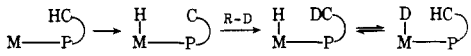
(16) C. A. Tolman, S. D. Ittel, A. D. English, and J. P. Jesson, *J. Am. Chem. Soc.*, **101**, 1742 (1979).
(17) An alternative explanation of the observed reaction chemistry has been put forth by one reviewer, and involves a ligand based radical according to the sequence shown. This proposal can be ruled out based on the following observations: (1) the product rhodium hydride complex is electrochemically inactive at the potential employed for electrolysis [−2.20 V vs. Ag/Ag(NO$_3$)]; (2) in dry CD$_3$CN as solvent, only the rhodium *deuteride* species is formed as the inorganic product in the electrolysis; and (3) once formed, the rhodium hydride or deuteride does not undergo exchange when placed in deuterated or nondeuterated solvents, respectively. The consequence of (1) is that each Rh center undergoes reaction only once. If the scheme above involving the ligand radical is correct, then the final step or equilibrium should lead to significant amounts of rhodium hydride product when deuterated solvents are used. However, this is in contradiction with (2). If H/D exchange is invoked to remove the contradiction, then a contradiction with (3) is necessitated. Thus, we can rule out the intermediacy of a ligand based radical scheme shown above, even though the absence of deuterium in the diphos ligands after electrolysis was not verified directly.

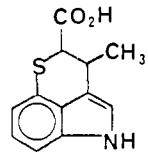


John A. Sofranko, Richard Eisenberg*
Jack A. Kampmeier*
Department of Chemistry, University of Rochester
Rochester, New York 14627
Received July 16, 1979

Total Synthesis of the Unique Indole Alkaloid Chuangxinmycin, Application of Nitro Group Displacement Reactions in Organic Synthesis

Sir:

Chuangxinmycin is a new antibiotic produced by the microorganism *Actinoplanes tsinanenis* n.sp., obtained from a soil sample collected in Tsinan, Shantung Province, China.[1] Chemical studies carried out by the Chuangxinmycin Research Group at the Institute of Materia Medica in Peking have led to the following structural assignment for this compound (the

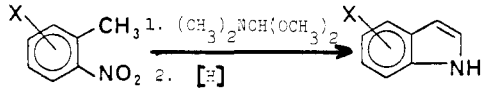


1

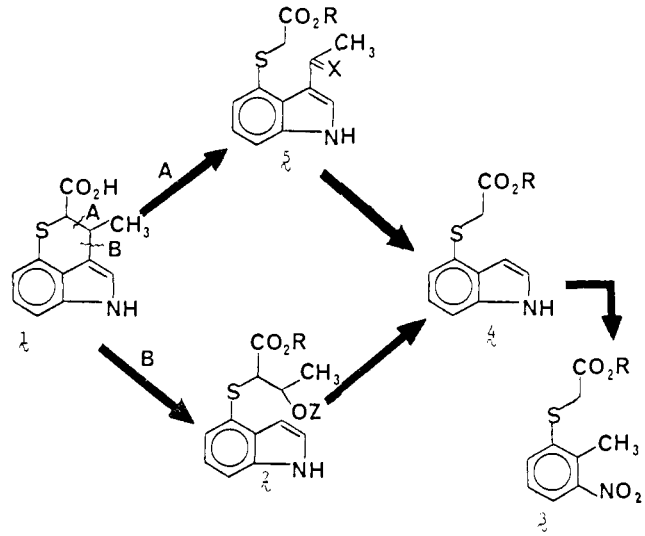
relative stereochemistry of the asymmetric centers was not established with any certitude). Preliminary clinical studies at the Chinese Academy of Medical Science have, moreover, shown chuangxinmycin to be 78% effective in the treatment of septicaemia and urinary and biliary infections.

The unique structural features (a new type of heterocyclic system) of chuangxinmycin, combined with its very promising biological activity, prompted us to attempt the total synthesis of this natural product.

