= 12.62 Hz), 5.17 (1 H, br s) [8.391, s, in Me_2SO]] showed the presence of two methyl groups on vinylic carbon(s). The presence of two symmetrical *n*-propyl groups in structure I is supported by the decoupling experiments: irradiation at δ 1.69 collapsed the triplet at δ 0.9393 into a singlet, and absorptions centered at δ 3.971 and 4.026 were also collapsed to simple triplets (J = 9.33 and 9.40 Hz, respectively), which is expected in phosphorus compounds because of the three-bond coupling between hydrogen and phosphorus;[23] similarly, irradiation at 0.9393 caused the multiplet at δ 1.69 to collapse into a simple triplet (J = 6.05 Hz) while irradiation around δ 3.99 collapsed the multiplet at δ 1.69 into a simple quartet (J = 6.30 Hz). Structure I is also supported by the mass spectral fragmentation pattern (m/z 278 indicates the loss of a hydroxyl group while the peaks at m/z 253 and 211 indicate the loss of C_3H_6 and C_6H_{12} from the molecule). The presence of a thiophosphonate moiety in I is indicated by the MS fragment at m/z 96.951.

Although the presence of phosphorus-containing toxic metabolites has been reported,[1] this is the first report on the structure of a phosphorus-containing compound from *G. breve*. Compound I (tentatively named Gb-4) has an ichthyotoxicity of 0.9 ppm against *Lebistes reticulatus*. The crude extract of *G. breve* has at least five more toxic compounds including Brevetoxin B. Work on the structure elucidation of the other ichthyotoxic compounds is in progress.

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Supplementary Material Available: Listings of bond angles, hydrogen atom parameters, anisotropic thermal parameters, and structure factors are available (14 pages). Ordering information is given on any current masthead page.

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Homogeneous Catalytic Hydrogenation. 1. Regiospecific Reductions of Polynuclear Aromatic and Polynuclear Heteroaromatic Nitrogen Compounds Catalyzed by Transition-Metal Carbonyl Hydrides

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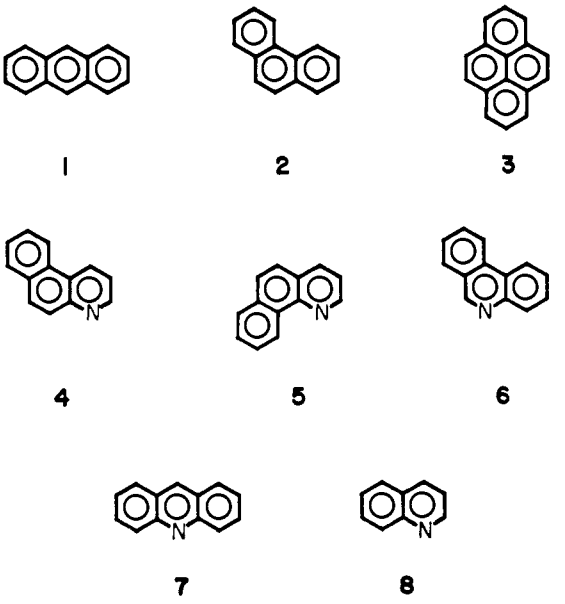
The various synthetic fuel products derived from coal or oil shale require additional hydroprocessing to minimize their nitrogen and sulfur content; therefore, the selective hydrogenation of polynuclear heteroaromatics becomes critical.[1] Thus, it is extremely important to have a basic understanding of which polynuclear aromatic and polynuclear heteroaromatic compounds are hydrogenated in these complex fossil fuel matrices.

Chart I. Model Synthetic Fuel Compounds Used in the Catalytic Hydrogenation with Transition-Metal Carbonyl Hydrides



Recently, Pettit and his co-workers[2-4] demonstrated, in an elegant manner, the use of carbon monoxide and water as an alternative reducing agent to that of hydrogen in the hydroformylation of olefins and the reduction of nitroarenes. These latter reactions were catalyzed by transition-metal carbonyl compounds ($M_x(CO)_y$) and thought to proceed via the formation of transition-metal carbonyl hydrides, (e.g., $H_2M_x(CO)_y$), by nucleophilic attack of water or base on coordinated carbon monoxide.[5] Other methods of generating transition-metal carbonyl hydrides from the corresponding carbonyls have used carbon monoxide and hydrogen and hydrogen alone as reagents.[6]

