UDC 615.779.931-011

70. **Zen-ichi Horii, Tatsuo Sakai, and Yasumitsu Tamura**: Studies on Oxytetracycline and Related Compounds. XV.[*1] Synthesis and Stereoisomers of 1-Methyl-4-oxo-1,2,3,4-tetrahydro-2-naphthoic Acid.[*2]

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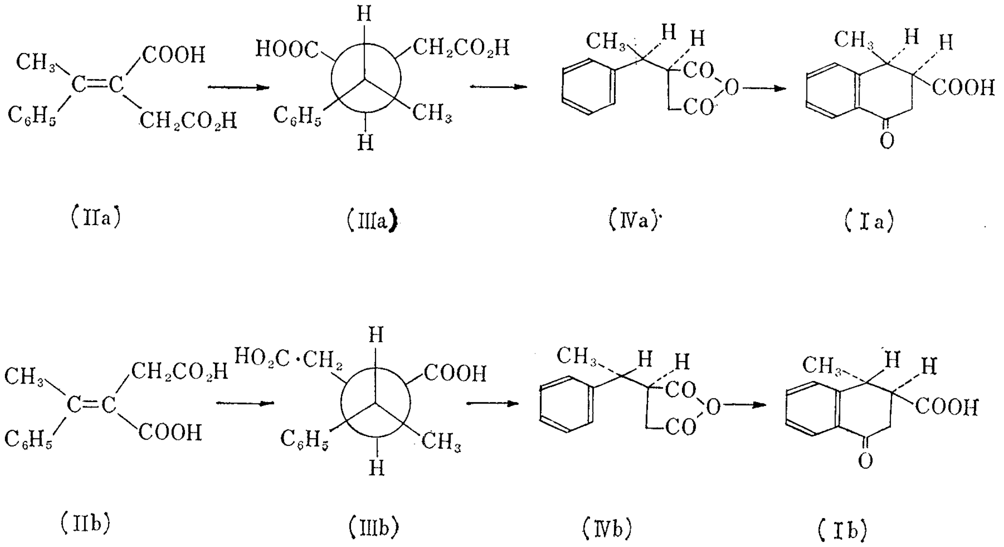
In the preceding work,[*1] the diastereoisomeric (α-methylbenzyl)succinic acids (IIIa and IIIb) were prepared and their configurations were determined. If these isomers are cyclized, *cis*- and *trans*-isomers of 1-methyl-4-oxo-1,2,3,4-tetrahydro-2-naphthoic acid (I) should be obtained. The compounds corresponding to these isomers of (I) were prepared by Urban and Beavers,1) but their structure was not reported. The present paper reports the syntheses of *cis*- and *trans*-isomers of (I) and the determination of their configurations.

In acid-catalyzed cyclization of (α-methylbenzyl)succinic acid (III), a six-membered ring would be expected to form in preference to a five-membered one2,3) and that the *threo*-isomer[*4] (IIIa) would form *cis*-tetralone (Ia) and the *erythro*-isomer[*4] (IIIb), *trans*-tetralone (Ib), as indicated by the Newman projections4) in Chart 1. Actually, when (IIIa) and (IIIb) were cyclized with aluminum chloride in nitrobenzene through their anhydrides (IVa and IVb), only the tetralone derivatives were obtained. Thus, the *threo*-isomer (IIIa), m.p. 167°, gave the *cis*-acid (Ia) of m.p. 170° in 75% yield and the *erythro*-isomer (IIIb), m.p. 174°, gave the *trans*-acid (Ib) of m.p. 108.5°. Other cyclization conditions using polyphos-



(IIa) (IIIa) (IVa) (Ia)

(IIb) (IIIb) (IVb) (Ib)

Chart 1.

[*1] Part XIV: This Bulletin, **9**, 451 (1961).

[*2] Presented before the 79th Annual Meeting of the Pharmaceutical Society of Japan, Osaka, April, 1959.

[*3] Toneyama, Toyonaka, Osaka-fu (堀井善一, 酒井立夫, 田村恭光).

[*4] *threo* and *erythro* were tentatively used to represent the structures of (IIIa) and (IIIb) shown in Chart 1, respectively.

