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STUDIES IN THE DIHYDROPYRIDINE SERIES IV[1]. BIPIPERIDYL SYNTHONS VIA COUPLING OF DIHYDROPYRIDINETRICARBONYLCHROMIUM (0) COMPLEXES.

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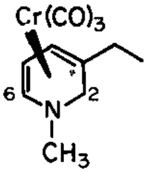
Abstract - The reaction of 1,2-dihydro-3-ethyl-N-methylpyridinetricarbonylchromium (0) complex with various alkyllithiums provides a high yield of three novel bipiperidyl intermediates. X-ray structures of these isomers are provided.

An earlier report[1] from these laboratories showed nucleophilic substitution in dihydropyridine tricarbonylchromium (0) systems (e.g. (1)) was indeed possible and unlike the analogous π-benzenoid tricarbonylchromium (0) complexes these heterocyclic systems exhibited remarkable regiospecificity.



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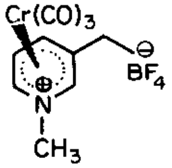

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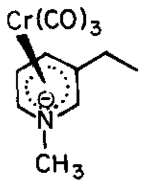
Based on earlier literature[2] we attempted to improve the efficiency of and/or change the position of nucleophilic substitution via the cation (2). As in other studies with similar systems[3] all attempts to prepare (2) by hydride abstraction (trityl fluoroborate) from (1) were unsuccessful, perhaps not surprising in light of the considerable electron withdrawing effect of the coordinated metal function and lack of stabilization from the nitrogen electrons. On the other hand the corresponding anion (3) seemed to be a plausible species.

On this basis attempts to abstract a proton from (1) and to alkylate (or acylate) the intermediate (e.g. (3)) were investigated. Initially the complex (1) was reacted in THF (-78°) with t-BuLi (1 equiv.) and the mixture subsequently treated with an excess of methyl iodide. Oxidation, of



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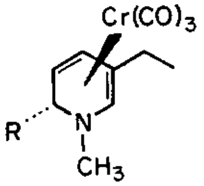


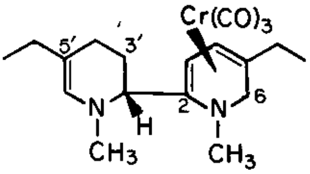
4 R = $\underline{t}$-Bu
5 R = CH_3

the resulting mixture, with iodine gave mainly decomposition products together with traces of (1) and a compound tentatively assigned as (4) based on mass spectral (M^+ 315) and ^{1}Hmr (δ($CDCl_3$): 5.76 (1H, d, J = 6 Hz, H-3), 4.83 (1H, bd, J = 6 Hz, H-4) 3.29 (2H, q, J = 8 Hz, H_2-6), 2.80 (3H, s, $-NCH_3$)) evidence. When the above reaction was repeated, omitting addition of methyl iodide, a low yield of (4) (7%) was obtained together with an isomeric compound and a "dimeric" product (mol. wt 382). Using methyllithium as base/nucleophile at -78° gave, directly without oxidation, a satisfactory yield (overall 84%) of "dimeric" materials (M^+ 382) together with ~ 1.5% of the nucleophilic substitution product (5) (M^+ 273). Chromatography (silica gel; hexane-ether, N_2 atmosphere) of the dimeric fraction afforded the three components:-

(6) (32%) red crystals from dichloromethane - hexane; mp. 99 - 101.5°; ms, m/e: 382, 354, 326, 298, 296, 245, 122; λmax: 402 nm (ε, 3821); νmax: 1945, 1863, 1845 cm^{-1}; ^{1}Hmr ($CDCl_3$) δ 5.82 (1H, d, J = 5.4 Hz, H-3), 5.79 (1H, s, H-6'), 4.94 (1H, d, J = 5.4 Hz, H-4), 3.92 (1H, s, H-2'), 3.33 (2H, s, H_2-6), 2.87 (3H, s, $-N'CH_3$), 2.63 (3H, s, $-NCH_3$), 1.02 (3H, t, J = 7.5 Hz, $-CH_2C\underline{H}_3$), 0.96 (3H, t, J = 7.5 Hz, $-CH_2C\underline{H}_3$); (C_6D_6) δ: 5.50 (1H, d, J = 5.4 Hz, H-3), 5.44 (1H, s, H-6'), 4.41 (1H, d, J = 5.4 Hz, H-4), 3.36 (1H, unresolved triplet, H-2'), 2.62 (3H, s, $-N'CH_3$), 2.31 (2H, ABq, $\Delta\nu_{AB}$ = 12.1 Hz, J = 10.8 Hz, H_2-6), 1.54 (3H, s, $-NCH_3$), 0.95 (3H, t, J = 7.5 Hz, $-CH_2C\underline{H}_3$), 0.56 (3H, t, J = 7.5 Hz, $-CH_2C\underline{H}_3$); Anal.[4]

