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New Routes to Oxindole Derivatives

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Summary. A new, practical synthesis of the antirheumatic oxindole derivative, tenidap, has been elaborated. The new approach has initiated studies on the mechanism of the acylation reactions of oxindoles. Methods have been developed for the synthesis of 1-[alkoxy(or aryloxy)carbonyl]- and 1,3-di[alkoxy(or aryloxy)carbonyl]oxindoles starting from oxindoles. The route designed for tenidap has provided a facile access to several analogues, too.

On another front, new reaction conditions are described, which turn *Wenkert*'s synthesis of 3-alkyloxindoles (by *Raney* nickel induced alkylation of oxindoles with alcohols) into a highly efficient synthetic tool. The method has been extended to the synthesis of 3-alkyloxindoles from isatins and to the preparation of 3-(ω-hydroxyalkyl)oxindoles from oxindoles and isatins.

Keywords. Acylation; Alkylation; Isatins; Oxindoles; Regioselectivity.

Introduction

The biological activity of oxindole (2-oxo-2,3-dihydroindole, 1,3-dihydro-2*H*-indol-2-one) derivatives and their structural relationship to indoles makes these compounds important targets in medicinal and synthetic organic chemistry [1–4]. Oxindoles showing cyclooxygenase inhibiting activity and cytokine modulating properties have been developed for the treatment of rheumatoid arthritis and osteoarthritis. An outstanding representative of these antirheumatic oxindoles, tenidap (**2**, (*Z*)-5-chloro-3-[1-hydroxy-1-(2-thienyl)methylene]-2-oxo-2,3-dihydro-1*H*-indole-1-carboxamide), was discovered and developed by Pfizer and regulatory approval was granted for its sodium salt in several countries [4–6]. Despite the very high market expectations, finally it was not launched because of concerns about reduced bone mineral density associated with its use.

The methods previously described for the synthesis of tenidap are shown in Scheme 1. Two routes were elaborated starting from 5-chlorooxindole (**1a)** [7, 8] just differing in the sequence of introduction of substituents. According to the first procedure, the thienoylation of compound **1a** with thiophene-2-carbonyl chloride

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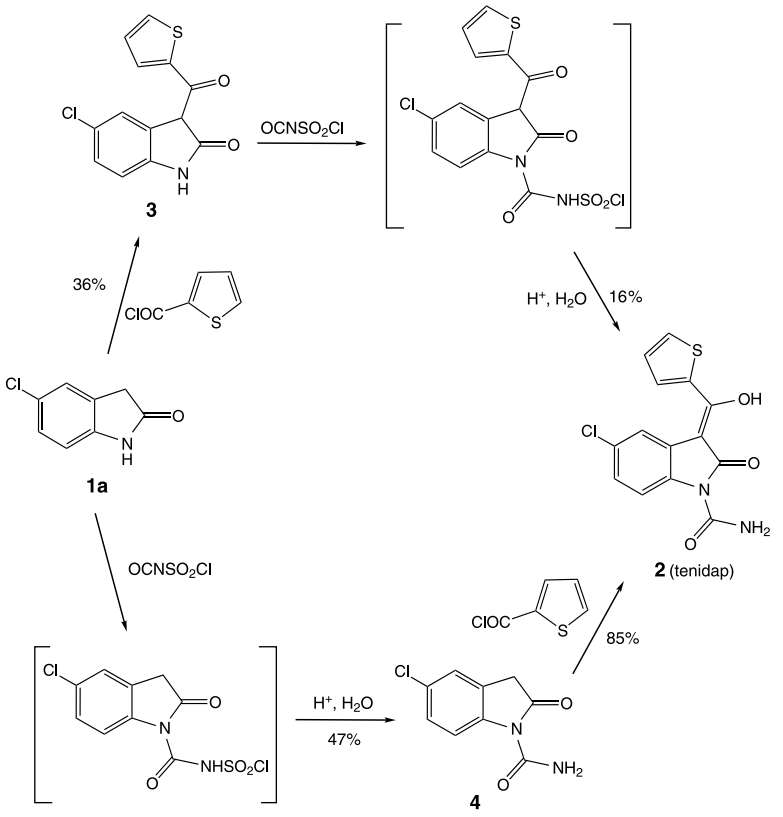


Scheme 1. The 3-acylated oxindoles may exist either in oxo or in enol form; in addition, the enol form may adopt an *E* or a *Z* configuration

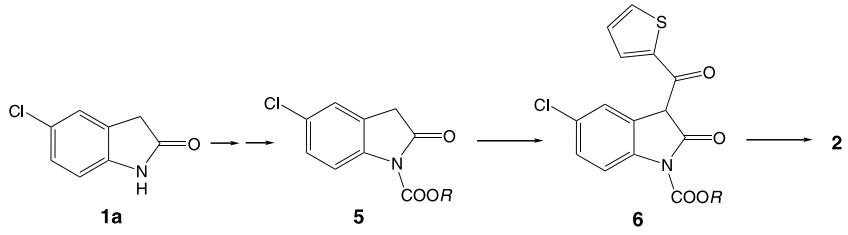
to compound **3** [8] is followed by *N*-amidation performed with chlorosulfonyl isocyanate and subsequent hydrolysis [9]. The second route involves the preparation of the 1-carbamoyl derivative **4** in the first step by the reaction of oxindole **1a** with chlorosulfonyl isocyanate and subsequent hydrolysis. Thienoylation of compound **4** afforded tenidap (**2**) [9, 10].

In the late nineties we were interested in the elaboration of a new patentable manufacturing synthesis of tenidap (**2**). Our activity in the field of oxindole chemistry has been initiated by this project.

