B. In Vitro Susceptibility Tests. MIC's of the compounds for the various bacterial strains were determined by a microtiter broth dilution assay.[8,9] For comparative purposes, MIC's of racemic compounds were divided by two to reflect the fact that only one oxazolidinone enantiomer possesses antibacterial activity.

Registry No. **3**, 139071-68-4; **3** isocyanato, 33484-67-2; **4**, 139071-69-5; **4** isocyanato, 59741-17-2; **5**, 139071-70-8; **5** isocyanato, 139072-17-6; **6**, 139071-71-9; **6** isocyanato, 139072-18-7; **7**, 139071-72-0; **7** isocyanato, 139072-19-8; **8**, 120912-42-7; **8** isocyanato, 120912-37-0; **9**, 139071-73-1; **9** isocyanato, 139072-20-1; **10**, 139071-74-2; **10** isocyanato, 2243-54-1; **11**, 139071-75-3; **11** isocyanato, 54132-75-1; **12**, 139071-76-4; **12** isocyanato, 54132-76-2; **13**, 139071-77-5; **13** isocyanato, 51163-27-0; **14**, 104421-21-8; **15**, 96800-17-8; **16**, 96800-41-8; **17**, 96800-15-6; **18**, 114992-51-7; **19**, 115006-55-8; **20**, 139071-78-6; **21**, 96799-96-1; **21** 3-(4-nitrophenyl), 96799-95-0; **22**, 139071-79-7; **23**, 139071-80-0; **24**, 139071-81-1; **25**, 139071-82-2; **27**, 139071-83-3; **28**, 139071-84-4; **29**, 139071-85-5; **30**, 139071-86-6; **31**, 139071-87-7; **32**, 139071-88-8; **33**, 139071-89-9; **34**, 139071-90-2; **35**, 139071-91-3; **35** (X = F), 139072-21-2; **36**, 139071-92-4; **36** (X = F), 139072-22-3; **37**, 139071-93-5; **38**, 139071-94-6; **39**, 139071-95-7; **40**, 139071-96-8; **41**, 139071-97-9; **42**, 139071-99-1; **43**, 139071-99-1; **44**, 139072-00-7; **45**, 139072-01-8; **46**, 139072-02-9; **47**, 139072-03-0; **48**, 139072-04-1; **49**, 139072-05-2; **50**, 139072-06-3; **51**, 114992-76-6; **52**, 114992-77-7; **53**, 139072-07-4; **54**, 139072-08-5; **55**, 139072-09-6; **56**, 139072-10-9; **57**, 139072-11-0; **57**, 139072-25-6; **57**, 139072-26-7; **57**, 139072-27-8; **58**, 139072-12-1; **59**, 139072-13-2; **60**, 139072-14-3; **61**, 139072-15-4; **62**, 139072-16-5; **63**, 120912-43-8; $PdCl_2(PPh_3)_2$, 13965-03-2; trimethylsilylacetylene, 1066-54-2; (*S*)-*N*-[[3-[4-[(trimethylsilyl)ethynyl]-3-(trifluoroacetamido)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide, 139072-23-4; (*S*)-*N*-[[3-[4-ethynyl-3-(trifluoroacetamido)-phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide, 139072-24-5.

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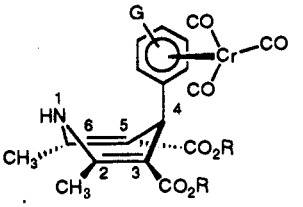
Communications to the Editor

Tricarbonylchromium Complexes of Hantzsch Esters Possess Robust Calcium Antagonist Activity†

4-Aryl-1,4-dihydropyridines (Hantzsch esters) are important cardiovascular drugs which exhibit calcium channel antagonist activity.[1] Interest in the synthesis of this class of compounds continues, both to elucidate the molecular basis of action and to improve their pharmacological profile.[2] (Arene)chromium tricarbonyl derivatives have found wide application in synthesis[3] and, more recently, in biological applications[4] as probes of drug–receptor binding. A central question for the potential use of a functionalized drug as a probe of any drug–receptor interaction is whether the structural change introduced perturbs the binding or abolishes biological activity.[5] We herein report the first preparation of tricarbonylchromium 4-aryl-1,4-dihydropyridines,[6] and present evidence that these molecules are robust and stable calcium antagonists which compete with [^{3}H]-1,4-dihydropyridine binding at Ca^{2+} channels in cardiac membranes.



