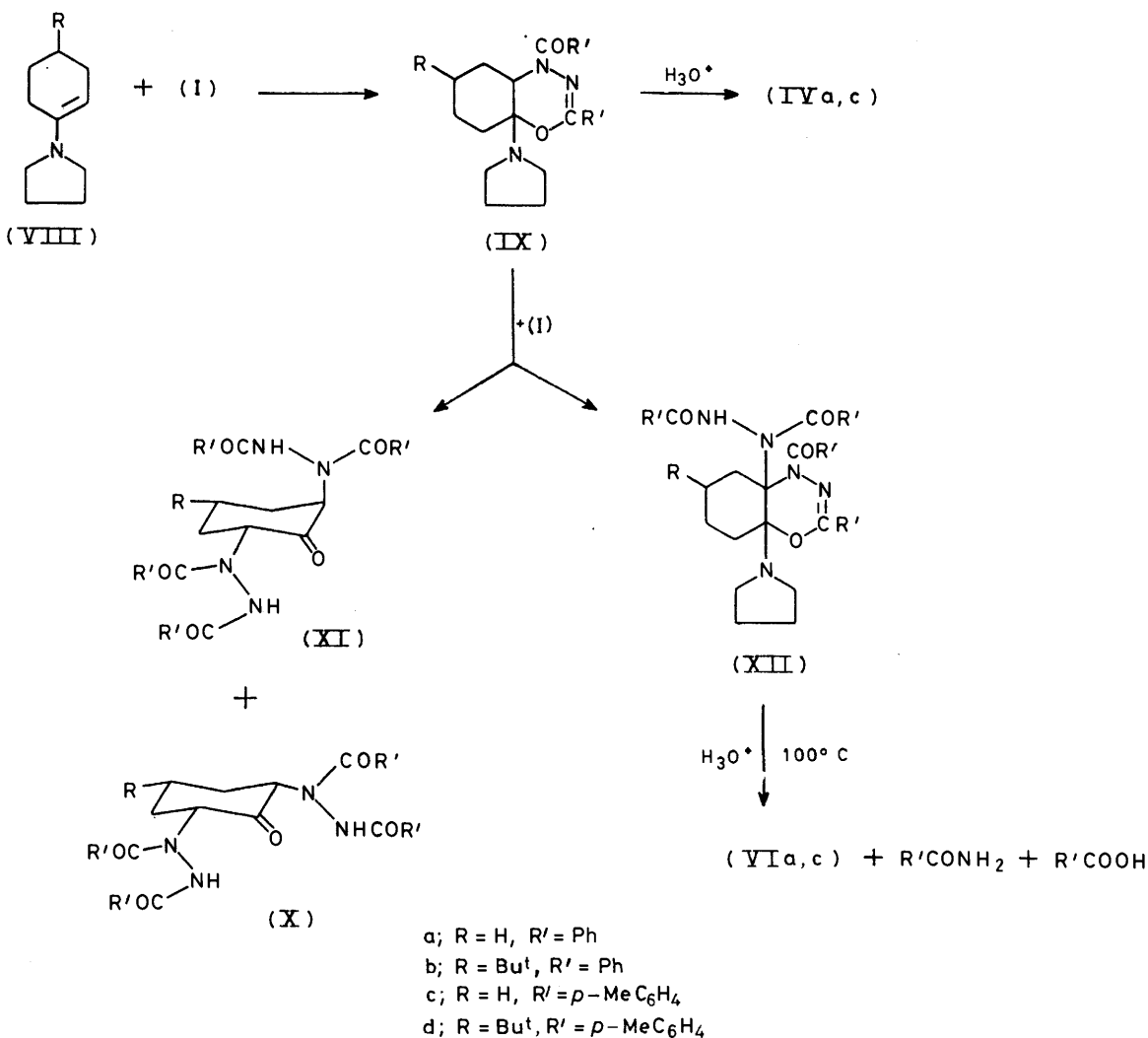
² A. Risaliti and L. Marchetti, *Ann. Chim. (Italy)*, 1963, **53**, 718.

(*NN'*-dibenzoyl)hydrazinocyclohexanone (IVa, c, and e), which can also be obtained from the cyclohexanones (Va and c) by treatment with (Ia and e) at 100 °C⁵



(Scheme 1). When an alcoholic solution of (IVa and e) containing HCl is refluxed, however, further hydrolysis takes place to give benzamide, benzoic acid, and cyclohexane-1,2-dione (VIa and e) probably by means of the

enamine (the molar ratio enamine : di-imide varying from 3 : 1 to 10 : 1) under rigorously anhydrous conditions. These adducts are hydrolysed very easily (*e.g.* by chromatography on silica) to afford the cyclohex-



monoimine derivative (VII) that we were not able to isolate.

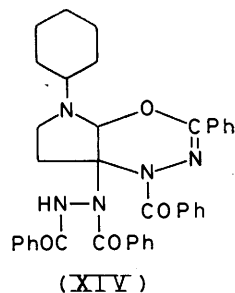
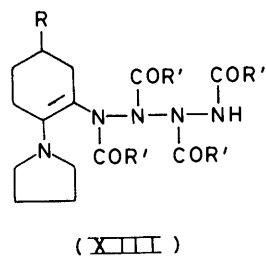
1-Pyrrolidino- (VIIIa) and 1-pyrrolidino-4-*t*-butylcyclohexene (VIIIb) reacted differently from the other

anones (IVa and c) in quantitative yield. The cyclic structure of the addition compounds (IXa and b) is

⁵ For similar reactions see ref. 2; R. Huigsen and F. Jakob, *Annalen*, 1954, **590**, 37.

demonstrated by the absence in the i.r. and n.m.r. spectra of bands for NH and by other spectroscopic data, which are similar to those of compounds (III); however, they react further with DBD and DTD, unlike (III), adding a second molecule and giving three compounds to which, on account of their analytical and spectroscopic data and their chemical behaviour, structures (X)—(XII) have been assigned. The n.m.r. spectra of compounds (X) and (XI) show peaks at δ 8.55—8.30 (2 H, NH) and 6.45—5.30 (2 H, $-CH-N$). A peak similar to the latter is also observed at δ 5.50—5.35 in the n.m.r. spectra of compounds (IV). The i.r. spectra of the same compounds exhibit bands at 3 240—3 280 (NH) and 1 740—1 750 (C=O) cm^{-1} . Compounds (Xa) are *cis-trans* stereoisomers; the *trans*-isomer (XIa) is very unstable and difficult to isolate, as it isomerizes easily in the *cis*-isomer, the reaction being complete after heating for a few minutes in chloroform solution. The reaction of cyclohexanone enamines with ethyl azodicarboxylate² follows a similar pattern, and we made our assignment on that basis.⁶ In the other cases, we were only able to isolate the more stable *cis*-isomer [(Xb, c, and d)].

The i.r. and n.m.r. spectra of compounds (XIIa and d) exhibit an NH band (1H) while no peak at all occurs between δ 3 and 7. This implies the absence of any $CH-N$ or vinyl proton, in accord with structures (XII) or (XIII).



