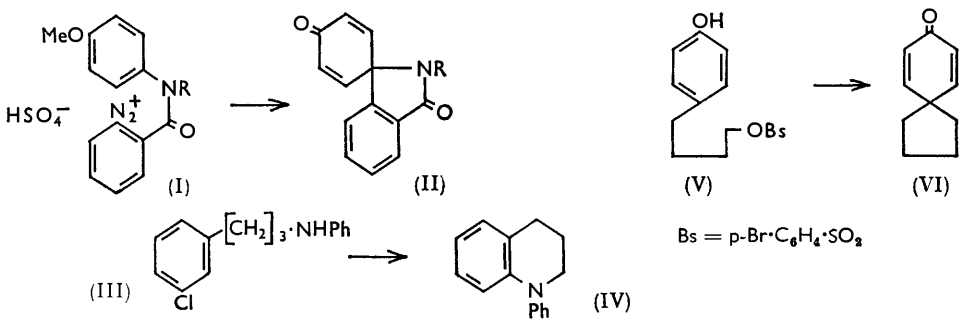
1003. *Internuclear Cyclisation. Part XX.*[1] *Synthesis of Spiro-dienones through Benzyne Intermediates.*

By D. H. Hey, J. A. Leonard, and C. W. Rees.

2-Bromo-4′-hydroxy-*N*-methylbenzanilide (VII; R = Me) and the 3-bromo-isomer (VIII) are converted by potassamide in liquid ammonia into 2-methylisoindoline-1-spiro-1′-cyclohexadiene-3,4′-dione (II; R = Me); 2-bromo-*N*-ethyl-4′-hydroxybenzanilide (VII; R = Et) is similarly converted into the corresponding dienone-lactam (II; R = Et). Thus the structures suggested for these lactams (II), previously obtained in the decomposition of certain diazonium salts, are confirmed. 2-Bromo-*N*-ethyl-3′-hydroxybenzanilide (X) is similarly converted into a mixture of 10-ethyl-2- and -4-hydroxyphenanthridone, thus providing a new synthesis of hydroxyphenanthridones. These reactions are considered to involve the formation of a benzyne intermediate and intramolecular addition to it of the phenoxide ion acting as an ambident nucleophile.

Thermal decomposition of aqueous solutions of the diazonium salts (I) prepared from 2-amino-*N*-methyl- and -*N*-ethyl-4′-methoxybenzanilide gave compounds which on the basis of their chemical and spectral properties were assigned the spiro-dienone-lactam structures (II; R = Me, Et).[2] Various attempts to synthesise these lactams have been described in Parts XVIII [3] and XIX [1] of this series. We now report a synthesis of these lactams which confirms the structure assigned to them.

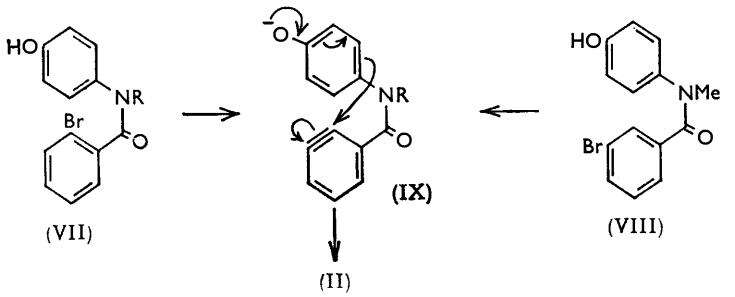


Intramolecular addition of a nucleophilic side-chain to a benzyne intermediate has recently been developed [4,5] as a route to certain benzo-heterocyclic compounds. For example, the amine (IV) has been prepared from the *m*-chloro-compound (III) with phenyl-lithium in ether or potassamide in liquid ammonia.[6] Formation of the same product from the *o*- and *m*-halogeno-compound is diagnostic of a benzyne intermediate. Furthermore, cyclohexa-2,5-dienones can be prepared from suitable *p*-hydroxyphenylalkyl halides,[7] toluene-*p*-sulphonates,[8] and related compounds by elimination, with aryl participation, under strongly basic conditions; for example, the reaction of 4-*p*-hydroxyphenylbutyl *p*-bromobenzenesulphonate (V) with potassium t-butoxide in t-butyl