Results and Discussions

New Practical Synthesis of Tenidap

The concept of our new synthetic route has been strongly influenced by the decision that we wanted to avoid the use of chlorosulfonyl isocyanate in our manufacturing process. Therefore our strategy for the new synthesis was to use the appropriate *N*-carboxylate as the precursor of the *N*-carbamoyl functionality, *i.e.* to introduce the *N*-carbamoyl moiety *via* alkoxy(or aryloxy)carbonylation of the oxindole nitrogen followed by treatment with ammonia. Compounds **3** and **4** could not be used in our synthesis for patent reasons. Therefore the *N*-carbamoyl group of



Scheme 2

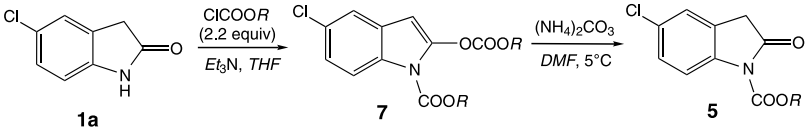
tenidap (**2**) would have to be introduced in the last step by ammonolysis of the key *N*-carboxylate **6** (Scheme 2) prepared by thienoylation of compound **5** [11, 12].

First we addressed the task of preparing *N*-alkoxy(or aryloxy)carbonyloxindoles **5**. The reaction of oxindole (**1b**) with one equivalent of ethyl chloroformate in the presence of triethylamine in *THF* is reported to give the corresponding *N*-ethoxycarbonyl derivative after chromatographic separation [13]. The low yield (20%) can be attributed to the simultaneous formation of *N*,*O*-diethoxycarbonylated product as indicated by our experiments.

N,*O*-Diethoxycarbonylation of some 3-substituted oxindoles with an excess of ethyl chloroformate has also been reported [14]. Considering these data we decided to carry out the synthesis of compounds **5** in a new two-step sequence starting from the readily available 5-chlorooxindole (**1a**) [7, 8]. In the first step, oxindole **1a** was treated with 2.2 equiv of ethyl chloroformate in the presence of triethylamine in *THF* to afford 5-chloro-1-ethoxycarbonyl-2-(ethoxycarbonyloxy)indole (**7a**) in excellent yield (Scheme 3). The corresponding methyl and phenyl esters (**7b** and **7c**) were obtained similarly. In the second step, selective *O*-ammonolysis of compounds **7** was accomplished with ammonium carbonate in *DMF* under mild conditions (0–6°C, ∼3 h, 25°C, ∼3 h, one equivalent of ammonium carbonate) to furnish oxindole-1-carboxylates **5** in good yield.

It is suggested in the patent literature that 3-thienoylation can be carried out in the presence of various amines, however, 4-(dimethylamino)pyridine (*DMAP*) is obviously preferred [9, 10]. Our observations, which helped us to understand the nature of the reaction, are summarized in Scheme 4.

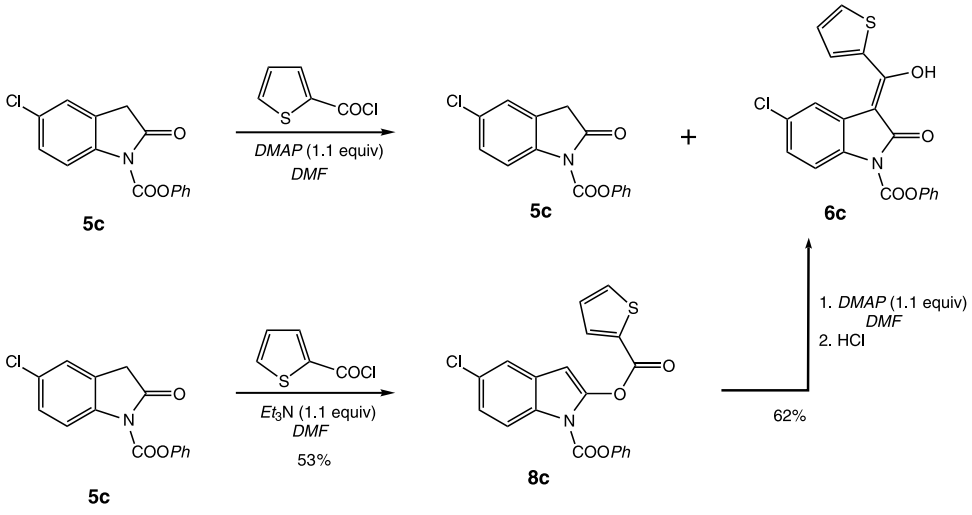
Thienoylation of the phenyl carbamate **5c** in the presence of 1.1 equiv of *DMAP* gave a mixture of the starting compound and the 3-thienoyl derivative **6c**. When the same reaction was carried out in the presence of 1.1 equiv of triethylamine, the *O*-thienoyl derivative **8c** was obtained. Treatment of the *O*-thienoyl