Results and Discussion

Dihydropyridine complexes of chromium are known wherein the η^6 tricarbonylchromium (TCC) is bound to the dienamine function.[6a–e] Recently, TCC–dihydropyridine complexes have been obtained by nucleophilic addition to TCC–pyridine complexes.[6f] We present here compounds which, to the best of our knowledge, represent the first examples of metalation selectively on the 4-aryl ring in the presence of a 1,4-dihydropyridine. Regioselectivity was clearly established as η^6 to the 4-aryl substituent by the

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0022-2623/92/1835-1165$03.00/0

^1H and ^{13}C NMR chemical shifts.[7] The assignments were made unambiguously by 2D ^1H–^{13}C correlation and off-resonance decoupling. The proton chemical shifts of the 4-phenyl substituent for the starting material (δ 7.0–7.2) shifted dramatically upfield (δ 4.9 to 5.6). Similarly, the carbon signals for the aromatic ring were also prominently shifted upfield, from 147.7 (ipso), 127.8, 127.7, and 126 to 118.9, 97.4, 96.0, and 87.7, respectively. In contrast, the signals for the vinylogous urethane functional group of the 1,4-dihydropyridine changed only slightly from 167.7 (CO_2R), 144 (C=CNH), and 103.8 (C=CNH) for the starting material to 167.1, 145.3, and 102.9 for the corresponding TCC complex. The characteristic spectroscopic features of the tricarbonylchromium derivative, which recommend its use as a drug–receptor probe, are the infrared carbonyl stretching absorptions at 1964 and 1884 cm^{-1} and the ^{13}C NMR chemical shift observed at 233 ppm for the TCC moiety. Both of these regions represent useful spectral "windows" for the study of TCC–DHP interaction with receptor protein.

In the structure–activity relationship (SAR) for the DHP calcium antagonists, electron-withdrawing substituents on the ortho or meta position of the 4-phenyl ring normally enhance biological activity. Therefore, the procedure was extended to the metalation of functionalized 4-phenyl rings. Representative electron-withdrawing groups (i.e., o-CF_3, 42% yield; o-Cl, 74%) and electron-donating groups (i.e., o-OCH_3, 59% yield; m-OCH_3, 66%; and p-OCH_3, 56%) can be incorporated. However, limitations were encountered with o-NO_2 and 4-isoxazolyl[5] substituents. In these cases, apparent reduction of the nitrogen–oxygen bond competes favorably with metalation.

The 4-aryl group in the solid state usually adopts a conformation in which the mean plane of the 4-aryl ring approximately bisects the mean plane of the 1,4-dihydropyridine (DHP),[8] and theoretical studies have suggested that this conformation represents an energy minimum.[9] For unsymmetrically disubstituted 4-aryl rings, there are two such conformations possible, that is, with the G-group endo or exo to the DHP.[8] Given the large size of a TCC group, an exo conformation would be expected. The conformation with respect to this ring juncture may significantly effect binding to the receptor; therefore, it was of interest to study the solution conformation of the tricarbonylchromium derivative. A 2D NOESY was undertaken of m-OCH_3-TCC–DHP to elucidate the relative conformation of the TCC–DHP in solution at room temperature (Figure 1).[11] As expected, a correlation was observed for the C-4 proton of the dihydropyridine and the C-2 proton of the aromatic ring, corresponding to the less hindered O-exo conformer. Prominent cross peaks were observed for the m-OCH_3 group with (1) the C-2,6 methyl signal of the DHP and (2) the methyl of the C-3,5 ester function. The former provides strong evidence for an O-endo conformation with respect to the ring juncture between the DHP and its 4-aryl substituent. In an O-endo conformation at the ring juncture, the latter correlation would be likely for the *ap* ester conformation. This assignment is corroborated by a cross peak observed from the C-2,6 methyl signal of the DHP and the methyl of the C-3,5 ester function.

