

Cyclisation of Biphenyl-2-carboxamides

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N-Methylbiphenyl-2-carboxamide was cyclised by treatment with lead(IV) acetate-iodine reagent to a mixture of *cis*- and *trans*-2-methyl-4'-acetoxy-3-oxoisindoline-1-spirocyclohexa-2',5'-dienes, which were hydrolysed to the corresponding alcohols and *N*-methylphenanthridone. Cyclisation of biphenyl-2-carboxamide and its *N*-methyl derivative by treatment with *t*-butyl hypochlorite-iodine reagent gave the corresponding 2-iodophenanthridones. The formation of the products is explained on the basis of cyclisation of the amido-radical at the 1'- and 2'-positions of biphenyl-2-carboxamide and, in the case of *t*-butyl hypochlorite-iodine reagent, subsequent iodination of the phenanthridone with ICl.

DIFFERENCES in the reactions of various free radicals has been explained on the basis of their nucleophilic and electrophilic properties.¹ The π state of amido-radicals, initially postulated by Chow and Joseph,² has recently been confirmed³ by e.s.r. spectroscopy and Neale⁴ has suggested that they can be placed between the extremes of basicity and nucleophilicity as defined by the neutral and protonated amino-radicals. In view of the electrophilic addition⁵ of amido-radicals to olefins, and our results⁶ concerning the rates of intramolecular hydrogen abstraction reactions of *p*-substituted 4-phenylbutyramides, we investigated the electrophilic addition of amido-radicals to aromatic compounds.

Recently Hey *et al.*⁷ reported that *N*-methylbiphenyl-2-carboxamide (I; R = Me) cyclised to *N*-methylphenanthridone (V; R = Me) on treatment with lead(IV) acetate-iodine reagent. We repeated this reaction and isolated a mixture which contained *N*-methylphenanthridone. However the major product was a mixture of *cis*- and *trans*-2-methyl-4'-acetoxy-3-oxoisindoline-1-spirocyclohexa-2',5'-diene (VII and VIII; R = Me, X = OAc). The acetate mixture was hydrolysed to the alcohols which were separated. The alcohol with higher R_F on t.l.c. was the major

component. On the basis of the mechanism for the formation of the acetates, as well as the polarity of the alcohol, it is proposed that the major spirocyclohexadiene component has the *trans*-structure (VIII). The n.m.r. spectra of the alcohols were identical except that the *N*-methyl hydrogen atom of the *cis*-compound resonated at lower field (δ 2.98) than those of the *trans*-isomer (δ 2.86).

The cyclisation of *N*-methylbiphenyl-2-carboxamide (I; R = Me) on treatment with *t*-butyl hypochlorite-iodine reagent gave 2-iodo-*N*-methylphenanthridone (IX; R = Me). Iodination of ring B under our conditions would not be expected to occur. The position of the iodine atom was eventually assigned on the basis of the n.m.r. spectrum (Figure). The cyclisation was accomplished by either heat or irradiation. Highest yields were obtained when the molar ratio of amide, iodine, and *t*-butyl hypochlorite was 1:2:3 and the reaction mixture was irradiated at room temperature.

These results with both positive iodinating reagents are in accord with the initial homolysis of the N-I bond, the stability of which has been investigated,⁸ to form the amido-radical (II; R = Me). The formation of the spirocyclohexadienyl acetates in the lead(IV) acetate-iodine reaction is clear evidence that the amido-radical cyclises at the 1' position of biphenylcarboxamide.

¹ C. Walling, 'Free Radicals in Solution,' Wiley, London, 1963; W. A. Pryor, 'Free Radicals,' McGraw-Hill, 1966; F. Minisci, R. Mondelli, G. P. Gardini, and O. Porta, *Tetrahedron*, 1972, **28**, 2403.

² Y. L. Chow and T. C. Joseph, *Chem. Comm.*, 1969, 490.

³ P. Tordo, E. Flesia, and J. M. Surzur, *Tetrahedron Letters*, 1972, 183; P. Tordo, E. Flesia, G. Labrot, and J. M. Surzur, *ibid.*, p. 1413; W. C. Danen and R. W. Gellert, *J. Amer. Chem. Soc.*, 1974, **94**, 6853.

