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Lactams. XVII.[1] Synthesis and Stereochemical Characterization of Diethyl *cis*- and *trans*-5-Ethyl-2-oxo-4-piperidinemalonate[2]

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The Michael addition of diethyl malonate to 1-acetyl-3-ethyl-2,3-dihydro-6(1*H*)-pyridone (**3**) in EtOH at 55° has been found to give the *trans* isomer (**4a**) and the *cis* isomer (**4b**) of diethyl 5-ethyl-2-oxo-4-piperidinemalonate in a ratio of 85 : 15. The stereochemical assignments were based on C-13 nuclear magnetic resonance spectroscopic evidence as well as chemical interrelation with substances of known configuration. The latter included decarbethoxylation of **4a** and **4b** in dimethyl sulfoxide–H_2O–NaCl to give the lactam monoesters **5a** and **5b**, conversion of **4a** into *trans*-1-benzyl-5-ethyl-2-oxo-4-piperidinemalonic acid (**7a**) through the lactim ether **9a** and its benzylated product **8a**, debenzylation of **7a** with sodium in liquid ammonia to give **6a**, and alkaline hydrolysis of **4a** to **6a**.

Keywords——dihydropyridone; lactam ester; Michael reaction; stereoselectivity; decarbethoxylation; lactim ether; benzylation; debenzylation; esterification; ^{13}C NMR

An interesting feature of our recent racemic syntheses of the Ipecac and *Alangium* alkaloids[4] and the structurally parallel indoloquinolizidine alkaloids[5] is that ethyl *dl-trans*-5-ethyl-2-oxo-4-piperidineacetate (**5a**) was used as a common starting material. Among the known synthetic routes[6] to this lactam ester is the synthesis from the lactam ketone **1** through **2**, **3**, and **4**, which was reported[6b] by one (T. F.) of the present authors in 1958. He was able to obtain a crystalline isomer (**4a**) of the title compound by the addition of diethyl malonate to the Michael acceptor **3**, but was unable to make a stereochemical assignment for the reasons described previously.[6b] In this paper we present evidence that **4a** has the *trans* configuration (in respect of the two side chains) and that a newly isolated crystalline isomer (**4b**) has the *cis* configuration.

The Michael acceptor **3** used in the present work was prepared from **1** according to a previously reported procedure,[6b] but the reduction of **1** to a diastereoisomeric mixture of the lactam alcohol **2** was effected by the use of $NaBH_4$ (EtOH, 0—20°, 4 hr) instead of Adams catalyst and hydrogen. Dehydration of the diastereoisomeric alcohols **2** with acetic anhydride (reflux, 4.5 hr) furnished **3** in 82% overall yield (from **1**). Condensation of **3** with diethyl malonate (NaOEt, EtOH, 55°, 1 hr) and separation of the resulting Michael products by column chromatography (alumina, benzene–EtOH; silica gel, AcOEt) provided **4a** (36% yield; mp 82—83°), which was identical with a sample previously characterized,[6b] together with **4b** (4% yield; mp 72.5—74°).