1) R. S. Urban, E. M. Beavers: J. Am. Chem. Soc., **76**, 3042 (1954).

2) Org. Reactions, **2**, 116 (1944).

3) D. Lednicer, C. R. Hauser: J. Am. Chem. Soc., **80**, 3409 (1958).

4) M. S. Newman: J. Chem. Educ., **32**, 344 (1955).

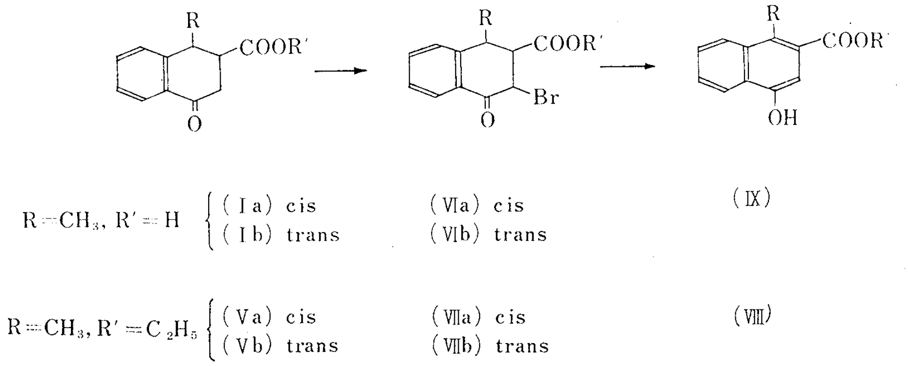


Chart 2

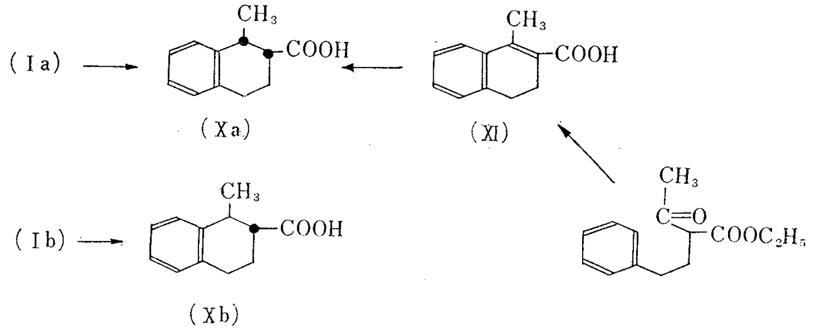


Chart 3.

phoric acid or sulfuric acid[5] gave a similar result, and (Ia) and (Ib) were obtained from (IIIa) and (IIIb), respectively.

The structures of (Ia) and (Ib) assigned above were further proved by the following two experimental procedures :

i) Aromatization of (Ia) and (Ib) by the method shown in Chart 2 gave the same naphthalene derivative.

Esterification of the *cis*-acid (Ia) and *trans*-acid (Ib) with ethanol and sulfuric acid produced an oily *cis*-ester (Va) and *trans*-ester (Vb) of m.p. 62.5°, respectively. Bromination with bromine in chloroform, followed by heating with 2,4,6-collidine converted both (Va) and (Vb) to ethyl 1-methyl-4-hydroxy-3-naphthoate (VIII), which was hydrolyzed to the known naphthoic acid[6] (IX). The preparation of naphthoic acid by bromination and subsequent dehydrobromination of the acid (Ia and Ib) was attempted, but in vain.

ii) The Clemmensen reduction of (Ia) furnished *cis*-1-methyl-1,2,3,4-tetrahydro-2-naphthoic acid (Xa) in a high yield which proved to be identical with a sample of (Xa) prepared by catalytic reduction or the Schwenk-Papa reduction of 1-methyl-3,4-dihydro-2-naphthoic acid.[7]

cis-1-Methyl-1,2,3,4-tetrahydro-2-naphthoic acid (Xa), m.p. 88°, was obtained in 90% yield by the Clemmensen reduction of (Ia) and also in a quantitative yield by the Schwenk-

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5) E. C. Horning, G. N. Walker : J. Am. Chem. Soc., **74**, 5147 (1952).