(7) (27%) red crystals; mp: 105 - 107°; ms. and uv. as for (6); νmax: 1950, 1875, 1850 cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 5.79 (1H, d, J = 5.4 Hz, H-3), 5.76 (1H, s, H-6'), 4.97 (1H, d, J = 5.4 Hz, H-4), 3.62 (1H, d, J = 9 Hz, H-2'), 3.43 (2H, ABq, $\Delta\nu_{AB}$ = 24.7 Hz, J = 10.8 Hz, H_2-6), 2.65 (3H, s, $N'-CH_3$), 2.50 (3H, s, NCH_3); (C_6D_6) δ: 5.60 (1H, s, H-6'), 5.32 (1H, d, J = 5.4 Hz, H-3), 4.50 (1H, d, J = 5.4 Hz, H-4), 3.42 (1H, dd, J = 10, 2.7 Hz, H-2'), 2.50 (2H, ABq, $\Delta\nu_{AB}$ = 15.5 Hz, J = 10.8 Hz, H_2-6), 1.97 (3H, s, $N'-CH_3$), 1.78 (3H, s, $-NCH_3$), 0.97 (3H, t, J = 7.5 Hz, $-CH_2C\underline{H}_3$), 0.72 (3H, t, J = 7.5 Hz, $-CH_2C\underline{H}_3$); Anal.[4]

(8) (25%) red crystals, mp: 138 - 142°; ms and uv as for (6); νmax: 1945, 1870, 1845 cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 5.67 (1H, d, J = 5.4 Hz, H-3), 5.62 (1H, bs, H-4'), 4.95 (1H, d, J = 5.4 Hz, H-4), 3.62 (1H, t, J = 5.4 Hz, H-2'), 3.36 (2H, ABq, J = 10.8 Hz, H_2-6), 3.19 (2H, ABq, J = 17.5 Hz, H_2-6'), 2.68 (3H, s, $-N'CH_3$), 2.40 (3H, s, $-NCH_3$), 1.03 (3H, t, J = 7.5 Hz, $-CH_2C\underline{H}_3$), 0.97



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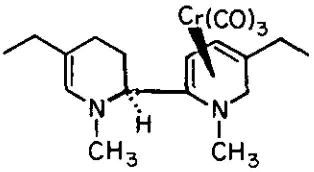

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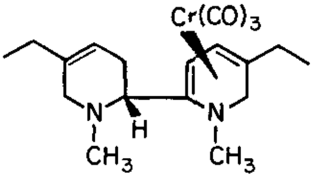

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(3H, t, J = 7.5 Hz, $-CH_2C\underline{H}_3$); (C_6D_6) δ: 5.39 (1H, bs, H-4'), 5.35 (1H, d, J = 5.4 Hz, H-3), 4.60 (1H, d, J = 5.4 Hz, H-4), 3.48 (1H, t, J = 5.4 Hz, H-2') 2.93 (2H, ABq, J = 17.5 Hz, H_2-6'), 2.63 (2H, ABq, J = 10.8 Hz, H_2-6), 2.19 (3H, s, $-N'CH_3$), 2.06 (3H, s, $-NCH_3$), 0.94 (3H, t, J = 7.5 Hz, $-CH_2C\underline{H}_3$), 0.78 (3H, t, J = 7.5 Hz, $-CH_2C\underline{H}_3$); Anal.[4] The above assignments were also supported by proton decoupling experiments on (8) in C_6D_6 solution. Here irradiation of the broad signal at δ 2.24 (H-3') caused collapse of the triplet at 3.48 ppm giving rise to a sharp singlet. Similarly irradiation at δ 5.35 gave rise to a sharp singlet at 4.60 ppm. The stereochemical relationships depicted in (6), (7) and (8) were determined by X-ray crystal analysis and the pertinent data are provided below. Notably, the diastereomer of (8) (corresponding to (7)) was not detected!

A mechanistic rationale for the formation of these "dimers" is given in Figure 1.

