36. *Steroids and Related Compounds. Part XIII.* The Preparation of 21-Hydroxypregna-4 : 17-dien-3-one.*

By D. K. Patel, V. Petrow, R. Royer, and (Mrs.) I. A. Stuart-Webb.

Novel methods for the conversion of 3β-acetoxyandrost-5-en-17-one into pregna-5 : 17-diene-3β : 21-diol (I) and 21-hydroxypregna-4 : 17-dien-3-one (VIII) are described. Attempts to hydroxylate an ethyl 20-cyanopregn-17-en-21-oate (V) in order to obtain an ethyl 17α-hydroxy-20-ketopregnan-21-oate are reported

In the course of studies (Magrath, Morris, Petrow, and Royer, *J.*, 1950, 2393) on the preparation of "Compound S" from 3β-acetoxyandrost-5-en-17-one, the latter was condensed with ethoxyethynylmagnesium bromide, and the resulting 3β-acetoxy-17α-ethoxyacetylenylandrost-5-en-17β-ol treated with ethanolic sulphuric acid. Reduction of the resultant ethyl 3β-acetoxypregna-5 : 17-dien-21-oate (II; R = Ac) with lithium aluminium hydride furnished pregna-5 : 17-diene-3β : 21-diol (I) (cf. Heusser, Eichenberger, and Plattner, *Helv. Chim. Acta*, 1950, **33**, 370, 1088), which was regarded as a key intermediate in this series of reactions. From it, by partial acetylation and oxidation, we hoped to obtain 21-hydroxypregna-4 : 17-dien-3-one (VIII), the facile conversion of which into "Compound S" has already been described by Miescher and Schmidlin (*ibid.*, p. 1840).

In contrast to results obtained with such compounds as 3α : 21-dihydroxypregn-17-en-11-one (Sarett, *J. Biol. Chem.*, 1946, **162**, 601), preferential acylation of the $C_{(21)}$-hydroxyl group of (I) proved only partly successful. Careful treatment with acetic anhydride or *p*-nitrobenzoyl chloride in pyridine gave only the diacyl derivatives admixed with unchanged material. Triphenylmethyl chloride in pyridine surprisingly failed to react. Succinic anhydride in pyridine gave an unsatisfactory yield of a product to which the structure 3β-hydroxypregna-5 : 17-diene-21-yl hydrogen succinate has been assigned

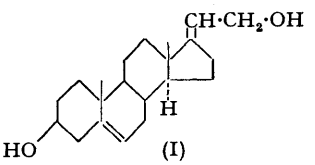
* Part XII, *J.*, 1951, 901.

(cf. Sarett, *loc. cit.*). Attempts to oxidise this compound by the Oppenauer method, however, proved unsuccessful, no doubt owing to its sparing solubility in appropriate solvents.

We, therefore, turned our attention to an alternative route to (VIII), employing ethyl 3β-hydroxypregna-5 : 17-dien-21-oate (II; R = H) as a starting material. Oppenauer oxidation of this compound proceeded with great facility to furnish ethyl 3-ketopregna-4 : 17-dien-21-oate (III) in excellent yield. Protection of the 3-keto-group in this compound before reduction of the carbethoxy-group was effected by conversion into the enol ether (see Meystre and Miescher, *Helv. Chim. Acta*, 1949, **32**, 1758) from which, by reaction with lithium aluminium hydride, 3-ethoxypregna-3 : 5 : 17-trien-21-ol (IV) was readily obtained in 90% yield. However, the final step in this series of reactions, the regeneration of the 3-keto-group, could not be effected by the usual procedure employing methanolic hydrochloric acid. In place of (VIII), an αβ-unsaturated ketone containing one methoxyl group was obtained, to which the formulation 21-methoxypregna-4 : 17-dien-3-one has been assigned. Conversion of (IV) into (VIII) was ultimately achieved by simply dissolving the enol ether in ordinary chloroform, which evidently contained sufficient acid to catalyse the required hydrolysis.

