elution to yield 0.14 g (64%) of 1,3-dimethyl-5-(3′,4′-dihydro-2′*H*-pyran-2′-yl)-2,4-pyrimidinedione (**3**) which exhibited λ_{max} (MeOH) 270 nm (ϵ 8000) and MS *m/e* 222.1008 (M^+; calcd for $C_{11}H_{14}N_2O_3$, 222.1004) and 166.0737 (calcd for $C_8H_{10}N_2O_2$, 166.0742); ^1H NMR ($CDCl_3$) δ 1.5–2.5 (m, 4 H, 3′- and 4′-H), 3.37 and 3.45 (s and s, NMe), 5.7–5.95 (m, 2 H, 2′- and 5′-H), 6.45 (d, J = 6 Hz, 1 H, 6′-H), 7.27 (s, 1 H, 6-H). In deuteriobenzene solution, the resonances for 2′-H and 5′-H are separated,[9] permitting facile assignment.

Anal. Calcd for $C_{11}H_{14}N_2O_3$: C, 59.5; H, 6.31; N, 12.6. Found: C, 59.3; H, 6.22; N, 12.5.

1,3-Dimethyl-5-(2′-tetrahydropyranyl)-2,4-pyrimidinedione (7). To a solution of 0.14 g of 1,3-dimethyl-5-(3′,4′-dihydro-2′*H*-pyran-2′-yl)-2,4-pyrimidinedione (**3**) in 50 mL of tetrahydrofuran was added 14 mg of 5% palladium on carbon. The resulting mixture was shaken under 2 atm of hydrogen pressure for 2 h. The catalyst was removed, and the solvent was evaporated to yield 0.10 g (71%) of 1,3-dimethyl-5-(2′-tetrahydropyranyl)-2,4-pyrimidinedione (**7**): mp 105–106 °C; UV λ_{max} (MeOH) 270 nm (ϵ 7900); MS *m/e* 224.1224 (M^+; calcd for $C_{11}H_{16}N_2O_3$, 224.1191); ^1H NMR ($CDCl_3$) δ 3.35 and 3.40 (NMe), 4.35 (d, J = 11 Hz, 2′-H), 7.24 (6-H).

Anal. Calcd for $C_{11}H_{16}N_2O_3$: C, 58.9; H, 7.14; N, 12.5. Found: C, 58.9; H, 7.16; N, 12.4.

Similar reductions of both **1** and **2** in methanol yielded **7**. Prolonged (>5 h) contact with the reducing conditions resulted in reduction of the pyrimidinedione ring, producing a tetrahydro product of M_r 226.

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Registry No.—**1**, 67464-93-1; **2**, 67464-94-2; **3**, 67464-95-3; **4**, 110-87-2; **5**, 65904-27-0; **6**, 40738-83-8; **7**, 67464-96-4; 1,3-dimethyluracil, 874-14-6; mercury(II) acetate, 1600-27-7.

Supplementary Material Available: Complete ^1H NMR and electron ionization mass spectra for compounds 1–3 (2 pages). Ordering information is given on any current masthead page.

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Reactions of Heteroaromatic Cations with Nucleophilic Reagents. Addition of Methoxide Ion to 2,6-Diphenyl- and 4-Methoxy-2,6-diphenylpyrylium Cations

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The title reactions have been studied mainly in methanol and 9:1 acetonitrile–methanol. 2,6-Diphenylpyrylium cation yields a 4*H*-pyran as the kinetically favored product and diphenylpentadienone **7**. The latter, which forms upon ring cleavage of a 2*H*-pyran, is the product of a thermodynamically favored pathway. In methanol the reaction of the methoxy-substituted cation yields comparable amounts of the isomeric 2*H*- and 4*H*-pyranic adducts; in this case the 2*H*-pyran apparently does not undergo ring cleavage. In 9:1 acetonitrile–methanol the only primary product is the 4*H*-pyran. The proticity of the medium seems to have an important role in promoting the interconversion of 4*H*-pyrans to other reaction products.

