Rearrangement of the Diels–Alder adduct of azodibenzoyl and cyclopentadiene

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The product of the thermal isomerization of the Diels–Alder adduct **1** of azodibenzoyl and cyclopentadiene has been identified by degradation and nuclear magnetic resonance analysis as the *cis*-bicyclic oxadiazine **2***a*, the dihydro derivative of which has been synthesized. The isomerization is quantitative and is first order throughout in solution in a range of solvents; kinetic and other evidence point to it being a sigmatropic rearrangement.

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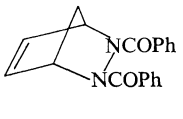
In earlier work by one of us and co-workers (1) it was found that the Diels–Alder adduct **1** of azodibenzoyl and cyclopentadiene was labile, isomerizing irreversibly on heating either near its melting point (m.p.) or in solution to a substance $C_{19}H_{16}O_2N_2$, m.p. 130–131.5°. The latter had a carbon–carbon double bond (dibromide, m.p. 144.5–147°) and its infrared (i.r.) spectrum had absorptions at 1652 and 1630 cm^{-1} in the carbonyl region, but no NH absorption, while its 60 Mc.p.s. nuclear magnetic resonance (n.m.r.) spectrum showed two non-equivalent phenyl groups and two vinyl, two tertiary, and two methylene hydrogens, each pair being non-equivalent. This stable isomer, like **1**, was thus evidently a bicyclic compound.

Carpino and Rundberg (2) have recently concluded that this isomer is **2***a* or **2***b*, tentatively the former, by reducing it to **3**, the structure of which was inferred by Raney nickel cleavage to *cis*-2-benzoylaminocyclopentanol. We wish to show that the stable isomer is indeed **2***a*, to describe the rational synthesis of **3**, and to present evidence regarding the mechanism of the rearrangement.

Catalytic reduction of the stable isomer with Pd–H_2 in benzene or by catalytic hydrogen transfer with Pd in refluxing cyclohexene (3) gave a mixture of mainly a dihydro-derivative, m.p. 143–143.5°, and small amounts (5–10%) of a tetrahydro-derivative, m.p. 197–198°. The latter had amide NH and CO absorption in the i.r. and was shown to be 1,2-dibenzoyl-1-cyclopentylhydrazine (**4**), synthesized by reduction of cyclopentanone benzoylhydrazone with sodium borohydride followed by benzoylation of the resulting hydrazine. The formation of **4** showed that the integrity of the original azodibenzoyl skeleton and of the C-5 ring had been preserved in the isomerization, and that the stable isomer contained at least one C—N bond at a ring junction.

The dihydro-derivative, which could be more conveniently made, in nearly quantitative yield, by reaction with di-imide (hydrazine-oxygen in methanol or *p*-toluenesulfonylhydrazine in refluxing dioxane), arose from reduction of the carbon–carbon double bond (2); its n.m.r.



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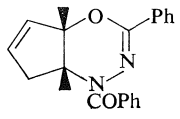
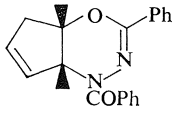
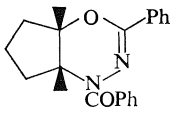


2*a*



2*b*



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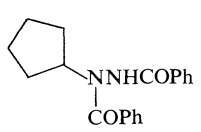

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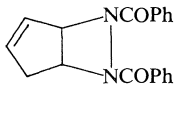

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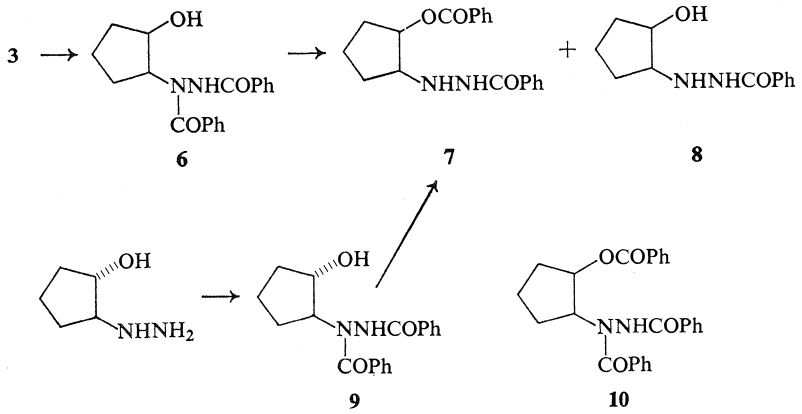


SCHEME 1

spectrum showed the phenyl groups and the tertiary hydrogens to be still non-equivalent. This ruled out the diazetidine **5** as a possible structure for the stable isomer and implied, therefore, a C—O link at the other ring junction which must have been the site of hydrogenolysis to **4**. The most plausible structures for the isomer and its dihydro-derivative were thus the bicyclic oxadiazines **2** and **3** or their epimers.

Confirmation of the structure and stereochemistry of **3** was obtained by hydrolyzing it with 0.8 *N* aqueous ethanolic hydrochloric acid (Scheme 1). Work-up gave the bases **7**, m.p. 88.5–89° (isolated directly as its hydrochloride in 37% yield), and **8**, m.p. 128–129° (11%), together with benzoic acid. The product expected from **3** was the *cis*-alcohol **6**, by analogy with the behavior of monocyclic 2-aryl-1,3,4-oxadiazines on hydrolysis (4). A control experiment, however, showed that **6** was efficiently converted into **7** under the conditions of the experiment, and its presence during the hydrolysis was indeed proven by thin-layer chromatography (t.l.c.).