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5) T. Fujii, S. Yoshifuji, and H. Ito, *Heterocycles*, **7**, 149 (1977).
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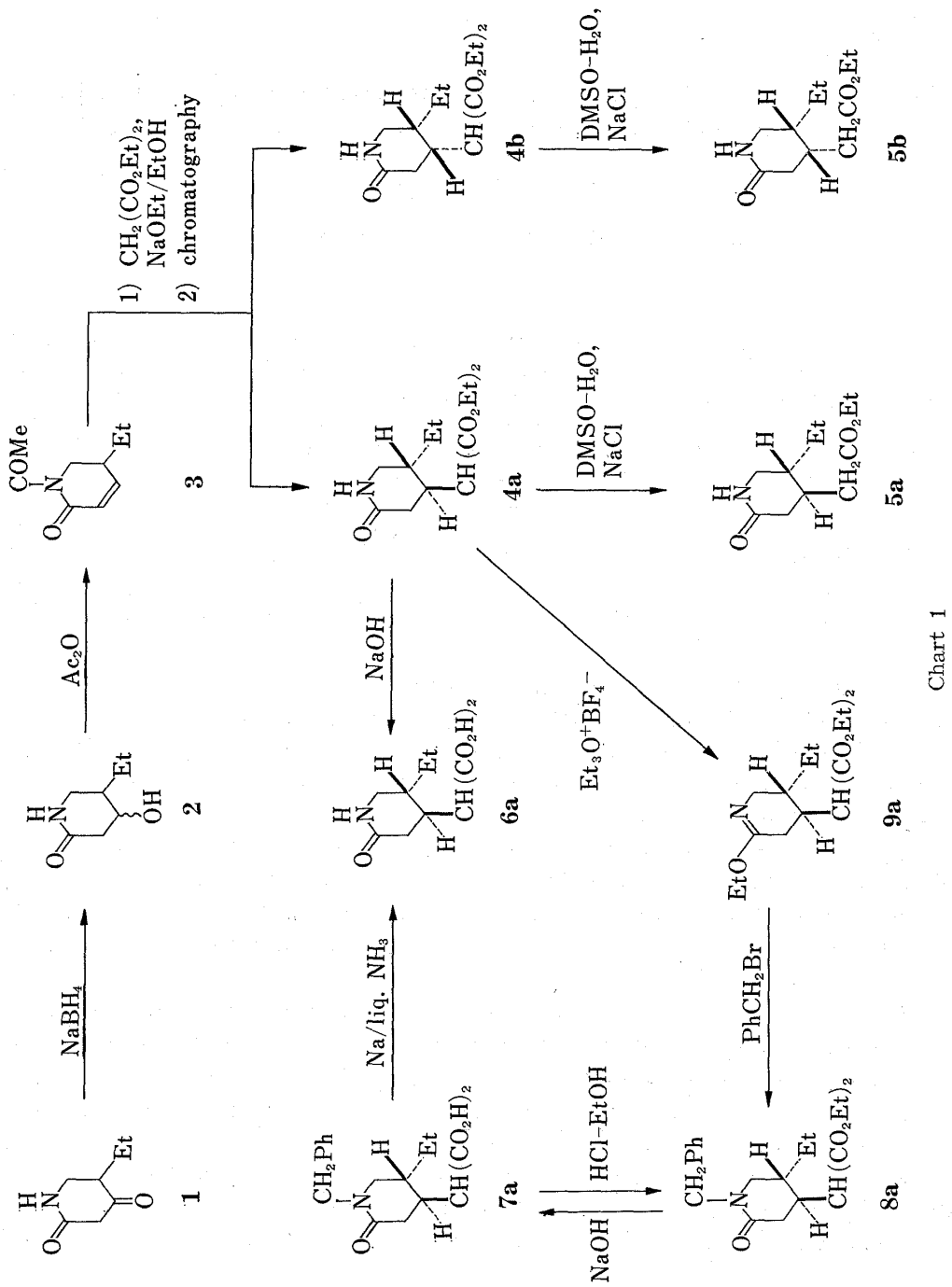

Chart 1

The two Michael products (**4a,b**) were characterized by appropriate analysis data for $C_{14}H_{23}NO_5$, and the mass spectra (MS), infrared (IR) spectra, and proton magnetic resonance (PMR) spectra also suggested that **4a** and **4b** were probably isomers with different stereochemical relationships between the two side chains. In the noise-decoupled C-13 nuclear magnetic resonance (NMR) spectrum in $CDCl_3$, **4a** exhibited methyl and methylene carbon signals of the $C_{(5)}$–Et group at 11.2 and 23.9 ppm (downfield from internal tetramethylsilane), whereas **4b** showed these signals at 11.8 and 20.5 ppm. Comparison of these band positions with those reported for the *trans* and the *cis* isomers of analogous compounds[6c,d,7] enabled us to assign the *trans* configuration to **4a** and the *cis* configuration to **4b**.

7) T. Fujii and S. Yoshifuji, *Chem. Pharm. Bull.* (Tokyo), **26**, 2253 (1978).