	7a	7b	7c
R	Et	Me	Ph
%	71	78	84

	5a	5b	5c
R	Et	Me	Ph
%	70	72	85

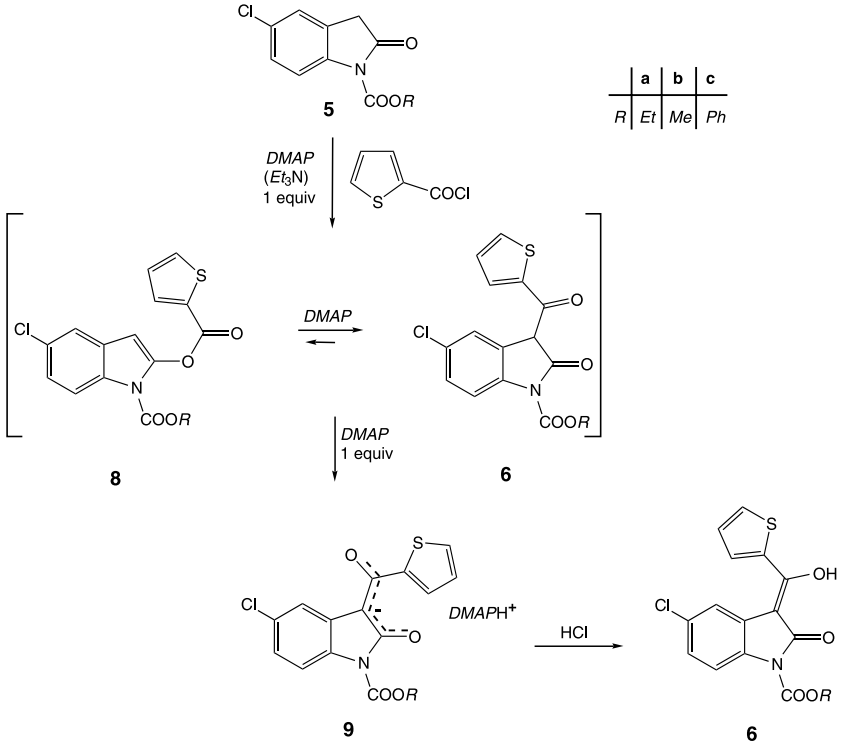
Scheme 3



Scheme 4

derivative **8c** with 1.1 equiv of *DMAP* afforded the required *C*(3)-thienoyl derivative **6c**. It is important to note that a catalytic amount of *DMAP* is not sufficient for the reaction.

The multistep reaction sequence of the thienoylation reaction is summarized in Scheme 5. Treatment of the oxindole-*N*-carboxylate **5** in the presence of one equiv



Scheme 5

of triethylamine or *DMAP* affords the *O*-thienoylated derivative **8**. The rearrangement to the *C*(3)-thienoylated product **6** takes place only in the presence of *DMAP*. Because of the β-keto amide structure of the product **6**, the $O \rightarrow C$ rearrangement should be reversible in the presence of a base, in principle. In spite of this fact the reaction can be accomplished, the equilibrium is driven by enolisation to the right as demonstrated by the isolation of the dimethylaminopyridinium enolate salts **9**, which were converted to the corresponding enols **6** by acidification (Scheme 5).

The *X*-ray structure analysis of compound **9a** revealed that the salt adopts an *E* configuration in the crystalline state [12]. The protonated *DMAP* cation (*DMAP*H^+) is linked with hydrogen bonds to the oxygen of the ring and the carbamate carbonyls. However, the temperature dependence of the chemical shifts of oxindole *C*(4) and thiophene *C*(3) hydrogen and the N*O*E observed between them in ^{1}H NMR studies shows the presence of the *Z* isomer in $CDCl_3$ solution, indicating the possibility of a rotation around the bond between oxindole *C*(3) and the carbon attached to the ring. The *E* isomer is expected to be the more stable one due to the electrostatic repulsion between the oxygens in the *Z* isomer.

The 3-thienoyl derivatives **6** obtained from the enolate salts **9** by acidification exhibit a *Z* enol structure both in solution and in the crystalline form as indicated by ^{1}H NMR and single crystal *X*-ray studies of compound **6a** [12]. A significant N*O*E between oxindole *C*(4) and thiophene *C*(3) hydrogens was detected.

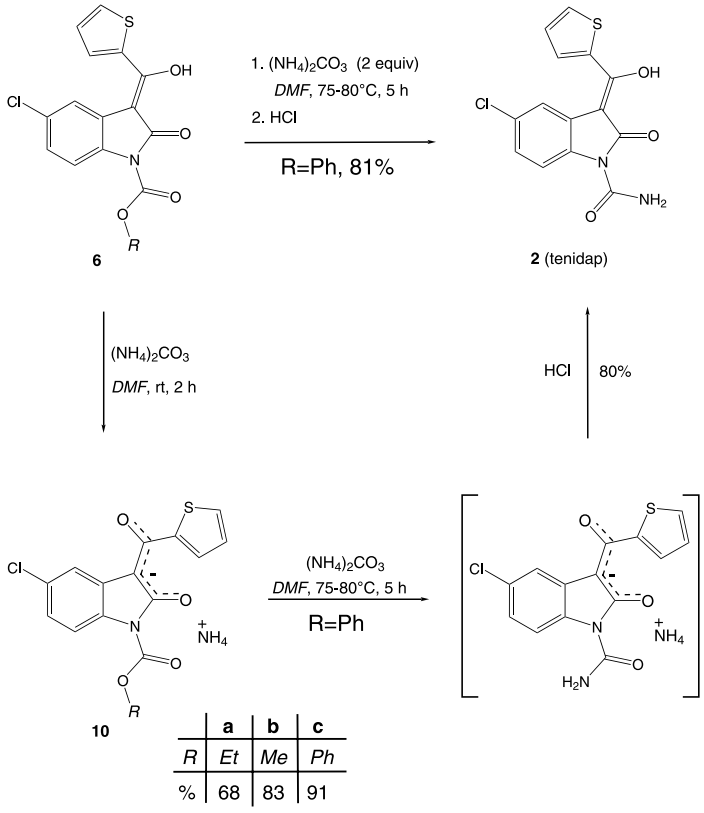
Attempts to convert ethyl carbamate **6a** to tenidap (**2**) failed. The reaction with ammonium carbonate in *DMF* at ambient temperature for 2 h resulted in the formation of the ammonium salt **10a** (Scheme 6). The starting material was recovered after further treatment of this ammonium salt with ammonium carbonate in *DMF* at 80°C for 6 h followed by acidification. The application of other ammonia sources and more vigorous reaction conditions resulted in the formation of substantial amounts of deethoxycarbonylated product and experiments with the methyl carbamate **6b** gave similar results: the initially formed ammonium salt could not be converted to tenidap (**2**).

