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THE THORPE-INGOLD EFFECT IN GLUTARIMIDE DERIVATIVES. PART II[†]

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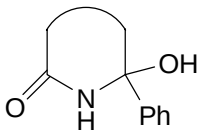
Abstract – Differently substituted glutarimides, 3-methylglutarimide (**12**), 3,3-dimethylglutarimide (**14**) and 3,3,4,4-tetramethylglutarimide (**18**) were prepared and their reactivity towards aryllithiums was investigated. The influence of Thorpe-Ingold effect on the distribution of products in tautomeric equilibrium was observed together with a total regioselectivity of the process. For imide (**12**) only keto amide (**13**) was isolated. Imide (**14**) resulted in formation both hydroxy lactam (**16**) and keto amide (**15**), and imide (**18**) gave only hydroxy lactam (**24**).

INTRODUCTION

Reactions between cyclic imides (such as succinic and glutaric imides) and organometallic compounds (such as Grignard and lithium compounds) are well-known synthetic procedures for the preparation of 1,4- and 1,5-dicarbonyl derivatives. The *N*-methylated or *N*-phenylated imides are in most cases used as starting materials. Numerous examples of this type of reaction can be found in the literature, including those leading to quite complex[1] or sensitive products.[2] Also, other nucleophiles (amines, hydroxylamines, hydrazines and alkoxides) were often employed.[3] Frequently, a selective reduction of the carbonyl group (with $NaBH_4/H^+$ or $Zn(BH_4)_2/H^+$) in the imide moiety is applied, leading to *N*-acyliminium intermediates of immense synthetic potential.

[†] Part I see ref. 12

In the case of five-membered ring imide derivative reaction leads surprisingly often to compounds having a hydroxy lactam (**1**) structure.



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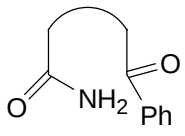

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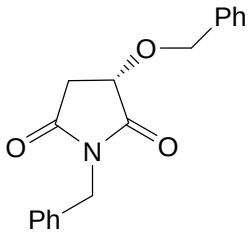
A reaction of a Grignard compound with (*S*)-1-benzyl-4-benzyloxy-2,5-pyrrolidinedione (**3**) that gave 1-benzyl-4-benzyloxy-5-hydroxy-5-(4-methoxybenzyl)pyrrolidin-2-one (**4**) as a sole product[4] is a good example. Another salient feature of this reaction is the observed regioselectivity. The formation of 1-benzyl-4-benzyloxy-5-hydroxy-5-(4-methoxybenzyl)pyrrolidin-2-one **4** as the only product[4] means that surprisingly the more hindered carbonyl group in (*S*)-1-benzyl-4-benzyloxy-2,5-pyrrolidinedione (**3**) underwent a nucleophilic attack.



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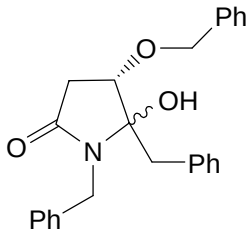

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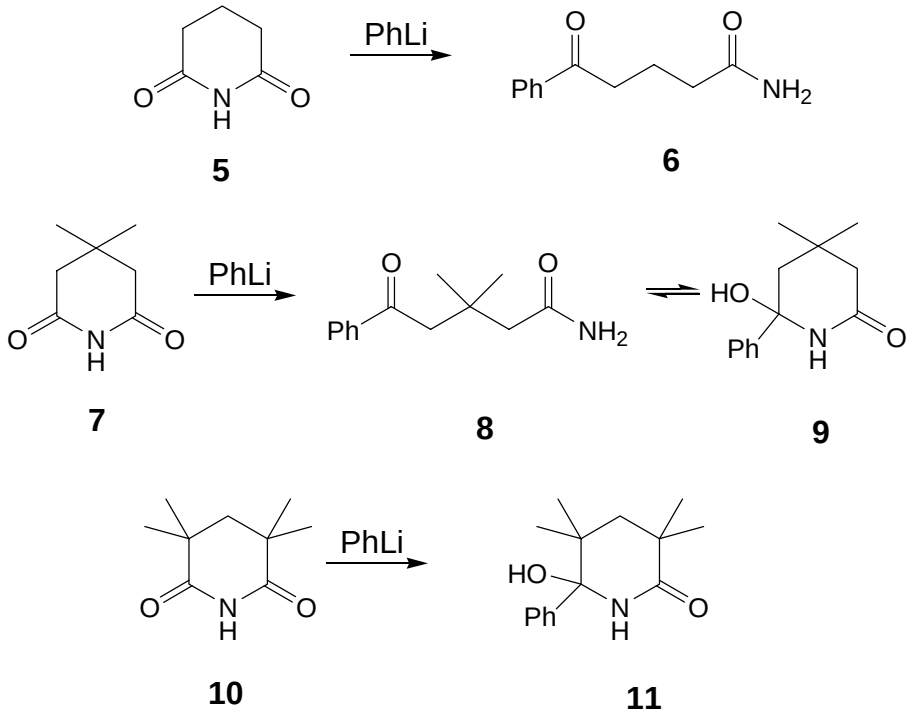
An attack on the more or less hindered site of the imide molecule depends on both the structure of the imide moiety and the type of nucleophilic reagent used in the reaction. In almost all cases described, not only 4- monosubstituted but sometimes also 4,4-disubstituted 2,5-pyrolidinediones and hence even much more crowded ones were formed.[5-7] An interesting explanation of this unusual behavior was offered.[6]

