methanol was added. The solution was refluxed overnight and the solvent was removed under a stream of nitrogen. The residue was extracted with 1 ml of ether and the solvent was removed leaving 4 mg. A sample was collected from column B (190°); the major peaks in its mass spectrum were at m/e 278, 249, 246, 228, 215, 205, 204, 197, 190. A sample of dimethyl 4-phenylsuberate which had been treated similarly with methanol-O-*d* contained >95% d_4 species by mass spectrometric analysis.

Molecular Asymmetry of Olefins. V. Resolution of *cis,trans*-1,5-Cyclooctadiene[1]

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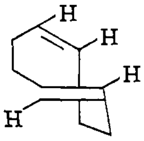
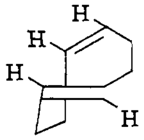
Contribution from the Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139. *Received November 6, 1965*

Abstract: Resolution of *cis,trans*-1,5-cyclooctadiene has been accomplished through platinum complexes containing optically active α-methylbenzylamine. Fractional crystallization of (+)-*trans*-dichloro(*cis,trans*-1,5-cyclooctadiene)(α-methylbenzylamine)platinum(II) to constant rotation and decomposition of this complex with sodium cyanide yielded optically active (−)-*cis,trans*-1,5-cyclooctadiene, $[\alpha]^0$D −152°.

The labile 1,5-cyclooctadiene obtained from N-methylgranatanine by two successive Hofmann exhaustive methylation reactions has been shown unequivocally to be *cis,trans*-1,5-cyclooctadiene.[4] Because of the rigid structure of the ring and the nonbonded hydrogen interactions which prevent rotation of the *trans*-olefinic bond with respect to the rest of the ring, the molecule should exist in two enantiomeric forms, **1a** and **1b**. Evidence that this is the case has been obtained by the asymmetric synthesis of *cis,trans*-1,5-cyclooctadiene from resolved N,N-dimethyl-*cis*-4-cycloocten-1-ylamine[5] and by partial resolution of the racemic diene *via* a platinum complex containing optically active (+)-α-methylphenethylamine (Dexedrine).[6]



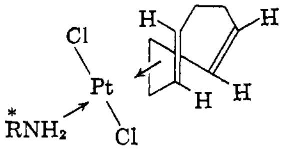
1a



1b

For the resolution of *trans*-cyclooctene, (+ or −)-α-methylbenzylamine was found to be more suitable as the optically active ligand in the platinum complex.[7] This paper reports the resolution of *cis,trans*-1,5-cyclooctadiene *via* the platinum complex containing optically active α-methylbenzylamine.

Unlike *trans*-cyclooctene, *cis,trans*-1,5-cyclooctadiene may form a bond with platinum in more than one way, since both ethylenic linkages are available as ligands.[8]



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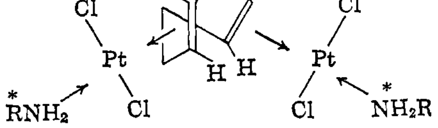

3

The *trans*-olefinic bond may form a coordination bond with one platinum as shown in the complex *trans*-dichloro(*cis,trans*-1,5-cyclooctadiene)(α-methylbenzylamine)platinum(II) (**2**), or both the *cis*- and *trans*-olefinic linkages may bond to two separate platinum atoms forming the bridged complex μ-(*cis,trans*-1,5-cyclooctadiene)-*trans,trans*-tetrachlorobis(α-methylbenzylamine)diplatinum(II) (**3**).

Displacement of ethylene from the complex (+)-*trans*-dichloro(ethylene)(α-methylbenzylamine)platinum(II) by *cis,trans*-1,5-cyclooctadiene in methylene chloride solution afforded as a less soluble fraction a material having the elemental composition expected for complex **2**. After fractional crystallization to constant rotation from methylene chloride, this material had $[\alpha]^{28}$D +97.2°.

Attempts to repeat the preparation of this complex and its enantiomer containing (−)-α-methylbenzylamine gave only the other complex **3**, characterized by elemental analysis, thin layer chromatographic properties, and lack of the infrared absorption at *ca.* 725 cm^{-1} associated with *cis* olefins. After fractional crystallization to constant rotation from methylene chloride–*n*-hexane, the complex **3** had $[\alpha]^{28}$D −94°.

It was possible to prepare complex **2** by cleavage of the bridged complex, di-μ-chloro-1,3-dichloro-2,4-bis(*cis,-trans*-1,5-cyclooctadiene)diplatinum(II) with (+)-α-

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[1] Supported in part by the Army Research Office (Durham) under Grant No. DA-AROD 31-124-G404.

