49. *Intramolecular Reactions of Amides. Part II.*[1] *Cyclisation of Amides of ω-Bromo-carboxylic Acids.*

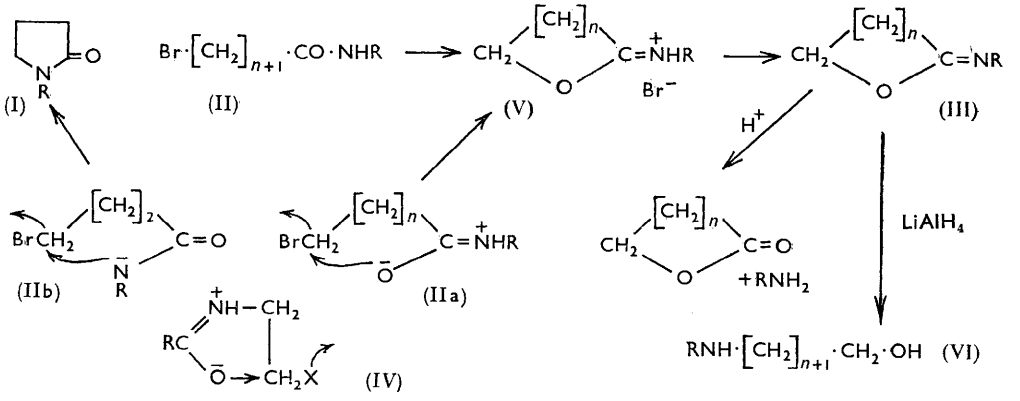
By C. J. M. Stirling.

Cyclisation of the bromo-amides (II and VIII) under various conditions has been investigated. In certain cases, cyclic imino-ethers (III and IX) are obtained. These are attacked at the imino-group by acids to give a lactone and an amine, and, with two exceptions, by lithium aluminium hydride with formation of acyclic ω-amino-alcohols. By contrast, acid-catalysed attack of ethanol occurs at the α-methylene carbon atom of the imino-ethers (III; R = C_6H_{11}; $n = 2$; and IX; R = $PhCH_2$) to give the ethoxy-amides (VII and XII).

The ultraviolet absorption spectra of the cyclic imino-ethers (IX) are compared with those of the isomeric lactams (XIII).

In a preparation of 1-cyclohexylpyrrolid-2-one (I; R = C_6H_{11}) by fusion of γ-bromo-*N*-cyclohexylbutyramide (II; R = C_6H_{11}; $n = 2$) with potassium hydroxide,[2] fusion of the bromo-amide alone was found to give the hydrobromide of a base. This hydrobromide was isomeric with the bromo-amide and gave a base isomeric with the pyrrolid-2-one. By further experiments described below, the base was identified as the cyclic imino-ether, 2-cyclohexyliminotetrahydrofuran (III; R = C_6H_{11}; $n = 2$).

Few cyclic imino-ethers of this type have been described: most have been obtained from ω-hydroxy-nitriles [3] and unsaturated nitriles.[4] Formation of cyclic imino-ethers by cyclisation of ω-halogeno-amides has previously been described only by Gabriel,[5] who obtained 1,3-dihydro-1-iminoisobenzofuran (IX; R = H) and its 5-nitro-derivative from 2-chloromethylbenzamide and 2-chloromethyl-5-nitrobenzamide, respectively, and by



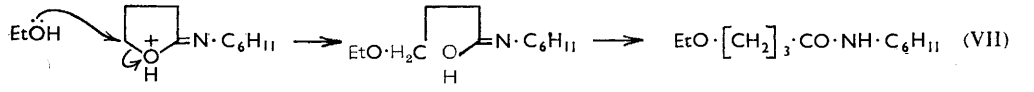
Craig [6] who showed that addition of bromine to *NN*-dialkylpent-4-enamides gave quaternary bromides of 2-dialkyliminotetrahydrofurans. Intermediate formation of a tetrahydroiminofuran in the oxidation of amides of 3-indolylpropionic acids has, however, been suggested,[7] and the ready formation of γ-butyrolactone from γ-bromo-*N*-(3,4-dimethoxyphenethyl)butyramide[8] is undoubtedly due to the formation and subsequent

[1] Part I, *J.*, 1958, 4531.
[2] Cf. Lipp and Caspers, *Ber.*, 1925, **58**, 1011.
[3] Topchiev and Kirmalova, *Doklady Akad. Nauk, S.S.S.R.*, 1948, **63**, 281; Schultz, Robb, and Sprague, *J. Amer. Chem. Soc.*, 1947, **69**, 2454.
[4] Raffauf, *J. Amer. Chem. Soc.*, 1952, **74**, 4460.
[5] Gabriel, *Ber.*, 1887, **20**, 2224; Gabriel and Landsberger, *ibid.*, 1898, **31**, 2732.
[6] Craig, *J. Amer. Chem. Soc.*, 1952, **74**, 129.
[7] Patchornik, Lawson, and Witkop, *J. Amer. Chem. Soc.*, 1958, **80**, 4748.
[8] Child and Pyman, *J.*, 1931, 36.

hydrolysis of a tetrahydro-2-iminofuran. In addition, imino-compounds of related structure have been obtained in the neutral solvolyses of ω-bromo-urethanes and ureides.[9] In no case has the isolation of free cyclic imino-ethers with an *N*-substituent been reported.

