

## 17. Stereoselective Effects in Reactions of Metal Complexes III<sup>1)</sup> Asymmetric Hydrogenation of 5,7,7,12,14,14-Hexamethyl- -1,4,8,11-tetraazacyclotetradeca-4,11-diene-nickel(II)

by Maurice Wermeille, Ewa Sledziowska<sup>2)</sup> and Klaus Bernauer

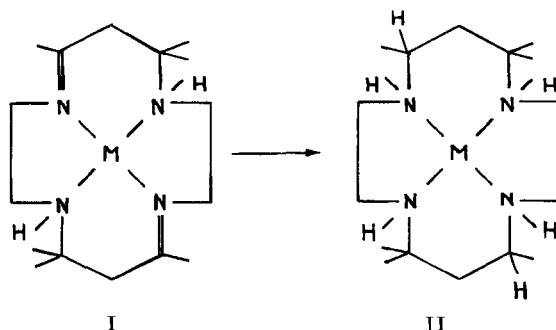
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(27. VI. 73)

*Summary.* The catalytic hydrogenation in acidic solution (pH  $\sim$  2) of the title compound<sup>3)</sup>  $[\text{Ni}(4,11\text{-dieneN}_4)]^{2+}$  (I) has been studied. The reaction yields only *C-meso*-5,7,7,12,14,14-hexamethyl-1,4,8,11-tetraaza-cyclotetradecane-nickel (II) (*C-meso*- $[\text{Ni}(4,11\text{-aneN}_4)]^{2+}$ ), when *meso*- $[\text{Ni}(4,11\text{-dieneN}_4)]^{2+}$  is the starting material. *Rac*- $[\text{Ni}(4,11\text{-dieneN}_4)]^{2+}$  yields the unstable  $\alpha$ -*C-rac*- $[\text{Ni}(4,11\text{-aneN}_4)]^{2+}$ . When optically active  $[\text{Ni}(4,11\text{-dieneN}_4)]^{2+}$  is reduced, optically active  $\alpha$ - $[\text{Ni}(4,11\text{-aneN}_4)]^{2+}$  is obtained, which in neutral or basic solution shows mutarotation due to conversion into optically active  $\beta$ - $[\text{Ni}(4,11\text{-aneN}_4)]^{2+}$ ; no racemization is observed. Reaction with cyanide ions yields the optically active free tetramine ligand.

The reaction mechanism of this asymmetric synthesis is discussed.

The absolute configuration of the two asymmetric nitrogen atoms of the title compound suggests that metal complexes such as I may exist in three isomeric forms: *R,S*, *R,R* and *S,S*. The stereochemistry of the *meso*- and the *rac*-forms has been established from NMR.-data [2] and X-ray diffraction [3].



Reduction of the two double bonds in I creates four new chiral elements in the molecule. Thus 20 diastereoisomers (16 *rac* and 4 *meso*) are theoretically possible [4];

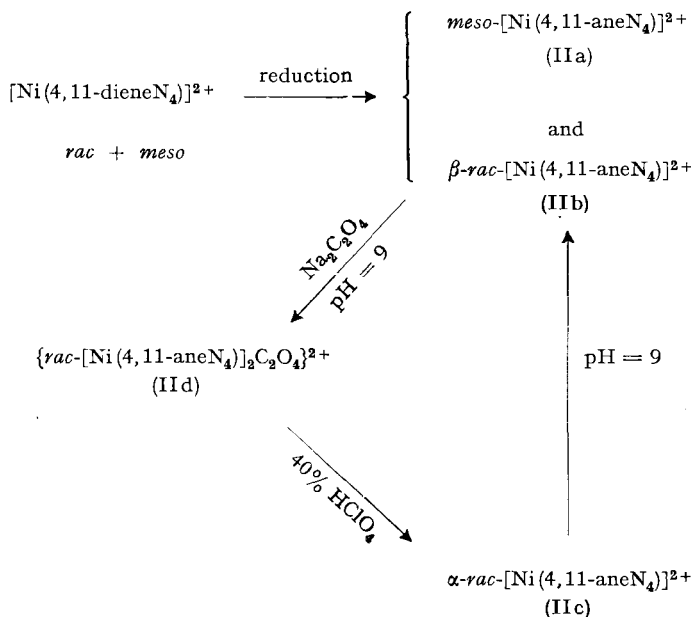
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<sup>3)</sup> In order to represent this and the related compounds by meaningful abbreviations, we shall adopt the numerotation system proposed in the literature [8] [12]. The complete abbreviation of the title compound is  $[\text{Ni}(5,7,7,12,14,14\text{-Me}_6\text{-[14]-4,11\text{-diene-1,4,8,11-N}_4)]^{2+}$ . As in the present work the 14-membered ring system with six methyl groups remains unchanged, we shall use  $[\text{Ni}(4,11\text{-dieneN}_4)]^{2+}$  and  $[\text{Ni}(4,11\text{-aneN}_4)]^{2+}$  for the complex with the unsaturated and saturated ligand, respectively.