An alternative approach to pregna-5 : 17-diene-3β : 21-diol (I) consisted of condensation of 3β-acetoxyandrost-5-en-17-one with compounds of the cyanoacetic ester type. Initial experiments revealed that the reaction could not be effected by means of catalysts such as piperidine acetate, acetic anhydride, or zinc chloride or by the procedure employed by Smith and Webb (*J.*, 1948, 1358) in the bile acid series. However, refluxing 3β-acetoxyandrost-5-en-17-one with ethyl cyanoacetate in benzene in the presence of a little acetic acid, with regular additions of ammonium acetate (cf. Cragoe, Robb, and Sprague, *J. Org. Chem.*, 1950, **15**, 381) readily gave ethyl 3β-acetoxy-20-cyanopregna-5 : 17-dien-21-oate (V; R = CO_2Et) in nearly quantitative yield. This structure was confirmed by (i) careful hydrolysis followed by Oppenauer oxidation, to give ethyl 20-cyano-3-ketopregna-4 : 17-dien-21-oate, and (ii) hydrolysis to give 20-cyano-3β-hydroxypregna-5 : 17-dien-21-oic acid, characterised by conversion into a highly crystalline methyl ester.

Hydroxylation of (V; R = CO_2Et) with osmium tetroxide was accompanied by fission * of the $C_{(17)}$–$C_{(20)}$ bond with formation, after acetylation, of 3β : 6α-diacetoxy-5α-



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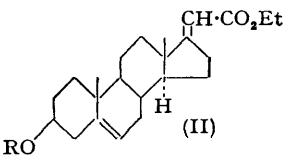

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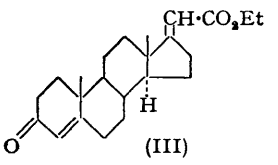

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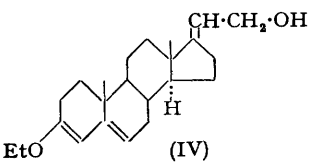

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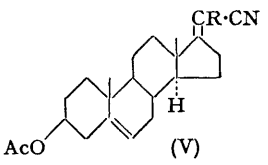

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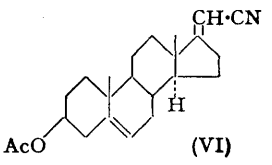

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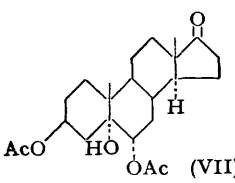

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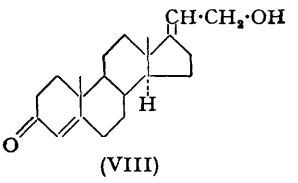

(VIII)

hydroxyandrostan-17-one (VII). Its behaviour on treatment with this reagent thus stands in marked contrast to that established by Sarett (*loc. cit.*) for the related 20-cyanopregn-17-en-21-ols, where formation of the ketol side chain typical of cortisone occurs.

* Possibly by the sodium sulphite used in working-up.

Similar results were obtained employing ethyl 3β-acetoxy-20-cyano*allo*pregn-17-en-21-oate (from 3β-acetoxyandrostan-17-one and ethyl cyanoacetate), hydroxylation of which likewise led to removal of the pregnane side chain with formation of 3β-acetoxyandrostan-17-one.

Decarboxylation of 20-cyano-3β-hydroxypregna-5 : 17-dien-21-oic acid invariably gave a complex mixture of products. By distillation at 140—160°/10^{-3} mm., however, followed by fractional crystallisation and acetylation, 3β-acetoxy-20-cyanopregna-5 : 17-diene (VI) could be obtained in *ca.* 30% yield; however, the cyano-group proved resistant to ethanolic sulphuric acid. Reduction with lithium aluminium hydride, followed by treatment with nitrous acid and acetylation, gave 3β : 21-diacetoxypregna-5 : 17-diene (cf. I).

Condensation of 3β-acetoxyandrost-5-en-17-one with malononitrile furnished 3β-acetoxy-20 : 20-dicyanopregna-5 : 17-diene (V; R = CN) in 95% yield. The cyano-groups present in this compound likewise (cf. VI above) proved resistant to hydrolysis.