Structure (XIII) may, in our opinion, be discounted for the following reasons. (i) Compounds with similar structure have never been obtained in other reactions of DBD with enamines or with cyclohexanone, whereas compound (XIV), which has a structure similar to that of (XII), has been obtained in the reaction between *N*-cyclohexylpyrrolidine and DBD.¹ It has also been demonstrated that (XIV) is formed from an enamine. (ii) 2-Methylcyclohexanone pyrrolidine enamine reacts with DBD to form exclusively a monocycloaddition product (see later) which does not react further with DBD. If the bisadduct of pyrrolidinocyclohexene had a structure similar to (XIII) a methyl group on C-6 in the cyclohexene ring should not prevent the addition

* Structure (XVIb) is hydrolysed to give ketone (XIX) in the n.m.r. spectrum of which the integral of the aliphatic proton peak is < 8 , in agreement with structure (XIX). However, it proved impossible to separate the peak for the protons α to carbonyl from that of the other protons of the cyclohexane ring. In the case of ketone (XVIII), on the other hand, the integral of the aliphatic proton peak is 8.

of the second molecule of DBD since it is a long way from the reaction centre. (iii) The bisaddition compounds obtained cannot be hydrolysed by an aqueous acid solution at room temperature, and this is not in agreement with the enamine structure (XIII), even if the latter is a more substituted enamine.

When compounds (XIIa and b) are treated with dilute HCl at room temperature, they yield the corresponding hydrochlorides which, when treated with alkali give back the starting compounds. However, when an alcoholic acid solution of (XIIa and b) is refluxed for several hours, dibenzoylhydrazine, benzoic acid, benzamide, and the cyclohexane-1,2-diones (VIa and c) are obtained. This behaviour is similar to that of (III) and (IV) and is in agreement with the proposed structure.

It would appear that the formation of the compounds obtained by the reaction of enamines with diacyldiimides can only be explained if it is accepted that the process follows the pattern set out in Scheme 3. The first phase is a two-stage addition⁷ *via* a dipolar intermediate (XV) from which the cycloadducts (III) and (IX) are generated. If it is allowed that, in the case of compound (IX) unlike that of (III), the closing of the ring under these reaction conditions may be reversed, the enamine structures (XVIa and b) can be generated from the intermediate (XV)^{8,9} by intramolecular transfer of a proton, a well known mechanism in the chemistry of enamines.¹⁰ The enamines (XVIa and b) may react with a molecule of DBD to give, respectively, compound (XII) and a bisadduct which is hydrolysed to yield the isomeric ketones (X) and (XI).

A proof of this mechanism was obtained by hydrolysing adducts (IIIb) and (IXa) with D_2SO_4 in D_2O . The first adduct gave ketone (XVII) (Scheme 3), the n.m.r. spectrum of which displays a peak at δ 5.45 (1 H, $\text{CO}-\text{CH}-\text{N}=\text{ND}$), thus demonstrating that deuterium has not been introduced α to the carbonyl group. On the other hand, when (IXa) was similarly hydrolysed, it gave a ketone (XVIII), the n.m.r. spectrum of which exhibits a peak at δ 5.45 but this time with an integrated intensity of *ca.* 0.6. This shows that in the case of adduct (IXa) a hydrolysis mechanism exists which is different from (and probably simultaneous with) the mechanism operating in the hydrolysis of (III). Since it is known that D_2O hydrolysis of enamines gives ketones with deuterium α to the carbonyl group, we may justifiably claim in our case that (XVIa) is present.* The low integral of the peak at δ 5.45 for (XVIII) and the absence in the spectrum of (XI) of peaks due to (XVIa and b) show that hydrolysis of the cyclic structure is slower than that of enamines. This agrees with the experimental finding

⁶ For the assignment of the *cis*- and *trans*-structure of 2,6-bis-(*NN'*-diethoxycarbonylhydrazino)cyclohexanones see S. Fatutta, A. Risaliti, C. Russo, and E. Valentin, *Gazzetta*, 1972, **102**, 1008.

⁷ For a discussion of the mechanisms of reaction of enamines see F. P. Colonna, S. Fatutta, A. Risaliti, and C. Russo, *J. Chem. Soc. (C)*, 1970, 2377.

⁸ G. Opitz and H. Haltmann, *Annalen*, 1965, **684**, 79.

⁹ I. Fleming and M. H. Karger, *J. Chem. Soc. (C)*, 1967, 226.

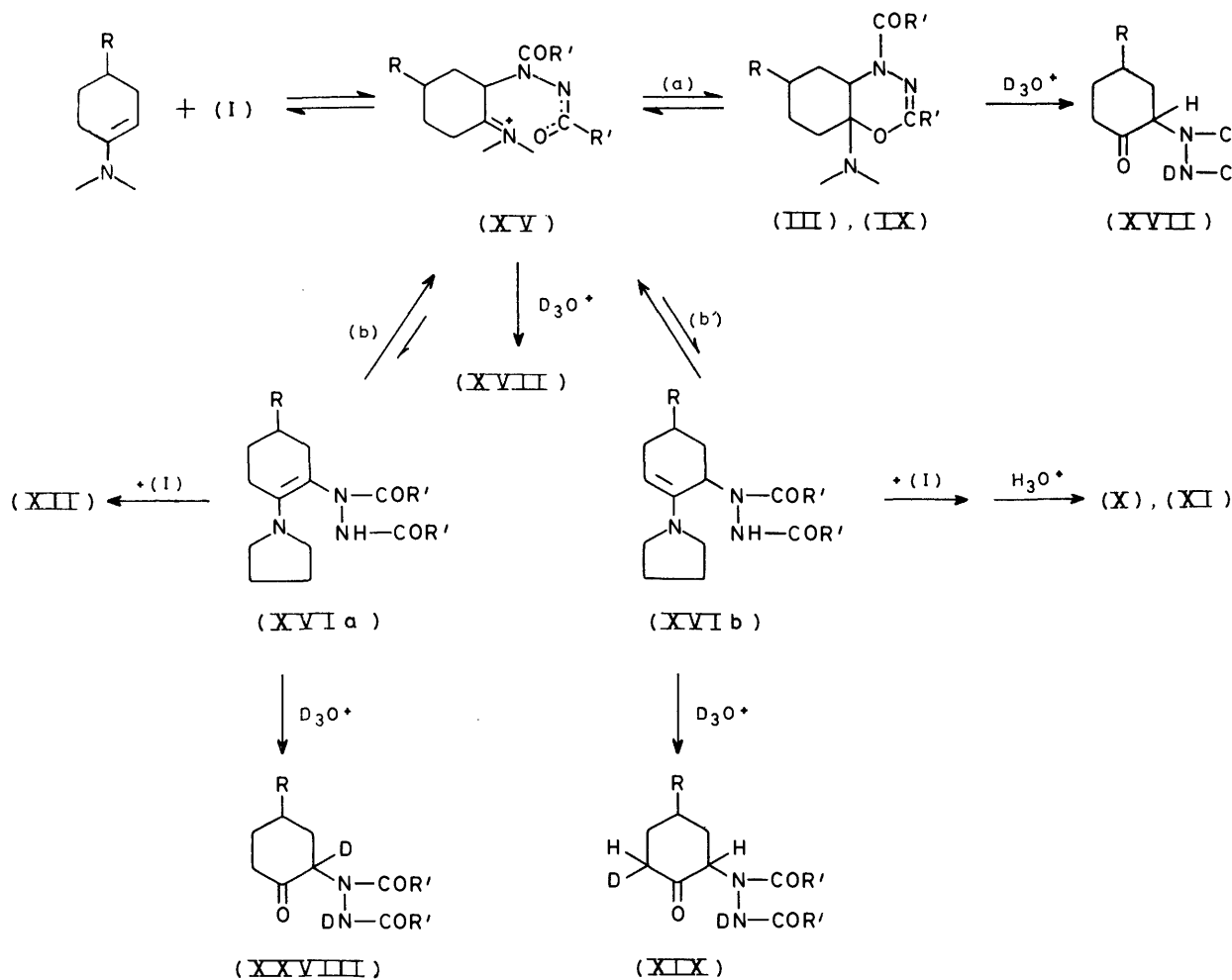
¹⁰ A. G. Cook, 'Enamines', Dekker, New York, 1959, p. 115 *et seq.*

that the addition compounds from pyrrolidine enamines are hydrolysed more rapidly than adducts (III).