[2] National Science Foundation Summer Fellow, 1962; National Institutes of Health Predoctoral Fellow, 1962–1963.

[3] National Science Foundation Science Faculty Fellow, 1960–1961.

[4] A. C. Cope, J. E. Bowers, C. F. Howell, and R. C. Lord, to be published.

[5] A. C. Cope, C. F. Howell, and A. Knowles, *J. Am. Chem. Soc.*, **84**, 3190 (1962).

[6] A. C. Cope, C. R. Ganellin, and H. W. Johnson, Jr., *ibid.*, **84**, 3191 (1962).

[7] A. C. Cope, C. R. Ganellin, H. W. Johnson, Jr., T. V. Van Auken, and H. J. S. Winkler, *ibid.*, **85**, 3276 (1963).

[8] The asterisk above RNH₂ indicates that (+ or −)-α-methylbenzylamine was used.

methylbenzylamine. The complex **2**, identified by elemental analysis and infrared absorption at 730 cm^{-1}, had $[\alpha]^{27}_{\mathrm{D}}$ +102.5° after fractional crystallization to constant rotation from methylene chloride.

Decomposition of this positively rotating complex **2** at −40° with sodium cyanide in a 1:1 mixture of methanol and ethylene glycol afforded *cis,trans*-1,5-cyclooctadiene, having $[\alpha]^{0}_{578}$ −160°, $[\alpha]^{0}_{\mathrm{D}}$ −152°. The product was identified by comparison of its infrared spectrum and vapor phase chromatographic (vpc) retention time with those of an authentic sample.

Previous attempts at resolution using (+)-α-methylphenethylamine (Dexedrine) as the optically active ligand in the platinum complex had given only partial resolution *via* a complex of the type **3**. The least soluble material had $[\alpha]^{28}_{\mathrm{D}}$ −18.3° and upon decomposition with aqueous potassium cyanide gave *cis,trans*-1,5-cyclooctadiene, $[\alpha]^{28}_{\mathrm{D}}$ +34°. The more soluble fraction, $[\alpha]^{28}_{\mathrm{D}}$ +55.2°, on decomposition gave the diene with $[\alpha]^{28}_{\mathrm{D}}$ −26°.[6]

cis,trans-1,5-Cyclooctadiene formed by the Hofmann degradation of resolved N,N-dimethyl-*cis*-4-cycloocten-1-ylamine had $[\alpha]^{25}_{\mathrm{D}}$ +121.3°, $[\alpha]^{25}_{\mathrm{D}}$ −120.5° (*c* 2.0, pentane) for the two enantiomers.[5] If the resolution presently reported was complete,[9] the diene was formed in about 80% optical purity (based on resolved olefin having $[\alpha]^{0}_{\mathrm{D}}$ −152°) by the asymmetric synthesis.

Experimental Section[10]

***cis,trans*-1,5-Cyclooctadiene.** The labile diene was prepared from N-methylgranatanine by two successive Hofmann degradations as previously described.[4,11]

Resolution of *cis,trans*-1,5-Cyclooctadiene. A. From (+)-*trans*-Dichloro(ethylene)(α-methylbenzylamine)platinum(II). A solution of 15.0 g of (+)-*trans*-dichloro(ethylene)(α-methylbenzylamine)platinum(II)[7] in 15 ml of methylene chloride was added to a solution of 4.83 g of freshly prepared *cis,trans*-1,5-cyclooctadiene in 5 ml of methylene chloride. After the evolution of ethylene was complete, the solution was cooled for 16 hr and 8.47 g of a less soluble fraction crystallized. From the mother liquor, 8.54 g of a more soluble material was recovered. Fractional crystallization[12] of the less soluble material from methylene chloride gave 2.42 g of (+)-*trans*-dichloro(*cis,trans*-1,5-cyclooctadiene)(α-methylbenzylamine)platinum(II) as yellow crystals, mp 124–125°, $[\alpha]^{28}_{\mathrm{D}}$ +97.2° (*c* 2.0, methylene chloride).

Anal. Calcd for $C_{16}H_{23}Cl_2NPt$: C, 38.79; H, 4.68; Pt, 39.38. Found: C, 38.93; H, 4.63; Pt, 39.21.

The infrared spectrum (KBr pellet) had a band at 725 cm^{-1}, characteristic of *cis*-HC=CH–.

cis,trans-1,5-Cyclooctadiene was liberated from 2.42 g of the above diastereoisomeric complex with aqueous potassium cyanide as described previously.[7] The resulting dried methylene chloride solution had $[\alpha]^{28}_{\mathrm{D}}$ −135° (*c* 5.3, methylene chloride).[13] The infrared spectrum and vpc analysis (4-methyl-4-nitropimelonitrile (NMPN), 80°) of the product showed that only *cis,trans*-1,5-cyclooctadiene was present.

