equiv were used per coupling; however, for Bpa only 2.5 equiv were employed. Activated esters were formed in situ using BOP, HOBT, and 0.451 M *N*-methylmorpholine in *N*,*N*-dimethylformamide (DMF). Coupling times varied from 1 to 2 h depending upon coupling efficiency of the particular amino acid. Deprotection of FMOC-protected amine groups was performed using a 7-min 20% piperidine/DMF wash. All peptides were acetyl capped on the resin using 21 equiv of acetic anhydride and 5 equiv of triethylamine in 3 mL of DMF. After shaking for 2 h with the acyl capping reagents, the resin was washed with dichloromethane and briefly air dried. The peptide was then cleaved from the resin using Reagent R as described by Milligen[12] and lyophilized from water. Purity was assessed by reverse-phase HPLC (H_2O/CH_3CN mixtures; UV 256, 228 nm detection) and 1D NMR. Impure peptides were purified using P2 gel filtration chromatography with 50 mM acetic acid as eluent. Fractions containing pure peptide were identified by HPLC and concentrated by lyophilization. Pure peptides were stored at −20 °C.

***N*-(Diphenylmethylene)-α-amino-(2,2′-bipyridine)-6-propanoic Acid *tert*-Butyl Ester (4).** *N*-(Diphenylmethylene)glycine *tert*-butyl ester (**2**) (1.3 g, 4.4 mmol), *N*-benzylcinchonidinum chloride (0.31 g, 0.736 mmol), and **3** (0.95 g, 3.68 mmol) were added to a suspension of 20 mL of dichloromethane (CH_2Cl_2) and 7.04 mL of 50% aqueous sodium hydroxide and stirred vigorously for 1 h at room temperature, at which time it was complete as evaluated by TLC. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (20 mL). The combined organic phases were concentrated in vacuo. The residue was redissolved in CH_2Cl_2 (40 mL) and water (20 mL). The organic phase was separated, washed with water (2 × 10 mL), dried (Na_2SO_4), and concentrated to afford the crude product. The product was purified by flash chromatography (eluent hexane/ethyl acetate, 7:1). Prior to loading the compound, the silica column was pretreated with several volumes of the eluent which also contained 0.5% triethylamine.[16] The pure yield was 1.37 g (83%). At this stage, 65 mg of material was removed for stereochemical analysis. The product was crystallized from hexane at 4 °C. The solid product (0.69 g) was removed and the filtrate concentrated to afford an oil (0.58 g). The chemical yield of optically pure material is approximately 40%, mp (DL) 90–91 °C, (L) oil; $[\alpha]^{25}_D$ −327° (*c* 1, EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.46 (s, 9 H), 3.40 (dd, 1 H, *J* = 9.2 and 13.4 Hz), 3.52 (dd, 1 H, *J* = 4.3 and 13.4 Hz), 4.63 (dd, 1 H, *J* = 4.3 and 9.2 Hz), 7.16 (m, 4 H), 7.27 (m, 5 H), 7.32 (t, 1 H, *J* = 6.1 Hz), 7.52 (d, 1 H, *J* = 8.1 Hz), 7.65 (t, 1 H, *J* = 7.9 Hz), 7.69 (dd, 1 H, *J* = 1.5 and 7.6 Hz), 8.09 (d, 1 H, *J* = 7.9 Hz), 8.18 (d, 1 H, *J* = 7.9 Hz), 8.64 (dd, 1 H, *J* = 1.5 and 3.5 Hz); ^{13}C NMR ($CDCl_3$) δ 28.0, 41.8, 66.5, 81.1, 118.4, 121.4, 123.4, 124.4, 127.8, 128.0, 128.1, 128.7, 130.0, 136.3, 136.5, 136.9, 139.6, 148.9, 155.4, 156.2, 158.0, 170.6, 170.9, 203.3. Anal. Calcd for $C_{30}H_{29}N_3O_2$: C, 77.72; H, 6.30; N, 9.06. Found: C, 78.08; H, 6.15; N, 9.09.