The pyrylium cation, one of the fundamental heteroaromatic systems, reacts easily with nucleophilic reagents. The nucleophilic attack occurs preferentially at the α or γ position;[1] in the absence of a good leaving group the reaction yields nonaromatic adducts (2*H*- or 4*H*-pyrans). The formation of a 2*H*-pyran is often followed by a ring-opening reaction, yielding a dienonic valence tautomer of the 2*H*-pyran.[2] If, on the other hand, the attacked position is bound to a good leaving group, the formation of the pyran is followed by the loss of this group and formation of a substituted pyrylium cation. Owing to the high reactivity of the pyrylium ring, substitution occurs easily, even with such poor leaving groups as alkoxy groups.[3,4]

Nucleophilic substitutions of pyrylium cations are similar to nucleophilic substitutions of pyridinium cations[5] and of activated benzenoid substrates,[6] where the intermediacy of σ adducts seems a general common feature.

While the equilibrium reactions of formation of Meisenheimer adducts from nitro-activated substrates[7] and of dihydropyridines from pyridinium cations[8] have been intensively investigated, reversible reactions of formation of pyrans from pyrylium cations have received limited attention so far.[9]

In view of the interest in the nucleophilic substitutions of pyrylium and related cations,[4,10,11] and in connection with our studies on the formation of adducts from heteroaromatic substrates,[12] we present the results concerning the course of the reaction of methoxide ion with 2,6-diphenylpyrylium (**1**) and 4-methoxy-2,6-diphenylpyrylium (**2**) cations and the structure assignment of the reaction products. Hydrogen and methoxyl groups are known to affect, in a different way, the structure and stability of Meisenheimer adducts.[13] The phenyl groups at the α positions were expected to have some hindering effect[14] toward attack at such positions and to decrease therein the reactivity, leaving virtually unaffected the reactivity of the γ position.

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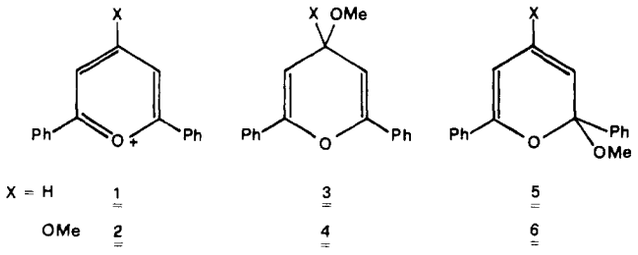
Table I. Chemical Shifts (δ) and Coupling Constants (Hz) for Compounds 1–4 and 6

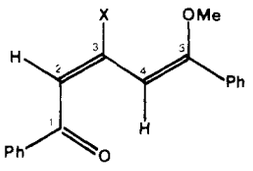
Compd	Solvent	H-3,5	H-4	C_6H_5	OCH_3	$J_{3,4}$	$J_{3,5}$
1	CD_3CN	8.51	8.95	7.5–8.4		8.6	
3	CD_3CN[a]	5.80	4.80	7.3–7.9	b	4.5	
	CH_3OD	5.85	4.9	7.1–8.1	b	4.5	
	CCl_4	5.60	4.88	7.2–7.9	3.16	4.5	
2	CD_3CN	7.90		7.6–8.3	4.40		
	$(CD_3)_2SO$	8.40		7.5–7.9, 8.3–8.6	4.45		
4	CD_3CN[a]	5.77		7.2–7.9	b		
	CH_3OD	5.80		7.3–8.1	b		
	$(CD_3)_2SO$[a]	6.02		7.3–8.1	b		
	CCl_4	5.65		7.1–7.9	3.22		
6	CH_3OD	4.55, 6.00		7.3–8.1	b		2
	CD_3CN[a]	4.6, 5.9		7.3–8.1	b		2
	CCl_4	4.34, 5.82		7.1–7.9	3.19, 3.57		2

[a] In the presence of methanol. [b] Concealed by the solvent.



X = H 1 3 5

OMe 2 4 6



X = H 7

OMe 8

Results and Discussion

Originally, we planned to study these reactions in methanol for a direct comparison with the formation of Meisenheimer adducts from nitro-activated benzenes. Spectrophotometric (UV) studies were carried out conveniently in this solvent. However, owing to the low solubilities of the salts of **1** and **2** in MeOH, NMR studies were at first carried out by recording the spectra of the salts in acetonitrile-d_3 and by adding subsequently the appropriate amount of a 4–5 M solution of sodium methoxide in MeOH. The medium was thus a mixture of acetonitrile-d_3 and methanol, approximately 9:1 (v/v).