however, only three of these have been isolated. Theoretical considerations suggest, that the other isomers would not be sufficiently stable to be formed in measurable amount [5]. *Scheme 1* shows the diastereomers obtained and the related reactions. These compounds have also been characterized by NMR.-data [6].

*Scheme 1. Formation and interconversion of  $[\text{Ni}(4,11\text{-aneN}_4)]^{2+}$  stereoisomers*



Forms (IIb) and (IIc) are interconvertible, since they differ only in the relative configuration of two nitrogen atoms. (IIb) is thermodynamically stable; (IIc) was obtained only by acidic decomposition of (II d). The latter is a binuclear complex of octahedral structure containing the macrocyclic ligand in a folded arrangement. (IIb) and (IIc) must each exist as optical antipodes, the separation of which has so far been unsuccessful. (IIa) is definitely *meso* with respect to the two pairs of nitrogen atoms as well as to C(5) and C(12) [5] [6].

In a preceding paper [7] we discussed the configurational stability of the nitrogen atoms in I, for which the rate of inversion was a function of acidity. At low pH and at room temperature inversion is so slow, that the optical antipodes may be considered stable. Consequently, we have studied the stereochemistry of the hydrogenation of I in acidic medium since this reaction has been performed hitherto only in neutral or basic solution [8]. In the latter case, the product is mainly the *meso*-form although the *rac*-form predominates in the unreduced compound. Since the equilibrium *meso*  $\rightleftharpoons$  *rac* is rapid under the reaction conditions used no information could be obtained about the stereochemical course of the reaction. In the present paper we show that the reaction, performed under conditions where N-inversion is much slower than reduction, is in fact highly stereoselective.

### Experimental Part

1. *Synthesis.*  $[\text{Ni}(4, 11\text{-dieneN}_4)](\text{ClO}_4)_2$  (I): from  $[\text{Ni}(\text{en})_3](\text{ClO}_4)_2$  and acetone [8] [9],  $[\text{Ni}(4, 11\text{-dieneN}_4)]\text{X}_2$  (Ia):  $\text{X} = \text{Cl}^-$ ,  $\text{SCN}^-$ ; these products were obtained by passing a solution of the perchlorate over an anion exchanger Dowex 1-X8, 50–100 mesh, loaded with chloride or thiocyanate, and evaporating the effluent solution; the perchlorate (I) can be regenerated by treating these products with  $\text{AgClO}_4$ .

$\{[\text{Ni}(4, 11\text{-aneN}_4)]_2(\text{C}_2\text{O}_4)\}(\text{ClO}_4)_2$  (II d) and  $\alpha\text{-}[\text{Ni}(4, 11\text{-aneN}_4)](\text{ClO}_4)_2$  (II b) are obtained as described in [5].