The alternative *trans*-stereochemistry for **3** can be excluded since the hydrolysis would have given the *trans*-alcohol **9**; however, no **9** was detected, though it was independently shown to be stable to these conditions.

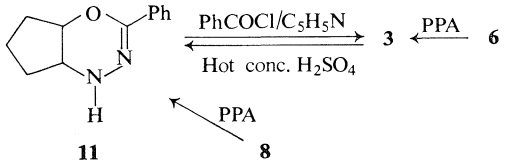
The synthesis of the hydrazine derivatives **6**–**10** was achieved as shown in Scheme 1. Cyclopentene oxide was cleaved with hydrazine to *trans*-2-hydrazinocyclopentanol, a dilute alkaline solution of which was shaken with two equivalents of benzoyl chloride, causing benzoylation at the nitrogens only to give the *trans*-*N*,*N*′-dibenzoyl alcohol **9**, m.p. 177.5–178°, in a good yield. Brief treatment of **9** with cold concentrated sulfuric acid, followed by neutralization, caused quantitative isomerization with inversion to the basic ester **7**, which was then hydrolyzed to **8** (80%) by 2 *N* aqueous methanolic sodium hydroxide. Benzoylation of **8** with an excess of benzoyl chloride in cold dilute alkali again occurred only at the nitrogen to give the *cis*-alcohol **6**, m.p. 170.5–171.5° in an excellent yield. The isomerization **9**→**7** is paralleled in cyclohexane chemistry (4).

The identity of the stereochemistries in **6**, **7**, and **8** followed from the fact that when treated with benzoyl chloride in pyridine they all gave the same tribenzoyl derivative **10**, m.p. 177.5–178.5°, which must have been *cis*, since it was different from the product, m.p. 139–140°, of benzoylation of the *trans*-compound **9**. Hydrolysis of **10** with alkali was hard to control to the dibenzoyl stage **6**, but proceeded smoothly, if allowed, to the monobenzoyl compound **8** in 90% yield; **8** could also be obtained from **7** under the conditions of hydrolysis of **3**, which probably accounted for its formation in that reaction.

The acid catalyzed intramolecular esterifications, under different conditions, of both epimeric alcohols **6** and **9** to the same benzoate **7** are part of a series of acyl transfer reactions of *cis*- and *trans*-2-hydrazinocyclopentanol derivatives presently being investigated.

In contrast to the degradation of the heterocyclic ring observed when **3** was heated with aqueous acid, reaction of **3** with hot concentrated sulfuric acid occurred only at the benzoyl substit-

uent, which was quantitatively removed to give, on neutralization, the oxadiazine **11** (Scheme 2), an oily base [λ_{max}(EtOH) 282 mμ; hydrochloride, m.p. 171–174° (decomposition)], from which **3** could be regenerated (>90%) by treating it with benzoyl chloride in pyridine.



SCHEME 2

Conditions for the cyclodehydration of 2-acyl-1-(2-hydroxyalkyl)hydrazines to 1,3,4-oxadiazines have been worked out in some detail by Trepanier *et al.* (5–9). Application of these to the *cis*-alcohol **6** gave the best results with polyphosphoric acid (PPA) at 60° for 24 h; gas–liquid chromatography (g.l.c.) indicated a modest yield of **3** (40–60%), which was separated from acidic and basic products, and then gave a single peak in the gas–liquid chromatogram. The stereochemical purity was high since two crystallizations gave **3** of satisfactory m.p. Similarly PPA, or alternatively concentrated sulfuric acid, converted the monobenzoyl compound **8** into the base **11**.

The ring closures to **3** and to **11** constitute a rational proof of the structure of **3** though not of its stereochemistry, since inversion of configuration may accompany cyclization (7, 8). However, in the only recorded examples of oxadiazine formation from cyclic hydroxy-hydrazides, both *cis*- and *trans*-1,2-dibenzoyl-1-(2-hydroxycyclohexyl)hydrazines cyclized with retention of configuration (4). Attempts were made to cyclize the *trans*-alcohol **9** to the *trans*-isomer of **3**, or, if inversion occurred to **3** itself, using a variety of reagents; with acids (H_2SO_4, P_2O_5) the rearrangement to **7**, already noted, was observed, and with bases (NaOEt, KO*t*-Bu) the starting material was recovered.

The position of the carbon–carbon double bond in **2** could be inferred from the fact that while **2** could be converted into **4**, **3** could not, being indefinitely stable to the hydrogenation conditions. Thus in the path from **2** to **4**, hydrogenolysis must have preceded hydrogenation, suggesting the presence of an allylic oxygen, i.e. that the stable isomer was **2***a*.

