N-Iodoamides. Cyclisation of Biphenyl-2-carboxamides

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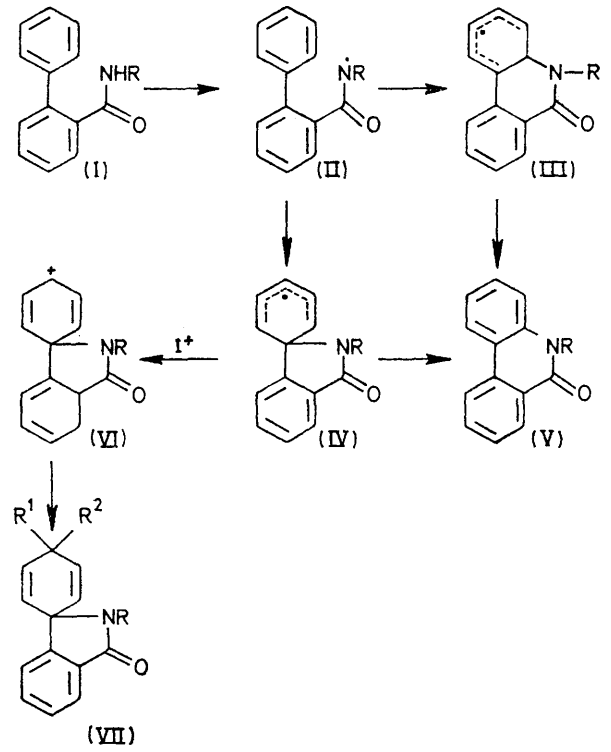
The reaction of biphenyl-2-carboxamide and its *N*-methyl and *N*-phenyl derivatives with t-butyl hypochlorite–iodine in t-butyl alcohol containing potassium t-butoxide gave phenanthridones, as well as the corresponding 4′-t-butoxy- and 4′-oxoisoindoline-1-spirocyclohexa-2′,5′-dien-3-ones. Both potassium t-butoxide and t-butyl alcohol suppress the iodination of aromatic substrates by iodine monochloride. The role of potassium t-butoxide and t-butyl alcohol in the formation of the isoindoline-1-spirocyclohexa-2′,5′-dien-3-ones and the mechanism of formation of the 4′-ketone from the 4′-t-butoxyisoindoline-1-spirocyclohexa-2′,5′-dien-3-ones are discussed.

THE addition reactions of amidyl radicals with olefins have been explained on the basis of their electrophilicity.[1] Furthermore the electrophilic nature of amidyl radicals has been invoked to account for the cyclisation of biphenyl-2-carboxamides (I) with lead tetra-acetate–iodine,[2] persulphate,[3] or t-butyl hypochlorite–iodine.[4] This last reagent, which has been shown to convert amides into *N*-iodo-derivatives,[5] gave the corresponding 2-iodophenanthridones [4] from biphenyl-2-carboxamide and its *N*-methyl derivative. *N*-Methylbiphenyl-2-carboxamide (I; R = Me) with lead tetra-acetate–iodine gave, in addition to *N*-methylphenanthridone (V; R = Me), *cis*- and *trans*-4′-acetoxy-*N*-methylisoindoline-1-spirocyclohexa-2′,5′-dien-3-one (VII; R = Me, R^1 = OAc, R^2 = H). These results were explained [4] on the basis of cyclisation of the amidyl radical (II; R = Me) at the 1′- and 2′-positions of biphenyl-2-carboxamide to form the intermediate radicals (IV; R = Me) and (III; R = Me), respectively.