However, the phenyl carbamate **6c** could be converted to tenidap (**2**) under simple conditions. Thus, treatment with 2 equiv of ammonium carbonate in *DMF* at 75–80°C for 5 h, followed by acidic work-up gave tenidap (**2**) in excellent yield (Scheme 6). An important requirement for a smooth reaction is an adequate solubility of the initially formed ammonium salt. Therefore the use of *DMF* as the reaction solvent is crucial. In less polar solvents the ammonium salt crystallizes out and does not react further.

These studies allowed the development of a patent-free one-pot process for the preparation of tenidap (**2**) starting from *N*,*O*-di(phenoxycarbonyl)-5-chlorooxindole (**7c**) by successive treatment in *DMF* with ammonium carbonate, thiophene-2-carbonyl chloride in the presence of *DMAP*, and once more with ammonium carbonate, in an optimized overall yield of 75% (Scheme 7). An appropriate one-pot treatment of the phenyl carbamate **5c** gave tenidap (**2**) in 79% overall yield.

New Synthesis of Oxindole-1-carboxamides

Together with tenidap (**2**), several oxindole-1-carboxamides have been described in the patent literature [4–6, 15]. The 1-carbamoyl moiety was introduced exclusively



	a	b	c
R	Et	Me	Ph
%	68	83	91

Scheme 6

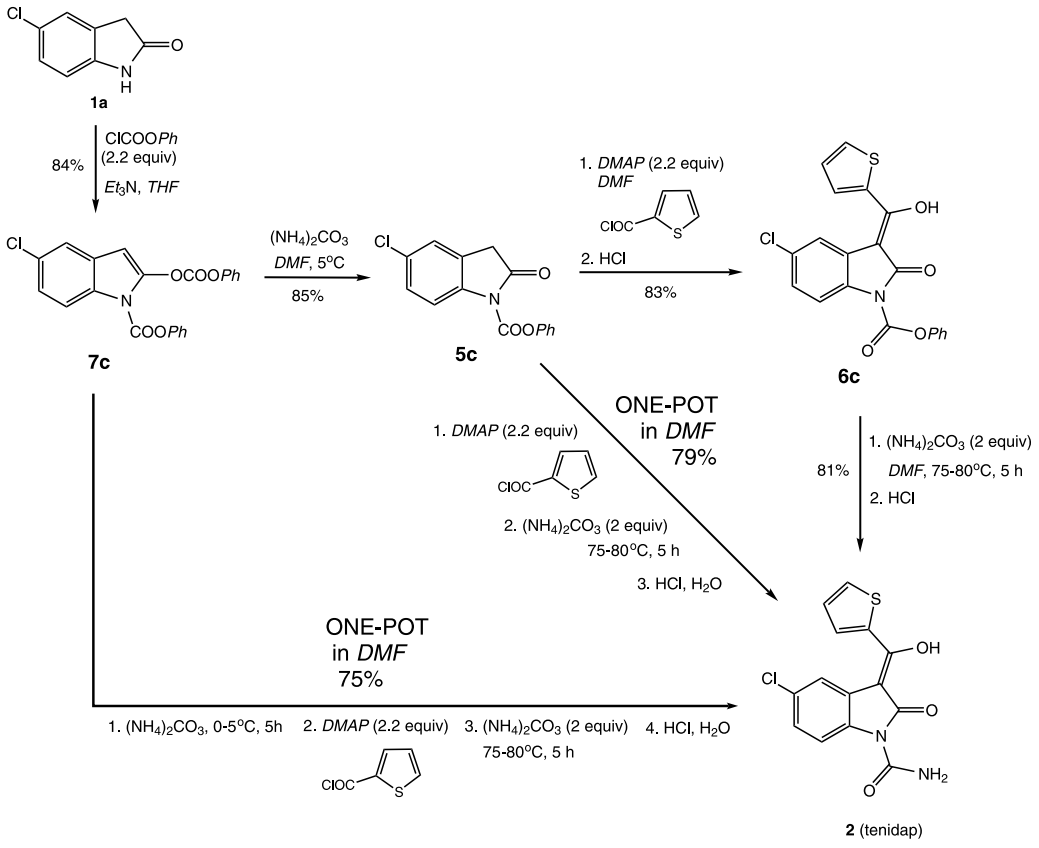
by treating an *N*-unsubstituted oxindole with alkyl, aryl, or acyl isocyanate. The use of isocyanates for the introduction of the 1-carbamoyl moiety has two major disadvantages: relatively few organic isocyanates are commercially available and *N*,*N*-disubstituted oxindole-1-carboxamides can not be synthesized by this method.

Taking advantage of our new key intermediate **6c** used in the synthesis of tenidap (**2**) we prepared a series of oxindole-1-carboxamides **11** by amidation of the phenyl carbamate **6c** with various amines (Scheme 8) [16]. For the most part, these compounds cannot be synthesized by the isocyanate method.