2. *Partial resolution and enrichment of Ia and of II b* [10]. 0,5 g of Ia are dissolved in 50 ml of  $\text{HCl } 10^{-2}\text{M}$ , introduced into a column (length 80 cm, internal diameter 3,5 cm) packed with potato starch and cluted with  $\text{HCl}$ -solution  $10^{-2}\text{M}$ . The pH of the optically active fractions is raised to 4,5 by adding sodium acetate. The solutions are then put on a weakly acidic Amberlite-CG 50 resin and washed with diluted acetate buffer solution to eliminate any optically active substance resulting from starch hydrolysis. When the washing solution is no longer optically active, the complex I is eluted with  $\text{HClO}_4$ -solution 0,1M.

Fractional concentration and crystallisation gives a product which is almost optically inactive, whereas the mother solution shows increased specific rotation. This operation is repeated as long as there is an increase in molar rotation of the solution.  $[\Phi]$ -values thus obtained (see Table 1) are markedly higher than those given in the literature.

3. *Reduction of (I).* Catalytic hydrogenations were carried out in acidic aqueous solution at room temperature with  $\text{PtO}_2$  as catalyst and a hydrogen pressure of about 4 atm. The pH was  $\leq 2$  and the quantity of the complex never exceeded 0,1 mmol. The reaction was considered complete when the absorption band due to the  $\text{C}=\text{N}$ -group at 280 nm had completely disappeared; reaction time was about two days.

4. *Physical Measurements.* All polarimetric measurements were carried out with a *Perkin-Elmer 141* Polarimeter; a *Unicam SP-800* was used for the UV. and visible spectra. ORD. curves

Table 1. *Molecular rotations*  $[\Phi]^{22}$   
 $(+)_365\text{-}[\text{Ni}(4, 11\text{-dieneN}_4)]\text{Cl}_2$  and optically active forms of  $[\text{Ni}(4, 11\text{-aneN}_4)]\text{Cl}_2$ .

Isomer	365 <sup>a)</sup>	436 <sup>a)</sup>	546 <sup>a)</sup>	578 <sup>a)</sup>
1. Non reduced	2340	4320	– 1895	– 1230
2. $\alpha$ from 1. by resolution	692	– 178	– 252	– 203
fwd. by reduction				
3. $\beta$ from 2.	95	– 522	116	70
4. $\alpha$ from 1. by reduction	248	– 62	– 112	– 91
fwd. by resolution				
5. $\beta$ from 4.	– 50	– 286	74	37
6. Free ligand [11] from 3.	– 120	– 74	– 43	– 37

$(-)_365\text{-}[\text{Ni}(4, 11\text{-dieneN}_4)]\text{Cl}_2$ and optically active forms of $[\text{Ni}(4, 11\text{-aneN}_4)]\text{Cl}_2$ .				
Isomer	365 <sup>a)</sup>	436 <sup>a)</sup>	546 <sup>a)</sup>	578 <sup>a)</sup>
1. Non reduced	– 2420	– 4620	1968	1270
2. $\alpha$ from 1. by resolution	– 704	166	248	203
fwd. by reduction				
3. $\beta$ from 2.	91	472	– 112	– 58
4. $\alpha$ from 1. by reduction	– 95	33	41	37
fwd. by resolution				
5. $\beta$ from 4.	25	149	– 37	– 21
6. Free ligand [11] from 3.	108	71	46	37

<sup>a)</sup> in nm.

were obtained using the spectropolarimeter constructed at *Hoffmann-La-Roche* and CD. spectra with a *Dichrographe Roussel Jouan* CD 185.

**Results.** – When a solution of a given enantiomer of  $rac$ -[Ni(4,11-dieneN<sub>4</sub>)]<sup>2+</sup> is completely reduced in acidic medium, a product is obtained which is still optically active. In neutral or basic solution this product undergoes mutarotation but no appreciable racemization occurs, shown by the fact that treatment of the basic solution with oxalate, followed by acidic decomposition of the product, regenerates the original reduction product with almost the same optical activity. Thus it seems probable that this first product is the unstable  $\alpha(+)$ - or  $\alpha(-)$ -[Ni(4,11-aneN<sub>4</sub>)]<sup>2+</sup>, which at higher pH-values is transformed into the stable  $\beta(+)$ - or  $\beta(-)$ -[Ni(4,11-aneN<sub>4</sub>)]<sup>2+</sup>. Typical results are summarized in Table 2. The  $\alpha$ -form which was previously obtained only *via* the octahedral oxalato-complex can now be synthesized directly.