Since no spirocyclohexadienes (VII) were isolated from the reaction of *N*-methylbiphenyl-2-carboxamide (I; R = Me) with t-butyl hypochlorite–iodine, the reaction was carried out in the presence of potassium t-butoxide in an effort to trap any spirocyclohexadienyl iodide (VII; R = Me, R^1 = I, R^2 = H) or carbocation (VI; R = Me) which could have been formed by oxidation of the intermediate radical (IV; R = Me). N.m.r. analysis of the crude product showed (from the characteristic *N*-methyl and olefinic resonances) the presence of the 4′-t-butoxyspirocyclohexadiene (VII; R = Me, R^1 = OBu^t, R^2 = H) [δ 2·86 (3H, s), 5·32 (2H, d), and 6·18 (2H, d)] and the spirocyclohexadien-4′-one (VII; R = Me, R^1R^2 = O) [δ 3·0 (3H, s) and 6·45—6·54 (4H, s)]. Surprisingly, the spectrum indicated that the major product was the *N*-methylphenanthridone (V; R = Me) and not the 2-iodo-derivative postulated to arise from the reaction of the phenanthridone with ICl, obtained in previous experiments [4] in which the reaction mixture did not contain potassium t-butoxide. In order to improve the yield of spirocyclohexadiene-type compounds the reaction was carried out with t-butyl alcohol as solvent. The reaction mixture gave the *N*-methylphenanthridone (V; R = Me) (33%), *N*-methyl-4′-t-butoxyisoindoline-1-spirocyclohexa-2′,5′-dien-3-one (VII; R = Me, R^1 = OBu^t,

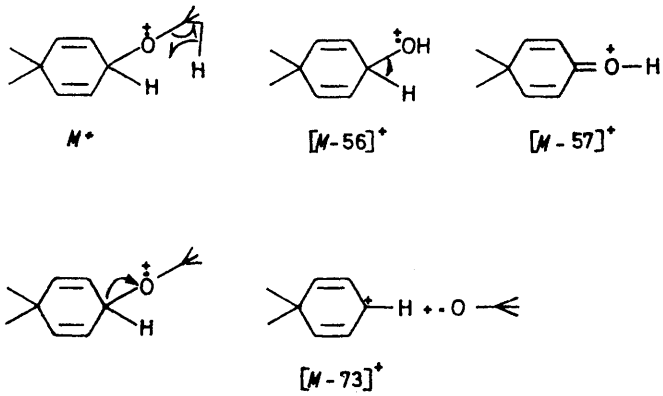
[1] D. Touchard and J. Lessard, *Tetrahedron Letters*, 1970, 4887.
[2] D. H. Hey, G. H. Jones, and M. J. Perkins, *J. Chem. Soc.* (*C*), 1971, 116.
[3] A. R. Forrester, A. S. Ingram, and R. H. Thomson, *J.C.S. Perkin I*, 1972, 1972.
[4] S. A. Glover, A. Goosen, and H. A. H. Laue, *J.C.S. Perkin I*, 1973, 1647.
[5] D. H. R. Barton, A. L. J. Beckwith, and A. Goosen, *J. Chem. Soc.*, 1965, 181.

R^2 = H) (16%), and *N*-methylisoindoline-1-spirocyclohexa-2′,5′-diene-3,4′-dione (VII; R = Me, R^1R^2 = O) (28%). Biphenyl-2-carboxamide (I; R = H) and the *N*-phenyl derivative (I; R = Ph) gave similar products



under the same conditions (Table 1). However *N*-phenylbiphenyl-2-carboxamide also gave 2-chloro-*N*-phenylphenanthridone (6%).

57]$^+$, and [*M* − 73]$^+$ peaks arising from α-fission (see displayed formulae).

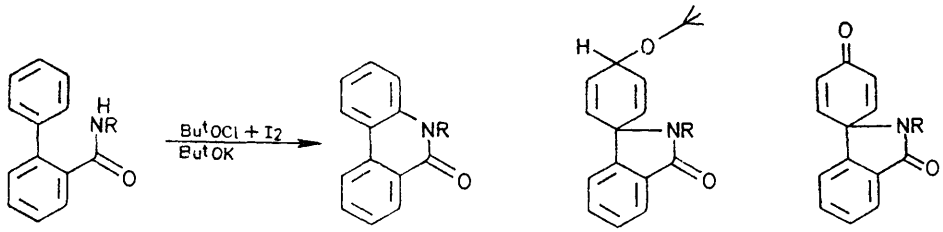


When the reaction with *N*-methylbiphenyl-2-carboxamide (I; R = Me) was carried out without the potassium t-butoxide, but with t-butyl alcohol as solvent, the total yield of cyclisation products was lower. However the relative yields of *N*-methylphenanthridone, t-butoxyspirocyclohexadiene, and spirocyclohexadienone were the same. This result indicates that t-butyl alcohol inhibits the aromatic iodination reaction of ICl and in addition that in the presence of an excess of t-butyl alcohol the potassium t-butoxide does not serve as a trapping reagent but merely increases the amount of positive iodinating species by reacting with ICl (to give Bu^tOI). This postulate was confirmed by the formation of an *N*-iodo-derivative when *p*-nitrobenzamide was treated with a filtered solution of potassium t-butoxide and iodine monochloride in benzene.