B. From Di-μ-chloro-1,3-dichloro-2,4-bis(*cis,trans*-1,5-cyclooctadiene)diplatinum(II). *trans*-Dichloro(*cis,trans*-1,5-cyclooctadiene)(α-methylbenzylamine)platinum(II) was also prepared by cleavage of the bridged complex di-μ-chloro-1,3-dichloro-2,4-bis(*cis,trans*-1,5-cyclooctadiene)diplatinum(II) with (+)-α-methylbenzylamine. To 4.22 g of di-μ-chloro-1,3-dichloro-2,4-bis(ethylene)diplatinum(II)[14] in 175 ml of methylene chloride, 1.55 g of *cis,trans*-1,5-cyclooctadiene was added. The orange solid (5.1 g, 95%) obtained on removal of the solvent was recrystallized from carbon tetrachloride and showed the same infrared absorption (730 cm^{-1}, KBr pellet) that had been present in the previously prepared complex containing one molecule of *cis,trans*-1,5-cyclooctadiene per atom of platinum. A 3.20-g sample of this complex was added to 1.035 g of (+)-α-methylbenzylamine in methylene chloride at 0°. The color of the solution changed from orange to yellow. The solvent was removed and the residue was recrystallized from methylene chloride until the specific rotation and the melting point did not change upon further crystallization. The yellow crystals had mp 122–123°, $[\alpha]^{27}_{578}$ +108°, $[\alpha]^{27}_{546}$ +127°, $[\alpha]^{27}_{\mathrm{D}}$ (calcd) +102.5° (*c* 1.5, methylene chloride).

Anal. Calcd for $C_{16}H_{23}Cl_2NPt$: C, 38.79; H, 4.68; Pt, 39.38. Found: C, 38.46; H, 4.70; Pt, 38.13.

The *cis,trans*-1,5-cyclooctadiene recovered from this complex in 98% yield (as determined by vpc analysis (NMPN, 80°)) by decomposition at −40° with sodium cyanide in 1:1 methanol–ethylene glycol had $[\alpha]^{0}_{578}$ −160°, $[\alpha]^{0}_{546}$ −182°, $[\alpha]^{0}_{\mathrm{D}}$ (calcd) −152° (*c* 0.87, methylene chloride). Its infrared spectrum and vpc retention time were identical with those of an authentic sample.

C. From μ-(*cis,trans*-1,5-Cyclooctadiene)-*trans,trans*-tetrachlorobis(α-methylbenzylamine)diplatinum(II). When the olefin displacement reaction was carried out with (−)-*trans*-dichloro(ethylene)(α-methylbenzylamine)platinum(II), the product differed from that obtained previously in thin layer chromatographic characteristics (silica gel G, elution with 4:1 benzene–methylene chloride) and infrared spectrum (lack of a strong absorption at 725 cm^{-1}, assigned to the *cis*-HC=CH– present in the previously prepared complex). Analysis of the product agreed with that expected for a complex formed by displacement of ethylene from 2 moles of the complex (−)-*trans*-dichloro(ethylene)(α-methylbenzylamine)platinum(II) by 1 mole of *cis,trans*-1,5-cyclooctadiene.[15] Fractional recrystallization to constant rotation from methylene chloride–*n*-hexane afforded yellow crystals, mp 128–130°, $[\alpha]^{28}_{578}$ −99°, $[\alpha]^{28}_{546}$ −117°, $[\alpha]^{28}_{\mathrm{D}}$ (calcd) −94° (*c* 1.65, methylene chloride).

Anal.[16] Calcd for $C_{24}H_{34}Cl_4N_2Pt_2$: C, 32.66; H, 3.86; Pt, 44.21. Found: C, 33.16; H, 3.95; Pt, 43.71.

The dried methylene chloride solution (8.8 ml), containing the *cis,trans*-1,5-cyclooctadiene, obtained on decomposition of 1.0 g of this complex with aqueous potassium cyanide as described previously,[7] had α_{578} (obsd) +1.33°. The specific rotation, $[\alpha]^{26}_{578}$ +103°, $[\alpha]^{26}_{546}$ +118°, $[\alpha]^{26}_{\mathrm{D}}$ (calcd) +98° (*c* 1.3, methylene chloride), was calculated from the observed rotation and the concentration determined by vpc using *cis,cis*-1,5-cyclooctadiene as an internal standard.[17]

Careful distillation of the solvent at 200 mm and 0° (bath temperature) yielded *cis,trans*-1,5-cyclooctadiene, $[\alpha]^{26}_{578}$ +114°, $[\alpha]^{26}_{546}$ +130°, $[\alpha]^{26}_{\mathrm{D}}$ (calcd) +109° (*c* 1.4, 1:1 methylene chloride–pentane), which was identified by comparison of its vpc retention time and infrared spectrum with those of authentic material.