In the case of six membered imide ring (glutarimide) derivatives the regioselectivity appears to be governed by much more complicated factors. In some instances, nucleophiles like hydrazine hydrate react at the less hindered site, as observed in the case of 3-ethyl-3-phenylpiperidine-2,6-dione.[8] Surprisingly, the introduction of fluorine at the aromatic ring changes the regiochemistry in favor of an attack at the more hindered site. The methoxide ion seems to behave in a similar manner.[9] The problem of the product

structure of the nucleophile action on glutarimide molecule seems to be even more complicated. Both open-chain (keto amide) (**2**)[3] and cyclic (hydroxy lactam) (**1**)[10] structures, sometimes being in tautomeric relationship, were detected. During our studies, we have gained some evidences for the presence of the tautomeric equilibrium between these forms.[11,12] The predominance of the particular form is strongly affected by stereoelectronic factors in the molecule – mainly the Thorpe-Ingold effect (*gem*-dialkyl effect) which is known to facilitate the cyclisation.[13,14] At least three explanations of this effect can be found in the literature. According to one of them, a *gem*-substitution of the methylene hydrogens causes compression of the internal angle of the carbon chain, pushing the reactive centers closer together.[15] Another rationale proposed for the effect is called a "reactive rotamer effect", according to which a ring closure reaction proceeds at a higher rate on geminally substituted reactant because of the resultant decrease in the disfavored rotamer distribution.[16] A higher rate for the cyclic transition state formation in the case of *gem*-dimethyl compounds has recently been supported by quantum chemical methods.[17]

The problem of the ring-chain tautomerism has far-reaching implications for chemical processes. Speckamp *et al.*[14] demonstrated that existence of the keto amide (**2**) form in the selective reduction of glutarimides causes overreduction of the carbonyl group in this tautomer.

In our previous publications we have demonstrated the significant influence of the Thorpe-Ingold effect on the structure of products derived from the action of phenyllithium on selected glutarimides.[12]



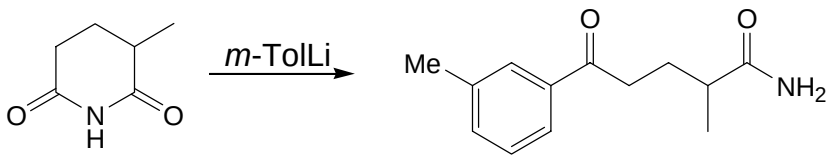
In the case of 4,4-dimethylglutarimide (**7**), the stereoelectronic stabilization is sufficiently strong to allow the separation and full spectroscopic characterization of both tautomers (**8**) and (**9**). The addition of

another pair of geminal methyls to the glutarimide ring completely shifts the tautomeric equilibrium towards the cyclic form (**11**), making the open-chain congener undetectable.[12] Following our earlier findings, we present here a further elaboration of the reactivity of the glutarimide system bearing various number of methyl substituents. That allows both the study of the regioselectivity of nucleophilic addition, and also the Thorpe-Ingold effect.

RESULTS AND DISCUSSION

Several non-symmetrically substituted glutarimides, namely: 3-methyl-, 3,3-dimethyl-, and 3,3,4,4-tetramethylglutarimide (**12, 14, 18**) were prepared, mostly by using well-known methods. They were subsequently treated with a multi-molar excess of phenyllithium and the compositions of the reaction mixtures were analysed after a standard workup.

In the case of 3-methylglutarimide (**12**)**,** only one product was obtained in a 9% yield and the starting material was recovered. The open chain structure of the product has already been proven.[18] A similar result was obtained when *m*-tolyllithium was used in this reaction. The product was isolated in a 17% yield along with approx. 80% of the recovered starting imide (**12**). Relatively low chemical yields obtained in the above mentioned reactions might be explained by the preliminary formation of the lithium salt at the imide nitrogen which decreased the electrophylicity in both carbonyls. Compound (**12**) revealed comparable spectral features to those obtained previously. Thus, in an aromatic region of ^{1}H NMR spectrum two groups of signals (7.33-7.39 and 7.75-7.76 ppm) were observed which are often attributed to the *ortho* deshielding effect of the carbonyl group attached to the aromatic ring. That supports the assignment of the open-chain structure (**13**) for this compound. The presence of the carbonyl carbon atom signal in ^{13}C NMR spectrum at 200.3 ppm is also consistent with this assignment.



12 **13**

The above was additionally confirmed by the X-Ray crystallographic analysis of product (**13**)**.** The experimental and refinement data are given in **Table 1**. The molecular structure obtained from crystallographic studies is shown in **Figure 1**. In the crystal structure two types of NH···O hydrogen bonds of similar dimensions which involve two amide hydrogen atoms and both carbonyl oxygens are observed.