Table 2. *Typical mutarotation results for stereoisomeric forms of [Ni(4,11-aneN<sub>4</sub>)] salts.* – Evidence for absence of racemisation;  $\alpha$  and  $[\Phi]^{22}$  are given in degrees.

Isomer	365 <sup>a)</sup>	436 <sup>a)</sup>	546 <sup>a)</sup>	578 <sup>a)</sup>	E <sup>b)</sup>
1. (+) <sub>365</sub> -[IIc]Cl <sub>2</sub>	0,425 690	-0,110 -179	-0,153 -247	-0,124 -210	0,32
2. (-) <sub>365</sub> -[IIb]Cl <sub>2</sub>	-0,048 -94	-	0,057 109	0,036 69	0,44
3. (+) <sub>365</sub> -[IIc](ClO <sub>4</sub> ) <sub>2</sub> <sup>c)</sup>	0,130 632	-0,021 -104	-0,050 -243	-0,044 -214	0,14

<sup>a)</sup> in nm; <sup>b)</sup> E = absorbance <sup>c)</sup> Obtained via II d by decomposition with 40% HClO<sub>4</sub>.

ORD. and CD. spectra should give further proof for the identity of the  $\alpha$ - and  $\beta$ -formes obtained as above. Unfortunately separation of the enantiomers of  $rac$ -[Ni(4,11-aneN<sub>4</sub>)] has not been achieved [6]; our attempts to separate the  $\beta$ -form by means of column chromatography on starch have also been unsuccessful. On the other hand, for the  $\alpha$ -form a slight activation could be obtained by the latter technique. The optical activity of these solutions may then be enhanced using the same procedure as described for (+)- or (-)-[Ni(4,11-dieneN<sub>4</sub>)]<sup>2+</sup>. Table 1 shows that the optical purity is only about 30%, but the mutarotation in alkaline medium takes place in the same way as for the substance which was separated into optical antipodes before reduction. This conclusion is also confirmed by ORD. and CD. spectra.

Finally, in order to determine whether the catalytic reduction of the two isomers of [Ni(4,11-dieneN<sub>4</sub>)]<sup>2+</sup> in acidic medium yields a mixture of products, as is the case of neutral or alkaline solutions, the *meso*- and *rac*-forms were reduced separately at pH  $\sim$  2. The solution obtained by reduction of the *meso*-form gives no reaction with oxalate and therefore contains only *meso*-[Ni-(4,11-aneN<sub>4</sub>)]<sup>2+</sup>, whereas the product of the reduced *rac*-form precipitates with oxalate at pH = 4. Precipitation is quantitative, and the absorption band at 446 nm, indicative of the planar complex, completely disappears. So, reduction in acidic medium, the relative configuration of the two new asymmetric carbon atoms in the product is entirely determined by the initial configuration of the two nitrogen atoms.

