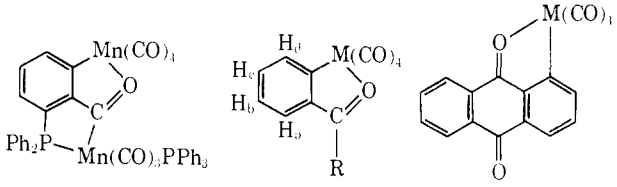
Metalation of Aromatic Ketones with Methylmanganese and Methylrhenium Carbonyl Complexes[1]

Sir:

Recent discovery of $Ph_2P[C_6H_3(CO)(Mn(CO)_4)]Mn(CO)_3PPh_3$[2] (**1**) has led us to investigate the reaction of aromatic ketones and quinones with $CH_3M(CO)_5$ (M = Mn or Re). We find that metalation of the aromatic ring in position ortho to the carbonyl group proceeds smoothly to give products such as **2** or **3**. We also



1 2, M = Mn or Re, R = CH_3, C_6H_5 3

find that the rate of reaction increases with decreasing carbonyl stretching frequency of the originating ketone. This is characteristic of increasing base strength of the carbonyl group[3] and, taken together with the specific metalation, leads us to believe that the entering metal is directed to the ortho position of the ring through initial donor–acceptor interaction with the carbonyl group; *cf.* directing effects of the carbonyl group in aromatic thallation[4a] or lithiation[4b] reactions.

In a typical reaction aryl ketone and the alkylmetal carbonyl in 1:1 ratio are heated under inert atmosphere in hydrocarbon solvents at temperatures ranging from 80 to 125° and reaction times up to 12 hr; see Table I.

Table I

Compound[a]	Originating ketone	Mol wt Obsd[b]	Mol wt Calcd	$\nu_{C\equiv O}$[c]	$\nu_{>C=O\rightarrow M}$[d]
$C_{12}H_7MnO_5$, **2a**	Aceto-phenone	286	286	2082 m, 1997 vs 1947 s	1578
$C_{17}H_9MnO_5$, **2b**	Benzo-phenone	348	348	2082 m, 1997 vs 1947 s	1519
$C_{17}H_9O_5Re$, **2c**	Benzo-phenone	478[e]	478[e]	2096 m, 1993 s 1988 sh, 1939 s	1501
$C_{18}H_7O_8Re$, **3**	Anthra-quinone	504[e]	504[e]	2096 w, 1996 s 1944 s	1512

[a] Reaction temperature, time, and solvent are as follows: **2a**, 126°, 0.5 hr, octane; **2b**, 80°, 5 hr, benzene; **2c**, 110°, 12 hr, toluene; **3**, 110°, 6 hr, toluene. [b] Mass spectral. [c] Cyclohexane solution, Beckman IR-4. [d] CCl_4 solution, Perkin-Elmer 421. [e] Based on the ^{185}Re peak of the multiplet pattern.

The progress of each reaction is followed by monitoring characteristic ir bands of starting materials and/or products in the carbonyl stretching region (*ca.* 1500–2100 cm^{-1}). Gas evolution is noted in each case. Products were purified through column chromatography (silica gel–hexane) followed by recrystallization from hexane–ether. Yields of the expected products were 60% or better.