NMR Studies in Acetonitrile-d_3–Methanol (9:1). The addition of an equivalent amount of methoxide ion to **1** and **2** brings about a general upfield shift of the NMR signals. Thus, the AB_2 system of **1** is replaced immediately after the addition of methoxide by the AX_2 system of **3** (Table I). The strong upfield shift of the hydrogen at position 4 indicates that the carbon atom in **3** has undergone change from sp^2 to sp^3 hybridization. The coupling constant between the adjacent positions of **3** is similar to the $J_{3,4}$ value in 1,4-dihydropyridines.[15] The NMR spectrum shows also weak signals at δ 6.5–7.0, whose intensities increase with time to become comparable with the signals of **3** after several hours.

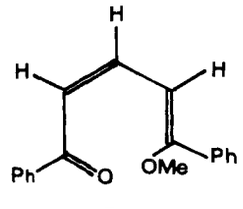
As to the reaction of **2**, the addition of the nucleophile leads immediately to the conversion of **2** to **4**. It can be excluded that the observed spectrum corresponds to that of a demethylation product because 2,6-diphenyl-4-pyranone shows a signal at δ 6.73. The signals of the methoxyls of **4** are concealed by the methanol introduced with the nucleophile. Besides the above described signals, the NMR spectrum shows very weak signals at δ 5.9 and 4.6, whose intensities increase very slowly to become in a few days comparable with the signal at δ 5.77. The nature of the slower reaction will be evident below.

NMR Studies in Methanol. (a) At Room Temperature. In the reaction of **1** the signals of adduct **3** are detected immediately after the addition of methoxide ion together with weak signals at δ 6.4–7.1. In a few minutes the signals of **3** decrease, with a corresponding increase of the signals at δ 6.4–7.1, and disappear completely in less than 1 h.

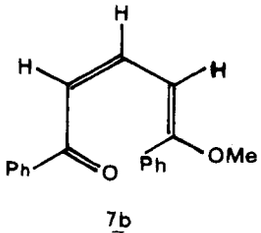
The final product was characterized as the dienone **7** by a 90 MHz spectrum in methanol: at δ 6.88 (H-3, triplet, J = 10.9 Hz); at nearly δ 6.6 (H-2, doublet of the same intensity, J = 10.9 Hz); intense multiplet in the range of the phenyl groups. Another proton, coupled only to H-3, was localized at δ 7.4 under the phenyl groups by a spin-tickling experiment; irradiation at δ 7.36 or 7.48 split each signal of the triplet into two doublets, leaving unchanged the doublet at δ 6.6. The signal at δ 7.4 corresponds to the proton at position 4, strongly deshielded by the adjacent carbonyl group, as already reported in dienones obtained upon ring opening of 2*H*-pyrans.[16] The methoxy group of **7** was detected at δ 3.90 in a CCl_4 solution, which otherwise showed the same pattern as in methanol. The difference between the chemical shift of H-4 in **7** (δ 7.4) and that reported for the dienone derived from 2,4,6-trimethyl-2*H*-pyran (δ 7.63)[16] is in better accordance with a *Z* configuration around the C_4–C_5 bond (δ_{calcd} 6.98)[17] than with an *E* configuration (δ_{calcd} 6.73).[17]

The value of $J_{2,3}$ (10.9 Hz), similar to that reported for ring-cleaved compounds formed after nucleophilic addition to pyridinium cations,[8c] shows the *Z* configuration of the double bond at C_2–C_3. The $J_{3,4}$ value (10.9 Hz) and the absence of coupling between positions 2 and 4, as previously reported for the dienone derived from 2,4,6-trimethyl-2*H*-pyran,[16] show that the more stable conformer of **7** is *s*-trans around the C_3–C_4 bond. Dienone **7** is presumably formed by the electrocyclic ring-opening reaction of 2*H*-pyran **5**. However, **5** is not detected as such by NMR spectroscopy. Weak signals in the alkene and methoxyl regions are in fact recorded, but their assignment to **5** is not straightforward. The absence of **5** shows that **7** is more stable and that, at the same time, a low energy barrier divides **7** from **5**.