Scheme 3 accounts for the formation of the products, but the high yield (>50%) of (XII) is surprising, since reactions (b) and (b') are reversible, as is (a). Since the distribution of compounds (IX) and (XVIa and b) is thermodynamically controlled, and since tetrasubstituted enamines are less stable than trisubstituted ones the percentage of (XVIa) should be less than that of (XVIb), and given that its reactivity should not be

analogous with the addition products from cyclohexanone enamines. The n.m.r. spectrum of (XXI) shows two doublets at δ 1.27 and 1.16 (3 H) due to methyl groups, whose integrated intensity ratio is *ca.* 55:45. The cycloadduct (XXI) is therefore a mixture of two stereoisomers, but all our attempts to separate them chromatographically failed.

Acid hydrolysis at room temperature of (XXI) gave 2-methyl-6-(*NN'*-dibenzoylhydrazino)cyclohexanone (XXII) whose n.m.r. spectrum shows again two doublets



SCHEME 3

greater than that of (XVIb), (X) and (XI) might be expected to be produced in greater yield than (XII). Further research is being conducted into this problem.

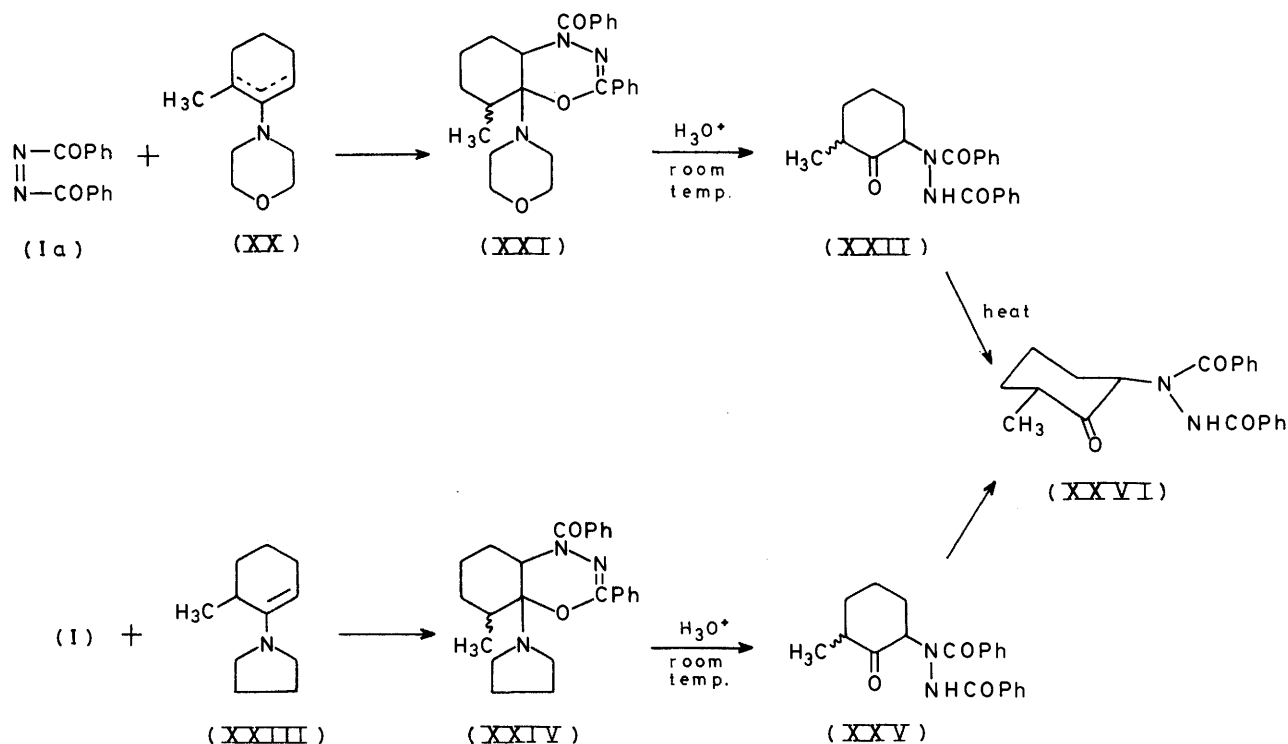
Dibenzoyldi-imide (Ia) also reacts with enamines from 2-methylcyclohexanone. The morpholine enamine (XX) (Scheme 4) is known to exist as a mixture of more and less substituted enamines;¹¹ nevertheless, upon treatment with DBD only the less substituted isomer reacts, producing a monoaddition compound, which was assigned the cyclic structure (XXI) because of the lack of NH bands in the i.r. and n.m.r. spectra, and by

¹¹ W. D. Gurowitz and M. A. Joseph, *Tetrahedron Letters*, 1965, 4433.

at δ 1.31 and 1.07 (3 H) due to methyl groups, with an intensity ratio of 55:45, as for (XXI). It seems then that mild hydrolysis conditions do not cause equilibration of the two isomers of the mixture (XXI). In this case, too, we were not able to separate the two *cis-trans* stereoisomers which differ in the orientation of the methyl group, as can be argued from the n.m.r. spectrum. In fact, the lower field signal, δ 1.31 (*J* 7 Hz), which is the more intense, is attributable to the axial methyl of the *trans*-isomer,¹² while that at higher field,

¹² For this assignment, see F. P. Colonna, M. Forchiassin, G. Pitacco, A. Risaliti, and E. Valentin, *Tetrahedron*, 1970, **26**, 5298 and references therein.

δ 1.07 (J 6 Hz), is due to the equatorial methyl of the *cis*-isomer.* A mixture of the two isomers (XXII), refluxed for a few hours in benzene containing a catalytic quantity of acetic acid, gave ketone (XVI) whose n.m.r. spectrum is identical with the spectrum of (XXII), except for a doublet for the methyl group at δ 1.07 (J 6 Hz); under these conditions, therefore, the *trans*-isomer is transformed into the more stable *cis*.



SCHEME 4

1-Pyrrolidino-6-methylcyclohexene (XXIII) is known to exist almost exclusively¹¹ in the less substituted enamine form; by treatment with DBD it gave the cycloaddition compound (XXIV) which is again a mixture of stereoisomers, δ 1.25 (d, J 6 Hz) and 1.03 (d, J 5 Hz) for the methyl groups; the intensity ratio is *ca.* 20 : 80, the more intense signal being at higher field, unlike the results for the morpholino-derivative.

By acid hydrolysis at room temperature of the adduct (XXIV) we obtained 2-methyl-6-(*NN'*-dibenzoylhydrazino)cyclohexanone (XXV) which is again a mixture of *cis*- and *trans*-isomers, δ 1.07 (d) and 1.31 (d) for the methyl groups, but which is different from (XXII) as the *cis*-isomer predominates over the *trans* in a *ca.* 90 : 10 ratio. Also (XXV) is easily isomerized to (XXVI) by reflux.