For each product we observe a strong ir band between 1500 and 1600 cm^{-1} which is characteristic of a ketonic carbonyl group coordinated to a metal through oxygen.[5] The nmr spectrum of the product derived from acetophenone, **2a**, includes, among other features, a characteristic pattern for the ortho-metalated aromatic ring:[6] at 100 MHz and 25°, τ (ppm) (multiplicity) H_a, 2.17 (2 × 2); H_b, 2.83 (3 × 2); H_c, 2.59 (3 × 2); H_d, 1.91 (2 × 2), CH_3, 7.4 (1). Coupling constants (Hz): J_{ab}, 7.5; J_{ac}, 1.5; J_{ad}, 0.7; J_{bc}, 7.0; J_{bd}, 1.1; J_{cd}, 7.0. The assignments are based on proton decoupling experiments and nmr analysis of the analogous para and meta methyl-substituted products. The products derived fom benzophenone show similar splitting for the metalated ring when the unmetalated phenyl signal is subtracted from the spectrum. The spectrum of **3** is quite complex. Regarding the effect of substituents, the following relative rates were observed at 101° (with carbonyl stretching frequency of originating ketone given in parentheses, in cm^{-1}): for para-substituted acetophenone, *p*-OMe (1675) > *p*-Me (1680) > *p*-Cl (1686) > H (1688); for meta-substituted acetophenones, *m*-OMe (1681) > *m*-Me (1685) > H (1688); for para,para′-disubstituted benzophenones, *p,p′*-$(OMe)_2$ (1649) > *p,p′*-$(Me)_2$ (1656) ≥ H (1959).

The alkylmetal carbonyl derivatives of manganese and rhenium thus differ significantly in their reactivity toward substituted aromatic substrates from that reported for other transition metal complexes; methanolic Na_2PdCl_4, which will metalate aromatic rings containing nitrogen functional substituents and form simple adducts with sulfur functional derivatives, is unreactive toward aromatic ketones,[7] and a reactive intermediate derived from $(C_5H_5)_2WH_2$ and butyllithium has been shown to metalate benzophenone in the para position.[8]

(1) Work supported by National Science Foundation (NSF) Grant No. 23267X2. Departmental instruments used in this work were supported as follows: nmr spectrometers, Varian A-60 and HA 100d, E. I. du Pont de Nemours and Co., Stauffer Chemical Co., Union Carbide Corporation, and NSF Grants No. G20207 and GP 8223; Beckman IR-4, E. I. du Pont de Nemours and Co.; AEI MS9 mass spectrometer, NSF Grant No., GP3627.

(2) R. J. McKinney, B. T. Huie, C. B. Knobler, and H. D. Kaesz, *J. Amer. Chem. Soc.*, **95**, 633 (1973).

(3) (a) L. J. Bellamy and R. J. Pace, *Spectrochim. Acta*, **19**, 1831 (1963); (b) M. Liler, *Spectrochim. Acta, Part A*, **23**, 139 (1963).

(4) (a) A. McKillop and E. C. Taylor, *Chem. Brit.*, **9**, 4 (1973); (b) see D. W. Slocum and B. P. Koonsvitsky, *J. Org. Chem.*, **38**, 1675 (1973), or D. W. Slocum and D. I. Sugarman, *Advan. Chem. Ser.*, in press.

(5) See B. P. Susz and P. Chalandon, *Helv. Chim. Acta*, **41**, 1332 (1950), and references cited therein.

(6) A. Baici, A. Camus, and G. Pellizer, *J. Organometal. Chem.*, **26**, 431 (1971).

(7) S. Trofimenko, *Inorg. Chem.*, **12**, 1215 (1973).

(8) B. R. Francis, M. L. H. Green, and G. G. Roberts, *Chem. Commun.*, 1290 (1971).

(9) Publication No. 3196

R. McKinney, G. Firestein, H. D. Kaesz*
Department of Chemistry,[9] University of California
Los Angeles, California 90024

Received July 30, 1973

Total Synthesis and Pharmacological Activities of N-Substituted 3,14-Dihydroxymorphinans. I

Sir:

A continuing challenge in medicinal chemistry centers on the search for effective analgetics and narcotic antagonists that would be devoid of physical dependence liabilities. We initiated a program designed to prepare, by total synthesis, 3,14-dihydroxymorphinans which would hopefully combine the potent and "pure"

narcotic antagonist activity of naloxone[1] with the good oral absorption and long duration of action of cyclorphan[2] and cyclazocine.[3,4] We have utilized the synthetic approach to morphinan-related structure designed by one of us several years ago,[5] since the classical Grewe synthesis of the morphinan and benzomorphan[6] ring systems does not lend itself to the introduction of the desired hydroxyl group at the 14-carbon atom of the morphinans.

