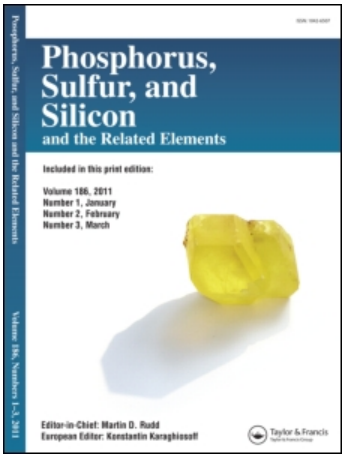

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THE REACTION OF SOME SUBSTITUTED BENZILS AND HETEROCYCLIC ANALOGS WITH CHLOROSULFONIC ACID

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THE REACTION OF SOME SUBSTITUTED BENZILS AND HETEROCYCLIC ANALOGS WITH CHLOROSULFONIC ACID

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The chlorosulfonation of a number of unsymmetrical benzils gave substituted benzofurans. Ring closure is dependent upon the electronic character of the substituent groups and can be controlled by electron-withdrawing groups. The reaction of the 2-thienyl analog gave one product but the 3-thienyl compound gave a mixture of isomers. The previously proposed mechanism can be used to explain these results.

Key words: Chlorosulfonic acid; substituted benzils; 2-arylbenzofuran derivatives.

INTRODUCTION

We have shown[1] that the treatment of benzil with an excess of chlorosulfonic acid at 40°C gave 3-chloro-2-phenylbenzofuran-6,4′-disulfonyl chloride. The proposed reaction pathway involved initial chlorohydrin formation, chlorosulfonation in the less deactivated phenyl ring, followed by ring closure—the latter being facilitated by the presence of the electron-withdrawing chlorosulfonyl group.[2]

Our previous investigations[1,2] were concerned primarily with symmetrical systems and have shown that cyclisation could be achieved except with 3,3′-dinitro- and 4,4′-dinitrobenzil.[2] In this paper, details of the optimum experimental conditions are described and the influence of substituents on the orientation of ring closure has been described. We have examined the reaction of a number of unsymmetrical benzils and some heterocyclic analogs with chlorosulfonic acid using these conditions.

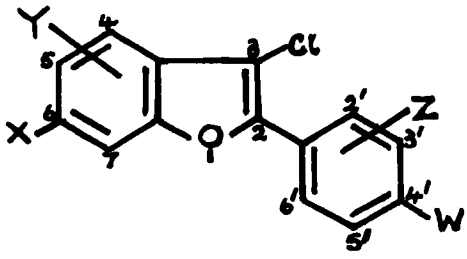
DISCUSSION

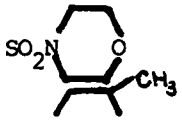
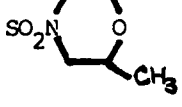
Previous work[1] suggested that the reaction of benzil with chlorosulfonic acid (6 equivalents), could be carried out above 40°C provided that dry chloroform was used as solvent, to avoid decomposition. However, examination of the reaction mixture by tlc indicated the presence of base-line material, which probably contained a sulfonic acid group. In order to complete the conversion of the sulfonic acid into the sulfonyl chloride, the excess of the reagent was increased to 12 equivalents.[3] However, under these conditions 3-chloro-2-phenylbenzofuran-4,6,4′-trisulfonyl chloride was isolated.

We have now prepared the 6,4′-disulfonyl chloride in excellent yield (>90%), by heating benzil with a smaller excess (3 equivalents) of the reagent in thionyl

chloride as chlorinating solvent. This product was characterized as the bis-N,N-dimethylsulfonamide (**1**). There was no evidence of the 4,6,4′-trisulfonyl chloride when the excess of the reagent was increased to 6 equivalents.

The reaction of each of the compounds described below was carried out using the optimised conditions—heating with 3 equivalents of the reagent in thionyl chloride.