By reaction of 3β-acetoxyandrost-5-en-17-one with ethyl cyanothiolacetate, ethyl 3β-acetoxy-20-cyanopregna-5 : 17-diene-20-thiolcarboxylate (V; R = CO·SEt) was readily obtained, but this compound could not be converted into the corresponding 3β-acetoxy-20-cyanopregna-5 : 17-dien-21-ol owing to concomitant reduction of the cyano-group.

Experimental

M. p.s are uncorrected. Ultra-violet absorption spectra were determined in alcoholic solution by Dr. R. E. Stuckey and Mr. P. Stross, B.Sc., Analytical Department, The British Drug Houses, Ltd.

3β : 21-*Di*-p-*nitrobenzoyloxypregna*-5 : 17-*diene*, prepared by treating pregna-5 : 17-diene-3β : 21-diol (1 g.) in pyridine (20 ml.) with *p*-nitrobenzoyl chloride (1·05 mols.) for 24 hours at room temperature, formed crystals (from benzene), m. p. 206—207° (Found : C, 68·5; H, 5·9; N, 4·6. $C_{35}H_{38}O_8N_2$ requires C, 68·4; H, 6·2; N, 4·6%). Unchanged material was recovered from the mother-liquors.

3β-*Hydroxypregna*-5 : 17-*diene*-21-*yl hydrogen succinate*, prepared by treating (I) (4·3 g.) for 2 hours at 28—29° with pyridine (22 ml.) saturated with succinic anhydride, formed crystals, m. p. 210—211°, $[\alpha]_D^{22}$ −48° ± 2° (*c*, 1·024 in dioxan), from ethanol (Found : C, 71·0; H, 8·8. $C_{25}H_{36}O_5$ requires C, 72·1; H, 8·7%).

Ethyl 3-*Ketopregna*-4 : 17-*dien*-21-*oate* (III).—Ethyl 3β-hydroxypregna-5 : 17-dien-21-oate (10 g.) in *cyclo*hexanone (66 ml.) was heated under reflux for 1 hour with a solution of aluminium *iso*propoxide (11 g.) in toluene (44 ml.). The mixture was then poured into water and steam-distilled for 4 hours. The non-volatile fraction was extracted with chloroform, and the product purified by passage in benzene through a column of alumina (activated; *ex* B.D.H.; 250 g. in a column 30 mm. wide), which was developed with benzene–ether. Evaporation of the bulked benzene and benzene–ether eluates left *ethyl* 3-*ketopregna*-4 : 17-*dien*-21-*oate* (70%), m. p. 181° (from methanol), $[\alpha]_D^{23}$ +88° (*c*, 1·044 in chloroform), $\lambda_{max.}$ 230 mμ (log ε = 4·4) (Found : C, 77·7; H, 9·2. $C_{23}H_{32}O_3$ requires C, 77·5; H, 9·0%).

Ethyl 3β-*Ethoxypregna*-3 : 5 : 17-*trien*-21-*oate*.—A mixture of the foregoing ester (3·0 g.), toluene-*p*-sulphonic acid (300 mg.) and ethyl orthoformate (30 ml.) was heated under reflux for 1 hour, whereafter the mixture was evaporated under reduced pressure. The partly crystalline residue was covered with methanol, one drop of pyridine added, and the mixture left overnight, after which the separated solids were collected, washed carefully with the minimum quantity of ice-cold methanol, and purified by crystallisation from methanol–ether. *Ethyl* 3β-*ethoxypregna*-3 : 5 : 17-*trien*-21-*oate* (81%) has m. p. 129—130°, $[\alpha]_D^{22}$ −177° (*c*, 0·580 in pyridine), $\lambda_{max.}$ 232 mμ (log ε = 4·5) (Found : C, 77·8; H, 9·3. $C_{25}H_{36}O_3$ requires C, 78·1; H, 9·4%).

3β-*Ethoxypregna*-3 : 5 : 17-*trien*-21-*ol* (IV).—A solution of the foregoing compound (1·6 g.) in dry ether (25 ml.) was added dropwise with stirring during 15 minutes to lithium aluminium hydride (800 mg.) in ether (100 ml.), and the mixture refluxed for 30 minutes. The product (91%), isolated in the usual way, was purified from methanol–ether, to give 3β-*ethoxypregna*-3 : 5 : 17-*trien*-21-*ol*, m. p. 118—119°, $[\alpha]_D^{22}$ −153° (*c*, 0·444 in pyridine), $\lambda_{max.}$ 241 mμ (log ε = 4·3) (Found : C, 80·2; H, 10·0. $C_{23}H_{34}O_2$ requires C, 80·7; H, 9·7%).