Alkylation of 7-methoxy-1-tetralone with 1,4-dibromobutane using sodium hydride in refluxing benzene gave the spiroketone **1** (Scheme I) (80%; bp 120–123° (0.04 mm)).[7] Cyanomethylation[8] of **1** gave the hydroxynitrile **2** which was reduced with $LiAlH_4$, without prior isolation, to the amino alcohol **3** (75%, based on **1**); oxalate, mp 179–180°. Rearrangement of the latter presumably *via* intermediate carbonium ion **4**, by refluxing in a mixture of concentrated hydrochloric acid and ether (24 hr; under nitogen), afforded the unsaturated amine **5** (74%; hydrochloride, mp 135°): nmr ($CDCl_3$) δ 5.66 (10 CH, t, $J \simeq 3.5$ Hz), 3.32, (9 CH_2, br s). Compound **5** in chloroform (1 *M* solution) was added to a 0.1 *M* solution of bromine in chloroform to give the bromohasubanan hydrobromide salt **6** (72%; mp 207–208°): nmr (CF_3CO_2H) δ 4.57 (unsharpened in D_2O; CHBr, t, J = 8.8 Hz), 3.18 (CH_2CHBr, d, J = 8.8 Hz). A methine hydrogen vicinal to NH_2^+ should show δ 3.87–3.40, sharpened in D_2O (unpublished observation with 14α-bromoisomorphinan). Treatment of **6** with sodium bicarbonate (1 equiv) in DMF at 130–135° for 1.5 hr gave 3-methoxy-$\Delta^{8,14}$-morphinan (**8**) (70%; oxalate; mp 187–189°): nmr ($CDCl_3$) δ 5.65 (8 CH, t, $J \simeq 4$ Hz). By carrying out the same reaction at a lower temperature, the aziridine hydrobromide **7** (mp 207–208.5°) was isolated which clearly indicates that **7** is an intermediate in the formation of **8**. Acylation of **8** by standard procedures readily afforded the corresponding amides such as **9** (95%; mp 125–128°), and **10** (94%; mp 94–96°). Epoxidation of these unsaturated amides with *m*-chloroperbenzoic acid yielded the expected 8,14-β-epoxides **11** (73%; mp 140–142°), and **12** (92%; mp 102–105°). Reduction of **11** with $LiAlH_4$ in refluxing THF gave the 14-hydroxymorphinan **16** (95%) which was demethylated with boron tribromide,[9] in dichloromethane, whereupon 3,14-dihydroxy-*N*-cyclopropylmethylmorphinan (**17**) was obtained (86%; hydrochloride, mp 255–257°). Resolution of **17** was accomplished with *l*-tartaric acid to give the tartrate salt of *l*-**17** [mp 178–180°; $[\alpha]^{23}D$ −91.3° ($CHCl_3$)].