	W	X	Y	Z
1	$SO_2N(CH_3)_2$	$SO_2N(CH_3)_2$	H	H
2	CH_3	$SO_2N(CH_3)_2$	H	3′-$SO_2N(CH_3)_2$
3	$SO_2N(CH_3)_2$	CH_3	5-$SO_2N(CH_3)_2$	H
4	CH_3	$SO_2N(CH_3)_2$	4-$SO_2N(CH_3)_2$	H
5	$SO_2N(CH_3)_2$	Cl	4-$SO_2N(CH_3)_2$	H
6	Cl	$SO_2N(CH_3)_2$	H	2′-$SO_2N(CH_3)_2$
7	NO_2	$SO_2N(CH_3)_2$	H	H
8	NO_2	$SO_2N(C_2H_5)_2$	H	H
9	NO_2		H	H
10	NO_2		H	H

4-Methylbenzil gave two products by tlc and after treatment with dimethylamine two new products were obtained. Micro-analysis and the mass spectrum (M^+ 458, 456) suggested these latter products were isomers with formula $C_{19}H_{21}ClN_2O_5S_2$ corresponding to bis-N,N-dimethylsulfonamides. The ^1H NMR spectrum supported this, on the basis of four peaks in the region of δ 3 due to 12 protons and two peaks in the region δ 2.5 due to 3 protons.

From the above evidence, 4-methylbenzil has undergone competitive cyclisation with probable formation of compounds **2** and **3**. The aromatic region of the ^1H NMR spesctrum due to 6 protons was too complicated to confirm the substitution patterns. However, the position of substitution in the fused ring in compound **2** can be supported by the combined electron-donating effects of the methyl substituent and the heterocyclic oxygen atom, while that in the tolyl ring of compound **3** could be expected due to stereoelectronic factors. It is unlikely that compound **4** was formed, as there was no evidence of 4,6-disubstitution in the case of benzil. Thus, there is little difference in the ease of chlorohydrin formation at either of the carbonyl groups, which consequently leads to the formation of two products.

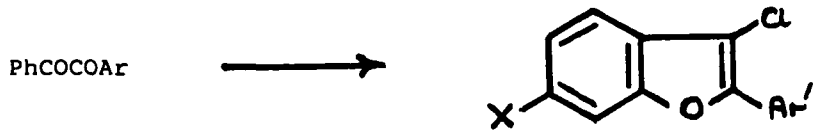
A mixture of two products was also obtained from 4-chlorobenzil. After treatment with dimethylamine, the mass spectrum (M^+ 480, 478, 476) and micro-analysis supported the formula $C_{18}H_{18}Cl_2N_2O_5S_2$, which corresponded to an isomeric mixture of the bis-N,N-dimethylsulfonamides. As with 4-methylbenzil it was not possible to determine the substitution patterns from the ^1H NMR spectrum, but on stereoelectronic grounds structures **5** and **6** seem possible. Thus, although the chloro substituent had a weakly-deactivating influence on chlorohydrin formation α to the substituted ring, this was not sufficient to inhibit competitive cyclisation.

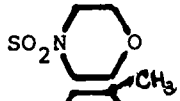
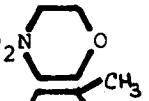
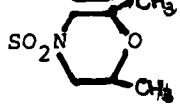
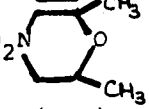
It was not surprising to observe that 4-chloro-4-methylbenzil also gave a similar mixture of products, in view of the inability of these substituents individually to control the course of the reaction.

The reaction of 4-nitrobenzil gave one product. After treatment with dimethylamine the mass spectrum of the derived product (M^+ 382, 380) and micro-analysis supported the formula $C_{16}H_{13}ClN_2O_5S$ and indicated that monosubstitution had occurred. The aromatic region of the ^1H NMR spectrum contained an AA'BB' pattern characteristic of *para*-disubstitution together with an ABC pattern. The protons assigned to the former pattern were more deshielded than the corresponding protons in product **1** from benzil. Consequently, as the nitro group has a greater electron-withdrawing effect than the chlorosulfonyl group, the structure of the product from the reaction with 4-nitrobenzil is considered to be **7**. The sulfonyl chloride was additionally characterized by reaction with diethylamine (**8**), morpholine (**9**) and 2,6-dimethylmorpholine (**10**).

