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STUDIES AIMING AT THE SYNTHESIS OF MORPHINE II[1]

Studies on Phenolic Coupling of N-Norreticuline Derivatives

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The synthesis of salutaridine derivatives via phenolic coupling on norreticuline derivatives can be performed in improved yields, using non-metallic oxidizing agents. The assumption of a coordination effect in the preformation of the desired structure is, thus, unnecessary.

It is a well-known conception[2,3] that the biosynthesis of morphine alkaloids is carried out in plants *via* salutaridine (2a), formed by intramolecular oxidative coupling of reticuline (1a). This para/ortho' phenolic oxidative cyclization of reticuline and its derivatives has been recognized as the key step of the biomimetic morphine synthesis as well. After a great number of futile attempts[4] to simulate the process Barton and coworkers[3] succeeded in detecting the formation of salutaridine, in 0.03 % yield. Even the oxidation[5,6] of 6'-bromoreticuline and 6'-bromo-N-ethoxycarbonylnorreticuline has not led to the desired morphinandienone structure; the bromo function did not protect the para' position and with HBr elimination an aporphine skeleton (3a,b) was formed by ortho/para' coupling.

The first satisfactory results on the transformation of N-acylnorreticulines into N-acylnorsalutaridine derivatives were published by Schwartz[7,8,9]. Thallium tristrifluoroacetate (TTFA) was used as oxidizing agent, and its favourable coordination effect was supposed to be responsible for the relatively high yields (13-35 %)[10].

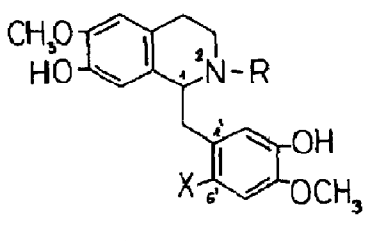
According to our experiments the desired cyclization can be accomplished with a relatively wide range of oxidizing agents irrespective of whether or not the oxidant and the additive are capable of exerting a coordination effect.

In our experience 1 → 2 oxidative coupling is generally successful in the presence of certain organic acids (preferably trichloroacetic, trifluoroacetic and picric acid) or their amine salts, or when the oxidizing agent itself

contains the anion of these acids. In other words the phenolic oxidative cyclization is mainly affected by the anion studied.

It has been stated that under strictly anhydrous conditions and indifferent gas atmosphere the reaction of N-ethoxycarbonyl- (1b)[6], N-formylnorreticuline (1e)[11] and their 6'-bromo or 6'-chloro derivatives (1c,d,f,g) with lead tetraacetate (LTA)[12] in CH_2Cl_2 in the presence of e.g. trichloroacetic acid at -25 °C leads to the corresponding N-acyl- (2b,e)[14] and 1-halogeno-N-acylnorsalutaridines (2c,d,f,g)[14], in 18-40 % yield[10]. In each case the yields of N-ethoxycarbonylnorsalutaridines were found to be higher than those of N-formyl derivatives.

In the course of LTA oxidation only a small amount of N-acylnorisoboldine (3b,c) was formed, especially in the case of 6'-halogeno derivatives, since, in contrast to previous observations[5,6], the halogen atom was found to protect the para' position.



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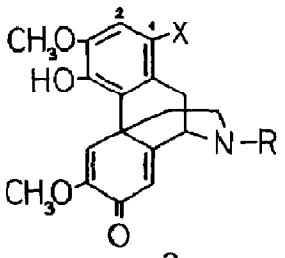

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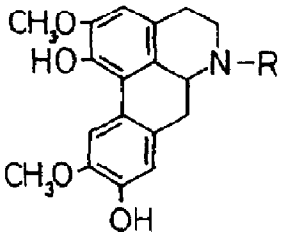
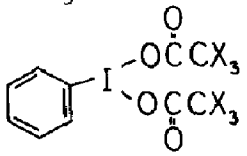


3

1, 2	R	X
a	CH_3	H
b	$CO_2C_2H_5$	H
c	$CO_2C_2H_5$	Br
d	$CO_2C_2H_5$	Cl
e	CHO	H
f	CHO	Br
g	CHO	Cl

3	R
a	CH_3
b	$CO_2C_2H_5$
c	CHO



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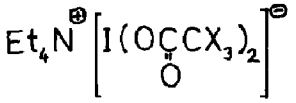

5

4,5	X
a	H
b	Cl
c	F

For 1 → 2 transformation non-metallic oxidizing agents have also been successfully applied. Thus, I,I-diacetoxyiodobenzene (4a) in the presence of organic acids, I,I-bis(trichloroacetoxy)- or I,I-bis(trifluoroacetoxy)iodobenzene (4b,c)[15,16] afforded 2b-g salutaridine derivatives in 14-32 % yields[10].

The different tetraethylammonium [di(acyloxy)iodate(I)] derivatives (5a,b,c)[17,18] proved to be even better oxidizing agents for the para/ortho' oxidative coupling of 6'-halogeno-N-acylnorreticulines (1c,d,f,g). Whereas 5b and 5c in CH_2Cl_2 at -45 — -25°C led to the desired 1-halogeno-N-acylnorsalutaridines (2c,d,f,g) in 25-58 % yield[10] without addition of acid or its salt, 5a gave the same results under similar conditions, but in the presence of piridinium trifluoroacetate.

In the cyclization with oxidants of type 5 the protective effect of the 6'-halogeno group is even more expressed than in the case of LTA; in the oxidation of 1b and 1e the N-acylnorisoboldine (3b,c)[14], formed with ortho/para' coupling, is the main product, and salutaridine derivatives (2b,e) can be obtained only as a minor product. On the other hand, when starting from the halogenated norreticulines only a slight amount of isoboldine derivatives can be detected; the process is highly selective for para/ortho' coupling.

Application of the oxidants in excess is definitely harmful, as the salutaridine derivatives, formed in the reaction, easily undergo further transformations. The use of less than 1 mole equivalent of the oxidizing agent gives better yields[10].

Separation of the starting material (1b-g) and the final product (2b-g) is carried out by extraction of their $CHCl_3$ solution with 0.5-5 % NaOH. In the course of the extraction the more acidic N-acylnorreticuline enters the alkaline phase and the salutaridine derivative remains in the organic solvent. Thus, a reaction mixture, containing mainly N-acylnorreticuline and the corresponding salutaridine derivative at a certain degree of conversion, can easily be worked up by this simple method.

According to our experiences, with $LiAlH_4$ in THF all 2b-g compounds can be reduced to 1:1 C-7 epimer mixture of salutaridinol, whose transformation to thebaine[19], then to codeine[20] and morphine[21] has already been solved.

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References and Notes

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12. By lead tetraacetate oxidation of 1-benzyl-1,2,3,4-tetrahydroisoquinolines Umezawa and coworkers[13] obtained the corresponding p-quinol acetate derivatives, the transformation of which into salutaridine compounds was unsuccessful.
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14. Melting points from ethyl acetate: 2b 198-200 °C (lit.[7]: 198-200 °C), 2c: 204-206 °C, 2d: 199-202 °C, 2e: 226-228 °C, 2f: 228-230 °C, 2g: 241-243 °C, 3b: oil, see Ref. 6. 3c: 225-226 °C. For all compounds UV, IR, NMR and MS spectra were found to be in good agreement with the proposed structures.
15. I,I-bis(trichloroacetoxy)iodobenzene (4b) was obtained from 4a with trichloroacetic anhydride in abs. $CHCl_3$ (yield: 85 %, mp: 124-125 °C). 4c was similarly produced with trifluoroacetic anhydride (mp.: 125-126 lit.[16]: 119-122, 122-124 °C).
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