Therefore, we thought that the rather facile generation of transition-metal carbonyl hydrides under water gas shift (CO, H_2O, base) and synthesis gas (1:1 CO:H_2) conditions as well as strictly hydrogenation conditions (H_2 alone) made these reagents very attractive for the purpose of testing their regioselectivities in the reductions of polynuclear aromatics and polynuclear heteroaromatic nitrogen compounds. Additionally, it is well-known that homogeneous catalytic reductions proceed at lower temperatures and pressures and, in fact, give the higher regioselectivities we were seeking when compared to their heterogeneous counterparts.[7]

Chart I shows the polynuclear aromatic and polynuclear heteroaromatic nitrogen compounds, **1-8**, that we used as model synthetic fuel compounds for the above stated purposes.

We reacted a wide variety of transition-metal carbonyl compounds with compounds **1-3** under water gas shift (wgs) and synthesis gas (sg) conditions[8] and found that only $Fe(CO)_5$,

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Table I. Reductions of Polynuclear Heteroaromatic Nitrogen Compounds, 4–8, under Water Gas Shift[a] (wgs) and Synthesis Gas (sg) Conditions[b] with Transition-Metal Carbonyls as Catalysts

substrate	catalyst	[sub]/[cat.]	temp, °C	time, h	condn	product	% product[d]
4	$Mn_2(CO)_8(Bu_3P)_2$	20	200	2	sg	1,2,3,4-tetrahydro-5,6-benzoquinoline	7
4	$Mn_2(CO)_8(Bu_3P)_2$	20	200	5	wgs		4
4	$Fe(CO)_4(Bu_3P)$	10	180	5	wgs		1
4	$Co_2(CO)_6(Ph_3P)_2$	20	200	2	sg		8
5	$Mn_2(CO)_8(Bu_3P)_2$	20	200	2	sg	1,2,3,4-tetrahydro-7,8-benzoquinoline	2
5	$Mn_2(CO)_8(Bu_3P)_2$	20	200	2	wgs	no product	
6	$Mn_2(CO)_8(Bu_3P)_2$	20	200	2	wgs	9,10-dihydrophenanthridine	1
6	$Mn_2(CO)_8(Bu_3P)_2$	20	200	2	sg		11
6	$Co_2(CO)_6(Ph_3P)_2$	20	200	2	sg		21
7	$Fe(CO)_5$[c]	10	180	2	wgs	9,10-dihydroacridine	100
7	$Mn_2(CO)_8(Bu_3P)_2$	10	200	2	wgs		38
7	$Mn_2(CO)_8(Bu_3P)_2$	20	200	2	sg		100
7	$Co_2(CO)_6(Ph_3P)_2$	20	200	2	sg		100
8	$Fe(CO)_5$	10	180	2	wgs	1,2,3,4-tetrahydroquinoline	0
8	$Mn_2(CO)_8(Bu_3P)_2$	20	200	5	wgs		4
8	$Mn_2(CO)_8(Bu_3P)_2$	20	200	5	sg		33
8	$Co_2(CO)_6(Ph_3P)_2$	20	200	1	sg		70

[a] Reaction run in THF (12 mL) with 0.2 M KOH (3 mL), 350 psi CO. [b] 350 psi H_2 and 350 psi CO in THF (15 mL). [c] 800 psi CO. [d] Determined by capillary GC using a digital integrator (HP 5880A). Isolated by column chromatography (Florisil) and identified by GC–MS and NMR spectroscopy (250 MHz, ^1H).

$Mn_2(CO)_8(Bu_3P)_2$, and $Co_2(CO)_6(Ph_3P)_2$ produced reduction products. For example, **1** was reduced to 9,10-dihydroanthracene, **9**, under wgs conditions with these carbonyls in rather poor yields of 8%, 13%, and 3%, respectively, while substrates **2** and **3** were totally unreactive.

In view of these discoveries, we decided to learn more about this reaction by using $Mn_2(CO)_8(Bu_3P)_2$ as the catalyst. The reaction of carbon monoxide and deuterium oxide (D_2O) with **1** provided only 9,10-dideuterioanthracene, **10**,[9] and this result strongly indicates that the hydrogen comes exclusively from water.