The inhibition of aromatic iodination by t-butyl

TABLE 1

Products from biphenyl-2-carboxamides and t-butyl hypochlorite–iodine



R	Solvent	%	%	%
Me	Bu^tOH	33	*ca.* 16	28
Me	Benzene	*ca.* 90	5,8	4,8
H	Bu^tOH	26	*ca.* 25	33
Ph	Bu^tOH	13	*ca.* 14	33

The t-butoxyspirocyclohexadienes could not be purified by distillation, as under these conditions rearrangement to the phenanthridone occurred. Their mass spectra showed characteristic M^+, [*M* − 56]$^+$, [*M* −

alcohol was further investigated. Iodine chloride [6] is well established as an aromatic iodinating agent and we have shown that t-butyl hypochlorite–iodine [7] also effects aromatic iodination. The rates of iodination of anisole with iodine chloride in methylene chloride and in t-butyl alcohol were compared by g.l.c. analysis of

[6] R. M. Keefer and L. J. Andrews, *J. Amer. Chem. Soc.*, 1956, **78**, 5623; L. J. Andrews and R. M. Keefer, *ibid.*, 1957, **79**, 1412; R. O. C. Norman and R. Taylor, 'Reaction Mechanism in Organic Chemistry,' Monograph 3, ed. C. Eaborn, Elsevier, Amsterdam, 1965.

[7] S. A. Glover, A. Goosen, and H. A. H. Laue, *J. S. African Chem. Inst.*, 1973, **26**, 77.

reaction mixtures. It has been shown [7] that the rate of disappearance of anisole when treated with ICl and t-butyl hypochlorite–iodine reagent corresponds to the rate of formation of *p*-iodoanisole. This study showed that the iodination reaction was completely suppressed by t-butyl alcohol. Further it was demonstrated that t-butyl alcohol also effectively quenches the iodination of anisole with t-butyl hypochlorite–iodine.

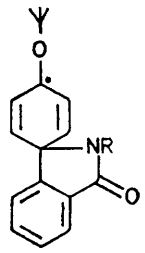
The results thus show that the t-butoxyspirocyclohexadiene is formed by reaction of the intermediate with potassium t-butoxide or t-butyl alcohol. However, when potassium t-butoxide and t-butyl alcohol are used in the reaction the potassium t-butoxide reacts with the excess of iodine [5] and iodine chloride and the t-butyl alcohol is thus mainly responsible for the ether formation. The potassium t-butoxide thus increases the amount of positive iodine; hence the oxidising power of the reaction mixture. Since the cyclisation reaction is effected by light it is proposed that the amidyl radical from the biphenyl-2-carboxamide cyclises either at the 1′- or the 2′-position to form the intermediate radical (IV) or (III), respectively. The butoxyspirocyclohexadiene (VII; R = Me, R^1 = OBu^t, R^2 = H) is thus either formed from the intermediate carbocation (VI; R = Me) [generated from the radical (IV; R = Me) by oxidation with a positive iodine species] by reaction with t-butyl alcohol or t-butoxide anion, or from the spirocyclohexadienyl iodide (VII; R = Me, R^1 = I, R^2 = H) [formed from iodine and the radical (IV; R = Me)] by an S_N-type reaction with t-butoxide anion or t-butyl hypoiodite.

