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3,3-Dialkylindolin-2-ones and 3,3-Dialkylisoindolin-1-ones. 2. Hofmann and Lossen Degradation of 4,4-Dialkyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolines (4,4-Dialkylhomophthalimides). A Mechanistic Study

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The Hofmann rearrangement reaction of 4,4-dialkylhomophthalimides and the Lossen rearrangement of 4,4-dialkyl-*N*-tosyloxyhomophthalimides afford indolinone or isoindolinone derivatives, or mixtures of both, depending on the nature of the 4-substituents. "Bulky" substituents give rise to isoindolinones, "small" substituents afford indolinones, and "medium sized" substituents give mixtures of both, though the actual size has less significance than their spatial geometry. The mechanisms of the reactions involved are discussed.

In a previous paper [1] we reported on the formation of 3,3-disubstituted indolinones and isoindolinones from 4,4-disubstituted homophthalimides * on treatment with alkali and sodium hypochlorite solution. Two reaction methods were used: in one (A), the homophthalimide derivative was treated with 2 M sodium hydroxide solution for various times prior to treatment with hypochlorite, and in the other (B), the alkaline homophthalimide solution was treated *immediately* with the hypochlorite. The products formed consisted of indolinone or isoindolinone derivatives, or mixtures of both, depending on the nature of the starting material and on the experimental conditions employed. Working with 4,4-tetramethylenehomophthalimide, it was concluded that in reaction A, the homophthalimide slowly underwent hydrolytic ring-opening to give a mixture of the two theoretically possible "amic" acids which, upon treatment with hypochlorite, rapidly underwent rearrangement to afford the indolinone and isoindolione derivatives.

Formation of the indolinones in method B, however, seems to rule out a corresponding mechanism initiated by a hydrolytic step, as the indolinones were formed at a much more rapid rate than hydrolysis of the imide. Consequently, a different reaction mechanism seems to be operating in method B, and it is the purpose of the present paper to report on the attempts made to elucidate this mechanism.

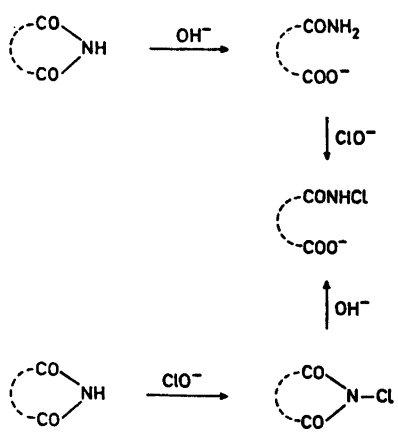
* As the correct names of these compounds are very cumbersome, they are designated as derivatives of homophthalimides in the following discussion.

DISCUSSION

The Hofmann amide degradation is generally believed to proceed through the following steps:[2]

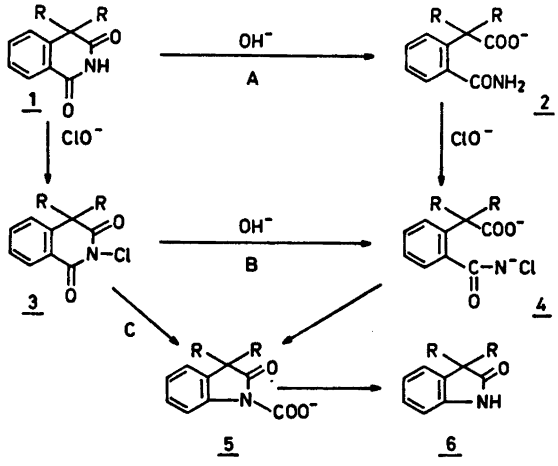
$$\mathrm{R-CONH_2} \xrightarrow{\mathrm{OHal^-}} \mathrm{R-CONHHal} \xrightarrow{\mathrm{OH^-}}$$
$$\mathrm{R-CON^-Hal} \rightarrow \mathrm{R-N=C=O} \rightarrow$$
$$\mathrm{R-NHCOOH} \rightarrow \mathrm{R-NH_2 + CO_2}$$