Titration of the acid extracts from the potassium cyanide decomposition with methyl red–brom cresol green mixed indicator afforded the appropriate titer for 2 moles of amine per mole of complex.

D. From μ-(*cis,trans*-1,5-Cyclooctadiene)-*trans,trans*-tetrachlorobis(α-methylphenethylamine)diplatinum(II). In the earlier work done on resolution of *cis,trans*-1,5-cyclooctadiene, (+)-α-methylphenethylamine had been employed as the optically active ligand on the platinum complex.[6] A solution of 2.59 g of (+)-*trans*-dichloro(ethylene)(α-methylphenethylamine)platinum(II)[7] in 15 ml of methylene chloride was added to a solution of 0.72 g of *cis*,-

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(9) It is possible that the complete resolution of the diene may not have been accomplished due to difficulties encountered in the formation and crystallization of the platinum complexes.

(10) Melting points were taken on a Kofler hot stage. Analyses were performed by Dr. S. M. Nagy and Scandinavian Microanalytical Laboratory. Optical rotations were measured with a Zeiss Precision Polarimeter or a Zeiss Photoelectric Precision Polarimeter. With the latter instrument, rotations measured at 546.1 and 577.8 mμ were used to calculate the value at the sodium D line (589.2 mμ). Gas chromatographic (vpc) analyses were carried out using 180 × 0.8 cm Pyrex tubes packed with 48–100 mesh firebrick which was coated with the appropriate stationary phase. The samples were eluted with helium at 15 psi and thermal conductivity cells were used as detectors.

(11) R. Willstätter and H. Veraguth, *Ber.*, **38**, 1975 (1905).

(12) The complexes were recrystallized to constant rotation and were pure diastereoisomers according to this criterion.

(13) The specific rotation was calculated on the basis that the theoretical amount of olefin was liberated.

(14) J. Chatt and M. L. Searle, *Inorg. Syn.*, **5**, 210 (1957).

(15) This result was obtained even if the displacement reaction was carried out at 0 and −60° or by simultaneous addition of the reactants.

(16) The sample analyzed was prepared in the manner described above.

(17) The response factor was determined previously with racemic *cis,trans*-1,5-cyclooctadiene.

trans-1,5-cyclooctadiene in 30 ml of methylene chloride. Fractional crystallization of the complex from benzene–cyclohexane gave 0.58 g of a more soluble material, mp 106–108° (after further recrystallization from carbon tetrachloride), and $[\alpha]^{28}{}_{D}$ +55.2° (*c* 2.5, methylene chloride).

Anal. Calcd for $C_{26}H_{38}Cl_4N_2Pt_2$: C, 34.28; H, 4.20; N, 3.08; Pt, 42.87. Found: C, 34.42; H, 4.05; N, 2.75; Pt, 43.22.

The least soluble diastereoisomer (0.62 g) had mp 155–157° and $[\alpha]^{28}{}_{D}$ −18.3° (*c* 2.5, methylene chloride).

Anal. Calcd for $C_{26}H_{38}Cl_4N_2Pt_2$: C, 34.28; H, 4.20; N, 3.08; Pt, 42.87. Found: C, 34.10; H, 4.33; N, 3.06; Pt, 42.46.

The diene obtained on decomposition of the more soluble diastereoisomer had $[\alpha]^{28}{}_{D}$ −26° (*c* 1.3, pentane); the diene from the least soluble diastereoisomer had $[\alpha]^{28}{}_{D}$ +34° (*c* 1.2, pentane).