The process whereby the spirocyclohexadien-4′-ones (VII; R^1R^2 = O) are formed was next investigated. The concurrent formation of spirocyclohexadien-4′-ones and 4′-t-butoxyspirocyclohexadienes by reaction of the spirocyclohexadienyl cation with water followed by oxidation of the alcohol seemed unlikely since the reactions were carried out in the presence of potassium t-butoxide. It seemed more probable that the spirocyclohexadienones were formed from the butoxyspirocyclohexadienes. This postulate was confirmed by the formation of the spirocyclohexadien-4′-one in good yield from 4′-t-butoxyisoindoline-1-spirocyclohexa-2′,5′-dien-3-one when it was irradiated in t-butyl alcohol or benzene with t-butyl hypochlorite–iodine at room temperature.

This reaction most likely takes place by abstraction of the diallylic proton by t-butoxyl radicals to yield a stabilised radical (VIII), which either suffers elimination of t-butyl radical or is trapped by iodine or oxidised to the carbocation. If the carbocation is formed it must readily suffer elimination of t-butyl carbocation, since the n.m.r. spectrum of the unprocessed reaction mixture showed the presence of the spirocyclohexadien-4′-one. The 4′-iodo-4′-t-butoxyspirocyclohexadiene (VII; R^1 = OBu^t, R^2 = I), if formed, must more readily eliminate t-butyl iodide than rearrange to the phenanthridone.

[8] C. Walling, ' Free Radicals in Solution,' Wiley, New York, 1957.

Since no evidence for the presence of t-butyl iodide was found in the reaction mixture which contained an excess of iodine, known to be an effective radical trap,[8]



(VIII)

the t-butyl group is most likely eliminated *via* an ionic process. However, efforts to trap and identify the t-butyl fragment were unsuccessful.

EXPERIMENTAL

M.p.s were determined with a Kofler hot-stage apparatus. Merck silica gel G was used for preparative t.l.c. N.m.r. spectra were determined with a Perkin-Elmer R12A spectrometer and mass spectra with an A.E.I. MS9 instrument at the N.C.R.L./C.S.I.R. laboratories. G.l.c. analyses were carried out with a Packard–Becker 420 instrument (flame ionisation detector).

Irradiation of N-Methylbiphenyl-2-carboxamide with t-Butyl Hypochlorite–Iodine in the Presence of Potassium t-Butoxide in t-Butyl Alcohol.—(*a*) t-Butyl hypochlorite (1·54 g, 0·014 mol) and iodine (4·12 g, 0·016 mol) in t-butyl alcohol (80 ml) were stirred in the dark at room temperature for 5 min. Potassium t-butoxide (2·5 g, 0·022 mol) was then added and stirring was continued for a further 5 min. *N*-Methylbiphenyl-2-carboxamide (1 g, 0·00476 mol) was added and the mixture irradiated with a 1000 W tungsten lamp at room temperature. The same quantities of t-butyl hypochlorite, iodine, and potassium t-butoxide were added after 2·5 h. After 5 h the mixture was poured into water (500 ml), treated with $Na_2S_2O_3$ and extracted with $CHCl_3$ (3 × 100 ml); the extract was washed, dried (Na_2SO_4), and concentrated to a gum (1·56 g). The gum was separated into two fractions by preparative t.l.c. on silica gel.

The fraction of the higher R_F value was a solid (0·329 g) which crystallised from CCl_4 as opaque crystals of *N*-methylphenanthridone, m.p. 105—107° (lit.,[4] 108—109°), identical (i.r., n.m.r.) with an authentic specimen.

The other fraction (0·41 g) was separated into a portion insoluble in benzene–petroleum (b.p. 40—60°) (0·13 g) and a soluble gum (0·2 g). The insoluble material crystallised from benzene–petroleum (b.p. 40—60°) as transparent plates of *N*-methylisoindoline-1-spirocyclohexa-2′,5′-diene-3,4′-dione, m.p. 218—219° (lit.,[9] 217—218°), M^+, 225, $\nu_{max.}$ 3458, 1699, and 1685 cm^{-1}, δ ($CDCl_3$) 3·0 (3H, s), 6·45—6·54 (4H, s), and 7·22—8·0 (4H, m).

The benzene–petroleum-soluble portion (0·2 g) was separated by preparative t.l.c., with numerous developments, into three bands. The middle band (0·16 g) contained the starting amide (12%), identified by n.m.r. spectroscopy, and *N*-methyl-4′-t-butoxyisoindoline-1-spirocyclohexa-2′,5′-dien-3-one, M^+ 284, $\nu_{max.}$ 1680 cm^{-1},

[9] D. H. Hey, J. A. Leonard, T. M. Moynehan, and C. W. Rees, *J. Chem. Soc.*, 1961, 232.