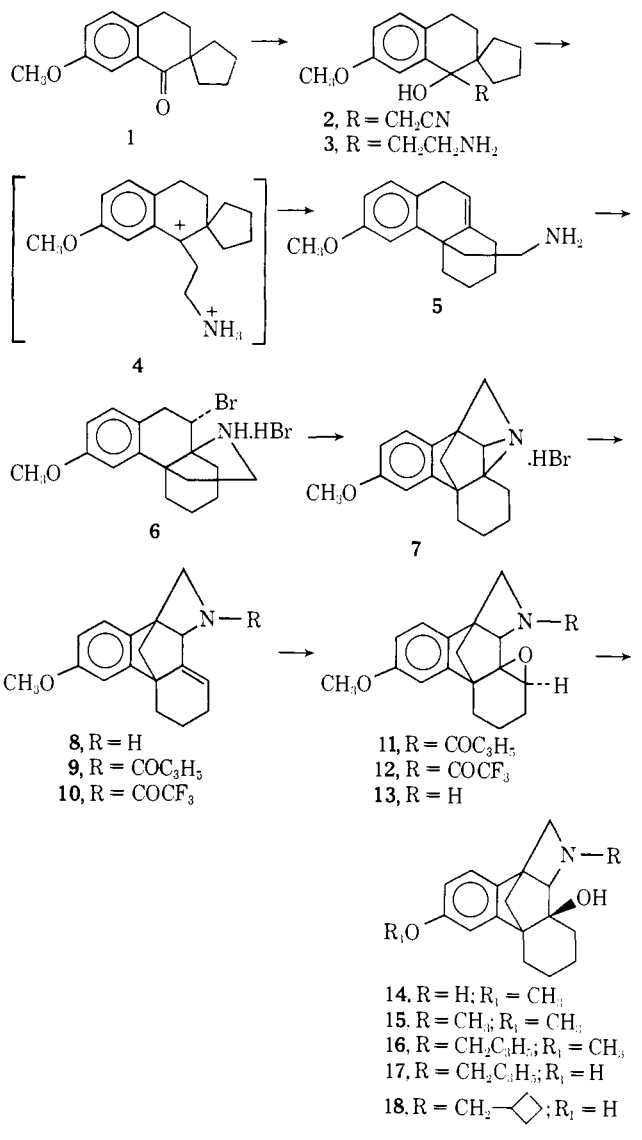
Alternatively, the epoxyamide **12** was treated with $NaBH_4$ in refluxing ethanol to give the base **13** (an oil) which was further reduced with $LiAlH_4$ to the amino alcohol **14** (75%; hydrochloride, mp 243–244°). Resolution of the latter with *l*-tartaric acid allowed the isolation of the levo base (*l*-**14**) [mp 110–112°; $[\alpha]^{23}D$ −44.9° ($CHCl_3$)]. Reductive N-methylation of *l*-**14** (CH_2O, Raney Ni, H_2) afforded *l*-3-methoxy-14-hydroxy-*N*-methylmorphinan (**15**), which was identical in every respect with an authentic specimen, derived from thebaine, as described by Sawa and Tada.[10]

Using the above-described general synthetic route, several N-substituted analogs of **17** (such as *l*-**18**) as well as several isomorphinans and hasubanan analogs were readily prepared.

In laboratory animals (including monkeys), *l*-**17** displayed narcotic antagonist activity comparable to naloxone in parenteral potency but almost equally effective orally as parenterally and with a prolonged duration of action comparable to cyclorphan or cyclazocine. In contrast, *l*-**18** proved to be a highly potent, dependence-free agonist in the same battery of tests. Preliminary clinical studies with *l*-**17** and *l*-**18** gave results comparable to the animal models.

Acknowledgment. We wish to thank Dr. A. Pircio[11] for the pharmacological tests and Dr. V. DiTullio and

Scheme I. Synthesis of 3,14-Dihydroxymorphinans



(1) (a) M. J. Lewenstein and J. Fishman, U.S. Patent 3,254,088 (1966); (b) H. Blumberg, H. B. Dayton, A. M. Rapoport, and D. N. Rapoport, *Fed. Proc., Fed. Amer. Soc. Exp. Biol.*, **20**, 311 (1961).

(2) M. Gates and T. Montzka, *J. Med. Chem.*, 7, 127 (1964).

(3) S. Archer, N. F. Albertson, L. S. Harris, A. K. Pierson, and J. G. Bird, *J. Med. Chem.*, 7, 123 (1964).

(4) For a review on this subject see: J. W. Lewis, K. W. Bentley, and A. Cowan, *Annu. Rev. Pharmacol.*, **4**, 241 (1971).

(5) B. Belleau, *J. Amer. Chem. Soc.*, **75**, 1159 (1953).

(6) (a) R. Grewe, *Naturwissenschafen*, **33**, 33 (1946); (b) E. L. May and G. L. Murphy, *J. Org. Chem.*, **20**, 257 (1955).

(7) All compounds described herein gave analytical and spectral data in agreement with the postulated structures.