⁴ R. S. Neale, *Synthesis*, 1971, **1**, 1.

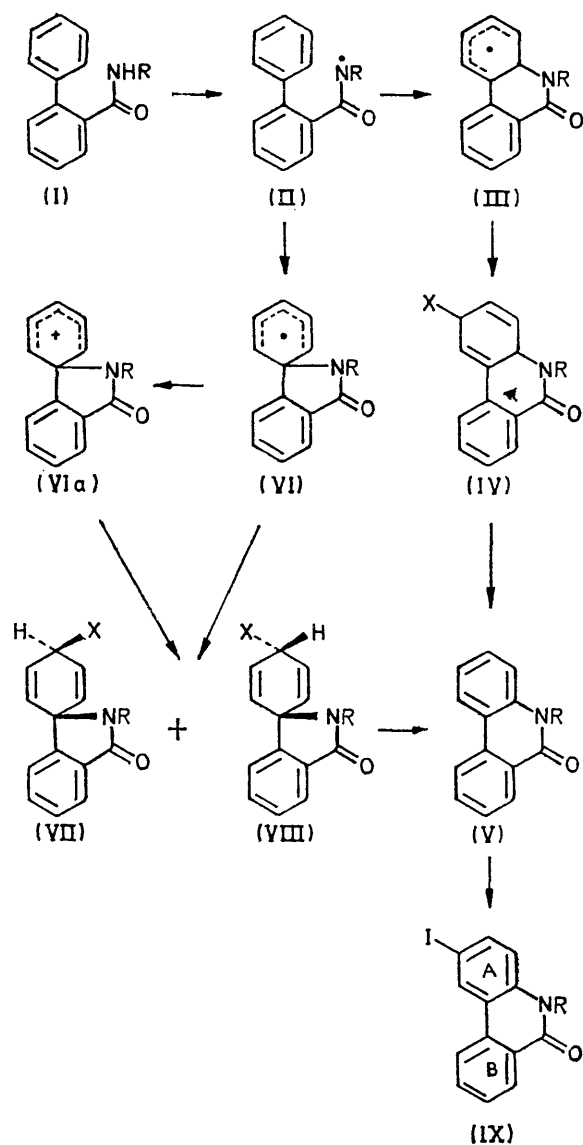
⁵ D. Touchard and J. Lessard, *Tetrahedron Letters*, 1971, 4425.

⁶ D. Graham, unpublished results.

⁷ D. H. Hey, G. H. Jones, and M. J. Perkins, *J. Chem. Soc. (C)*, 1971, 116.

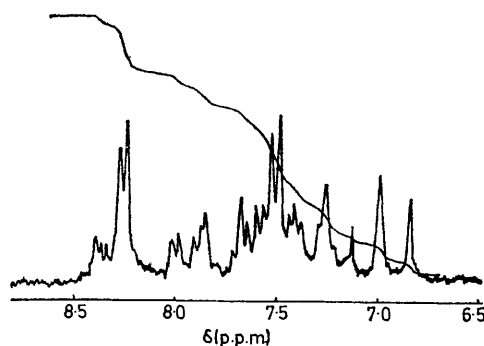
⁸ D. H. R. Barton, A. L. J. Beckwith, and A. Goosen, *J. Chem. Soc.*, 1965, 181.

The intermediate radical (VI; R = Me) could then be trapped by iodine to form the spirocyclohexadienyl iodides (VII and VIII; R = Me, X = I). However, it is extremely unlikely that the intermediate radical



could be trapped by acetoxy radicals since these, if formed, would readily decarboxylate.⁹ The formation of the spirocyclohexadienyl acetates (VII and VIII; R = Me, X = OAc) therefore most likely occurs by reaction of the carbocation (VIa; R = Me), formed by oxidation¹⁰ of the intermediate radical (VI; R = Me) with iodine, with acetate species in the reaction mixture. In support of the above proposal for an N -