Cyclisation of ω-halogeno-amides in neutral conditions occurs by displacement of the halide ion by the carbonyl oxygen of the amido-group (IIa) and is analogous to the formation of oxazolines from *N*-acyl-halogeno-amines,[10] whereupon an endocyclic imino-group is obtained (IV). In basic conditions, a proton is lost from the amido-nitrogen atom (IIb) and cyclisation gives an *N*-substituted pyrrolid-2-one.[2,11] In the present work, cyclisation of *N*-monosubstituted ω-bromo-amides (II and VIII) under various conditions has been examined. In certain cases, *N*-substituted imino-ethers have been obtained and their reactions have been compared with those of both open-chain imino-ethers and of cyclic imino-ethers without an *N*-substituent.

Reactions with Butyramides.—Fusion of γ-bromo-*N*-cyclohexylbutyramide (II; R = C_6H_{11}; $n = 2$) at 100° gave the tetrahydroiminofuran hydrobromide (V; R = C_6H_{11}; $n = 2$) quantitatively. The free base was more stable than the acyclic analogues and distilled without decomposition. Acid hydrolysis gave γ-butyrolactone and cyclohexylamine. The base readily formed a methiodide and reduction with lithium aluminium hydride[12] gave 4-cyclohexylaminobutanol (VI; R = C_6H_{11}; $n = 2$). Reaction with phenylmagnesium bromide[13] was slow and no identifiable products were obtained. Attempts to isomerise[14] the imino-ether to the pyrrolidone (I; R = C_6H_{11}) failed, the compound being recovered even from reactions at 290°, but the pyrrolidone was obtained by potassium hydroxide fusion of the bromo-amide. Cyclisation of the bromo-amide to the tetrahydroiminofuran hydrobromide also occurred when the compound was heated in ethanol for short periods. The chief product of prolonged heating, however, was *N*-cyclohexyl-γ-ethoxybutyramide (VII), together with small amounts of cyclohexylamine and γ-butyrolactone. The same products were obtained from ethanolysis of the tetrahydroiminofuran hydrobromide. These results suggest the occurrence of two competing reactions: (i) slow hydrolytic fission of the $C_{(2)}$–N bond of the imino-ether to give amine and lactone, and (ii) a faster attack of ethanol at $C_{(5)}$, facilitated by protonation of the ring oxygen atom, which causes ring fission and formation of the unstable tautomer of the γ-ethoxy-amide:



N-Cyclohexyl-γ-hydroxybutyramide, the corresponding intermediate in aqueous hydrolysis, was looked for but could not be isolated.

Fusion of γ-bromobutyranilide (II; R = Ph; $n = 2$) failed to give the cyclic imino-ether; only aniline and γ-butyrolactone were obtained. Ethanolysis of the anilide also gave aniline and γ-butyrolactone. In this case, hydrolysis of the imino-ether at the C–N bond must be so rapid that $C_{(5)}$ attack is not competitive. Attempts to prevent hydrolysis by carrying out the reaction in the presence of, *e.g.*, triethylamine gave the pyrrolidone (I; R = Ph).

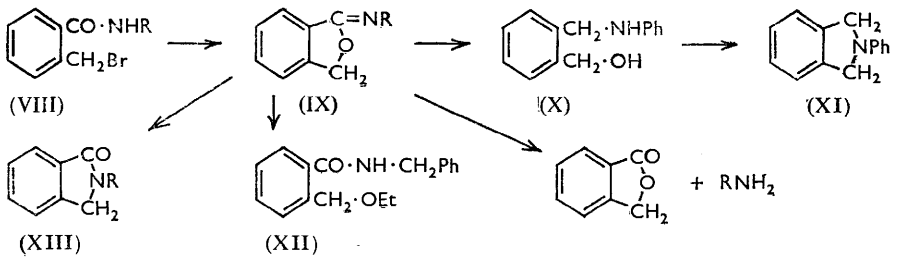
Similar results were obtained with *N*-benzyl-γ-bromobutyramide (II; R = $PhCH_2$; $n = 2$), but small yields of 2-butyliminotetrahydrofuran (III; R = Bu^n; $n = 2$) were obtained by fusion of the corresponding bromo-amide, although the intermediate hydrobromide could not be isolated, and the reaction was much slower than with the cyclohexyl

[9] Scott, Glick, and Winstein, *Experientia*, 1957, **13**, 183.
[10] Fry, *J. Org. Chem.*, 1949, **14**, 887; Heine, *J. Amer. Chem. Soc.*, 1956, **78**, 3708.
[11] Heine, Love, and Bove, *J. Amer. Chem. Soc.*, 1955, **77**, 5420.
[12] Cf. Easton and Fish, *J. Amer. Chem. Soc.*, 1955, **77**, 1776.
[13] Cf. Easton, Lukach, Nelson, and Fish, *J. Amer. Chem. Soc.*, 1958, **80**, 2519.
[14] Cf. Chapman, *J.*, 1925, 1992; 1927, 1743.

analogue. The structure of the imino-ether was confirmed by acid hydrolysis to butylamine and γ-butyrolactone, and by reduction with lithium aluminium hydride to the amino-butanol (VI; R = Bu^n; $n = 2$).