Our synthetic approach to this compound was guided by our experience with the preparation of variously substituted indoles by the Leimgruber–Batcho methodology.[2] This process consists of simply heating an *o*-nitrotoluene with *N,N*-dimethylformamide dimethyl acetal to yield an *o*-nitrophenylacetaldehyde enamine. Subsequent reduction of the nitro group [Fe(II), H_2, dithionite, etc.] directly furnishes the indole. This chemistry thus resembles the Reissert indole synthesis, but bypasses the final decarboxylation step.



Scheme I, Retrosynthetic Analysis of Chuangxinmycin



Several retrosynthetic pathways from the target structure now become apparent based on the utilization of this chemistry. Two possibilities, displayed in Scheme I, lead to the sulfur-bearing nitrotoluene **3** as the required starting material.

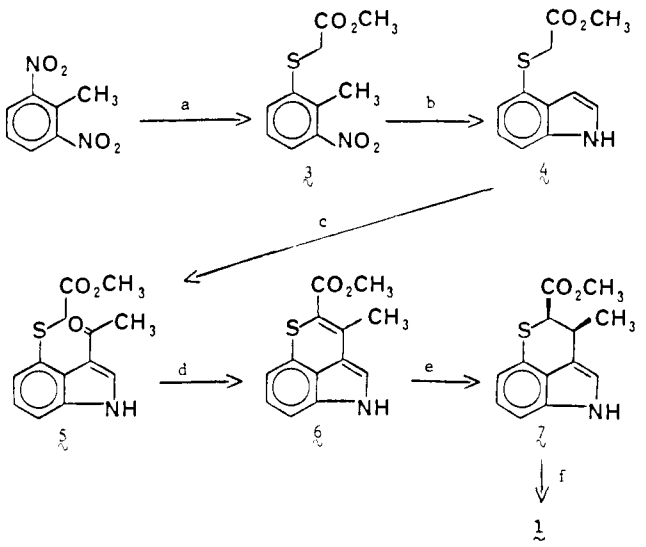
Our preliminary efforts to prepare **3** were founded on an observation recorded by Piers and co-workers in their synthesis of 4-mercaptoindole.[3] They had shown that the halogen atom of 2-bromo-6-nitrotoluene could be displaced by potassium benzylmercaptide in DMF to afford the corresponding thioether in 26% yield. We, in fact, attempted to carry out this experiment, using the commercially available 2-chloro-6-nitrotoluene with HMPA as solvent. To our initial surprise, displacement of the nitro group had occurred instead. This result was, however, quite in line with previously reported data concerning the relative rates of displacement of various activated aromatic groups with several different nucleophiles ($Me_2S^+ > Me_3N^+ > F \simeq NO_2 > Cl$).[4] This information moreover suggested that the commercially available 2,6-dinitrotoluene might serve as a suitable precursor to the thioether **3**.[5] Indeed, simply adding powdered lithium hydroxide to an HMPA solution of methyl thioglycolate and 2,6-dinitrotoluene at room temperature and stirring for 1 day afforded **3** in good yield (70%): mp 46–47 °C; IR ($CHCl_3$) 1736, 1523, 1352 cm^{-1}; NMR ($CDCl_3$) δ 6.90–7.70 (m, 3 H), 3.76 (s, 3 H), 3.63 (s, 2 H), 2.60 (s, 3 H).

The conversion of this product into the corresponding indole now required treatment with *N,N*-dimethylformamide dimethyl acetal. As might have been anticipated, while enamine formation did take place with this substrate, reaction occurred exclusively at the more acidic methylene group rather than at the methyl substituent. To shift the regiochemical course of this reaction, the methylene site was deactivated by converting the ester into the potassium salt (KOH, MeOH) of the corresponding acid, thereby enabling the reaction to occur exclusively at the site of the methyl group. The enamine produced was hydrolyzed directly to acid aldehyde by treatment with cold 6 N HCl, and this crude product immediately was reduced with $FeSO_4/NH_4OH$.[6] The crude indole acid was esterified with diazomethane and chromatographed on silica gel to afford in 43% overall yield for these four steps[7] (Scheme II) the ester **4**: mp 83–85 °C; IR ($CHCl_3$) 1730 cm^{-1}; NMR ($CDCl_3$) δ 7.20 (m, 4 H), 6.65 (m, 1 H), 3.70 (s, 2 H), 3.67 (s, 3 H).