Obviously, the reaction requires an ionizable hydrogen atom at the amide nitrogen of the haloamide, that is, the reaction can proceed only with *primary* amides. Many imides, especially phthalimides, do however undergo this reaction which has usually been explained by an initial hydrolytic ring-opening, either of the free imide [2] or of the *N*-chloro derivative formed from this,[3] followed by rearrangement of the haloamide formed:

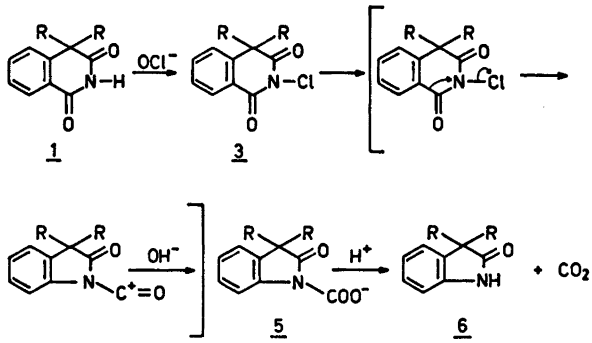


(For alternative hypotheses see Ref. 4, 5). Our results with 4,4-tetramethylenehomophthalimide, although only qualitative, clearly demonstrate that the hydrolysis of this imide is a slow reaction requiring several hours at room temperature to proceed to any considerable extent. In sharp contrast to this is the rapid formation of the indolinone derivative from this imide on reaction with alkaline sodium hypochlorite solution: almost 90 % of the indolinone derivative is obtained after a reaction time of less than 15 min. at room temperature. It can therefore be concluded that at least in this case hydrolysis of the free imide (Scheme 1, route A) is not the initial step but that the reaction is initiated by *N*-chlorination of the imide. The *N*-chloro derivative *3* might then either undergo hydrolysis to the *N*-chloro primary amide *4* (Scheme 1, route B) or rearrange directly (Scheme 1, route C). The direct rearrangement C may conceivably proceed either without participation of OH^- ions according to Scheme 2, or by the "concerted" mechanism outlined in Scheme 4. Whatever the operating mechanism may be, the carbamic acid derivative *5* is an intermediate, since its sodium salt was isolated on cooling the reaction mixture and characterised by conversion to the methyl ester with dimethyl sulphate.[1]

The Scheme 2 mechanism appeared at first sight to be a very plausible alternative, its greatest merit being the fact that it obviates the necessity for hydrolytic ring-opening of the imide. In order to test the validity of this mechanism, the reaction was carried out in the presence of $H_2{}^{18}O$: non-incorporation of ^{18}O into the indolinone formed would strongly support the proposed mechanism. MS measurements showed that formation of the indolinone *6* was accompanied by incorporation of ^{18}O. As, however, independent experiments with heavy water showed that whereas *5* did not exchange ^{18}O with the medium, the imide *1* did so very rapidly, this observation was without meaningful interpretation. Consequently, the *N*-chloro derivative *3* was prepared separately and made to react with sodium hydroxide solution. It was found that already



Scheme 1.



Scheme 2.

after about ten minutes, an 80 % yield of the indolinone *6* could be isolated after acidification of the reaction mixture, and that it contained incorporated ^{18}O to the extent required by 100 % participation of OH^- ions from the medium. Although a rapid exchange of oxygen in the chloroimide followed by rearrangement according to Scheme 2 is not entirely ruled out by these experiments this apparently means that the *N*-chloro derivative *3* rearranges either *via* a conventional hydrolysis reaction (Scheme 1 route B) or by way of the "concerted" reaction (Scheme 4) as all efforts to effect the rearrangement with for example silver salts in an inert solvent have failed so far. That rapid hydrolysis of *3* is not inconceivable may be deduced from the fact that *N*-methoxy-4,4-tetrahydrohomophthalimide, which both sterically and electronically closely resembles the *N*-chloro analogue *3*, is virtually completely hydrolysed by 1 M sodium hydroxide in 50 % aqueous dioxane at room temperature in less than 5 min. (The resistance offered by the imide *1* to alkaline hydrolysis must apparently by ascribed to the effect exerted by its anion, which would tend to repel the approach of OH^- ions from the medium). Since no experiments could be devised to distinguish between these two mechanisms (Scheme 1, route B and Scheme 4), the choice was finally made on the basis of indirect evidence derived from the Lossen reaction, as discussed further on.