In order to confirm the structures of **4a,b**, we next attempted to interrelate them chemically with substances of known stereochemistry. Krapcho and co-workers[8] have recently reported that geminal diesters undergo decarbalkoxylation when heated with NaCl in wet dimethyl sulfoxide (DMSO) at 140—183°. Under similar reaction conditions (DMSO–H_2O–NaCl, 160°, 3 hr),[8b] the diester **4a** produced the monoester **5a** (92% yield; mp 93—94°), which was identical with authentic ethyl *trans*-5-ethyl-2-oxo-4-piperidineacetate.[6b,c] Likewise, **4b** afforded **5b** (88% yield) as an oil; this was identical with an authentic sample[7] of ethyl *cis*-5-ethyl-2-oxo-4-piperidineacetate.[9] The *trans* structure of **4a** was further supported by its conversion into the N-benzyl derivative **8a** *via* our recent "lactim ether method".[10] The steps involved were the ethylation of **4a** with triethyloxonium fluoborate[11] to give the lactim ether **9a** and the benzylation of **9a** with benzyl bromide (60°, 15 hr) to furnish **8a** (54% yield from **4a**) as an oil. This sample of **8a**, identical with that obtained quantitatively by the Fischer-Speier esterification of *trans*-1-benzyl-5-ethyl-2-oxo-4-piperidinemalonic acid (**7a**),[6d] furnished **7a** in 85% yield on alkaline hydrolysis.

In addition, when **7a** was treated with sodium in liquid ammonia according to the general procedure of Sugasawa and Fujii[12] for the debenzylation of N-benzylated lactams and amides, **6a** was obtained in 25% yield.[13] It was identical with a sample prepared previously[6b] by alkaline hydrolysis of **4a**. This interrelation of **4a** with **7a** through **6a** not only provides further evidence in support of the assignments of the *trans* configuration to **4a** and of the *cis* configuration to **4b**, but also made it possible to establish the stereochemistry of **6a**.

In the Michael reaction of **3** described above, the ratio of the two isomeric products was measured more precisely by C-13 NMR spectroscopy in a manner similar to that reported previously,[6c,d,7] and a ratio of **4a**:**4b**=85:15 was obtained. Although it was not clear whether the two isomers had been equilibrated[14] under the reaction conditions adopted, the observed stereoselectivity is roughly comparable to that reported for similar Michael reactions of analogous derivatives[15–17] and may reflect a preference for the formation of the *trans* isomer **4a** over that of the *cis* isomer **4b** in both the kinetically controlled and the thermodynamically controlled processes.[14]

Experimental

All melting points are corrected; boiling points are uncorrected. See ref. 10 for details of instrumentation and measurements. The following abbreviations are used: b=broad, d=doublet, m=multiplet, q=quartet, s=singlet, t=triplet.

1-Acetyl-3-ethyl-2,3-dihydro-6(1*H*)-pyridone (3)——To a stirred, ice-cooled solution of the lactam ketone **1**[6b] (2.12 g, 15 mmol) in EtOH (15 ml) was added portionwise $NaBH_4$ (288 mg, 7.61 mmol). After

8) *a*) A. P. Krapcho and A. J. Lovey, *Tetrahedron Lett.*, **1973**, 957; *b*) A. P. Krapcho, E. G. E. Jahngen, Jr., A. J. Lovey, and F. W. Short, *ibid.*, **1974**, 1091; *c*) A. P. Krapcho, J. F. Weimaster, J. M. Eldridge, E. G. E. Jahngen, Jr., A. J. Lovey, and W. P. Stephens, *J. Org. Chem.*, **43**, 138 (1978).

9) It is known[6c] that heating *cis*- or *trans*-5-ethyl-2-oxo-4-piperidineacetic acid at 180—210° for 8 min gives an equilibrated 33:67 mixture of the *cis* and *trans* acids, whereas the corresponding methyl or ethyl esters (**5a,b**) completely failed to undergo such *cis–trans* isomerization at 180° during 1 or 5 hr. We have also confirmed that neither the *cis* nor the *trans* isomer of the lactam monoester **5** undergoes isomerization under these particular decarbethoxylation conditions.