[1] Part XIX, Hey, Leonard, and Rees, preceding paper.
[2] Hey, Leonard, Moyenhan, and Rees, *J.*, 1961, 232.
[3] Hey, Leonard, and Rees, *J.*, 1963, 5251.
[4] Bunnett and Hrutfiord, *J. Amer. Chem. Soc.*, 1961, **83**, 1691.
[5] Huisgen, König, and Lepley, *Chem. Ber.*, 1960, **93**, 1496.
[6] König and Huisgen, *Chem. Ber.*, 1959, **92**, 429.
[7] Dreiding, *Helv. Chim. Acta*, 1957, **40**, 1812; Dorling and Harley-Mason, *Chem. and Ind.*, 1959, 1551.
[8] Masamune, *J. Amer. Chem. Soc.*, 1961. **83**, 1009; Mandell, Caine, and Kilpatrick, *ibid.*, p. 4457.

alcohol gave the spiro-dienone (VI).[9] A consideration of the spiro-dienone-lactam structure (II) suggested that such compounds might be synthesised, in one step, by a suitable combination of these two types of reaction, as shown in (VII) or (VIII) ⟶ (IX) ⟶ (II).

2-Bromo-4′-hydroxy-*N*-methylbenzanilide (VII; R = Me), prepared from *p*-methylaminophenol and *o*-bromobenzoyl chloride followed by hydrolysis of the ester group, was treated with potassamide (3 mol.) in liquid ammonia for 8 hours. The desired product, 2-methylisoindoline-1-spiro-1′-cyclohexadiene-3,4′-dione (II; R = Me), was obtained in 75% yield, based on the starting material consumed. From a similar reaction for 2 hours, more starting material was recovered and the yield of lactam was 66%. This product was identical with that obtained [2] by decomposition of diazotised 2-amino-4′-methoxy-*N*-methylbenzanilide (I; R = Me). That reaction with potassamide proceeded through a benzyne intermediate, and not by concerted displacement of the bromine atom, was shown by the similar preparation of the lactam (II; R = Me) from 3-bromo-4′-hydroxy-*N*-methylbenzanilide (VIII). In this case more potassamide (5 mol.) was required and the yield was lower (35%), presumably because of other reactions of the alternative benzyne



intermediate, derived by removal of a proton from position 4. These reactions are therefore considered to involve formation of the benzyne intermediate and intramolecular addition to it of the phenoxide ion acting as an ambident nucleophile (as in IX). The use of sodamide in boiling benzene with the phenol (VII; R = Me) gave only starting material and none of the dienone-lactam.

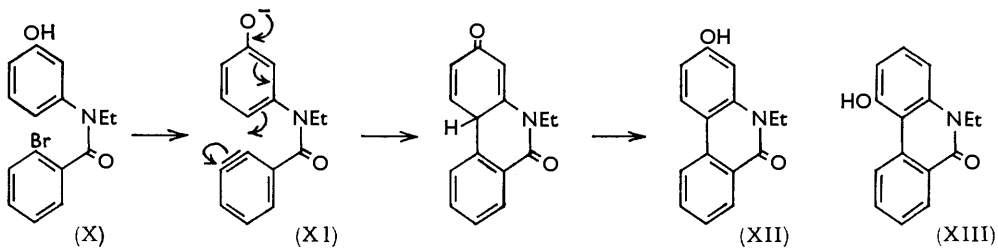
An attempt was also made to prepare the parent dienone-lactam (II; R = H). Treatment of *p*-aminophenol with *o*-bromobenzoyl chloride gave the *ON*-di-*o*-bromobenzoyl compound which on hydrolysis gave 2-bromo-4′-hydroxybenzanilide (VII; R = H). This compound, with potassamide (5 mol.) in liquid ammonia, gave only starting material; with more potassamide (10 mol.) the recovery was small but no other product could be isolated. Presumably the reluctance of this secondary amide to undergo intramolecular cyclisation arises from electrostatic repulsion between the amide anion and the phenoxide ion.