21-*Hydroxypregna*-4 : 17-*dien*-3-*one* (VIII).—A solution of the foregoing enol ether (250 mg.) in " reagent-grade " chloroform (50 ml.) was kept at room temperature for 72 hours. After evaporation of the solvent the pale yellow oil was treated with hexane containing a trace of

acetone, to give 21-hydroxypregna-4 : 17-dien-3-one (63%), needles, m. p. 137°, $[\alpha]_D^{24}$ +112° (*c*, 0·838 in ethanol) (Found : C, 79·9; H, 9·5. Calc. for $C_{21}H_{30}O_2$: C, 80·3; H, 9·6%). Ruzicka and Muller (*Helv. Chim. Acta*, 1939, **22**, 416) give m. p. 138—139° (corr.), $[\alpha]_D$ +116° ± 2° (in ethanol).

21-*Methoxypregna*-4 : 17-*dien*-3-*one*.—A solution of 3β-ethoxypregna-3 : 5 : 17-trien-21-ol (500 mg.) in methanol (30 ml.) was heated under reflux with 2N-hydrochloric acid for 1 hour. Dilution with water, followed by extraction with ether, afforded an oil which was dissolved in benzene and chromatographed on alumina (9 g. in a column of 12 mm. diameter). The benzene and benzene–ether eluates yielded 21-*methoxypregna*-4 : 17-*dien*-3-*one* (27%), m. p. 106—107° (from hexane), $[\alpha]_D^{24}$ +103° (*c*, 0·428 in ethanol) (Found : C, 79·6; H, 9·8; OMe, 11·1. $C_{22}H_{32}O_2$ requires C, 80·5; H, 9·8; OMe, 9·5%). The presence of an αβ-unsaturated ketonic residue in the compound was indicated by the formation of a scarlet dinitrophenylhydrazone.

Ethyl 3β-*Acetoxy*-20-*cyanopregna*-5 : 17-*dien*-21-*oate* (V; R = CO_2Et).—3β-Acetoxyandrost-5-en-17-one (6·6 g.) and ethyl cyanoacetate (4·5 g.) in benzene (80 ml.) and pure acetic acid (19 ml.) were heated under reflux in a flask fitted with a Dean and Stark separator, ammonium acetate (7 g.) being added every 3 hours during a total of 30 hours. The cooled reaction mixture was poured on ice, and the product isolated with ether. Crystallisation from ethanol afforded *ethyl* 3β-*acetoxy*-20-*cyanopregna*-5 : 17-*dien*-21-*oate* (90—95%), m. p. 182—184°, $[\alpha]_D^{27}$ −39·4° (*c*, 0·674 in chloroform), $\lambda_{max.}$ 238 mμ (log ε = 4·1) (Found : C, 73·5; H, 8·0; N, 3·4. $C_{26}H_{35}O_4N$ requires C, 73·4; H, 8·2; N, 3·3%).

20-*Cyano*-3β-*hydroxypregna*-5 : 17-*dien*-21-*oic Acid*.—To a solution of the foregoing ester (1·0 g.) in methanol (15 ml.), potassium carbonate (600 mg.) in water (5 ml.) was added and the mixture heated under reflux for 30 minutes. Addition of dilute sulphuric acid (to pH 2—3) gave 20-*cyano*-3β-*hydroxypregna*-5 : 17-*dien*-21-*oic acid* (80%), m. p. 253—254° (decomp.) (from acetone) (Found : C, 73·9; H, 8·2. $C_{22}H_{29}O_3N$ requires C, 74·3; H, 8·2%).

The *methyl* ester, crystallised from ether–light petroleum, m. p. 190—192°, $[\alpha]_D^{20}$ −44·8° (*c*, 1·084 in chloroform) (Found : C, 74·5; H, 8·3. $C_{23}H_{31}O_3N$ requires C, 74·8; H, 8·5%), was obtained by treating a suspension of the acid in dry ether with excess of diazomethane.

