28. *Photochemical Transformations. Part XVI.* A Novel Synthesis of Lactones.*

By D. H. R. Barton, A. L. J. Beckwith, and A. Goosen.

The photolysis of *N*-iodoamides has been shown to provide a general route to γ-lactones. The mechanism and stereochemical aspects of the reaction have been investigated. A general reagent for the preparation of *N*-iodoamides has been found in t-butyl hypochlorite–iodine. Lactonisation is most conveniently effected by photolysis of the amide in presence of excess of iodinating agent (t-butyl hypochlorite or lead tetra-acetate with iodine).

The synthesis of saturated lactones from *saturated* acids by oxidative procedures has not hitherto been accomplished in high yield or by a general method.[1] In contrast the oxidative cyclisation of aromatic acids has been well attested.[2] In connection with the interrelationship of sesquiterpenoid lactones [3] there was need for a general method for converting saturated acids into γ-lactones. The present Paper reports the solution of this problem. A preliminary communication has already appeared.[4]

Our first approach to the problem was to attempt the generation of acyloxy-radicals by photochemical methods. Since the photolysis of alkyl hypohalites,[5] especially hypoiodites,[6] is a convenient and efficient procedure for inducing intramolecular attack of derived alkoxy-radicals on non-activated hydrogen, we studied the photolysis of acyl hypoiodites. However, in this system, decarboxylation is so rapid that there is little if any indication of the formation of γ-iodo-acids or of γ-lactones. In fact, the photolysis of acyl hypoiodites provides a good method for decarboxylation.[7]

We next turned to a general proposition which is summarised as (I) ⟶ (II) ⟶ (III) ⟶ (V) ⟶ (IV) ⟶ (VII) ⟶ (VIII) with possible competition from the process (IV) ⟶ (VI). Reduction to practice involves the selection of X such that the radical ·CO·X·

* Part XV, *J.*, 1964, 2518.

[1] Cf. Clutterbuck, Raistrick, and Rintoul, *Phil. Trans.*, 1931, **220***B*, 301; Kenyon and Symons, *J.*, 1953, 3580; Bonnett, Cannon, Clark, Johnson, Parker, Smith, and Todd, *J.*, 1957, 1158; Cason, Tars, and Weiss, *Tetrahedron*, 1962, **18**, 437; Wiberg and Fox, *J. Amer. Chem. Soc.*, 1963, **85**, 3487.

[2] Kenner, Murray, and Tylor, *Tetrahedron*, 1957, **1**, 259.

[3] Cf. Barton, Pinhey, and Wells, *J.*, 1964, 2518.

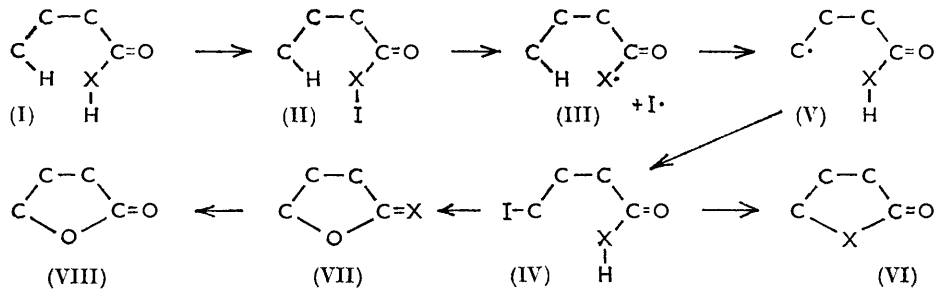
[4] Barton and Beckwith, *Proc. Chem. Soc.*, 1963, 335.

[5] Akhtar and Barton, *J. Amer. Chem. Soc.*, 1964, **86**, 1528, and references there cited.

[6] Meystre, Heusler, Kalvoda, Wieland, Anner, and Wettstein, *Experientia*, 1961, **17**, 475; *Helv. Chim. Acta*, 1962, **45**, 1317; Heusler, Kalvoda, Meystre, Anner, and Wettstein, *ibid.*, 1962, **45**, 2161; Heusler, Kalvoda, Wieland, Anner, and Wettstein, *ibid.*, p. 2575.

[7] Barton and Serebryakov, *Proc. Chem. Soc.*, 1962, 309; Barton, Faro, Serebryakov, and Woolsey, unpublished observations.

will abstract hydrogen intramolecularly as indicated. We have shown that the amide function (X = NH) satisfies these requirements.



For the generation of iodoamides *in situ* we first investigated the use of the lead tetra-acetate–iodine reagent which works well for alcohols [6] and for carboxylic acids.[7] Irradiation of 3β-acetoxy-11-oxo-5α-pregnane-20-carboxamide (IX; R = Ac, R′ = NH_2) with this reagent afforded, after alkaline hydrolysis and reacetylation of the crude lactonic product, the known [8] lactone (X) in about 55% yield. Similar oxidation of toluamide gave phthalide. Stearamide in the same way gave γ-stearolactone as well as, in minor amount, δ-stearolactone. The constitution of the latter was established by hydrolysis to the known [9] 5-hydroxystearic acid. Treatment of δ-stearolactone with benzylamine furnished *N*-benzyl-5-hydroxystearamide.

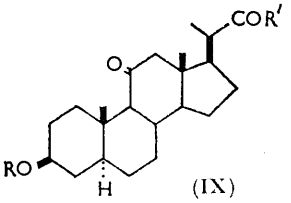
The properties of the *N*-iodoamides (II) postulated as intermediates in these reactions were next examined. With lead tetra-acetate–iodine benzamide gave *N*-iodobenzamide. This combination has, however, disadvantages as a general reagent for iodoamides, a group of compounds which has been little investigated.[10] We found that the t-butyl hypochlorite–iodine mixture [5] is an excellent reagent for the preparation of *N*-iodo-derivatives of benzamide, succinimide, n-butyramide, n-hexanamide, and n-octadecanamide all of which were obtained crystalline. The *N*-iodo-derivative of n-octadecanamide was isolated in two forms. These may be different crystal forms, but it is also possible that, since the " less stable " form appeared not to be converted into the " more stable " one simply by seeding, that they may be geometrical isomers of types [(XII) and (XIII; R = $C_{17}H_{35}$)], an isomerism in amide derivatives not hitherto detected. The phenomenon deserves further study. Benzanilide gave *N*-*p*-iodophenylbenzamide and acetanilide gave *p*-iodoacetanilide with the t-butyl hypochlorite–iodine reagent. In comparative experiments it was found that t-butyl hypochlorite in the presence of a catalytic amount of bromine was also an effective *N*-chlorinating agent for amides. Similar results have been obtained previously in polar solvents without catalysis by bromine.[11] Anilides gave the corresponding *p*-chloro-derivatives with this reagent.