Reactions with Pentanamides.—Cyclisation of 5-bromo-*N*-cyclohexylpentanamide (II; R = C_6H_{11}; $n = 3$) to 2-cyclohexyliminotetrahydropyran hydrobromide (V; R = C_6H_{11}; $n = 3$) was very slow by comparison with the butyramide, as was expected for the formation of a six-membered ring. Hydrolysis of the imino-ether gave δ-valerolactone and cyclohexylamine, and lithium aluminium hydride reduction yielded 5-cyclohexylaminopentanol (VI; R = C_6H_{11}; $n = 3$). In view of the extremely slow cyclisation of the *N*-cyclohexylamide, cyclisation of other amides was not attempted. Ethanolysis of the anilide, however, gave δ-valerolactone and aniline, again presumably *via* the tetrahydroiminopyran.

Reactions with 2-Bromomethylbenzamides.—The anilide (VIII; R = Ph) was cyclised at 130° to give 1,3-dihydro-1-phenyliminoisobenzofuran hydrobromide from which the free imino-ether (IX; R = Ph) was obtained. Acid hydrolysis of the imino-ether gave aniline and phthalide; reduction with lithium aluminium hydride yielded the amino-alcohol (X) which was dehydrated to the known isoindoline (XI). The imino-ether isomerised at 300° to the isoindolinone (XIII; R = Ph) which was also obtained by treatment of the bromo-anilide with sodium ethoxide.



The *N*-benzylamide (VIII; R = CH_2Ph) cyclised so readily that it could not be purified. The free iminoisobenzofuran (IX; R = CH_2Ph) was obtained from the cyclisation product and acid hydrolysis, which was much slower than that of the phenyl analogue, gave aniline and phthalide. The same results were obtained with the cyclohexyl-amide (VIII; R = C_6H_{11}) and neither imino-ether was reduced by lithium aluminium hydride under the conditions used for the other imino-ethers that have been studied. Attempted isomerisation of both imino-ethers at 300° caused considerable decomposition, and in neither case was the *N*-substituted isoindolinone (XIII) isolated. Ethanolysis of 1-benzyl-1,3-dihydroisobenzofuran hydrobromide yielded only a small amount of *N*-benzyl-2-ethoxymethylbenzamide (XII). Evidently, cleavage of the C–N bond is preferred to attack at $C_{(3)}$ in this instance.

Ultraviolet absorption data of the *N*-substituted 1,3-dihydro-1-iminoisobenzofurans are given in Table 1 together with those of the isomeric isoindolinones (XIII), which show absorption at slightly shorter wavelengths. Similar comparisons have been made by several workers [15] who found slight but distinct differences between the spectra of acyclic amides and imino-ethers.

Experimental

The light petroleum used had b. p. 40—60°. Extracts were dried over Na_2SO_4. Ultraviolet spectra refer to ethanolic solutions and were determined on the Unicam S.P. 500 spectrophotometer.

γ-Bromo-N-cyclohexylbutyramide.—Cyclohexylamine (45 g.) in ether (100 ml.) was added

[15] Ley and Specker, *Ber.*, 1939, **72**, 192; Edward and Meacock, *Chem. and Ind.*, 1955, 536; Grob and Fischer, *Chem. and Ind.*, 1955, 1063.

with cooling and stirring to γ-bromobutyryl chloride (from 38 g. of the acid [16]) in ether (300 ml.). The mixture was washed with water, dilute hydrochloric acid, and 10% aqueous sodium carbonate. Evaporation under reduced pressure and treatment of the residue with light petroleum gave the *amide* (38 g.). The m. p. (about 60°) could not be accurately determined, as slow heating gave the cyclisation product (m. p. 132°) (below) (Found: C, 48·5; H, 7·2; N, 5·6. $C_{10}H_{18}ONBr$ requires C, 48·4; H, 7·3; N, 5·6%).

2-Cyclohexyliminotetrahydrofuran.—The amide, when heated at 100°, fused and immediately resolidified. Crystallisation of the product from ethanol–ether gave *2-cyclohexyliminotetrahydrofuran hydrobromide*, m. p. 132° (Found: C, 48·2; H, 7·2; N, 5·9%). The hydrobromide (26 g.) in water (75 ml.) was basified with 10% aqueous sodium carbonate; extraction with ether gave *2-cyclohexyliminotetrahydrofuran* (16·2 g.), b. p. 134°/7 mm., n_D^{20} 1·4945 (Found: C, 71·5; H, 10·2; N, 8·3. $C_{10}H_{17}ON$ requires C, 71·9; H, 10·2; H, 8·4%). A 20% solution of the imino-ether in methyl iodide was kept at 25° for 1 hr.; addition of ether then precipitated the *methiodide*, m. p. 187—188° (from methanol–ether) (Found: C, 43·0; H, 6·3; N, 4·5. $C_{11}H_{20}ONI$ requires C, 42·7; H, 6·5; N, 4·5%).

Reactions with 2-Cyclohexyliminotetrahydrofuran.—(a) *Hydrolysis.* The imino-ether (2 g.) in 20% aqueous sulphuric acid (20 ml.) was heated at 100° for 16 hr. Saturation of the solution with sodium chloride and extraction with ether gave γ-butyrolactone (0·5 g.), b. p. 97°/18 mm., n_D^{22} 1·4350 (lit.,[17] $n_D^{26·5}$ 1·4343). The aqueous solution was basified with sodium hydroxide and re-extracted with ether. The ethereal extract was halved: (i) was evaporated, and distillation of the residue gave only cyclohexylamine (0·5 g.), b. p. 60°/7 mm., n_D^{24} 1·4569; (ii) was benzoylated giving *N*-cyclohexylbenzamide (0·97 g.), m. p. and mixed m. p. 150°. The imino-ether was largely recovered after treatment for 24 hr. with cold dilute or concentrated hydrochloric acid.