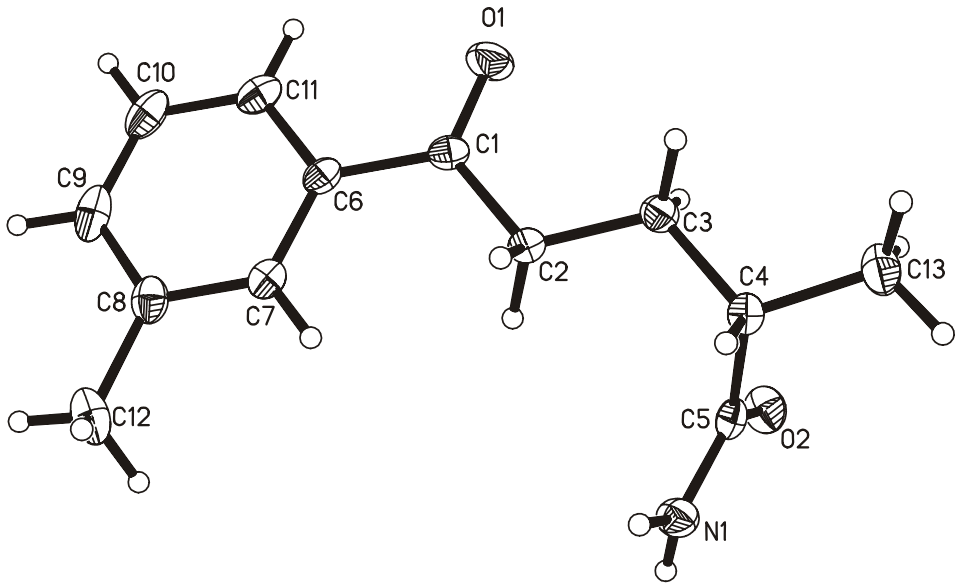
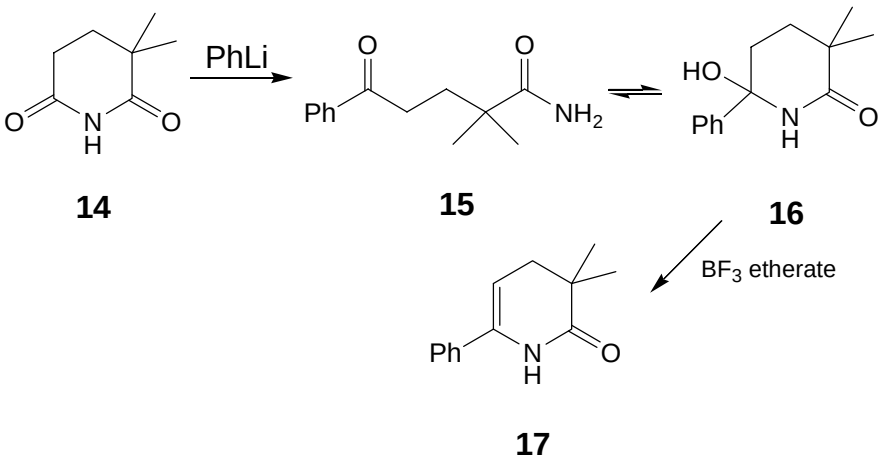


Figure 1. Molecular structure of **13**. The non hydrogen atoms are shown as 20% probability ellipsoids.

No other tautomeric forms were detected by spectroscopic methods.

An additional unexpected feature of this type of reaction is a high degree of regioselectivity observed. Compound (**13**) was the only product indicated by high field NMR spectra of the crude reaction mixture. Therefore it is not surprising that in the case of 3,3-dimethylglutarimide (**14**) again only one carbonyl group was attacked by phenyllithium under the same conditions. Interestingly, two compounds (**15**) and (**16**) were formed in 38% and 19% yields, respectively.



14 **15** **16** **17**

No traces of other regioisomers were detected. In the case of compound (**15**), a very similar shape of the ^{1}H NMR spectrum was observed. Again, an *ortho* deshielding effect in the aromatic region (signals at 7.40-7.59 and 7.94-7.99 ppm), together with the presence of carbonyl group resonance at 200.0 ppm

showed up in ^{13}C NMR spectrum. Careful column chromatography allowed the separation of compounds (**15**) and (**16**). An X-Ray analysis of a single crystal of **15** proved its open chain structure, also in the solid state. The experimental and refinement data are shown in **Table 1**. The molecular structure of **15** observed in the crystalline state is shown in **Figure 2**. The crystal shows considerable thermal motions in the phenyl ring region which might be interpreted as librations and shown as a partial disorder of this region (see **Figure 2**). Although the bond dimensions in the phenyl ring region are somewhat distorted by thermal motion, the whole molecular structure seems rational and similar to **13**. Also the hydrogen bonds characteristic of (**13**), NH···O intermolecular interactions, are observed and all donor and acceptor functions are employed.