(*S*)-α-Amino-(2,2′-bipyridine)-6-propanoic Acid (1). A suspension of optically pure **4** (0.5 g) was refluxed in 6 N hydrochloric acid (10 mL) for 4 h. The hydrolyzed reaction mixture was then cooled, extracted with ether (3 × 5 mL), and concentrated to dryness. The residual material was lyophilized several times from water to afford 0.3 g (100%) of the amino acid hydrochloride: mp 220 °C dec; $[\alpha]^{25}_D$ −18.6° (*c* 1, H_2O; pH 7.0) −12.9° (*c* 1, 5 N HCl); MS (M^+) 244; ^{1}H NMR (D_2O) δ 3.30 (dd, 1 H, *J* = 6.6 and 12.5 Hz), 3.35 (dd, 1 H, *J* = 5.0 and 12.5 Hz), 4.09 (dd, 1 H, *J* = 5.0 and 6.6 Hz), 7.29 (d, 1 H, *J* = 7.4 Hz), 7.49 (t, 1 H, *J* = 6.1 Hz), 7.79 (t, 1 H, *J* = 7.6 Hz), 7.82 (t, 1 H, *J* = 7.7 Hz), 7.98 (t, 1 H, *J* = 7.7 Hz), 8.07 (d, 1 H, *J* = 7.9 Hz), 8.50 (d, 1 H, *J* = 4.1 Hz); ^{13}C NMR (D_2O) δ 37.8, 54.9, 121.7, 123.9, 126.1, 140.2, 141.5, 148.2, 154.0, 154.6, 157.2, 174.1; UV (H_2O, free zwitterion) λ_{max} 238 (ϵ = 8.95 × 10^3), 284 (ϵ = 13.42 × 10^3).

***N*-[(9*H*-Fluoren-9-ylmethoxy)carbonyl]-α-amino-(2,2′-bipyridine)-6-propanoic Acid (5).** A solution of FMOC azide (0.81 g, 3.1 mmol) in 10 mL of 1,4-dioxane was added dropwise with stirring to a solution of **1** (0.75 g, 3.0 mmol) in 10 mL of 10% aqueous sodium carbonate at 0 °C, over 2 h. The reaction was then allowed to warm to room temperature and stirred for 36 h. The mixture was diluted with 100 mL of distilled water and extracted 3 times with 50 mL of ether. The aqueous phase was cooled in an ice bath and brought to pH 2 with concentrated hydrochloric acid. The suspension was then centrifuged (5000 rpm) for 10 min. The aqueous phase was decanted and the solid washed with water (2 × 50 mL), centrifuged, and decanted. The solid was taken up in methanol and concentrated in vacuo to yield 1.36 g (90%) of white powder: $[\alpha]^{25}_D$ −61.3° (*c* 1, MeOH); ^{1}H NMR (CD_3OD) δ 3.34 (m, 1 H), 3.62 (m, 1 H), 4.02 (t, 1 H, *J* = 7.2 Hz), 4.28 (m, 2 H), 5.13 (m, 1 H), 7.07 (m, 1 H), 7.20 (t, 1 H, *J* = 7.4 Hz), 7.26 (m, 1 H), 7.32 (t, 1 H, *J* = 7.3 Hz), 7.44 (d, 1 H, *J* = 7.4 Hz), 7.46 (d, 1 H, *J* = 7.4 Hz), 7.59 (t, 1 H, *J* = 7.9 Hz), 7.65 (d, 1 H, *J* = 7.4 Hz), 7.69 (d, 1 H, *J* = 7.5 Hz), 8.00 (t, 1 H, *J* = 5.2 Hz), 8.05 (t, 1 H, *J* = 7.8 Hz), 8.28 (d, 1 H, *J* = 7.8 Hz), 8.65 (d, 1 H, *J* = 7.5 Hz), 8.69 (d, 1 H, *J* = 8.0 Hz), 8.78 (d, 1 H, *J* = 4.9 Hz); ^{13}C NMR (CD_3OD) δ 39.7, 39.8, 48.2, 54.0, 67.8, 120.9, 122.1, 125.4, 126.0, 128.0, 128.1, 128.3, 128.7, 128.8, 128.9, 140.7, 142.4, 143.4, 144.8, 145.0, 145.1, 146.8, 148.3, 148.4, 149.3, 158.8, 158.9, 160.0, 160.1, 173.8, 175.1; high res MS [M^+], calcd for $C_{28}H_{24}N_3O_4$ 466.1767, obsd 466.1781.