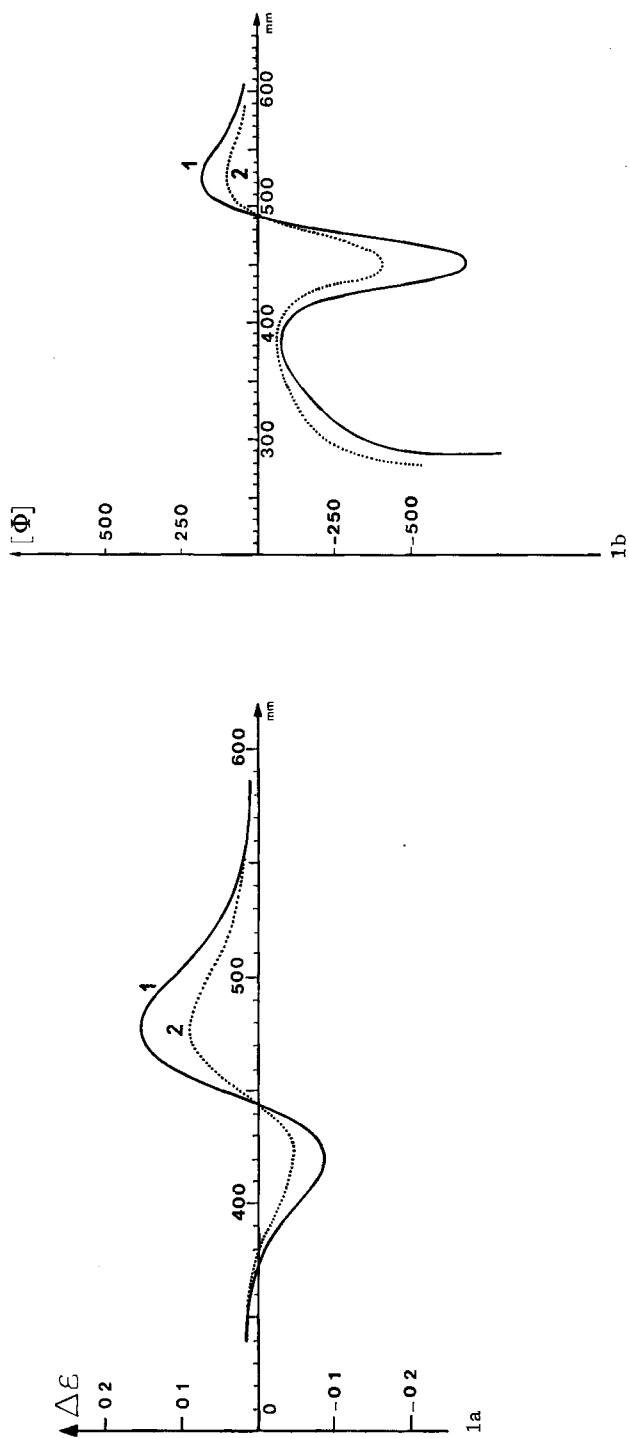
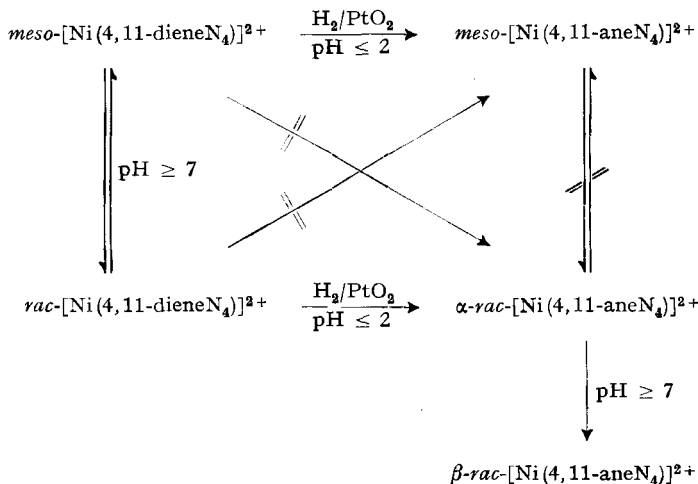


Fig. 1. ORD, (fig. 2a) and CD, (fig. 2b) spectra of stereoisomeric forms of  $\beta$ - $(-)$  $_{\text{abs}}[\text{Ni}(4,11\text{-aneN}_4)]^{2+}$  obtained: a) by resolution of  $[\text{Ni}(4,11\text{-dieneN}_4)]^{2+}$ , followed by reduction; b) reduction of  $[\text{Ni}(4,11\text{-dieneN}_4)]^{2+}$ , and then resolution of the  $\alpha$ - $[\text{Ni}(4,11\text{-aneN}_4)]^{2+}$ .

