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AN UNUSUALLY SIMPLE PROCEDURE FOR THE SYNTHESIS OF CANTHIN-ALKALOID DERIVATIVES USING DIALKYL OXALATES AS NEW REGIOSELECTIVE N-ALKYLATING AGENTS

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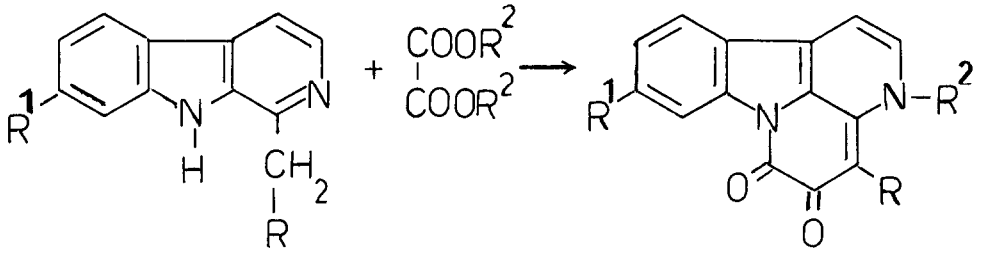
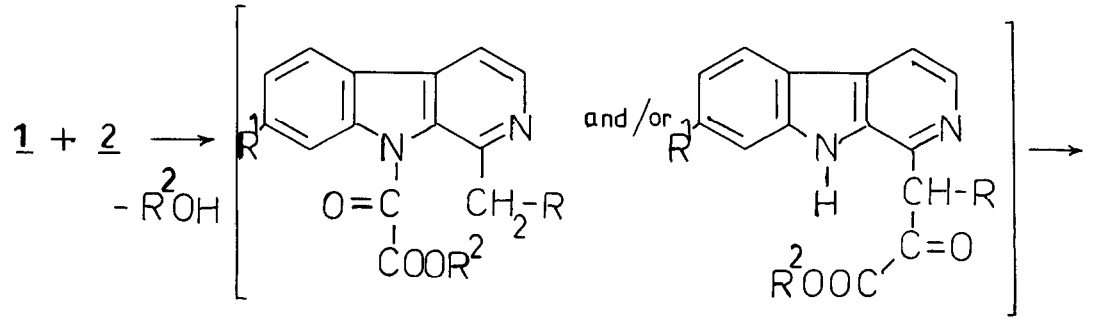
Abstract: 1-Alkyl-β-carbolines were treated with dialkyl oxalates to give N-alkylated canthin-alkaloid derivatives in one step

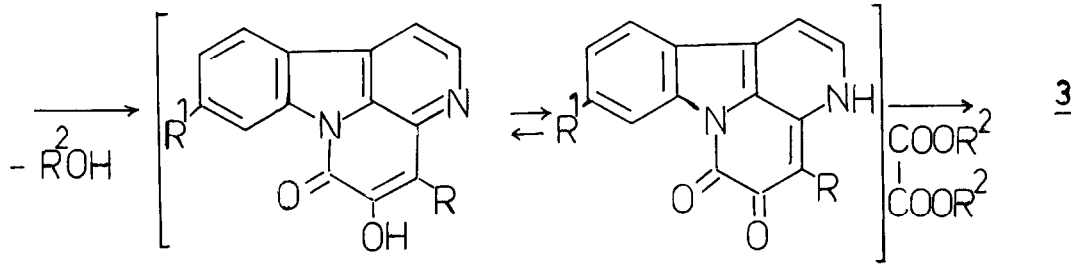
During the reproduction of the experiments described by Atta-ur-Rahman[1] we found that the reaction of 1-alkyl-β- carbolines (1) with excess dialkyl oxalates (2) between 155-175°C for 8-12 hours did not afford the pyrrolizine derivatives described by the authors. However, canthin-alkaloid derivatives (3) were formed in one step with yields between 20-65 %.



1 **2** **3**

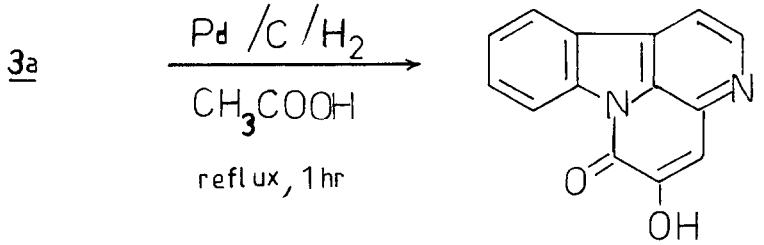
Compounds 3 have yellow colour and a green fluorescence under uv-lamp (254 and 366 nm). Products and reaction conditions are summarized in Table 1. Only in the case of dimethyl oxalate we could not get any product. We suggest the following mechanism for the formation of N-alkylated 3H-5,6-dihydro-5,6-dioxo-indolo [3,2,1-de] [1,5] - naphthyridines (3):