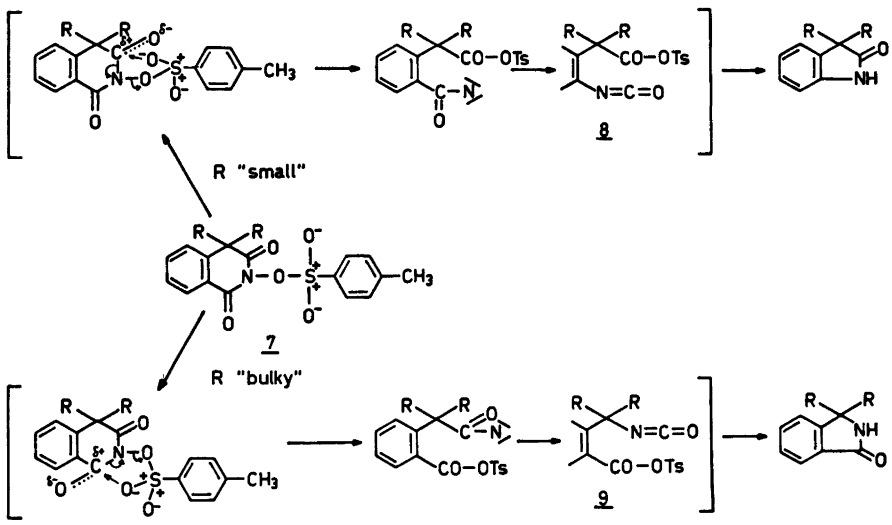
Both of the above rearrangement mechanisms would also explain the role played by the 4-substituent in governing the course of the reaction: increasing "bulkiness" of the substituent would shift attack from the more electrophilic but more hindered aliphatic carbonyl group to the less electrophilic but less hindered aromatic one, thus favouring transition from indolinone to isoindolinone formation. This is in complete alignment with the finding that the 4,4-dimethyl-, 4,4-tetramethylene-, and 4,4-pentamethylenehomophthalimides gave high yields of the corresponding indolinones, 4,4-diallylhomophthalimide gave moderate yields of both indolinone and isoindolinone derivatives, and 4,4-diethylhomophthalimide afforded solely the isoindolinone derivative in moderate yield. The 4,4-dipropyl- and 4,4-dibutylhomophthalimides did not react at all, indicating that here the steric effect extends to block reaction even at the imide nitrogen or aromatic carbonyl group.

A semi-quantitative indication of the relative degrees of reactivity of the carbonyl groups in the various 4,4-dialkylhomophthalimides could be obtained by determining the rate of ^{18}O incorporation. It can be seen from Table 4 that the velocity of exchange decreases in the series

$$R = -(CH_2)_4- \gg C_2H_5-;$$
$$CH_2=CHCH_2- > n\text{-}C_3H_7-$$

This is in agreement with the found reactivities of the homophthalimides with respect to the Hofmann rearrangement reaction.

In order to obtain further insight into the mechanism of the Hofmann reaction, the Lossen rearrangement of the corresponding *N*-tosyloxyhomophthalimide derivatives *7* was studied, as it is known that these two reactions