6) Z. Horii, Y. Tamura, K. Tanaka, T. Momose : This Bulletin, **7**, 281 (1959).

7) K. Auwers, K. Möller : J. prakt. Chem., [2], **102**, 124 (1925).

Papa reduction or by catalytic reduction of 1-methyl-3,4-dihydro-2-naphthoic acid[7] (XI) using palladium-carbon and acetic acid. The Clemmensen reduction of (Ib) gave the *trans*-acid (Xb), m.p. 82°, in 83% yield. These facts indicate that (Xa) and (Ia) should have *cis*-configurations in respect to the relative position of the methyl and carboxyl groups, and accordingly (Xb) and (Ib) should have *trans*-configurations.

Experimental

***threo*-(α-Methylbenzyl)succinic Anhydride (IVa)**——A solution of 1.5 g. of (IIIa) (*threo*, m.p. 167°) in 20 cc. of AcCl was allowed to stand overnight and AcCl was distilled off in a reduced pressure. Benzene was added and removed in a reduced pressure, and this procedure was repeated several times, giving a pale yellow oil. Two crystallizations from Et_2O furnished colorless prisms of m.p. 78.5~80.5°. *Anal.* Calcd. for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92. Found : C, 70.72; H, 5.89.

***cis*-1-Methyl-4-oxo-1,2,3,4-tetrahydro-2-naphthoic Acid (Ia)**——a) To a solution of 1.3 g. of (IVa) in 15 cc. of nitrobenzene, 2.5 g. of anhyd. $AlCl_3$ was added dropwise with stirring and ice-cooling. The reaction mixture was stirred for 2 hr. and allowed to stand overnight before pouring into ice-water containing HCl. The aqueous layer was extracted with Et_2O. The nitrobenzene layer and the Et_2O extracts were combined and subjected to steam-distillation. The residual aqueous solution was filtered while hot and concentrated to colorless blades, m.p. 157~163°. Yield, 0.9 g. (75%). Recrystallization from H_2O furnished colorless needles, m.p. 168.5~170°. The mixed melting point with a sample of (Ia) prepared according to the procedure of Urban and Beavers[1] showed no depression. *Anal.* Calcd. for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92. Found : C, 70.72; H, 5.96.

b) A mixture of 28 g. of polyphosphoric acid and (IVa) prepared from 1.4 g. of (IIIa) was stirred on a boiling water bath for 2 hr. The dark violet-brown reaction mixture obtained was cooled and poured into 100 cc. of ice-water with stirring, and the yellow-brown solid which separated was collected. The solid was washed with H_2O, dissolved in Et_2O, and dried over anhyd. Na_2SO_4. Evaporation of Et_2O gave 1.05 g. (82%) of a white solid, which was recrystallized from H_2O to colorless needles, m.p. 168~170°. The melting point was not depressed when mixed with a sample of (Ia) prepared by method (a) described above. *Anal.* Calcd. for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92. Found : C, 70.81; H, 5.90.

c) A mixture of 18 cc. of conc. H_2SO_4 and (IVa) prepared from 1.6 g. of (IIIa) was allowed to stand overnight at room temperature. The resulting dark red solution was poured into ice-water with stirring and extracted with Et_2O. The extract was washed with H_2O, dried over anhyd. Na_2SO_4, and concentrated, giving 1.05 g. (71%) of a white solid. Recrystallization from H_2O gave colorless needles, m.p. 168~170°. The melting point was not depressed when mixed with samples of (Ia) prepared by methods (a) and (b) described above. *Anal.* Calcd. for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92. Found: C, 70.68; H, 5.75.

***erythro*-(α-Methylbenzyl)succinic Anhydride (IVb)**——A pale yellow oil (crude IVb) was obtained from 0.8 g. of (IIIb) (*erythro*, m.p. 174°) and 10 cc. of AcCl by the same procedure as described for (IVa). This oil was used without further purification.