The *N*-ethyl-dienone-lactam (II; R = Et) was synthesised in high yield in the same way as the *N*-methyl derivative. Numerous attempts were made to ethylate the above *ON*-di-*o*-bromobenzoyl compound; reaction was effected with diethyl sulphate and anhydrous potassium carbonate in boiling dimethylformamide but the product, m. p. 156—157°, which was alkali-insoluble, was *N*-*o*-bromobenzoyl-4-phenetidide and not the required isomer, 2-bromo-*N*-ethyl-4′-hydroxybenzanilide (VII; R = Et), m. p. 160·5°. This ready hydrolysis of the ester, followed by *O*-ethylation and a striking reluctance to undergo *N*-ethylation, despite the use of a large excess of diethyl sulphate, has also been noted for *p*-benzamidophenyl benzoate.[1] The phenol (VII; R = Et) was therefore prepared by treatment of *p*-ethylaminophenol, from *p*-aminophenol and ethyl bromide, with an excess of *o*-bromobenzoyl chloride followed by hydrolysis of the ester group. When this phenol was treated with potassamide (3 mol.) no reaction was observed but with more base (5 mol.)

[9] Winstein and Baird, *J. Amer. Chem. Soc.*, 1957, **79**, 756.

cyclisation proceeded as before to give 2-ethylisoindoline-1-spiro-1′-cyclohexadiene-3,4′-dione (66%), identical with the product of decomposition of diazotised 2-amino-*N*-ethyl-4′-methoxybenzanilide (I; R = Et).[2]

By analogy with these successful internuclear cyclisations it was envisaged that the use of a 3′-hydroxybenzanilide, such as (X), might provide a new synthesis of hydroxyphenanthridones. The ambident phenoxide ion should now add to the benzyne *via* the *p*- (shown in XI ⟶ XII) or the *o*-carbon atom to give 10-ethyl-2-hydroxyphenanthridone (XII) or the 4-hydroxy-isomer (XIII), respectively, rather than spirans. 2-Bromo-*N*-ethyl-3′-hydroxybenzanilide (X), prepared in the standard way, was treated with potassamide (10 mol.) in liquid ammonia, and the alkali-soluble product (60%) was eluted from silica gel in one fraction, but fractional crystallisation separated it into equal amounts of two isomers, $C_{15}H_{13}NO_2$, m. p. 256° and 282°, shown by an independent synthesis [10] to be 10-ethyl-2- (XII) and -4-hydroxyphenanthridone (XIII), respectively.



Finally, the possibility of the production of a benzyne intermediate with a nitro-group replacing halogen as the leaving group was briefly examined. 4′-Hydroxy-*N*-methyl-2-nitrobenzanilide was therefore prepared from *p*-methylaminophenol and *o*-nitrobenzoyl chloride, but treatment with potassamide (5 mol.) in the standard way gave no identifiable products.

Part of this work has been briefly reported.[11]

Experimental

For general directions see Part XVIII.[3]

Procedure for Reactions with Potassamide in Liquid Ammonia.—Liquid ammonia (~ 250 ml.) contained in a round-bottomed Quickfit Dewar flask was treated with small pieces of potassium with stirring until a permanent deep blue colour was observed. A single crystal of ferric nitrate was added, followed by the required amount of potassium. When the initial blue colour had faded to grey (*ca.* 10 min.) the dry, finely powdered phenol was added in small portions. Any reactant adhering to the neck of the flask was washed down with a small quantity of dry ether. After the required reaction time an excess of ammonium chloride was added. The mixture was diluted with ether (800 ml.) and the ammonia allowed to evaporate overnight.

