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5-AMINOMETHYL-8-METHOXYPSORALEN

John B. Hansen and Ole Buchardt

Chemical Laboratory II, The H. C. Ørsted Institute, University of Copenhagen,

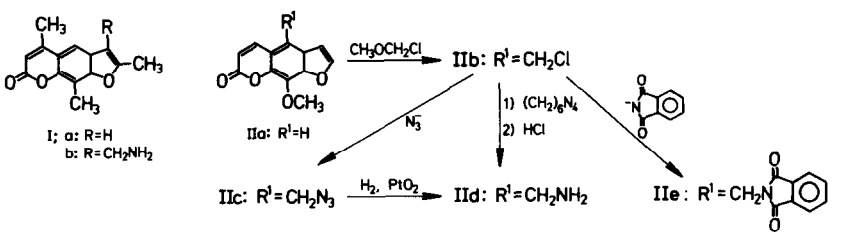
Universitetsparken 5, DK-2100 Copenhagen, Denmark

Summary: The synthesis of a new DNA-intercalating agent, the psoralen derivative 5-aminomethyl-8-methoxypsoralen, is described.

Some of the naturally occurring psoralens, e.g., Ia, IIa, are widely used in photochemotherapy of the wide-spread dermatological disease, psoriasis, the action of the therapy presumably being due to irreversible photoaddition of the drug to DNA.[1]

By increasing the affinity and the photoreactivity of such a drug towards DNA, it is conceivable that the efficiency of the therapy could be improved. Such an attempt was made by Isaacs et al.,[2] who prepared 4'-aminomethyl-4,5',8-trimethylpsoralen (Ib) as its hydrochloride, and reported its superior photoreactivity toward DNA and RNA.

Since 8-methoxypsoralen is by far the most clinically important drug in this treatment, we decided to attempt to prepare a simple hydrophilic derivative of this compound, the results of which are reported below.



5-Chloromethyl-8-methoxypsoralen (IIb) was synthesized from IIa and chloromethyl methyl ether in acetic acid as reported by Aboulez et al.[3] Reflux of IIb with NaN_3 gave 5-azidomethyl-8-methoxypsoralen (IIc) in 80% yield upon recrystallization from toluene, mp 150-152°C; NMR, 90MHz, $CDCl_3$, δ-values: 8.00(d,J=10Hz,1H); 7.74(d,J=2Hz,1H); 6.97(d,J=2Hz,1H); 6.46(d,J=10Hz,1H); 4.73(s,2H); 4.32(s,3H). IR(KBr,cm^{-1}): 2080, 1722, 1590. MS,m/e: 271(M^+), 229(M-N_3, base peak).

The reduction of the azido group was accomplished by catalytic hydrogenation in methanol (1 atm, 22°C, 35 min), using PtO_2 as catalyst. The free amine, MS,m/e: 245(M^+), 229(M-NH_2, base peak), was dissolved in abs. ethanol/conc. HCl and IId,HCl precipitated upon addition of ether in 65% yield. Mass spectrometry of (IId) showed the presence of about 2% of a peak at M+2, presumably due to the presence of 4',5'-dihydro-5-aminomethyl-8-methoxypsoralen.[4] Prolonged hydrogenation resulted in an increase in the yield of this byproduct,

whereas imcomplete reduction was observed at shorther reaction times.

The Délepine procedure proved to be more convenient in the synthesis of IId.[5] Compound IIb and 1.5-2 eq. of hexamethylenetetramine were refluxed in dry $CHCl_3$ for 40 h. The resulting precipitate was suspended in ethanol: conc. HCl, 3:1, at room temperature, for 72 h. The solution was concentrated, in vacuo, and the residue taken up in dil. NaOH, followed by extraction with $CHCl_3$ to give IId in 85% yield. IId was dissolved in ethanol/conc. HCl and the hydrochloride precipitated by addition of ether: mp. 250-251°C; NMR, 90MHz, D_2O, δ-values: 8.23(d,J=10Hz,1H); 7.93(d,J=2Hz,1H); 7.13(d,J=2Hz,1H); 6.47(d,J=10Hz,1H); 4.58(s,2H); 4.20 (s,3H). Anal. calc. for $C_{13}H_{12}ClNO_4,H_2O$ (found): C: 53.64(53.52); H: 4.25(4.47); N: 4.70 (4.80); Cl: 11.93(12.18).

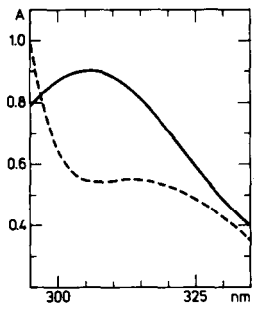


Fig. 1. UV-spectrum of IId,HCl ($8x10^{-2}$mM) alone —— and in the presence of DNA (Calf Thymus DNA, 0,5 mg/ml in 5mM Tris, pH 7.4)-----.

The solubility of IId,HCl in H_2O (20°C), $1.25x10^{-1}$M, is higher than those of IIa ($1.7x10^{-4}$M) and Ib,HCl ($3.4x10^{-2}$M).[2] The UV-absorption of IId, HCl shows a significant decrease in absorbancy, and a red shift in the presence of DNA, as expected for a compound which intercatales with DNA (Fig.1). Attempts to prepare IIb by hydrazinolysis of 5-phthalimidomethyl-8-methoxypsoralen[6] (IIe) as described by Isaacs et al.[2] for the synthesis of Ib were not successful.

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References

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4. Identified by NMR. M. E. Brokke and B. E. Christensen, J. Org. Chem. 23, 589(1958) have reported that catalytic hydrogenation of IIa gives 4',5'-dihydro-8-methoxypsoralen.
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6. IIe, mp. 261°C, was prepared in 65% yield by treatment of IIb with potassium phthalimide in acetone, and showed satisfactory elementary analysis and spectral properties.

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