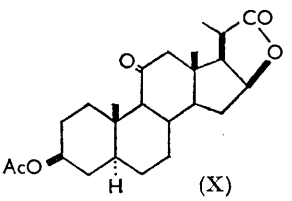
t-Butyl hypochlorite–iodine converted amides into lactones on photolysis in the same way as lead tetra-acetate–iodine. It has been suggested [5] that t-butyl hypochlorite and iodine interact to give t-butyl hypoiodite and iodine chloride. It is the t-butyl hypoiodite that should be the active iodinating agent for amides. In agreement, iodine chloride does not iodinate amides or convert the typical amide (IX; R = Ac, R′ = NH_2) into the lactone (X) under the usual photolytic conditions. On the other hand, t-butyl hypoiodite,[5] prepared from potassium t-butoxide and excess of iodine, gave the " stable " *N*-iodo-derivative with *n*-octadecanamide and converted the parent amide itself on photolysis

[8] Cameron, Evans, Hamlet, Hunt, Jones, and Long, *J.*, 1955, 2807.
[9] Bergstrom, Aulin-Erdtman, Rolander, Stenhagen, and Ostling, *Acta Chem. Scand.*, 1952, **6**, 1157.
[10] See Djerassi and Lenk, *J. Amer. Chem. Soc.*, 1953, **75**, 3493; Arsem, U.S.P. 2,472,361/1949.
[11] Zimmer and Audrieth, *J. Amer. Chem. Soc.*, 1954, **76**, 3856; Chalsty and Israelstam, *Chem. and Ind.*, 1954, 1452; Israelstam, *J.S. African Chem. Inst.*, 1956, **9**, 30.

under the usual conditions into a mixture of γ- and δ-stearolactones comparable with that obtained in earlier experiments.

We now turn to a more detailed consideration of the mechanism of the γ-lactonisation


(IX)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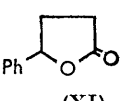
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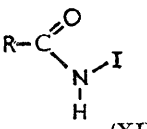
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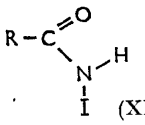
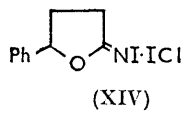
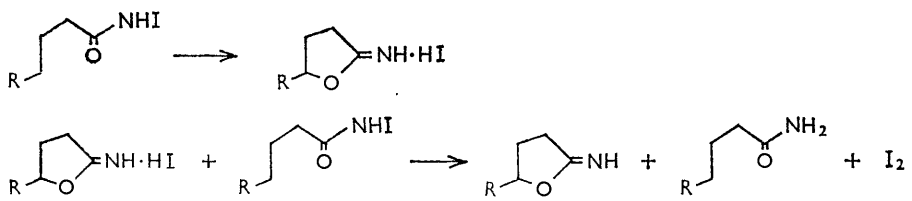

(XIII)


(XIV)

reaction. Photolysis of amides with t-butyl hypochlorite–iodine, or comparable irradiation of *N*-iodoamides themselves, gave solutions which showed no γ-lactone band in the infrared spectrum. A strong band at about 1680 cm.$^{-1}$ was, however, present which could be interpreted as due to amide or to the (C=N) band of an iminolactone. Washing of the solutions with aqueous sodium hydrogen sulphite caused the expected γ-lactone band to appear. This behaviour is consistent with the presence of either a γ-iodoamide (IV; X = NH), which cyclises very easily, or of an iminolactone (VII; X = NH), which hydrolyses with water. γ-Iodoamides appear to be hardly known, so as a model compound γ-iodobutyramide was prepared by iodide-ion displacement on γ-chlorobutyramide. The γ-iodobutyramide cyclised spontaneously at room temperature in a humid atmosphere to give γ-lactone (infrared spectrum).

In order to determine if the γ-iodoamide or the iminolactone were present at the end of the photolysis and before hydrolysis the photolysis of the " stable " *N*-iodo-octadecanamide was studied quantitatively. As the reaction proceeded iodine was liberated. *All* the iodine originally present as *N*-iodo was found as molecular iodine at the end of the reaction. This was shown by conventional titration or, more convincingly, by running the reaction in an ultraviolet–visible spectrometer and determining iodine as it appeared by its absorption band at 490 mμ. This result suggests the sequence

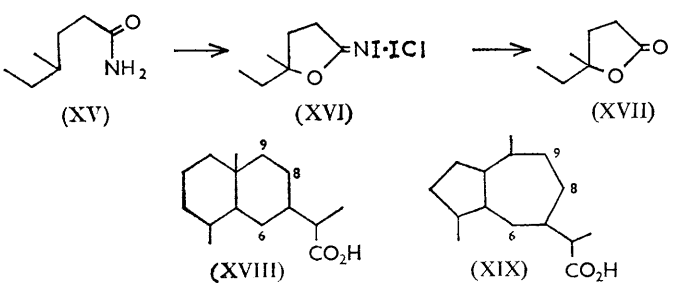


In agreement the yield of γ-lactone from the photolysis of an *N*-iodoamide was always less than 50%. Yields in excess of 50% were only obtained with excess of oxidant. A further study of the photolysis of the " stable " *N*-iodo-octadecanamide, following the appearance of iodine and interrupting the course of the photolysis in ultraviolet light by periods of darkness, gave interesting results. During an initial period of darkness there was no appearance of iodine. Irradiation caused a rapid development of iodine. During a further period of darkness about 10% of the iodine liberated during the light period was produced. Further periods of light and darkness produced the same effects. We consider that γ-iodoamide (IV; X = NH) is produced on photolysis and that this is spontaneously converted into iminolactone (VII; X = NH). The rate of this latter reaction is, however, somewhat slower than the rate of production of γ-iodoamide so that a residual rate of cyclisation remains evident during the periods of darkness.