2*H*-Pyran **5** could yield both **7a** and **7b**; the preferential formation of **7** as a stable conformer of **7a** shows that the



7a



7b

smaller methoxy group rotates inward during the ring-opening reaction because of a sterically favored transition state and finally turns out to be situated trans at H-4.

As to the reaction of **2**, this yields immediately a deep yellow solution of both 4*H*-pyran **4** and 2*H*-pyran **6**. The characterizing feature of the latter is given by two coupled signals of the same intensity. The $J_{3,5}$ value of **6** is in the range observed in 1,2-dihydropyridines[8c] and α-pyrones[18] (J = 1.5–3 Hz). The intensity ratio between each of the doublets and the singlet is nearly 0.5. At variance with the reaction of **1**, both 2*H*- and 4*H*-pyrans are observed separately in the reaction of **2**. Moreover, the electrocyclic ring opening of **6** is not observed. This spectrum changes slowly with time; after one day a signal is detected at δ 6.85, owing to the formation of a small amount of the demethylation product (2,6-diphenyl-4-pyranone).

(b) At Low Temperature. The disappearance of the signals of both substrates is complete within the time necessary to add the nucleophile and record the spectra.

The reaction of **1** at −30 °C yields only adduct **3**, which is converted to the open-chain dienone **7** on raising the temperature.

The reaction of **2** was performed at −50 °C. Even at this temperature, **2** yields both adducts **4** and **6** in a ratio not too different from that observed at room temperature.

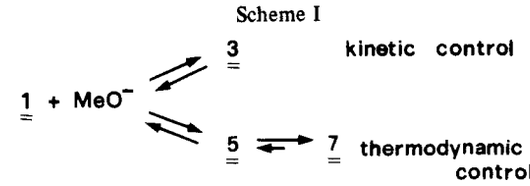
NMR Studies in Me_2SO-d_6–MeOH (9:1 v/v). Only the reaction of **2** was studied in Me_2SO because of the fast decomposition of **1** in this solvent. Upon addition of an equivalent amount of MeO^-, **2** yields adduct **4**. After one week at room temperature, this adduct is still almost unchanged, even if weak broad signals are detected at δ 7.1–7.2, probably owing to some decomposition. The demethylation product, 2,6-diphenyl-4-pyranone, is not detected.

Spectrophotometric Studies. 2,6-Diphenylpyrylium cation (**1**) in methanol has two absorption maxima at 277 nm (ϵ 1.62×10^4 M^{-1} cm^{-1}) and 400 (2.51×10^4). Upon addition of a slight excess of sodium methoxide to a 4.5×10^{-5} M solution of **1**, these maxima disappear immediately to be replaced by new maxima at 243 and 353 nm. With time the absorbance at 243 nm decreases, whereas that at 353 nm increases further. This conversion is characterized by the presence of an isosbestic point at 270 nm. After 15 min the reaction is practically finished, and a residual absorbance is observed in the range 230–260 nm together with the maximum at 353 nm. Upon addition of HCl in methanol the reaction products are converted back to pyrylium cation **1**. On the basis of the NMR data we attribute the absorbance maximum at 243 nm to 4*H*-pyran **3**. This hypothesis is in accordance with literature data[19] reporting that nonconjugated 4*H*-pyrans have maxima in the region of 225 and 250 nm. The absorbance maximum at 353 nm, again on the basis of the NMR and literature data[19] concerning the electronic spectra of 2*H*-2-benzyl- and 4*H*-4-benzyl-2,4,6-triphenylpyrans, is assigned to the open-chain dienone **7**. A clear distinction between 2*H*-pyrans and their open-chain valence tautomers does not seem feasible on the basis of the UV spectral data alone.[20]

In methanol, 4-methoxy-2,6-diphenylpyrylium cation (**2**) shows two absorption maxima at 274 nm (ϵ 2.45×10^4 M^{-1} cm^{-1}) and 355 (2.57×10^4). Upon addition of a slight excess of sodium methoxide, the spectrum of **2** disappears immediately and the formation of two maxima at 237 and 320 nm is observed (of intensity nearly 1:2). The disappearance of **2** is complete even with a methoxide ion concentration as low as 10^{-4} M. Upon acidification, the reaction products are converted back to cation **2**. On the basis of NMR and literature data[19] we assign the shorter wavelength maximum to 4*H*-pyran **4** and the longer wavelength one to 2*H*-pyran **6**. At variance with the reaction of **1**, small changes of the spectrum are observed only after several hours.