The nitro group clearly controls the course of this reaction. The carbonyl group α to the substituted ring is sufficiently deactivated for the chlorohydrin to be formed preferentially at the other carbonyl group. A similar result was obtained with 4-N,N-dimethylaminobenzil due to protonation of the substituent under the reaction conditions, leading to electron withdrawal and deactivation of the adjacent carbonyl group.[2]

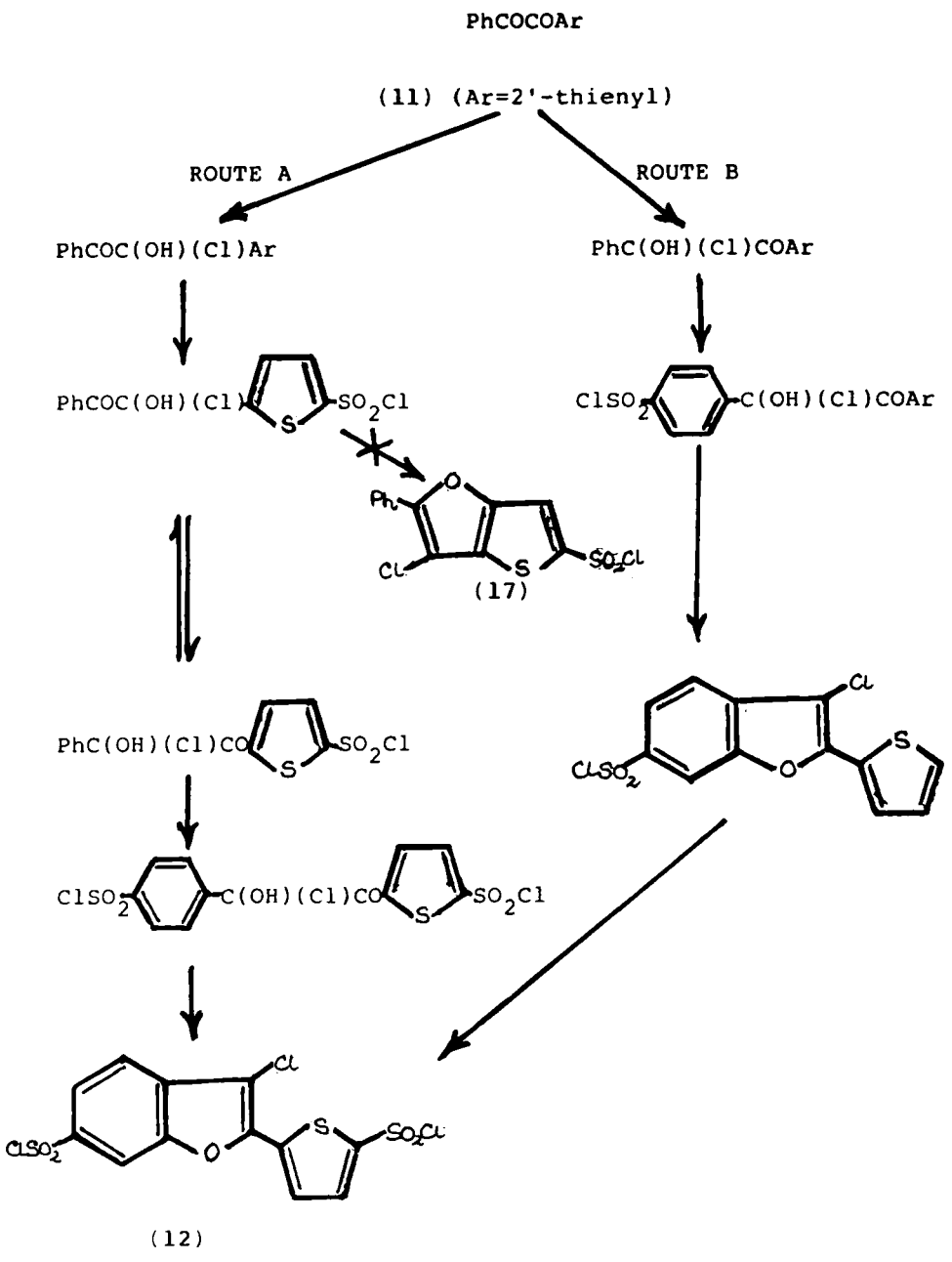
As we have clearly demonstrated that the reaction of an unsymmetrical system with chlorosulfonic acid can be controlled by sufficiently strong electron-withdrawing groups, it was appropriate to investigate the influence of electron donation. A