In an experiment to elucidate the stereochemistry of the anthracene reaction, we reacted an analogue of **1**, 9,10-dimethylanthracene, **11**, with $Mn_2(CO)_8(Bu_3P)_2$ under wgs conditions (180 °C, 5 h, 350 psi CO, 0.2 M KOH in THF, [substrate]/[catalyst] = 20) to provide a 30% yield of *cis*- and *trans*-9,10-dihydro-9,10-dimethylanthracene, **12** and **13**, in a ratio of 53:47.[10] A similar result was recently reported by Sweany et al.[11a] for the reaction of **11** and $HMn(CO)_5$ and Taylor and Orchin[11b] with $HCo(CO)_4$ under sg conditions (1:1 CO:H_2, ~200 °C).

We also found that under sg conditions ($CO/H_2 = 1$)[8] better yields of reduced polynuclear aromatic products could be obtained with $Mn_2(CO)_8(Bu_3P)_2$ as the catalyst and compounds **1–3** as substrates. Thus, reaction of **1** with $Mn_2(CO)_8(Bu_3P)_2$ provided **9** in 30% yield, while reaction with **2** gave no product and with **3** produced 4,5-dihydropyrene, **14**, in 3% yield.

From these results, it is evident that bent polynuclear aromatic compounds are extremely unreactive under either wgs or sg conditions, when compared to **1**, a linear polynuclear aromatic compound.[12a,b]

As previously stated, the polynuclear heteroaromatic nitrogen compounds are important to study under various homogeneous hydrogenation conditions, since they are prevalent in all coal and oil shale products. Few examples of their reactivity have been published under either wgs or sg conditions or, for that matter, under strictly hydrogenation conditions (H_2 alone). For example, Laine et al.[13] reported on the hydrogenation of the mononuclear heterocyclic compound pyridine under wgs conditions with $Rh_6(CO)_{16}$ as catalyst and Derencsenyi and Vermeulen[12b] reported that under sg conditions quinoline, **8**, was regioselectively reduced to 1,2,3,4-tetrahydroquinoline with $Mn_2(CO)_8(Bu_3P)_2$ as a catalyst. Furthermore, Jardine and McQuillin[14] also reported that **8** was reduced to 1,2,3,4-tetrahydroquinoline with $RhCl_2Py_2(dmf)BH_4$ as the catalyst.

As seen in Table I, we found a greater reactivity for the polynuclear heterocyclic nitrogen compounds, **4–8**, under either wgs or sg conditions than for their carbon analogues, e.g., acridine, **7**, is more reactive than anthracene, **1**. It is also important to note the high regioselectivity observed with compounds **4–8**, where only the nitrogen ring was hydrogenated. This regioselectivity might be explained by the lowered aromaticity of the nitrogen-containing ring vs. the carbon analogues, which would provide a lower activation energy for hydrogenation.[15]

The fact that Fe, Mn, and Co carbonyls did provide reduced product, under wgs conditions, while other transition-metal carbonyls did not, may be indicative of the former compounds being very poor shift-catalysts.[16] Moreover, Mn and Co catalysts were also able to hydrogenate the substrates studied under sg conditions, while the other transition-metal carbonyls were unreactive under these reaction conditions.

We examined the various reaction parameters and found that a dramatic increase in reduced product resulted when carbon monoxide was removed from the reactions catalyzed by ruthenium carbonyls.

In initial experiments, we utilized $Ru(Cl)_2(CO)_2(Ph_3P)_2$ as a catalyst. We found, interestingly, with this catalyst that both