(b) *Reduction.* The imino-ether (10 g.) in benzene (50 ml.) was added to a suspension of lithium aluminium hydride (2 g.) in ether (100 ml.). After the mixture was refluxed for 6 hr., acetone was added to destroy excess of the reagent. Water (25 ml.) was cautiously added and the mixture was filtered. 20% Aqueous sodium hydroxide (40 ml.) was added to the filtrate, and the ethereal layer was separated. Fractional distillation gave 4-cyclohexylaminobutanol (4·6 g.), b. p. 153°/9 mm., n_D^{21} 1·4830 (supercooled), m. p. 45—46° (from light petroleum) (lit.,[18] m. p. 45—46°) (Found: C, 70·5; H, 11·9; N, 7·8. Calc. for $C_{10}H_{21}ON$: C, 70·2; H, 12·3; N, 8·2%).

(c) *Reaction with phenylmagnesium bromide.* The imino-ether (5 g.) in benzene (50 ml.) was added to a solution of phenylmagnesium bromide [from bromobenzene (15 g.) and magnesium (2·4 g.)] in ether (100 ml.). The mixture was refluxed for 3 hr. and then was added to saturated aqueous ammonium chloride. Separation of the ethereal layer and subsequent distillation gave two fractions. Fraction (i) (2·6 g.), b. p. 130—140°/8 mm., n_D^{19} 1·5340, was separated by successive extraction with dilute hydrochloric acid and aqueous sodium hydroxide into (*a*) recovered starting material (1·3 g.), b. p. 133°/10 mm., n_D^{22} 1·4940; (*b*) phenol [phenyl benzoate (0·08 g.), m. p. and mixed m. p. 69°]; (*c*) biphenyl (0·3 g.), m. p. and mixed m. p. 65°. Fraction (ii) (0·4 g.) had b. p. 138°/0·1 mm., n_D^{20} 1·5525 (Found: C, 77·9; H, 8·9; N, 3·4. Calc. for $C_{16}H_{23}ON$: C, 78·4; H, 9·4; N, 5·7%).

(d) *Attempted isomerisation.* The imino-ether (3·4 g.) was refluxed (bath temp. 290°) for 2 hr. in a stream of nitrogen. Distillation gave recovered starting material (2·1 g.), b. p. 138°/12 mm., n_D^{15} 1·4931, and a glassy residue.

Reactions with γ-Bromo-N-cyclohexylbutyramide.—(a) *Ethanolysis.* (i) The amide (3·5 g.) in ethanol (10 ml.) was refluxed for 1 hr. and ether (250 ml.) was then added. The precipitate (1·2 g.) had m. p. 118—121°, alone or mixed with 2-cyclohexyliminotetrahydrofuran hydrobromide. Further addition of ether (250 ml.) gave cyclohexylammonium bromide (0·3 g.), m. p. and mixed m. p. 188—192°.

(ii) The previous experiment was repeated except that the mixture was heated for 24 hr. Addition of ether (500 ml.) precipitated cyclohexylammonium bromide (0·77 g.), m. p. and mixed m. p. 199—200°. Evaporation of the filtrate and distillation of the residue gave γ-butyrolactone (0·34 g.), b. p. 85°/10 mm., n_D^{25} 1·4389 (contaminated with ester). The residue (2·4 g.), m. p. 47—51°, in ether (300 ml.), was washed with water (20 ml.), 10% aqueous sodium

[16] Henry, *Compt. rend.*, 1886, **102**, 368.
[17] Marvel and Birkhimer, *J. Amer. Chem. Soc.*, 1929, **51**, 260.
[18] Barry and Twomey, *Proc. Roy. Irish Acad.*, 1952, **55***B*, No. 1.

carbonate (20 ml.), and water (20 ml.). Evaporation of the ethereal solution gave N-*cyclohexyl-γ-ethoxybutyramide* (2·1 g.), m. p. 62—64° raised to 68·5° (from light petroleum) alone or mixed with an authentic specimen (below) (Found: C, 67·7; H, 11·0. $C_{12}H_{23}ON$ requires C, 67·6; H, 10·8%).

(b) *Potassium hydroxide fusion.* The amide (5 g.) and powdered potassium hydroxide (15 g.) were heated at 100° for 3 min. Water (100 ml.) was added and the suspension was extracted with ether. Distillation of the extracts gave slightly impure 1-cyclohexylpyrrolid-2-one (1·2 g.), b. p. 154°/7 mm., n_D^{14} 1·5005 (lit.,[1] b. p. 154°/7 mm., n_D^{15} 1·5043), probably contaminated with the imino-ether.

Reactions with 2-Cyclohexyliminotetrahydrofuran Hydrobromide.—(a) *Ethanolysis.* The hydrobromide (3 g.) in ethanol (10 ml.) was refluxed for 24 hr. Treatment of the mixture as for the experiment with the amide gave cyclohexylammonium bromide (0·64 g.), m. p. and mixed m. p. 199—200°, γ-butyrolactone (0·4 g.), b. p. 85°/12 mm., n_D^{25} 1·4403 (contaminated with ester), and *N*-cyclohexyl-γ-ethoxybutyramide (1·85 g.), m. p. and mixed m. p. 64—65°.