10) T. Fujii, S. Yoshifuji, and K. Yamada, *Chem. Pharm. Bull.* (Tokyo), **26**, 2071 (1978).

11) H. Meerwein, "Organic Syntheses," Coll. Vol. 5, ed. by H. E. Baumgarten, John Wiley and Sons, Inc., New York, 1973, p. 1080.

12) S. Sugasawa and T. Fujii, *Chem. Pharm. Bull.* (Tokyo), **6**, 587 (1958).

13) About 50% of the starting material (**7a**) was recovered from the reaction mixture. The low yield of **6a** and the recovery of a large amount of **7a** were probably due to the poor solubility of the disodium salt of **7a**, which was formed initially, in liquid ammonia.

14) H. O. House, "Modern Synthetic Reactions," 2nd ed., W. A. Benjamin, Menlo Park, 1972, pp. 595—623.

15) J. Ueyanagi, H. Nawa, R. Nakamori, T. Matsuoka, and Y. Ueno, *Yakugaku Zasshi*, **77**, 603 (1957).

16) A. R. Battersby and J. C. Turner, *J. Chem. Soc.*, **1960**, 717.

17) K. Kariyone, *Yakugaku Zasshi*, **83**, 398 (1963).

the mixture had been stirred at room temp. for 4 hr, AcOH (1 ml) was added under ice-cooling and the solvent was removed by vacuum distillation. The residue containing the resulting lactam alcohol(s) **2** was well dried in a desiccator. The total amount of the dried residue was treated with boiling Ac_2O (15 ml) for 4.5 hr. After excess Ac_2O had been removed with a flash evaporator, the residual gel was extracted with benzene by trituration and decantation. The insoluble solid was dissolved in H_2O (5 ml), and the solution was salted out with NaCl and then extracted with benzene. The combined extracts were dried over anhyd. Na_2SO_4 and evaporated *in vacuo* to leave a reddish brown oil (2.76 g). Vacuum distillation of the oil gave **3** (2.05 g, 82%) as a colorless oil, bp 139° (18 mmHg) [lit.[6b] bp 155—156° (32 mmHg)]. The IR spectrum of this sample was identical with that of authentic **3**.[6b]

Diethyl *trans*- and *cis*-5-Ethyl-2-oxo-4-piperidinemalonate (4a and 4b)——The Michael acceptor **3** (3.11 g, 186 mmol) was allowed to react with diethyl malonate (NaOEt/EtOH, 55°, 1 hr) and the reaction mixture was worked up as described previously.[6b] After first and second crops of the *trans* isomer **4a** had been isolated from the ethereal solution of the distilled product [2.75 g, 52% yield; bp 176—179° (0.085 mmHg)], the mother liquor was concentrated *in vacuo* to leave a light brown oil (847 mg). The oil was purified by column chromatography [alumina (85 g), benzene–EtOH (20: 1, v/v)] and fractions showing a spot of *Rf* 0.49 on a thin-layer chromatography (TLC) plate [alumina, benzene–EtOH (20: 1, v/v)] were collected. The fractions were combined and evaporated *in vacuo*. The resulting oily residue was chromatographed on a column packed with silica gel (85 g) using AcOEt as an eluent. The *cis* isomer **4b** was found in earlier fractions [*Rf* 0.66 on a silica gel TLC plate (AcOEt)], and the *trans* isomer **4a** in later fractions (*Rf* 0.56). The two products were characterized as follows.

The *trans* isomer **4a** (1.89 g, 36% yield) was recrystallized from hexane–ether (3: 1, v/v) to give colorless prisms, mp 82—83° (lit.[6b] mp 80—81.5°), identical (by mixed melting-point test, IR spectrum, and TLC) with a previous sample;[6b] IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3412 (NH), 1739 and 1721 (ester CO), 1661 (lactam CO); PMR ($CDCl_3$) δ: 0.93 (3H, t, J=7 Hz, $CCH_2\underline{Me}$), 1.28 (6H, t, J=7 Hz, two $OCH_2\underline{Me}$'s), 2.88—3.58 (2H, m, $H_{(6)}$'s), 3.56 [1H, d, J=7 Hz, $C\underline{H}(CO_2Et)_2$], 4.21 (4H, q, J=7 Hz, two $OC\underline{H}_2Me$'s), 7.16 (1H, b, NH); ^{13}C NMR (see the text).