***trans*-1-Methyl-4-oxo-1,2,3,4-tetrahydro-2-naphthoic Acid (Ib)**——a) To a solution of 0.8 g. of the crude (IVb) in 10 cc. of nitrobenzene, 2 g. of anhyd. $AlCl_3$ was added dropwise with stirring and ice-cooling, and worked up as in the synthesis of (Ia) by method (a). Colorless needles, m.p. 79~82.5°; Yield, 0.5 g. (68%). Three recrystallizations from H_2O furnished colorless needles, m.p. 82.5~85°.[*1] When dried at 50° for 20 hr. over P_2O_5 *in vacuo*, it melted at 107~108.5°. *Anal.* Calcd. for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92. Found : C, 70.34; H, 5.78.

b) From 25 g. of polyphosphoric acid and (IVb) prepared from 1.2 g. of (IIIb), 0.6 g. (54%) of colorless needles, m.p. 89~104°, was obtained by the same procedure as method (b) in the synthesis of (Ia). Recrystallization from H_2O furnished crystals of m.p. 106~108°. The melting point was not depressed when mixed with the authentic sample obtained by method (a). *Anal.* Calcd. for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92. Found : C, 70.63; H, 5.74.

c) From 15 cc. of conc. H_2SO_4 and (IVb), prepared from 1.2 g. of (IIIb), 0.8 g. (73%) of colorless needles, m.p. 89~104°, was obtained by the same procedure as method (c) in the synthesis of (Ia). Recrystallization from H_2O furnished crystals of m.p. 105~108°. The melting point was not depressed when mixed with the authentic sample obtained by method (a). *Anal.* Calcd. for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92. Found : C, 70.83; H, 5.92.

Ethyl 1-Methyl-4-hydroxy-2-naphthoate (VIII)——i) A solution of 3.0 g. of (Ia), 0.5 cc. of conc. H_2SO_4, and 30 cc. of dehyd. EtOH was refluxed for 15 hr. and concentrated on a water bath to about 10 cc. The reaction mixture was diluted with 30 cc. of H_2O, neutralized with Na_2CO_3, and concentrated, yielding 2.9 g. (93%) of a pale yellow oil (Va), b.p$_{0.2}$ 160~161°.

To the solution of 0.5 g. of (Va) in 2 cc. of $CHCl_3$, a solution of 0.14 cc. of Br_2 in 2 cc. of $CHCl_3$ was added dropwise and the reaction mixture was stirred for 2 hr. after completion of the addition of Br_2. Et_2O was added to the mixture, which was washed successively with H_2O and 10% Na_2CO_3 solution, and dried over anhyd. Na_2SO_4. Distillation of the solvent gave a pale yellow oil (crude VIIa) in a quantitative yield.

A mixture of the crude (VIIa) and 3 cc. of 2,4,6-collidine was heated for 2 hr. on a water bath. When cool, two volumes of Et_2O was added to complete precipitation of inorganic salt. The precipitate was collected and washed with Et_2O. The Et_2O washings and the filtrate were combined, shaken several times with 5% HCl, and dried over anhyd. Na_2SO_4. Evaporation of Et_2O gave a brown solid; yield, 0.45 g. (91%). Recrystallization from benzene-petr. benzine gave 0.4 g. of colorless plates, m.p. 128~129.5°. *Anal.* Calcd. for $C_{14}H_{14}O_3$: C, 73.02; H, 6.13. Found : C, 73.11; H, 6.14.

ii) A solution of 2.7 g. of (Ib), 0.5 cc. of conc. H_2SO_4, and 25 cc. of dehyd. EtOH was heated under reflux for 12 hr. and worked up by the same procedure as that for (VIII) from (Ia). The yield of the crude ester (Vb), m.p. 59~61°, was 2.5 g. (89%). The analytical sample was recrystallized from petr. benzine to colorless plates, m.p. 60.5~62.5°. *Anal.* Calcd. for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found : C, 72.43; H, 6.82.

The crude bromo-ester (VIIb) was obtained as a pale yellow oil in a quantitative yield from the crude (Vb). Attempted crystallization from petr. benzine or Me_2CO-benzene was not successful. The crude (VIIb) gave 0.43 g. (95%) of (VIII) as a pale brown solid, which was recrystallized from benzene to 0.37 g. of colorless plates, m.p. 129~129.5°. The melting point was not depressed when mixed with a sample of (VIII) prepared from (Ia). *Anal.* Calcd. for $C_{14}H_{14}O_3$: C, 73.02; H, 6.13. Found : C, 73.15; H, 6.11.