A rigid proof was provided by the 60 Mc.p.s. n.m.r. analysis of the tertiary hydrogens in the base **11** and its dideuterio analogue. In **11** these were found centered at 5.5 and 6.8 τ (CCl_4), both essentially quartets, and must have been adjacent to oxygen and to basic nitrogen respectively since protonation by trifluoroacetic acid made the high-field absorption more complex (due to splitting by the extra proton on the adjacent nitrogen) and moved it down by 0.9 p.p.m., while it moved the other absorption correspondingly less (0.6 p.p.m.) (10). When **2** was reduced by *p*-toluenesulfonylhydrazine-d_3 in refluxing dioxane and the product was de-benzoylated with concentrated sulfuric acid to the base, only the absorption for the tertiary hydrogen next to the oxygen was affected, being simplified to a triplet. This located a deuterium in the methylene nearest the oxygen and so the stable isomer is (±)-*cis*-4-benzoyl-4,4*a*,5,7*a*-tetrahydro-2-phenylcyclopenta-1,3,4-oxadiazine (**2***a*).

The adduct **1** in the solid phase was stable for at least 15 h at 80°, but was completely isomerized in 10 h at 120°, and, in the molten state, in 10 min at 140°, the i.r. spectrum of the product being superimposable on that of purified **2***a*. The most striking demonstration of the completeness of the rearrangement was provided by the mass spectra of **1** and **2***a*, which were identical in every detail when run under the same conditions at an inlet temperature of 205°.

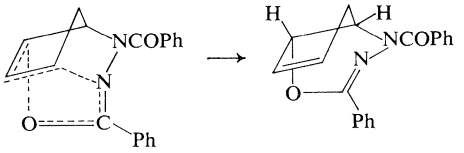
On heating in solution the rearrangement was again quantitative and could be conveniently followed by ultraviolet (u.v.) spectrometric analysis which showed first order kinetics throughout and one or more isosbestic points in a variety of solvents (Table 1). The log plot of the rate constants in 71% aqueous ethanol at various temperatures between 65° and 80° against $1/T$ gave a good straight line fit from which an energy of activation of 23.2 kcal mole^{-1} and an entropy of activation of about −9 e.u. (350 °K) were obtained (11). These values and the rather small solvent effect (12), together with the failure of added dienophiles to divert the reaction path (thus when **1** was refluxed with a 5-fold excess of maleic anhydride in iso-octane **2***a* was obtained quantitatively) strongly point to a concerted cyclic mechanism which can formally be interpreted as a [3,3]-sigmatropic shift **12**→**2***a*.

The rearrangement of the heterocycle **1** thus provides an exact parallel to the recently reported

TABLE 1

First order rate constants for the thermal isomerization of **1**

Solvent	Temperature (°C)	Isobestic points (mμ)	$k \times 10^4$ (s^{-1})
iso-Octane	77.5	231,253,335	1.82
Dioxane	77.0	232,258	1.96
Acetonitrile	77.0	230,259	0.60
29% Aqueous ethanol	77.5	228,259	4.50
48% Aqueous ethanol	77.5	228,258	3.67
71% Aqueous ethanol	77.5	227,258	2.54
	75.2	—	2.04
	73.5	—	1.77
	69.3	—	1.15



12 **2a**

(13) rearrangement of the carbocyclic Diels–Alder adducts of fulvenes and *cis*-hex-3-ene-2,5-dione.

A detailed study is now being made using a range of Diels–Alder adducts with structural variation both in the diene and in the azo components. A complete understanding of the mechanism must accommodate our observations to this point that **13** is stable indefinitely on heating, while **14** rearranges more slowly than **1** to give **15** only, and **16** rearranges rather faster than **1** to give both **17** and **18**. Steric factors may also play a role since the adduct **19** is extremely labile, having a transient existence at room temperature, detectable by n.m.r. analysis, when 1,4-dimethyl-2,3-diphenylcyclopentadiene (14) and azodibenzoyl are allowed to react: the product isolated is an oxadiazine, presumably **20**, whose structure has yet to be confirmed.

Experimental

Infrared spectra were taken on a Beckman IR9 or IR10 spectrophotometer. A Bausch and Lomb Spectronic 505 or a Coleman EPS-3T Hitachi spectrophotometer were used for measuring u.v. spectra. The n.m.r. analyses were done on a JEOL C60 or a Varian HA 100 spectrometer and absorptions are quoted in τ values against tetramethylsilane as standard; all values are from 60 Mc.p.s. spectra unless otherwise stated. The mass spectra were taken on a CEC 110 spectrometer.[2]

[2]We thank from this department, Dr. A. J. Carty for obtaining the 100 Mc.p.s. n.m.r. spectra and Dr. F. W. Karasek for obtaining the mass spectra.

Anhydrous magnesium sulfate was used as drying agent for solutions in organic solvents. Melting points are uncorrected.

1,2-Dibenzoyl-1-cyclopentylhydrazine(4)

Benzoylhydrazine and cyclopentanone (0.2 mole each) were refluxed in 70% aqueous acetic acid (100 ml) for ½ h and the solution was concentrated. The hydrazone separated out on cooling and was recrystallized from aqueous ethanol, m.p. 144–145°.

Cyclopentanone benzoylhydrazone (10 g, 50 mmole) and sodium borohydride (5 g, 130 mmole) were allowed to react in ethanol solution (100 ml) at room temperature for 3 days. The solvent was removed, the residue was decomposed with very dilute acetic acid, and the product was crystallized from aqueous ethanol giving an excellent yield of 2-benzoyl-1-cyclopentylhydrazine as needles, m.p. 101–101.5°.