Ac-Bpa-Thr-Pro-D-Ala-Val-Bpa-NH$_2$ (6): ^{1}H NMR (D_2O) δ 8.29 (s, 2 H), 7.63 (m, 8 H), 7.21 (m, 2 H), 7.10 (m, 2 H), 4.30 (d, 1 H, *J* = 5.8 Hz), 3.99 (d, 1 H, *J* = 7.14 Hz), 3.86 (t, 1 H, *J* = 7.52 Hz), 3.77 (t, 1 H, *J* = 6.1 Hz), 3.66 (d, 1 H, *J* = 7.23 Hz), 3.36 (m, 2 H), 3.16 (m, 1 H), 2.93 (m, 4 H), 1.64 (m, 13 H), 0.99 (d, 3 H, *J* = 7.2 Hz), 0.90 (d, 3 H, *J* = 6.4 Hz), 0.39 (d, 3 H, *J* = 6.8 Hz), 0.36 (d, 3 H, *J* = 6.8 Hz); high res MS [M^+], calcd for $C_{45}H_{56}N_{11}O_8$ 878.4313, obsd 878.4285.

Ac-Bpa-Thr-Pro-D-Ala-Val-Phe-NH$_2$ (7): ^{1}H NMR (DMSO-d_6) δ 8.75 (d, 1 H, *J* = 4.4 Hz), 8.52 (d, 1 H, *J* = 7.9 Hz), 8.30 (m, 2 H), 8.09 (t, 1 H, *J* = 7.1 Hz), 7.91 (m, 5 H), 7.58 (t, 1 H, *J* = 6.6 Hz), 7.40 (d, 1 H, *J* = 7.6 Hz), 7.24 (m, 7 H), 4.98 (m, 1 H), 4.58 (t, 1 H, *J* = 6.3 Hz), 4.40 (m, 1 H), 4.32 (m, 2 H), 4.40 (m, 2 H), 3.73 (m, 1 H), 3.63 (m, 1 H), 3.32 (m, 1 H), 3.11 (m, 2 H), 2.86 (m, 1 H), 2.04 (m, 2 H), 1.81 (m, 6 H), 1.20 (d, 3 H, *J* = 7.0 Hz), 1.11 (d, 3 H, *J* = 6.2 Hz), 0.77 (d, 3 H, *J* = 6.8 Hz), 0.70 (d, 3 H, *J* = 6.8 Hz); high res MS [M^+], calcd for $C_{41}H_{54}N_9O_8$ 800.4095, obsd 800.4135.

Acknowledgment. Financial support from the Caltech Consortium in Chemistry and Chemical Engineering (E.I. du Pont de Nemours & Co., Inc., Eastman Kodak Co., and Minnesota Mining and Manufacturing Co.) and the National Science Foundation is gratefully acknowledged. S.L.F. is a Department of Education Predoctoral Fellow. We also thank Thomas Prins for help in optimizing the procedures described.

Registry No. **1**·HCl, 137495-60-4; **2**, 81477-94-3; **3**, 83478-63-1; **4**, 137495-61-5; **5**, 137495-62-6; **6**, 136391-83-8; **7**, 136391-83-8; (8*S*,9*R*)-(−)-*N*-benzylcinchonidinium chloride, 69257-04-1.

Supplementary Material Available: ^{1}H and ^{13}C NMR spectra of compounds 1–7 and HPLC traces of amino acid derivatives and peptides (13 pages). Ordering information is given on any current masthead page.

(16) This treatment was found necessary to avoid decomposition of the acid-labile imine product.

Wavelength Dependence of the Photolysis of Some Anthracene-Containing Sulfonium Salts

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Received April 1, 1991

Considerable interest is currently focused on photoacid generating systems.[1,2] Sulfonium salts are among the most

(1) PMSE Symposium on Photoacid Generating Compounds, ACS Annual Conference, Miami, Sept 1989.