(8) For the following carbonyls: $Fe(CO)_4Bu_3P$, $Mn_2(CO)_8(Bu_3P)_2$, $Co_2(CO)_6(Ph_3P)_2$, $W(CO)_6$, $Re_2(CO)_{10}$, $Fe(CO)_5$, $Ru(Cl)_2(CO)_2(Ph_3P)_2$, $Rh_6(CO)_{16}$, $Mo(CO)_5Bu_3P$, and $Os_3(CO)_{12}$, the wgs reaction conditions were as follows: A 45-mL Parr minireactor was used with tetrahydrofuran (12 mL) as solvent, 0.2 M KOH (3 mL), P_{CO} 350 psi, 5-h reaction time, temperature 200 °C, 1 mmol of **1–3**, 0.1 mmol of transition-metal carbonyl catalyst (10:1 substrate to catalyst ratio). The product percentage was found by area ratio of starting material and product by using a HP 5880A capillary column gas chromatograph with digital integration (12 m × 0.1 mm i.d. OV 101 at 60 to 200 °C (10 °C/min)) and flame ionization detection. The reactions of **1–3** with $M_2(CO)_8(Bu_3P)_2$ as catalyst were run under sg conditions in a 45-mL Parr minireactor at 200 °C, 350 psi H_2, 350 psi CO in THF for 2 h with a 10:1 substrate: catalyst ratio. Other carbonyls such as $Fe(CO)_4Bu_3P$, $Cr(CO)_6$, $Mo(CO)_6$, $W(CO)_6$, $Re_2(CO)_{10}$, $Os_3(CO)_{12}$, and $Ru_3(CO)_{12}$ produced no reduced product with 1–3 as substrates.

(9) GC–EI mass spectral analysis showed *m/e* 182 (100%), consistent with two deuteriums being incorporated into compound **1** (*m/e* 178).

(10) The cis and trans isomers of 9,10-dihydro-9,10-dimethylanthracene, **12** and **13**, could be cleanly separated on a 12 m × 0.1 mm i.d. fused silica capillary column (OV 101) using a HP 5880a instrument with flame ionization detection (temperature programming 60 to 200 °C, 10 °C/min).

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(16) For example, we found that $Mn_2(CO)_8(Bu_3P)_2$ did not produce CO_2 and H_2 to any significant extent in the absence of substrates **1–8** under wgs conditions (350 psi CO, 0.2 M KOH, 200 °C for 5 h gave 10 psi H_2). Additionally, selected gas analysis under wgs conditions gave a qualitative order of wgs activity as follows: $Rh_6(CO)_{16} > Ru_3(CO)_{12} > Cr(CO)_6 > Mo(CO)_6 > W(CO)_6 > Fe(CO)_5 > Mn_2(CO)_{12} > Co_2(CO)_8$.

Table II. Reductions of Compounds 1-8 with $Ru(Cl)_2(CO)_2(Ph_3P)_2$ and $H_4Ru_4(CO)_{12}$ as Catalysts

substrate	catalyst	product	% product[b]
1	$Ru(Cl)_2(CO)_2(Ph_3P)_2$[a]	1,2,3,4-tetrahydroanthracene	30
1	c	no product	
2	a,c	no product	
3	a,c	no product	
4	a	1,2,3,4-tetrahydro-5,6-benzoquinoline	10
4	c		92
5	a	1,2,3,4-tetrahydro-7,8-benzoquinoline	0
5	c		72
6	a	9,10-dihydrophenanthridine	5
6	c		15
7	a	9,10-dihydroacridine	100
7	c		74
8	a	1,2,3,4-tetrahydroquinoline	42
		5,6,7,8-tetrahydroquinoline	5
8	c	1,2,3,4-tetrahydroquinoline	100
4	$H_4Ru_4(CO)_{12}$[d]	1,2,3,4-tetrahydro-5,6-benzoquinoline	75
5	d	1,2,3,4-tetrahydro-7,8-benzoquinoline	8
6	d	9,10-dihydrophenanthridine	15
7	d	9,10-dihydroacridine	100
8	d	1,2,3,4-tetrahydroquinoline	100

[a] Experiments were performed in a 45-mL Parr minireactor containing 1 mmol of substrate, 0.1 mmol of $Ru(Cl)_2(CO)_2(Ph_3P)_2$ in THF (12 mL), 0.2 M KOH (3 mL), 180 °C, 350 psi H_2 for 5 (1-7) or 2 h (8). [b] Analyzed by gas chromatography on a 12 m × 0.1 mm i.d. fused silica capillary column (OV101) using a HP-5880A instrument with flame ionization and digital integration. The percent product conversion was obtained by integration of product and any starting material remaining and normalizing to 100%. Products were isolated by column chromatography (Florisil) and identified by GC-MS and NMR spectroscopy (250 mHz, ^1H). [c] 180 °C, THF (12 mL), 0.1 mmol of $Ru(Cl)_2(CO)_2(Ph_3P)_2$, 1 mmol of substrate, 350 psi H_2 for 2 h. [d] Experiments were performed in a 45-mL Parr minireactor containing 1 mmol of substrate, 0.1 mmol of $H_4Ru_4(CO)_{12}$ (10:1 substrate to catalyst ratio) in 15 mL of cyclohexane with 350 psi H_2 for 2 h at 150 °C.