δ ($CDCl_3$) 1·35 (9H, s), 2·86 (3H, s), 4·40—4·63 (H, m), 5·32 (2H, dd), 6·18 (2H, dd), and 7·3—7·9 (4H, m).

This procedure was employed for other analogous experiments.

(*b*) The experiment was carried out as in (*a*) with benzene as solvent. The crude product, analysed by comparing the *N*-methyl n.m.r. signals, contained *N*-methylphenanthridone (90%) (δ 3·58) and spirocyclohexadienes (δ 2·98 and 2·86) (10%).

(*c*) An experiment carried out as in (*a*) without potassium t-butoxide gave starting material (δ 2·63) (56%), 4′-t-butoxyisoindoline-1-spirocyclohexa-2′,5′-dien-3-one (δ 2·86) (6·8%), isoindoline-1-spirocyclohexa-2′,5′-diene-3,4′-dione (δ 2·98) (12%), and *N*-methylphenanthridone (δ 3·72) (25%).

Irradiation of Biphenyl-2-carboxamide.—Irradiation of the amide (1·5 g, 0·00714 mol) gave *isoindoline-1-spirocyclohexa-2′,5′-diene-3,4′-dione* (0·5 g), m.p. 215—240° (decomp.), M^+ 211, $\nu_{max.}$ 3420, 1706, and 1678 cm^{-1}, δ ($CDCl_3$) 6·48 (4H, s) and 7·2—8·0 (4H, m) (Found: C, 73·7; H, 4·3; N, 6·1. $C_{13}H_9NO_2$ requires C, 73·9; H, 4·3; N, 6·65%); phenanthridone (0·36 g), m.p. 288—290° (lit.,[3] 290—292°), M^+ 195, $\nu_{max.}$ 3165sh and 1663 cm^{-1}; and 4′-t-butoxyisoindoline-1-spirocyclohexa-2′,5′-dien-3-one, M^+ 287, $\nu_{max.}$ 3425 and 1695 cm^{-1}, δ ($CDCl_3$) 1·32 (9H, s), 4·28—4·68 (1H, m), 5·01 (2H, dd), 6·05 (2H, dd), and 7·25—7·9 (4H, m).

Irradiation of N-Phenylbiphenyl-2-carboxamide.—Irradiation of the amide (1·3 g, 0·00476 mol) gave *N-phenylisoindoline-1-spirocyclohexa-2′,5′-diene-3,4′-dione* (0·52 g), m.p. 205—207°, M^+ 287, $\nu_{max.}$ 1709 and 1678 cm^{-1}, δ ($CDCl_3$) 6·38 (2H, d), 6·7 (2H, d), and 7·15—8·1 (9H, m) (Found: C, 79·0; H, 4·6; N, 5·0. $C_{19}H_{13}NO_2$ requires C, 79·45; H, 4·55; N, 4·85%); *N*-phenyl-4′-t-butoxyisoindoline-1-spirocyclohexa-2′,5′-dien-3-one (0·23 g), m.p. 155—158°, M^+ 345, $\nu_{max.}$ 1696 cm^{-1}, δ ($CDCl_3$) 1·24 (9H, s), 4·14—4·35 (1H, m), 5·1 (2H, dd), 6·04 (2H, dd), and 7·1—8·0 (9H, m); *N*-phenylphenanthridone (0·17 g), m.p. 227—229° (lit.,[3] 222—224°), M^+ 271, $\nu_{max.}$ 1655 cm^{-1}, δ ($CDCl_3$) 6·57—6·82 (1H, m), 7·15—7·91 (9H, m), and 8·14—8·61 (3H, m) (Found: C, 84·0; H, 4·6; N, 5·2. Calc. for $C_{19}H_{13}NO$: C, 84·1; H, 4·85; N, 5·15%); and 2-*chloro*-N-*methylphenanthridone* (0·11 g), m.p. 197—198·5°, M^+ 305, $\nu_{max.}$ 1660 cm^{-1}, δ ($CDCl_3$) 6·62 (1H, d), 7·03—7·87 (8H, m), and 7·99—8·56 (3H, m) (Found: C, 74·6; H, 4·0; N, 4·7. $C_{19}H_{12}ClNO$ requires C, 74·3; H, 3·95; N, 4·55%).

