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LATERAL CONTROL OF SKELETAL REARRANGEMENT BY COMPLEXATION OF THEBAINE WITH $Fe(CO)_3$

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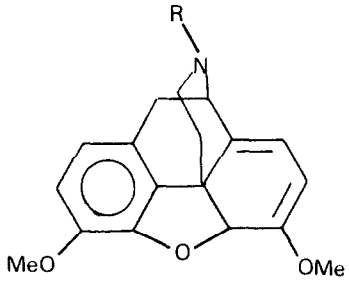
Summary

Temporary attachment of $Fe(CO)_3$ to thebaine allows access to northebaine, 14α-substituted thebainone derivatives, and a rearranged codeinone analogue lacking the oxide ring and in which the dihydrophenanthrene nucleus is replaced by a dihydrofluorene one.

Lateral attachment of a complexed transition metal to the π-system of unsaturation can control organic synthetic reactions in a number of useful ways.[1] The $Fe(CO)_3$ complexes of substituted cyclohexa-1,3-dienes have been examined with the aim of elucidating such general aspects.[1,2] Complexation abolishes the normal polarisability and reactivity of an olefin, but induces other properties. Reactions are therefore altered in ways from which new synthetic capabilities can be derived.

One feature is to reduce or abolish the reactivity of the diene to some reagents, that is, to protect it reversibly since the $Fe(CO)_3$ is readily removed. Another is to provide internal activation leading to formation of the equivalent of a carbenium ion because of the ability of the Fe to accommodate a positive charge, under experimental conditions not requiring external application of acids, Lewis or otherwise. This may permit two new types of experimental process, one of which, the application of an anion or a base, would be incompatible with the usual acidic experimental conditions; the other leading to the possibility of Wagner-Meerwein rearrangements new in type because of internal nucleophilic capabilities of the nitrogen atom.[3] Some reactions of (2,R=Me), readily available[3] from thebaine (1,R=Me), illustrate these three aspects, and in the course of doing so lead to potentially useful substances related to the morphinane series.



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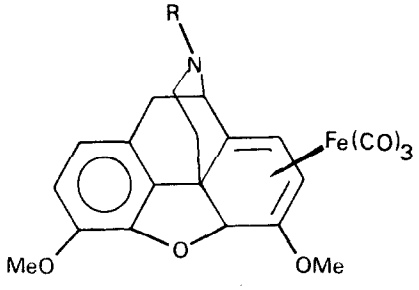

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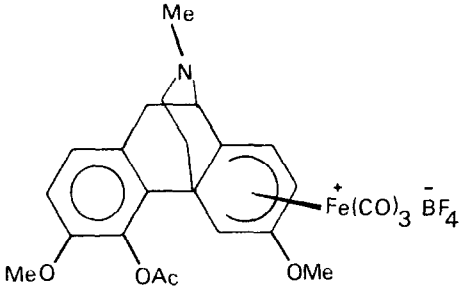

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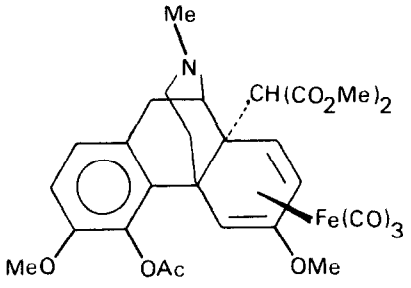

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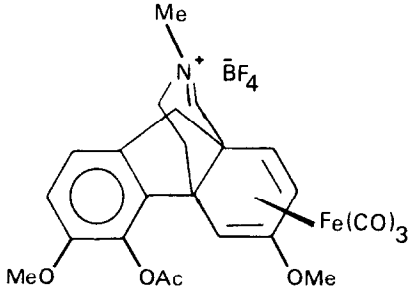
N-Demethylation of thebaine is desirable to give ready access to N-substituted analogues, but classical reagents such as BrCN induce skeletal rearrangement via carbenium ions. The neutral reagent ethyl azodicarboxylate has been used with some success for the purpose.[4]

With the methoxydiene system locked up by the superimposed $Fe(CO)_3$ it has been shown that BrCN replaces Me in the normal fashion to yield (2,R=CN). We now find that hydrolysis of this with aqueous trifluoroacetic acid (25%) at 20°/20 h gave (2,R=$CONH_2$) (91%) m.p. 215° which reacted with $Me_3NO.2H_2O$ in dimethylacetamide to form (1,R=$CONH_2$) (46%) m.p. 223-226°. However we failed to remove the $CONH_2$ by hydrolysis either from this or the $Fe(CO)_3$ precursor. However, the action[5] on (2,R=Me) of 2,2,2-trichloroethyl chloroformate and 1,2-epoxypropane gave (2,R=$CO_2CH_2CCl_3$) (86%) m.p. 170-172°, which with $FeCl_3.6H_2O$ in formamide at 15°/22 h, led to (1,R=$COCH_2CCl_3$) (61%) m.p. 180-182°. Reduction of this carbamate with Zn-acetic acid at 10-15°/1 h produced northebaine (1,R=H) (64%) m.p. 159-160°. The structures of all of these substances were supported by NMR, mass spectra and elemental analyses, identical with known compounds when the data are available.