hydrogen and base were needed for the reduction of compound **1**.[17] No reaction occurred in the presence of carbon monoxide or in the absence of base. The reduction of **1** was highly regiospecific and gave exclusively 1,2,3,4-tetrahydroanthracene, **15**, in 30% yield.[18] A control experiment was performed to establish that 9,10-dihydroanthracene, **9**, was not the initial product formed, which then rearranged to compound **15**. We reacted **9** under similar reaction conditions and found that it did not produce compound **15** and hence no rearrangement occurred.

Compounds **2** and **3** were unreactive under the reaction conditions, and this result is consistent with the previous finding that bent aromatic compounds were extremely unreactive vs. linear aromatics such as **1**. The polynuclear heteroaromatic nitrogen compounds **4–8** were reacted under similar conditions to produce poor to moderate yields of reduced product (Table II). However, we found that the removal of base (KOH) in the reactions of **4–6** and **8** with $Ru(Cl)_2(CO)_2(Ph_3P)_2$ as catalyst provided an increase in the yields of all reduced products with the exception of **7** (Table II). For example, compound **5** provided no reduced product with base present, while affording a 72% yield of 1,2,3,4-tetrahydro-7,8-benzoquinoline, **16**, in the absence of base. Additionally, as with compound **1**, carbon monoxide totally inhibited reduced product formation in the reactions of **4–8** with $Ru(Cl)_2(CO)_2(Ph_3P)_2$ as catalyst. Interestingly, compound **8**, with H_2 and base, provided a small amount (5%) of reduced aromatic ring compound (5,6,7,8-tetrahydroquinoline), which was not produced when base was omitted.

In concurrent experiments, we discovered that tetrahydridotetraruthenium dodecacarbonyl ($H_4Ru_4(CO)_{12}$)[19] was also an excellent catalyst for the hydrogenation of compounds **4–8**, but was inactive for the reductions of compounds **1–3** under the conditions studied. Tetrahydridotetraruthenium dodecacarbonyl was not the initial catalyst used; rather, we pursued the catalytic activity of triruthenium dodecarcarbonyl, ($Ru_3(CO)_{12}$). We found that under our reaction conditions $H_4Ru_4(CO)_{12}$ readily formed (IR and MS analysis) by reaction of $Ru_3(CO)_{12}$ with hydrogen gas (eq 1).[19b] Under the latter reaction conditions, reduction of

$$4Ru_3(CO)_{12} + 6H_2 \rightarrow 3H_4Ru_4(CO)_{12} + 12CO \quad (1)$$

4–8 was evident; however, catalytic activity increased dramatically if $H_4Ru_4(CO)_{12}$ was formed prior to substrate addition. In this process CO was flushed from the system. Evidently, even a small partial pressure of CO (~10 psi CO was generated in the formation of $H_4Ru_4(CO)_{12}$ from $Ru_3(CO)_{12}$) was sufficient to cause a possible inhibition of substrate coordination to ruthenium and greatly reduced product yield. For example, $Ru_3(CO)_{12}$ provided a 7% yield of 1,2,3,4-tetrahydro-5,6-benzoquinoline, **17**, from **4**, while $H_4Ru_4(CO)_{12}$ produced the same product in 75% yield.

Tetrahydridotetraruthenium dodecacarbonyl has been previously described as a hydrogenation catalyst for olefins, carboxylic acids and ketones[20] but, to our knowldege, never for polynuclear heteraromatic nitrogen compounds.[21] The results of these catalytic hydrogenations with $H_4Ru_4(CO)_{12}$ is indicative, as with $Ru(Cl)_2(CO)_2(Ph_3P)_2$, of the high regioselectivity for the nitrogen heterocyclic ring.