The hydrazine (0.5 g, 2.5 mmole) was refluxed for 16 h with benzoyl chloride (0.35 ml, 3.0 mmole) in pyridine (5 ml). The addition of water precipitated a solid which after two crystallizations from benzene–petroleum ether (b.p. 60–80°) afforded **4** as fine needles, m.p. 197–198°; ν(Fluorolube) 3230 (NH), 1685, 1630 cm^{-1} (*sec, tert*-amide C=O); τ($CDCl_3$) 1.5(NH), 2.3–2.9(10 phenyl H), 5.4(*tert* H), 7.9–8.8 p.p.m. (8 methylene H).

Anal. Calcd. for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54; N, 9.09. Found: C, 74.42; H, 6.54; N, 9.08.

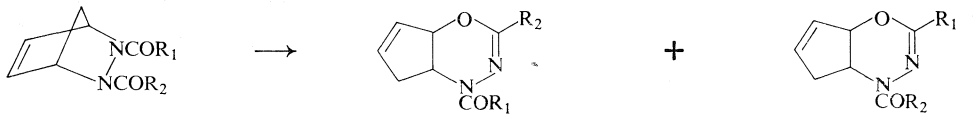
trans-2-Hydrazinocyclopentanol

Cyclopentene oxide (15) (80 g, 0.95 mole) was heated at 100° with an excess of 95% hydrazine for 20 h. Water and unreacted hydrazine were then removed at reduced pressure and the oily residue was distilled giving the hydroxyhydrazine as a colorless, viscous, hygroscopic liquid (96%), b.p. 105°/0.4 mm; τ($CDCl_3$) 5.7 sharp (OH, 3NH), 5.9(OC—H), 7.0(NC—H, $J_{1,2}$ = 3.5 c.p.s., determined by spin decoupling), 7.7–9.0 p.p.m. (6 methylene H).

Anal. Calcd. for $C_5H_{12}N_2O$: C, 51.69; H, 10.41. Found: C, 52.49; H, 10.68.

trans-1,2-Dibenzoyl-1-(2-hydroxycyclopentyl)-hydrazine (9)

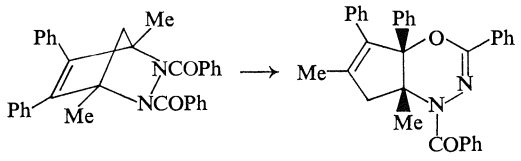
A solution of benzoyl chloride (230 ml, 2.0 mole) in benzene (1.7 l) was added portionwise and with vigorous shaking to a solution of *trans*-2-hydrazinocyclopentanol (111 g, 0.96 mole) in 2 *N* sodium hydroxide (2.5 l). The



13 $R_1 = R_2 = OEt$
14 $R_1 = OEt$; $R_2 = Ph$
16 $R_1 = Ph$; $R_2 = p\text{-}BrC_6H_4$

15 $R_1 = OEt$; $R_2 = Ph$
17 $R_1 = Ph$; $R_2 = p\text{-}BrC_6H_4$

18 $R_1 = Ph$; $R_2 = p\text{-}BrC_6H_4$



19 **20**

mixture was then stirred for 3 h and filtered to remove the product. The benzene layer was evaporated and the residue was combined with the filtered material. The whole was washed thoroughly with water and recrystallized from aqueous methanol to give **9** (80%) as prisms, m.p. 173–174°, raised to 177.5–178° on further recrystallization; ν($CHCl_3$) 3600–3200 (H-bonded OH, NH), 1685, 1655 cm^{-1} (*sec*, *tert*-amide C=O); τ($CDCl_3$) 1.2 (NH), 2.2–2.8 (10 phenyl H), 5.4–6.2 (2 *tert* H),[3] 6.4 (OH), 7.9–8.6 p.p.m. (6 methylene H).

Anal. Calcd. for $C_{19}H_{20}N_2O_3$: C, 70.35; H, 6.22; N, 8.64. Found: C, 70.40; H, 6.26; N, 8.71.

The *benzoate* was obtained as a gum, which slowly crystallized, by treating **9** (0.50 g, 1.5 mmole) in pyridine (5 ml) with benzoyl chloride (0.5 ml, 4 mmole) for 2 days at 5°, and then pouring the reaction mixture on ice. The solid (93%) was recrystallized from benzene–petroleum ether (b.p. 60–80°) as fine prisms, m.p. 139–140°; ν(CCl_4) 3365 (NH), 1702, 1672 cm^{-1} (ester, amide C=O); τ($CDCl_3$) 0.8 (NH), 1.8–3.0 (15 phenyl H), 4.6, 5.1 (2 *tert* H), 7.4–8.5 p.p.m. (6 methylene H).

Anal. Calcd. for $C_{26}H_{24}N_2O_4$: C, 72.88; H, 5.65; N, 6.54. Found: C, 73.15; H, 5.83; N, 6.71.

Compound **9** was unaffected when refluxed for 16 h with sodium ethoxide in ethanol or with potassium *t*-butoxide in *t*-butanol or benzene: the recovery was quantitative.

