Photochemical Cyclisation of 3-*N*-(Dialkylaminomethyl)imidazole-2,4-diones to 1,3,7-Triazabicyclo[3.3.0]octanes

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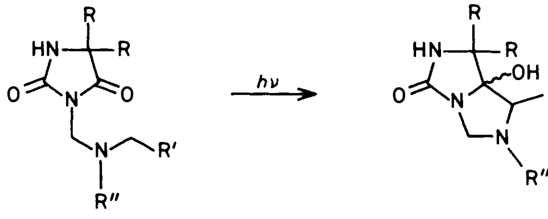
Ultraviolet irradiation of *N*-3 Mannich bases derived from hydantoin or from 5,5-disubstituted hydantoins (imidazole-2,4-diones), provides an efficient route to 1,3,7-triazabicyclo[3.3.0]octane derivatives by photocyclisation to the C-4 carbonyl group.

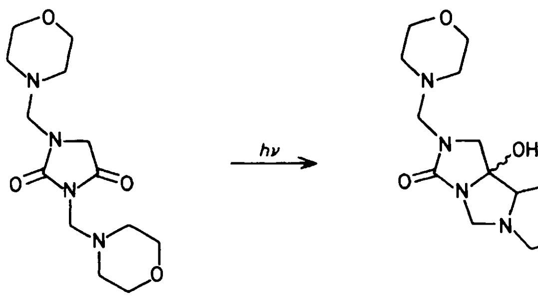
Irradiation of *N*-substituted imides often gives rise to cyclised products by way of an intramolecular hydrogen transfer process involving one of the imide carbonyl groups.[1] *N*-Alkyl imides lead to azepinediones or azocinediones by ring-opening of the initial fused azetidinol.[2]

With other substitutents, particularly those containing O, S, or N groups, photocyclisation can give polycyclic products,[3] and for phthalimides this includes products with new macrocyclic rings.[4] *N*-(Dialkylaminomethyl)hydantoins have been reported in studies of pharmacologically active Mannich bases,[5] but there is no report of their photochemistry. Our interest in the photocyclisation of hydantoins was partly to see if the reaction was regioselective, and we now report that the products are 1,3,7-triazabicyclo[3.3.0]octane derivatives formed by selective reaction at the C-4 carbonyl group.



(1) (2)

a; R = Ph, R′ = H, R″ = Me
b; R = Ph, R′ - R″ = $CH_2OCH_2CH_2$
c; R = Ph, R′ - R″ = $CH{=}CHCH_2CH_2$
d; R = Ph, R′ - R″ = o-$C_6H_4CH_2CH_2$
e; R = Me, R′ - R″ = $CH_2OCH_2CH_2$
f; R = H, R′ - R″ = $CH_2OCH_2CH_2$



(3) (4)

Results and Discussion

Substituted hydantoins (imidazole-2,4-diones) (1) were prepared by standard Mannich procedures, and on irradiation (medium-pressure mercury arc, quartz filter, MeCN solvent) they gave photocyclised products (2). Yields ranged from 33 to 73% (based on unrecovered starting material), and from (1f) hydantoin (40%) was also isolated. Products from the 5,5-disubstituted hydantoins (2b—e) appeared to be single diastereoisomers, but (2f) was a mixture of stereoisomers from which one could be isolated in a pure state by partial crystallisation from chloroform. In a similar way irradiation of the bis-Mannich base (3) gave hydantoin (25%) and a mixture (77%) of two stereoisomers of (4); the two isomers could be separated by silica-gel chromatography, but in solution a slow isomerisation of one to the other occurred.