In a further experiment the " stable " *N*-iodo-octadecanamide was photolysed and the product divided into two portions. One was processed in the normal way, the other was treated with zinc dust and acetic acid under mild conditions before applying the normal hydrolytic procedure. Both portions gave the same yield of lactone. Since γ-iodobutyramide was smoothly reduced to butyramide under these reduction conditions, the experiment suggests, but does not prove, that the γ-iodo-octadecanamide was cyclised to iminolactone during the course of the photolysis.

The isolation of a derivative of the postulated iminolactone (VII; X = NH) was finally achieved during the photolysis of γ-phenylbutyramide in the presence of an excess of t-butyl hypochlorite and iodine. A nicely crystalline and sparingly soluble yellow compound was formed in good yield during the photolysis. We regard it as the iodine chloride complex (XIV) of *N*-iodo-γ-phenylbutyroiminolactone on the basis of the following evidence. Treatment with aqueous sodium hydrogen sulphite followed by mild acid hydrolysis gave γ-phenylbutyrolactone (XI) in good yield. With pyridine the complex afforded the pyridine–iodine chloride complex. With triethylamine in tetrahydrofuran a precipitate of the amine hydrochloride and amine hydroiodide was produced. Analysis revealed two atoms of iodine and one of chlorine the oxidizing part of the complex being two equivalents. The infrared spectrum showed a band at 38·5 μ (260 cm.$^{-1}$) corresponding to an (I–Cl) frequency (cf. pyridine–iodine chloride which absorbs at 268 cm.$^{-1}$). The nuclear magnetic resonance spectrum in dimethyl sulphoxide showed the benzylic proton at τ 4·2 split into a complex multiplet. The benzylic proton of γ-hydroxy-γ-phenylbutyramide in deuterochloroform at τ 5·3 is split, in contrast, into a well-defined triplet. The evidence favours, therefore, a ring structure in the complex rather than a γ-iodo- or γ-chloro-type of formulation. Finally, shaking with an excess of active Raney nickel gave γ-phenylbutyramide.

If the lactonisation reaction of amides proceeds in the sense (X = NH): (I) ⟶ (II) ⟶ (III) ⟶ (V) ⟶ (IV), etc., then, if the γ-position be asymmetric this asymmetry should be lost in passing through radical (V) and a racemic product should result. This was confirmed in the following way. (+)-Citronellol was transformed into (+)-4-methylhexan-1-ol [12] and thence into (+)-4-methylhexanamide (XV). Photolysis of this amide in the presence of t-butyl hypochlorite and iodine gave in high yield a crystalline iodine chloride complex (XVI) analogous to that from γ-phenylbutyramide. On hydrolysis this afforded racemic 4-methyl-4-hexanolactone (XVII). An insertion type of mechanism is thus excluded.



(XV) (XVI) (XVII)

(XVIII) (XIX)

We have also studied in outline several variants of X in the scheme (I) ⟶ (II), etc. (see above). For this purpose several derivatives of the acid (IX; R = Ac, R′ = OH) were prepared, including the *N*-methylamide, the *N*-phenylamide, the *N*-methoxyamide, and the *N*-methylhydroxamic acid. Repeated attempts at oxidation of the *N*-methylamide (IX, R = Ac, R′ = NHMe) with lead tetra-acetate and iodine under irradiation gave no lactone. The same results were obtained in preliminary experiments with the *N*-methoxyamide (IX; R = Ac, R′ = NH·OMe) and the *N*-methylhydroxamic acid (IX; R = Ac,

[12] Cason, Brewer, and Pepper, *J. Org. Chem.*, 1948, **13**, 239.

R′ = N·MeOH). The *N*-phenylamide (IX; R = Ac, R′ = NHPh), on the other hand, afforded a moderate yield of lactone (X).

The yields in the lactonisations reported in this Paper parallel to the strengths of the (C–H) bonds that are broken in the hydrogen abstraction step (III) ⟶ (V) (X = NH). Thus the abstraction of benzylic hydrogen (γ-phenylbutyramide) and of tertiary hydrogen [the amide (XV)] gives high yields. The abstraction of secondary hydrogen [octadecanamide; the amide (IX; R = Ac, R′ = NH_2)] affords satisfactory yields. The abstraction of primary hydrogen, however, (as in *n*-butyramide) gave a very poor yield. The same relative yields are observed in nitrite photolysis.[13] Further applications of the lactonisation reaction will be reported in due course.

Although the lactonisation reaction described in this Paper is obviously not directly involved in biogenetic processes, it is of interest that in sesquiterpenoid lactones of types based on (XVIII) or (XIX) hydroxylation is observed at C-6 and/or C-8,[14] but *not* at C-9. This suggests that acids of types (XVIII) and (XIX) may be formed first in biogenesis and that oxidative processes, conceivably based on the amides, are then employed to insert oxygen at C-6 and/or C-8. The carbonyl function would thus be assigned a direct role in selecting the (γ) positions for subsequent hydroxylation.

Experimental

Melting points were determined on the Kofler hot-stage apparatus unless otherwise specified. Infrared spectra were taken on the Unicam S.P. 200. t-Butyl hypochlorite [15] was stored over calcium chloride at 0° in the dark. Lead tetra-acetate was a commercial sample dried *in vacuo* and stored in a desiccator over phosphorus pentoxide and potassium hydroxide pellets. AnalaR chloroform was filtered through alumina (Grade V) to remove ethanol and stored over calcium chloride. Methylene dichloride and carbon tetrachloride were dried over calcium chloride; benzene and ether were dried over sodium wire. Irradiations were carried out under dry oxygen-free nitrogen with a 150w tungsten lamp or a 125w high-pressure mercury-arc lamp. For irradiations in the cold the Pyrex flask was partially immersed in circulating cold water in a large Pyrex Petri dish the lamp being placed underneath the dish. Light petroleum was of b. p. 40—60°.

Preparation of N-*Chloroamides and of Chloroanilides.*—The following preparation of *N*-chlorobenzamide is illustrative. Benzamide (1·2 g.), suspended in methylene dichloride (20 ml.) containing t-butyl hypochlorite (1·3 g.), was treated with bromine (2 drops) and left at ambient temperature for 10 min. Removal of the solvent *in vacuo* and crystallisation from methylene dichloride–light petroleum gave *N*-chlorobenzamide (1·3 g.).[16]

Similarly, octadecanamide (1·4 g.) gave N-*chloro-octadecanamide* which crystallised from methanol in plates (1·3 g.), m. p. 83°, $\nu_{max.}$ (Nujol) 3240 and 1660 $cm.^{-1}$ (Found: Cl, 11·6. $C_{18}H_{36}ClNO$ requires Cl, 11·15%). *N*-Methyloctadecanamide (1·0 g.) gave N-*chloro*-N-*methyl-octadecanamide*. Recrystallised from methanol this (970 mg.) had m. p. 65°, $\nu_{max.}$ (in $CHCl_3$) 1660 $cm.^{-1}$ [Found: Cl, 10·5, 10·6 (iodimetry). $C_{19}H_{38}ClNO$ requires Cl, 10·7%].