iodo-intermediate, the starting material was recovered when the amide was treated with lead(IV) acetate alone. The formation of the phenanthridone in this reaction could thus arise by rearrangement of the spirocyclohexadienyl acetate or iodide. This type of rearrangement is well documented.¹¹ However we were unsuccessful in rearranging the spirocyclohexadienyl acetates (VII and VIII; R = Me, X = OAc) under more extreme conditions of temperature and acidity than could be encountered during the reaction. Since no spirocyclohexadienyl iodides, whose stability has been investigated,¹² were isolated from the reaction mixture they must have rearranged with loss of hydrogen iodide to the phenanthridone (V; R = Me). However the phenanthridone could also have been formed by cyclisation of the amido-radical (II; R = Me) at the 2' position.



N.m.r. spectrum of 2-iodo- N -methylphenanthridone in $CDCl_3$.

The same intermediate radicals (VI) and (III) were proposed by Hey *et al.*⁷ in their studies on the cyclisation of N -methyl- N -phenylcarbamoylbenzene diazonium fluoroborate and 2-iodo- N -methylbenzanilide. Chottard and Julia¹³ have elegantly demonstrated that two cyclisations of the radical generated by decarboxylation of 5-(1-naphthyl)pentanoic acid occur, forming five- and six-membered ring products. Cyclisation at the 2' position would produce the intermediate radical (III; R = Me) which could either be trapped or oxidised to the carbocation by iodine prior to reaction with iodine or acetate species. These dihydrophenanthridones (IV; R = Me, X = I or OAc) would readily lose hydrogen iodide or acetic acid on rearomatisation.

Cyclisation with t -butyl hypochlorite-iodine reagent would thus occur in the same way producing the phenanthridone (V; R = Me) either *via* the spirocyclohexadienyl iodide (IV; R = Me, X = I) or by reaction at the 2' position. However, when t -butyl hypochlorite-iodine reagent was used the product was 2-iodo- N -methylphenanthridone (IX; R = Me) which would arise by the fast reaction of the initially formed N -methylphenanthridone with ICl, which is established¹⁴

⁹ J. K. Kochi, *J. Amer. Chem. Soc.*, 1965, **87**, 2500; D. H. R. Barton, H. P. Faro, E. P. Serebryakov, and N. F. Woolsey, *J. Chem. Soc.*, 1965, 2438.

¹⁰ K. Heuster and J. Kalvoda, *Angew. Chem. Internat. Edn.*, 1964, **3**, 525.

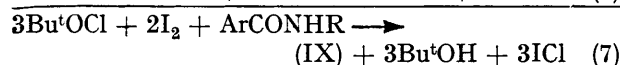
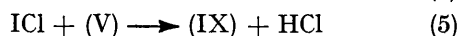
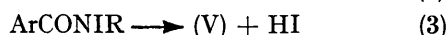
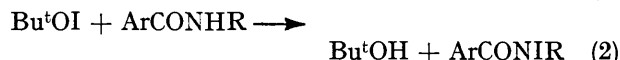
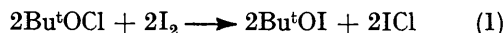
¹¹ D. H. Hey, G. H. Jones, and M. J. Perkins, *J.C.S. Perkin I*, 1972, 105, 113.

¹² D. H. Hey, G. H. Jones, and M. J. Perkins, *J.C.S. Perkin I*, 1972, 1155.

¹³ J. C. Chottard and M. Julia, *Tetrahedron Letters*, 1971, 2561.

¹⁴ L. J. Andrews and R. M. Keefer, *J. Amer. Chem. Soc.*, 1965, **78**, 5623; 1957, **79**, 1412; R. O. C. Norman and R. Tayler, 'Reaction Mechanisms in Organic Chemistry,' ed. C. Eaborn, Elsevier, Amsterdam, 1965.

as an efficient aromatic iodinating reagent. In support of this postulate it was found that *N*-methylphenanthridone readily reacted with ICl to give 2-iodo-*N*-methylphenanthridone. On this basis it is then possible to account for the molar ratio of reagents which give best yields of 2-iodo-*N*-methylphenanthridone by the reaction sequence (1)–(7).