(b) *Hydrolysis.* The hydrobromide (4 g.) was refluxed in water (12 ml.) for 16 hr. Working-up as for the hydrolysis of the imino-ether gave γ-butyrolactone (1·0 g.), b. p. 94°/15 mm., n_D^{25} 1·4335, and *N*-cyclohexylbenzamide (3·08 g., 94%), m. p. and mixed m. p. 150°.

N-*Cyclohexyl-γ-ethoxybutyramide.*—γ-Ethoxybutyric acid, obtained in low yield from γ-butyrolactone [19] had b. p. 127°/12 mm., n_D^{19} 1·4250 (lit.,[20] b. p. 116—117°/8 mm., n_D^{20} 1·4253). The acid chloride (from 1·7 g. of acid), in anhydrous ether (50 ml.), was treated with cyclohexylamine (4 g.) in ether (25 ml.). The mixture was washed with dilute hydrochloric acid; evaporation of the ethereal solution gave the amide (1·5 g.), m. p. 68·5° (Found: C, 67·9; H, 10·7; N, 6·5. $C_{12}H_{23}ON$ requires N, 6·6%).

Attempted Cyclisation of γ-Bromobutyranilide.—(*a*) The amide [1,11] was heated at 150° for 5 min. Extraction of the melt with anhydrous ether left anilinium bromide, m. p. and mixed m. p. 282°. Evaporation of the extracts gave recovered amide, m. p. and mixed m. p. 70—73°. Variations of time and temperature failed to give the cyclised product.

(*b*) The amide (5 g.) was refluxed for 3 hr. in ethanol (15 ml.). Addition of ether (250 ml.) gave anilinium bromide (3 g., 84%), m. p. and mixed m. p. 288—290°. Evaporation of the filtrates and subsequent distillation of the residue gave γ-butyrolactone (1·7 g., 100%), b. p. 85°/8 mm., n_D^{19} 1·4350. The same results were obtained after refluxing for 1 hr.

(*c*) The amide (7 g.) and triethylamine (3·1 g.) were refluxed in ethanol (25 ml.) for 1 hr. Dilution with ether precipitated triethylammonium bromide (4·85 g., 95%), m. p. 250°; subsequent distillation of the filtrates gave first a mixture of aniline and γ-butyrolactone (1·1 g.) and then 1-phenylpyrrolid-2-one (3·3 g.), b. p. 188°/14 mm., m. p. and mixed m. p. 66—68° (lit.,[21] m. p. 64—68°). Repetition of the experiment with benzylamine gave the pyrrolidone as the only high-boiling product.

2-*Butyliminotetrahydrofuran.*—γ-Bromo-*N*-butylbutyramide was obtained as a liquid by the method used for the cyclohexyl compound. Distillation was not attempted. The tetrahydroiminofuran hydrobromide could not be isolated from fusion of the amide, and varying yields of the imino-ether were obtained by aqueous extraction of the melts from runs at different temperatures and periods of heating. The best procedure was as follows: the amide (25 g.), in 5 g. portions, was kept at 125° for 1½ hr. The combined product, suspended in benzene, was extracted with water and the aqueous extracts were basified with 5% aqueous potassium hydroxide. Extraction with ether and subsequent distillation gave 2-*butyliminotetrahydrofuran* (2·4 g.), b. p. 92°/9 mm., n_D^{18} 1·4593 (Found: C, 68·2; H, 10·7; N, 10·0. $C_8H_{15}ON$ requires C, 68·1; H, 10·6; N, 10·0%). A crystalline methiodide could not be obtained.

Reactions with 2-Butyliminotetrahydrofuran.—(a) *Hydrolysis.* The imino-ether (0·9 g.), in 20% sulphuric acid (10 ml.), was kept at 100° for 24 hr. By the procedure described for the cyclohexyl compound, γ-butyrolactone (0·2 g.), b. p. 88°/10 mm., n_D^{23} 1·4340, was obtained, and *n*-butylamine was obtained as the *p*-nitrobenzoyl derivative (0·55 g., 78%), m. p. and mixed m. p. 100—101° (lit.,[22] m. p. 102·5—103°), *p*-nitrobenzoyl chloride being used instead of

[19] Fittig and Ström, *Annalen*, 1892, **267**, 186.
[20] Palomaa and Kenetti, *Ber.*, 1931, **64**, 797.
[21] Baillie and Tafel, *Ber.*, 1899, **32**, 68.
[22] Coleman and Howells, *J. Amer. Chem. Soc.*, 1923, **45**, 3084.

benzoyl chloride. No imino-ether was recovered, as it was from 20% sulphuric acid after 24 hr. at room temperature.

(b) *Reduction.* The procedure for the cyclohexyl compound was followed, using the imino-ether (2·9 g.) and lithium aluminium hydride (1 g.). Distillation of the product gave three fractions: (i) (0·4 g.), b. p. 60—80°/10 mm., which was not further investigated; (ii) 4-butylaminobutanol (1·1 g.), b. p. 132°/10 mm., n_D^{21} 1·4508 (Found: C, 66·2; H, 13·5; N, 9·1. Calc. for $C_8H_{19}ON$: C, 66·3; H, 13·1; N, 9·7%) (lit.,[23] b. p. 84—90°/1 mm.); (iii) (0·9 g.), b. p. 174°/10 mm., n_D^{25} 1·4699 (Found: C, 66·4; H, 11·6; N, 7·1%), which was not identified.