Course of the Reaction. The reaction of 2,6-diphenylpyrylium cation **1** yields 4*H*-pyran **3** as the kinetically controlled product. Nucleophilic addition occurs more easily at the γ position probably because of the lower steric requirement with respect to the α positions. This reaction is the only one observed in methanol at low temperature and in the 9:1 acetonitrile–methanol mixture.

Scheme I



When the reaction is run in methanol at room temperature, the initial formation of **3** is followed by the appearance of the ring-cleaved dienone **7**. Subsequently, **3** is completely transformed into the latter. The same behavior is observed when the reaction mixture is initially kept at low temperature and then warmed to room temperature.

Compound **7** is the result of a thermodynamically controlled pathway; the formation of a strongly conjugated dienone may then be considered a driving force. The reaction goes probably according to Scheme I. This involves the interaction of small amounts of the starting reactants, which are in equilibrium with **3** and may alternatively react to yield 2*H*-pyran **5**, the immediate precursor of **7**. So far it has not been possible to detect by NMR spectroscopy the presence of **5**. However, owing to the relatively low sensitivity of the NMR method and the expected complexity of the spectrum of **5**, we cannot exclude the presence of a small amount at equilibrium. In Scheme I methanol, as a hydrogen bond donor, is likely to act as a promoter of the departure of the methoxyl from **3** and of the return to pyrylium cation **1**; the use of a solvent with a low content of methanol slows down the conversion of the 4*H*-pyran to dienone **7** and allows even the isolation, upon removal of the solvent, of a mixture containing substantial amounts of adduct **3**.

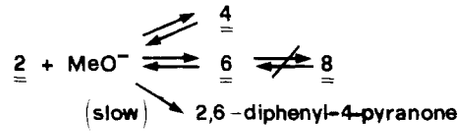
In the reaction of 4-methoxy-2,6-diphenylpyrylium cation **2**, the behavior is again strongly dependent upon the nature of the solvent. In methanol **4** is detected along with its isomeric 2*H*-pyran **6**; the ratio **4**/**6**, as measured by NMR spectroscopy, is independent of the temperature and does not change dramatically with time. The observed ratio seems thus to be a measure of the relative stability of **4** and **6**. On the other hand, in the acetonitrile-rich medium the observed product is only the 4*H*-pyran adduct **4**. On standing at room temperature, this adduct is slowly converted into a mixture of the isomeric adducts **4** and **6**. The conversion **4** → **6** is even slower in a Me_2SO-rich medium, where the hydrogen bond donor ability of methanol is presumably lower than in the acetonitrile-rich medium.

At variance with the behavior of the undetected 2*H*-pyran **5**, 2*H*-pyran **6** apparently does not undergo the ring-opening reaction to dienone **8**. This difference in behavior is related to the presence at position 4 of a substituent; while it seems difficult to estimate the role of electronic effects in the ring-opening reaction, the stability of 2*H*-pyran **6** may be connected to the fact that an increase of steric hindrance generally shifts the equilibrium 2*H*-pyran ⇌ dienone toward the left, probably because bulky groups decrease the conjugation degree in the dienone system.[20]

An assessment of the tendency of **6** to undergo the ring-opening reaction (**6** → **8**) is complicated by the fact that **2** is finally demethylated to 2,6-diphenyl-4-pyranone. This irreversible reaction, which can occur on small amounts of **2** and methoxide (Scheme II), could effectively compete with a possible slow ring-opening reaction.

The equilibria for the reactions of **1** and **2** with CH_3O^- are largely shifted to the pyrans, even in methanol solutions

Scheme II



containing very dilute methoxide ion. Under this aspect, the tendency of pyrylium cations to undergo nucleophilic addition seems qualitatively higher than that of pyridinium cations under similar conditions.[21] Further work will be necessary in order to assess quantitatively this tendency.