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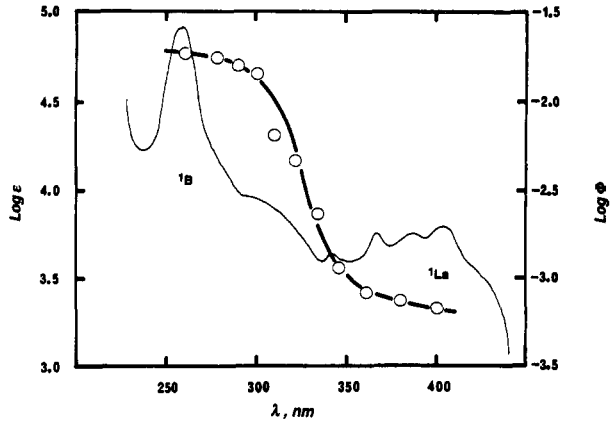
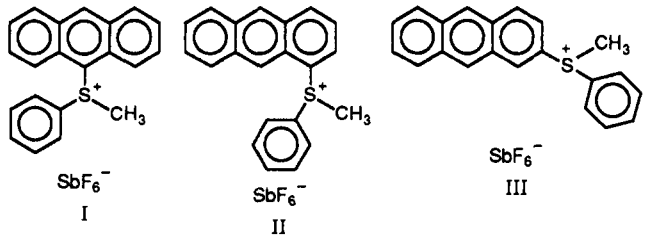


Figure 1. The effect of wavelength of irradiation on the quantum yield of acid formation. The experimental points were obtained by monochromatic irradiation of a 5×10^{-4} M solution of I in dichlormethane at the indicated wavelengths. The data are overlayed over the absorption spectrum of I. The absorption bands at 400 and 260 nm, respectively, correspond to the ^1L_a and the ^1B states of anthracene.

effective acid generators, but they absorb in general below 300 nm and for many applications it is desirable to extend their spectral sensitivity to longer wavelength. One way of doing this is to incorporate a suitable chromophore directly into the sulfonium ion. Saeva[3-6] and his colleagues have taken this route, using anthracene as the light-gathering chromophore. We have investigated a group of anthracene-containing sulfonium salts and in some of these have observed an unusual wavelength dependence of photolytic efficiency. We report here on three isomeric anthrylphenylmethylsulfonium hexafluorantimonates.



In early experiments it had been found that exposure of I to 254-nm radiation produced acid more efficiently than irradiation at 365 nm. To investigate this effect in more detail, identical samples of a 5×10^{-4} M solution of I in dichloromethane were exposed to the radiation of a monochromator–xenon lamp combination over a range of wavelengths from 400 to 260 nm.

The result of these experiments is shown in Figure 1 where the quantum yield of acid formation and the absorption spectrum of I are plotted logarithmically as a function of wavelength. It can be seen that there is a significant change in the quantum yield when the excitation of the anthracene system changes from the ^1L_a to the ^1B state. In the case of I the quantum yield increases by a factor of 28, from 0.000 66 to 0.018. A similar behavior was observed in the isomers II and III where the quantum yield of acid formation again increases on transition from the ^1L_a to the ^1B state, but here only by a factor of 2. The experimental data are collected in Table I.[7]

Table I. Quantum Yield of Acid Formation by the Anthracene-Containing Sulfonium Salts I–III as a Function of the Wavelength of Irradiation

λ (nm)	I	II	III
400	0.000 66	0.012	0.011
380	0.000 73	0.014	0.012
360	0.001 26	0.014	0.012
345	0.001 07	0.015	0.014
335	0.0023	0.014	0.012
320	0.0045	0.016	0.014
310	0.0054	0.020	0.017
300	0.014	0.028	0.019
290	0.016	0.026	0.016
280	0.018	0.027	0.017
260	0.019	0.025	0.019

The photolysis of mixed aromatic–aliphatic sulfonium salts is thought to occur predominantly via a homolytic route.[8-11] The primary event is the formation of a sulfonium cation radical, and acid is formed by the reaction of this radical with the solvent. Since our experiments are carried out at different wavelength but under otherwise identical conditions it is reasonable to assume that the rate of acid formation in these experiments is a measure of the rate of radical production and hence of the rate of primary bond scission. We believe, therefore, that the abrupt change in the quantum yield of acid production reflects a change in the efficiency of photolytic bond scission.