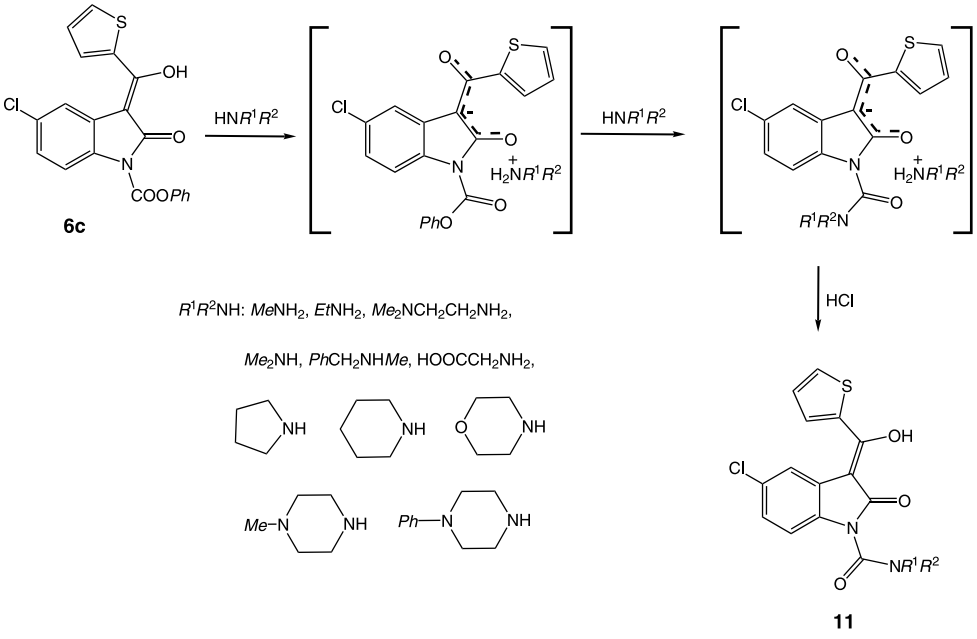
Aminolysis of compound **6c** with various amines is expected to follow a similar pathway as shown in Scheme 6. Therefore at least two equivalents of the amine have to be used in the reactions.

Synthesis of 1,3-Di[alkoxy(or aryloxy)carbonyl]oxindoles

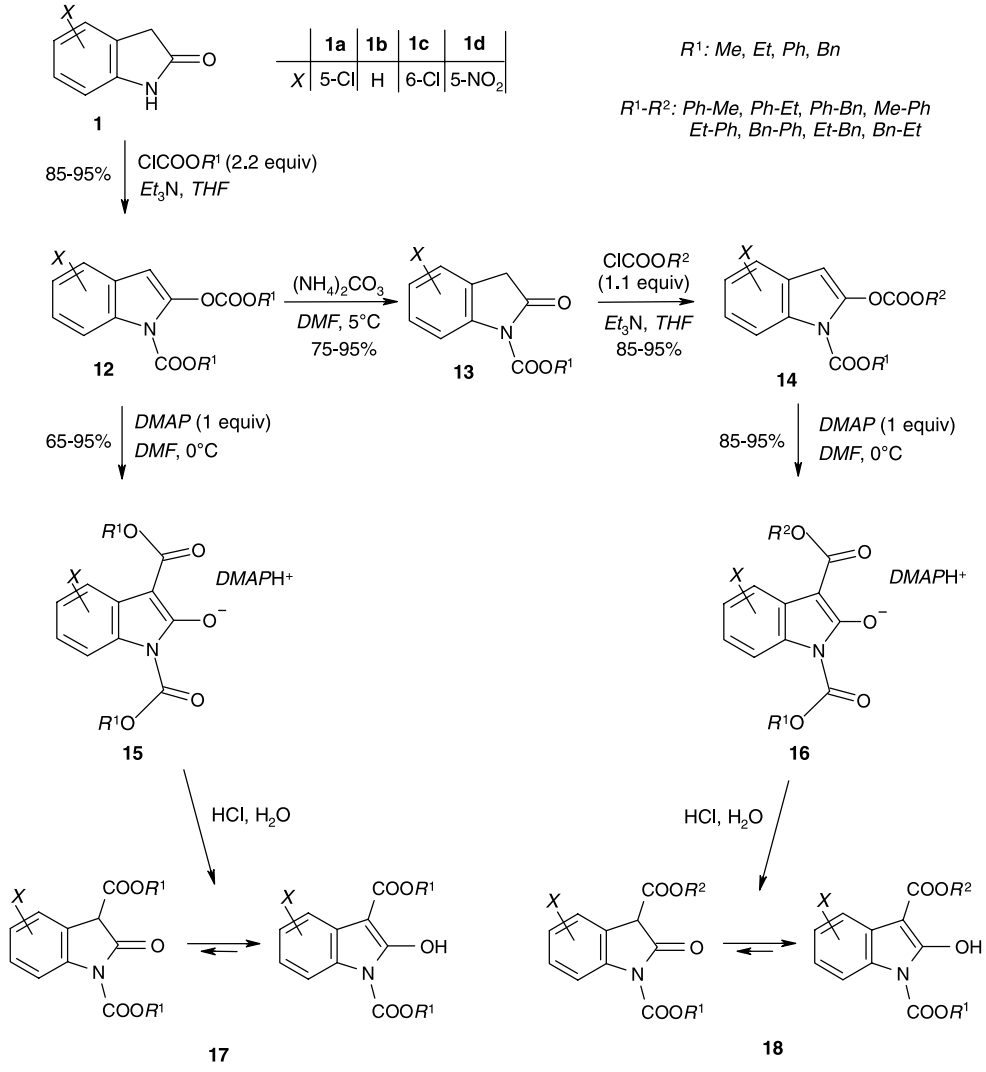
Oxindole-1,3-dicarboxamides are also interesting targets in medicinal chemistry. According to the procedure described in the patent literature [10, 17], the two carbamoyl moieties were introduced successively into the oxindole. Refluxing with alkyl, aryl, or acyl isocyanates in toluene afforded oxindole 1-carboxamides. The 3-carbamoyl group was then introduced by further treatment with an isocyanate in *DMF* in the presence of a base. Based on the experience obtained in the course of the synthesis of tenidap (**2**), we decided to synthesize new



