All the experiments were carried out under a nitrogen stream on capped vials. The anaerobic conditions were maintained with a disposable anaerobic indicator (Gas Pac Becton Dickinson Co., Orangeburg, NY).

The incubations were carried out at 37 °C, and 4, 8, 16, 24, 72 h after the addition of the corresponding BA, the reaction was stopped with addition of 150 μL of a 30% solution of KOH.

Tubes were centrifuged at 3500 rpm for 10 min, and 2 mL of the supernatant was transferred into a tube to which 18 mL of 0.1 M NaOH solution was added. The solution was applied to a C_{18} Bond Elut cartridge, previously activated according to the manufacturer's instructions.

The solution was eluted at a flow rate of 1 mL/min and the cartridge washed with 10 mL of water and the BA collected with 4 mL of methanol. The elute was dried under a N_2 stream and reconstituted with 0.5 mL of CH_3OH. BA were separated by using TLC and HPLC techniques. Conjugated BA were separated from the free BA with use of silica gel 0.25-μm-thickness plates (Merck GRF) with a solvent system composed by $CHCl_3/CH_3OH/H_2O$ (75/25/3, v/v/v).

The qualitative–quantitative compositions were obtained by HPLC with a 5-μm C-18 reverse-phase column (Waters Associates). The mobile phase was composed of a mixture of CH_3OH/KH_2PO_4 (0.01 M, pH 5.8, 130/70 v/v).

The analysis was carried out in isocratic conditions at a flow rate of 0.3 mL/min with use of an UV detector at 200 nm.

After TLC separation the radioactivity of the different spots was measured by zonal scanning. The different fractions were transferred into scintillation vials, and 1 mL of ethanol/acetic acid (9:1, v/v) was added. Ten milliliters of Unisolve (Kooklight, England) as liquid scintillation cocktail was then added and the radioactivity measured in a β scintillation counter.

Conclusion

In conclusion, the in vitro experiments suggest that TCUDCA should be superior to TUDCA in vivo in therapy for gallstones owing to its much greater resistance to biotransformation to inactive or potentially toxic products.

Acknowledgment. We thank Professor Alan Hofmann for helpful discussion and suggestions. Two of us (B.G. and S.C.) acknowledge gratefully a fellowship from Gipharmex, Milano, Italy.

Registry No. 4, 93060-76-5; 5·Na, 93001-12-8; 6, 93038-89-2; NaOH, 1310-73-2; EEDQ, 16357-59-8; ethanol, 64-17-5; taurine, 107-35-7; ^{35}S-taurine, 2782-32-3.

Synthesis and Antitumor Activity of a Series of Ftorafur Analogues: The Effect of Varying Electronegativity at the 1′-Position

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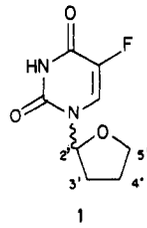
To test the effect of changes in electronegativity within the alicyclic N-1 substituent of substituted 5-fluorouracil analogues on cytotoxic activity, a series of derivatives of ftorafur, 1-(2′-tetrahydrofuranyl)-5-fluorouracil, was synthesized and tested for antitumor activity in the P388 lymphocytic leukemia screen and cytotoxic activity in the L1210 cell culture screen. Two compounds of N-1 substituent with high electronegativity, the 2′-tetrahydrothiophene 1′-oxide and the 2′-tetrahydrothiophene 1′,1′-dioxide derivatives, demonstrated the highest in vitro L1210 cell inhibition (84.5% and 92.0%, respectively). Furthermore, against P388 lymphocytic leukemia in vivo, the 2′-tetrahydrothiophene 1′-oxide derivative showed significant activity (T/C = 143). Other compounds of similar or lower electronegativity within the N-1 cyclic substituent were inactive against P388 lymphocytic leukemia and less active against L1210 cells.