It is known that in trisubstituted enamines from 2-methylcyclohexanone the methyl group is always in the

axial position¹³ for steric requirements;¹⁴ the formation of the adducts (XXI) and (XXIV) in both the isomeric structures (even if in a different amount) seems to indicate that the attack of DBD on the enamines can be both parallel and antiparallel¹⁵ and either of these predominates depending on the enamine. However an antiparallel attack on the conformer with the axial methyl is greatly hindered by a 1,3-diaxial interaction

* See ref. 6. We assume that the *NN'*-dibenzoylhydrazino-group behaves as does *NN'*-bismethoxycarbonyl.

¹³ F. Johnson, N. A. Starkovsky, A. C. Patton, and A. A. Carlson, *J. Amer. Chem. Soc.*, 1964, **86**, 118; 1966, **88**, 149.

¹⁴ F. Johnson, *Chem. Rev.*, 1968, **68**, 375.

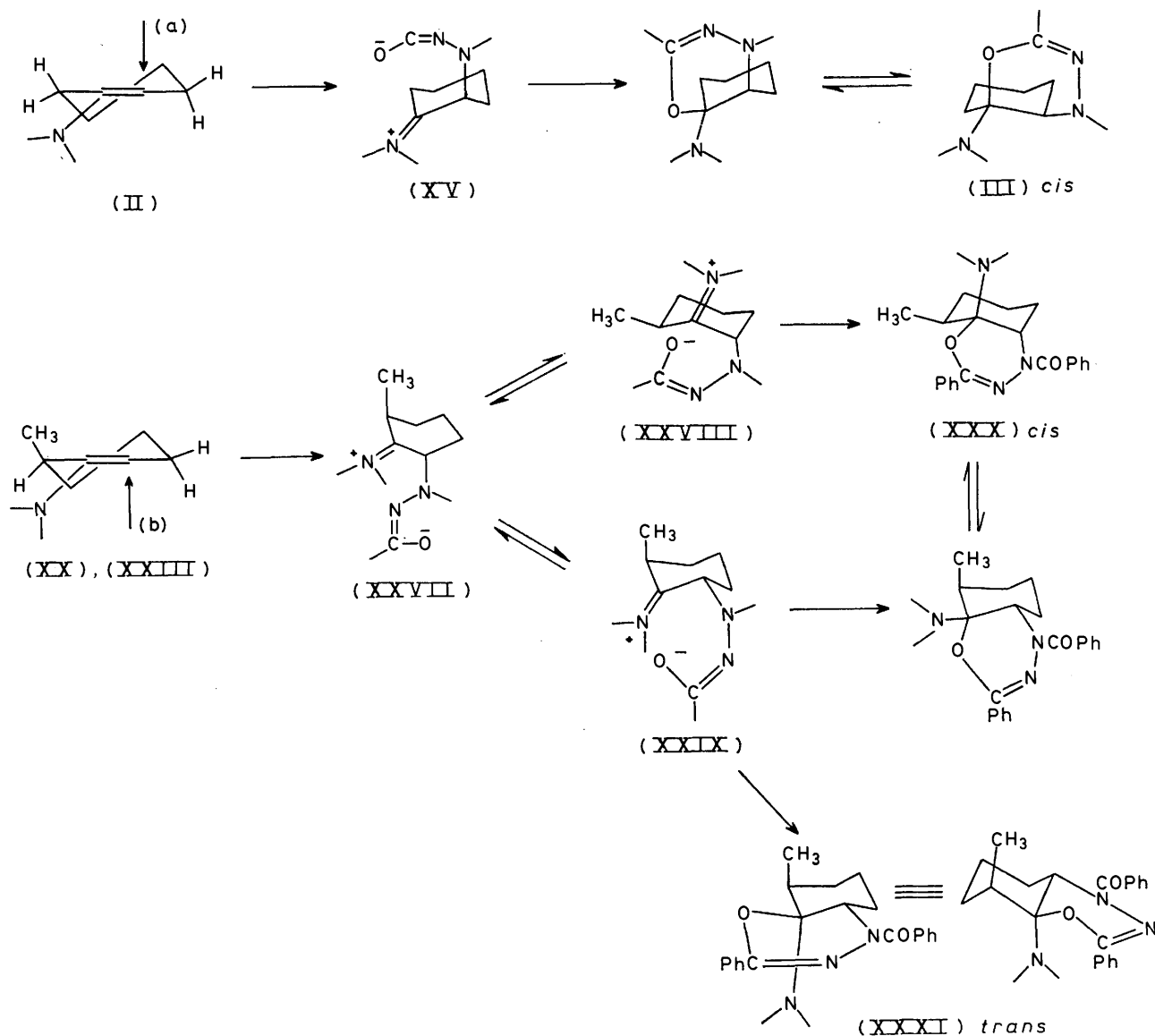
¹⁵ J. Valls and E. Toromanoff, *Bull. Soc. chim. France*, 1961, 758.

¹⁶ E. L. Eliel, N. A. Allinger, S. J. Angyal, and G. A. Morrison, 'Conformational Analysis', Interscience, New York, pp. 307—314.

cis-isomer (XXX); however, the dipolar ion (XXIX), which has an equatorial dibenzoylhydrazino-group, can close giving two different bicyclic systems, (XXX) and (XXXI), with *cis*- and *trans*-ring junctions, respectively.

The ratio between the two isomers is different for (XXI) and (XXIV) (45:55 versus 80:20), probably because of the different interactions of the enamine with the groups in positions 2 and 6 in (XXVII)—(XXIX). The cycloaddition compound (XXIV) does not react further with excess of DBD, unlike the corresponding compound from cyclohexanone enamine.

solutions in CDCl_3 . U.v. spectra were recorded with a Beckman DK-2A spectrometer for solutions in cyclohexane. Molecular weights were measured with a Hewlett-Packard 301 A steam-pressure osmometer, benzil being used as calibration standard and benzene as solvent. T.l.c. was carried out on silica gel G (Merck) (eluent benzene-acetone 9:1). Column chromatography was carried out on extra-pure Merck silica (70—325 mesh ASTM) as stationary phase the eluent being benzene-acetone 9:1 or 6:4. G.l.c. was carried out on a Fractovap GV column with Carbowax 20 M (60—80 mesh), nitrogen being used as carrier gas.



SCHEME 5 (a) Antiparallel attack, (b) parallel attack

EXPERIMENTAL

M.p.s are not corrected. The following procedures were used unless otherwise indicated. I.r. spectra were recorded for Nujol by a Beckman R 12 spectrophotometer. N.m.r. spectra were recorded with a JEOL JMN-C-60 HL spectrometer, with tetramethylsilane as internal standard, for

Dibenzoyldi-imide (Ia) was prepared by the method of Leffler and Bond,^{4,17} slightly modified, the mercury salt of *NN'*-dibenzoylhydrazine being oxidized in ether solution with bromine, m.p. 120—121° (from ligroin) (lit.,¹⁸ 119.5—

¹⁷ R. Stollé, *Ber.*, 1912, **45**, 279.

¹⁸ H. H. Hatt, *Org. Synth.* 1943, Coll. Vol. II, p. 208.

121.5°), ν_{\max} 1 730 (C=O) and 1 680 cm^{-1} (C=C), $\delta(\text{CCl}_4)$ 8.0 (4 H, m, ArH) and 7.55 (6 H, m, ArH).

NN'-Dibenzoylhydrazine was prepared by the usual method,²⁰ m.p. 240—242° (from acetic acid), ν_{\max} 3 230 (NH), 1 670 (C=O), and 1 635 cm^{-1} (C=C), $\delta([\text{H}_6]\text{DMSO})$ 9.55 (2 H, s, NH), 8.0 (4 H, m, ArH), and 7.5 (6 H, m, ArH).

