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NEW TOTAL SYNTHESIS OF ESERINE-TYPE ALKALOIDS VIA REGIOSELECTIVE $NaBH_4$-REDUCTION OF IMIDES.

by

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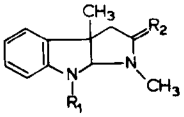
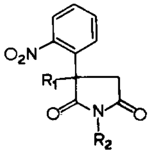
The synthesis of structurally simple eserine skeleton 1 has been investigated recently by various groups$^{1)}$ All of the syntheses presently known start from an indole-type precursor to which ring C is attached. We wish to report a short and stereoselective synthesis in which the B-ring of 1 is constructed in the final step and which is based on the $NaBH_4/H^{\oplus}$-reduction of succinimides$^{2)}$.

As a central compound in the present approach the o-nitrophenylimide 2 was chosen, the synthesis of which is realized in a simple manner starting from o-nitrobenzaldehyde. $TiCl_4$/malonate condensation$^{3)}$ followed by $CN^{\ominus}$ attachment$^{4)}$ and hydrolysis (H_2SO_4 conc./$0^{\circ}C$) of the cyanodiester so-formed led to the amido-diester 3 which was cyclized (NaCl/DMSO $145^{\circ}C$)directly to the imide 4 via adaptation of a recently described method for decarboxylation of malonates$^{5)}$. N-Methylation of 4$^{6)}$ (CH_2N_2) gave 5 which after C-methylation (CH_3I, K_2CO_3/DMF) afforded 2: m.p. 148-150°C, PMR $\delta(CDCl_3)$ 1·78 (s, 3H, $CC\underline{H}_3$) 3·05 (s, 3H, $NC\underline{H}_3$). Alternatively both steps could be combined (0°, CH_3I, K_2CO_3/DMF) to give 2 in 70% yield.

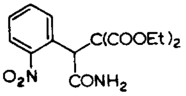
Initially the conversion $NO_2 \rightarrow NH_2$ was planned at this stage; instead of the desired imide 10, however, the product obtained upon catalytic hydrogenation in hydroxylic solvents was the oxindole 11$^{7)}$. Therefore the $NaBH_4/H^{\oplus}$-reduction was directly applied to imides 2 and 5 which showed strikingly dissimilar reaction behaviour. In both instances quantitative carbinolamide formation occurred albeit in completely different product ratios. Thus reduction of 2 afforded a mixture



1 $R_1 = CH_3$, $R_2 = H_2$
12 $R_1 = H$, $R_2 = O$



2 $R_1 = CH_3$, $R_2 = CH_3$
4 $R_1 = H$, $R_2 = H$
5 $R_1 = H$, $R_2 = CH_3$



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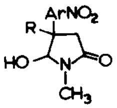
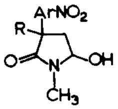
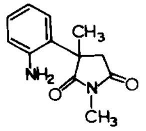


6 $R = CH_3$
7 $R = H$



8 $R = CH_3$
9 $R = H$



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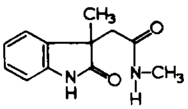

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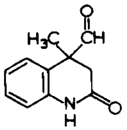

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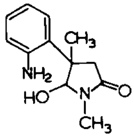

14

of 6: m.p. 189-191°C, PMR δ($CDCl_3$) 1·52 (s, 3H, CCH_3) 2·79 (s, 3H, NCH_3) 4·90 (d, 1H, J = 8 cps, N—CH—O) and 8 in a ratio of 84:16 (PMR) while the corresponding reaction of 5 gave 7 and 9: m.p. 160-164°C, PMR δ($CDCl_3$) 2·75 (s, 3H, NCH_3) 5·15 (m, 1H, N—CH—O), in a ratio of 17:83 (PMR). These results unequivocally support our earlier hypothesis of steric factors being responsible for the observed regioselectivity in the reduction of α,α disubstituted succinimides[8). In the case of 5 electronic factors may well explain the preferential attack at the least hindered side in view of the possible participation of an enolic type structure in the alkaline $NaBH_4$ medium. The latter phenomenon has also been observed in the $NaBH_4/H^{\oplus}$-reduction of other monosubstituted C-aryl-imides, the degree of regioselectivity being determined by the electronic character of the Ar- substituents.

The eserinederivative 12: m.p. 123-126°C, PMR $\delta(CDCl_3)$ 1·45 (s, 3H, $C\underline{H}_3$) 2·84 (s, 3H, $NC\underline{H}_3$) 4·88 (s, 1H, N–C$\underline{H}$–NH) was finally obtained in 78% yield after Pd/C hydrogenation of 6 followed by reflux in $H^{\oplus}$/EtOH. Interestingly as a second compound 13: m.p. 147-150°C, PMR $\delta(CDCl_3)$ 1·51 (s, 3H, $CC\underline{H}_3$) 9·44 (s, 1H, C$\underline{H}$O), 9.78 (broad s, 1H, N$\underline{H}$) was isolated.

Most remarkably 13 was formed in 66% yield after pTsOH/PhH reflux of 14, the latter derivative being provided upon Pd/C hydrogenation of 6 in 97% yield.

In conclusion two points of general interest should be mentioned. Firstly, the present approach allows synthetic access into a broad category of eserine type derivatives. Secondly gem-disubstituted dihydrocarbostyrils can be also obtained via the carbinol amide method thus adding another dimension to this versatile intermediate.

ACKNOWLEDGEMENT

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