Ftorafur (1) [NSC 148958, 1-(2′-tetrahydrofuranyl)-5-fluorouracil] is under clinical investigation as a less toxic alternative to 5-fluorouracil (5-FU) (2) in the treatment of cancer. Although ftorafur offers the advantage of decreased myelosuppression and possible oral effectiveness, its role in cancer chemotherapy is probably limited to combination chemotherapy.[3] Some effectiveness in the treatment of adenocarcinoma and breast cancer has been demonstrated.[3]



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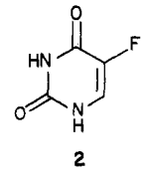

2

It is generally accepted that ftorafur is a repository form of 5-FU. This conversion has been demonstrated in rat liver microsomes,[4] rat and mouse liver soluble fraction,[5] and human plasma and tumor tissue.[6,7]

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(1) This paper was presented in part at the APhA 130th Annual Meeting, Academy of Pharmaceutical Science Section, April 10–14, 1983, New Orleans, LA.

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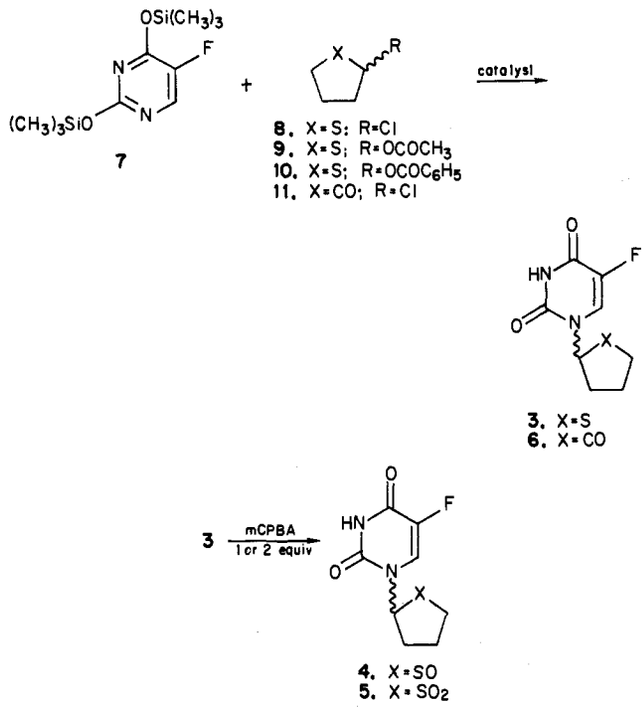
Scheme I. Synthesis of Analogues of 1-(2′-Tetrahydrofuranyl)-5-fluorouracil[a]



[a] mCPBA = *m*-chloroperbenzoic acid.

The enzymatic mechanism of this conversion remains speculative. More than one enzyme system is probably capable of cleavage of the N-1–C-2′ bond. Furthermore, it has been suggested that such a cleavage may involve a prior 2′- or 5′-hydroxylation.[5]

Consequently, many N-1 substituted 5-FU derivatives which demonstrate antitumor activity have been synthesized.[8] Isosteric replacement within the tetrahydrofuran ring of ftorafur has also been accomplished.[9] However, a systematic synthesis and antitumor testing of a series of derivatives of varying electronegativity at the 1′-position of the five-membered ring has not been accomplished. Therefore, a short series of analogues of ftorafur was prepared and each compound tested for antitumor activity in the murine P388 lymphocytic leukemia screen and for cytotoxic activity in the L1210 cell culture screen.

Chemistry. A number of schemes for the synthesis of ftorafur appear in the literature.[2,10] Most are modifications of the Hilbert–Johnson method of nucleoside synthesis and utilize an activated pyrimidine base and an α-substituted tetrahydrofuran catalyzed by a Lewis acid.[11] Specificity is often a problem and the 1,3-bis(tetrahydrofuranyl) derivative of the pyrimidine has been formed especially when stannic chloride is employed as a catalyst.[9a] Specificity has been demonstrated in the reaction of 5-FU with 2,3-dihydrofuran in the presence of phosphorus pentachloride.[10e]

Activation of the pyrimidine has been accomplished by salt formation,[2a] 2,4-dialkylation,[11] and trimethylsilylation at the 2 and 4 oxygen atoms.[5] The latter method was chosen since it afforded a better N-1 directing effect. Reaction of **2** with hexamethyldisilazane with a few milligrams of ammonium sulfate to protect from moisture afforded a quantitative yield of the liquid **7**. Reaction of this liquid with a 2-substituted tetrahydrothiophene afforded compound **3** (see Scheme I).