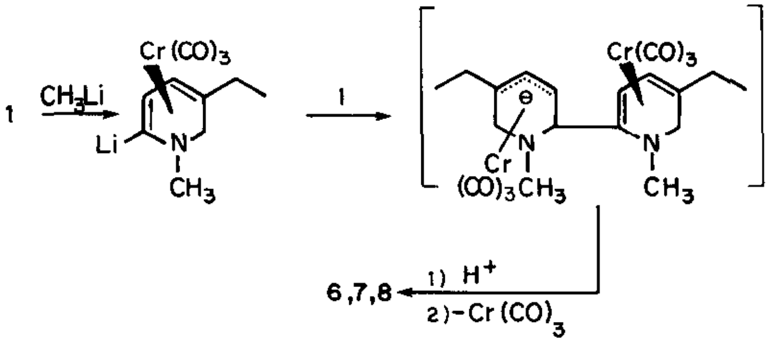


Figure 1

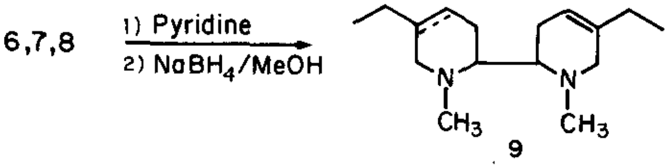
In order to confirm the structural assignments uniquely and to determine the finer stereochemical details, compounds (6), (7) and (8) were subjected to X-ray analysis and their structures are represented as (6a), (7a), and (8a) respectively (Figure 2). Data sets were collected on a Nonius CAD-4 automated diffractometer using $Mo\underline{K}\alpha$ radiation. The structures were solved by direct methods[5] and refined by full-matrix anisotropic least-squares techniques. The results are summarized in Table 1.

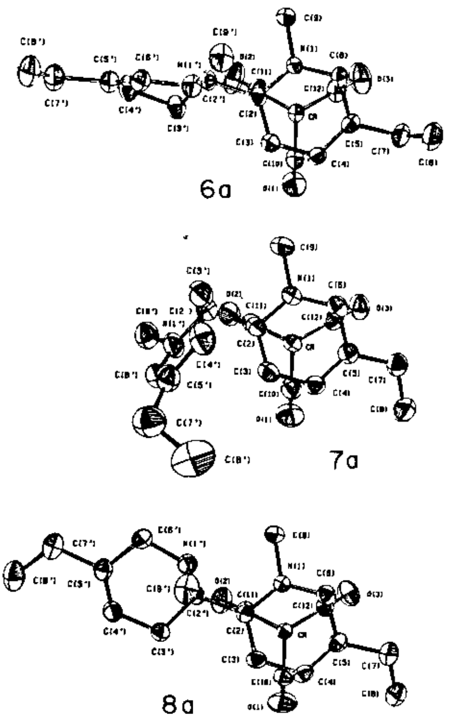
Table 1. Summary of X-ray Crystallographic Data

	6a	7a	8a
a(Å)	29.537(5)	11.430(2)	19.226(4)
b	11.323(3)	10.440(2)	10.567(2)
c	14.594(2)	19.566(2)	9.457(1)
α(°)	90	90	90
β	128.55(4)	123.43(10)	90
γ	90	90	90
Space group	$C2/c$	$P2_1/c$	$P2_12_12_1$
Z	8	4	4
Obs. data	1801	2474	1819
R	0.031	0.035	0.028
C(3')-C(4')(Å)	1.520(6)	1.510(10)	1.508(4)
C(4')-C(5')	1.495(5)	1.495(13)	1.320(4)
C(5')-C(6')	1.326(15)	1.317(5)	1.498(4)

Figure 2 compares all three isomers, each viewed from the same perspective relative to its chromium tricarbonyl group. In each molecule the metal atom interacts with the double bonds [C(2) - C(3) and C(4) - C(5)] and the lone pair of the dihydropyridine system to achieve a distorted octahedral configuration. The position of the double bond in the tetrahydropyridine ring of each isomer is established by the observed C - C bond lengths (Table 1) and direct location of the hydrogen atoms.

Removal of the chromium from (6), (7) and (8) in the previously described manner[6] afforded the bipiperidyl systems generally shown by (9). Full details and further applications of these synthons will be discussed later.





6a

7a

8a

Figure 2

In summary, reaction of dihydropyridinetricarbonylchromium (0) complexes with lithium alkyls provides an interesting and novel route to bipiperidyl synthons of value in the synthesis of natural products and related systems. Studies in this direction are presently underway.

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