Bis-(4-methylbenzoyl)*di-imide* (Ie) was prepared in the same way as (Ia), m.p. 130° (from ligroin) (Found: C, 72.25; H, 5.15; N, 10.25. $\text{C}_{16}\text{H}_{15}\text{N}_2\text{O}_2$ requires C, 72.15; H, 5.3; N, 10.5%), ν_{\max} 1 730 (C=O) and 1 680 cm^{-1} (C=C), δ 7.97 (4 H, d, *J* 10 Hz, ArH), 7.37 (4 H, d, *J* 10 Hz, ArH), and 2.50 (6 H, s, 6, Me).

NN'-*Bis*-(4-methylbenzoyl)*hydrazine* was prepared as for dibenzoylhydrazine, m.p. 252° (from acetic acid) (lit.,¹⁹ 253—254°), ν_{\max} 3 270 (NH), 1 670 (C=O), and 1 630 cm^{-1} (C=C), $\delta([\text{H}_6]\text{DMSO})$ 9.86 (2 H, s, NH), 7.57 (4 H, d, *J* 9.0 Hz, ArH), 7.06 (4 H, d, *J* 9.0 Hz, ArH), and 2.36 (6 H, s, Me).

4-Benzoyl-4a,5,6,7,8,8a-hexahydro-8a-morpholino-2-phenyl-4H-1,3,4-benzoxadiazine (IIIa).—Dibenzoyl-di-imide (2.38 g, 10 mmol) in anhydrous benzene (100 ml) was added dropwise with stirring to a solution of 1-morpholinocyclohexene (1.67 g, 10 mmol) in anhydrous benzene (30 ml) under nitrogen, the mixture being kept at 7—8° in an ice-bath. The solution was left for 24 h at room temperature under nitrogen and then evaporated without heating under vacuum. The residue was crystallized from ligroin to give (3.3 g, 81%), m.p. 154—155° (Found: C, 70.9; H, 6.75; N, 10.3. $\text{C}_{24}\text{H}_{27}\text{N}_3\text{O}_3$ requires C, 71.1; H, 6.7; N, 10.35%), ν_{\max} 1 637 and 1 626 cm^{-1} , δ 7.85 (4 H, m, ArH), 7.40 (6 H, m, ArH), 5.05br (1 H, CH-N), 3.65 (4 H, m, $\text{CH}_2\text{-O-CH}_2$), 2.75 (4 H, m, $\text{CH}_2\text{-N-CH}_2$), and 2.0—1.2 (8 H, complex m, aliphatic).

The reaction was also carried out with a two-fold excess of (Ia) under the conditions described above. No discoloration of the solution occurred, even after 48 h, and chromatography on alumina of the residue gave (IIIa) and (IVa) (total yield 80%). Biphenyl (identified by comparison with an authentic sample) and benzaldehyde (identified by g.l.c.) were also obtained.⁴

2-(*NN'*-Dibenzoyl)*hydrazinocyclohexanone* (IVa).—10% HCl was added to an ethanol solution of (IIIa) and the resulting mixture shaken at room temperature for 24 h. The precipitate was filtered off and crystallized from benzene-ligroin to give (IVa) in quantitative yield, m.p. 142° (Found: C, 71.45; H, 5.85; N, 8.45. $\text{C}_{24}\text{H}_{27}\text{N}_3\text{O}_3$ requires C, 71.4; H, 6.0; N, 8.35%), ν_{\max} 3 345 (NH), 1 712 (ketone C=O), 1 676, 1 664, and 1 648 cm^{-1} , δ 8.45 (1 H, s, NH), 7.8—7.2 (10 H, complex m, ArH), 5.35br (1 H, CH-N), and 2.7—1.7 (8 H, complex m, aliphatic), R_F 0.36 (AcOEt-light petroleum 1:1).

Piperidinobenzoxadiazine (IIIb).—This was prepared from 1-piperidinocyclohexene and (Ia) in 87% yield as indicated for (IIIa), m.p. 154—156° (from ligroin) (Found: C, 74.1; H, 7.3; N, 10.35. $\text{C}_{25}\text{H}_{30}\text{N}_3\text{O}_2$ requires C, 74.25; H, 7.5; N, 10.35%), ν_{\max} 1 636 and 1 626 cm^{-1} , δ 7.75 (4 H, m, ArH), 7.45 (6 H, m, ArH), 5.0br (1 H, CH-N), 2.7 (4 H, m, $\text{CH}_2\text{-N-CH}_2$), and 1.8—1.3 (14 H, complex m, aliphatic). Acid hydrolysis of (IIIb), carried out as for (IIIa), gave (IVa) in quantitative yields. The reaction was also carried out using an excess (2:1) of (Ia), as indicated

for 1-morpholinocyclohexene; only (IIIb) and (IVa) were obtained, together with the decomposition products of (Ia).

Morpholinobenzoxadiazine (IIIc).—This was prepared (74%) from 1-morpholino-4-*t*-butylcyclohexene and (Ia), as indicated for (IIIa), m.p. 187—189° (from ligroin) (Found: C, 73.1; H, 7.75; N, 9.2. $\text{C}_{28}\text{H}_{35}\text{N}_3\text{O}_3$ requires C, 72.85; H, 7.65; N, 9.1%), ν_{\max} 1 645 cm^{-1} , δ 8.7 (4 H, m, ArH), 8.3 (6 H, m, ArH), 5.6br (1 H, CH-N), 4.0 (4 H, m, $\text{CH}_2\text{-O-CH}_2$), 3.1 (4 H, m, $\text{CH}_2\text{-N-CH}_2$), 2.8—1.1 (7 H, complex m, aliphatic) and 1.0 (9 H, s, Bu^t), R_F 0.7 (benzene-acetone 9:1).

2-(*NN'*-Dibenzoyl)*hydrazino-4-t-butylcyclohexanone* (IVc).—This was prepared in quantitative yield by acid hydrolysis of (IIIc) as described for (IVa), powder, m.p. 167° (from benzene-ligroin) (Found: C, 73.05; H, 7.15; N, 7.1. $\text{C}_{34}\text{H}_{38}\text{N}_2\text{O}_3$ requires C, 73.45; H, 7.2; N, 7.15%), ν_{\max} 3 316 (NH), 1 735 (ketone C=O), and 1 667—1 650 cm^{-1} , δ 8.2 (1 H, s, NH), 7.5 (10 H, m, ArH), 5.5br (1 H, CH-N), 2.8—1.5 (7 H, complex m, aliphatic), and 1.0 (9 H, s, Bu^t), R_F 0.57 (benzene-acetone 9:1).

Piperidinobenzoxadiazine (IIIId).—This was prepared from 1-piperidino-4-*t*-butylcyclohexene and (Ia) as indicated for (IIIa), crystals (79%), m.p. 153° (from ligroin) (Found: C, 76.1; H, 8.15; N, 9.15. $\text{C}_{29}\text{H}_{37}\text{N}_3\text{O}_2$ requires C, 75.8; H, 8.1; N, 9.15%), ν_{\max} 1 647 cm^{-1} , δ 8.06 (4 H, m, ArH), 7.5 (6 H, m, ArH), 5.2br (1 H, CH-N), 2.75 (4 H, m, $\text{CH}_2\text{-N-CH}_2$), and 2.2—1.1 (13 H, complex m, aliphatic), R_F 0.7 (benzene-acetone 9:1). Acid hydrolysis of (IIIId) carried out as for (IIIa) gave (IVc) in quantitative yield.