The racemic 2-chloro derivative **8** was synthesized by free-radical chlorination of tetrahydrothiophene with *N*-chlorosuccinimide.[12] Compounds **9** and **10** were synthesized by reaction of tetrahydrothiophene with *tert*-butyl peracetate and *tert*-butyl perbenzoate, respectively, in the presence of cuprous bromide and were used as racemic mixtures.[14] Yields of **3** varied with leaving group in an unexpected manner. Reaction with the acetoxy derivative **9** provided the highest yields (45%). Compound **8** underwent spontaneous dehydrochlorination to 2,3-dihydrothiophene during the reaction. Similarly, heat-catalyzed debenzoylation occurred when **10** was utilized. The major recovered product was benzoic acid. Consequently, use of **9** and **10** produced yields of less than 5%.

Table I. Effect of N-1 Substituted 5-FU Derivatives on P388 Lymphocytic Leukemia Growth[a]

compd	av days survived[b]	T/C,[c] %	compd	av days survived[b]	T/C,[c] %
0.05% Tween 80 in NS	10.17		**4**	14.50	143
			5	12.17	119
1	10.00	98	**6**	10.50	103
2[d]	17.60	173	FUDR[e]	15.17	149
3	10.17	100			

[a] 10^6 tumor cells were injected ip into six female CDF_1 mice. The mice were dosed for 9 days at 20 mg/kg with each test compound. [b] Treated mice. [c] T/C of greater than 125% is required for significant activity. No weight loss vs. control was observed for test animals in this experiment. [d] Sigma Chemical Co. [e] Hoffmann-La Roche, Inc.

Table II. Effect of N-1 Substituted 5-FU Derivatives on in Vitro L1210 Cell Growth[a]

compd	concn,[b] μM		
	1	10	100
2	79.8	81.2	90.3
1	17.2	67.5	81.8
3	16.9	52.5	68.5
4	64.9	82.9	84.5
5	59.2	85.0	92.0
6[c]	40.0	49.1	65.5

[a] Maximum cell kill within a 72-h period. Numbers represent percent inhibition versus control ($N = 9$). All values differ significantly from control; $p < 0.05$. [b] Suspensions or solutions in phosphate buffered saline. [c] $N = 4$ for this compound.

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Due to the ease of workup, sodium iodide was used as a catalyst for the synthesis of compound 3. Use of a Lewis acid such as stannic chloride did not increase yields significantly. Moreover, the synthesis of compound 6 required catalysis by a Lewis acid. Reaction utilizing stannic chloride and the readily available (±)-2-chlorocyclopentanone (11) afforded 6 in low yields.

Oxidation of the sulfide 3 was accomplished with *m*-chloroperbenzoic acid in relative molar amounts to form 4 and 5 in high yields.

Results and Discussion

Classical and nonclassical isosteric replacement has led to the discovery of more active and less toxic drugs. Ftorafur (1) is important in that it has a higher therapeutic index than 5-FU (2) but a lower efficacy. Isosteric replacement at the 1′-position could provide substances which may (1) optimize efficacy and toxicity, (2) provide insight into the mechanism of 5-FU release through the C-2′–N-1 bond cleavage, and (3) have a mechanism potentially different from the liberation of 5-FU.

The synthesized derivatives were tested for in vivo antitumor activity and in vitro cytotoxicity. In the P388 lymphocytic leukemia screen, ftorafur (T/C = 98) surprisingly demonstrated no antitumor activity. Similarly, compounds 3, 5, and 6 also proved to be inactive. However, the sulfoxide analogue 4 demonstrated good antitumor activity (T/C = 143). In the L1210 cell culture all compounds demonstrated some cytotoxic activity within 72 h at concentrations ranging from 1 to 100 μM (Table II). The order of decreasing activity did not correlate with that of the P388 lymphocytic leukemia screen. However, in the series of tetrahydrothiophene derivatives in vitro L1210 cytotoxicity was correlated with increasing electronegativity. Compound 4 demonstrated significant activity in both assays.