The (arene)chromium carbonyl group is usually considered an electron-withdrawing moiety.[3] We expected

(6) Chromium carbonyl complexes with electron-rich dihydropyridines are well-known: (a) Bear, C. A.; Cullen, W. R.; Kutney, J. P.; Ridaura, V. E.; Trotter, J.; Zanarotti, A. Studies in the Dihydropyridine Series. I. Novel and Stable Complexes of N-Methyl-3-ethyl-1,2-dihydropyridine and N-Methyl-3-ethyl-1,6-dihydropyridine. *J. Am. Chem. Soc.* **1973**, *95*, 3058–3060. (b) Kutney, J. P.; Greenhouse, R.; Ridaura, V. E. Studies in the Dihydropyridine Series. II. Unstable Dihydropyridines Generated from their Chromium Complexes and their C-Alkylation. *J. Am. Chem. Soc.* **1974**, *96*, 7364–7365. (c) Kutney, J. P.; Noda, M.; Worth, B. R. Studies in the Dihydropyridine Series. III. Piperideine Synthons by Nucleophilic Substitution to Dihydropyridinetricarbonyl Chromium(0) Complexes. *Heterocycles* **1979**, *12*, 1269–1273. (d) Kutney, J. P.; Mak, T. C. W.; Mostowicz, D.; Trotter, J.; Worth, B. R. Studies in the Dihydropyridine Series. IV. Bipiperidyl Synthons via Coupling of Dihydropyridinetricarbonylchromium(0) Complexes. *Heterocycles* **1979**, *12*, 1517–1521. (e) Kutney, J. P.; Noda, M.; Lewis, N. G.; Monteiro, B.; Mostowicz, D.; Worth, B. R. Studies in the Dihydropyridine Series. V. Synthesis of Pyridocarbazole Alkaloids: Olivacine and Guatambuine. *Heterocycles* **1981**, *16*, 1469–1472. (f) Davies, S. G.; Shipton, M. R. Pyridine Tricarbonylchromium Complexes: Complete Stereoselective α,α-Dialkylation of 2-Methylpyridine Tricarbonylchromium. *J. Chem. Soc., Chem. Commun.* **1990**, 1780–1781.

(7) A representative preparation is described below: 3,5-dicarbethoxy-1,4-dihydro-2,6-dimethyl-4-[η^6-tricarbonylchromiophenyl]pyridine. Obtained from 3,5-dicarbethoxy-1,4-dihydro-2,6-dimethyl-4-phenyl-pyridine by reaction with chromium hexacarbonyl at reflux in *n*-butyl ether/tetrahydrofuran solution (9:1). The product was obtained as a bright yellow crystalline solid by recrystallization from benzene/hexanes, in 76% yield. IR: 1964, 1884, 1695. ^1H NMR ($CDCl_3$) δ 5.87 (br s, 1 H), 5.6 (d, 2 H), 5.43 (t, 1 H), 4.98 (t, 2 H), 4.82 (s, 1 H), 4.22 (q, 4 H), 2.41 (s, 6 H), 1.29 (t, 6 H). ^{13}C NMR: 233.3 (CrCO), 167.1, 145.3, 118.9, 102,9, 97.4, 96.0, 87.7, 60.3, 36.7, 19.55, 14.3. Mass spectrum: *m/z* 465 (1.1% relative intensity, M^+), 437 (3), 409 (8.4), 381 (91), 392 (3.2), 336 (10.2), 252 (100). Anal. ($C_{22}H_{23}NO_7Cr$) Calculated: C, 56.77; H, 4.98; N, 3.01. Found: C, 56.53; H, 4.83; N, 3.08. Complete spectroscopic characterization of all new compounds has been provided to the Editor.

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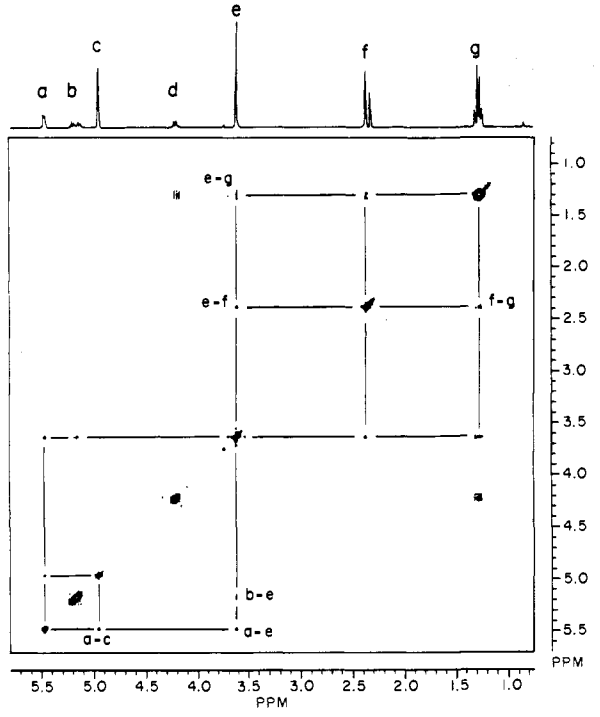