(8) E. M. Kaiser and C. R. Hauser, *J. Org. Chem.*, **33**, 3402 (1968).

(9) J. F. W. McOmie, M. L. Watts, and E. E. West, *Tetrahedron*, **24**, 2289 (1968).

(10) Y. K. Sawa and H. Tada, *Tetrahedron*, **24**, 6185 (1968).

Mr. J. Chapuis for their technical assistance. This work was supported in part by the National Research Council of Canada with a grant through its Industrial Research Assistance Programme.

(11) Bristol Laboratories, Syracuse, N. Y. 13201.

I. Monković,* T. T. Conway, H. Wong
Y. G. Perron, I. J. Pachter,[11] B. Belleau
Bristol Laboratories of Canada
Candiac, P. Q. J5R 1J1, Canada
Received August 3, 1973

Use of Tris(dipivalomethanato)praseodymium(III) for the Determination of the Chirality of Simple Amines and Cyclic 1,2-Amino Alcohols[1]

Sir:

Our interest in biologically important simple amines and 1,2-amino alcohols has prompted us to seek a rapid, convenient micromethod for determining the absolute stereochemistry of these compounds. A recent report has shown that the chirality of cyclic α-glycols can be established from the induced Cotton effects (CE) observed in the circular dichroism (CD) spectra of a mixture of the α-glycol and tris(dipivalomethanato)praseodymium(III) [Pr(DPM)$_3$] in carbon tetrachloride.[2,3] Since the sign of the CD at *ca.* 310 nm was a measure of the chirality of the α-glycols, the extension of this method to 1,2-amino alcohols was proposed.[2] In this communication we report our observations on the CD spectra of Pr(DPM)$_3$ complexes with simple amines and the extension of the α-glycol method to cyclic 1,2-amino hydroxy compounds with known chirality and fixed conformation.

Although steroidal monoalcohols showed no CE when combined with Pr(DPM)$_3$,[2] the isolation of crystalline lanthanide adducts such as Ho(DPM)$_3$(4-picoline)$_2$[4] led us to expect that Cotton effects may be observed with Pr(DPM)$_3$ and optically active amines. Sanders and Williams had also shown that Eu(DPM)$_3$ coordinates more strongly with many amines than with alcohols.[5] The effects of Pr(DPM)$_3$ on the CD spectra of some optically active simple amines are summarized in Table I. In every case a first Cotton effect was observed at *ca.* 315 nm and a second effect of opposite sign and similar magnitude was observed at *ca.* 290 nm.[6] The value of $[\theta]$ increased rapidly as the ratio of Pr(DPM)$_3$ to **1** increased to 0.5 and was relatively insensitive to further increases in Pr(DPM)$_3$ concentration. This is consistent with the results of Reuben's work with β-picoline where he found that association of the type Pr(DPM)$_3$(amine)$_2$ was dominant over a large range of reagent to substrate ratios.[7] The Pr(DPM)$_3$-(amine)$_2$ adducts listed in Table I show an induced CE that can be correlated with the Cahn, Ingold, and Prelog *R* and *S* designations of absolute configuration.[8] In this study, amines of the *S* configuration have a first CE of one sign (positive) while those of the *R* configuration have the opposite sign (negative). This observation is probably fortuitous and is not related directly to the configuration based on the *R,S* system. The observed correlation with the Cahn, Ingold, and Prelog designation of absolute configuration is more likely due to the circumstance that in all the cases studied the substituents (other than nitrogen) on the asymmetric center followed a decreasing size sequence which is the same as the Cahn, Ingold, and Prelog sequence rule order. These observations suggest the possibility of using Pr(DPM)$_3$ for determining the stereochemistry of amines.[9] However, in order to establish the usefulness of this method, it will be necessary to study additional amines possessing various types of substituents.