2-*Bromo*-4′-*hydroxy*-N-*methylbenzanilide* (VII; R = Me).—*o*-Bromobenzoyl chloride, prepared from the acid (17·3 g.), in ether (50 ml.) was slowly added to a stirred suspension of *p*-methylaminophenol sulphate (10·1 g.) in dry pyridine (40 ml.) and ether (50 ml.); a brown oil slowly separated. After 3 hr. the mixture was poured into dilute hydrochloric acid and extracted with methylene chloride. The organic layer was further washed with dilute acid and then with water. The solvent was removed and the residue was boiled with 10% aqueous sodium hydroxide (150 ml.) under reflux for 1 hr. The alkaline solution was acidified and extracted with ether. The ethereal extract was washed with saturated aqueous sodium hydrogen carbonate and then with 10% aqueous sodium hydroxide. Acidification of the first

[10] Hey, Rees, and Todd, unpublished work.
[11] Hey, Leonard, and Rees, *Chem. and Ind.*, 1962, 1025.

alkaline extract gave *o*-bromobenzoic acid (7 g.) and the second a brown solid (9·7 g.). Recrystallisation of the latter from benzene–light petroleum gave *2-bromo-4′-hydroxy-*N*-methylbenzanilide* in prisms, m. p. 170° (Found: C, 55·2; H, 4·2. $C_{14}H_{12}NO_2Br$ requires C, 54·9; H, 4·0%).

*3-Bromo-4′-hydroxy-*N*-methylbenzanilide* (VIII).—This was prepared as for the 2-bromo-isomer but a better yield was obtained by using *p*-methylaminophenol instead of its sulphate. Recrystallisation from benzene gave the *anilide*, m. p. 176° (Found: C, 55·5; H, 4·1%).

2-Methylisoindoline-1-spiro-1′-cyclohexadiene-3,4′-dione (II; R = Me).—(*a*) 2-Bromo-4′-hydroxy-*N*-methylbenzanilide (2 g.) was treated with potassamide prepared from potassium (0·83 g.) in liquid ammonia. In two separate experiments the reaction mixture was stirred for (i) 2 hr. and (ii) 8 hr. Extraction of the ethereal mixture with 10% aqueous sodium hydroxide and acidification of the extract gave (i) 1·31 g. and (ii) 0·68 g. of starting material. Removal of solvent from the dried ethereal solution gave (i) 0·33 g. (66%) and (ii) 0·73 g. (75%) of 2-methylisoindoline-1-spiro-1′-cyclohexadiene-3,4′-dione (II; R = Me) in small prisms, m. p. 228°; yields are based on unrecovered starting material. (*b*) Sodamide (8·1 g.) was ground to a fine suspension in dry benzene (50 ml.). 2-Bromo-4′-hydroxy-*N*-methylbenzanilide (3 g.) in benzene (100 ml.) was added and the mixture boiled under reflux for 65 hr. Standard treatment gave only starting material (2·23 g.)

(*c*) 3-Bromo-4′-hydroxy-*N*-methylbenzanilide (2 g.) was treated with potassamide (3 mol). in liquid ammonia. After 5 hours' stirring, only starting material (1·77 g.) was isolated. The reaction with potassamide (5 mol.) for 8 hr. yielded starting material (0·68 g.) and 2-methylisoindoline-1-spiro-1′-cyclohexadiene-3,4′-dione (0·34 g., 35%), m. p. 228°. These samples of 2-methylisoindoline-1-spiro-1′-cyclohexadiene-3,4′-dione and that from the diazonium salt decomposition [2] gave undepressed mixed m. p.s and had identical infrared spectra.

p-o′-*Bromobenzamidophenyl* o-*Bromobenzoate*.—*o*-Bromobenzoyl chloride prepared from the acid (17·3 g.), in ether (50 ml.) was added to a solution of *p*-aminophenol (5·42 g.) in dry pyridine (30 ml.) and ether (50 ml.). After being stirred for 2 hr. the mixture was poured into dilute hydrochloric acid and extracted with chloroform. Removal of the solvent from the dried extract and recrystallisation of the residue from ethanol gave the ON-*di*-o-*bromobenzoyl derivative* (11 g.) in needles, m. p. 163·5° (Found: C, 50·2; H, 2·8. $C_{20}H_{13}NO_3Br_2$ requires C, 50·6; H, 2·8%).