Biphenyl-2-carboxamide (I; R = H) similarly gave 2-iodophenanthridone (IX; R = H). The *N*-iodoamide could not be isolated in pure form from the reaction mixture. This *N*-iodoamide cyclised in the dark at room temperature to produce 2-iodophenanthridone.

EXPERIMENTAL

M.p.s were determined on a Kofler hot stage. Silica gel for preparative t.l.c. was G according to Stahl. Irradiations were performed with a Phillips 125 W low pressure mercury lamp through Pyrex containers. I.r. spectra were determined with a Unicam SP 200 G spectrophotometer. N.m.r. spectra were determined with a Perkin-Elmer R12A spectrometer with tetramethylsilane as internal standard. Mass spectra were recorded on an A.E.I. MS 9 at the N.C.R.L./C.S.I.R. laboratories in Pretoria.

N-Methylbiphenyl-2-carboxamide and biphenyl-2-carboxamide were synthesised according to standard procedures.¹⁵

Lead(IV) Acetate-Iodine Oxidation of N-Methylbiphenyl-2-carboxamide.—*N*-Methylbiphenyl-2-carboxamide (1 g, 4.76×10^{-3} mol) and iodine (1.3 g, 5.12×10^{-3} mol) in boiling benzene were treated with lead(IV) acetate (2.11 g, 4.76×10^{-3} mol) for 30 min. The mixture was treated successively with ethylene glycol, water, and aqueous $\text{Na}_2\text{S}_2\text{O}_3$, dried (Na_2SO_4), and concentrated to give a solid (1.0893 g) which was separated by preparative t.l.c. to give two fractions. The fraction with highest R_F crystallised from light petroleum (b.p. 60–80°) to give *N*-methylphenanthridone, m.p. 108–109° (lit.,¹⁶ 107–108°), M^+ 209, ν_{max} 1650 cm^{-1} , δ (CDCl_3) 3.65 (3H, s) and 6.9–8.5 (8H, m).

The other component contained starting material and an isomeric mixture of 2-methyl-4'-acetoxyl-3-oxoisindoline-1-spirocyclohexa-2',5'-diene (A) ν_{max} 1694 and 1736 cm^{-1} , δ (CDCl_3) 2.16 (3H, d), 2.97–2.89 (3H, d), 5.7–5.4 (2H, m), 5.98–5.74 (1H, m), 6.28–6.12 (2H, m), and 7.96–7.03 (4H, m).

¹⁵ E. A. Rudzit, G. Kh. Khixamutdinov, A. K. Motorina, V. V. Kazakova, G. I. Efimova, V. K. Kiselev, M. B. Lis, I. B. Abaza, Z. V. Nefedora, I. D. Brazhnikova, and V. E. Chistyakov, *Khim. farm. Zhur.*, 1967, 1, 5, 14 (*Chem. Abs.*, 1967, 67, 108,584r).

The isomeric mixture (A) (0.5953 g) in ethanol (50 ml) was treated with 10% aqueous sodium hydroxide solution (10 ml) and shaken for 2.5 h. The mixture gave a solid (0.502 g) which when separated by preparative t.l.c. gave *cis*-2-methyl-4'-hydroxy-3-oxoisindoline-1-spirocyclohexa-2',5'-diene, m.p. 196–199°, M^+ 227, ν_{max} 1694, 3400, and 3600 cm^{-1} , δ (CDCl_3) 2.5–3.5 (1H), 2.98 (3H, s), 4.7–4.95 (1H, m), 5.4 (2H, q), 6.35 (2H, q), and 7.00–7.96 (4H, m) (Found: C, 73.35, 74.05; H, 5.7, 4.8. $\text{C}_{14}\text{H}_{13}\text{NO}_2$ requires C, 74.0; H, 5.7%) and the *trans*-isomer (0.1032 g), m.p. 130–132°, M^+ 227, ν_{max} 1690, 3400, and 3600 cm^{-1} , δ (CDCl_3) 2.86 (3H, s), 3.4–4.5 (1H), 4.63–4.9 (1H, m), 5.34 (2H, q), 6.39 (2H, q), and 7.28–7.94 (4H, m) (Found: C, 74.3; H, 5.7%).