This study provides evidence for the individual reactivity of a number of model synthetic fuel compounds under various homogeneous catalytic hydrogenation conditions. However, their relative reactivities need to be ascertained, especially in a mixture of these compounds and in the presence of other polynuclear heterocyclic compounds (e.g., sulfur and oxygen heterocycles). Additionally, work on the many mechanistic details, as well as expansion to the reactivities of polynuclear heterocyclic compounds of oxygen and sulfur, and the activity of heterogenized forms of the reported catalysts is being pursued.[22]

Finally, our results point to the possible usefulness of these homogeneous catalysts and others in future synthetic fuel processes concerned with ultimately removing nitrogen from the regioselectively reduced nitrogen-containing ring in polynuclear heterocyclic nitrogen compounds.[23] The reported catalysts may also find some important uses in synthetic organic chemistry.

(17) $Ru(Cl)_2(CO)_2(Ph_3P)_2$ has been described as a homogeneous hydrogenation catalyst (H_2) for aliphatic and aromatic aldehydes (Strohmeier, W.; Weigelt, L. *J. Organomet. Chem.* **1978**, *145*, 189); however, no references to its use as a homogeneous catalyst for polynuclear aromatic or heteraromatic compounds have been found.

(18) A similar regioselectivity was obtained with **1** and a ruthenium anion hydride under strictly H_2 conditions. See: Grey, R. A.; Pez, G. P.; Wall, A. H. *J. Am. Chem. Soc.* **1980**, *102*, 5948 and references therein.

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(21) Infrared analysis of the yellow reaction solutions of compounds **4–8** clearly shows $H_4Ru_4(CO)_{12}$ still present after reaction. More importantly, no "heterogeneous component" was found after reaction at 150 °C for the $H_4Ru_4(CO)_{12}$-catalyzed hydrogenations. The infrared analysis does not unequivocally demonstrate that $H_4Ru_4(CO)_{12}$ is the actual active catalyst, as pointed out by a referee, and we are presently running these reactions in a spectraclave (high-pressure IR cell) to clarify this point.

(22) A preliminary account of the work was presented at the 182nd National Meeting of the American Chemical Society, New York, Aug 1981; INOR 49, and the Pacific Conference on Chemistry and Spectroscopy, Anaheim, CA, Oct 1981, abstract 188. A similar study using $Se(CO)_5$ as a catalyst has been accepted for publication: Kaesz, H. D.; Banah, M.; Lynch, T. J.; Porter, C. *J. Mol. Catal.*, in press.

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Registry No. 1, 120-12-7; **2**, 85-01-8; **3**, 129-00-0; **4**, 85-02-9; **5**, 230-27-3; **6**, 229-87-8; **7**, 260-94-6; **8**, 91-22-5; **11**, 781-43-1; **12**, 82706-19-2; **13**, 82706-20-5; **15**, 2141-42-6; **16**, 5223-80-3; **17**, 40174-35-4; H_2O, 7732-18-5; $Mn_2(Co)_8(Bu_3P)_2$, 15609-33-3; $Fe(CO)_4(Bu_3P)$, 18474-82-3; $Co_2(CO)_6(Ph_3P)_2$, 24212-54-2; $Fe(CO)_5$, 13463-40-6; $H_4Ru_4(CO)_{12}$, 34438-91-0; $RuCl_2(CO)_2(Ph_3P)_2$, 14564-35-3; $Ru_3(CO)_{12}$, 15243-33-1; $RhCl_2(py)_2(dmp)BH_4$, 24436-16-6; $Rh_6(CO)_{16}$, 28407-51-4; $Cr(CO)_6$, 13007-92-6; $Mo(CO)_6$, 13939-06-5; $W(CO)_6$, 14040-11-0; $Mn_2(CO)_{10}$, 10170-69-1; $Co_2(CO)_8$, 10210-68-1; $Re_2(CO)_{10}$, 14285-68-8; $Mo(CO)_5(Bu_3P)$, 15680-62-3; $Os_3(CO)_{12}$, 15696-40-9; 9,10-dihydrophenanthridine, 82692-08-8; 9,10-dihydroacridine, 92-81-9; 1,2,3,4-tetrahydroquinoline, 635-46-1; 5,6,7,8-tetrahydroquinoline, 10500-57-9.