Benzoxadiazine (IIIe).—This was prepared (81%) from 1-morpholinocyclohexene and (Ie) as described for (IIIa),* crystals, m.p. 149—151° (from ligroin, b.p. 80—120°) (Found: C, 71.85; H, 7.2; N, 9.4. $\text{C}_{26}\text{H}_{31}\text{N}_3\text{O}_3$ requires C, 72.05; H, 7.2; N, 9.7%), ν_{\max} 1 620—1 612 cm^{-1} , δ 7.76 (4 H, 2 \times d, ArH), 7.20 (4 H, 2 \times d, ArH), 5.0br (1 H, CH-N), 3.60 (4 H, m, $\text{CH}_2\text{-O-CH}_2$), 2.75 (4 H, m, $\text{CH}_2\text{-N-CH}_2$), 2.45 (3 H, s, Me), 2.30 (3 H, s, Me), and 1.70 (8 H, complex m, aliphatic).

2-(*NN'*-*Bis*-(4-methylbenzoyl)*hydrazinocyclohexanone* (IVe).—This was prepared in quantitative yield by acid hydrolysis of (IIIe) as described for (IIIa) and (IVa), m.p. 171—173° (from benzene-ligroin) (Found: C, 72.3; H, 6.7; N, 7.7. $\text{C}_{22}\text{H}_{24}\text{N}_2\text{O}_3$ requires C, 72.5; H, 6.65; N, 7.7%), ν_{\max} 3 250 (NH), 1 720 (ketone C=O), and 1 640 cm^{-1} , δ 8.30 (1 H, s), 7.3 (8 H, m, ArH), 5.4br (1 H, CH-N), 2.37 (3 H, s, Me), 2.32 (3 H, s, Me), and 2.7—1.5 (8 H, complex m, aliphatic).

Reaction of Cyclohexanones (Va and c) with Dibenzoyl-di-imide.—Compound (Ia) (2.38 g, 10 mmol) was mixed with an excess of (Va or e) (5—10 g). The mixture was heated in an oil-bath at 100—110° for 20 h, then a small quantity of *NN'*-dibenzoylhydrazine, which had formed, was filtered out, the unchanged cyclohexanone was distilled under vacuum and the residue, dissolved with benzene-acetone (9:1), was filtered on an alumina column to give (IVa or c) (0.6—0.8 g, 20—25%).

Hydrolysis of 2-(NN'-Dibenzoyl)hydrazinocyclohexanones (IVa and c).—Compounds (IVa or c) were refluxed with 5% aqueous HCl for 8 h. The solution obtained was evaporated to small volume and benzoic acid (50—60%) was precipitated. G.l.c. of the filtrate revealed the presence of cyclohexane-1,2-dione (VIa) and 4-*t*-butylcyclohexane-1,2-dione

²⁰ C. C. Hoch, C. V. Banks, and H. Diehl, *Org. Synth.*, 1963, Coll. Vol. IV, p. 229.

* The corresponding piperidino-derivative is also known.³

¹⁹ W. Autenrieth and G. Thomae, *Ber.*, 1924, 57, 436.

(VIc). When toluene-*p*-sulphonic acid was used instead of HCl, benzamide was obtained in the place of benzoic acid.

Pyrrolidinobenzoxadiazine (IXa).—Compound (Ia) (2.38 g, 10 mmol) dissolved in anhydrous benzene (100 ml) was added dropwise under stirring for 45 min to a benzene solution of 1-pyrrolidinocyclohexene (4.53 g, 30 mmol), the temperature being maintained at 7–8° by an ice-bath. In order to obtain good yields it was necessary to operate under anhydrous conditions and an inert atmosphere. The solution was left in an ice-bath for 2 h and was then evaporated under vacuum at room temperature. Purification of the residue from benzene–ligroin gave *crystals* (90%), m.p. 100–101° (Found: C, 74.15; H, 7.15; N, 10.65. $C_{24}H_{27}N_3O_2$ requires C, 74.0; H, 7.0; N, 10.8%), ν_{\max} 1 644 cm^{-1} , $\delta(CCl_4)$ 7.75 (4 H, m, ArH), 7.30 (6 H, m, ArH), 4.85br (1 H, CH-N), 2.80 (4 H, m, CH_2-N-CH_2), and 2.0–1.5 (12 H, complex m, aliphatic), R_F 0.75 (benzene–acetone 9 : 1).

Hydrolysis of Compound (IXa).—10% Aqueous HCl was added to an ethanol solution of (IXa) and the mixture was shaken for 30 min. The precipitate (IVa) was obtained in quantitative yield.

Reaction of Compound (IXa) with *Dibenzoyldi-imides*.—Compound (Ia) (0.72 g, 3 mmol), dissolved in anhydrous benzene (10 ml), was added dropwise to a benzene solution of (IXa) (1.17 g, 3 mmol) with stirring under dry nitrogen. The solution rapidly became colourless and was filtered on a column of silica; elution with benzene gave (IVa) and (Xa)—(XIIa), together with a small quantity of dibenzoylhydrazine.

Reaction of 1-Pyrrolidinocyclohexene with Dibenzoylhydrazine (molar ratio 1 : 2).—1-Pyrrolidinocyclohexene (0.75 g, 5 mmol) in anhydrous benzene (30 ml) was added dropwise with stirring to a benzene solution of (Ia) (2.38 g, 10 mmol), cooling being effected with an ice-bath to maintain the temperature at 7–8°. The solution was left at room temperature under nitrogen for 48 h, then evaporated under vacuum without heating. The residue was dissolved in benzene–acetone (8 : 2; 20 ml) and passed through a column of silica. Elution with benzene–acetone (8 : 2) gave (XIIa) (1.7 g, 55%), then (Xa) (0.3 g, 10%). Elution with acetone gave (XIa) (0.3 g, 10%), with traces of (IVa).

4-Benzoyl-4a-NN'-dibenzoylhydrazino-4a,5,6,7,8,8a-hexahydro-2-phenyl-8a-pyrrolidino-4H-1,3,4-benzoxadiazine (XIIa) was a powder, m.p. 133° (from benzene) (Found: C, 72.55; H, 6.0; N, 11.0. $C_{38}H_{37}N_5O_4$ requires C, 72.7; H, 5.95; N, 11.15%), ν_{\max} 3 357 (NH), 1 705, 1 660, 1 640, and 1 630 cm^{-1} , δ 8.80 (1 H, s), 7.7 (8 H, m, ArH), 7.35 (12 H, m, ArH), and 3.0–1.8 (16 H, complex m, aliphatic), R_F 0.33 (benzene–acetone 9 : 1) (Found: M , 640. $C_{38}H_{37}N_5O_4$ requires M , 627.72).

2,6-Bis(dibenzoylhydrazino)cyclohexanone (Xa) was a powder, m.p. 166° (from chloroform–light petroleum) (Found: C, 70.85; H, 5.15; N, 9.55. $C_{34}H_{30}N_4O_5$ requires C, 71.05; H, 5.2; N, 9.75%), ν_{\max} (Nujol) 3 260 (NH), 1 738 (ketone C=O), 1 667–1 652, and 1 640 cm^{-1} , ν_{\max} (CCl_4) 3 393 (NH), 1 705 (ketone C=O), 1 677, 1 645, and 1 631 cm^{-1} , δ 8.30 (2 H, s, NH), 7.7–7.2 (20 H, m, ArH), 5.45br (2 H, 2, CH-N), and 2.9–1.7 (6 H, complex m, aliphatic), R_F 0.38 (benzene–acetone 8 : 2), 0.11 (benzene–acetone 9 : 1). The *isomer* (XIa) was a powder, m.p. 199–201° (from cold chloroform–light petroleum) (Found: C, 70.9; H, 5.05; N, 9.95%) ν_{\max} 3 261 (NH), 1 747 (ketone C=O), 1 694, 1 680, 1 668, and 1 651 cm^{-1} , δ 8.5 (2 H, s, NH), 7.8–7.2 (20 H, complex m, ArH), 5.45br (2 H, CH-N),

and 2.9–1.7 (6 H, complex m aliphatic), R_F 0.38 (benzene–acetone (8 : 2) and 0.11 (benzene–acetone 9 : 1).