2-Iodo-N-methylphenanthridone.—The results of this preparation under various conditions are summarised in the Table.

Yield of 2-iodo-*N*-methylphenanthridone under various reaction conditions

Reaction conditions (h)				Product yield (%)
Irradiation	Heat	Dark		
3.5	3.5			17
	3.5			29.4
3.5				48
		3.5		0

N-Methylbiphenyl-2-carboxamide (0.5 g, 2.28×10^{-3} mol) and iodine (1.21 g, 4.76×10^{-3} mol) in CCl_4 (20 ml) was treated with *t*-butyl hypochlorite (0.238 g, 2.38×10^{-3} mol) initially and after 1.5 h (0.238 g, 2.38×10^{-3} mol). After 3.5 h the mixture was washed (aqueous $\text{Na}_2\text{S}_2\text{O}_3$, water), dried, and concentrated to a solid which was either gravimetrically analysed after separation (t.l.c.) and/or analysed by n.m.r. spectroscopy. The product in all cases crystallised from chloroform–light petroleum (b.p. 60–80°) as opaque prisms of 2-iodo-*N*-methylphenanthridone, m.p. 212–214°, M^+ 335, ν_{max} 1650 cm^{-1} , δ (CDCl_3) 3.67 (3H, s, NMe), 6.91 (1H, d, J 9 Hz, 4-H), 7.1–7.76 (3H, m, 7-, 8-, and 9-H), 7.94 (1H, dd, J 9 and 3 Hz, 3-H), 8.26 (1H, d, J 3 Hz, 1-H), and 8.4 (1H, m, 10-H). (Found: C, 50.6; H, 2.6. $\text{C}_{14}\text{H}_{10}\text{INO}$ requires C, 50.2; H, 3.0%). The highest yield of 2-iodo-*N*-methylphenanthridone (83.6%) was obtained when *t*-butyl hypochlorite (0.771 g, 7.14×10^{-3} mol) was added in three equal portions after 1.5 h intervals and irradiated for 5.5 h.

N-Methylphenanthridone (0.0345 g, 0.1775×10^{-3} mol) and iodine chloride (0.0755 g; 0.455×10^{-3} mol) were shaken in dry chloroform (25 ml) for 20 min. The washed ($\text{Na}_2\text{S}_2\text{O}_3$) mixture gave a solid (0.0524 g) which crystallised from chloroform–light petroleum (b.p. 60–80°) as needles of 2-iodo-*N*-methylphenanthridone, m.p. 211–213°, identical (i.r., n.m.r.) with that obtained from the cyclisation.

2-Iodophenanthridone.—Biphenyl-2-carboxamide (1.3685 g, 6.65×10^{-3} mol) and iodine (3.38 g, 1.33×10^{-2} mol) treated as above gave a solid (0.8813 g) which crystallised from pyridine as opaque needles of 2-iodophenanthridone, m.p. 329–331° (lit.,¹⁷ 323.5–325°), M^+ 321, ν_{max} 3161 and 1660 cm^{-1} .

Attempted Isolation of N-Iodobiphenyl-2-carboxamide.—

¹⁶ D. H. Hey, C. W. Rees, and A. R. Todd, *J. Chem. Soc. (C)*, 1967, 1518.

¹⁷ H. Gilman and J. Eisch, *J. Amer. Chem. Soc.*, 1957, 79, 5479.

Biphenyl-2-carboxamide (0.5 g, 2.54×10^{-3} mol) and t-butyl hypochlorite (1.3 g, 1.2×10^{-2} mol) in benzene (3 ml) were stirred in the dark at room temperature for 3 h. Addition of light petroleum (b.p. 40—60°) deposited a gum which was washed with light petroleum (b.p. 40—60°) and triturated with acetone to give a solid. The solid crystallised from pyridine as needles of 2-iodophenanthri-

done, m.p. 327—328°, identical (i.r., m.p.) with an authentic specimen.

We thank the South African Council for Scientific and Industrial Research for financial support and the recording of mass spectra (Dr. R. H. Hall).

[3/003 Received, 1st January, 1973]