Figure 1. 2D NOESY spectrum of m-OCH_3-TCC-DHP. The correlations of a–e and b–e correspond to the m-OCH_3 group and its ortho and para protons. The correlation a–c corresponds to the ortho proton and the C-4 DHP proton, and thus provides evidence for the O-exo conformation. The e–f correlation arises from interaction between the m-OCH_3 and the C-2/6 methyl groups of the DHP, and therefore provides evidence for the O-endo conformation. The f–g correlation, between the C-2/6 methyl groups of the DHP and the C-3/5 ethyl esters, must arise from an *ap* ester conformation. The g–e correlation probably arises from the m-OCH_3 group in the O-endo conformation and an *ap* ester.

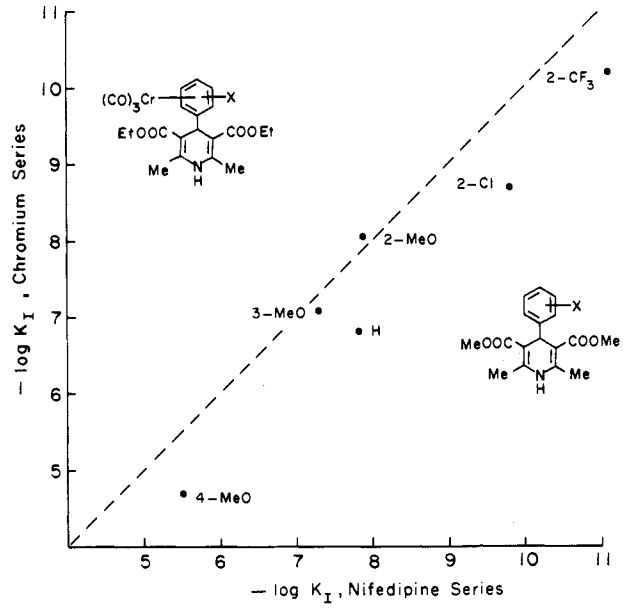

Figure 2. Relationship of competitive binding of the TCC-DHP series with [^{3}H]PN 200 110 to guinea pig heart membranes versus the 4-aryl-DHP series. The correlation is consistent with both series interaction at the same site.

that the biological activity could be comparable to or greater than that of the uncomplexed Hantzsch esters, if the large steric bulk of the TCC group can be presented in a favorable orientation in the receptor "cavity". In accord with this expectation the K_I values of TCC-DHPs (Figure 2) compare favorably with the values for the 4-aryl-1,4-dihydropyridines.[1,8b,13] In fact, the o-OCH_3-TCC-DHP is more active than its unmetalated counterpart. The same general trend in the Hansch relationship[14] for substitution at the 4-aryl moiety is observed for the TCC-DHPs as for their unmetalated counterparts: binding follows the order EWG > H > EDG, and para substitution greatly diminishes binding. The observation of robust activity of TCC-DHPs is consistent with the recently proposed drug–receptor model of Langs, Strong, and Triggle[15] in that the conformation evidenced for the 4-aryl moiety of TCC-DHP should allow for facile adaptation to the receptor site during binding to the voltage sensor moiety of the membrane-bound enzyme which serves as the DHP receptor.[12]