When the reaction was carried out in other solvents the same products are obtained with the following yields: (XIIa) 28, (Xa) 59, (XIa) 4%.

Isomerization of (XIa) to (Xa).—A chloroform solution of (XIa) was refluxed for 30 min, then evaporated under vacuum. The residue was identical to (Xa) (m.p., mixed m.p., i.r. and n.m.r. spectra, R_F).

Hydrolysis of Compound (XIIa).—Compound (XIIa) dissolved in aqueous AcOH was heated in a steam-bath for 5 h. The solution was cooled, diluted with water, neutralized with Na_2CO_3 , saturated with NaCl, and extracted with $CHCl_3$ ($\times 5$). The extracts were combined, dried, concentrated, and chromatographed. Elution with benzene–acetone gave (VIa), benzamide, benzoic acid, (IVa), and small quantities of dibenzoylhydrazine. G.l.c. confirmed the presence of cyclohexane-1,2-dione (VIa), identified by comparison with authentic sample (Fluka).

4-Benzoyl-4a,5,6,7,8,8a-hexahydro-2-phenyl-8a-pyrrolidino-6-t-butyl-4H-1,3,4-oxadiazine (IXb).—This was prepared (90%) from 1-pyrrolidino-4-t-butylcyclohexene and (Ia), as for (IXa), m.p. 132–133° (from benzene–ligroin) (Found: C, 75.35; H, 8.0; N, 9.3. $C_{28}H_{35}N_3O_2$ requires C, 75.45; H, 7.9; N, 9.45%), ν_{\max} 1 635, 1 630, and 1 625 cm^{-1} , $\delta(CCl_4)$ 7.7 (4 H, m, ArH), 7.3 (6 H, m, ArH), 4.8br (1 H, CH-N), 2.8 (4 H, m, $CH-N-CH_2$), 2.0–1.1 (11 H, complex m, aliphatic), and 0.90 (9 H, s, Bu^t).

Hydrolysis of Compound (IXb).—10% Aqueous HCl was added to an ethanol solution of (IXb) and the mixture was stirred at room temperature for 30 min. The solid (IVb) was obtained in quantitative yield.

Reaction of Compound (IXb) with *Dibenzoyldi-imides*.—The reaction was carried out as for (IXa). *NN'*-Dibenzoylhydrazine, (XIIb), (IVb), and (Xb) were isolated from the reaction solution.

Reaction of 1-Pyrrolidino-4-t-butylcyclohexene with Dibenzoyldi-imides (molar ratio 1 : 2).—The reaction was carried out in the same way as that of (VIIIa) with (Ia). Using benzene as solvent, the following were isolated, (XIIb) (78%), (IVc) (15%), and traces of (Xb). When ethyl ether was used, however, (Xb) (13%), (XIIb) (50%), and traces of (IVc) were obtained. The *t-butyl derivative* (XIIb) was a powder, m.p. 175° (from CCl_4 –light petroleum) (Found: C, 73.95; H, 6.75; N, 10.2%; M , 692. $C_{42}H_{45}N_5O_4$ requires C, 73.75; H, 6.65; N, 10.25%; M , 684), ν_{\max} 3 240 (NH), 1 691, 1 632, and 1 615 cm^{-1} , δ 8.50 (1 H, s, NH), 7.8 (20 H, m, ArH), 3.2–1.3 (14 H, complex m, aliphatic), and 0.95 (9 H, s, Bu^t). The *ketone* (Xb) was a powder, m.p. 197–199° (from chloroform–ligroin) (Found: C, 72.4; H, 6.25; N, 8.75. $C_{38}H_{38}N_4O_5$ requires C, 72.35; H, 6.05; N, 8.9%), ν_{\max} 3 240 (NH), 1 750 (ketone C=O), and 1 680–1 650 cm^{-1} , δ 8.35 (2 H, s, NH), 7.8–7.3 (20 H, complex m, aromatic), 5.4br (2 H, CH-N), 2.8–1.6 (5 H, m, aliphatic), 0.90 (9 H, s, Bu^t), R_F 0.21 (benzene–acetone 9 : 1).

Acid Treatment of Compound (XIIb).—(a) *With HCl*. 10% Aqueous HCl was added to an ethanol solution of (XIIb) and the mixture left for 48 h under stirring. The resulting precipitate was filtered and crystallized from chloroform–ligroin, m.p. 182°, containing chlorine [when treated with alkali it gives back (XIIb)], to which the structure of (XIIb) hydrochlorate was assigned.

(b) *With acetic acid*. A solution of (XIIb) in aqueous AcOH was refluxed for 5 h, then cooled, diluted with water,

neutralized with Na_2CO_3 , saturated with NaCl , and extracted with CHCl_3 ($\times 5$). The chloroform extracts were combined, dried (Na_2SO_4), concentrated, and passed through a column of silica. *NN'*-Dibenzoylhydrazine, (VIc), (IVc), benzamide, and benzoic acid were obtained in low yield. Compound (VIc) was identified by comparison with an authentic sample prepared by a procedure similar to that for cyclohexane-1,2-dione;²⁰ its presence in the reaction mixture was confirmed by g.l.c.

Reaction of 1-Pyrrolidino-cyclohexene with Bis-(4-methylbenzoyl)di-imide.—The reaction was carried out as described for that of (VIIIa) with (Ia). With ether as solvent, (XIIc) and (Xc) were obtained in yields of 46 and 32%, respectively. The *amide* (XIIc) was a powder, m.p. 166° (from benzene-ligroin) (Found: C, 73.6; H, 6.75; N, 10.0. $\text{C}_{42}\text{H}_{45}\text{N}_5\text{O}_4$ requires C, 73.75; H, 6.65; N, 10.25%), ν_{max} 3 324—3 140 (NH), 1 680, 1 655, and 1 650 cm^{-1} , δ 8.30 (1 H, s, NH), 7.8—7.1 (16 H, complex m, ArH), 3.0—1.4 (16 H, complex m, aliphatic), and 2.42 (12 H, s, Me), R_F 0.36 (benzene-acetone 9 : 1). The *ketone* (Xc) was a powder, m.p. 204° (from CHCl_3) (Found: C, 72.6; H, 6.2; N, 8.9. $\text{C}_{38}\text{H}_{38}\text{N}_4\text{O}_5$ requires C, 72.35; H, 6.05; N, 8.9%), ν_{max} 3 248 (NH), 1 740 (ketone C=O), and 1 670—1 616 cm^{-1} , δ 8.55 (2 H, s, NH), 7.5—6.8 (16 H, m, ArH), 5.3br (2 H, CH-N), 2.2 (12 H, s, Me), 2.7—1.5 (6 H, complex m, aliphatic), R_F 0.15 (benzene-acetone 9 : 1).