Similarly benzanilide (2·0 g.) gave *N*-*p*-chlorophenylbenzamide [17] (1·7 g.), acetanilide (1·4 g.) gave *p*-chloroacetanilide (1·1 g.), and octadecanilide (750 mg.) gave *p*-chloro-octadecanilide [18] (650 mg.).

Preparation of N-*Iodoamides and of Iodoanilides.*—The following preparation of *N*-iodobenzamide is illustrative. Benzamide (1·2 g.), suspended in carbon tetrachloride (20 ml.) containing iodine (3·0 g.), was stirred at room temperature (no illumination) with addition of t-butyl hypochlorite (1·3 g.) added dropwise (5 min.) and then for a further 30 min. The precipitate was filtered off and washed with carbon tetrachloride to give N-*iodobenzamide* (1·9 g.), m. p. 120°.

[13] Cf. Kabasakalian, Townley, and Yudis, *J. Amer. Chem. Soc.*, 1962, **84**, 2718; and other Papers in this series.
[14] See, for example, Romo, Joseph-Nathan, and Diaz, *Tetrahedron*, 1964, **20**, 79, and references there cited.
[15] Teeter and Bell, *Org. Synth.*, 1952, **32**, 20.
[16] Elliot, *J.*, 1922, **121**, 202.
[17] Edwards, *J.*, 1956, 222.
[18] King and Orton, *J.*, 1911, **99**, 1377.

Recrystallised from acetone–light petroleum this formed pale yellow needles, m. p. 123—124° (decomp.), $\nu_{max.}$ (Nujol) 3240 and 1600 cm.$^{-1}$ (Found: C, 34·2; H, 2·3; I, 50·9; N, 5·4. C_7H_6INO requires 34·1; H, 2·45; I, 51·35; N, 5·7%).

N-Iodobenzamide was also prepared in the following way. Benzamide (1·2 g.) and lead tetra-acetate (2·2 g.) suspended in chloroform (20 ml.) were stirred under nitrogen at room temperature with powdered iodine at such a rate as to maintain the iodine colour. After 1 hr. (1·2 g. of iodine added) the precipitate of *N*-iodobenzamide was filtered off and washed with chloroform to give as residue the *N*-iodoamide (1·3 g.).

Similarly, by using t-butyl hypochlorite, succinimide (1·1 g.) gave *N*-iodosuccinimide [19] (2·35 g.) and hexanamide (1·1 g.) gave N-*iodohexanamide* (2·1 g.). Recrystallised from methylene dichloride–light petroleum this formed rods, m. p. 97°; $\nu_{max.}$ (Nujol) 3300, 1600, and 1570 cm.$^{-1}$ [Found: I, 52·6 (iodometric). $C_6H_{12}INO$ requires I, 52·6%]. Similarly, n-butyramide gave N-*iodobutyramide*. Recrystallised from chloroform–light petroleum (b. p. 60—80°) this had m. p. 95—98° (decomp.) [Found: I, 59·2 (iodometric). C_4H_8INO requires I, 59·6%].

In view of the unexpected results with octadecanamide the experimental is given in more detail. t-Butyl hypochlorite (1·35 g.) and iodine (3·0 g.) in methylene dichloride (30 ml.) were stirred at room temperature for 10 min. (pale brown colour). Addition of octadecanamide (2·8 g.) caused a colour change (yellow) and precipitation. Filtration after 10 min. and washing with light petroleum gave N-*iodo-octadecanamide* (isomer A) (94%) m. p. *ca.* 114° (decomp.). Crystallised quickly from chloroform–light petroleum this formed minute plates, m. p. 114—115° (decomp.), $\nu_{max.}$ (Nujol) 3270 and 1640 cm.$^{-1}$ [Found: I, 31·2, 30·8 (iodometric). $C_{18}H_{36}INO$ requires I, 31·0%]. The same product was obtained when this procedure was repeated at 0° with benzene as solvent.

In an alternative procedure t-butyl hypochlorite (1·35 g.) was added to a stirred suspension of octadecanamide (2·8 g.) and iodine (3·0 g.) in methylene dichloride (30 ml.) at room temperature. The mixture became warm, the colour changed to pale brown and a precipitate formed. After 10 min. the suspension was diluted with light petroleum and filtered to give N-*iodo-octadecanamide* (isomer B) (74%), m. p. *ca.* 120°. This crystallised from acetone as rods, m. p. 120—122° (decomp.); $\nu_{max.}$ (Nujol) 3280, 1565, 1600, and 1635 cm.$^{-1}$ [Found: I, 31·0, 31·3% (iodometric)]. The mixed m. p. of isomer A with isomer B was *ca.* 114—118°.

The same isomer B was obtained when isomer A was crystallised from ethyl acetate or from acetone or when the t-butyl hypochlorite–iodine reagent was stirred with octadecanamide in benzene for 5 hr. Treatment of isomer B (100 mg.) in chloroform (7 ml.) with tetramethylammonium iodide (200 mg.) gave iodine immediately.

t-Butyl hypochlorite (0·72 g.) was added to a stirred suspension of benzanilide (1·0 g.) and iodine (1·5 g.) in benzene (20 ml.). After 15 min. the mixture was diluted with light petroleum (40 ml.) and filtered. Crystallisation from chloroform–ethanol gave *N*-*p*-iodophenylbenzamide [20] (1·3 g.). Similarly acetanilide (1·4 g.) gave *p*-iodoacetanilide [20] (2·2 g.) and octadecanilide (0·75 g.) gave p-*iodo-octadecanilide* (1·0 g.). This crystallised from benzene or ethanol as laths, m. p. 132—133° (Found: I, 26·3. $C_{24}H_{40}INO$ requires I, 26·15%).