$$Ar_3S^+ X^- \xrightarrow{h\nu} Ar_2S^{\bullet+} + Ar^\bullet$$

Saeva et al.[6] have convincingly demonstrated that bond scission in the anthracene–sulfonium system is caused by the transfer of an electron from the excited anthracene moiety to the σ^* S–C orbital of the leaving group. In the excited state the S^+–C bond is weakened by the presence of an electron in the antibonding σ^* orbital, but the excited state is still a bonding state with a minimum in the potential energy function, and bond scission occurs when the system escapes from the potential energy well of the bond. The probability of escape depends on the point of entry onto the potential energy surface. In most systems where anthracene is the light-absorbing chromophore, the transition from a higher anthracene excited state to a side-chain state occurs from the lowest vibrational level of the lowest excited state (^1L_a) of anthracene, the rate of interaction between the two systems being slower than the rate of internal conversion within the anthracene manifold. In the case of I and of its isomers the coupling between the orbitals of anthracene and those of the sulfonium system appears to be so close that there is the possibility

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(7) In the photochemical transformation of 9-anthrylmethyl(*p*-cyanobenzyl)sulfonium hexafluorophosphate, Saeva et al.[5] find a quantum yield of acid formation (and of the formation of sulfides) of 0.77. This high reaction efficiency is caused by several factors: the S---benzyl bond is weakened by the electron-attractive power of the cyano group and that promotes bond scission in the primary photolytic step. The ensuing *p*-cyanobenzyl radical is stabilized by the presence of the substituent which militates against radical recombination, and finally, the anthrylmethylsulfonium radical cation is highly reactive. The anthrylphenylmethylsulfonium salts of this study are less well adapted to the purpose of acid generation. The S---methyl bond is stronger than in Saeva's compound, recombination between the radical cation and the methyl radical is prevalent, and the anthrylphenylsulfonium radical cation is somewhat less reactive than its counterpart in the Saeva study.
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of a small energy leak from the higher anthracene state (^1B) directly into the σ^* orbital of the S^+–C bond. This is not a large effect. Even in I most of the excitation energy takes the usual route via ^1L_a, and for that reason the quantum yield of acid production by I is very much lower than, e.g., that of triphenylsulfonium salts where the critical σ^* orbital is populated exclusively from a relatively high-lying excited state of the phenyl group.

Experimental Section

Compounds I to III were prepared from the respective anthryl phenyl sulfides by treating these with silver hexafluoroantimonate and methyl iodide.

In the first phase of synthesis, 5.5. g (0.05 mol) of thiophenol and 50 mL of dimethylformamide were placed into a 250-mL three-necked, round-bottom flask equipped with a paddle stirrer, an addition funnel, and a condenser. The mixture was cooled to 0 °C in an ice–water bath, and then 1.2 g (0.05 mol) of sodium hydride was added in small portions. In the synthesis of I, 5.14 g of 9-bromoanthracene in 25 mL of dimethylformamide was introduced into the solution, and this was refluxed for 10 h. After being cooled, the contents were poured into ice–water and the precipitate of the product filtered off and recrystallized from hexane: yellow crystals, yield 64%, mp 90–91 °C.

In the preparation of II, bromoanthracene was replaced by 1-chloroanthracene, dimethylformamide by dimethylacetamide. The product was obtained in 52% yield; pale yellow crystals, mp 103–104 °C.

In the preparation of III 2-chloroanthracene and dimethylacetamide were used. The product yield was 68%: pale yellow crystals, mp 149–150 °C.

In the second phase of synthesis silver hexafluoroantimonate was added to a solution of the appropriate anthryl phenyl sulfide as well as 1 g of methyl iodide in 20 mL of methylene chloride. The mixture was stirred at room temperature for 3 h. The insoluble silver salt was then filtered off, and the volume of the solution was reduced to about 3 mL. The solution was added dropwise to diethyl ether where the product precipitated. The ether was decanted, and the raw product (a yellow gum) was recrystallized from acetonitrile–ether.