While this indole **4** could readily be transformed to a 1:1 diastereomeric mixture of alcohols **2** (Scheme I, Z = H; LDA, CH_3CHO), all attempts to effect ring closure of this mixture by converting the hydroxyl group into a good leaving group

0002-7863/80/1502-1165$01.00/0

Scheme II, Synthesis of (±)-Chuangxinmycin[a]



[a] (a) $HSCH_2CO_2CH_3$, HMPA, LiOH, room temperature. (b) (i) KOH, MeOH; (ii) $(CH_3)_2NCH(OCH_3)_2$, DMF, reflux, then cold 6 N HCl; (iii) $FeSO_4$, NH_4OH; (iv) CH_2N_2, Et_2O. (c) CH_3COCl, $SnCl_4$. (d) NH_4OAc, HOAc, PhH, reflux. (e) H_2/Pd–S. (f) *n*-PrSLi, HMPA.

(e.g., tosylate or mesylate) led to decomposition of the starting material. The failure of this reaction pathway may be attributable to the difficulty encountered in correctly aligning the reaction centers for this electrophilic substitution process.

Since this chemistry would have led, in any event, to the stereorandom production of both the cis and trans isomers of chuangxinmycin, we opted at this point to examine path A where X = O.

Pursuant to pathway A, indole **4** was acylated in quantitative yield with acetyl chloride in benzene employing stannic chloride as catalyst.[8] This product was directly subjected to an internal Knoevenagel condensation (NH_4OAc/HOAc in benzene) to afford in quantitative yield dehydrochuangxinmycin methyl ester (**6**) as a bright yellow-orange solid: mp 167–168 °C; IR ($CHCl_3$) 1710 cm^{-1}; NMR ($CDCl_3$) δ 7.92 (br m, 1 H), 6.40–6.92 (m, 4 H), 3.77 (s, 3 H), 2.30 (s, 3 H).

Since we desired to firmly establish the stereorelationship of the asymmetric centers of chuangxinmycin, we now sought an efficient procedure for reducing dehydrochuangxinmycin by hydrogenation. Because the required site of this reduction is a trisubstituted vinyl sulfide which also experiences conjugative electron release from the indolic nitrogen, we were somewhat skeptical at the outset of being able to accomplish this in an efficient manner. While numerous conditions using homogeneous and heterogeneous catalysts in various solvents with or without added traces of acid at a range of pressures were examined, only a single successful procedure has emerged to date. Hydrogenation using a sulfided 5% palladium catalyst at 70 psi in ethyl acetate provided stereochemically homogeneous chuangxinmycin methyl ester in nearly quantitative yield: mp 145–146 °C; IR ($CHCl_3$) 1730 cm^{-1}; NMR ($CDCl_3$) δ 7.88 (br m, 1 H), 6.76–7.12 (m, 4 H), 4.08 (d, 1 H, J = 4 Hz), 3.64 (overlapping m, 1 H, and s, 3 H), 1.28 (d, 3 H, J = 7 Hz); M^+ 247.0666. This ester was identical by IR, NMR, and LC with a sample prepared from natural chuangxinmycin, procured from the Peking research group, by diazomethane treatment. Since the hydrogenation can be expected to deliver hydrogen in a cis fashion to **6**, the stereorelationship of the methyl and the carboxyl substituent of **1** has been established as cis. The synthetic ester was further converted into racemic chuangxinmycin (mp 186–189 °C; M^+ 233.0511) by treatment with *n*-PrSLi in HMPA at room temperature.[9] This material was identical in all respects (TLC, IR, ^1H NMR, and MS) with the authentic sample.

In summary, this work has led to the development of an efficient synthesis of the unique alkaloid chuangxinmycin, thus rigorously establishing the relative stereochemistry of its asymmetric centers. This work further emphasizes the usefulness of the nitro group displacement reaction as a tool for the construction of diversely functionalized aromatics. Further studies in these laboratories will focus on the synthesis of selected analogues of chuangxinmycin.