γ-Iodobutyramide.—γ-Chlorobutyramide (310 mg.) and sodium iodide (2·0 g.) in acetone (12 ml.) were refluxed for 12 hr. Filtration, removal of the solvent *in vacuo* and crystallisation from benzene gave *γ-iodobutyramide* (237 mg.), m. p. 70—73° (Found: C, 23·0; H, 4·0. C_4H_8INO requires C, 22·55; H, 3·8). During 3 days at room temperature the crystals turned into a dark brown oil which showed strong γ-lactone absorption (1760 cm.$^{-1}$). When γ-iodobutyramide (50 mg.) in benzene (10 ml.) and methanol (10 ml.) was shaken with 10% palladised calcium carbonate (35 mg.) under hydrogen there was no uptake of gas. The product showed only γ-lactone absorption.

γ-Iodobutyramide (160 mg.) in glacial acetic acid (5 ml.) and benzene (5 ml.) was shaken with zinc dust (1·2 g.) for 48 hr. Filtration, removal of the solvent *in vacuo*, hydrolysis with 2N-sodium hydroxide on the steam-bath for 2 hr., and extraction with ether gave a negligible neutral fraction. Acidification with 2N-aqueous sulphuric acid, heating on a steam-bath for 2 hr. (to complete lactonisation), and continuous extraction with ether for 48 hr. gave no indication of γ-butyrolactone either in the infrared spectrum or in g.l.c. A repetition of this experiment omitting zinc dust gave γ-butyrolactone in good yield.

[19] Djerassi and Lenk, *loc. cit.*, see ref. 10.
[20] Chattaway and Constable, *J.*, 1914, **105**, 124.

Derivatives of 3β-*Acetoxy*-11-*oxo*-5α-*pregnane*-20-*carboxylic Acid*.—The acid chloride (prepared from the acid [21] with excess of oxalyl chloride) (1·7 g.) in benzene (10 ml.) was shaken vigorously with concentrated aqueous ammonia (2 ml.) in water (8 ml.) for 5 min. Cyclcohexane (10 ml.) was added and the shaking continued for a further 5 min. Crystallisation of the insoluble amide from methylene dichloride–methanol gave 3β-*acetoxy*-11-*oxo*-5α-*pregnane*-20-*carboxyamide* (IX; R = Ac, R′ = NH_2) (1·4 g.) as rods or plates, m. p. 293—295° (evac. tube), $[\alpha]_D$ +31° (*c* 1·41 in 1 : 1 EtOH–$CHCl_3$); $\nu_{max.}$ (in $CHCl_3$) 3550, 3450, 1720, 1700, 1680, and 1595 cm.$^{-1}$ (Found: C, 71·3; H, 9·3; N, 3·2. $C_{24}H_{32}NO_4$ requires C, 71·4; H, 9·2; N, 3·5%). The amide was also obtained by passing anhydrous ammonia over the acid chloride in benzene (94%). This amide (100 mg.) in dioxan (5 ml.) and methanol (5 ml.) was refluxed with potassium hydroxide (33 mg.) for 10 min. Crystallisation of the product from chloroform–benzene gave 3β-*hydroxy*-1-*oxo*-5α-*pregnane*-20-*carboxyamide* (72 mg.) as needles, m. p. 273°, $[\alpha]_D$ +49° (*c* 0·99 in 1 : 1 EtOH–$CHCl_3$) (Found: C, 73·3; H, 9·7; N, 4·05. $C_{22}H_{35}NO_3$ requires C, 73·1; H, 9·8; N, 3·9%).

Similarly the acid chloride (2·0 g.) in benzene (10 ml.) was shaken vigorously with methylamine hydrochloride (2·0 g.) and sodium hydrogen carbonate (1·4 g.) in water (15 ml.). After 5 min. light petroleum (10 ml.) was added and the shaking continued for a further 5 min. Crystallisation of the precipitate from chloroform–methanol gave 3β-*acetoxy*-N-*methyl*-11-*oxo*-5α-*pregnane*-20-*carboxyamide* (IX; R = Ac, R′ = NH_2) (1·9 g.) as prisms, m. p. 308—309° (evac. tube), $[\alpha]_D$ +37° (*c* 1·13 in 1 : 1 $CHCl_3$–EtOH); $\nu_{max.}$ (in $CHCl_3$) 3500, 1720, 1705, and 1665 cm.$^{-1}$ (Found: C, 71·7; H, 9·3; N, 3·4. $C_{25}H_{39}NO_4$ requires C, 71·9; H, 9·4; N, 3·4%).

Similarly the acid chloride (1·50 g.) with methoxyammonium chloride (500 mg.) and sodium hydrogen carbonate (500 mg.) gave 3β-*acetoxy*-N-*methoxy*-11-*oxo*-5α-*pregnane*-20-*carboxyamide* (I; R = Ac, R′ = NHOMe). Recrystallised from methylene dichloride–ethanol this formed plates (1·03 g.), m. p. 258—259°, $[\alpha]_D$ +35° (*c* 1·20), $\nu_{max.}$ (Nujol) 3460, 1710, and 1700 cm.$^{-1}$ (Found: C, 69·2; H, 8·9; N, 3·25. $C_{25}H_{39}NO_5$ requires C, 69·25; H, 9·1; N, 3·2%).

Similarly the acid chloride (2·4 g.) in benzene (10 ml.) and dry ether (10 ml.) was treated with aniline (2·0 ml.) at room temperature for 30 min. Crystallisation of the product from aqueous methanol gave 3β-*acetoxy*-11-*oxo*-N-*phenyl*-5α-*pregnane*-20-*carboxyamide* (IX; R = Ac, R′ = NHPh) (2·6 g.) as rods, m. p. 245—246°, $[\alpha]_D$ +39° (*c* 1·12); $\nu_{max.}$ (in $CHCl_3$) 3480, 1720, 1700, 1690, and 1600 cm.$^{-1}$ (Found: N, 3·1. $C_{30}H_{41}NO_4$ requires N, 2·9%).

Similarly the acid chloride (500 mg.) in benzene (5 ml.) with *N*-methylhydroxyammonium chloride (500 mg.) and sodium hydrogen carbonate gave 3β-*acetoxy*-N-*methyl*-11-*oxo*-5α-*pregnane*-20-*carboxyhydroxamic acid*. Crystallised from methanol–benzene this formed plates (380 mg.), m. p. 226°, $[\alpha]_D$ +50° (*c* 1·05); $\nu_{max.}$ (in $CHCl_3$) 3300, 1720, 1700, and 1620 cm.$^{-1}$ (Found: C, 69·3; H, 9·0; N, 3·4. $C_{25}H_{39}NO_5$ requires C, 69·25; H, 9·1; N, 3·2%).