It was also stable when refluxed (0.50 g) for 17 h in a mixture of ethanol (7 ml), water (3 ml), and 12 *N* hydrochloric acid (0.6 ml), the conditions for hydrolysis of the oxadiazine **3**. Addition of an excess of potassium hydrogen carbonate, evaporation to dryness, and several extractions with ether led to a recovery of **9** (80%) in a pure state.

Anhydrous acidic conditions however, caused isomerization (see below).

Isomerization of ***9*** *to cis-2-Benzoyl-1-(2-benzoyloxycyclopentyl)hydrazine (****7****)*

Finely powdered **9** (1.00 g, 3.1 mmole) was dissolved in concentrated sulfuric acid (5 ml) at room temperature and after 5 min the solution was poured into an excess of ice-cold aqueous ammonia. The liberated oil readily crystallized and was extracted with methylene chloride; the extracts were dried and evaporated to give a quantitative yield of **7** which was twice crystallized from aqueous ethanol as prisms, m.p. 88.5–89°; ν(CCl_4) 3400, 3300 (NH), 1707, 1661 cm^{-1} (ester, amide C=O); τ(CCl_4) 1.5 (amide NH), 2.0–2.9 (10 phenyl H), 4.7 (C_2—H), 5.1 (amine NH), 6.7 (C_1—H), 7.8–8.7 p.p.m. (6 methylene H).

Anal. Calcd. for $C_{19}H_{20}N_2O_3$: C, 70.35; H, 6.22; N, 8.64. Found: C, 70.23; H, 6.24; N, 8.69.

The *hydrochloride* separated out in methanolic hydrochloric acid, and was recrystallized from the same solvent medium; it had m.p. 162–164°, with previous decomposition and loss of water.

Anal. Calcd. for $C_{19}H_{21}ClN_2O_3$: C, 63.24; H, 5.87; Cl, 9.83; N, 7.76. Found: C, 63.71; H, 5.99; Cl, 9.91; N, 7.83.

The *cis*-ester **7** could also be obtained by isomerization of **9** at room temperature either with thionyl chloride (5 h) or phosphoric oxide in methylene chloride (12 h). In each case the work-up entailed addition to aqueous alkali and extraction with methylene chloride.

*cis-2-Benzoyl-1-(2-hydroxycyclopentyl)hydrazine (****8****)*

A solution of the ester **7** (0.50 g, 1.55 mmole) in 2 *N* 50% aqueous methanolic sodium hydroxide (15 ml) was refluxed for ½ h and evaporated. Addition of an excess of dilute aqueous acetic acid and then of sodium hydrogen carbonate, followed by extraction with methylene chloride, gave the alcohol **8** (82%), the i.r. spectrum of which was identical with that of material recrystallized from aqueous methanol, m.p. 128–129°; ν(CCl_4) 3435, 3305, 3360 (OH, NH), 1662 cm^{-1} (amide C=O); τ($CDCl_3$) 1.2 (amide NH), 1.7–2.7(5 phenyl H), 5.3 one peak (OH, amine NH), 5.9 (C_2—H), 6.8 (C_1—H), 7.9–8.8 p.p.m. (6 methylene H).

Anal. Calcd. for $C_{12}H_{16}N_2O_2$: C, 65.43; H, 7.32; N, 12.72. Found: C, 65.34; H, 7.46; N, 12.47.

*cis-1,2-Dibenzoyl-1-(2-hydroxycyclopentyl)hydrazine (****6****)*

The alcohol **8** (0.20 g, 0.91 mmole) was dissolved with warming in 2 *N* sodium hydroxide (10 ml), ice was added followed by benzoyl chloride (0.21 ml, 1.82 mmole), and

[3]The tertiary hydrogens in all the *cis*- and *trans*-hydroxycyclopentylhydrazine derivatives studied, whether overlapping or distinguishable, showed little fine structure. The quoted τ values are the centers of the absorptions.

the whole was shaken vigorously until odorless. A small amount of precipitate was filtered off and the solution was treated in turn with an excess of dilute aqueous acetic acid and sodium hydrogen carbonate which brought down the crystalline dibenzoyl-derivative. Isolation with methylene chloride gave material (83%) of high purity (i.r.), which was twice recrystallized from aqueous methanol and afforded **6** as small prisms, m.p. 170.5–171.5°; $\nu(CHCl_3)$ 3395 broad (OH, NH), 1688, 1655 cm^{-1} (*sec*, *tert*-amide C=O); $\tau(CD_3SOCD_3)$ 2.0–2.7 (10 phenyl H), 5.3 overlapping (NH and *tert* H), 5.6 (*tert* H), 6.7 (OH), 7.8–8.6 p.p.m. (6 methylene H).

Anal. Calcd. for $C_{19}H_{20}N_2O_2$: C, 70.35; H, 6.22; N, 8.64. Found: C, 70.41; H, 6.24; N, 8.62.