	Ar	X	Ar'
11	2'-thienyl	12 SO_2Cl	2'-thienyl-5'-SO_2Cl
		13 $SO_2N(CH_3)_2$	2'-thienyl-5'-$SO_2N(CH_3)_2$
		14 $SO_2N(C_2H_5)_2$	2'-thienyl-5'-$SO_2N(C_2H_5)_2$
		15 	2'-thienyl-5'- 
		16 	2'-thienyl-5'- 
18	3'-thienyl	19 $SO_2N(CH_3)_2$	3'-thienyl-4'-$SO_2N(CH_3)_2$
		20 $SO_2N(CH_3)_2$	3'-thienyl-5'-$SO_2N(CH_3)_2$
21	2'-furyl		

suitable substrate for this purpose is 2-(1′,2′-dioxo-2′-phenyl)ethylthiophene (**11**), as the thiophene ring is activated to electrophilic attack and such a study would extend to heterocyclic compounds. The reaction of compound (**11**) with chlorosulfonic acid under the prescribed reaction conditions gave the disulfonyl chloride (**12**). The identity of this compound was determined by conversion into a number of derivatives (**13–16**), by condensation with the secondary amines used in the characterization of the product obtained from 4-nitrobenzil. Examination of the spectral data of the N,N-diethylsulfamoyl derivative (**14**) confirmed the structure unambiguously. Micro-analytical data together with the mass spectrum (M^+ 506, 504) supported the formula $C_{20}H_{24}ClN_2O_5S_3$. The ^1H NMR spectrum showed in the aromatic region (δ 8.0–7.0), a typical ABC pattern together with an AB pattern for which the coupling constant of 3.9 Hz confirmed 5′-substitution indicative of cyclisation onto the phenyl rather than the thienyl ring.

The mode of formation of the 2-thienylbenzofuran derivative (**12**) could occur by either of the two routes depicted in Scheme 1. In *route A*, chlorohydrin formation occurs α to the thiophene ring which then undergoes electrophilic attack at the 5-position. Cyclisation of this intermediate is probably precluded at this stage due to the ring strain present in the fused system (**17**). Consequently equilibration of the chlorohydrin with that α to the phenyl ring facilitates cyclisation. However,



SCHEME 1

route B cannot be entirely ruled out, although initial chlorohydrin formation α to the phenyl ring is less favoured on the basis of the relative +M effects of the phenyl and thienyl rings. Treatment of the regio-isomer, 3-(1',2'-dioxo-2'-phenyl)ethylthiophene (**18**) contaminated with benzil (see experimental), under the prescribed conditions followed by reaction with dimethylamine, gave a mixture of

three products. LCMS confirmed the presence of compound **1**, by the addition of an authentic sample. The remaining products were shown to be isomers with highest mass ions m/Z 450, 448 corresponding to the formula $C_{16}H_{17}ClN_2O_5S_3$. It seems probable that by analogy with the reaction of compound (**11**) the products are the bis-dimethylsulfonamides (**19**) and (**20**).

Treatment of the furan analog (**21**) of compound (**11**) with chlorosulfonic acid was unsuccessful. The reaction proceeded vigorously and gave a tar. This result is not unexpected in view of the greater reactivity of the furan ring and its sensitivity to strongly acidic reagents.

EXPERIMENTAL

Melting points were determined using an electrical Gallenkamp apparatus and are uncorrected. IR spectra were measured as KBr discs on a Pye Unicam SP3/100 spectrophotometer. ^{1}H NMR spectra were recorded with a Bruker WP80 spectrometer in deuterochloroform as solvent using tetramethylsilane as internal reference standard. Mass spectra were determined with a VG Micromass V15 instrument. TLC was carried out on Camlab Polygram silica gel plates sensitized to UV 254 nm, using cyclohexane-ethyl acetate 1:1 as eluant. Micro-analyses were carried out by courtesy of ICI (Pharmaceuticals Division) plc, Macclesfield, Cheshire, England.