The acylation and ring closure reactions are similar to the work described by Bartlett and Taylor[2], where 4-hydroxy-canthin-6-one (4) was formed from harman and diethyl oxalate under mild conditions. However, in this case the nucleophilicity of harman was increased by forming its dilithium salt. The finishing step of the reaction is a regioselective N-alkylation of 4 derivatives to give the compounds 3. Recently Bergman and Sand[3] published similar N-alkylation reactions using dialkyl oxalates. In their cases the reactions were carried out in the presence of alkoxides.

The structure of compounds 3 were elucidated by the following reactions:
1./ the cathalytic hydrogenation of the N-benzyl derivative (3a) afforded 5-hydroxy-canthin-6-one (4)[2] which was found to be identical with the product described in literature,
2./ compounds 3 are very resistant against acidic hydrolysis, even by refluxing in 48 % HBr only starting materials were recovered, whereas they could be smoothly hydrolyzed under basic conditions, e.g. 3b was hydrolyzed to give green-coloured 1-methyl-2-ethyl-2H-pyrido [3,4-b] indol (5) with the characteristic uv-absorption (λ max by pH > 11,5 : 275 and 325 nm)[4].



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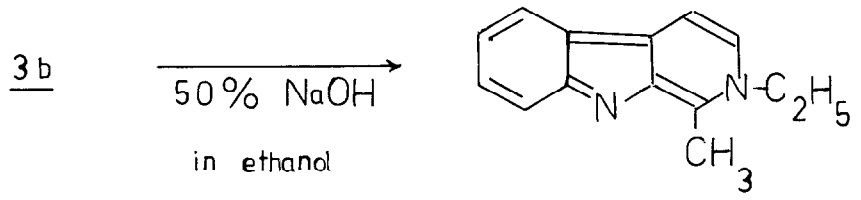

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m.p.: 194-6°C

The position of R^2 could be established by comparing the regioisomeric O- and N-methyl derivatives of 5-hydroxy-canthin 6-one (6 and 7) with the help of their nmr-spectra. The N-methyl signal of 7 (3,86 ppm) was shifted to 4,57 ppm after adding CF_3COOH to the DMSO-d_6 solution, whereas the O-methyl signal of 6 (4,00 ppm) was only shifted to 4,13 ppm following CF_3COOH addition. Compound 6 is known from the literatur[5] and compound 7 could be isolated from the neat reaction mixture of 4 and dimethyl oxalate at 175°C.

Compounds 3 show M-28 and M-56 fragments in mass spectrum as a consequence of two consecutive CO-splittings. The compound 3b was investigated also by x-ray crystallography by Kálmán[6]. The mechanism of the above regioselective N-alkylation with dialkyl oxalates should be further investigated.

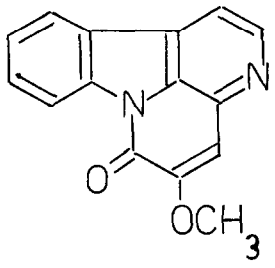
Table 1 New canthin-alkaloid derivatives (3)

	R	R^1	R^2	Reaction temp./°C	Reaction time (h)	Yield (%)	M.p.[b] (°C)
a	H	H	CH_2Ph[a]	155	8	42	275-302
b	H	H	C_2H_5	175	10	44	309-310
c	H	H	n-butyl	175	12	20	262-265
d	CH_3	H	C_2H_5	175	8	39	266-274
e	C_2H_5	H	C_2H_5	165	8	47	244-253
f	C_2H_5	H	CH_2Ph[a]	160	10	64	234-245
g	H	OCH_3[c]	C_2H_5	160	10	29	286-290

a/ Ph = phenyl

b/ the melting points are not sharp; because of the insolubility in organic solvents, compounds 3 could not be recrystallized

c/ this product had identical physical constants as described also in the literature[1], however, it is N-ethyl-9-methoxy-3H-5,6-dihydro-5,6-dioxo-indolo [3,2,1-de] [1,5] - naphthyridine



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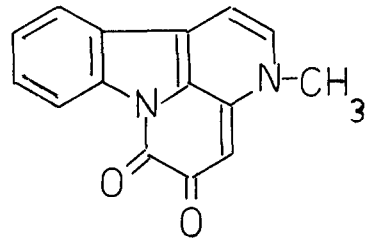

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