The structures of (2) and (4) are assigned on the basis of microanalytical and spectroscopic data. Compounds (1) and (3) show two i.r. bands at 1 700—1 720 and 1 760—1 770 cm^{-1}, corresponding to the urea-like C-2 and the imide-like C-4 carbonyl groups; (2) and (4) show a single band near 1 700 cm^{-1}, suggesting that only the C-2 carbonyl remains. In the ^{1}H n.m.r. spectra of all the photoproducts there is an AB pattern in the 4.3—4.9 and 3.9—4.5 p.p.m. regions, which is characteristic of the cyclic $N-CH_2-N$ unit in a five-membered ring.[6] For the photoproduct (2a) there is another AB pattern at 2.7 and 2.5 p.p.m., which is derived from the second CH_2 group in the new imidazolidine ring. The ^{13}C n.m.r. spectra of (1) and (3) show two carbon signals in the 171—175 and 157—160 p.p.m. ranges (from C-4 and C-2 respectively), and (2) and (4) show only one signal in the range 161—165 p.p.m. (pyrrolidinones would be expected to give a signal around 175 p.p.m.). The carbon spectra of (2) and (4) also show signals characteristic of the new quaternary carbon of the bridgehead alcohol (90—100 p.p.m.) and the new CH-(R′)N centre in the imidazolidine ring (68—72 p.p.m.). An unusual feature in the ^{1}H n.m.r. spectrum of (2d) is the signal for one of the aromatic protons that appears at very high field (δ = 5.4 p.p.m.). This signal arises from the proton on C-8′ of the tetrahydroisoquinoline part of the molecule, which lies above the plane of one of the phenyl groups and quite close to the π-electron system.

In the corresponding photoproducts derived from phthalimide Mannich bases the stereochemistry can be assigned [7] on the basis of an *X*-ray crystallographic analysis supported by results from ^{1}H and ^{13}C n.m.r. studies. The information for the present photoproducts is less extensive, but the lower ^{1}H chemical shift value (4.35 p.p.m., compared with 4.84 p.p.m.) for the lower field proton of the AB system in the spectrum of the crystalline isomer of (4), and the lower ^{13}C chemical shift value (90.5 p.p.m., compared with 92.2 p.p.m.) for the quaternary carbon (carrying the OH group), suggest that this isomer has the OH group *trans* to the CH_2OR group at the adjacent bridgehead position.

It is evident from the structure of the photoproducts that the C-4 carbonyl group in the hydantoin ring provides the preferred site of reaction, and we have no evidence for formation of the corresponding products resulting from attack at

C-2.* So the excited hydantoin chromophore acts in the same way as the excited succinimide chromophore, but with selective reaction at the imide-like C-4 carbonyl. In the bis-Mannich compound (3) reaction occurs at only one of the possible sites of reaction, and the *N*-substituted urea derivative (4) shows no signs of undergoing further photochemical reaction. Overall the photocyclisation of hydantoin Mannich bases offers a convenient route to the 1,3,7-triazabicyclo[3.3.0]octane system.

Experimental

The Mannich bases were prepared by conventional methods,[8] the appropriate hydantoin, formaldehyde, and amine in equimolar proportions being warmed in ethanol. Of those derived from 5,5-disubstituted hydantoins, only (1a) and (1b) have been reported previously; [9] in our hands the yields of these were 73% (from ethanol; m.p. 117—118 °C, lit.,[9] 114—115 °C) and 78% (from propan-2-ol; m.p. 159.5—161 °C, lit.,[9] 156—157 °C), respectively. Of the two unsubstituted hydantoin derivatives only the bis-compound (3) has been reported previously,[10] and not the mono-compound (1f); we obtained (3) in 54% yield (from ethanol; m.p. 142—144 °C, lit.,[10] 144—145.5 °C) using 1 : 2 : 2 ratios of hydantoin, formaldehyde, and amine.

5,5-*Diphenyl*-3-(1,2,5,6-*tetrahydropyridin*-1-*ylmethyl*)*imidazole*-2,4-*dione* (1c). This was obtained as white crystals (76% from ethanol), m.p. 123—125 °C), $\bar{\nu}_{max.}$ (Nujol) 3 210, 3 100, 1 770, and 1 720 cm^{-1}; δ_H (90 MHz, $CDCl_3$) 7.35 (s, 10 H), 5.63 (s, 2 H), 4.59 (s, 2 H), 3.3—3.0 (m, 2 H), 2.77 (t, *J* 6 Hz, 2 H), and 2.35—1.95 (m, 2 H) (Found: C, 72.5; H, 6.15; N, 12.0. $C_{21}H_{21}N_3O_2$ requires C, 72.60; H, 6.09; N, 12.10%.