Formation of the dienyl salt (3) is made possible by ready fission of the ether linkage due

to stabilisation of the resulting positive charge on Fe. This cation salt has been shown[3] to react with $OH^{\ominus}$ and $H^{\ominus}$ at the terminus of the carbon system 'ortho' to OMe in contrast to the simple 2-OMe cation salt which with these nucleophiles reacts only at the 'para' position. Surprisingly, therefore, upon treatment with the anion of dimethylmalonate the cation (3) gave a product corresponding to attack at the angular C-14 position, m.p. 148-149° (petrol). The structure of the complex (4) was supported by comparison of its 270 MHz ^1H NMR with that of the thebaine complex; in it are the key resonances of a 1-OMe group and two 'inner' diene protons. The malonate adduct shows resonances characteristic of a 2-OMe (δ 3.51, s) derivative having only one 'inner' proton (δ 4.86, dd, J=6.7, 2.4 Hz).

This procedure, using possible reactions of cation salt (3) with nucleophiles, represents an entry into 14-functionalised morphinanes lacking the 4,5-oxide bridge (e.g. the series related to thebainone).



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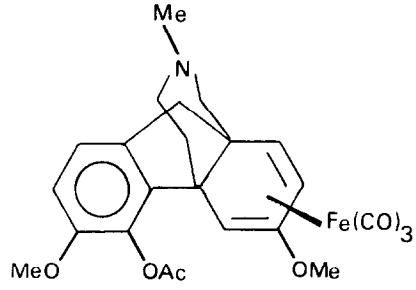

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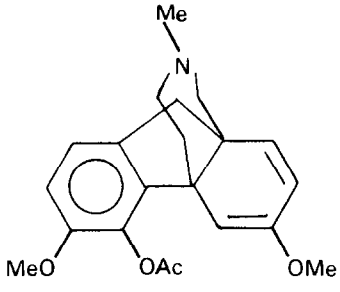

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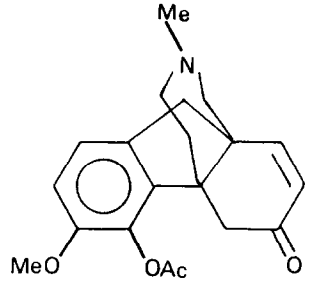

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Numerous rearrangements of the morphinane skeleton are based on carbenium ion sequences[6], in turn dependent for their character on the nature of the unsaturation present as well as the reagents. In thebaine, for instance, rearrangements induced by the action of either Bronsted or Lewis acids result finally in opening of the N-containing ring with formation of the aromatic phenanthrene nucleus. Members of the aporphine group of alkaloids have been synthesised in this

way.[7]

Heating (3) in ethanol produces[3] iminium salt (5) by a type of rearrangement not observed in the series lacking the $Fe(CO)_3$. The structure of (5) was defined by X-ray crystallography.[8] This rearrangement has been utilised to produce novel codeine-related structures for biological testing. Thus, reduction of iminium salt (5) using $NaBH_4$ in methoxyethanol (0°, 20 min) gave the known[3] amine (6) which upon treatment with $Me_3NO.2H_2O$ (10 fold excess) in dimethylacetamide (70°, 3 h) gave the new diene (7). Without purification this was converted by aqueous acid in THF (room temp., overnight) into the enone (8) purified over silica using $CHCl_3$-MeOH (4:1) as eluant (75% yield from the iminium salt). The compound displayed the following spectral characteristics, which together with elemental analyses, are supportive of the structure shown: υ_{max} ($CHCl_3$) 1680, 1770 cm^{-1}; δ_H ($CDCl_3$, 270 MHz) 7.04 (d, J=8.1 Hz, 1H), 6.81 (d, J=8.1 Hz, 1H), 6.73 (d, J=10.2 Hz, 1H), 6.06 (d, J=10.2 Hz, 1H), 3.80 (s, 3H), 2.96 (br, s, 2H), 2.7-2.5 (m, 4H), 2.32 (s, 3H), 2.3-2.1 (m, 2H), 2.20 (s, 3H), 1.86 (m, 2H); m/e 341 (M^+, 29%), 313 (7%), 270 (17%), 228 (16%), 71 (100%).

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