Similarly the acid chloride (800 mg.) in ether (10 ml.) and benzene (5 ml.) containing pyridine (0·25 ml.) was treated at −30° with *m*-chloroperoxybenzoic acid (470 mg.) in ether (10 ml.) and left at ambient temperature for 15 min. After addition of cold aqueous potassium carbonate solution the organic phase was separated and washed with 2N-aqueous sulphuric acid and then with water. Removal of the solvent *in vacuo* and crystallisation from chloroform–light petroleum gave m-*chlorobenzoyl* 3β-*acetoxy*-11-*oxo*-5α-*pregnane*-20-*carbonyl peroxide* (900 mg.) as rods, m. p. 163°, $[\alpha]_D$ +34° (*c* 1·16); $\nu_{max.}$ (in $CHCl_3$) 1800, 1740, 1720, and 1705 cm.$^{-1}$ (Found: C, 66·6; H, 7·2; O, 20·4. $C_{31}H_{39}ClO_7$ requires C, 66·6; H, 7·0; O, 20·0%).

Lactonisation of n-*Butyramide*.—Butyramide (1·3 g.) and iodine (10·5 g.) in benzene (40 ml.) containing t-butyl hypochlorite (3·3 ml.) were irradiated with a mercury arc lamp at <30° for 7 hr. At the end of the first three successive hours further t-butyl hypochlorite (3 × 1·0 ml.) was added. After irradiation the solution was divided into two portions (A, 27 ml., and B, 18 ml.). Solution A was washed with saturated aqueous sodium hydrogen sulphite (60 ml.), the solvent removed *in vacuo*, and the residue hydrolysed with 4N-aqueous sodium hydroxide (30 ml.) on the steam-bath for 2 hr. The solution was extracted with ether, then acidified (2N-aqueous sulphuric acid), and heated on the steam-bath for 2 hr. Continuous extraction with ether for 48 hr. gave a product (737 mg.) shown to contain γ-butyrolactone (0·3%) by quantitative g.l.c. Solution B was concentrated *in vacuo* and then treated with zinc dust (10 g.) and glacial acetic acid (20 ml.) at room temperature for 2 hr. Processing as above gave γ-butyrolactone in essentially the same yield.

[21] Chamberlain, Ruyle, A. E. Erickson, Chemerda, Aliminosa, R. L. Erickson, Sita, and Tishler, *J. Amer. Chem. Soc.*, 1951, **73**, 2396; Cameron, Hunt, Oughton, Wilkinson, and Wilson, *J.*, 1953, 3864.

Lactonisation of 3β-*Acetoxy*-1-*oxo*-5α-*pregnane*-20-*carboxyamide* (IX; R = Ac, R′ = NH_2).—(*a*) *With lead tetra-acetate.* The amide (1·5 g.), lead tetra-acetate (5 g.), and iodine (3 g.) in benzene (40 ml.) were irradiated in Pyrex flask at 15° with a 125w high-pressure mercury arc lamp for 5 hr. After filtration and washing with chloroform the filtrate was shaken with water and with aqueous sodium hydrogen sulphite. Removal of the solvent *in vacuo* afforded a gum (1·52 g.). This residue in ethanol (40 ml.) containing potassium hydroxide (2·5 g.) in water (10 ml.) was refluxed for 2 hr. Most of the solvent was removed *in vacuo*, water added, and the resulting solution extracted with ethyl acetate to give a small neutral and/or basic fraction (68 mg.) which was discarded. The aqueous solution was acidified with 2N-aqueous sulphuric acid and heated on the steam-bath for 2 hr. (to complete lactonisation). After separation into acidic and neutral (lactonic) fractions the latter was acetylated with acetic anhydride (4 ml.) and pyridine (4 ml.) on the steam-bath for 15 min. Chromatography on alumina (Wœlm, acid, act. IV) and elution with benzene gave the derived lactone (X). Crystallised from benzene–cyclohexane this formed plates (700 mg.), m. p. 265—267°, $[\alpha]_D$ −23° (*c* 1·16), identical with an authentic specimen.[8]

(*b*) With t-butyl hypochlorite. The amide (1·5 g.) was stirred in suspension with iodine (3·0 g.) in benzene (40 ml.) with addition of t-butyl hypochlorite (0·54 g.) and irradiated as above for 7 hr. Further portions (3 × 0·36 g.) of t-butyl hypochlorite were added at the end of the first and of two subsequent hours. Working up as above gave the derived lactone (X) (422 mg.).

Attempted Lactonisation of 3β-*Acetoxy*-N-*methyl*-11-*oxo*-5α-*pregnane*-20-*carboxyamide.*—The *N*-methylamide (2·0 g.) and lead tetra-acetate (2·8 g.) in chloroform (50 ml.) were irradiated under reflux with a tungsten lamp during addition of iodine (800 mg.) in the same solvent (25 ml.). The iodine was rapidly consumed at first, but later (*ca.* 1 hr.) the colour was regenerated. After 1·5 hr. the mixture was filtered and the filtrate washed with aqueous sodium hydrogen sulphite. Removal of the solvent *in vacuo* gave a crude product (2·1 g.). A portion (150 mg.) of this was hydrolysed with alkali in the usual way. There was no lactonic fraction but 3β-*hydroxy*-N-*methyl*-11-*oxo*-5α-*pregnan*-20-*carboxyamide* (IX; R = H, R′ = NHMe) was found in the neutral fraction. This crystallised from acetone in prisms, m. p. 283—284° (evac. tube), $[\alpha]_D$ +54° (*c* 1·24 in 1 : 1 EtOH–$CHCl_3$); $\nu_{max.}$ (in $CHCl_3$) 3500, 3450, 1700, and 1665 $cm.^{-1}$ (Found: C, 73·7; H, 9·8; N, 3·7. $C_{23}H_{37}NO_3$ requires C, 73·6; H, 9·9; N, 3·7%).

The remainder of the crude product (see above) was re-oxidised twice by essentially the same procedure but only minor amounts of non-crystalline lactonic material were produced.