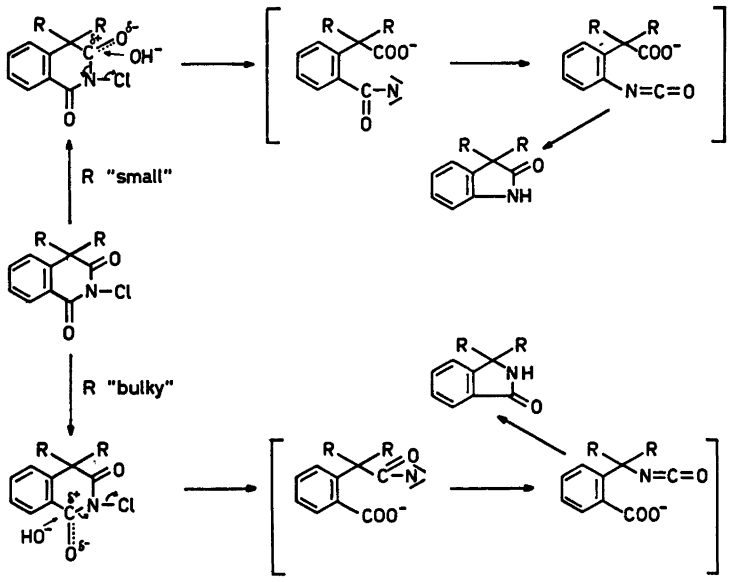


Scheme 3.

proceed according to the same mechanism. It was found that when the *N*-tosyloxy derivatives of homophthalimide substituted with the 4,4-dimethyl-, 4,4-tetramethylene-, 4,4-diallyl-, 4,4-diethyl-, and 4,4-dibutyl groups were warmed in aqueous dioxane containing potassium carbonate, the first two members of the series afforded the corresponding indolinone derivatives, the allyl derivative gave a mixture of indolinone and isoindolinone, the ethyl derivative gave only isoindolinone, and the butyl derivative also afforded small amounts of the isoindolinone. It is obvious that the substituent in the 4-position has a profound directive influence on the course of the reaction. Also, since the electronic effects of the methyl group must be very similar to that of the ethyl group, this influence must be steric rather than electronic in nature. Furthermore, experiments in heavy water revealed that *incorporation of ^{18}O occurred neither in the indolinones nor in the isoindolinones formed* which means that in this case the attacking species is not an OH^- ion and the reaction does not involve hydrolytic opening of the imide ring. An attractive mechanism reconcilable with this finding would be the one outlined in Scheme 3, since this would explain in a satisfactory manner the directive influence of the 4-substituent. This mechanism is entirely analogous to the one proposed for the Hofmann reaction, with the difference that the leaving group here is a toluene sulphonate instead of a chloride ion and the attacking species is an intramolecular sulphonyl oxygen instead of an external hydroxyl ion. The increasing steric hindrance exerted by the 4-substituent with increasing bulk would progressively shift the attack from the aliphatic to the aromatic carbonyl group, resulting in formation of indolinone or isoindolinone as the case may be.

As was mentioned above in the discussion of the Hofmann rearrangement, the experiments devised cannot distinguish between a reaction involving normal hydrolysis of the *N*-chlorohomophthalimide (Scheme 1, route B) and a "concerted" reaction not involving a distinct hydrolytic step (Scheme 4). However, if we accept the Lossen mechanism as a justifiable model for the closely related Hofmann reaction, we would favour the entirely analogous "concerted" mechanism as outlined below (Scheme 4) in preference to the stepwise hydrolysis and subsequent rearrangement.

It was a fortuitous circumstance for the elucidation of the mechanism of the Lossen rearrangement that in these compounds the unique structural constellation of the postulated mixed anhydride derivatives *8* and *9* imparted to these intermediates a much greater tendency to ring-closure than to reaction with the



Scheme 4.

environmental water, for otherwise correct interpretation of the heavy water experiments would not have been possible.

EXPERIMENTAL

All melting points were taken with a Heræus Fus-O-Mat apparatus. Mass spectra were determined on an LKB 9000 instrument. Microanalyses were carried out by Prof. K. J. Karrman, University of Lund, Lund, Sweden.

N-Chloro-4,4-tetramethylenehomophthalimide and its Hofmann rearrangement. A mixture of 4,4-tetramethylenehomophthalimide (16 g; 0.147 mol) and *tert*-butyl hypochlorite (16 g; 0.147 mol) was stirred in a waterbath at 60°C for 3 h, by when a clear orange solution had formed. Excess hypochlorite was removed in vacuum and the residual oil was recrystallized from 175 ml of diisopropyl ether, giving 15.3 g (83 %) of white crystals, m.p. 85 – 94°C. An analytically pure sample melted at 90 – 94°C. (Found: C 62.8; H 4.86; N 5.60; O 12.8; Cl 13.9. $C_{13}H_{12}ClNO_2$ requires: C 62.5; H 4.85; N 5.61; O 12.8, Cl 14.2).