2-Bromo-4′-hydroxybenzanilide (VII; R = H).—The preceding *ON*-di-*o*-bromobenzoyl derivative (5·5 g.) in 10% aqueous sodium hydroxide (125 ml.) was boiled under reflux for 1 hr. The alkaline solution was acidified and the precipitate stirred with aqueous sodium hydrogen carbonate. The insoluble material crystallised from benzene–ethanol, to give *2-bromo-4′-hydroxybenzanilide* (3·5 g.) in needles, m. p. 191—192° (Found: C, 53·6; H, 3·4. $C_{13}H_{10}NO_2Br$ requires C, 53·4; H, 3·5%). This compound (2 g.) was treated in two experiments with potassamide (5 and 10 mol.) in liquid ammonia. After 8 hr., only starting material (1·71 g. and 0·21 g., respectively) was isolated.

Attempted Ethylation of the ON-*Di*-o-*bromobenzoyl Derivative*.—The phenol (0·5 g.) with dimethylformamide (5 ml.) and anhydrous potassium carbonate (1 g.) was treated with diethyl sulphate (1 ml.), and the mixture was boiled under reflux for 4 hr. The solvent was removed under reduced pressure, the residue triturated with water, and the mixture extracted with chloroform. Removal of solvent from the extract gave a yellow oil (0·39 g.) which was dissolved in benzene, adsorbed on alumina (1 × 15 cm.), and eluted as follows: (i) Benzene–light petroleum (1 : 1; 200 ml.); benzene (400 ml.) and benzene–ether (1 : 1; 200 ml.) yielded nothing. (ii) Ether (200 ml.) and ether–methanol (4 : 1; 200 ml.) gave a brown solid (0·19 g.), which on crystallisation from ether gave N-o-*bromobenzoyl-4-phenetidide* in prisms, m. p. 156—157° (Found: C, 56·6; H, 4·6. $C_{15}H_{14}NO_2Br$ requires C, 56·3; H, 4·4%), $\nu_{max.}$ 3257 (N–H) and 1647 cm.$^{-1}$ (amide-carbonyl). Application of chromatography as above to the *ON*-di-*o*-bromobenzoyl derivative (0·07 g.) yielded only 2-bromo-4′-hydroxybenzanilide (0·033 g.), indicating that ready hydrolysis of the ester had occurred. The starting material could be recovered by rapid elution with methanol.

N-*Ethylation of* m- *and* p-*Aminophenol* (cf. ref. 12).—The aminophenol (20 g.) in ethanol (60 ml.) and ethyl bromide (20 g.) was boiled under reflux for 2 hr. The solution was poured into aqueous sodium carbonate and extracted with ether (3 × 150 ml.). The oil obtained after removal of the solvent was distilled at reduced pressure. *p*-Ethylaminophenol was

[12] Foerster, *J. prakt. Chem.*, 1866, **21**, 346.

collected as an oil (15 g.), b. p. 132°/2 mm., that solidified; exposure to the air caused oxidation and the oil rapidly assumed a red and finally a black colour. Crystallisation from ether–light petroleum gave *p*-ethylaminophenol, m. p. 102—104° (decomp.) (lit.,[13] 103—104°). *m*-Ethylaminophenol distilled as a pale yellow oil (19·7 g.), b. p. 132°/2 mm., which slowly crystallised.

2-Bromo-N-ethyl-4′-hydroxybenzanilide (VII; R = Et).—*o*-Bromobenzoyl chloride, prepared from the acid (18 g.), in ether (50 ml.) was added with stirring to *p*-ethylaminophenol (6 g.) in dry pyridine (30 ml.) and ether (50 ml.). After 2 hr. at room temperature, the mixture was poured into dilute hydrochloric acid and extracted with chloroform. The solvent was removed and the residue, with 10% aqueous sodium hydroxide (125 ml.), was boiled under reflux for 2 hr. Acidification of the alkaline solution, treatment of the precipitate with saturated aqueous sodium hydrogen carbonate and filtration, yielded a brown solid (8·4 g.). Recrystallisation of this from ethanol afforded *2-bromo-N-ethyl-4′-hydroxybenzanilide* in needles or prisms, m. p. 160·5° (Found: C, 55·9; H, 4·2. $C_{15}H_{14}NO_2Br$ requires C, 56·3; H, 4·4%).