The basic premise that variation of electronegativity at the 1′-position will influence the rate of cleavage of the N-1–C-2′ linkage is still speculative and few structural correlations can be made. Compounds 4 and 5 contain the highly electronegative sulfoxide and sulfone groups, respectively, and demonstrate good L1210 inhibition properties. The enigma of all structure–activity relationships is the relative inactivity of compound 6, which contains a carbonyl group at the 1′-position. However, this correlates with the low activity characteristic of other carbocyclic analogues of pyrimidines.[13] Preliminary studies have indicated that the three compounds of highest water solubility, 2, 4, and 5, are more active in general than the compounds of highest lipid solubility (1 and 3). Further research is underway to determine the mode of activation of these compounds.

Experimental Section

Chemistry. All melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Thin-layer chromatography was performed on precoated TLC plates (silica gel 60-F-254, EM Reagents) with fluorescent backing and visualized by ultraviolet light. Elemental analyses were done by Atlantic Microlab, Atlanta, GA, and agreed with theoretical values within ±0.4%.

Infrared spectra were obtained with a Perkin-Elmer Model 257 infrared spectrophotometer. Proton NMR spectra were taken on a JEOL FX-90Q spectrometer using tetramethylsilane as an internal standard. All IR and NMR spectra were consistent with assigned structures. Unless otherwise specified, all reagents were used as received from suppliers. Ftorafur was synthesized by the method of Sakuai et al.[10e] Purity was established by comparison of instrumental values with an authentic sample. Fluorodeoxyuridine was kindly supplied by Dr. W. E. Scott, Hoffmann LaRoche, Inc., Nutley, NJ.

1-(2′-Tetrahydrothienyl)-5-fluorouracil (3). Compound 3 was synthesized from the bis(trimethylsilyl) intermediate 7.[5] Hence, 1.3 g (10 mmol) of 5-FU and 2.0 g (12.4 mmol) of hexamethyldisilazane with 5 mg of $(NH_4)_2SO_4$ for protection from moisture were refluxed 4 h at 150–160 °C under N_2. The temperature was then lowered to 100 °C and 5 mL of toluene added and distilled from the solution. The resulting liquid, compound 7, was cooled to 60 °C; 7 mL of dry acetonitrile and 2.5 g (17 mmol) of 2-acetoxytetrahydrothiophene[14] were added dropwise over 1 h. To this solution 750 mg (5 mmol) of NaI was added and the mixture refluxed for 7 h. The mixture was then cooled and the solvent evaporated. The resulting brown powder was taken up into 100 mL of chloroform and extracted with three 60-mL portions of water. The chloroform layer was dried over $MgSO_4$ and evaporated. The light yellow powder yielded 950 mg (45%) of white crystals from ethyl acetate: mp 183–184 °C; TLC (SilG, ethyl acetate) R_f 0.50; IR (KBr) 1725, 1660 (C=O); NMR ($CDCl_3$) δ 7.79 (d, J_{F-H} = 8.1 Hz, 1, 6 H), 6.28–6.13 (m, 1, 2′ H), 3.17–2.85 (m, 2, 5′ H), 2.63–1.65 (m, 4, 3′ H and 4′ H). Anal. C, H, S.

1-(2′-Tetrahydrothienyl)-5-fluorouracil 1′-Oxide (4). A solution of 0.5 g (2.3 mmol) of compound 3 in 30 mL of dry methylene chloride was stirred at room temperature while a solution of 0.4 g (2.3 mmol) of *m*-chloroperbenzoic acid in 10 mL of methylene chloride was added dropwise over 1 h. After 4 h of stirring at room temperature, a whitish precipitate had formed which was filtered and recrystallized from 95% EtOH to give 0.443 g (83%) compound 4: mp 213–215 °C dec; IR (KBr) 1690, 1668 (C=O), 1025 (SO); NMR (Me_2SO-d_6) δ 8.05 (d, J_{F-H} = 6.3 Hz, 1, 6 H), 5.60 (dd, J = 1 Hz, 1, 2′ H), 3.39–2.60 (m, 6, 3′, 4′, and 5′ H). Anal. C, H, N.