The above chloro derivative (1.25 g; 0.005 mol) was treated with ice-cold 2 M sodium hydroxide solution (10 ml; 0.02 mol) and stirred at room temperature for 10 min. Acidification with acetic acid afforded 730 mg (78 %) of 3,3-tetramethyleneindolin-2-one, m.p. 113°C.

When the rearrangement reaction was carried out in a medium containing 20 atom-% of $H_2{}^{18}O$, the indolinone isolated contained about 9 % of the labelled isomer of M.W. 189.

N-Chloro-4,4-diethylhomophthalimide and its Hofmann rearrangement. A mixture of 4,4-diethylhomophthalimide (10.9 g; 0.05 mol) and *tert*-butyl hypochlorite (10 ml; 0.092 mol) in dry benzene (50 ml) was stirred at room temperature overnight. Removal of volatile material in vacuum afforded 12.4 g (99 %) of a thick oil which slowly crystallized on standing. An analytical sample recrystallized from petroleum ether melted at 51 – 56°C. (Found: C 61.6; H 5.5; Cl 14.8; N 5.5; O 12.9. $C_{13}H_{14}ClNO_2$ requires: C 62.0; H 5.6; Cl 14.1; N 5.6; O 12.7).

The above chloro derivative (2.5 g; 0.01 mol) was warmed and stirred with 2 M sodium hydroxide solution (20 ml; 0.04 mol) for 45 min, the reaction mixture was cooled, acidified with acetic acid and the product collected, giving 1.4 g (74 %) of 3,3-diethylisoindolin-1-one, m.p. 166 – 169 °C.

General method for the preparation of 4,4-dialkyl-N-hydroxy-homophthalimides. Sodium (2.5 g; 0.11 mol) was added to dry methanol (50 ml) and when reaction was complete the solution was cooled and treated with a hot solution of hydroxylamine hydrochloride (7.7 g; 0.11 mol) in water (5 ml). To the stirred solution was added the appropriate substituted homophtalic acid (or, preferably, the anhydride, obtained by heating the acid) and the mixture was refluxed for 4 to 6 h, then stirred at ambient temperature overnight. Dilute hydrochloric acid was added, the solution taken to dryness

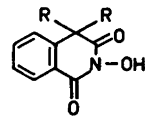


Table 1. Data for 4,4-dialkyl-*N*-hydroxyhomophthalimides.

R	M.p. °C	Yield %	Recryst. solv. [a]	Formula	Analysis Calc. C	H	N	O	Found C	H	N	O
CH_3	82	95	DIP/PET	$C_{11}H_{11}NO_3$	64.4	5.4	6.8	23.0	64.4	5.4	6.8	23.5
C_2H_5	128–130	69	DIP	$C_{13}H_{15}NO_3$	66.9	6.5	6.0	20.6	67.1	6.5	5.7	20.7
C_4H_9	184–186	70	MET	$C_{17}H_{15}NO_3$	70.6	8.0	4.8	16.6	68.7	8.0	4.7	16.1
$CH_2=CHCH_2$	123–128	93	DIP/PET	$C_{15}H_{15}NO_3$	70.0	5.9	5.4	18.7	70.0	5.9	5.4	18.9
$-(CH_2)_4-$ (–R–R–)	116–118	82	CHL/PET	$C_{13}H_{13}NO_3$	67.5	5.7	6.1	20.8	67.2	5.7	6.0	20.9

[a] DIP = Diisopropyl ether, PET = petroleum ether, MET = methanol, and CHL = chloroform.

under vacuum, the residue taken up in hot acetone, the sodium chloride filtered off and the filtrate taken to dryness, giving an oil which became crystalline on cooling. The data of the derivatives thus prepared are presented in Table 1.