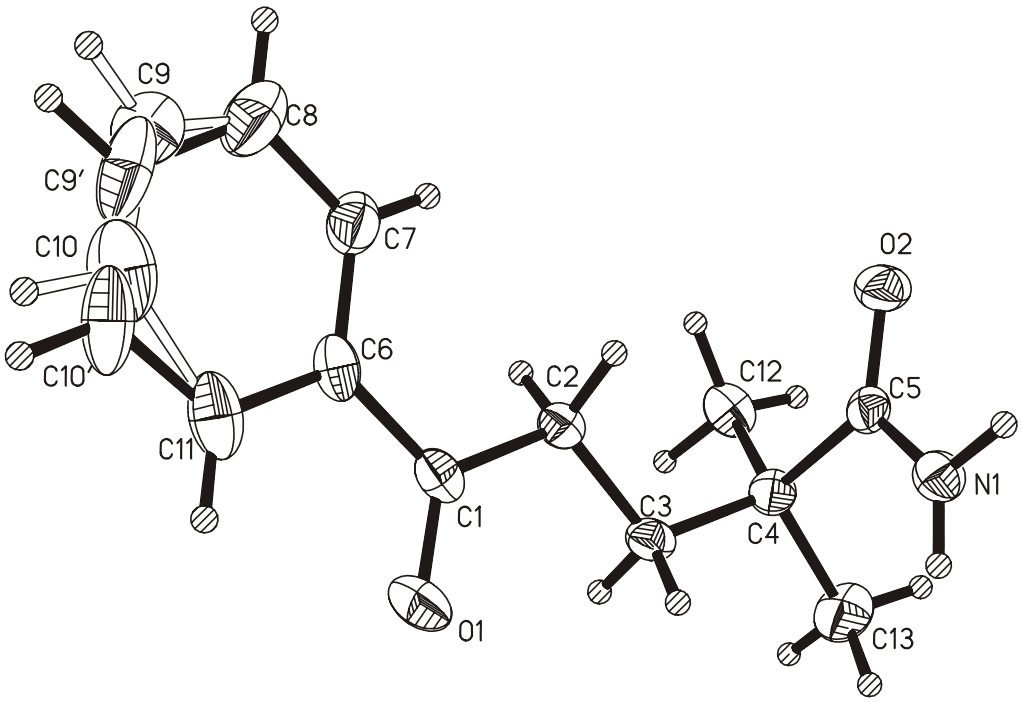


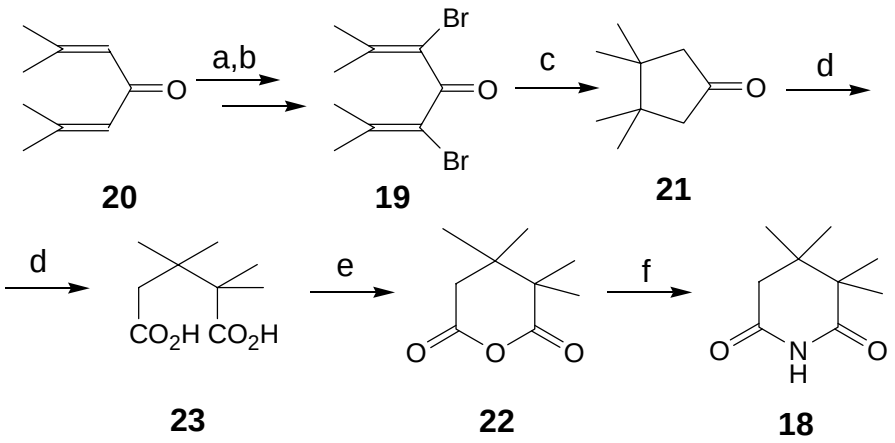
Figure 2. Molecular structure of **15**. The non hydrogen atoms are shown as 20% probability ellipsoids. Two alternative positions of the disordered phenyl ring are visualized.

Despite repeated efforts we were unable to obtain a single crystal of **16** suitable for X-Ray analysis. However, in our opinion both ^{1}H and ^{13}C NMR spectrum unambiguously pointed the hydroxy lactam structure of **16**. Quite indicative was the absence of the *ortho* deshielding effect, the presence of both methyl groups as singlets at 0.80 ppm and 0.99 ppm in ^{1}H NMR spectrum, together with the extinction of the carbonyl carbon group signal in ^{13}C NMR spectrum at 200.0 ppm in favor of the appearance of a tertiary alcohol resonance at 88.8 ppm. An additional drawback in handling compounds (**15**) and (**16**) was the fact that both of them existed in a relatively fast tautomeric relationship, accompanied by a facile dehydration process that brought about the formation of enamide (**17**) whose structure was confirmed by

the presence of the olefin hydrogen triplet (5.39 ppm, J=5 Hz) in ^{1}H NMR spectrum and the olefin carbon signal at 101.7 ppm in ^{13}C NMR spectrum.

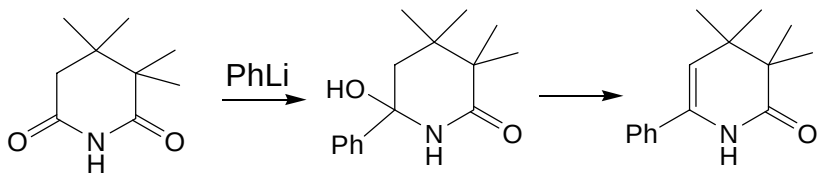
The presence of hydroxy lactam structure (**16**) derived from compound (**14**) seems to be the consequence of the Thorpe-Ingold effect. A similar behaviour has previously been observed in the case of 4,4-dimethylglutarimide.[12]

Analogously, we prepared 3,3,4,4-tetramethylglutarimide (**18**) according to the modified procedure given by Ingold[19] in which dibromophorone (**19**) (obtained from phorone (**20**)) was subjected to cyclisation by hydroiodic acid – red phosphorus treatment. The cyclopentanone derivative (**21**) thus formed was subsequently oxidized by HNO_3 followed by the anhydride (**22**) formation from acid (**23**). The reaction with aqueous ammonia and pyrolysis of the salt produced imide (**18**) in a moderate yield.



Reagents and conditions: (a) Br_2, CCl_4, 95%; (b) pyridine, 0°C, 24 h, 85%; (c) HI, P_{red}, reflux, 42%; (d) HNO_3, reflux, 67%; (e) AcCl, reflux, 98%; (f) NH_3(aq.), 230°C, 2 h, 90%.

The introduction of yet another pair of methyl groups to the imide ring of **18** shifts the tautomeric equilibrium between the cyclic and the open-chain forms even further. Thus, when (**18**) was used, the only product detected after the reaction with phenyllithium was the hydroxy lactam (**24**), which was formed in a 59% yield.



This compound was extremely prone to the dehydration process and even carefully purified solvents promoted its transformation into **25**. The result of the X-Ray structure analysis of this product is shown in **Figure 3**, whereas the experimental and refinement details are given in **Table 1**. The crystal structure is build up from molecular hydrogen bonded dimers bonded *via* pairs of NH···O hydrogen bonds between symmetry related molecules.