Scheme 7



Scheme 8



Scheme 9

oxindole-1,3-dicarboxamides starting from the corresponding oxindole-1,3-dicarboxylates. Since these latter compounds had not been described in the literature, we have set as an aim to synthesize 1,3-di[alkoxy(or aryloxy)carbonyl]oxindoles (exemplified by compounds **17** and **18**, Scheme 9), containing identical or different alkoxy(or aryloxy)carbonyl groups in these two positions.

Similarly to the synthesis of compounds **6** and **7** (Scheme 3), oxindoles **1** were treated with 2.2 equiv of chloroformic acid esters and triethylamine in *THF* affording *N*,*O*-diacylated derivatives **12**. The *O*-acyl moiety was removed by reaction with ammonium carbonate in *DMF* to give *N*-[alkoxy(or aryloxy)carbonyl]oxindoles **13** in good yields. The reaction of the *N*-acylated derivatives with 1.1 equiv of chloroformic acid esters and triethylamine in *THF* afforded mixed *N*,*O*-diacylated derivatives **14**. Attempts to rearrange the *N*,*O*-diacylated compounds **12** and **14** to the desired *N*,*C*(3)-diacylated derivatives using catalytic amounts of

triethylamine or *DMAP* as well as one equivalent of triethylamine resulted in formation of product mixtures. Treatment of **12** and **14** with one equivalent of *DMAP* in *DMF* followed by addition of water gave the *N*,*C*(3)-diacylated dimethylaminopyridinium enolate **15** and **16** in good yields (Scheme 9).

The stereostructure of compounds **15** and **16** depicted in Scheme 9 corresponds to the structure of the dibenzyloxycarbonyl derivative determined by single crystal *X*-ray study [18].

The acidic treatment of the enolate of diesters having an alkoxycarbonyl group in the 3-position results in the conjugate acids **17** and **18** (Scheme 9), which exist as oxo-enol mixtures in $CDCl_3$ solutions as demonstrated by the NMR spectra. However, derivatives with aryl- or benzyloxycarbonyl group in the 3-position were unstable towards the acidic work-up. Hydrolysis and decarboxylation was observed [18].

Single crystal *X*-ray analysis of the bis(ethoxycarbonyl) compound **17** has shown that it exhibits the enol form in the crystalline state [18].

We have recently started studying the amidation reactions of oxindole-1,3-dicarboxylates. Several unexpected reactions have been observed and the elaboration of the project is in progress.

Raney Nickel Induced 3-Alkylation of Oxindole with Alcohols and Diols

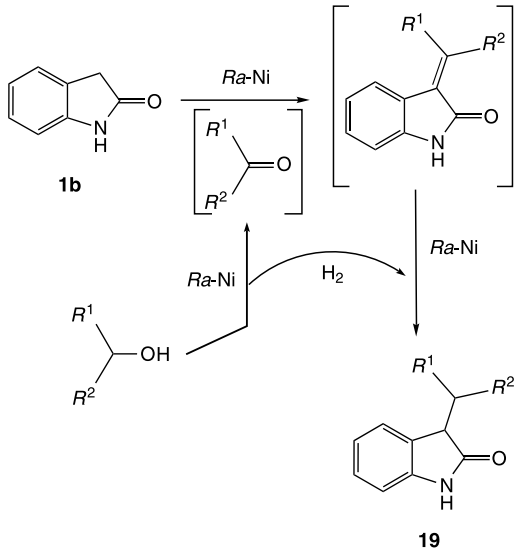
In continuation of our studies on acylation reactions of oxindoles we sought a simple method for the synthesis of 3-alkyl- and 3-(ω-hydroxyalkyl)oxindoles. Direct alkylation of deprotonated oxindole (**1b**) has been studied in detail [19]. However, the lack of regioselectivity and the formation of dialkylated products have rendered this synthetic route limited use.

The two-step reductive alkylation of oxindole (**1b**) with ketones and aromatic aldehydes through 3-alkylideneoxindoles is a convenient method for the preparation of 3-alkyloxindoles. However, in the case of aliphatic aldehydes the yields are moderate because of aldol-type side reactions [20].

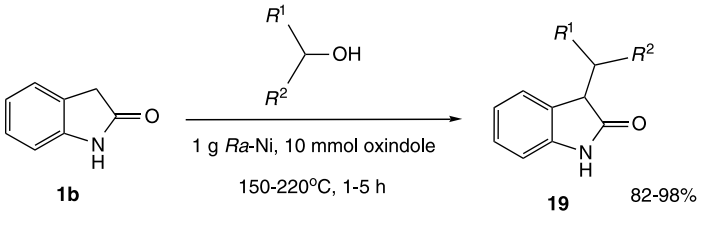
Wenkert has described the formation of 3-alkyloxindoles **19** by long refluxing ($>$70 h) of oxindole (**1b**) in alcohols in the presence of ten fold mass of *Raney* nickel (*Ra*-Ni) [21]. *Raney* nickel plays various roles in this multistep reaction (Scheme 10): it acts as the oxidizing agent in the transformation of the alcohol to the corresponding carbonyl compound, as the base in the condensation of oxindole (**1b**) with the carbonyl compound to form 3-alkylideneoxindoles, and as the reducing agent in the last step, affording 3-alkyloxindoles **19**.