5,5-*Diphenyl*-3-(1,2,3,4-*tetrahydroisoquinolin*-2-*ylmethyl*)-*imidazole*-2,4-*dione* (1d). This was obtained as white crystals (77% from chloroform–light petroleum, m.p. 181—183 °C), $\bar{\nu}_{max.}$ (Nujol) 3 330, 1 773, and 1 710 cm^{-1}; δ_H (90 MHz, $CDCl_3$) 7.40 (s, 10 H), 7.25—7.05 (m, 4 H), 4.75 (s, 2 H), 3.84 (s, 2 H), and 2.90 (s, 4 H), δ_C (90 MHz, $CDCl_3$) 174.7, 157.6, 139.2, 134.5, 133.7, 129.7, 128.8, 128.7 128.5, 127.6, 126.8, 126.6, 126.1, 125.8, 125.6, 70.4, 60.6, 52.5, 48.5, and 29.3 (Found: C, 75.7; H, 5.9; N, 10.45. $C_{25}H_{23}N_3O_2$ requires C, 75.55; H, 5.83; N, 10.57%).

5,5-*Dimethyl*-3-(*morpholin*-4-*ylmethyl*)*imidazole*-2,4-*dione* (1e). This was obtained as white crystals (71% from ethanol, m.p. 154—156 °C), $\bar{\nu}_{max.}$ (Nujol) 3 250, 1 770, and 1 725 cm^{-1}; δ_H (60 MHz, $CDCl_3$) 6.64br (s, 1 H, disappears on addition of D_2O), 4.42 (s, 2 H), 3.85—3.55 (m, 4 H), 2.8—2.5 (m, 4 H), and 1.45 (s, 6 H) (Found: C, 52.7; H, 7.55; N, 18.6. $C_{10}H_{17}N_3O_3$ requires: C, 52.85; H, 7.54; N, 18.49%).

3-(*Morpholin*-4-*ylmethyl*)*imidazole*-2,4-*dione* (1f). This was obtained as white crystals (72% from ethanol, m.p. 134—136 °C), $\bar{\nu}_{max.}$ (Nujol) 3 300, 1 760, and 1 700 cm^{-1}; δ_H (60 MHz, $CDCl_3$) 6.59br (s, 1 H, reduced in D_2O), 4.24 (s, 2 H), 4.05 (s, 2 H), 3.9—3.6 (m, 4 H), and 2.8—2.55 (m, 4 H); δ_C (90 MHz, $CDCl_3$) 172.3, 159.2, 66.9, 60.4, 50.8, and 46.4 (Found: C, 48.3; H, 6.7; N, 21.1. $C_8H_{13}N_3O_3$ requires C, 48.24; H, 6.58; N, 21.10%).

Photochemical Reactions.—These were carried out using *ca*. 0.01 mol of Mannich base in each case. The photoproducts were isolated by silica-gel column chromatography using chloroform–methanol as eluant.

5-*Hydroxy*-7-*methyl*-4,4-*diphenyl*-1,3,7-*triazabicyclo*[3.3.0]-*octan*-2-*one* (2a). Irradiation of (1a) gave (2a) as a sticky solid (51%), from which white crystals (m.p. 103—105 °C) could be isolated by further silica-gel chromatography, $\bar{\nu}_{max.}$ (Nujol) 3 240 and 1 710 cm^{-1}; δ_H (90 MHz, $CDCl_3$) 7.3 (m, 11H), 4.33 (d, *J* 7 Hz, 1 H), 3.89 (d, *J* 7 Hz, 1 H), 2.72 (d, *J* 11 Hz, 1 H), 2.62 (s, 1 H), 2.47 (d, *J* 11 Hz, 1 H), and 2.29 (s, 3 H). The AB pattern at 2.47 and 2.67 was also evident in the spectrum when [$^2H_4$]methanol was used as solvent, but not when [$^2H_5$]-pyridine was used; δ_C (90 MHz, $CDCl_3$) 162.5, 140.9, 139.1, 128.8, 128.3, 127.9, 126.3, 99.4, 69.5, 69.3, 63.3, and 41.17 (not all of the aromatic signals are resolved) (Found: *m/z* 309.1475 $C_{18}H_{19}N_3O_2$ requires *m/z* = 309.1475).