*cis-1,2-Dibenzoyl-1-(2-benzoyloxycyclopentyl)-hydrazine (**10**)*

The *cis*-ester **7** (0.324 g, 1 mmole) was set aside in pyridine (3 ml) with benzoyl chloride (0.17 ml, 1.5 mmole) for 12 h at 5°. The solution was evaporated to remove most of the pyridine and was then made slightly acidic with dilute hydrochloric acid. Extraction of the precipitate with methylene chloride, removal of the solvent, and trituration of the residue with methanol gave the tribenzoyl derivative **10** (94%) directly pure (i.r.), recrystallized from aqueous methanol as fine needles, m.p. 178–179°; $\nu(CCl_4)$ 3420, 3310 (free, bonded NH), 1730, 1704, 1680 cm^{-1} (ester, *sec*-amide, *tert*-amide C=O); $\tau(CDCl_3)$ 1.7–2.9 (15 phenyl H, NH), 4.3, 5.0 (2 *tert* H), 7.4–8.5 p.p.m. (6 methylene H).

Anal. Calcd. for $C_{26}H_{24}N_2O_4$: C, 72.88; H, 5.65; N, 6.54. Found: C, 72.94; H, 5.70; N, 6.60.

Similar treatment of the monobenzoyl derivative **8** or the dibenzoyl derivative **6** with the appropriate amount of benzoyl chloride also gave **10** in excellent yields.

*Alkaline Hydrolysis of **10***

Attempts to hydrolyze only the ester group in **10** met with little success, even when cold very dilute alkali was used; the reaction usually proceeded further to give mixtures of **6** and **8**. Hydrolysis to **8** could be achieved in a high yield using hot alkali.

A solution of the ester **10** (1.00 g, 2.3 mmole) in 2 *N* 50% aqueous methanolic sodium hydroxide (30 ml) was refluxed for ½ h and then evaporated. The residue was dissolved in dilute aqueous acetic acid and an excess of sodium hydrogen carbonate was added to liberate the basic alcohol **8**, which was isolated with methylene chloride and obtained directly (90%) in a pure state.

*Labile Adduct **1***

A final crystallization of **1**(1) from aqueous acetone raised the m.p., which should be taken fairly rapidly, to 138–139°; $\nu(CCl_4)$ 1698, 1675 cm^{-1} (C=O doublet); λ_{max}(EtOH) 224 (ε 21 600), 255 mμ (ε 12 800); n.m.r. described previously (1); the mass spectrum was identical with that of **2***a*.

*Rearrangement to Stable Isomer **2a***

(a) Preparative Scale

A solution of **1** (3.0 g, 9.9 mmole) was refluxed in 80% aqueous methanol (50 ml) for 2 h and evaporated. The residue (quantitative) had an i.r. spectrum superimposable on that of purified **2***a*. Recrystallization from aqueous methanol gave prisms, m.p. 130–130.5°; $\nu(CCl_4)$ 1652 (C=O), 1635 cm^{-1} (C=N); λ_{max}(EtOH) 220 (ε 21 900), 290 mμ (ε 19 800); $\tau(CDCl_3$, 100 Mc.p.s.)[4] 2.1–2.9 (10 phenyl H), 3.71, 3.93 (C_7—H and C_6—H, AB quartet with further small splittings, $J_{6,7}$ = 7 c.p.s.), 5.05 (C_{4a}—H and C_{7a}—H overlapping, total width 33 c.p.s., $J_{4a,7a}$ at least 6 c.p.s.), 6.91, 7.64 p.p.m. (C-5 methylene H, AB quartet of doublets, further splittings, $J_{5A,5B}$ = 17.5, $J_{5A,4a} = J_{5B,4a}$ = 6 c.p.s.); mass spectrum 304(M^+, 30), 105 ($PhCO^+$, 100), 77 (Ph^+, 34).

(b) Direct Heating of Solid

The effect of temperature is qualitatively illustrated by the following: 80°, 15 h: no change; 120°, 5 h: mixture; 120°, 10 h: complete isomerization; 140° (melt), 10 min: complete isomerization.

(c) Kinetic Determinations

A Bausch and Lomb Spectronic 505 with a cell compartment heated by a constant temperature circulating pump was used. The spectra of dilute (ca. 5×10^{-5} *M*) solutions of **1** were run directly in 1 cm stoppered cells at suitable times (t) until there was no further change in absorbance (A_∞). Isosbestic points were observed throughout (Table 1). A plot of ln ($A_\infty - A_t$) against t gave a good straight line fit of slope $-k$, the first order rate constant; a Guggenheim first order plot (15) also gave the same value of k. The effect of temperature (T) on k was examined in 71% aqueous ethanol. Determinations were made at 6 temperatures between 65 and 80° and from the plot of log k against $1/T$ the energy of activation, ΔE^*, and entropy of activations, ΔS^*, were obtained as described by Foster *et al.* (11).

(d) Effect of Maleic Anhydride

The adduct **1** (100 mg, 0.33 mmole) and maleic anhydride (200 mg, 2.1 mmole) were refluxed together in a mixture of iso-octane (8 ml) and benzene (2 ml) for 1 day. The solvent was evaporated and the maleic anhydride allowed to sublime off at room temperature. The i.r. spectrum of the remaining crystalline material was that of analytically pure **2***a*.