Reaction of Iodine Monochloride with Anisole.—Iodine chloride (1·625 g, 0·9 mol) and anisole (0·463 g, 0·005 mol) were made up to 50 ml with solvent and shaken at room temperature. Samples (2 ml) withdrawn at intervals were treated with 0·27M-sodium iodide in acetone (2 ml) and a 0·005M internal standard solution of nitrobenzene in t-butyl alcohol (2 ml). The samples were analysed by g.l.c. [Carbowax 20M on Chromosorb M (80—100 mesh) 15 : 25 column; *T* 190°, carrier gas 45 ml min^{-1}; retention times anisole 47 s, nitrobenzene 165 s, *p*-iodoanisole 316 s]. The results are in Table 2.

Reaction of t-Butyl Hypochlorite–Iodine with Anisole.—t-Butyl hypochlorite (0·543 g, 0·005 mol) and iodine (1·27 g, 0·005 mol) were made up to 80 ml with t-butyl alcohol and shaken in the dark at room temperature for 10 min. Anisole (0·463 g, 0·005 mol) was added and the mixture was analysed as before (see Table 3).

TABLE 2

Reactions of iodine chloride with anisole: (a) in t-butyl alcohol; (b) in methylene chloride

Time (min)	Anisole concn. (%)	Time (min)	Anisole concn. (%)
(a)			
½	97·5	8	96·50
1	96·25	16	94·75
2	96·25	30	92·5
4	95·00	90	93·45

	Time (min)	Anisole concn. (%)	*p*-Iodoanisole concn. (%)
(b)			
	½	4	96
	1	0	100

TABLE 3

Reaction of t-butyl hypochlorite–iodine with anisole

Time (min)	Anisole concn. (%)	Time (min)	Anisole concn. (%)
½	97·5	8	100
1	100	16	96
2	98	30	98
4	99		

Irradiation of 4′-t-Butoxyisoindoline-1-spirocyclohexa-2′,5′-dien-3-one in the Presence of t-Butyl Hypochlorite–Iodine.—(*a*) t-Butyl hypochlorite (0·03 g, 0·00028 mol) and iodine (0·071 g, 0·00028 mol) in t-butyl alcohol (20 ml) were stirred in the dark at room temperature for 5 min. 4′-t-Butoxyisoindoline-1-spirocyclohexa-2′,5′-dien-3-one (0·05 g, 0·000186 mol) was added and the mixture was irradiated at room temperature for 2·5 h. The mixture was then diluted with water (200 ml), treated with an excess of aqueous sodium thiosulphate, and extracted with chloroform (50 ml). The extract was dried (Na_2SO_4) and concentrated to a gum (0·05 g). N.m.r. analysis showed the presence of isoindoline-1-spirocyclohexa-2′,5′-diene-3,4′-dione (δ 6·48) (76%) and 4′-t-butoxyisoindoline-1-spirocyclohexa-2′,5′-dien-3-one (δ 5·01—6·05) (24%).

(*b*) Experiment (*a*), repeated with benzene as solvent, gave isoindoline-1-spirocyclohexa-2′,5′-diene-3,4′-dione (δ 6·48) (73%) and 4′-t-butoxyisoindoline-1-spirocyclohexa-2′,5′-dien-3-one (δ 5·01—6·05) (27%) (n.m.r. analysis).

Reaction of p-Nitrobenzamide with the Filtered Solution from the Reaction of Iodine Monochloride with Potassium t-Butoxide.—Iodine monochloride (0·41 g, 0·005 mol) and potassium t-butoxide (0·56 g, 0·005 mol) in benzene (25 ml) were shaken in the dark at 0 °C for 5 min. Filtration gave a purple solution which on treatment with an excess of *p*-nitrobenzamide gave *N*-iodo-*p*-nitrobenzamide [containing 100% positive halogen (iodometry)], identical with an authentic specimen.

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