1-Methyl-4-hydroxy-2-naphthoic Acid (IX)——A mixture of 0.35 g. of (VIII) and 7 cc. of 10% KOH solution was heated under reflux for 2.5 hr. The reaction mixture was washed with Et_2O and acidified with 15% HCl. The separated white crystals were collected and washed with H_2O. Yield, 0.3 g. (98%). Two recrystallizations from AcOH furnished colorless plates, m.p. 203~205°. The melting point was not depressed when mixed with the authentic sample of (IX), m.p. 202~206°, reported in a previous paper.[6] *Anal.* Calcd. for $C_{12}H_{10}O_3$: C, 71.28; H, 4.99. Found : C, 71.62; H, 5.00.

***cis*-1-Methyl-3-bromo-4-oxo-1,2,3,4-tetrahydro-2-naphthoic Acid (VIa)**——To a suspension of 1.6 g. of (Ia) in 5 cc. of $CHCl_3$ a solution of 0.43 cc. of Br_2 in 1 cc. of $CHCl_3$ was added. Discoloration of the first drop of Br_2 required about 40 min. After the addition of Br_2, an equal volume of Et_2O was added to the reaction mixture, washed with H_2O, and dried over anhyd. Na_2SO_4. Evaporation of Et_2O in a reduced pressure gave a pale brown solid, which crystallized from Me_2CO-benzene to 0.9 g. (41%) of colorless plates, m.p. 145~147°. *Anal.* Calcd. for $C_{12}H_{11}O_3Br$: C, 50.90; H, 3.92. Found: C, 51.22; H, 4.04.

Treatment of (VIa) with 2,4,6-collidine by the procedure of Haworth, *et al.*[8] gave only a resinous substance.

***trans*-1-Methyl-3-bromo-4-oxo-1,2,3,4-tetrahydro-2-naphthoic Acid (VIb)**——By the same procedure as that described for (VIa), 1.2 g. of (Ib) was brominated with 0.34 cc. of Br_2 in 4 cc. of $CHCl_3$. Discoloration of the first drop of Br_2 required about 1 hr. The resulting brown solid was recrystallized from Me_2CO-benzene to 0.5 g. (30%) of colorless plates, m.p. 158°. *Anal.* Calcd. for $C_{12}H_{11}O_3Br$: C, 50.90; H, 3.92. Found : C, 50.89; H, 3.83.

Treatment of (VIb) with 2,4,6-collidine by the procedure of Haworth, *et al.*[8] only gave a resinous substance.

***cis*-1-Methyl-1,2,3,4-tetrahydro-2-naphthoic Acid (Xa)**——i) A mixture of Zn-Hg (prepared from 30 g. of Zn and 3.0 g. of $HgCl_2$), 18 cc. of H_2O, 38 cc. of conc. HCl, 40 cc. of toluene, and 6.0 g. of (Ia) was heated under reflux for 30 hr. Three 9-cc. portions of conc. HCl was added at 6 hr. intervals during the refluxing period. When cool, 36 cc. of H_2O was added to the reaction mixture and the aqueous layer was extracted with Et_2O. The organic layer and the Et_2O extracts were combined, washed with H_2O, and dried over anhyd. Na_2SO_4. Distillation of the solvent yielded a pale brown viscous oil, which readily solidified. The solid was extracted with warm petr. ether and the extract was concentrated, yielding 5.0 g. (90%) of pale yellow crystals, m.p. 78~85°. Two recrystallizations from petr. ether furnished pale yellow plates, m.p. 86~88°. *Anal.* Calcd. for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found : C, 75.92; H, 7.60.

ii) 1.5 g. of (XI)[5] was reduced at 90° by the Schwenk-Papa method using 2 g. of Raney Ni alloy and 20 cc. of 8% NaOH solution. Upon working up as usual, 0.45 g. (89%) of a white solid, m.p. 77~82°, was obtained. Two recrystallizations from petr. ether furnished crystals of m.p. 85~87°. The melting point was not depressed when mixed with a sample of (Xa) prepared by the Clemmensen reduction of (Ia) (method (i)).