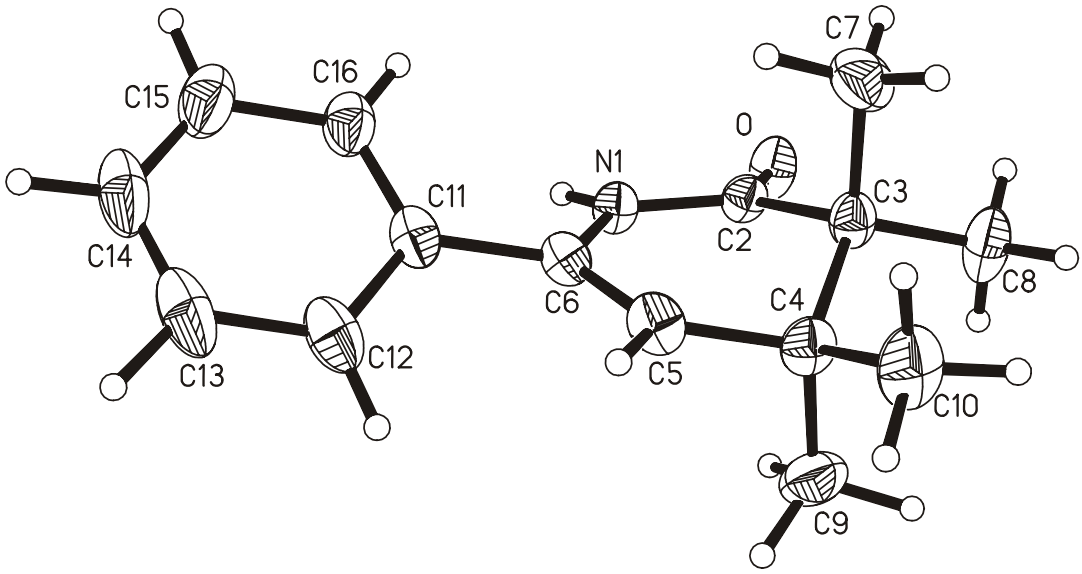


Figure 3. The molecular structure of **25** together with the numbering scheme. The non-hydrogen atoms are shown as 30% probability ellipsoids

We managed to collect spectral data for compound (**24**) in which similar phenomena to those for **16** were observed. In ^{1}H NMR the presence of four methyl resonances (at 0.54, 0.86, 1.02 and 1.15 ppm) confirmed the cyclic structure of this compound. Also, in ^{13}C NMR spectrum there was a signal at 84.0 ppm, which was indicative of a tertiary hydroxy group. The *ortho* deshielding effect in ^{1}H NMR spectrum and a carbonyl carbon atom resonance at 200.0 ppm in ^{13}C NMR spectrum were not present for this compound, which excluded the open-chain tautomer structure. We were unable to detect any traces of the other regioisomer of compound (**24**) in the crude reaction mixture. We obtained a monocrystal of compound (**24**). Its X-Ray analysis is in full accordance with all previous assignments. To prevent the crystal from decomposition, the crystallographic measurements were performed at a low temperature. The molecular structure of **24** is shown in **Figure 4** whereas the experimental and refinement data are given in **Table 1**. In the crystal structure strong OH···O hydrogen bonds between hydroxyl hydrogen and carbonyl oxygen atoms from symmetry related molecules are present. Some much weaker CH···O and CH···π interactions are also visible.

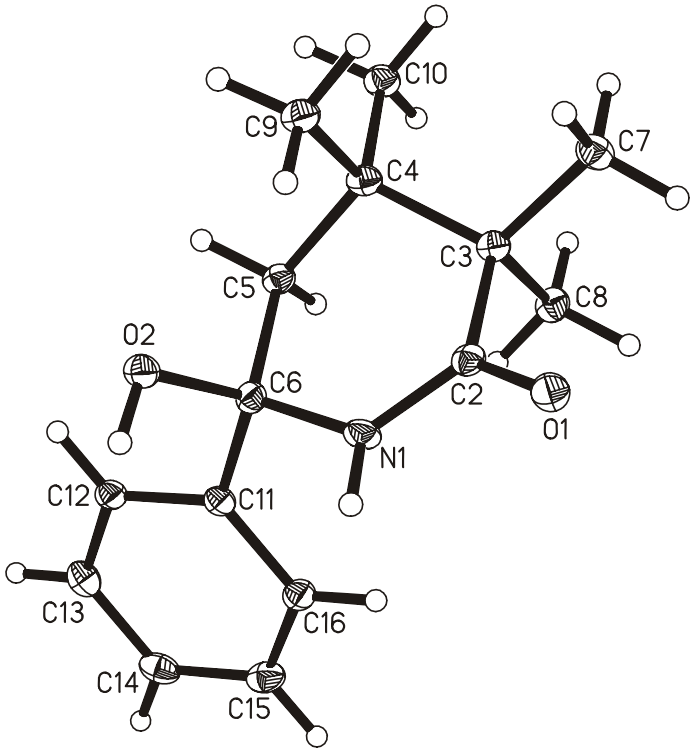


Figure 4. Molecular structure of **24** together with the numbering scheme. The non-hydrogen atoms are shown as 30% probability ellipsoids.

EXPERIMENTAL

GENERAL

The NMR spectra were recorded on a Varian Unity Plus spectrometer operating at 500 MHz or 200 MHz for ^{1}H NMR and 125 MHz or 50 MHz for ^{13}C NMR, respectively. Tetramethylsilane (TMS) was used as the internal standard. Chemical shifts are reported in ppm. Coupling constants (J) are reported in hertz. Melting points are uncorrected. Column chromatographic separations were carried out on silica gel (70-230 mesh or 230-400 mesh) or on neutral aluminum oxide (activity III) and were monitored by TLC on silica gel or aluminum oxide plates, which were visualized by UV radiation and/or iodine vapours. Diethyl ether was distilled from CaH_2 before use. Bromobenzene and chloroform were also distilled before use. In the case of sensitive compounds solvents for chromatography were redistilled and stored over neutral aluminum oxide. Most of the X-Ray crystallographic data were collected at room temperature on a Kuma KM4 single crystal κ-axis diffractometer using MoKα radiation. The data for **24**, however, were collected at 143 K using a Kuma KM4CCD apparatus. The data were corrected for Lorentz and polarization effects but not for absorption. Crystal structures were solved using dirrect methods from SHELXS97[22] and refined by the application of the SHELXL97 [23] software. X-Ray data are collected in **Table 1**.