The *cis* isomer **4b** (211 mg, 4% yield) was recrystallized from hexane–ether (3: 1, v/v) to give colorless prisms, mp 72.5—74°; MS *m/e*: 285 (M^+); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3408 (NH), 1725 (ester CO), 1666 (lactam CO); PMR ($CDCl_3$) δ: 0.95 (3H, t, J=7 Hz, $CCH_2\underline{Me}$), 1.27 and 1.30 (3H each, t, J=7 Hz, two $OCH_2\underline{Me}$'s), 2.94—3.54 (2H, m, $H_{(6)}$'s), 3.31 [1H, d, J=7 Hz, $C\underline{H}(CO_2Et)_2$], 4.16 and 4.24 (2H each, q, J=7 Hz, two $OC\underline{H}_2Me$'s), 7.00 (1H, b, NH); ^{13}C NMR (see the text). *Anal.* Calcd. for $C_{14}H_{23}NO_5$: C, 58.93; H, 8.13; N, 4.91. Found: C, 58.66; H, 8.06; N, 4.87.

In a separate experiment, a portion (128 mg) of the distilled product described above was dissolved in $CDCl_3$ (2 ml) prior to recrystallization and chromatographic purification. Quantitative analysis of the resulting $CDCl_3$ solution by means of ^{13}C FT NMR spectroscopy was carried out as described previously,[6c,d,7] and showed the solution to contain an 85: 15 mixture of **4a** and **4b**.

Ethyl *trans*-5-Ethyl-2-oxo-4-piperidineacetate (5a)——A mixture of **4a** (143 mg, 0.5 mmol) and powdered NaCl (6 mg, 0.1 mmol) in Me_2SO (1 ml) containing H_2O (18 mg, 1 mmol) was heated at 160° (bath temp.) for 3 hr. After cooling, the reaction mixture was diluted with H_2O (10 ml), salted out with NaCl, and extracted with ether. The ethereal extracts were washed with sat. aq. NaCl, dried over anhyd. Na_2SO_4, and concentrated *in vacuo* to leave **5a** (98 mg, 92%) as a colorless solid, mp 92—93°. Recrystallization of the solid from isopropyl ether yielded colorless pillars of mp 93—94°, identical (by mixed melting-point test, TLC, and IR spectrum) with authentic **5a**.[6b,c,d]

Ethyl *cis*-5-Ethyl-2-oxo-4-piperidineacetate (5b)——The lactam diester **4b** was decarbethoxylated as described above for the reaction **4a**→**5a**, producing **5b** (88% yield) as a colorless oil. This sample was identical with authentic **5b**[7] on comparison of their TLC behavior and IR spectra.

***trans*-5-Ethyl-2-oxo-4-piperidinemalonic Acid (6a)**——To a stirred solution of **7a**[6d] (3.32 g, 10.4 mmol) in liquid NH_3 (1.6 l) was added, without external cooling, Na (1.25 g, 0.0544 g.-atom) in small pieces over a period of 3 hr. The resulting turbid mixture was allowed to evaporate and the residual solid was dissolved in H_2O (20 ml). The aqueous solution was washed with ether, made acid to Congo red paper with conc. aq. HCl, and extracted with AcOEt. NaCl was added to the residual aqueous solution until it was almost saturated, and the resulting mixture was kept in a refrigerator for a day. The colorless prisms that deposited were collected by filtration, washed with a little cold H_2O, and dried to give **6a** (590 mg, 25%) of mp 142—143° (dec.), identical (by mixed melting-point test and IR spectrum) with a sample obtained previously[6b] by alkaline hydrolysis of **4a**.

The AcOEt extracts described above were washed with H_2O, dried over anhyd. Na_2SO_4, and concentrated *in vacuo* to recover the starting material **7a** (1.69 g, 51%).