2-*Hydroxy*-3,3-*diphenyl*-11-*oxa*-4,6,8-*triazatricyclo*[6.4.-0.0^{2,6}]*dodecan*-5-*one* (2b). Irradiation of (1b) gave (2b) as an oil (36%) after further purification by column chromatography on silica-gel; $\bar{\nu}_{max.}$ (thin film) 3 230 and 1 710 cm^{-1}; δ_H (90 MHz, C_5D_5N), 7.6—7.1 (m, 11 H), 4.55 (d, *J* 5 Hz, 1 H), 4.39 (d, *J* 5 Hz, 1 H), 3.8—3.2 (m, 4 H), and 3.0—2.3 (m, 4 H); δ_C (90 MHz, C_5D_5N), 163.7, 145.7, 140.9, 130.1, 129.1, 128.6, 128.3, 128.2, 127.9, 127.6, 127.2, 99.4, 69.7, 68.4, 67.6, 65.4, 64.5, and 50.4 (Found: *m/z* 351.1575. $C_{20}H_{21}N_3O_3$ requires *m/z* = 351.1626).

2-*Hydroxy*-3,3-*diphenyl*-4,6,8-*triazatricyclo*[6.4.0.0^{2,6}]*dodec*-11-*en*-5-*one* (2c). Irradiation of (1c) gave (2c) as white crystals (42%), m.p. 134—136 °C); $\bar{\nu}_{max.}$ (Nujol) 3 225 and 1 700 cm^{-1}; δ_H (90 MHz, C_5D_5N) 7.6—7.1 (m, 11 H), 5.6—5.1 (m, 2 H), 4.95 (d, *J* 6 Hz, 1 H), 4.27 (d, *J* 6 Hz, 1 H), 4.2br (s, 1 H), and 3.1—1.2 (m, 5 H); δ_C (90 MHz, C_5D_5N) 163.0, 144.8, 142.5, 129.5, 128.9, 128.6, 127.9, 127.7, 127.3, 125.8, 99.7, 69.6, 66.5, 62.4, 42.4, and 18.5.

16-*Hydroxy*-15,15-*diphenyl*-10,12,14-*triazatetracyclo*[8.6.0-0^{2,7}.0^{12,16}]*hexadeca*-2,4,6-*trien*-13-*one* (2d). Irradiation of (1d) gave (2d) as white crystals (73%), m.p. 176—178 °C; $\bar{\nu}_{max.}$ (Nujol) 3 400 and 1 722 cm^{-1}; δ_H (60 MHz, $CDCl_3$) 7.4—6.5 (m, 13 H), 6.08 (s, 1 H, reduced with D_2O), 5.38 (d, *J* 7 Hz, 1 H; becomes a singlet with selective decoupling at 6.7 p.pm.), 4.85 (d, *J* 8 Hz, 1 H), 4.46 (s, 1 H), 4.05 (d, *J* 8 Hz, 1 H), and 3.4—2.3 (m, 5 H, reduces to 4 H with D_2O); δ_C (60 MHz, $CDCl_3$) 161.1, 141.9, 139.3, 130.2, 129.4, 129.1, 128.7, 128.5, 128.2, 127.8, 127.3, 125.5, 98.8, 71.9, 65.2, 65.0, 47.1, and 26.7; *m/z* 397 (M^+) and 145 (base) (Found: C, 75.5; H, 6.0; N, 10.3. $C_{25}H_{23}N_3O_2$ requires C, 75.55; H, 5.83; N, 10.57%).

2-*Hydroxy*-3,3-*dimethyl*-11-*oxa*-4,6,8-*triazatricyclo*-[6.4.0.0^{2,6}]*dodecan*-5-*one* (2e). Irradiation of (1e) gave (2e) as white crystals (60%), m.p. 168—170 °C; $\bar{\nu}_{max.}$ (Nujol) 3 335, 3 210, and 1 710 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.84br (s, 1 H), 5.0br (1 H), 4.50 (d, *J* 5 Hz, 1 H), 4.33 (dd, *J* 11 and 3 Hz, 1 H), 4.23 (d, *J* 5 Hz, 1 H), 4.01 (t, *J* 10.5 Hz, 1 H), 3.84 (dd, *J* 11 and 3 Hz, 1 H), 3.56 (dt, *J* 11 and 3 Hz, 1 H), 2.92br (d, *J* 11 Hz, 1 H), 2.74 (dd, *J* 10 and 3 Hz, 1 H), 2.54 (dt, *J* 11 and 3 Hz, 1 H), 1.64 (s, 3 H), and 1.42 (s, 3 H); δ_C (90 MHz, $CDCl_3$) 162.6, 97.2, 68.3, 67.8, 65.7, 63.7, 57.9, 50.7, 26.6, and 25.1 (Found: C, 52.8; H, 7.65; N, 18.6. $C_{10}H_{17}N_3O_3$ requires C, 52.85; H, 7.54; N, 18.49%).