*cis-4-Benzoyl-4,4a,5,6,7,7a-hexahydro-2-phenylcyclopenta-1,3,4-oxadiazine (**3**)*

(a) Hydrogenation

A solution of the stable isomer (**2***a*) (0.50 g, 1.7 mmole) in benzene (20 ml) in the presence of palladium black (25 mg) consumed slightly more than one equivalent of hydrogen at room temperature and atmospheric pressure. The mixture was heated and filtered, the cooled solution depositing crystalline 1,2-dibenzoyl-1-cyclopentylhydrazine (**4**) (<10%), m.p. and mixed m.p. 197–198°. The benzene soluble fraction, obtained by evaporation, was the dihydro-derivative (90%) which was crystallized 3 times from aqueous methanol to give an analytical sample as large prisms, m.p. 143–143.5° (lit. m.p. 143.5–145° (2)); $\nu(CCl_4)$ 1650 (C=O), 1646 cm^{-1} (C=N); λ_{max}(EtOH) 220 (ε 14 000), 290 mμ (ε 13 300); $\tau(CDCl_3$, 100 Mc.p.s.) 2.1–2.8 (10 phenyl H), 5.05 (C_{4a}—H, octet[5]

[4]For numbering of **2***a* see text. The splitting constants were determined by spin decoupling.

[5]A 4-line X portion of an ABX system split into 4 doublets. The determination of the $J_{4a,7a}$ and $J_{7a,7}$ values is possible in conjunction with the spectrum of the dideuteriated derivative (see (*d*)). The assignment of the correct values to the tertiary hydrogens follows from the spectrum of the de-benzoylated oxadiazine **11**.

$J_{4a,7a} = 3.6, |J_{4a,5A} + J_{4a,5B}| = 18$ c.p.s.), 5.55 (C_{7a}—H, triplet $J_{7a,7A} = 3, J_{7a,7B} < 0.5$ c.p.s.), 7.3–8.7 p.p.m. C-5, C-6, C-7 methylene H); mass spectrum 306 (M^+, 23), 105 ($PhCO^+$, 100), 77 (Ph^+, 29).

(b) Catalytic Hydrogen Transfer

2*a* (1.5 g, 5 mmole) was refluxed for 2 days in cyclohexene (15 ml) containing palladium black (50 mg). Work-up as described in (*a*) again gave **3** (90%) and a small amount of **4**.

(c) Di-imide

2*a* (1.0 g, 3.3 mmole) was dissolved in a mixture of methanol (3.60 ml), water (120 ml), and 95% hydrazine (2.5 ml), and the p*H* was adjusted to 9 using acetic acid. Air was bubbled through the solution for 2 days, evaporation losses being made up by the addition of methanol. Removal of the solvent gave a residue which after crystallization from aqueous methanol or benzene–petroleum ether (b.p. 60–80°) gave **3** (>90%), m.p. 143–143.5°.

The use of hydrogen peroxide in place of the air stream also proved successful.

(d) Dideuterio-di-imide

p-Toluenesulfonylhydrazine (5 g) was dissolved in tetrahydrofuran (10 ml) and D_2O (5 ml) was added. The solution was evaporated, the whole operation was repeated twice more, and the residue finally dried *in vacuo*.

The hydrazine-d_3 (0.19 g, 1.0 mmole) and **2***a* (0.18 g, 0.6 mmole) were refluxed in dry dioxane for 16 h. The solvent was removed and the resulting solid treated with ether and water. The ether layer was shaken out in turn with dilute sodium hydrogen carbonate and dilute hydrochloric acid and was then dried and evaporated. The residue showed an i.r. absorption at 1150 cm^{-1}, probably due to a sulfone by-product, which disappeared after one crystallization from aqueous methanol. A second crystallization gave the 6,7-dideuterio-derivative containing 1.5 atom D per molecule (determined by mass spectrometric analysis); the n.m.r. showed the expected differences in the methylene region and the C_{7a}—H at 5.5 τ as a doublet, $J_{4a,7a} = 3.6$ c.p.s.

*cis-4,4a,5,6,7,7a-Hexahydro-2-phenylcyclopenta-1,3,4-oxadiazine (**11**)*

The oxadiazine **3** (0.49 g, 1.6 mmole) was heated in concentrated sulfuric acid (10 ml) at 100° for 1 min, and set aside at room temperature for 3 h. The clear almost colorless solution was then poured into an ice-cold mixture of carbon tetrachloride and an excess of dilute sodium hydroxide. The organic layer and two carbon tetrachloride washings were combined, dried, and evaporated to give the oily base **11** (90%), which was directly pure (g.l.c.). An analytical sample was distilled at a bath temperature <200°/0.4 mm. pressure; ν(CCl_4) 3370 (NH weak, but very strong in Nujol), 1631 cm^{-1} (C=N); λ_{max}(EtOH) 282 mμ; τ(CCl_4) 2.0–2.9 (5 phenyl H), 4.7 (NH, sharp), 5.53 (C_{7a}—H, quartet), 6.80 (C_{4a}—H, quartet), 7.9—8.8 p.p.m. (C-5, C-6, C-7 methylene H); τ(CF_3CO_2H—CCl_4) 4.9 (C_{7a}—H), 5.9 p.p.m. (C_{4a}—H).

Anal. Calcd. for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.98; N, 13.85. Found: C, 71.11; H, 6.95; N, 13.73.

The *hydrochloride*, prepared in ether by passage of hydrogen chloride, and crystallized from ether–methanol had m.p. 171–174° (decomposition).

Anal. Calcd. for $C_{12}H_{15}ClN_2O$: N, 11.70. Found: N, 11.88.