Lactonisation of 3β-*Acetoxy*-11-*oxo*-N-*phenyl*-5α-*pregnane*-20-*carboxyamide.*—The *N*-phenylamide (2·5 g.) and lead tetra-acetate (4·0 g.) in chloroform (40 ml.) were irradiated (tungsten lamp) under reflux with addition of iodine (1·0 g.) in the same solvent (25 ml.) during 30 min. Initially the iodine was completely consumed, but its colour returned 10 min. after completion of the addition. After 4 hrs. irradiation the reaction solution was washed with 2N-aqueous hydrochloric acid, aqueous sodium hydrogen sulphite, and water, and then evaporated *in vacuo* (3·13 g.). A portion (1·31 g.) of the product was hydrolysed in the usual way to give a lactonic fraction (168 mg.). Acetylation with pyridine–acetic anhydride and crystallisation from methylene dichloride–ether gave the lactone (X) (116 mg.).

Lactonisation of o-*Toluamide.*—(*a*) *With lead tetra-acetate.* *o*-Toluamide (1·0 g.) and lead tetra-acetate (4·0 g.) in chloroform (50 ml.) were stirred at room temperature with addition of powdered iodine until a permanent colour was attained (*ca.* 1 g. of iodine). The mixture was irradiated (tungsten lamp) under reflux for 2·5 hr. and then filtered and the residue washed with methylene dichloride. The filtrate was evaporated *in vacuo* and further processed as above. The lactonic fraction (250 mg.) gave some phthalide on crystallisation from methylene dichloride–light petroleum.

(*b*) *With t-butyl hypochlorite.* *o*-Toluamide (1·1 g.) in chloroform (40 ml.) containing t-butyl hypochlorite (1·3 g.) was treated with iodine (1·62 g.) and irradiated under reflux with a mercury-arc lamp for 3·5 hr. Processing as above gave phthalide (100 mg.), *o*-toluamide (570 mg.), and a crude acid (170 mg.) affording phthalic acid (10 mg.) on crystallisation from chloroform.

Lactonisation of Octadecanamide.—(*a*) *With lead tetra-acetate.* Octadecanamide (2·0 g.), lead tetra-acetate (9·4 g.), and iodine (5 g.) in benzene (40 ml.) were photolysed at 20—30° using a 125w mercury-arc lamp for 5 hr. Working up as above gave, on crystallisation of the lactonic fraction from aqueous methanol, γ-stearolactone[22] (1·2 g.), m. p. 49—50°. The mother-liquor, evaporated *in vacuo*, gave a lactonic residue (675 mg.). This was chromatographed over silica

[22] Fosbinder and Rideal, *Proc. Roy. Soc.*, 1933, *A*, **143**, 61.

gel. Elution with methylene dichloride afforded δ-*stearolactone* (340 mg.). This crystallised from light petroleum as needles, m. p. 38—39° (Found: C, 76·0; H, 11·95; O, 11·5. $C_{18}H_{34}O_2$ requires C, 76·5; H, 12·1; O, 11·3%).

γ-Stearolactone (497 mg.) was refluxed with potassium hydroxide (800 mg.) in water (25 ml.) for 1 hr. Cooling and acidification furnished 4-hydroxyoctadecanoic acid. Recrystallised from methylene dichloride this formed plates (323 mg.), m. p. 86—87°,[9] $\nu_{max.}$ (in $CHCl_3$) 1705 cm.$^{-1}$. γ-Stearolactone (80 mg.) was heated with benzylamine (0·2 ml.) at 100° (sealed tube) for 1 hr. Crystallisation of the product from methanol gave N-*benzyl*-4-*hydroxyoctadecanamide* as plates (70 mg.), m. p. 96—97°, $\nu_{max.}$ (in $CHCl_3$) 3480 and 1660 cm.$^{-1}$ (Found: C, 77·0; H, 11·0; O, 8·2. $C_{25}H_{43}NO_2$ requires C, 77·1; H, 11·1; O, 8·2%). δ-Stearolactone was similarly converted into 5-hydroxyoctadecanoic acid,[9] m. p. 81° (Found: C, 72·2; H, 12·0. Calc. for $C_{18}H_{36}O_3$: C, 71·95; H, 12·1%), and into N-*benzyl*-5-*hydroxyoctadecanamide*, m. p. 90—92° (from methanol), $\nu_{max.}$ (in $CHCl_3$) 3480 and 1660 cm.$^{-1}$ (Found: C, 76·9; H, 11·0. $C_{25}H_{43}NO_2$ requires C, 77·1; H, 11·1%).

(*b*) *With t-butyl hypochlorite.* Octadecanamide (2·3 g.) and iodine (5·0 g.) in benzene (50 ml.) were treated with t-butyl hypochloride (3·8 g.) with stirring for 15 min. and then photolysed with a mercury-arc lamp at <30° for 7 hr. Processing the reaction mixture as before gave γ-stearolactone (1·4 g.) and δ-stearolactone (510 mg.).

(*c*) *With t-butyl hypoiodite.* Potassium t-butoxide (made by dissolving potassium (800 mg.) in excess of t-butyl alcohol and then removing the excess azeotropically with benzene) in benzene (100 ml.) was treated with iodine (8·17 g.) and the potassium iodide filtered off (exclusion of moisture). Octadecanamide (940 mg.) was added to the filtrate and the solution stirred for 30 min. at room temperature. Withdrawal of a portion and dilution with light petroleum gave a precipitate which on crystallisation from acetone afforded isomer B of *N-iodo-octadecanamide*. The reaction solution was photolysed with a mercury-arc lamp at room temperature for 7 hr. Working up as before gave γ-stearolactone (180 mg.) and δ-stearolactone (20 mg.).

(*d*) *Blank experiment.* Octadecanamide (2·0 g.), iodine (5 g.), and t-butyl hypochlorite (1·6 mg.) in benzene (40 ml.) were stirred at 20° in the dark (flask shielded with foil) for 5 hr. Further t-butyl hypochlorite (3 × 0·6 ml.) was added at the end of the first three successive hours. The precipitate, which was filtered off (2·334 g.), and washed with benzene and with light petroleum, was the more stable isomer B of *N*-iodo-octadecanamide (see above). The filtrate and combined washings were washed with aqueous sodium hydrogen sulphite and the solvent removed *in vacuo*. The residue (497 mg.) was hydrolysed as before. There was *no* lactonic fraction.