Ethyl 20-*Cyano*-3-*ketopregna*-4 : 17-*dien*-21-*oate*.—The ester (V; R = CO_2Et) (6·4 g.) dissolved in absolute ethanol (10 ml.) containing sulphuric acid (0·75 ml.; *d* 1·84) was heated under reflux for 2 hours, and then the mixture was poured into ice-water. The neutral fraction, isolated in the usual way, gave the 3-hydroxy-ester (85—90%), m. p. 151—153°, from aqueous ethanol. This compound (1·0 g.) was mixed with a solution (9 ml.; 16%) of aluminium *tert.*-butoxide in benzene, and the mixture evaporated to dryness. The residue in dry toluene (7 ml.) and *cyclo*hexanone (6 ml.) was heated under reflux for 2 hours and the product isolated in the usual way. *Ethyl* 20-*cyano*-3-*ketopregna*-4 : 17-*dien*-21-*oate* (85%) [from ether–light petroleum (b. p. 40—60°)] had m. p. 132—134°, $[\alpha]_D^{22}$ +143·2° (*c*, 1·980 in chloroform) (Found : C, 75·7; H, 8·3; N, 3·7. $C_{24}H_{31}O_3N$ requires C, 75·6; H, 8·2; N, 3·7%).

3β : 6α-*Diacetoxy*-5α-*hydroxyandrostan*-17-*one* (VII).—To ethyl 3β-acetoxy-20-cyanopregna-5 : 17-dien-21-oate (2·0 g.) in dry ether (50 ml.) was added a solution of osmium tetroxide (2·0 g.) in dry ether (20 ml.), followed by pyridine (0·2 ml.). After being kept overnight at room temperature, the mixture was taken to dryness and the residue heated under reflux for 3 hours with sodium sulphite (10·5 g.) in water (24 ml.) and ethanol (35 ml.). The hot mixture was filtered and the residue extracted with successive 100-ml. portions of 60, 70, 80, and 90%, and absolute ethanol. The bulked extracts were taken to dryness and the residue dissolved in water (50 ml.) and repeatedly extracted with chloroform (6 × 30 ml.). The combined extracts were washed until neutral and the solvent removed. Acetylation of the residue gave 3β : 6α-diacetoxy-5α-hydroxyandrostan-17-one (550 mg.), needles, m. p. 242—245°, $[\alpha]_D^{24}$ +57·7° (*c*, 1·952 in chloroform) (Found : C, 68·1; H, 8·3. Calc. for $C_{23}H_{34}O_6$: C, 68·0; H, 8·4%). Ehrenstein and Decker (*J. Org. Chem.*, 1940, **5**, 544) give m. p. 253—254°, $[\alpha]_D$ +63·6° (in acetone).

Ethyl 3β-*acetoxy*-20-*cyano*allo*pregn*-17-*en*-21-*oate*, prepared (90%) from 3β-acetoxyandrostan-17-one and ethyl cyanoacetate by the procedure described for (V; R = CO_2Et) and crystallised from ethanol, had m. p. 164—166°, $[\alpha]_D^{20}$ +30·1° (*c*, 2·832 in chloroform) (Found : C, 73·1; H, 8·4; N, 3·6. $C_{26}H_{37}O_4N$ requires C, 73·1; H, 8·4; N, 3·3%).

Hydroxylation with osmium tetroxide gave 3β-acetoxyandrostan-17-one, m. p. 115—117°, not depressed on admixture with an authentic specimen. Reduction of the latter compound with lithium aluminium hydride, followed by acetylation, furnished 3β : 17β-diacetoxyandrostane, m. p. 125—127°, $[\alpha]_D$ −2·0° (*c*, 1·76 in acetone). Shoppee (*Helv. Chim. Acta*, 1940, **23**, 740) gives m. p. 127—129°, $[\alpha]_D$ −1·0° ± 1° (in acetone).