The higher yield of the *meso*-form found in the products obtained by reduction in alkaline solution must then be due to a higher rate of reduction for the *meso*-form compared with that for the *rac*-form. The reaction *scheme 1* may then be changed to that indicated in *scheme 2*.

*Scheme 2. Formation and interconversion of stereoisomers of [Ni(4,11-aneN<sub>4</sub>)]<sup>2+</sup> at pH ≤ 2*



**Discussion.** – The results obtained for catalytic hydrogenation of (+)- or (–)-[Ni(4,11-dieneN<sub>4</sub>)] show that the two hydrogen molecules must approach the complex from the same side which is necessarily that where no methyl group is in an axial position.

For the mechanism, different hypotheses may be proposed. If one supposes that addition of two hydrogen atoms on a C=N-double bond is *cis*, then a rapid inversion of the nitrogen atoms (set N(2)<sup>4</sup>) adjacent to the new asymmetric carbon atoms must necessarily occur, leading to the unstable  $\alpha$ -[Ni-(4,11-aneN<sub>4</sub>)]<sup>2+</sup>.

Assuming that the configuration of the N(2) atoms is determined by these new asymmetric carbon atoms, transformation into  $\beta$ -[Ni-(4,11-aneN<sub>4</sub>)]<sup>2+</sup> can only happen by inversion of the nitrogen atoms N(1), which are the original centers of dissymmetry. So we may speak of a threefold asymmetric induction: (i) the configuration of the N(1) atoms determines the conformation of the two six-membered chelate rings, which fixes the configuration of the asymmetric carbon atoms obtained in the reaction, (ii) these carbon atoms determine the configuration of the N(2) atoms and finally, (iii) the conformation of the six-membered rings changes from skew boat to chair form by inversion of the N(1) atoms [7].

In this connection, it seems interesting to note, that we can observe, in this system, a *Walden*-type inversion taking place without any participation of the centers involved in the reaction producing the inversion.

<sup>4</sup>) The two nitrogens adjacent to the geminal carbon atoms are designated as nitrogen set N(1) and the two nitrogen atoms adjacent to the two asymmetric carbon atoms are designated as nitrogen set N(2).

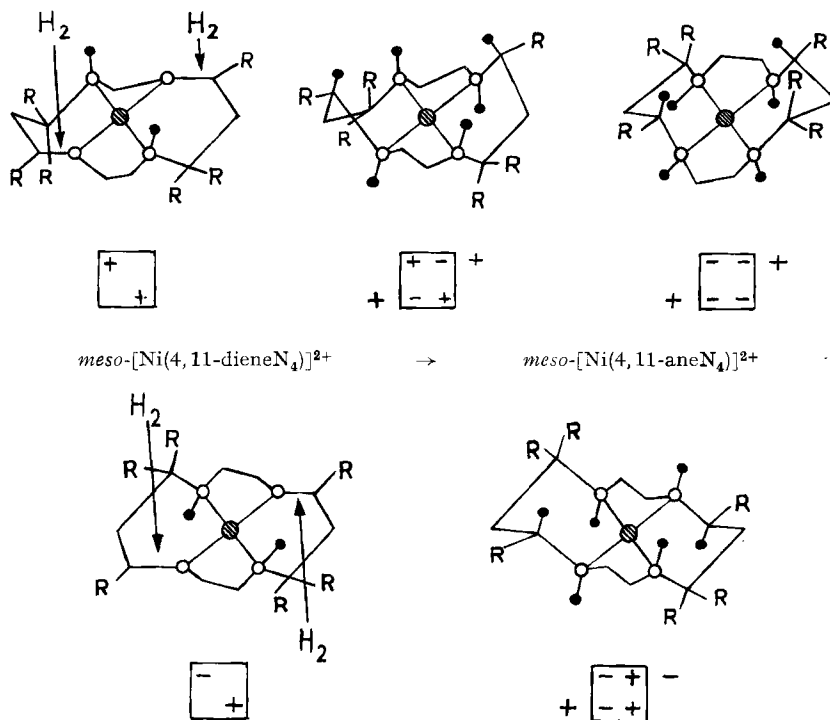
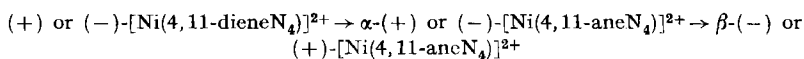