Table 1. Crystal data and structure refinement details.

Identification code	**13**	**15**	**25**	**24**
Empirical formula	C_{13} H_{17} N O_2	C_{13} H_{17} N O_2	C_{15} H_{19} N O	C_{15} H_{21} N O_2
Formula weight	219.28	219.28	229.31	247.33
Temperature	293(2) K	293(2) K	293(2) K	173(2) K
Wavelength	0.71073 Å	0.71073 Å	0.71073 Å	0.71073 Å
Crystal system	Monoclinic	Triclinic	Monoclinic	Monoclinic
Space group	$P2_1/n$	P -1	$P2_1/n$	P $2_1/c$
Unit cell dimensions	a = 9.572(2) Å, α= 90°.	a = 7.578(2) Å, α= 111.76(3)°.	a = 10.056(2) Å, α= 90°.	a = 7.5878(15) Å, α= 90°
	b = 9.191(2) Å, β= 106.30(3)°.	b = 9.262(2) Å, β= 99.93(3)°.	b = 10.734(2) Å, β= 111.70(3)°.	b = 20.742(4) Å, β= 101.90(3)°.
	c = 14.406(3) Å, γ = 90°.	c = 10.127(2) Å, γ = 102.32(3)°.	c = 13.595(3) Å, γ = 90°.	c = 8.7157(17) Å, γ = 90°.
Volume	1216.4(4) $Å^3$	619.7(2) $Å^3$	1363.4(5) $Å^3$	1342.3(5) $Å^3$
Z	4	2	4	4
Density (calculated)	1.197 Mg/m^3	1.175 Mg/m^3	1.117 Mg/m^3	1.224 Mg/m^3
Absorption coefficient	0.080 mm^{-1}	0.079 mm^{-1}	0.069 mm^{-1}	0.081 mm^{-1}
F(000)	472	236	496	536
Crystal size	0.5 x 0.4 x 0.3 mm^3	0.6 x 0.4 x 0.4 mm^3	0.7 x 0.6 x 0.4 mm^3	0.3 x 0.25 x 0.2 mm^3
θ range for data collection	2.29 to 25.00°.	2.25 to 30.00°.	2.18 to 28.00°.	3.37 to 25.00°.
Index ranges	$-11\le h\le 0$, $0\le k\le 10$, $-16\le l\le 17$	$-9\le h\le 10$, $-13\le k\le 12$, $0\le l\le 14$	$-12\le h\le 13$, $-14\le k\le 0$, $-12\le l\le 17$	$-9\le h\le 9$, $-24\le k\le 24$, $-10\le l\le 10$
Reflections collected	2269	3728	3370	21284
Independent reflections	2134 [R(int) = 0.0626]	3542 [R(int) = 0.0162]	3234 [R(int) = 0.0104]	2359 [R(int) = 0.0850]
Refinement method	Full-matrix least-squares on F^2			
Data / restraints / parameters	2134 / 0 / 197	3542 / 9 / 213	3234 / 0 / 230	2359 / 0 / 171
Goodness-of-fit	1.008	0.997	1.025	1.082
Final R1 and wR2 [I>2sigma(I)]	R1 = 0.0360, wR2 = 0.0962	R1 = 0.0440, wR2 = 0.1223	R1 = 0.0444, wR2 = 0.1245	R1 = 0.0540, wR2 = 0.1299
R1 and wR2 (all data)	R1 = 0.0906, wR2 = 0.1179	R1 = 0.1192, wR2 = 0.1574	R1 = 0.0785, wR2 = 0.1498	R1 = 0.0671, wR2 = 0.1386
Largest diff. peak and hole	0.186 and -0.189 $e.Å^{-3}$	0.161 and -0.264 $e.Å^{-3}$	0.258 and -0.167 $e.Å^{-3}$	0.239 and -0.228 $e.Å^{-3}$
CCDC deposition number	2134 / 0 / 197	218694	218696	218697

3,3,4,4-Tetramethylcyclopentanone (21). According to modified Ingold's procedure,[19] 3,5-dibromo-2,6-dimethylhepta-2,5-dien-4-one (α,α'-dibromophorone **19**, 25 g, 85 mmol), hydriodic acid (250 mL, 54 wt. %) and red phosphorus (30 g, 1 mol) were gently refluxed for 4 h. After cooling down to rt, 1 L of water was added and the mixture was steam distilled. A first 250 mL portion of the distillate was collected and extracted with dichloromethane (5×25 mL). Combined organic layers were dried over anhydrous $MgSO_4$ and concentrated. The residue was chromatographed on silica gel using dichloromethane/hexane (2:1 v/v) as an eluent resulting in compound (**21**) (5 g, 42%) as a white solid, mp 130-131°C (lit.,[19] mp 130°C). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.03 (s, 12H), 2.20 (s, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 23.93, 40.22, 52.48, 218.83.

2,2,3,3-Tetramethylpentanedioic acid (23). Compound (**21**) (5 g, 36 mmol), 10 mL of water and 10 mL of 68% nitric acid were mixed and the reaction mixture was refluxed until the evolution of brown nitrogen oxides ceased. After cooling down to rt a white solid was obtained (4.5 g, 67%), mp 144-145°C (lit.,[19] mp 144°C). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.15 (s, 6H) 1.19 (s, 6H) 2.47 (s, 2H), 10.0 (br s, 2H, disappeared with D_2O); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.0, 22.9, 37.7, 42.3, 48.4, 179.1, 183.4; MS (ES) (m/z) $[M+Na]^+$ = 211, $[M-H]^-$ = 187; IR (KBr, cm^{-1}) 2980, 1695, 1290.