1-(2′-Tetrahydrothienyl)-5-fluorouracil 1′,1′-Dioxide (5). Synthesis was carried out from compound 3 according to the reaction above except 2 equiv of *m*-chloroperbenzoic acid was used. 5: white crystals (80%) from 95% EtOH; mp 281–282 °C; IR (KBr) 1720, 1660 (C=O), 1305, 1175 (SO_2); NMR (Me_2SO-d_6) δ 8.26 (d, J_{F-H} = 7.2 Hz, 1, 6 H), 5.75 (dd, J = 1 Hz, 1, 2′ H), 3.29 (s, 6, 3′, 4′, and 5′ H). Anal. C, H, S.

1-(1′-Oxocyclopentan-2′-yl)-5-fluorouracil (6). Compound 7 (10 mmol) at 50 °C was treated dropwise with a solution of 1.18 g (10 mmol) of 2-chlorocyclopentanone, 5 mL of methylene chloride, and 2.6 g (10 mmol) of stannic chloride (previously stirred at room temperature for 30 min). The addition was made over 2 h after which the mixture was refluxed 12 h. The mixture was then cooled and fractioned between methylene chloride and water. The organic layer was dried over $MgSO_4$ and evaporated. Repeated recrystallization from chloroform afforded 0.210 g (10%) light brown crystals: mp 222–223 °C dec; IR (KBr) 1750, 1705, 1660 (CO); NMR (Me_2SO-d_6) δ 7.69 (d, J_{F-H} = 6.3 Hz, 1, 6 H), 4.64 (dd, J = 1 Hz, 1, 2′ H), 3.41–3.10 (m, 2, 5′ H), 2.38–2.10 (m, 4, 3′, and 4′ H). Anal. C, H, N.

Tumor Screens. P388 Lymphocytic Leukemia Screen. All test compounds were sonicated in 0.05% Polysorbate 80 (Tween 80) in sterile normal saline and were administered intraperitoneally. Dosing was based on the optimum dose of 5-fluorouracil (20 mg/kg) in this test screen in order that structure–activity relationships could be determined. The P388 lymphocytic leukemia screen was performed according to NIH protocol,[15] using female CDF_1 mice (~25 g). On day 0, 1×10^6 cells were injected ip. Test compounds were administered on days 1–9. T/C values were calculated, and a T/C of greater than 125% was considered significant activity. Six mice were used per test group. 5-FU and fluorodeoxyuridine were used as positive internal standards.

L1210 Cell Culture Cytotoxicity Screen. All test compounds were suspended or dissolved in sterile phosphate buffered saline (5 mM) and sonicated for 3 min to disperse the particles. Serial dilution resulted in micromolar concentrations used for testing. The L1210 cells were maintained as continuous suspension cultures in growth medium containing Roswell Park Memorial Institute-1640 supplemented with 10% fetal calf serum, 10 units/mL of penicillin, and 100 mg/mL of streptomycin (Gibco Laboratories, Grand Island, NY). Cultures were incubated in a CO_2 incubator (Forma Scientific, Marietta, OH) at 37 °C, 98%

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humidity, and 5% CO_2. Exponentially growing cells (4×10^5 cells/mL) were incubated with test compounds at concentrations of 1, 10, or 100 μm. Cell counts were taken at 24, 48, and 72 h. Cell viability was measured by the trypan blue exclusion technique.[16] Stability of all suspensions was monitored throughout the test period by thin-layer chromatography.

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Acknowledgment. This research was supported partly by Grant 903A awarded by the Northeast Louisiana University Research Committee and in part by the Northeast Louisiana School of Pharmacy. Annette Shipp is a Silas M. Burroughs Fellow of the American Foundation for Pharmaceutical Education.

Registry No. **2**, 51-21-8; **3**, 93473-97-3; **4**, 70758-92-8; **5**, 93473-98-4; **6**, 93473-99-5; **7**, 17242-85-2; **9**, 93474-00-1; **11**, 93474-01-2; hexamethyldisilazane, 999-97-3.