Attempted Cyclisation of N-Benzyl-γ-bromobutyramide.—The *amide*, prepared as described for the cyclohexyl compound, had m. p. 58° (from ether–light petroleum) (Found: C, 51·2; H, 5·2; N, 5·2. $C_{11}H_{14}ONBr$ requires C, 51·5; H, 5·5; N, 5·5%). No cyclised product was obtained by heating the amide for varying periods between 100° and 150°. Attempts to isolate the imino-ether directly as for the butyl analogue gave a basic product, but attempted distillation gave only glasses.

5-Bromo-N-cyclohexylpentanamide.—The *amide*, obtained from 5-bromopentanoyl chloride [24] and cyclohexylamine, had m. p. 80·5—81·5° (from ether–light petroleum) (Found: C, 50·7; H, 7·4; N, 5·1. $C_{11}H_{20}ONBr$ requires C, 50·4; H, 7·6; N, 5·4%).

2-Cyclohexyliminotetrahydropyran Hydrobromide.—Cyclisation of the amide was very much slower than that of the butyramide. In the best procedure the amide was kept at 100° for 1 hr., anhydrous ether was then added, and the precipitate was filtered off. The process was repeated after evaporation of the ethereal filtrates. Recrystallisation of the combined precipitates (7 g.) from twenty repetitions of the procedure with amide (12 g. in all) gave the *hydrobromide* as hygroscopic needles (from ethanol–ether), m. p. 101—102°. Solvent of crystallisation was removed by heating the salt *in vacuo* at 70°; the m. p. was then 108—109° (Found: C, 50·3; H, 7·6; N, 5·9. $C_{11}H_{20}ONBr$ requires C, 50·4; H, 7·6; N, 5·3%).

2-Cyclohexyliminotetrahydropyran.—The preceding hydrobromide (4·6 g.), in water (20 ml.), was added to saturated brine (100 ml.). Ether (200 ml.) was added, followed by 10% aqueous potassium hydroxide (20 ml.). The liberated base was quickly extracted and the ethereal extract was washed with saturated brine. Evaporation of the extracts and distillation of the residue gave cyclohexylamine (0·3 g.), b. p. 60°/15 mm., n_D^{25} 1·4585 (*N*-benzoyl derivative, m. p. and mixed m. p. 150°), and then the *imino-ether* (1·9 g.), b. p. 134°/8 mm., n_D^{21} 1·4980 (Found: C, 72·6; H, 10·5; N, 7·8. $C_{11}H_{19}ON$ requires C, 72·9; H, 10·5; N, 7·7%). After 3 weeks, the compound had changed to a viscous oil which could not be redistilled.

Reduction of 2-Cyclohexyliminotetrahydropyran.—The imino-ether (1·6 g.) and lithium aluminium hydride (0·5 g.) by the previous procedure gave 5-cyclohexylaminopentanol (0·89 g.), m. p. 74—75° (from ether) (lit.,[25] m. p. 79—80·5°) (Found: C, 71·7; H, 12·1; N, 7·6. Calc. for $C_{11}H_{23}ON$: C, 71·4; H, 12·4; N, 7·6%).

Ethanolysis of 5-Bromo-N-cyclohexylpentanamide.—The amide (2 g.), in ethanol (10 ml.), was refluxed for 3 hr. Dilution of the mixture with ether (500 ml.) and recrystallisation of the precipitate from ethanol–ether gave cyclohexylammonium bromide (0·7 g.), m. p. and mixed m. p. 192°. Evaporation of the filtrates and distillation of the residue gave δ-valerolactone (0·3 g.), b. p. 110°/12 mm., n_D^{25} 1·4573 (lit.,[26] b. p. 88°/4 mm., n_D^{20} 1·4568).

Hydrolysis of 2-Cyclohexyliminotetrahydropyran Hydrobromide.—The hydrobromide (0·6 g.), in 20% sulphuric acid (10 ml.), was kept at 100° for 16 hr. Saturation of the mixture with sodium chloride and extraction with ether gave δ-valerolactone (0·05 g.), b. p. 115°/13 mm., n_D^{22} 1·4550. Treatment of the aqueous extracts as for the furan analogue gave *N*-cyclohexylbenzamide (0·55 g., 98%), m. p. and mixed m. p. 148°.

Ethanolysis of 5-Bromopentananilide.—The anilide (3 g.) [from 5-bromopentanoyl chloride and aniline; it had m. p. 96—97° (lit.,[27] m. p. 98—99°)], in absolute ethanol (10 ml.), was refluxed for 3 hr. Addition of ether (500 ml.) precipitated anilinium bromide (1·27 g., 62%), m. p. and mixed m. p. 282°. Distillation of the filtrate gave δ-valerolactone (0·5 g.), b. p. 116°/15 mm., n_D^{23} 1·4555. After 24 hours' refluxing, the yield of anilinium bromide was 78%.

[23] Wilson and Tishler, *J. Amer. Chem. Soc.*, 1951, **73**, 3635.
[24] Merchant, Wickert, and Marvel, *J. Amer. Chem. Soc.*, 1927, **49**, 1828.
[25] Drake, Hayes, German, Johnson, Kelley, Melamed, and Peck, *J. Amer. Chem. Soc.*, 1949, **71**, 455.
[26] Linstead and Rydon, *J.*, 1933, 580.
[27] Normant and Voreux, *Compt. rend.*, 1950, **231**, 703.