Reaction of 1-Pyrrolidino-4-t-butylcyclohexene with Bis-(4-methylbenzoyl)di-imide.—The reaction was carried out as for that of (VIIIa) with (Ia). Compounds (XIId) and (Xd) were obtained in yields of 51 and 23%, respectively. The *amide* (XIId) was a powder, m.p. 193° (from benzene-ligroin) (Found: C, 74.75; H, 7.05; N, 9.3. $\text{C}_{46}\text{N}_5\text{H}_{53}\text{O}_4$ requires C, 74.65; H, 7.2; N, 9.5%), ν_{max} 3 240 (NH) and 1 680—1 616 cm^{-1} , δ 8.28 (1 H, s, NH), 7.9—7.1 (16 H, complex m, ArH), 2.40 (12 H, s, $\text{C}_6\text{H}_4\text{CH}_3$), 0.92 (9 H, s, Bu^t), and 2.2—1.3 (15 H, complex m, aliphatic), R_F 0.26 (benzene-acetone 9 : 1). The *ketone* (Xd) was a powder, m.p. 214—215° (from chloroform) (Found: C, 73.3; H, 6.85; N, 8.05. $\text{C}_{42}\text{H}_{46}\text{N}_4\text{O}_5$ requires C, 73.45; H, 6.75; N, 8.15%), ν_{max} 3 285—3 244 (NH), 1 748 (ketone C=O), and 1 680—1 616 cm^{-1} , δ ([$^2\text{H}_6$]DMSO) 8.30 (2 H, s, NH), 7.7—7.1 (16 H, complex m, ArH), 5.3br (2 H, CHN), 2.32 (12 H, s, $\text{C}_6\text{H}_4\text{CH}_3$), 2.7—1.7 (5 H, complex m, aliphatic), and 0.85 (9 H, s, Bu^t), R_F 0.33 (benzene-acetone 9 : 1).

Hydrolysis with D_2SO_4 - D_2O .—Compounds (IIb) and (IXa) were hydrolysed with D_2SO_4 - D_2O (10 : 90) in dioxan, by the procedure for hydrolysis with aqueous HCl. In both cases, 2-(*NN'*-dibenzoylhydrazine)cyclohexanone was obtained, with physical data identical with those above, except for the n.m.r. parameters.

The ketone obtained from (IIb) displays a broad peak at δ 5.45 (intensity 1) corresponding to CH-N. The ketone obtained from (IXa) displays a broad peak also at δ 5.45 (intensity ca. 0.6) and a peak at δ 2.7—1.7 corresponding to aliphatic protons (intensity 7—8). 2-(*NN'*-Dibenzoylhydrazine)cyclohexanone dissolved in dioxan and treated with D_2SO_4 - D_2O (10 : 90) does not exchange 2-H with deuterium.

4-Benzoyl-4a,5,6,7,8,8a-hexahydro-8-methyl-8a-morpholino-2-phenyl-4H-1,3,4-benzoxadiazine (XXI).—DBD (2.38 g, 10 mmol) in anhydrous benzene (100 ml) was added

dropwise with stirring to a solution of 1-morpholino-6(2)-methylcyclohexene (1.81 g, 10 mmol) in anhydrous benzene (30 ml) under nitrogen and with cooling in an ice-bath to 7—8 °C. The solution was left at room temperature under nitrogen for 24 h, then evaporated under vacuum at room temperature; crystallization of the residue from ligroin gave (XXI), crystals (50%), m.p. 154—156 °C (Found: C, 71.75; H, 7.0; N, 10.25. $\text{C}_{25}\text{H}_{29}\text{N}_3\text{O}_3$ requires C, 71.6; H, 6.95; N, 10.0%), ν_{max} 1 971, 1 652, and 1 633 cm^{-1} , δ 7.8 (4 H, m, ArH), 7.35 (6 H, m, ArH), 5.0br (1 H, CH-N), 3.55 (4 H, m, $\text{CH}_2\text{-O-CH}_2$), 2.8 (4 H, m, $\text{CH}_2\text{-N-CH}_2$), 2.0—1.0 (10 H, complex m, aliphatic), and 1.27—1.16 (3 H, 2 \times d, Me), R_F 0.50.

The reaction was also carried out with excess of DBD (2 : 1 and 3 : 1) with the same experimental conditions. No discolouration of the solution occurred, even after several days, and chromatography of the residue obtained after evaporation of the reaction solution again gave (XXI) together with biphenyl and decomposition products of DBD.

*2-(*NN'*-Dibenzoylhydrazino)-6-methylcyclohexanone* (XXII).—This was obtained by suspending (XXI) in aqueous 10% HCl and stirring the mixture for 48 h at room temperature, giving a powder (100%), m.p. 167—169 °C (from benzene-ligroin) (Found: C, 72.05; H, 6.35; N, 8.5. $\text{C}_{21}\text{H}_{22}\text{N}_2\text{O}_3$ requires C, 72.0; H, 6.35; N, 8.0%), ν_{max} 3 300 (NH), 1 715 (ketone C=O), and 1 680—1 640 cm^{-1} , δ 8.40 (1 H, s, NH), 7.8—7.2 (10 H, complex m, ArH), 5.5br (1 H, CH-N), 2.9—1.7 (7 H, complex m, aliphatic), and 1.31—1.07 (3 H, 2 \times d, Me), R_F 0.74.

Isomerization of (XXII) to (XXVI).—A benzene solution of (XXII) containing a catalytic quantity of acetic acid was refluxed for 5 h; cooling and addition of ligroin caused the precipitation of isomer (XXVI) (100%), m.p. 193 °C, (Found: C, 72.05; H, 6.3; N, 8.0%), ν_{max} 3 302 (NH), 1 715 (ketone C=O), 1 637—1 676 cm^{-1} , δ 8.40 (1 H, s, NH), 7.7—7.2 (10 H, complex m, ArH), 5.35br (1 H, CH-N), 2.9—1.8 (7 H, complex m, aliphatic), and 1.07 (3 H, d, Me), R_F 0.74.

4-Benzoyl-4a,5,6,7,8,8a-hexahydro-8-methyl-2-phenyl-8a-pyrrolidino-4H-1,3,4-benzoxadiazine (XXIV).—This was prepared from (XXIII) and (Ia) as indicated for (XXI), but it was necessary to exclude moisture from the reaction medium, powder, m.p. 175—176 °C (from ligroin) (Found: C, 74.3; H, 7.3; N, 10.35. $\text{C}_{25}\text{H}_{29}\text{N}_3\text{O}_2$ requires C, 74.4; H, 7.25; N, 10.4%), ν_{max} 1 670—1 645 cm^{-1} , δ 7.7—7.1 (10 H, complex m, ArH), 5.4br (1 H, CH-N), 3.6 (4 H, m, $\text{CH}_2\text{-N-CH}_2$), 1.85 (11 H, m, aliphatic), 1.26—1.05 (3 H, 2 \times d, Me).

In this case, as for the morpholine enamine, when the reaction was carried out with excess of DBD, no other addition product was obtained, but decomposition compounds from DBD were isolated.

Hydrolysis of Compound (XXIV).—Hydrolysis of (XXIV), carried out as for the hydrolysis of (XXI), gave ketone (XXVI), m.p. 193 °C, in quantitative yield, δ 1.31 (d) and 1.07 (d) (3 H, Me, intensity ratio ca. 10 : 90). Ketone (XXV) refluxed in benzene containing acetic acid, as indicated for (XXII), gave the *cis*-isomer (XXVI) in quantitative yield.

[7/575 Received, 1st April, 1977]