Fig. 2. Mechanism of the asymmetric hydrogenation of the diastereomers of  $[\text{Ni}(4,11\text{-dieneN}_4)]^{2+}$

Another possibility would be a *trans*-addition of the hydrogen atoms to each double bond, leading directly to  $\alpha\text{-}[\text{Ni}(4,11\text{-aneN}_4)]^{2+}$ .

For the  $meso\text{-}[\text{Ni}(4,11\text{-dieneN}_4)]^{2+}$  on the other hand, the approach of the two hydrogen molecules must occur from opposite sides of the plane of the complex. We may assume that for each double bond, the approach will occur from the opposite side relative to that containing the axial methyl group of the same six-membered chelate ring.

For further insight into the importance of steric hindrance in catalytic hydrogenation, it would be interesting to study similar systems, for example, optically active 5,12-dimethyl-1,4,8,11-tetra-azacyclotetradeca-4,11-diene-nickel(II) perchlorate, a compound containing no axial methyl groups.

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## 18. The Molecular and Crystal Structure of $\psi$ -Retroprogesterone

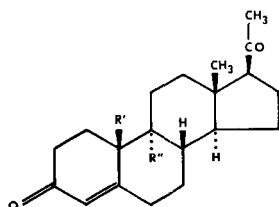
by H. P. Weber and E. Galantay

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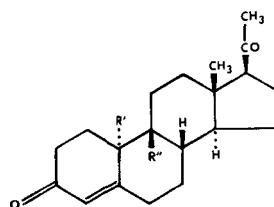
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**Summary.** The crystal structure of synthetic, racemic  $\psi$ -retroprogesterone (9 $\alpha$ -methyl-19-norprogesterone) has been determined by X-ray analysis and refined to  $R = 0.050$ . The analysis was carried out to establish the relative configuration at positions 9, 10 and 17 in connection with the biological activity of the compound.

An important chapter in the history of steroids [1] grew out from the recognition that the steric 'bulk', represented by the 10 $\beta$ -methyl group (*i.e.*, C(19)) of *corpus luteum* hormone progesterone (**1**) is actually detrimental to what has been defined as



- 1:** R' = CH<sub>3</sub>; R'' = H: progesterone  
**2:** R' = H; R'' = H: 19-norprogesterone  
**4:** R' = H; R'' = CH<sub>3</sub>:  $\psi$  = retroprogesterone



- 3:** R' = CH<sub>3</sub>; R'' = H: retroprogesterone

Table 1. *Crystal Data and Intensity Statistic*

$\psi$ -Retroprogesterone, C<sub>21</sub>H<sub>30</sub>O<sub>2</sub>, M = 314,469

Monoclinic, space group: P2<sub>1</sub>/c

Cell dimensions: a = 7.55(1), b = 22.93(3), c = 10.63(2) Å  
 $\beta = 107.5(1)^\circ$ , V = 1755 Å<sup>3</sup>  
 D<sub>m</sub> = 1.18(1), D<sub>x</sub> = 1.19 Z = 4

Intensities: total number of observations: 2734 (sin  $\theta/\lambda \leq 0.56$  Å<sup>-1</sup>)  
 number of significant reflexions: 1494 (I  $\geq 3\sigma(I)$ )  
 $\bar{B}$  (overall) = 4.3 Å<sup>2</sup>  
 $\langle |E| \rangle = 0.789$   $\langle |E^2 - 1| \rangle = 1.057$   $\langle E^2 \rangle = 1.050$