2-Bromomethylbenzanilide.—*o*-Bromomethylbenzoyl bromide [28] (23 g.) was treated with aniline (17 g.) in ether (300 ml.). The mixture was filtered and the dry residue was repeatedly extracted with hot benzene. Addition of light petroleum to the benzene extracts gave the *anilide* (15 g.), m. p. about 83° (Found: C, 58·6; H, 4·4; N, 4·5. $C_{14}H_{12}ONBr$ requires C, 58·0; H, 4·1; N, 4·8%); the m. p. of a slowly heated sample was that of the cyclisation product (below).

1,3-Dihydro-1-phenyliminoisobenzofuran Hydrobromide.—The anilide fused at 130° and resolidified. The product, after unchanged material had been extracted with hot benzene, was crystallised to constant m. p. (164—165°) from ethanol–ether, but did not give satisfactory analyses. Satisfactory results were, however, obtained on a specimen of the same m. p. regenerated from the pure imino-ether (below) which was heated slowly from 20° to 110° *in vacuo* before analysis (Found: C, 58·1; H, 4·3; N, 4·5%).

1,3-Dihydro-1-phenyliminoisobenzofuran.—The hydrobromide (14 g.), in water (100 ml.) was basified with 10% aqueous sodium carbonate. Extraction with ether and evaporation of the extracts gave the *imino-ether* (10 g.), m. p. 99·5° with softening at 95° (from benzene–light petroleum) (Found: C, 80·9; H, 5·3; N, 6·5. $C_{14}H_{11}ON$ requires C, 80·5; H, 5·3; N, 6·7%). A crystalline methiodide could not be obtained.

Reactions with 1,3-Dihydro-1-phenyliminoisobenzofuran.—(a) *Hydrolysis.* A solution of the imino-ether (0·75 g.) in 20% aqueous sulphuric acid (12 ml.) was kept at 100° for 1½ hr. Extraction of the solution with benzene gave phthalide (0·40 g., 93%), m. p. and mixed m. p. 73—74°. The aqueous solution was basified and re-extracted with ether. Treatment of the extract as before with benzoyl chloride and pyridine gave benzanilide (0·65 g., 92%), m. p. and mixed m. p. 164—165°.

(b) *Isomerisation.* The imino-ether (1 g.) was kept at 300° for 2 hr. The cold melt was extracted with chloroform. Evaporation of the extracts and treatment of the residue with light petroleum gave *N*-phenylisoindolinone (0·7 g.), m. p. 166—167° after crystallisation from ethanol (Found: C, 80·5; H, 5·5; N, 6·4%) (lit.,[29] m. p. 160°).

(c) *Reduction.* The previous procedure with imino-ether (3·5 g.) and lithium aluminium hydride (1 g.) was followed. Distillation of the product gave *2-hydroxymethyl-N-phenylbenzylamine* (2·7 g.), b. p. 156°/0·03 mm., m. p. 59—60° (from ether–light petroleum) (Found: C, 79·0; H, 6·6; N, 6·6. $C_{14}H_{15}ON$ requires C, 79·0; H, 7·0; N, 6·6%). The hydroxy-amine (0·9 g.) was converted into the hydrochloride which was then refluxed with thionyl chloride (5 ml.) until evolution of gases ceased. The excess of thionyl chloride was removed, and the residue treated with hot 10% aqueous sodium carbonate. Extraction with ether gave *N*-phenylisoindoline (0·4 g.), m. p. 174—175° (from ethanol) (lit.,[30] m. p. 169—170°) (Found: 86·4; H, 6·8; N, 7·0. Calc. for $C_{14}H_{13}N$: C, 86·1; H, 6·7; N, 7·2%).

1-Benzylimino-1,3-dihydroisobenzofuran.—2-Bromomethylbenzoyl bromide (21 g.) was treated with benzylamine (18 g.) in ether (250 ml.). Dilute hydrochloric acid was added and the mixture was filtered. Evaporation of the filtrate and treatment of the residue with light petroleum gave a solid (5 g.), m. p. 64—67°, but attempted recrystallisation gave only cyclised product (below). The dry residue was kept at 100° for 10 min.; crystallisation from ethanol–ether then gave a salt (10·5 g.), m. p. 145—146°. Satisfactory analytical results for 1-benzylimino-1,3-dihydroisobenzofuran hydrobromide could not be obtained, probably owing to the retention of solvent of crystallisation. Heating the compound *in vacuo* was unsuccessful and satisfactory analytical figures could not be obtained on a specimen of the hydrobromide which was regenerated from the pure *imino-ether* (below). The salt (10 g.), in water (50 ml.), was basified with 10% aqueous sodium carbonate. Extraction with ether gave 1-benzylimino-1,3-dihydroisobenzofuran (7 g.), m. p. 37—38° (from light petroleum), n_D^{25} 1·6103 (supercooled) (Found: C, 80·8; H, 5·6; N, 6·4. $C_{15}H_{13}ON$ requires C, 80·7; H, 5·8; N, 6·3%). Treatment of the imino-ether with methyl iodide under reflux gave the *methiodide*, m. p. 143—144° (from ethanol–ether) (Found: C, 53·0; H, 4·6. $C_{16}H_{16}ONI$ requires C, 52·6; H, 4·4%).

Reactions with 1-Benzylimino-1,3-dihydroisobenzofuran.—(a) *Hydrolysis.* The imine (1·0 g.), in 20% aqueous sulphuric acid (15 ml.), was kept at 100° for 24 hr. Working up as for the phenyl analogue gave phthalide (0·53 g., 88%), m. p. and mixed m. p. 73°, and *N*-benzylbenzamide (0·92 g.; 97%), m. p. and mixed m. p. 104—105°.