General method for the preparation of 4,4-dialkyl-N-tosyloxyhomophthalimides. A solution made up from the appropriate 4,4-dialkyl-*N*-hydroxyhomophthalimide (0.05 mol), DMF (200 ml) and 1 M sodium hydroxide solution (50 ml; 0.05 mol) was added dropwise at room temperature to a solution of tosyl chloride (10 g; 0.052 mol) in chloroform (150 ml). The mixture was stirred at room temperature for 2 to 20 h, the layers were separated and the aqueous phase was extracted with chloroform. The combined chloroform phase was washed with water, with dilute hydrochloric acid and finally with sodium carbonate solution. After drying, the solvent was removed, giving an oil which generally crystallized on standing. The data of the derivatives thus prepared are presented in Table 2.

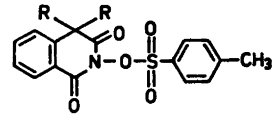
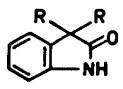
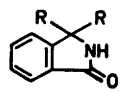


Table 2. Data for 4,4-dialkyl-*N*-tosyloxyhomophthalimides.

R	M.p. °C	Yield %	Recryst. solv.[a]	Formula	Analysis Calc. C	H	N	O	Found C	H	N	O
CH_3	135	50 [b]	AC/DIP	$C_{16}H_{17}NO_5S$	60.2	4.8	3.9	8.9	60.1	4.9	3.9	8.9
C_2H_5	132–133	75	MET	$C_{20}H_{21}NO_5S$	62.0	5.5	3.6	8.3	61.8	5.4	3.6	8.2
C_4H_9	94–98	90	MET	$C_{24}H_{29}NO_5S$	65.0	6.6	3.2	7.2	64.8	7.0	3.2	7.3
$CH_2=CHCH_2$	64–68	73	MET	$C_{22}H_{21}NO_5S$	64.2	5.1	3.4	7.8	64.3	5.2	3.4	7.8
$-(CH_2)_4-$ (–R–R–)	118–120	65	MET	$C_{20}H_{19}NO_5S$	62.3	5.0	3.6	8.3	62.6	5.0	3.7	8.1

[a] AC = acetone, MET = methanol, and DIP = diisopropyl ether. [b] Also obtained 36 % yield of 3,3-dimethylindolin-2-one.

Table 3. Lossen rearrangement of 4,4-dialkyl-*N*-tosyloxyhomophthalimides.

R	% Products isolated 		Remarks
CH_2	68	–	
C_5H_8	–	58	Reaction in $H_2{}^{18}O$: 2 % ^{18}O incorporated.
C_4H_9	–	26	M.p. 81 – 84 °C. Product isolated by silica-gel column chromat. Found: C 77.7; H 9.5; N 5.8; O 7.0. $C_{13}H_{23}NO$ requires C 78.3; H 9.5; N 5.7; O 6.5.
$CH_2=CHCH_2$	47	31	Products separated by silica-gel column chrom.
$-(CH_2)_4-$ (–R–R–)	74	–	Reaction in $H_2{}^{18}O$: < 1 % ^{18}O incorporated.

General procedure for the Lossen rearrangement reaction. A mixture made up from the 4,4-dialkyl-*N*-tosyloxyhomophthalimide (0.01 mol), dioxane (10 ml), potassium carbonate (1.5 g; 0.011 mol) and water (5 ml) was stirred in an oil-bath (80 °C) overnight. Volatile material was removed under vacuum, the residue was treated with water, extracted with chloroform, the organic extract was washed with water, dried (K_2CO_3), the solvent was removed and the residual product was recrystallized. Pertinent data of the products obtained are presented in Table 3. In the experiments with isotope labelling, water containing 20 atom-% of $H_2{}^{18}O$ was used.

In the reaction with the dibutyl derivative, the product was characterised as isoindolinone by the NMR spectrum, in which the aromatic H-atoms appear at τ 2.0 – 2.6 in contrast to their appearance at τ 2.8 – 3.0 in the indolinones. In addition, the UV-spectrum in methanol exhibits a peak at 225 nm, as did also other isoindolinones, in contrast to the peak appearing at 247 nm in the indolinones (*cf.* Ref. 1).