Deglycobleomycin: Total Synthesis and Oxygen Transfer Properties of an Active Bleomycin Analogue

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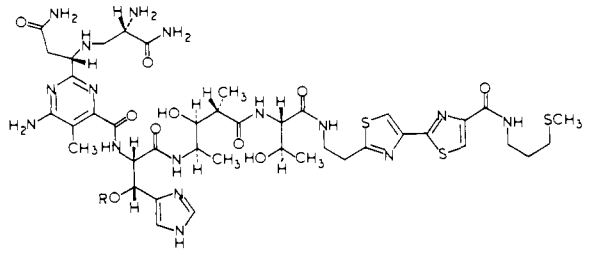
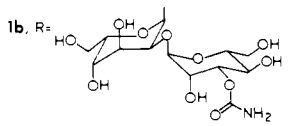
Bleomycin is the generic name that has been given to a family of clinically useful antitumor antibiotics.[1,2] The bleomycins are believed to mediate their therapeutic effect via oxidative degradation of DNA.[1] This transformation has been investigated intensively, in part because such studies may permit the design of structurally simpler congeners of bleomycin having analogous biological properties. Presently, we describe a practicable total synthesis of deglycobleomycin (**1a**),[3] a redox-active analogue of



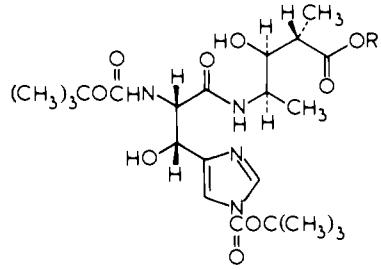
1a, R = H



1b, R =

bleomycin (**1b**) capable of oxidative degradation of DNA.[4] Also reported is the anaerobic activation of Fe(III) and Cu(II) deglycobleomycin by iodosobenzene and the abilility of the active species to degrade DNA and to transfer oxygen to simple olefins in analogy with cytochrome P-450.

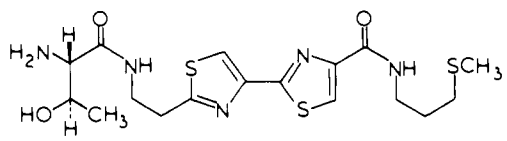
Coupling of N^{α},N^{im}-di-*tert*-butoxycarbonyl-L-erythro-β-hydroxyhistidine[5] and benzyl (2*S*,3*S*,4*R*)-4-amino-3-hydroxy-2-methylvalerate[5] (DCC, HOBt, DMF, 25 °C, 16 h) provided dipeptide **2a** as a glassy solid in 62% yield, $[\alpha]^{24}_D$ +20.3° (*c* 2.72,



2a, R = $CH_2C_6H_5$

2b, R = H

CH_3OH).[6] Following hydrogenolysis of the dipeptide (1 atm H_2, 10% Pd/C, 1.5 h), **2b**[6] was condensed with bithiazole derivative **3**[7] via the agency of DCC–HOBt (DMF, 40 h), to provide the



3

N-protected derivative of **4** as a glassy solid after chromatographic purification on silica gel (yield 56%), $[\alpha]^{24}_D$ +15.1° (*c* 1.50, CH_3OH).[6] The carbamate protecting groups were removed

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(1) (a) Umezawa, H. *Biomedicine* **1973**, *89*, 459. (b) Umezawa, H. In "Bleomycin: Current Status and New Developments"; Carter, S. K.; Crooke, S. T.; Umezawa, H., Eds.; Academic Press: New York, 1978; p 15 ff. (c) Hecht, S. M. In "Bleomycin: Chemical, Biochemical and Biological Aspects"; Hecht, S. M., Ed.; Springer-Verlag: New York, 1979; p 1 ff.

(2) (a) Umezawa, H. *Prog. Biochem. Pharmacol.* **1976**, *11*, 18. (b) Ichikawa, T. *Ibid.* **1976**, *11*, 143. (c) Carter, S. K.; Blum, R. H. *Ibid.* **1976**, *11*, 158. (d) Bonadonna, G.; Tancini, G.; Bajetta, E. *Ibid.* **1976**, *11*, 172. (e) Depierre, A. *Ibid.* **1976**, *11*, 195. (f) Rygard, J.; Hansen, H. S. *Ibid.* **1976**, *11*, 205. (g) Rathert, P.; Lutzeyer, W. *Ibid.* **1976**, *11*, 223.

(3) Other workers have recently described what is presumably a relay synthesis of deglycobleomycin A_2. See: Saito, S.; Umezawa, Y.; Morishima, H.; Takita, T.; Umezawa, H.; Narita, M.; Otsuka, M.; Kobayashi, S.; Ohno, M. *Tetrahedron Lett.* **1982**, *23*, 529.