Table I. CD Data for Optically Active Amine–Pr(DPM)$_3$ Complexes in Carbon Tetrachloride[a]

No.	Entry[b]	10^3M	10^3[Pr(DPM)$_3$], M	$[\theta] \times 10^{-2}$ (nm)[c-e]
1	(*R*)-α-Methylphenethylamine	1.1	0.60	−31 (313)
2	(*S*)-α-Methylphenethylamine	1.1	0.60	+32 (313)
3	(*R*)-α-Methylbenzylamine	1.2	0.60	−26 (313)
4	(*S*)-α-Methylbenzylamine	1.1	0.63	+22 (313)
5	(*R*)-α-(1-Naphthyl)ethylamine	1.2	0.56	−23 (313)
6	(*S*)-α-(1-Naphthyl)ethylamine	1.0	0.52	+24 (313)
7	Dehydroabietylamine	0.73	1.05	−3.6 (310)
		2.3		+0.18 (310)[f]
8	(*R*)-*N*-Methyl-α-methylphenethylamine [deoxy-(+)-ephedrine]	1.0	0.62	−20 (311)
9	(17*R*)-17α-Amino-5α-androstan-3β-ol	1.0	1.0	−32 (318)

[a] CD measurements were made at room temperature using a Durrum-Jasco Model J-20 recording spectropolarimeter. The solution of the compound studied and Pr(DPM)$_3$ were prepared in CCl_4 which had been distilled from P_2O_5 and stored over molecular sieve. The CD curves were recorded within a few hours after preparation. [b] Compounds **1**–**7** were obtained from Aldrich Chemical Co. and used without further purification. Compound **8** was prepared as described by K. W. Rosenmund and E. Karg, *Ber.*, **75**, 1850 (1942), substituting 10% Pd/C. Compound **9** was prepared as described by M. Davis, E. W. Parnell, and D. Warburton, *J. Chem. Soc. C*, 1688 (1966). [c] Only the high wavelength CE is given. [d] The CD curves of the amines in the absence of Pr(DPM)$_3$ showed no or only negligible CE when carried out under similar conditions. [e] Unless the liquid amine was weighed directly into solvent, a five–ten fold reduction of $[\theta]$ was sometimes observed. This was attributed to carbonate formation. [f] This is $[\theta]$ for **7** at 310 nm in the absence of Pr(DPM)$_3$ but is not the λ_{max} for **7**.

The results obtained in Table II show that the method for determining the chirality of cyclic α-glycols can be extended to cyclic β-amino alcohols. The chirality of the β-amino alcohols is defined, as for the α-glycols,[2] as being negative or positive, respectively, when the Newman projection represents an anticlockwise (left handedness) or clockwise (right handedness) rotation from the forward hetero atom to the rearward hetero atom as illustrated for **11**.

As entries **10**, **11**, **13**, and **15** indicate, the sign of the first CE is the same as the predicted chirality. Al-

(1) This work was carried out under Contract No. PH-43-65-1057 with the Pharmacology–Toxicology Program, National Institute of General Medical Sciences, National Institutes of Health.
(2) K. Nakanishi and J. Dillon, *J. Amer. Chem. Soc.*, **93**, 4058 (1971).
(3) N. Harado and K. Nakanishi, *Accounts Chem. Res.*, **5**, 257 (1972).
(4) W. DeW. Horrocks, Jr., J. P. Sipe, III, and J. R. Luber, *J. Amer. Chem. Soc.*, **93**, 5258 (1971).
(5) J. K. M. Sanders and D. H. Williams, *J. Amer. Chem. Soc.*, **93**, 641 (1971).
(6) The α-glycols showed similar CD curves, although the observed $[\theta]$ values were generally somewhat larger than those for the amines.[2]
(7) J. Reuben, *J. Amer. Chem. Soc.*, **95**, 3534 (1973).
(8) R. S. Cahn, C. Ingold, and V. Prelog, *Angew. Chem., Int. Ed. Engl.*, **5**, 385 (1966).
(9) Entry **7** is of particular interest because the amino group is not at the asymmetric center but separated from it by a methylene group, suggesting the possibility of using Pr(DPM)$_3$ adducts with amines to determine the stereochemistry of more remote asymmetric centers.