2-Ethylisoindoline-1-spiro-1′-cyclohexadiene-3,4′-dione (II; R = Et).—2-Bromo-*N*-ethyl-4′-hydroxybenzanilide (2 g.) was treated with potassamide (3 ml.) in liquid ammonia. After 6 hours' stirring, starting material (1·77 g.) only was isolated. The reaction with potassamide (5 mol.) for 8 hr. yielded starting material (0·42 g.) and 2-ethylisoindoline-1-spiro-1′-cyclohexadiene-3,4′-dione (0·81 g., 68·5%) in rods, m. p. and mixed m. p. with the product from the diazonium salt decomposition,[2] 139—140°.

2-Bromo-N-ethyl-3′-hydroxybenzanilide (X).—*m*-Ethylaminophenol (6·5 g.) was treated in a similar way to the *para*-isomer as above. After hydrolysis of the intermediate ester, an alkali-insoluble oil (3 g.) remained. Acidification of the alkaline solution and removal of *o*-bromobenzoic acid from the precipitate as before gave a colourless solid (3 g.). Crystallisation from benzene–ethanol afforded *2-bromo-N-ethyl-3′-hydroxybenzanilide* in rods, m. p. 152° (Found: C, 56·5; H, 4·3%).

10-Ethyl-2- (XII) *and -4-hydroxyphenanthridone* (XIII).—2-Bromo-*N*-ethyl-3′-hydroxybenzanilide (2 g.) was added to potassamide (10 mol.) in liquid ammonia. After 8 hours' stirring, the reaction mixture in ether was extracted with 10% aqueous sodium hydroxide. Acidification gave a brown solid (1·2 g.), which was dissolved in benzene–chloroform, adsorbed on silica gel (2 × 20 cm.), and eluted with benzene (500 ml.), benzene–ether (10 : 1; 500 ml.) and benzene–ether (3 : 1; 1200 ml.). The solids obtained from several fractions had identical infrared spectra. The fractions were combined (0·72 g.) and, on crystallisation from benzene, gave a mixture of needles and prisms. Fractional crystallisation from benzene afforded *10-ethyl-2-hydroxyphenanthridone* (0·3 g.), m. p. 256° (Found: C, 74·9; H, 5·6; N, 5·9. $C_{15}H_{13}NO_2$ requires C, 75·3; H, 5·5; N, 5·9%) and *10-ethyl-4-hydroxyphenanthridone* [10] (0·3 g.), m. p. 282° (Found: C, 75·3; H, 5·2; N, 5·9%).

4′-Hydroxy-N-methyl-2-nitrobenzanilide.—*o*-Nitrobenzoyl chloride, prepared from the acid (14·5 g.), in ether (50 ml.) was added to a stirred solution of *p*-methylaminophenol (5·6 g.) in dry pyridine (30 ml.) and ether (50 ml.). After 2 hr. the mixture was poured into dilute hydrochloric acid and extracted with chloroform. The solvent was removed from the extract, and the residue in 10% aqueous sodium hydroxide (125 ml.) was boiled under reflux for 1 hr. Acidification of the alkaline solution, treatment of the precipitated solid with aqueous sodium hydrogen carbonate, and filtration yielded a residue (7·5 g.). Recrystallisation of this from benzene–ethanol gave *4′-hydroxy-N-methyl-2-nitrobenzanilide* in colourless prisms, m. p. 195° (Found: C, 61·7; H, 4·7. $C_{14}H_{12}N_2O_4$ requires C, 61·8; H, 4·4%).

Grateful acknowledgment is made to the Department of Scientific and Industrial Research for a Research Studentship to J. A. L.

King's College (University of London),
Strand, London W.C.2. [*Received, April 27th,* 1963.]

[13] Galatis, *Ber.*, 1927, **60**, 1402.