The 6,7-dideuterio analogue of **11** was prepared similarly from the deuteriated analogue of **3**; its n.m.r. spectrum (CCl_4) differed from that of the unlabelled isomer as expected in the methylene region and in the assignment: τ 5.5 p.p.m. (C_{7a}—H, triplet $J_{4a,7a} = J_{7a,7} = 4.5$ c.p.s.).

*Benzoylation of **11***

The base **11** (44 mg, 0.22 mmole) and benzoyl chloride (0.1 ml) were allowed to react in pyridine (2 ml) at room temperature for 18 h. The product was worked up by quenching with dilute hydrochloric acid and washing the precipitate (71%, 1 peak in g.l.c.) with aqueous ammonia. Two crystallizations from methanol gave **3**, m.p. 142–143° in admixture with material obtained by reduction of **2***a*.

*Acid Hydrolysis of **3***

A solution of **3** (1.45 g, 4.73 mmole) in a mixture of ethanol (20 ml), water (10 ml), and 12 *N* hydrochloric acid (2 ml) was refluxed for 17 h. The course of the reaction was monitored by removing and neutralizing small portions and subjecting them to t.l.c. In the early stages the starting material **3** and all three products **6**, **7**, and **8** were observed. As the reaction progressed **7** and **8** increased at the expense of **3**. The spot due to **6** was at all stages faint, indicating a low concentration of it (see control experiment below on isomerization of **6** to **7**).

When hydrolysis was complete the solution was cooled and a little 3 *N* hydrochloric acid added, causing the precipitation of the crystalline hydrochloride of **7** (0.64 g, 37%), directly pure. The mother liquor was basified with sodium carbonate, the solution was evaporated, and the residue extracted several times with ether. The combined extracts afforded a solid which was crystallized from aqueous ethanol to give the monobenzoyl derivative **8** (0.118 g, 11%). The ether insoluble fraction was acidified with dilute hydrochloric acid, taken to dryness, and again extracted with ether, from which benzoic acid (0.32 g, representing a total recovery of 71%) was obtained.

*Control Experiments Pertaining to Hydrolysis of **3***

*(a) Isomerization of cis-Alcohol **6** to Ester **7***

The alcohol **6** (20 mg, 0.06 mmole) was dissolved and refluxed in a mixture of ethanol (2 ml), water (1 ml), and 12 *N* hydrochloric acid (0.2 ml), the medium for the hydrolysis of the oxadiazine **3**. After 1 h (oxadiazine hydrolysis for 17 h) the solution was concentrated, made basic with aqueous sodium hydrogen carbonate, and extracted with methylene chloride. The dried extracts on evaporation gave a gum (95%) of i.r. spectrum identical with that of the ester **7**. Crystallization from aqueous methanol gave a pure product which did not depress the m.p. of authentic ester.

*(b) Hydrolysis of Ester **7** to Alcohol **8***

A solution of **7** (40 mg, 0.12 mmole) in ethanol (4 ml), water (2 ml), and 12 *N* hydrochloric acid (0.4 ml) was refluxed for 17 h (the conditions for the hydrolysis of the oxadiazine **3**). Addition of an excess of potassium carbonate, evaporation to dryness, and extraction with methylene chloride yielded a gum (33 mg), the i.r. spectrum of which showed it to be mainly starting material with a small amount of the product **8**. This mixture was

dissolved in methanol (5 ml) and a few drops of 12 *N* hydrochloric acid were added causing the hydrochloride of **7** to precipitate. The alcohol soluble fraction was basified with ammonia, evaporated, and extracted with methylene chloride giving a gum in which the i.r. absorption bands of the alcohol **8** were now predominant.

Synthesis of Oxadiazines by Ring Closure

(a) Oxadiazine 3

The *cis*-alcohol **6** (37 mg, 0.12 mmole) was mixed intimately with polyphosphoric acid (1 ml, K. and K. Laboratories) and heated for 24 h at 60°, and the clear mass was dissolved into a slight excess of ice-cold aqueous ammonia. Extraction with methylene chloride gave a gum (34 mg, two peaks of about equal area in g.l.c.) which was taken up in ether and then shaken in turn with dilute hydrochloric acid and dilute sodium hydroxide. The ether solution was then dried and evaporated to give a residue which crystallized and showed a single peak in its g.l.c. Two recrystallizations from aqueous methanol gave the oxadiazine **3**, m.p. 140.5–141.5°, alone or in admixture with material obtained by hydrogenation of **2***a*.

(b) Oxadiazine 11

The *cis*-alcohol **8** (245 mg, 1.1 mmole) was similarly heated in PPA (3 ml), and the reaction products worked up with aqueous sodium hydroxide and carbon tetrachloride. The n.m.r. spectrum of the carbon tetrachloride solution indicated the presence of **11** of at least 70% purity. Evaporation gave the oily oxadiazine (125 mg, corresponding to a 40% yield of **11**) which on benzoylation as described before gave the oxadiazine **3**, m.p. and mixed m.p. 142.5–143.5°, after crystallization from methanol.

The use of concentrated sulfuric acid in place of PPA also caused cyclodehydration of **8** to **11**. Heating at 100° for 5 min followed by treatment with ice and then aqueous sodium hydroxide gave an oil, isolated as before. Gas–liquid chromatography indicated a yield of about 50%.

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