3,3,4,4-Tetramethyldihydro-2*H*-pyran-2,6(3*H*)-dione (22). Compound (**23**) (4 g, 21 mmol) and acetyl chloride (30 mL, 420mmol) were gently refluxed for 2 h. Then volatile reagents were removed in *vacuo* and the resulting precipitate was recrystallized from hexane to give compound (**22**) (3.3 g, 98%) mp 183-184°C (lit.,[19] mp 184°C). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.08 (s, 6H), 1.30 (s, 6H), 2.70 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.3, 23.8, 34.1, 42.4, 45.8, 166.0, 172.7; IR (KBr, cm^{-1}) 3440, 2985, 1805, 1770, 1175, 1050, 1005.

GENERAL PROCEDURE OF IMIDES PREPARATION.

To a solution of acid anhydride (24 mmol) in dioxane (10 mL) concentrated aqueous ammonia (20 mL) was added. After 30 min all solvents were evaporated under vacuum and the residue was heated neat at 230°C for 2 h. The resulting brownish solid was chromatographed on silica gel using chloroform as an eluent to afford an appropriate imide. Each sample of imide taken to the subsequent step was vacuum dried over P_2O_5.

3-Methylpiperidine-2,6-dione (12). mp 92-93°C (lit.,[20] mp 91-92°C). Yield 89%. Spectral data were in accordance with the literature.[20]

3,3-Dimethylpiperidine-2,6-dione (14). mp 142-143°C (lit.,[21] mp 137-144°C). Yield 94%. Spectral data were in accordance with the literature.[21]

3,3,4,4-Tetramethylpiperidine-2,6-dione (18). mp 202-203°C (lit.,[19] mp 202°C). Yield 90%. ^{1}H NMR ($CDCl_3$, 200 MHz) δ1.05 (s, 6H), 1.24 (s, 6H), 2.53 (s, 2H), 8.29 (br s, 1H, disappeared with D_2O); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 20.3, 24.0, 35.2, 44.0, 45.6, 171.5, 178.9; IR (KBr, cm^{-1}) 3205, 2990, 2965,

1725, 1680, 1285; MS (EI) m/z (rel intensity in %) 169 (M^+, 49), 154 (11), 113 (42), 110 (10), 100 (15), 87 (31), 86 (29), 84 (76), 83 (100), 70 (37), 69 (47), 57 (12), 56 (11), 55 (31).

GENERAL PROCEDURE FOR REACTIONS BETWEEN IMIDES AND PHENYLLITHIUM.

To the lithium turnings (250 mg, 36 mmol) in 30 mL of ether either bromobenzene or *m*-bromotoluene (54 mmol) in 5 mL of ether was slowly added at rt with stirring during a period of 1 h. After additional 1 h the solution was cooled down to -78°C and an appropriate imide (3.6 mmol) suspended in 5 mL of anhydrous ether was added in one portion. After 30 min of stirring at -78°C the mixture was allowed to reach rt overnight. 5 mL of water was carefully added and the reaction mixture was evaporated and extracted with ethyl acetate (5x20 mL). Combined organic layers were evaporated and the residue was chromatographed giving the following products:

2-Methyl-5-(3-methylphenyl)-5-oxopentanamide (13). Obtained from imide (**12**) (457 mg, 3.6 mmol) and isolated by column chromatography on basic aluminum oxide using chloroform as eluent with yield 17% (124 mg) along with 361 mg (79%) of the recovered imide (**12**). Recrystallized from $CHCl_3$ mp 128-129ºC. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.21 (d, J=7 Hz, 3H), 1.87 (m, 1H), 2.05 (m, 1H), 2.41(s, 3H), 2.45 (app. sextet, 1H), 2.98 (m, 1H), 3.11 (m, 1H), 5.70 and 5.75 (two br s, 2H, *s-cis* NH and *s-trans* NH), 7.36 (m, 2H), 7.76 (d, J= 9 Hz, 1H), 7.77 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 17.9, 21.4, 28.6, 35.9, 39.6, 125.3, 128.5, 128.6, 134.0, 136.7, 138.4, 178.6, 200.3; MS (ES) $[M+H]^+$ = 220, $[M+Na]^+$ = 242; HRMS m/z calcd for $C_{13}H_{17}NO_2Na$ 242.1157 found 242.1136.Anal. Calcd for $C_{13}H_{17}NO_2$: C 71.21, H 7.81, N 6.39. Found: C 71.28, H 7.69, N 6.27.

2,2-Dimethyl-5-oxo-5-phenylpentanamide (15) and **6-hydroxy-3,3-dimethyl-6-phenylpiperidin-2-one (16)**. The products (**15**) and (**16**) were prepared from **14** (508 mg, 3.6 mmol) and isolated by column chromatography on neutral aluminum oxide using chloroform as eluent: **15** with yield 38% (300 mg), mp 133-134°C and **16** with yield 19% (150 mg), mp 155-156°C along with 208 mg (41%) of recovered imide (**14**).

2,2-Dimethyl-5-oxo-5-phenylpentanamide (15). Recrystallized from ethyl acetate. ^{1}H NMR ($CDCl_3$, 200 MHz) 1.27 (s, 6H), 1.94 (m, 2H), 3.01 (m, 2H), 5.87 and 6.17 (two br s, 2H, *s-cis* NH and *s-trans* NH), 7.40 – 7.60 (m, 3H), 7.97 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 25.6, 34.4, 35.0, 41.6, 128.1, 128.5, 133.0, 136.7, 180.2, 200.0; IR (KBr, cm^{-1}) 3425, 3160, 1670, 1445 MS; (ES) $[M+Na]^+$ = 242; HRMS m/z calcd for $C_{13}H_{17}NO_2Na$ 242.1157 found 242.1146. Anal. Calcd for $C_{13}H_{17}NO_2$: C 71.21, H 7.81, N 6.39. Found: C 71.31, H 7.72, N 6.30.