In a later publication *Wenkert* remarked that 'dependence on heterogenous catalysis for success of the alkylations could be predicted to make the results erratic' [22]. This might explain why the method has not been mentioned later in the literature for the synthesis of 3-alkyloxindoles.

We managed to elaborate new reaction conditions, which turned *Wenkert*'s synthesis of 3-alkyloxidoles **19** into a reproducible and highly efficient synthetic tool. The reactions of oxindole (**1b**) with various primary and secondary alcohols were carried out by heating the mixture in an autoclave at 150–220°C for 1–5 hours in the presence of less than one mass equivalent (0.1 g/mmol of oxindole) of *Raney* nickel (Scheme 11) [23].



Scheme 10



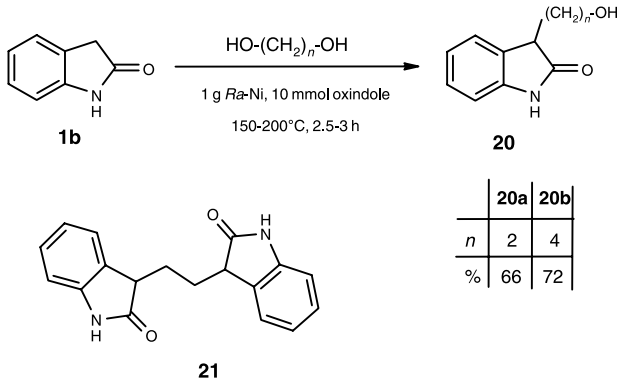
	19a	19b	19c	19d	19e	19f	19g	19h	19i
R^1	H	*Me*	*Et*	*Pr*	*Ph*	*Bn*	*Me*	*Me*	-$(CH_2)_5$-
R^2	H	H	H	H	H	H	*Me*	*Et*	

Scheme 11

We succeeded in extending the *Raney* nickel induced 3-alkylation reactions of oxindole (**1b**) to the preparation of 3-(ω-hydroxyalkyl)oxindoles **20** in good yields. The treatment of oxindole with diols under the conditions shown in Scheme 12 afforded the ω-hydroxyalkyl compounds, which are convertible into a range of new derivatives. Alternative methods for the preparation of 3-(2-hydroxyethyl)oxindole (**20a**) involve complicated multistep procedures [24].

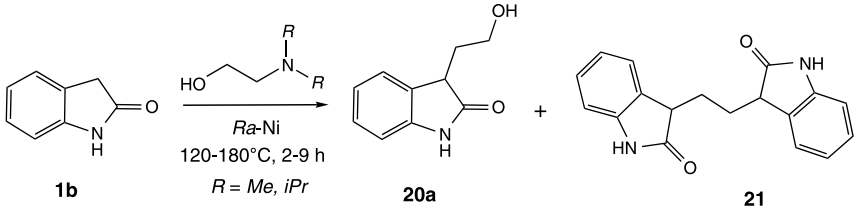
Byproduct **21** ($\sim$5%, mixture of diastereomers) was isolated when the reaction of oxindole (**1b**) was performed with ethylene glycol. The formation of a similar byproduct has not been observed in the case of butane-1,4-diol (Scheme 12).

We tried to extend the reaction to the 3-aminoalkylation of oxindole. The reaction of oxindole (**1b**) with 2-(dimethylamino)ethanol and 2-(diisopropylamino)ethanol under various conditions (*Ra*-Ni, 120–180°C, 2–9 h) afforded 3-(2-hydroxyethyl)oxindole (**20a**) and the dimeric byproduct **21** (Scheme 13). The expected 3-(2-dialkylaminoethyl)oxindoles could not be detected in the product



	20a	20b
n	2	4
%	66	72

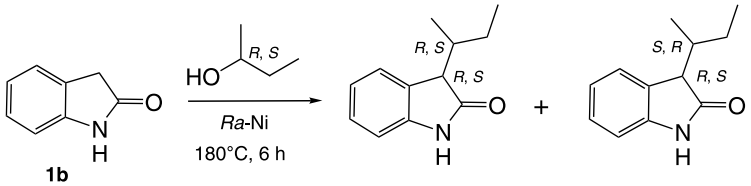
Scheme 12



Scheme 13

mixture. Higher temperatures and longer reaction times led to an increased amount of **21**.

Preliminary studies have been carried out on the stereochemical aspects (possibility of asymmetric induction) of the alkylation reaction. The alkylation of oxindole (**1b**) with (±)-2-butanol (*Ra*-Ni, 180°C, 6 h) gave practically equal amounts (47:53, 49:51, and 53:47 molar ratio in three runs, measured by ^{1}H NMR) of the two expected diastereomeric racemates **19h** (Scheme 14). However, this result might be the consequence of an epimerization at *C*(3) due to the basicity of *Raney* nickel and the high reaction temperature. Further investigations regarding the stereochemical control of this reaction type are in progress in our laboratory.