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(13) Radioligand binding was assayed as described below. Microsomal membranes from guinea pig heart ventricles were prepared as previously described. Binding of the 1,4-dihydropyridine (+)-[^{3}H]-PN 200 110 (isopropyl 4-(2,1,3-benzoxadiazol-4-yl)-1,4-dihydro-5-(methoxycarbonyl)-2,6-dimethyl-3-pyridinecarboxylate) and its competitive displacement by the tricarbonylchromium 4-aryl-1,4-dihydropyridines were carried out as previously described. Briefly, membrane protein (40–120 μg) was incubated in 5 mL of 50 mM tris[(hydroxymethyl)amino]methane (Tris) buffer at pH 7.2 for 90 min at 25 °C with 5×10^{-11} (+)-[^{3}H]-PN 200 110 and varying concentrations of competing compounds. Duplicate tubes contained 10^{-7} M (+)-PN 200 110 to define nonspecific binding. Tubes were filtered and washed rapidly with two 5-mL portions of ice-cold Tris buffer in a Brandel cell harvester [Model M-24R, Brandel Instruments Ltd., Gaithesburg, MD]. Trapped radioactivity was counted by liquid scintillation spectrometry at an efficiency of 40–45%. Competing compounds were prepared in ethanol as 10^{-3} stock solutions in 100% ethanol. Subsequent dilutions were made in 50% ethanol (10^{-4} M) or distilled water (10^{-5} onward). All dilutions were prepared on the day of the experiment. Concentrations of ethanol to 0.2% (v/v) did not affect specific binding. Binding data were analyzed by iterative curve fitting programs (BDATA, CDATA, EMF Software, Knoxville, TN). (+)-[^{3}H]-PN 200 110 with a specific activity of 70 Ci/mol [1 Ci = 3.7×10^{10} bq) was purchased from DuPont-New England Nuclear (Boston, MA). (a) Bolger, G. T.; Gengo, P.; Klockowski, R.; Luchowski, E.; Siegel, H.; Janis, R. A.; Triggle, A. M.; Triggle, D. J. Characterization of binding of the Ca^{2+} channel antagonist [^{3}H]nitrendipine, to Guinea Pig Ileal Smooth Muscle. *J. Pharmacol. Exp. Ther.* **1983**, *225*, 291. (b) Janis, R. A.; Sarmiento, J. G.; Maurer, S. C.; Bolger, G. T.; Triggle, D. J. Characteristics of the binding of [^{3}H]nitrendipine to rabbit ventricular membranes: modification of the Ca^{2+} channel Antagonist Bay K 8644. *J. Pharmacol. Exp. Ther.* **1984**, *231*, 291.

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Knerr of the Idaho NMR facility. We also thank the National Science Foundation (Grant No. CHE-8504253) and the M. J. Murdock Charitable Trust of Research Corp. for their part in funding the purchase of the IBM AF-300 NMR spectrometer.

Registry No. $Cr(CO)_6$, 13007-92-6; DHP (unsubstituted), 1165-06-6; o-OCH_3-DHP, 42972-42-9; m-OCH_3-DHP, 58029-73-5; p-OCH_3-DHP, 34014-60-3; o-CF_3-DHP, 23191-75-5; o-Cl-DHP, 34148-67-9; TCC-DHP (unsubstituted), 139276-23-6; o-OCH_3-TCC-DHP, 139276-24-7; m-OCH_3-TCC-DHP, 139276-25-8; p-OCH_3-TCC-DHP, 139276-26-9; o-CF_3-TCC-DHP, 139276-27-0; o-Cl_3-TCC-DHP, 139276-28-1; 2.

(16) (a) A referee expressed concern about the stability of TCC complexes in the buffered aqueous media; however, it should be pointed out that such complexes are well-known to be quite stable under such conditions. A good example is the reduction of carbonyl–TCC complexes to carbinol–TCC complexes using Baker's yeast in aqueous media at 35 °C, without decomposition of the TCC moiety: Top, S.; Jaouen, G.; Gillois, J.; Baldoli, C.; Maiorana, S. Enantioselective Microbial Reduction of Planar Chiral Organometallics of Synthetic Interest. *J. Chem. Soc., Chem. Commun.* **1988**, 1284–1285. (b) Another referee expressed concern for the toxicity of chromium compounds. Chromium hexacarbonyl has an LD_{50} of 100 mg/kg iv in mice (Merck Index, 10th Ed.). Although the toxicologial properties of TCC–DHPs are not known, and they should be handled with due respect, this level of toxicity does not appear to represent an unreasonable hazard to properly trained technicians.

† Dedicated to Professor Albert I. Meyers on the occasion of his 60th birthday.

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Book Reviews

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