6-Hydroxy-3,3-dimethyl-6-phenylpiperidin-2-one (16). Recrystallized from $CHCl_3$. ^{1}H NMR ($CDCl_3$, 200 MHz) 0.79 (s, 3H), 0.98 (s, 3H), 1.43 (m, 1H), 2.30 – 2.60 (m, 3H), 3.88 (s, 1H, disappeared with D_2O), 6,37 (br s, 1H, disappeared with D_2O), 7.30 – 7.40 (m, 3H), 7.40 – 7.50 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 23.0, 23.8, 28.6, 31.0, 36.9, 88.8, 127.5, 127.7, 127.8, 128.3, 128.4, 141.0, 174.1; IR (KBr, cm^{-1}) 3320, 2925, 1640, 1390; MS (EI) m/z (rel intensity in %) 219 (M^+, 15), 218(100), 202 (42), 190

(25), 177(12), 176 (44), 162 (13), 148 (22), 136 (33), 134 (14), 122 (37), 105 (80), 104 (33), 77 (37), 56 (12), 55 (11), 51 (10), 41 (17); HRMS m/z calcd for $C_{13}H_{17}NO_2Na$ 242.1147 found 242.1169. Anal. Calcd for $C_{13}H_{17}NO_2$: C 71.21, H 7.81, N 6.39. Found: C 71.25, H 7.74, N 6.14.

6-Hydroxy-3,3,4,4-tetramethyl-6-phenylpiperidin-2-one (24). Obtained from compound (**18**) (608 mg, 3.6 mmol) and purified by column chromatography on silica gel using benzene and ethyl acetate as eluents, starting from pure benzene to benzene:ethyl acetate (1:1 v/v). It gave 525 mg of **24**, 59%, mp 143-144°C. Recrystallized from benzene. ^{1}H NMR (benzene-d_6, 500 MHz) δ 0.54 (s, 3H), 0.86 (s, 3H), 1.02 (s, 3H), 1.15 (s, 3H), 1.85 (q_{AB}, J=14.5 Hz), 5.00 (s, 1H, disappeared with D_2O), 7.08 (tt, 1H, J_1=7.8, J_2=1.5 Hz), 7.17 (td, 2H, J_1=7.8, J_2=1.5 Hz), 7.29 (s, 1H, disappeared with D_2O), 7.55 (dt, 2H, J_1=7.7, J_2=1.5 Hz); ^{13}C NMR (benzene-d_6, 125 MHz) δ 19.3, 23.2, 24.7, 26.2, 35.6, 44.4, 48.0, 84.0, 125,4, 127.8, 128.6, 148.5, 179.6; MS (EI) m/z (rel intensity in %) 247 (M^+, 4), 230 (39), 229 (23), 215 (16), 214 (100), 199(11), 191 (18), 170 (21), 160 (23), 128 (10), 122 (18), 105 (19), 104 (10), 84 (82), 83 (10), 77 (21), 70 (12), 69 (41), 55 (12), 41 (24); IR (KBr, cm^{-1}) 3295, 2975, 1655, 1625, 1405, 1170; HRMS m/z calcd for $C_{15}H_{21}NO_2Na$ 270.1470 found 270.1476. Anal. Calcd for $C_{15}H_{21}NO_2$: C 72.84, H 8.56, N 5.66. Found: C 73.01, H 8.66, N 5.48.

3,3-Dimethyl-6-phenyl-3,4-dihydropyridin-2(1*H*)-one (17). Keto amide (**15**) (100 mg, 0.46 mmol) was dissolved in 5 mL of chloroform and one drop of BF_3 etherate was added. After 30 min the solvents were removed and a short-path chromatography on neutral aluminum oxide was performed with chloroform as eluent, giving compound (**17**) (90 mg, 98%), mp 143°C. Recrystallized from $CHCl_3$. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.25 (s, 6H), 2.37 (d, J=5.0 Hz, 2H), 5.41 (td, 1H, J_1=5.0, J_2=1.8 Hz), 7.10 (br s, 1H, disappeared with D_2O), 7.40 (m, 5H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 24.5, 36.0, 36.9, 101.7, 124.7, 128.7, 128.9, 135.0, 136.3, 177.1; MS (ES) $[M+H]^+$ = 202. Anal. Calcd for $C_{13}H_{15}NO$: C 77.58, H 7.51, N 6.96. Found: C 77.42, H 7.39, N 6.61.

3,3,4,4-tetramethyl-6-phenyl-3,4-dihydropyridin-2(1*H*)-one (25). Attempted purification of compound (**24**) (100 mg, 0,4 mmol) by recrystallization from chloroform gave compound 25 (92 mg, 99%), mp 137°C. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.09 (s, 6H), 1.17 (s, 6H), 5.17 (d, 1H, J=1.8 Hz), 7.11 (bs, 1H, disappeared with D_2O), 7.34-7.41 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 19.2, 23.0, 37.4, 44.3, 114.5, 124.7, 128.6, 128.9, 133.0, 134.9, 178.0; IR (KBr, cm^{-1}) 3200, 3105, 2975, 1675, 1660, 1345; MS (EI) m/z (rel intensity in %) 229 (M^+, 30), 215 (15), 214 (100), 199 (12), 160 (22), 143 (10); HRMS m/z for $C_{15}H_{19}NONa$ 252.1364 found 252.1335. Anal. Calcd for $C_{15}H_{19}NO$: C 78.56, H 8.35, N 6.11. Found: C 78.65, H 8.21, N 5.89.

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