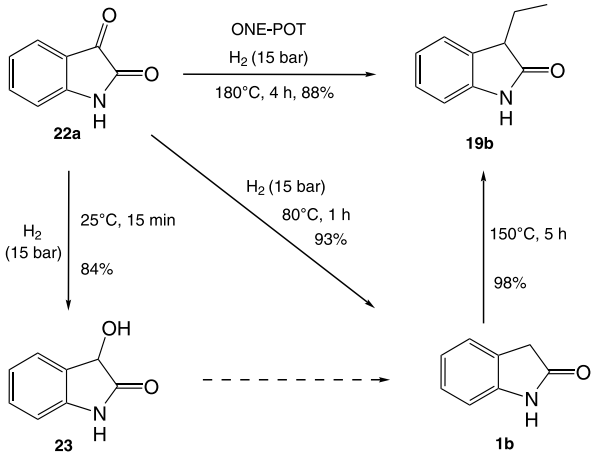
Scheme 14

One-pot Synthesis of 3-Alkyl- and 3-(ω-Hydroxyalkyl)oxindoles from Isatins

Since oxindoles can be prepared by catalytic reduction of easily available isatins [25], an opportunity arose that the complex reaction sequence, which involves the reduction of isatin (**22a**) to oxindole (**1b**) and the regioselective alkylation of oxindole at the 3-position with alcohols in the presence of *Raney* nickel, might be carried out in one pot.

Therefore, the reaction of isatin (**22a**) with ethanol was performed by heating the reactants in an autoclave at 150°C for 5 h in the presence of *Raney* nickel. As expected, 3-ethyloxindole (**19b**) was obtained as the main product. However, the conversion of isatin (**22a**) to 3-ethyloxindole (**19b**) was substantially lower than the conversion of oxindole (**1b**) to 3-ethyloxindole (**19b**) under the same conditions [23], which indicates that the multistep reaction sequence suffers from the slow reduction of isatin (**22a**) to oxindole (**1b**). Although longer reaction times and higher temperatures resulted in better conversions, the yield of the isolated product was unsatisfactory because of the formation of unidentified impurities.

It was reasoned that the use of hydrogen atmosphere could accelerate the rate of the first two, reductive steps of the complex reaction sequence (**22a** → **23** → **1b** → **19b**, Scheme 15). Detailed experiments have shown that 3-hydroxyoxindole (**23**) is formed from isatin (**22a**) in *Et*OH in the presence of *Raney* nickel under 15 bar hydrogen (25°C, 15 min). More vigorous conditions (80°C, 1 h, *Ra*-Ni, 15 bar hydrogen) lead to the formation of oxindole (**1b**). As described above [23], at higher reaction temperatures (150°C, 5 h, *Ra*-Ni) oxindole (**1b**) can be transformed to 3-ethyloxindole (**19b**). These results demonstrate that the introductory reaction steps of the overall transformation of isatin to 3-alkyloxindole are faster in hydrogen atmosphere than the final step, *i.e.* the 3-alkylation of oxindole. This relation of the individual reaction rates is supposed to facilitate the overall reaction. Indeed, the reaction of isatin with ethanol in the presence of *Raney* nickel at 180°C under



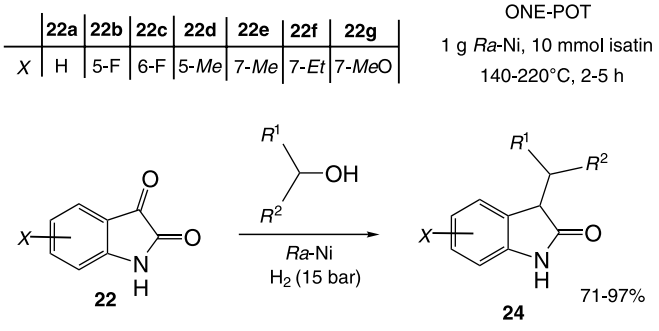
Scheme 15

15 bar hydrogen affords a high yield (88%) of 3-ethyloxindole after 4 h reaction time.

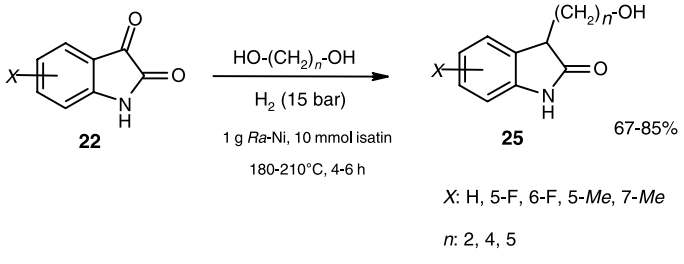
The reaction studied above can be applied to other alcohols and isatins. A new and efficient one-pot procedure has been developed for the synthesis of 3-alkyloxindoles **24** from isatins **22** by treatment with alcohols in the presence of *Raney* nickel, under hydrogen atmosphere [26]. The reactions of isatins **22** with various primary and secondary alcohols were accomplished in an autoclave at 140–220°C for 2–5 h in the presence of less than one mass equivalent of *Raney* nickel under 15 bar hydrogen, and the corresponding 3-alkyloxindoles **24** were isolated in high yields (Scheme 16).

The alkylation reaction of isatins with alcohols under hydrogen atmosphere, in the presence of *Raney* nickel has also been extended to the synthesis of 3-(ω-hydroxyalkyl)oxindoles **25** by treatment of isatins with diols under the conditions shown in Scheme 17 [26].

This publication gives an overview on our recent achievements in the field of oxindole chemistry. In connection with our novel manufacturing route to tenidap, new methods have been developed for the preparation of 1-acylated and 1,3-diacylated oxindoles. Furthermore, we have studied the alkylation reactions of this family in detail, elaborating the first one-pot synthesis of 3-alkyl- and 3-(ω-hydroxyalkyl)oxindoles from isatins.



Scheme 16



Scheme 17

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