N-[2-Hydroxy-5-[2-(methylamino)ethyl]phenyl]methanesulfonamide. A Potent Agonist Which Releases Intracellular Calcium by Activation of α_1-Adrenoceptors

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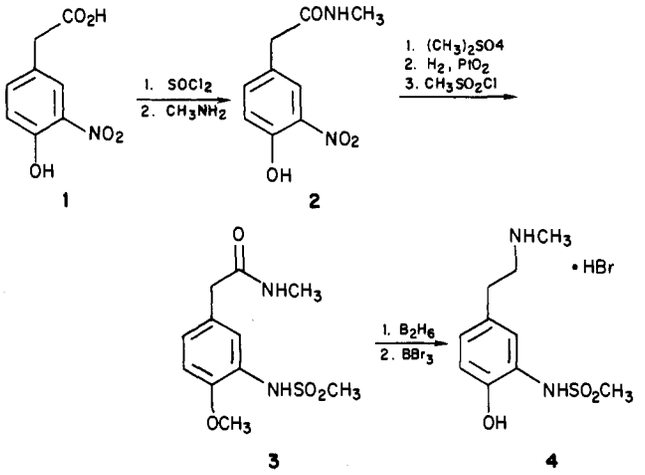
N-[2-Hydroxy-5-[2-(methylamino)ethyl]phenyl]methanesulfonamide (SK&F 102652) has been prepared and characterized pharmacologically. It is a potent agonist with an EC_{50} of 25 nM at α_1-adrenoceptors as determned in the isolated perfused rabbit ear artery. On the presynaptic α_2-adrenoceptors of the guinea pig atrium it was considerably weaker, demonstrating an EC_{50} for inhibition of neurotransmission of 1200 nM and thus an overall α_1/α_2 selectivity ratio of ≥48. In the vascular smooth muscle of the canine saphenous vein an EC_{100} concentration of this agonist in the presence of zero external Ca^{2+} induced 37.9 ± 1.4% of the maximal contractile response due to this agent while the endogenous ligand norepinephrine evoked only 14.5 ± 0.4% of the maximum. In the presence of low (1 μM) external calcium, this agent produced 78.3 ± 5.3% of maximum while norepinephrine gave 45.3 ± 7.4%. This agent produces α_1-adrenoceptor-mediated contraction primarily by release of intracellular Ca^{2+} and should provide a useful tool for characterizing α_1-receptor subtypes.

In the last several years, it has been amply demonstrated that two distinct types of postsynaptic α-adrenoceptors (α_1, α_2) are present on vascular smooth muscle and that activation of either subtype causes vasoconstriction.[1-3] Evidence has been produced from both in vitro and in vivo experiments to indicate that there is a pharmacological difference in the Ca^{2+} utilization process of smooth muscle after stimulation of α_1- or α_2-adrenoceptors.[4-6] Studies from a number of laboratories have shown that activation of postsynaptic α_2-adrenoceptors causes the influx of extracellular Ca^{2+} across the cell membrane and that it is this translocation of Ca^{2+} that mediates the contractile process.[6-8] On the other hand, activation of postsynaptic α_1-adrenoceptors can induce both extracellular Ca^{2+} influx and intracellular Ca^{2+} release to initiate vascular smooth muscle contractions.[9-11]

Activation of the postsynaptic α_1-adrenoceptor may use either extracellular Ca^{2+}, intracellular Ca^{2+}, or both to initiate contraction and the pathway taken can be dependent on the chemical structure of the α_1-agonist employed to produce the contraction. We have shown previously that there are differences in the responses to α_1-agonist-mediated vasoconstriction produced by two different chemical classes of α_1-agonists.[11] These results suggest that agonists such as methoxamine and SK&F l-89748 (*l*-1,2,3,4-tetrahydro-8-methoxy-5-(methylthio)-2-naphthalenamine)[12] primarily use extracellular Ca^{2+} to produce contractions of smooth muscle. α_1-Agonists of a different general structural type, such as phenylephrine or norepinephrine, which have protonic containing substituents on the meta position of the aromatic ring, are able to induce contraction by both translation of extracelular Ca^{2+} and by internal release of Ca^{2+} stores.[13] The compound described in this report, *N*-[2-hydroxy-5-[2-(methylamino)ethyl]phenyl]methanesulfonamide (SK&F 102652) is a selective α_1-adrenoceptor agonist which has

Scheme I



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