2-*Hydroxy*-11-*oxa*-4,6,8-*triazatricyclo*[6.4.0.0^{2,6}]*dodecan*-5-*one* (2f). Irradiation of (1f) gave hydantoin (40%) and (2f) as a mixture of stereoisomers (62%). One of the isomers was isolated as white crystals (m.p. 137.5—139 °C) by partial crystallisation from chloroform, $\bar{\nu}_{max.}$ (Nujol) 3 345, 3 196, 3 100, and 1 710 cm^{-1}; δ_H (60 MHz, C_5D_5N) 8.05br (s, 1 H), 4.6—3.4 (m, 9 H, including 2 doublets 4.55 and 4.04, *J* 4.5 Hz), and 2.9—2.3 (m, 3 H); δ_C (C_5D_5N) 164.2, 93.9, 69.1, 66.7, 66.6, 65.9, 50.3, and 50.1; *m/z* 199 (M^+), 181, and 99 (base) (Found: C, 48.15; H, 6.5; N, 21.25. $C_8H_{13}N_3O_3$ requires C, 48.24; H, 6.58; N, 21.10%). The signals for the ^{13}C spectrum of the second isomer were identified from the spectrum of the mixture: δ 166.4, 95.0, 70.2, 69.1, 66.4, 65.6, (50.3) and 49.1 p.p.m.

2-*Hydroxy*-11-(*morpholin*-4-*ylmethyl*)-11-*oxa*-4,6,8-*triazatricyclo*[6.4.0.0^{2,6}]*dodecan*-5-*one* (4). Irradiation of (3) gave

* Our unpublished results of studies on derivatives of 2-phenylsuccinimide show that in this system products arise by both modes of cyclisation.

hydantoin (25%) and also (4) as a mixture of stereoisomers (77%). The isomers were separated by column chromatography on silica gel. The first was obtained as white crystals, m.p. 123—125 °C, $\bar{\nu}_{max.}$ (Nujol) 3 285 and 1 685 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 4.35 (d, J 5 Hz, 1 H), 3.99 (dd, J 11.5 and 3.5 Hz, 1 H), 3.93 (d, J 12.5 Hz, 1 H), 3.80 (d, J 12.5 Hz, 1 H), 3.66—3.45 (m, 10 H, including 2 doublets 3.60 and 3.47, J 10 Hz), 2.95 (dt, J 11 and 2.5 Hz, 1 H), 2.50—2.43 (m, 6 H), and 2.19 (dd, J 9 and 3 Hz, 1 H); δ_C (90 MHz, $CDCl_3$) 161.2, 90.5, 68.7, 66.7, 66.0, 65.9, 65.8, 65.6, 52.7, 50.8, and 49.9; m/z 298 (M^+), 280, and 100 (base) (Found: C, 52.2; H, 7.5; N, 18.8. $C_{13}H_{22}N_4O_4$ requires C, 52.34; H, 7.43; N, 18.78%). The second isomer was obtained as an oil, $\nu_{max.}$ (liquid film) 3 360 and 1 700 cm^{-1}; δ_H (90 MHz, C_5D_5N) 4.84 (d, J 8 Hz, 1 H), 4.3—3.4 (m, 13 H), 3.0 (m, 1 H), 2.8—2.3 (m, 6 H); δ_C (90 MHz, C_5D_5N) 164.4, 92.2, 70.0, 69.5, 66.9, 66.5, 66.1, 65.7, 54.4, 51.3, and 49.1; m/z 298 (M^+), 280, and 100 (base).

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