(b) *Ethanolysis.* (i) The imino-ether (4 g.), in ether, was treated with hydrogen bromide.

[28] Davies and Perkin, *J.*, 1922, **121**, 2202.
[29] Rowe, Levin, Burns, Davies, and Tepper, *J.*, 1926, 690.
[30] Wittig, Closs, and Mindermann, *Annalen*, 1955, **594**, 89.

The precipitated hydrobromide (5 g.), in ethanol (10 ml.), was refluxed for 5 hr. Addition of ether (500 ml.) and crystallisation of the precipitate (2·76 g.) from ethanol–ether gave benzylammonium bromide (1·62 g.), m. p. and mixed m. p. 225°. The filtrates were washed with water and 10% aqueous sodium carbonate. Evaporation of the ethereal solution and distillation of the residue gave phthalide (1·13 g.), b. p. 164°/15 mm.; m. p. 73—74° (from benzene–light petroleum) alone or mixed with an authentic specimen. The residue (1·0 g.), m. p. 68—70°, crystallised from light petroleum to give *N-benzyl-2-ethoxymethylbenzamide* (0·5 g.), m. p. 86·5° (Found: C, 75·3; H, 7·1; N, 5·2. $C_{17}H_{19}O_2N$ requires C, 75·8; H, 7·1; N, 5·2%).

(ii) The previous experiment was repeated with hydrobromide (3·5 g.) and a refluxing period of 18 hr. Benzylammonium bromide (1·79 g., 83%), m. p. and mixed m. p. 226°, phthalide (0·93 g.), m. p. and mixed m. p. 70°, and *N*-benzyl-2-ethoxymethylbenzamide (0·2 g.), m. p. and mixed m. p. 82°, were obtained.

2-Benzylisoindolinone.—Phthalide (3 g.) and benzylamine (4 g.) were kept at 260° (sealed tube) for 3 hr. The product was dissolved in chloroform and the excess of amine was removed with dilute hydrochloric acid. Evaporation of the chloroform solution gave the *amide* (3·2 g.), m. p. 90° after crystallisation from ether (Found: C, 80·3; H, 6·0; N, 5·7. $C_{15}H_{13}ON$ requires C, 80·7; H, 5·8; N, 6·3%).

1-Cyclohexylimino-1,3-dihydroisobenzofuran.—2-Bromomethylbenzoyl bromide (10·5 g.) was treated with cyclohexylamine (7·2 g.) in ether (150 ml.). Dilute hydrochloric acid was added and the suspension was filtered. The residue was taken up in chloroform and evaporation of the solution gave a solid (9·6 g.), which could not be purified. Fusion and immediate resolidification of the compound occurred at 100°, and the product was recrystallised from ethanol–ether. On slow heating from 90° or below, it had m. p. 185—186° but melted on insertion at 130° or above. Correct analytical figures for 1-cyclohexylimino-1,3-dihydroisobenzofuran hydrobromide could not be obtained either on this specimen or on one regenerated from the pure *imino-ether* (below). The salt (12 g.), in water (50 ml.), was basified with 10% aqueous sodium carbonate. Extraction with ether gave 1-cyclohexylimino-1,3-dihydroisobenzofuran (4 g.), m. p. 79—80° (from light petroleum) (Found: C, 78·6; H, 7·7; N, 6·4. $C_{14}H_{17}ON$ requires C, 78·2; H, 7·9; N, 6·5%). Treatment with methyl iodide as before gave the *methiodide*, m. p. 202° (from ethanol) (Found: C, 50·6; H, 5·8; N, 3·6. $C_{15}H_{20}ONI$ requires C, 50·5; H, 5·6; N, 3·9%). Hydrolysis of the imino-ether with 20% aqueous sulphuric acid, as for the benzyl analogue, gave phthalide (92%), m. p. and mixed m. p. 73—74°, and *N*-cyclohexylbenzamide (87%), m. p. and mixed m. p. 150°.

2-Cyclohexylisoindolinone.—Phthalide (10 g.) and cyclohexylamine (10 g.) were kept (sealed tube) at 310° for 4 hr. Working up as for the benzyl analogue gave the *amide* (12 g.), m. p. 112—113° (from ethanol) (Found: C, 78·3; H, 8·0; N, 6·2. $C_{14}H_{17}ON$ requires C, 78·0; H, 7·9; N, 6·5%).

TABLE 1. *Light absorption of dihydroiminoisobenzofurans and isoindolinones.*

($\lambda_{max.}$ *in* mμ; $10^{-2}\varepsilon$ *in parentheses*).

(IX; R = Ph)	240 (139)	293 (106)	(IX; R = C_6H_{11})	242 (140)	284 (53)
(XIII; R = Ph)	228 (136)	282 (133)	(XIII; R = C_6H_{11})	229 (115)	278 (19)
(IX; R = CH_2Ph)	242 (154)	284 (55)			
(XIII; R = CH_2Ph)	230 (132)	279 (17)			

The author is grateful to Professor E. L. Hirst, F.R.S., for his interest and encouragement and the University of Edinburgh is thanked for the award of an I.C.I. Fellowship.

DEPARTMENT OF CHEMISTRY, UNIVERSITY OF EDINBURGH.
(Present address: DEPARTMENT OF CHEMISTRY,
THE QUEEN'S UNIVERSITY OF BELFAST.)

[*Received, July 2nd,* 1959.]