(4) Oppenheimer, N. J.; Chang, C.; Chang, L.-H.; Ehrenfeld, G.; Rodriguez, L. O.; Hecht, S. M. *J. Biol. Chem.* **1982**, *257*, 1606.

(5) N^{α},N^{im}-Di-*tert*-butoxycarbonyl-L-erythro-β-hydroxyhistidine was formed by treatment of L-erythro-β-hydroxyhistidine (Hecht, S. M.; Rupprecht, K. M.; Jacobs, P. M. *J. Am Chem .Soc.* **1979**, *101*, 3982) with *tert*-butyl azidoformate (DMF, 25 °C, 20 h, 66%); benzylation ($C_6H_5CH_2OH$, HCl, 25 °C, 12 h) of (2*S*,3*S*,4*R*)-4-amino-3-hydroxy-2-methylvaleric acid (Ohgi, T.; Hecht, S. M. *J. Org. Chem.* **1981**, *46*, 1232) provided the requisite ester in quantitative yield as a glassy solid.

(6) (Partial) ^1H NMR spectra: **2a** ($CDCl_3$–D_2O, $(CH_3)_4Si$) δ 1.00 (d, 3), 1.18 (d, 3), 1.36 (s, 9), 1.54 (s, 9), 2.47 (m, 1), 3.73 (m, 1), 3.89 (m, 1), 4.41 (q, 1), 4.88 (d, 1), 5.05 (s, 2), 5.93 (d, 1), 6.74 (d, 1), 7.28 (s, 6), 7.96 (s, 1); **2b** ($CDCl_3$–D_2O, $(CH_3)_4Si$) δ 1.05 (d, 3), 1.15 (d, 3), 1.31 (s, 9), 1.55 (s, 9), 2.3–2.6 (m, 1), 3.7–4.0 (m, 2), 4.37 (d, 1), 4.81 (d, 1), 7.30 (s, 1), 8.00 (s, 1); **3** (D_2O, DSS) δ 1.75 (t, 2), 1.98 (s, 3), 2.45 (t, 2), 7.69 (s, 1), 7.86 (s, 1); di-*N*-BOC-**4** ($CDCl_3$–D_2O, $(CH_3)_4Si$) δ 1.40 (s, 9), 1.60 (s, 9), 1.94 (t, 2), 2.11 (s, 3), 2.58 (t, 2), 4.49 (d, 1), 4.90 (d, 1), 7.37 (s, 1), 7.81 (s, 1), 8.02 (s, 1), 8.08 (s, 1); **4** (D_2O, DSS) δ 1.81 (t, 2), 2.01 (s, 3), 2.51 (t, 2), 7.11 (s, 1), 7.73 (s, 1), 7.90 (s, 1), 8.00 (s, 1).

(7) Bithiazole derivative **3** was formed in analogy with tripeptide S (Levin, M. D.; Subrahamanian, K.; Katz, H; Smith, M. B.; Burlett, D. J.; Hecht, S. M. *J. Am. Chem. Soc.* **1980**, *102*, 1452), by treatment of the acid chloride of 2′-(2-(trifluoroacetamido)ethyl)-2,4′-bithiazole-4-carboxylic acid with 3-(methylthio)propylamine (CH_2Cl_2, Et_3N, DMAP). The fully blocked product was isolated as colorless crystals from CH_2Cl_2–hexane (67%, mp 126–128 °C) and converted to the free amine by treatment with aqueous NH_4OH in CH_3OH. The amine was isolated as a colorless oil in 87% yield (NMR ($CDCl_3$, $(CH_3)_4Si$) δ 1.66 (br s, 2), 1.90 (m, 2), 2.10 (s, 3), 2.57 (t, 2), 3.17 (m, 4), 3.53 (m, 2), 7.66 (br s, 1), 7.87 (s, 1), 8.10 (s, 1)) and condensed with 2,4-dinitrophenyl-*N*-(*o*-nitrophenylsulfenyl)threoninate to give the NPS derivative of **3** (68%, mp 108 °C). Conversion to **3** was accomplished by treatment of the blocked derivative with concentrated HCl in 1:1 $CHCl_3$–CH_3OH at 25 °C. Compound **3** (·HCl) was obtained as a pale yellow glass in 94% yield.[6]

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