iii) A solution of 0.7 g. of (XI) in 50 cc. of 80% EtOH was subjected to catalytic hydrogenation using 0.7 g. of 5% Pd-C at atmospheric pressure. Uptake of one molar equivalent of H_2 required about 1 hr. The catalyst was filtered off, the filtrate was diluted with an equal volume of H_2O,

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[8] R. D. Haworth, B. Jones, Y. M. Way : J. Chem. Soc., **1943**, 10.

and concentrated to one-half its original volume in a reduced pressure in a water bath. The concentrated solution was weakly basified with Na_2CO_3, washed with Et_2O, acidified with HCl, and extracted with Et_2O. The extract was dried over anhyd. Na_2SO_4 and the solvent evaporated, giving 0.6 g. of a white solid, m.p. 80~84°. Recrystallization from petr. ether furnished colorless plates, m.p. 86~88°.

***trans*-1-Methyl-1,2,3,4-tetrahydro-2-naphthoic Acid (Xb)**——Four g. of (Ib) was reduced by refluxing with Zn-Hg (prepared from 20 g. of Zn and 2.0 g. of $HgCl_2$) for about 25 hr. as in the synthesis of (Xa) by method (i). The petr. ether-soluble substance (3.1 g; 83%) was obtained. Two recrystallizations from petr. ether furnished colorless plates, m.p. 80~82°. The melting point was depressed when mixed with a sample of (Xa); mixed m.p. 55~68°. *Anal.* Calcd. for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.92; H, 7.59.

Summary

The configurations of (Ia) and (Ib) were confirmed by the aromatization of these compounds to the same naphthalene derivative (IX) and by the transformation of (Ia) to *cis*-1-methyl-1,2,3,4-tetrahydro-2-naphthoic acid (XVIa), which was prepared by the *cis*-reduction of 1-methyl-3,4-dihydro-2-naphthoic acid (XVII).

(Received September 9, 1960)

UDC 547.92.07

71. Saburo Akagi and Kyosuke Tsuda: Steroid Studies. XXIII. Dehydrobromination of 7-Bromostigmasteryl Benzoate.

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Much work had hitherto been carried out by many workers on the dehydrobrominating reaction of 7α-bromocholesteryl benzoate. In the present investigation, dehydrobromination of 7-bromostigmasteryl benzoate, obtained by bromination with N-bromosuccimide, was carried out and details of the results are set herein.

Bromination of stigmasteryl benzoate was carried out with N-bromosuccimide in the same manner as for cholesteryl benzoate.[1~3] The resulting bromo compound was a stable one which showed optical rotation of $[\alpha]^{26}_{D}$ −123°. Comparing with $[\alpha]^{18}_{D}$ −172° for 7α-bromocholesteryl benzoate, it should have the same configuration as the more levorotatory 7α-bromocholesteryl benzoate.[2][*3]

When 7-bromostigmasteryl benzoate was treated with collidine, the chief reaction products were 7-dehydrostigmasteryl benzoate and 4,6,22-stigmastatrienyl benzoate. 7-De-

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[*3] Nowacki, *et al.* reported[4] that the more levorotatory 7-bromo derivatives of 3β-methoxycholest-5-ene and 3β-bromocholest-5-ene would be 7α-derivatives deduced from the results of their X-ray crystallography.

1) A. E. Bide, H. B. Henbest, E. R. H. Jones: J. Chem. Soc., **1948**, 1783; F. Hunziker: Helv. Chim. Acta, **38**, 1316 (1955); W. R. Nes: J. Am. Chem. Soc., **78**, 440 (1956); S. Bernstein, L. J. Binovi: J. Org. Chem., **14**, 433 (1949).

2) H. Schaltegger, F. X. Mullner: Helv. Chim. Acta, **34**, 1096 (1951); E. J. Corey, G. A. Gregoriou: J. Am. Chem. Soc., **81**, 3127 (1959).

3) K. Tsuda, K. Arima, R. Hayatsu: J. Am. Chem. Soc., **76**, 2934 (1954).

4) W. Nowacki, N. Burki: Chimia (Switz.), **10**, 254 (1956).