The possibility of rapid interconversions between the reaction products (isomeric pyrans and/or dienones) has some implication on the chemistry of pyrylium and related heteroaromatic cations in the sense that the relative reactivities of different positions in these cations cannot be immediately related to the yield of the respective addition product. Under this view, an important role is also played by the nature of the medium, which can strongly affect the rate of return of the adducts to the starting reagents, allowing the easy detection of the less stable reaction products in the media containing minor amounts of the hydroxylic solvent.

Experimental Section

Published procedures were followed for the synthesis of the perchlorates of **1**[22] and **2**.[23] We found it convenient to purify these salts by dissolving them in the least amount of dry acetonitrile and precipitating with dry ethyl ether.

Electronic spectra were recorded on a Perkin-Elmer 402 instrument; molar absorption coefficients of **1** and **2** in methanol were recorded in the presence of $HClO_4$ in order to avoid the methanolysis reaction. NMR experiments at 60 MHz were done on a Jeol C60-HL instrument; the spin-tickling experiment at 90 MHz was done on an HX90 Bruker apparatus. Since the perchlorates of **1** and **2** are poorly soluble in methanol, the NMR spectra of the reaction products can be conveniently recorded upon addition of an equivalent amount of sodium methoxide to a suspension of the perchlorates in this solvent (20–30 mg in 0.5 mL of CD_3OD). This operation brings about the complete solubilization of the substrates. In order to avoid any interference of the signals of the products with those of any residual light methanol, the reagent was freed from CH_3OH by alternating several times vacuum pumping and addition of CD_3OD.

Isolation of Adducts. General Procedure. To a solution of the perchlorate of **1** or **2** in acetonitrile (ca. 5×10^{-2} M) was added an equivalent amount of potassium methoxide as a 2.8 M solution in methanol. The solvents were rapidly removed under reduced pressure at room temperature, and the organic materials were dissolved in CCl_4 or ethyl ether. The oily residue of evaporation was induced to crystallize by scratching or prolonged cooling. Attempted purification of these solids by recrystallization or chromatography led to decomposition.

Adduct from 1: mp 54–66 °C dec; MS, weak peak at *m/e* 264 corresponding to the molecular peak from a 1:1 adduct between **1** and CH_3O^-, intense peak (base peak) at *m/e* 233 $(M - OCH_3)^+$, and absence of peaks beyond *m/e* 264. The NMR spectrum (CCl_4) is in accordance with the formation of 4*H*-pyran **3** (Table I), except for the somewhat higher intensity of the phenyl region, presumably related to the overlapping with phenyl groups of otherwise undetected side products.

Adduct from 2: mp 65–75 °C dec; MS, weak peak at *m/e* 294 (M^+ of 1:1 adduct), intense peak at *m/e* 263 $(M - OCH_3)^+$, and absence of peaks beyond *m/e* 294. The NMR spectrum (CCl_4) shows the presence of 4*H*-pyran adduct **4** and a minor amount of 2,6-diphenyl-4-pyranone.

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Registry No.—**1**, 41044-52-4; **1** perchlorate, 3558-68-7; **2**, 47075-64-9; **2** perchlorate, 17539-77-4; **3**, 53856-27-2; **4**, 67069-64-1; **6**, 67069-65-2; **7**, 67069-66-3.

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Synthesis of 3-Aryl-5-bromo-2(5*H*)-furanones[1]

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A synthetic route to 3-aryl-5-bromo-2(5*H*)-furanones (**7**) based on treating a methyl 2-aryl-4-oxobutyrate (**5**) with bromine in acetic acid has been developed. The methyl 2-aryl-4-oxobutyrates were prepared in high yield by the following sequence: alkylation of an arylacetic acid using lithium diisopropylamide and allyl bromide, esterification with diazomethane to yield a methyl 2-aryl-4-pentenoate (**4**), and ozonolysis (**4** → **5**).

Continued interest in the synthesis of cardenolides[2] and isocardenolides[3] for biological evaluation led us to consider simpler 2(5*H*)-furanones[4,5] for antineoplastic and/or cytotoxicity studies. Semonsky and co-workers[6] have examined

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