Acknowledgment. We are indebted to the National Institutes of Health (Grant No. R01 HL2059-03) for partial support of these investigations and to Dr. C.-P. Chang for a sample of chuangxinmycin. The technical assistance of Edward Ryan is also gratefully acknowledged.

References and Notes

(1) H.-T. Liang, H.-D. Hsu, C.-P. Chang, H.-E. Ku, and W.-S. Wang, *Hua Hsueh Hsueh Pao*, **34**, 129 (1976); *Chem. Abstr.*, **87**, 165948z (1977); *Sci. Sin. (Engl. Ed.)*, **20**, 106 (1977); *Chem. Abstr.*, **87**, 98565g (1977). C.-P. Chang, H.-D. Hsu, L.-C. Huang, Y.-C. Lin, H.-S. Li, C.-L. Yu, and C.-L. Chao, *Acta Chim. Sin.*, **34**, 133 (1976); *Chem. Abstr.*, **88**, 62309h (1978).
(2) W. Leimgruber and A. D. Batcho, Third International Congress of Heterocyclic Chemistry, Japan, Aug 23–27, 1971; U.S. Patent 3 976 639 (1976).
(3) E. Piers, V. B. Haarstad, R. J. Cushley, and R. K. Brown, *Can. J. Chem.*, **40**, 511 (1962).
(4) J. R. Beck, *Tetrahedron*, **34**, 2057 (1978).
(5) The displacement of the nitro group in *m*-dinitrobenzene by several nucleophiles has previously been described: N. Kornblum, L. Cheng, R. C. Kerber, M. M. Kestner, B. N. Newton, H. W. Pinnick, R. G. Smith, and P. A. Wade, *J. Org. Chem.*, **41**, 1560 (1976).
(6) K. G. Blaikie and W. H. Perkin, *J. Chem. Soc.*, 296 (1924); H. N. Rydon and J. C. Tweddle, *ibid.*, 3499 (1955).
(7) An alternate route to indole **4** involving prior reaction of the 2,6-dinitrotoluene with *N,N*-dimethylformamide dimethyl acetal with subsequent conversion of enamine into protected aldehyde followed by nitro group displacement with the anion of methyl thioglycolate has been examined. This route will be reported in detail in the full paper; M. Greco and S. Gordon, unpublished results.
(8) J. I. Degraw, J. G. Kennedy, and W. A. Skinner, *J. Heterocycl. Chem.*, **3**, 9 (1966).
(9) P. A. Bartlett and W. S. Johnson, *Tetrahedron Lett.*, 4459 (1970). Some of the trans product is also generated in this dealkylation reaction. The spectral data of chuangxinmycin have been published; see ref 1.
(10) All new compounds reported had spectral properties and high resolution mass spectral data for the molecular ion fully compatible with the assigned structures. Melting points are uncorrected.
(11) Fellow of the Alfred P. Sloan Foundation.

Alan P. Kozikowski,*[11] Michael N. Greco
Department of Chemistry, University of Pittsburgh
Pittsburgh, Pennsylvania
Received July 12, 1979

Chiral Recognition by ^{15}N NMR Spectroscopy, 8-Benzyl-5,6,7,8-tetrahydroquinoline[1]

Sir:

Chiral recognition through diastereomeric complex formation with optically active solvents or solutes and detected by chemical-shift differences in ^1H or ^{19}F NMR spectroscopy has many applications, including for the determination of absolute configurations.[2] The NMR shift differences observed in many chiral recognition experiments are not large and, because the reported changes of ^{15}N chemical shifts of pyridine-type nitrogens on hydrogen-bond formation and protonation are, respectively, usually 15–30 and ~100 ppm,[3] it seemed possible that differential complexation between an optically active proton donor and the separate enantiomers of chiral pyridine derivatives might lead to substantial ^{15}N chemical-shift differences. This expectation has been realized with racemic 8-benzyl-5,6,7,8-tetrahydroquinoline (**1**)[4] with several optically active acids and β-cyclodextrin[5] as complexing agents in various solvents. Most of the successful experiments

0002-7863/80/1502-1166$01.00/0