The Stereochemical Course of a Robinson–Schöpf Biogenetic-Type Reaction. The Conformation of Certain Tricyclic Tropane Congeners[1]

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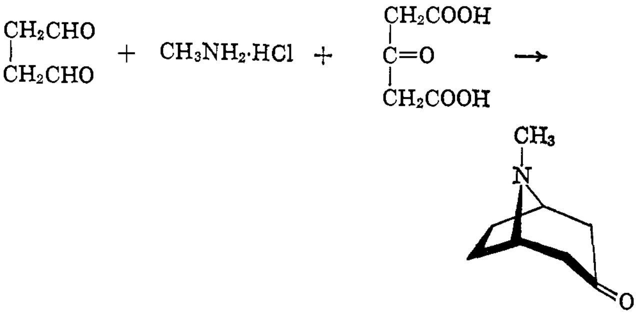
Contribution from the Department of Chemistry, The Ohio State University, Columbus, Ohio 43210. *Received November 1, 1965*

Abstract: The Robinson–Schöpf reaction of *cis*-cyclopentane-1,3-dialdehyde, methylamine hydrochloride, and acetonedicarboxylic acid leads to a tricyclic amino ketone in which the nitrogen and carbon bridges are *anti* to each other. Furthermore, the N-methyl group is shown to exist almost totally, if not exclusively, in the axial conformation (with respect to the piperidone ring). The stereochemical course of the reduction of the amino ketone with various reagents has been studied and a variety of data is presented which contributes to the elucidation of the stereochemistry and conformational analysis of the resulting amino alcohols. The possible significance of the stereochemical outcome of the Robinson–Schöpf reaction on the mechanistic course of double Mannich reactions is discussed.

The elegant synthesis[3] of tropane alkaloids "under physiological conditions" ingeniously devised by Robinson[4] and later improved by Schöpf[5] has proved widely applicable, and is illustrated below for the

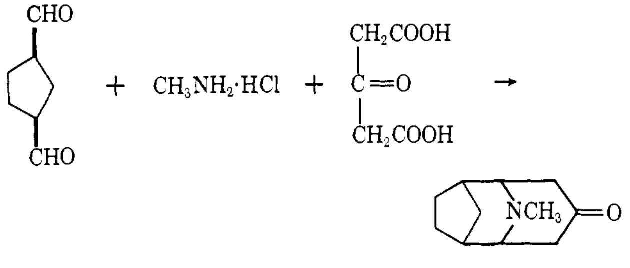


$$\begin{matrix}CH_2CHO\\|\\CH_2CHO\end{matrix} + CH_3NH_2{\cdot}HCl + \begin{matrix}CH_2COOH\\|\\C{=}O\\|\\CH_2COOH\end{matrix} \longrightarrow$$

1

case of tropinone (1). The Robinson–Schöpf reaction is often cited as the epitome of a double Mannich condensation involving aldehydes other than formaldehyde,[6] although the actual mechanistic details (except for the nondescript lasso symbolism) of the process have never been discussed to the authors' knowledge and are undoubtedly not clearly understood.[7] In addition, the influence of steric factors on the course of Mannich reactions in general, and of the Robinson–Schöpf reaction in particular, has been little investigated.

Alder, Wirtz, and Koppelberg[8] have reported that the condensation of *cis*-cyclopentane-1,3-dialdehyde with methylamine hydrochloride and acetonedicarboxylic acid results in the formation of the tricyclic tropane congener 2, but these workers were unable to determine the geometry of this amino ketone. We have investigated the synthesis of 2 with a view to elucidating the stereochemical course of this reaction and in the anticipation that knowledge of the configuration of 2 will shed some light on the mechanistic course of the Robinson–Schöpf reaction.



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Results

When a methyl acetate solution of *cis*-cyclopentane-1,3-dialdehyde was added to an aqueous phosphate-buffered solution of methylamine hydrochloride and

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(1) We are indebted to the National Institutes of Health of the U. S. Public Health Service for financial support (Grant No. GM-11975).

(2) (a) Alfred P. Sloan Foundation Research Fellow; (b) undergraduate research participant.

(3) Once characterized by Willstätter as "von bewundernswerter Eleganz": E. Winterstein and G. Trier, "Die Alkaloide," Gebrüder Borntraeger, Berlin, 1931, p 295.

(4) R. Robinson, *J. Chem. Soc.*, **111**, 762, 876 (1917).

(5) For early extensive reviews of such reactions see C. Schöpf, *Angew. Chem.*, **50**, 779, 797 (1937).

(6) See, for example, H. O. House "Modern Synthetic Reactions," W. A. Benjamin, Inc., New York, N. Y., 1965, p 233.

(7) Our understanding of the mechanism of simple Mannich condensations is much more complete: (a) ref 6, p 230; (b) H. Hellmann and G. Opitz, *Angew. Chem.*, **68**, 265 (1956); (c) T. F. Cummings and J. R. Shelton, *J. Org. Chem.*, **25**, 419 (1960); (d) M. Brown and W. S. Johnson, *ibid.*, **27**, 4706 (1962); (e) H. O. House and B. M. Trost, *ibid.*, **29** 1339 (1964).

(8) K. Alder, H. Wirtz, and H. Koppelberg, *Ann.*, **601**, 138 (1956).