I: light yellow crystals, yield 30%, mp 140–141 °C; ^1H NMR δ 4.45 (3 H), 7.8–9.5 (14 H). Anal. Calcd: C, 46.95; H, 3.19; S, 5.97. Found: C, 46.93; H, 3.03; S, 6.14.

II: light yellow crystals, yield 29%, mp 170–171 °C; ^1H NMR δ 4.2 (3 H), 7.9–9.2 (14 H). Anal. Calcd: C, 46.95; H, 3.19; S, 5.97. Found: C, 46.91; H, 3.03; S, 5.86.

III: light yellow crystals, yield 19%, mp 201–203 °C; ^1H NMR δ 4.3 (3 H), 7.9–9.3 (14 H). Anal. Calcd: C, 46.95; H, 3.19: S, 5.97. Found: C, 46.98; H, 3.07; S, 6.13.

Solutions (5×10^{-4} M) in analytical-grade dichloromethane were exposed in a standard 1-cm spectroscopic cell to the radiation beam of a Bausch and Lomb monochromator. The light source was a 150-W xenon lamp (Osram) attached to a stabilized power supply. The spectral width of the radiation beam was ±3 nm; its intensity was determined for each wavelength setting by ferrioxalate actinometry.[12] In the range from 400 to 260 nm the radiation intensity varied from 2.51×10^{-10} to 0.169×10^{-10} einstein/cm^2 s. Exposure times were in the range from 10 to 120 min. The optical density of the solutions varied between 1.5 and 4. For exposures at 260 and 280 nm the solutions were diluted to keep their optical density below a value of 4.

Acid formation was determined by mixing the photolyte with a standard solution of an indicator dye[13] and monitoring the degree of bleaching of that dye. The indicator system was calibrated with monomethylsulfonic acid.

Registry No. I, 137719-80-3; II, 137719-82-5; III, 137719-84-7; 9-bromoanthracene, 1564-64-3; thiophenol, 108-98-5; 1-chloroanthrazene, 4985-70-0; 2-chloroanthracene, 17135-78-3.

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Azatetralone Synthesis via Regioselective Grignard Coupling and Parham Cyclization

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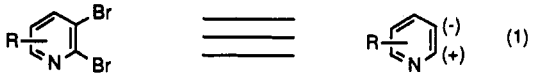
Received May 6, 1991

During the course of efforts directed toward the novel aldose reductase inhibitors **20** and **21**, the need for an asymmetric synthesis of azatetralone **16** was encountered. Methods have been reported for the synthesis of achiral azatetralone **15**, but were not amenable for the preparation of chiral azatetralone **16**.[1] To this end, a novel sequence of pyridine functionalization was developed from a 2,3-dibromopyridine derivative depicted by the synthon below. The pyridine annulation route to azatetralones **15** and **16**, via a 2,3-dibromopyridine derivative, allows access to other 2,3-disubstituted pyridines.



(1)

Electrophilic and nucleophilic elaboration of pyridines was known. Kumada has demonstrated alkylation and arylation of halopyridines, bromothiophenes, haloquinolines, halobenzenes, and haloisoquinolines by Grignard reagents, catalyzed by nickel/phosphine complexes (1,2-bis(diphenylphosphino)ethane(dppe)nickel(II) chloride and 1,3-bis(diphenylphosphino)propane(dppp)nickel(II) chloride).[2] These bromide displacements were facile in pyridine systems independent of the position of the halide as evidenced by the displacement of bromide in 2-, 3-, and 4-bromopyridine with dppe/$NiCl_2$ and 2-methylbutylmagnesium chloride in ether at reflux affording the alkylated products in 67%, 72%, and 53% yields, respectively.[3]

In previous transmetalation studies with pyridines by Parham and co-workers, halogen–metal exchange on 2,5-dibromopyridine afforded 2-bromo-5-lithiopyridine as determined by proton and deuterium quenching.[4] These workers had not anticipated metalation at the 5-position because the 2-position is more electronegative and initial coordination of butyllithium with the heteroatom would favor metalation at the 2-position. This halogen–metal exchange and other pyridine metalations led these workers to suggest that the reactions were the result of thermodynamic control.[5] Thus, functionalization of halopyridines by cross coupling with Grignard reagents, catalytic in nickel/phosphine complexes, and by transmetalation was precedented.

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