3β-*Acetoxy*-20-*cyanopregna*-5 : 17-*diene* (VI).—20-Cyano-3β-hydroxypregna-5 : 17-dien-21-oic acid (2·0 g.) was distilled at 140—160°/10^{-3} mm. and the glassy product crystallised by addition of light petroleum. Purification from ether–light petroleum gave the hydroxy-nitrile, m. p. 144—146°, in *ca.* 30% yield, acetylation of which furnished 3β-*acetoxy*-20-*cyanopregna*-5 : 17-*diene* (95%), m. p. 176—178°, $[\alpha]_D^{22}$ −71·5° (*c*, 2·466 in chloroform) (Found : C, 78·0; H, 8·8; N, 4·1. $C_{23}H_{31}O_2N$ requires C, 78·1; H, 8·9; N, 4·0%).

3β : 21-*Diacetoxypregna*-5 : 17-*diene*.—To the foregoing compound (1·7 g.) in dry ether (100 ml.) was added a solution of lithium aluminium hydride (1·5 g.) in ether (100 ml.), and the mixture heated under reflux for 2 hours. The product formed a viscous liquid which gave a positive test for a primary aliphatic amine. It (1·0 g.) was dissolved in acetic acid (2 ml.) and water (0·4 ml.) and the ice-cooled solution was treated with sodium nitrite (1·0 g.) in the minimum quantity of ice-water, after which the mixture was allowed to warm to room temperature. Further quantities of acetic acid (2 ml.) and sodium nitrite (500 mg.) were then added, after which the mixture was heated for 1 hour on the steam-bath, cooled, and poured into water. Ether-extraction gave a product which, after acetylation overnight with acetic anhydride (1 ml.) in pyridine (1 ml.), was purified by chromatography (30 g. alumina) in 95% light petroleum–benzene, to give 3β : 21-*diacetoxypregna*-5 : 17-*diene* (300 mg.), needles (from methanol), m. p. 135—136°, $[\alpha]_D^{24}$ −52·7° (*c*, 0·902 in chloroform) (Found : C, 75·2; H, 9·3. Calc. for $C_{25}H_{36}O_4$: C, 75·0; H, 9·0%), not depressed on admixture with authentic material (Heusser, Eichenberger, and Plattner, *loc. cit.*).

3β-*Acetoxy*-20 : 20-*dicyanopregna*-5 : 17-*diene* (V; R = CN), prepared from 3β-acetoxyandrost-5-en-17-one (3·3 g.) and malononitrile (1·0 g.), formed prisms (from ethanol), m. p. 184—186°, $[\alpha]_D^{20}$ −56·2° (*c*, 1·880 in chloroform) (Found : C, 76·1; H, 8·1; N, 7·5. $C_{24}H_{30}O_2N_2$ requires C, 76·0; H, 8·3; N, 7·4%).

Ethyl 3β-*Acetoxy*-20-*cyanopregna*-5 : 17-*diene*-20-*thiolcarboxylate* (V; R = CO·SEt).—Recrystallised cyanoacetic acid (17 g.) was dissolved in dry ether (75 ml.) and the cooled solution treated with phosphorus pentachloride (40 g.) in portions during 20 minutes. After removal of ether and phosphorus halides under reduced pressure, cyanoacetyl chloride was obtained, b. p. 58°/0·1 mm. (cf. Schroeter, *J. pr. Chem.*, 1922, **105**, 165). It was treated, in dry ether (50 ml.), with the lead salt of ethanethiol (17 g.), in portions, during 15 minutes. Lead halide was removed and washed with ether, and the filtrate and washings were taken to dryness and distilled, to give *ethyl cyanothiolacetate* (7 g.), b. p. 126°/10 mm. (Found : C, 46·3; H, 5·5; N, 10·7; S, 24·7. C_5H_7ONS requires C, 46·5; H, 5·4; N, 10·9; S, 24·8%).

Condensation of this ester with 3β-acetoxyandrost-5-en-17-one gave *ethyl* 3β-*acetoxy*-20-*cyanopregna*-5 : 17-*diene*-20-*thiolcarboxylate*, large prisms (95%) (from chloroform–*n*-hexane), m. p. 216—218°, $[\alpha]_D^{21}$ −40·6° (*c*, 1·364 in chloroform) (Found : C, 70·7; H, 7·6; N, 3·2; S, 6·8. $C_{26}H_{35}O_3NS$ requires C, 70·7; H, 8·0; N, 3·2; S, 7·2%).

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