Diethyl *trans*-6-Ethoxy-3-ethyl-2,3,4,5-tetrahydro-4-pyridinemalonate (9a)——A solution of triethyloxonium fluoborate[11] (1.1 g, 5.8 mmol) and **4a** (566 mg, 1.98 mmol) in CH_2Cl_2 (6 ml) was refluxed for 4 hr. The solvent was removed by vacuum distillation, 10% aq. K_2CO_3 (7 ml) was added to the residue under ice-cooling, and the mixture was extracted with CH_2Cl_2. The CH_2Cl_2 extracts were dried over anhyd. Na_2SO_4, and concentrated *in vacuo* to leave **9a** (619 mg) as a yellowish brown, thick oil, IR ν_{max}^{film} cm^{-1}: 1746 and 1727 (ester CO), 1684 (C=N). The oil was used directly in the next benzylation step without further purification.

Diethyl *trans*-1-Benzyl-5-ethyl-2-oxo-4-piperidinemalonate (8a)——i) From **9a**: A mixture of **9a** (615 mg, 1.96 mmol) and benzyl bromide (1.10 g, 6.43 mmol) was heated at 60° (bath temp.) for 15 hr. To remove the excess benzyl bromide, the reaction mixture was stirred with pyridine (5 ml) at room temp. overnight, and concentrated *in vacuo*. The residue was dissolved in benzene and the benzene solution was washed successively with 5% aq. HCl and H_2O, and dried over anhyd. Na_2SO_4. Removal of the solvent from the dried benzene solution by evaporation left a pale brown oil (601 mg), which was purified by column chromatography [silica gel (60 g), AcOEt–hexane (1: 5; 1: 1, v/v)] to furnish **8a** (399 mg, 54% overall yield from **4a**) as an oil. This sample was identical (by TLC and IR spectrum) with that prepared by method (ii) (see below).

ii) From **7a**: A solution of **7a**[6d] (639 mg, 2 mmol) in 10% (w/w) ethanolic hydrogen chloride (20 ml) was kept at 15° for 24 hr. The solution was then concentrated *in vacuo*, H_2O (20 ml) was added to the residue, and the aqueous mixture was extracted with benzene. The benzene solution was washed successively with sat. aq. $NaHCO_3$ and H_2O, dried over anhyd. Na_2SO_4, and concentrated *in vacuo* to leave **8a** (750 mg, 100%) as a colorless, thick oil, MS *m/e*: 375 (M^+); IR ν_{max}^{film} cm^{-1}: 1727 (ester CO), 1642 (lactam CO); PMR ($CDCl_3$) δ: 0.80 (3H, t, J=7 Hz, $CCH_2\underline{Me}$), 1.27 and 1.28 (3H each, t, J=7 Hz, two $OCH_2\underline{Me}$'s), 2.83—3.44 (2H, m, $H_{(6)}$'s), 3.54 [1H, d, J=6.5 Hz, $C\underline{H}(CO_2Et)_2$], 4.24 and 4.25 (2H each, q, J=7 Hz, two $OC\underline{H}_2Me$'s), 4.51 and 4.71 (1H each, AB type d's, J=15 Hz, $C\underline{H}_2Ph$), 7.30 (5H, s, Ph).

***trans*-1-Benzyl-5-ethyl-2-oxo-4-piperidinemalonic Acid (7a)**——A solution of **8a** (360 mg, 0.96 mmol), derived from **9a** by benzylation, in EtOH (2 ml) containing 2 N aq. NaOH (1 ml) was kept at 40° for 16 hr. The solvent was removed from the reaction mixture by evaporation, and H_2O (2 ml) was added to the residue. The aqueous solution was acidified (pH 1) with 10% aq. HCl and extracted with $CHCl_3$. After washing with H_2O and drying over anhyd. Na_2SO_4 for a while, the $CHCl_3$ solution was concentrated *in vacuo* to leave a colorless solid (262 mg, 85%). Recrystallization from 35% (v/v) aq. EtOH provided **7a** as colorless prisms, mp 152—153° (dec.), which were identical (by mixed melting-point test and IR spectrum) with an authentic sample.[6d]

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