N-Methoxy-4,4-tetramethylenehomophthalimide. A mixture of *N*-hydroxy-4,4-tetramethylenehomophthalimide (23.1 g; 0.1 mol), potassium carbonate (13.8 g; 0.1 mol) and water (100 ml) was warmed until a clear solution had been obtained when dimethyl sulphate (10.3 ml; 0.11 mol) in acetone (50 ml) was added dropwise. After stirring in the water-bath for 2.5 h, an additional 10 ml of dimethyl sulphate was added, whereafter the mixture was stirred in the water-bath for a further 4 h. After standing at room temperature overnight, most of the acetone was removed by distillation, causing a heavy oil to separate out. This was washed with water by decantation whereupon it solidified, giving 22.4 g (91.5 %) of white crystals, m.p. 75 – 80 °C. Recrystallization from methanol gave white crystals m.p. 77 – 81°C. (Found: C 68.6; H 6.1; N 5.7; O 19.7. $C_{14}H_{15}NO_3$ requires: C 68.6; H 6.1; N 5.7; O 19.6).

α,α-Diallylhomophthalic acid. Ethyl *o*-carbethoxyphenyl acetate (59 g; 0.25 mol) in DMF (100 ml) was added dropwise at room temperature under vigorous stirring to a mixture of allyl bromide (72 ml; 0.8 mol) and sodium hydride (50 % in oil; 30 g; *ca.* 0.7 mol) in DMF (400 ml). The stirred mixture was warmed on the water bath (*ca.* 70 °C) for 5 h, then stood at room temperature overnight. The inorganic salt was filtered off, the filtrate was taken to dryness under vacuum, the residual oil was treated with 5.5 M sodium hydroxide solution (100 ml) and the mixture refluxed overnight. After dilution with water, the solution was extracted with chloroform, the aqueous phase was treated with dilute hydrochloric acid to incipient turbidity (pH *ca.* 5), the solution was stirred with decolourising carbon, filtered through a Celite pad, and the filtrate strongly acidified with hydrochloric acid. The resulting viscous oil was extracted into chloroform, the extract was washed with brine, dried (Na_2SO_4) and taken to dryness under vacuum, giving a crystalline residue weighing 51 g (78.5 %), m.p. *ca.* 140 °C. Fractional crystallization from a mixture of chloroform-ether-petroleum ether 1:1:1 afforded 27.7 g (42 %) of the diacid, m.p. 139 °C dec., and 20.0 g (30.3 %) of a colourless oil which was identified by NMR as practically pure anhydride. (Found: C 69.0; H 6.2; O 24.5.

$C_{16}H_{16}O_4$ requires: C 69.2; H 6.2; O 24.6 %).

Experiments with ^{18}O-labelling. ^{18}O-Labelling of 4,4-dialkylhomophthalimides. The homophthalimide derivative (0.1 mmol) and sodium hydroxide (0.25 mmol) in 0.1 ml of water containing 20 atom-% of $H_2{}^{18}O$ was allowed to stand at room temperature for various times, then acidified with acetic acid and the precipitated imide isolated. The amount of incorporated ^{18}O was determined by MS. The results are presented in Table 4.

Table 4. ^{18}O-Exchange of 4,4-dialkylhomophthalimide (*1*).

R	Reaction time	Content of labelled isomer %
$-(CH_2)_4-$	12 min	11
	25 min	20
	4 h	20
	96 h[a]	30
C_2H_5	24 h	10
$CH_2=CHCH_2$	24 h	10
C_3H_7	24 h	4–5

[a] Also contains 5 % of isomer M. W. 219.

^{18}O-Exchange of N-carboxy-4,4-tetramethyleneindolin-2-one. The sodium salt of the carbamic acid derivative *5*[1] (26 mg; 0.1 mmol) was dissolved in a solution of sodium hydroxide (9.1 mg; 0.23 mmol) in 0.2 ml of water containing 10 atom-% of $H_2{}^{18}O$. After 3 h at room temperature the solution was warmed on a water bath for 10 min, cooled, acidified with dilute acetic acid and the resulting 4,4-tetramethyleneindolin-2-one was isolated. MS measurements showed that it contained practically no incorporated heavy oxygen.

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