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# THE REACTIVITY OF 1,4-DIHYDRONICOTINAMIDES TOWARDS REDUCTION OF 1,1',1"-TRIFLUORO-ACETOPHENONE : INFLUENCE OF METHYL SUBSTITUTION ON THE PYRIDINE RING.

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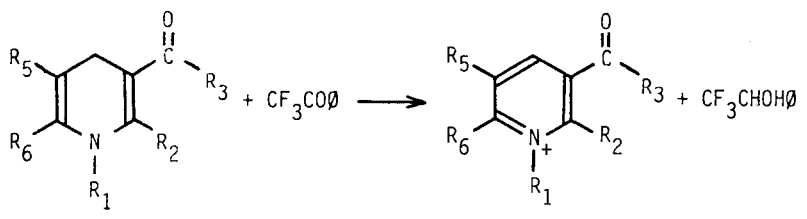
*Summary :* In a series of methyl substituted 1-(2',6'-dichlorobenzyl)-1,4-dihydronicotinamides those compounds with the methyl α to the pyridine nitrogen are at least one order of magnitude more reactive than the analogues without methyl or methyl on the 5-position.

A new series of 1,4-dihydronicotinamides is used to study the reduction of ketones by NADH-model compounds. Many papers already described the reductive properties of different 1,4-dihydropyridines towards different types of substrates[1]. However, reports with variation of any other substituent than the one on the pyridine nitrogen or the electron acceptor groep on carbon atom $C_3$ are very rare. R. Dommisse et al. reported on the oxidation of 3,5-diethoxy-carbonyl-2,6-dimethyl-1,4-dihydropyridine ( Hantzsch ester ) by chloranil in $CHCl_3$[2]. As no such oxidation of 3,5-diethoxycarbonyl-1,4-dihydropyridine or of 3,5-dicyano-2,6-dimethyl-1,4-dihydropyridine was observed, it was assumed that the reactivity of the Hantzsch ester was induced by steric hindrance between the ring substituents. If the ethoxycarbonyl moiety is not coplanar with the dihydropyridine ring, conjugation between these groups is decreased and reactivity towards oxidation by chloranil is increased. On the other hand, X-ray analysis proved the Hantzsch ester to be completely flat[3]. This suggests that the origin of this methyl-effect lies in the methyl groups *in se*. In order to study the influence of a methyl group on the oxido-reduction behaviour of 1,4-dihydropyridines, a series of ring-substituted methyl-1-(2',6'-dichlorobenzyl)-1,4-dihydronicotinamides were synthesized[4] and subjected to reaction with a suitable substrate.




Ia : $R_2$=$R_5$=$R_6$=H
Ib : $R_5$=$R_6$=H, $R_2$=$CH_3$
Ic : $R_2$=$R_6$=H, $R_5$=$CH_3$
Id : $R_2$=$R_5$=H, $R_6$=$CH_3$
I(a-d) : $R_3$=$NH_2$,
$R_1$=2,6-dichlorobenzyl

Figure 1 : reaction of 1,4-dihydronicotinamides with 1,1',1"-trifluoracetophenone. Medium : 21.7% (v:v) sulfolane - borate buffer pH=8.3.

The reaction of 1,1',1"-trifluoroacetophenone (II) with 1,4-dihydronicotinamides ( see Figure 1 ) is well documented[5,6,7] . Although the reversible formation of a competitive adduct between analogues of I ( with $R_1 = CH_2\phi$ or n-prop, $R_2=R_5=R_6 = H$ ) and II has been reported, the contribution of this compound is not so important in the case of 1-(2',6'-dichlorobenzyl)-derivatives, possibly due to steric hindrance[6].

The initial rate of disappearance of I(a-d) was spectrophotometrically followed ( UV at $\lambda_{max}$). In the presence of a large excess of II, the reaction is pseudo first order in I(a-d)[4,5,6], after correction for decomposition of I(a-d). Most 1,4-dihydronicotinamides are instable in aqueous solutions as they undergo hydration[1]. Correction was made by subtracting the decomposition rate $k_{dec.}$ from the pseudo first order rate constant $k_1'$, yielding $k_1$.

In aqueous solutions, the balance between the keto form and the hydrate of II is shifted towards the hydrate[8]. The concentration of free ketone can be calculated according to Stewart[7]. The second order rate constant $k_2$ was derived from $k_1$ through division by the free ketone concentration. For the fastest compounds (Ib and Id), the excess of II was varied from a 100 to 600 times the concentration of I(b,d). As reported[7], the rate of formation in the ketone-hydrate equilibrium did not interfere with the reaction.

Table 1 : rate constants in function of methyl substitution.

| comp. | $\lambda_{max}$ ( nm ) | $k_1'$ ( $h^{-1}$ ) | $k_{dec}$ ( $h^{-1}$ ) | $k_1$ ( $h^{-1}$ ) | $k_2$ ( $M.h)^{-1}$ | ratio |
|---|---|---|---|---|---|---|
| Ia | 356.8 | .00614 ± .00015 | .000222 ± .000009 | .00592 ± .00015 | 18.0 ± .4 | 1 |
| Ib | 347.6 | .57 ± .03 | .0317 ± .0008 | .53 ± .03 | 1150 ± 60 | 64 |
| Ic | 357.9 | .01264 ± .00017 | .00032 ± .00004 | .01232 ± .00017 | 26.7 ±.3 | 1.5 |
| Id | 354.7 | .294 ± .007 | .0100 ± .0001 | .284 ± .007 | 617 ± 15 | 34 |

$k_1 = k_1' - k_{dec.}$ $\quad k_2 = k_1$ / concentration free ketone $\quad$ ratio $= k_2(Ia\text{-}d)/k_2(Ia)$

From table 1, it can be seen that the introduction of a methyl group on carbon atom $C_5$ enhances rate slightly. Introduction of a methyl on carbon atoms $C_2$ or $C_6$ enhances the rate at least an order of magnitude. From these results it can be concluded that - in this case - the difference in reactivity is probably not a result of steric influence of the methyl group on the rotation of the carbamoyl moiety. Determination of the activation parameters is in progress[4], and the nature of the "methyl-effect" is being further investigated.

REFERENCES


1. Kuthan J., Kurfuerst A., Ind. Chem. Prod. Res. Dev. 21 191 '82
2. Dommisse R.A., Lepoivre J.A., Alderweireldt F.C., Bull. Soc. Chim. Belg. 86 633 '77
3. Lenstra A.T., Petit G.H., Dommisse R.A., Alderweireldt F.C., *ibid.* 88 133 '79
4. Bossaerts J., Dommisse R.A., Alderweireldt F.C., to be published.
5. Steffens J.J., Chipman D.M., J.A.C.S. 93 6694 '71
6. van Eikeren P., Grier D.L., Eliason J., *ibid.* 101 7406 '79
7. Stewart R., Teo K.C., Ng L.K., Can. J. Chem. 58 2497 '80
8. Stewart R., Van Dyke J.D., *ibid.* 50 1992 '72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