(*e*) *Comparative experiments involving zinc dust reduction.* *N*-Iodostearamide (2·0 g.) in chloroform (100 ml.) was photolysed with a mercury-arc lamp at <30° for 6½ hr. The solution was divided into two equal portions and the solvent removed *in vacuo*. The first half of the product in glacial acetic acid (45 ml.) was shaken with zinc dust (10·0 g.) for 12 hr., filtered, and poured into water. Hydrolysis with excess of alkali and further processing as above gave a lactone fraction (180 mg.). The second half of the product in glacial acetic acid (45 ml.) was kept for 12 hr. and then worked up as for the first half to give a lactone fraction (160 mg.).

Lactonisation of 4-*Phenylbutyramide.*—4-Phenylbutyramide (1·60 g.) and iodine (7·40 g.) in benzene (50 ml.) were treated with t-butyl hypochlorite (2·4 ml.) with stirring for 15 min. at room temperature. The stirred reaction mixture was photolysed with a 125w mercury-arc lamp at <30° for 7 hr., more t-butyl hypochlorite (3 × 0·8 ml.) being added after the first three successive hours. The precipitate was filtered off (2·34 g.) and crystallised quickly from methylene dichloride to furnish N-*iodo*-4-*phenylbutyroiminolactone iodine chloride complex*, m. p. 110—122°, $\lambda_{max.}$ 224 mμ (ε 2800 in tetrahydrofuran), $\nu_{max.}$ (Nujol) 1600, 260, and 210 cm.$^{-1}$ (Found: C, 26·7; H, 2·55; Cl, 8·75; I, 56·7. $C_{10}H_{10}ClI_2NO$ requires C, 26·7; H, 2·25; Cl, 7·9; I, 56·5%). This complex (300 mg.) was heated with saturated aqueous sodium hydrogen sulphite (2 ml.) and 2N-aqueous sulphuric acid (5 ml.) on the steam-bath for 10 min. Extraction into ethyl acetate gave 4-phenylbutyrolactone (69 mg.), identical with an authentic specimen. This lactone (30 mg.) in ethanol (2 ml.) was saturated with ammonia at 0° and set aside for 12 hr. Removal of the solvent *in vacuo* and crystallisation from ether gave 4-hydroxy-4-phenylbutyramide, m. p. 84—85°.

The iodine chloride complex (465 mg.) in benzene (5 ml.) was treated with pyridine (103 mg.) and the small precipitate discarded. On addition of light petroleum the pyridine–iodine chloride complex (m. p., and mixed m. p., and u.v. and i.r. spectra) was deposited.

The iodine chloride complex (130 mg.) in tetrahydrofuran (3 ml.) was treated with triethylamine (1 ml.). The precipitate was filtered off and fractionally crystallised to furnish triethylamine hydrochloride (m. p. and mixed m. p.) and triethylamine hydriodide (m. p. and mixed m. p.).

The iodine chloride complex (200 mg.) in tetrahydrofuran (25 ml.) was shaken with Raney nickel (2 g.) for 12 hr. Filtration, removal of the solvent *in vacuo*, and crystallization from benzene–light petroleum gave 4-phenylbutyramide (40 mg.), m. p. 81—82°.

Preparation and Lactonisation of 4-*Methylhexanamide.*—(+)-Citronellol (25 g.) was treated overnight with excess of toluene-*p*-sulphonyl chloride in pyridine at room temperature and the derived toluene-*p*-sulphonate was purified by filtration in light petroleum through alumina (Grade V) to give an oil (27 g.), $[\alpha]_D$ +1° (*c* 1·07). This toluene-*p*-sulphonate (15 g.) in methylene dichloride (150 ml.) was ozonised at 0° for 16 hr. After removal of the solvent *in vacuo* the ozonide was reduced with excess of ethereal lithium aluminium hydride. Working up gave 4-methylhexan-1-ol [12] (3 g.), b. p. 80—84°/22 mm., $[\alpha]_D$ +2·6° (*c* 1·50). This alcohol (3·0 g.) in acetone (22·5 ml.) was added to chromium trioxide (5·1 g.) in concentrated sulphuric acid (8·1 g.) and water (25·5 ml.) and left for 1½ hr. Working up gave 4-methylhexanoic acid [23] (1·75 g.) b. p. 114—117°/15 mm., $[\alpha]_D$ +5° (*c* 1·02). This acid (1·75 g.) was treated with excess of thionyl chloride and the excess removed *in vacuo*. The derived acid chloride in dry ether was added to concentrated aqueous ammonia with shaking. Removal of the ether *in vacuo* gave 4-methylhexanamide [24] (1·3 g.), m. p. (from light petroleum), 97—98°, $[\alpha]_D$ +11° (*c* 0·85).

4-Methylhexanamide (1·0 g.) and iodine (5·3 g.) in benzene (40 ml.) was treated with t-butyl hypochlorite (1·8 ml.) and stirred for 15 min. The reaction mixture was then photolysed with a 125w mercury-arc lamp at <30° for 7 hr. More t-butyl hypochlorite (3 × 0·6 ml.) was added after the first three successive hours. After cooling to 0° part of the crystalline precipitate (1·11 g.) was filtered off. The remainder and the filtrate were combined and the solvent removed *in vacuo*. The residue was hydrolysed in the usual manner and afforded (±)-4-methyl-4-hexanolactone [25] (360 mg.), b. p. 75—78°/6 mm., $[\alpha]_D$ ±0° (*c* 1·06), rotation 0° at all accessible wavelengths (Found: C, 65·7; H, 9·5. Calc. for $C_7H_{12}O_2$ C, 65·6; H, 9·4%).

The crystalline precipitate referred to above was crystallised from methylene dichloride to give N-*iodo*-4-*methyl*-4-*hexanoiminolactone iodine chloride complex*, m. p. 113—115°, $\nu_{max.}$ (Nujol) 1610 cm.$^{-1}$ (Found: C, 20·05; H, 2·6; I, 61·5. $C_7H_{12}ClI_2NO$ requires C, 20·25; H, 2·9; I, 61·1%). This compound (280 mg.) was heated with saturated aqueous sodium hydrogen sulphite (2 ml.) and 1N-aqueous sulphuric acid (5 ml.) on the steam-bath for 10 min. Extraction into ethyl acetate gave 4-methyl-4-hexanolactone, identical with material described above.

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[23] Kenyon and Symons, *loc. cit.*, see ref. 1.
[24] Dewael and Weckering, *Chem. Zent.*, 1925, I, 358.
[25] Porter, *J. Amer. Chem. Soc.*, 1923, **45**, 1086.