General procedure for benzil preparation. The two aldehydes (0.5 mole of each) were dissolved in ethanol (500 ml) and potassium cyanide (20 g) in water (50 ml) was added. The solution was heated under reflux for 1.5 hours, cooled and the precipitate of benzoin washed well with water to remove cyanide.

The benzoin (0.2 mole) was added to a solution of copper sulfate (50 g) in pyridine (50 ml) and water (50 ml) at 80°C and the mixture maintained at that temperature for 2 hours. It was cooled, filtered, washed with water (5x200 ml) and air dried. The crude benzil was dissolved in dichloromethane (300 ml) and stirred with activated charcoal to remove any residual copper sulfate. The solution was filtered, washed with 2 M hydrochloric acid (5 × 100 ml), 1 M sodium bicarbonate solution (2 × 100 ml), water (2 × 100 ml) and dried ($MgSO_4$). The solvent was evaporated *in vacuo* to give the benzil.

The benzils prepared by this route were:
(**11**), (35%), m.p. 60–61°C, (lit.[4] 59–60°C);
(**18**), (45%), m.p. 72–73°C, (lit.[5] 81–83°C);
(This product was contaminated with benzil which could not be removed.)
(**21**), (22%), m.p. 140–142°C, (lit.[6] 142°C)

The following benzils were supplied by courtesy of ICI (Pharmaceuticals Division) plc: 4-chloro, 4-chloro-4'-methyl, 4-methyl, 2,3,4,5,6-pentamethyl.

4-Nitrobenzil. Benzoin (100 g, 0.47 mole) was dissolved in a mixture of concentrated sulfuric acid (100 g) and acetic anhydride (500 ml). The solution was cooled to −10°C and powdered potassium nitrate (55 g) was added, while retaining the temperature below −5°C and the mixture allowed to stand for 3 days. The precipitate was filtered off to give 4-nitro-O-acetylbenzoin (80 g, 27%), m.p. 195–196°C.

The benzoin was added to hot (90°C) fuming nitric acid (200 ml). The mixture was stirred until the evolution of nitrogen dioxide ceased. The solution was cooled, poured onto ice to give a gum which was washed with boiling water (2 × 500 ml). Recrystallization (ethanol) gave yellow needles of 4-nitrobenzil (65 g, 54%), m.p. 141–142°C, (lit.[7] 142°C).

General procedure for chlorosulfonation. The benzil (5 g) was dissolved in thionyl chloride (50 ml) and chlorosulfonic acid (3 mole equivalents) was added. The solution was heated under reflux for 1 hour, left overnight and the product filtered off. The crude product was used for derivative preparation without purification.

General procedure for derivative preparation. The crude sulfonyl chloride (2 g) was added to a stirred solution of the amine (2.5 mole equivalents) in 50% aqueous acetone (30 ml) at room temperature. The mixture was added to an equal volume of water and the precipitate filtered off, washed with water and recrystallized (ethanol).

Compound **7**. (75%), m.p. 225–226°C, TLC one spot R_F 0.50. (Found: C, 50.5; H, 3.3; N, 7.4. $C_{16}H_{13}ClN_2O_5S$ requires C, 50.5; H, 3.4; N, 7.4%). IR ν_{max} 1600 (Ar C=C) 1520, 1330 (NO_2), 1340, 1160 (SO_2) cm^{-1}. ^1H NMR δ: 8.5–8.3 (4H, AA'BB', ArH), 8.2–7.8 (3H, ABC, ArH), 2.7 (6H, s, CH_3). MS m/Z 382, 380 (M^+), 274, 272 (M^+—$SO_2N(CH_3)_2$); accurate mass measurement for M^+, found 380.0242, requires 380.0235.

Compound **8**. (60%), m.p. 194–195°C, TLC one spot R_F 0.50. (Found: C, 52.7; H, 4.2; N, 6.8. $C_{18}H_{17}ClN_2O_5S$ requires C, 52.9; H, 4.2; N, 6.9%). IR ν_{max} 1610 (Ar C=C), 1520, 1330 (NO_2), 1360, 1160 (SO_2) cm^{-1}. ^1H NMR δ: 8.5–7.7 (7H, m, ArH), 3.25 (4H, q, 2 × CH_2), 1.2 (6H, t, 2 × CH_3). MS m/Z 410, 408 (M^+), 395, 393 (M^+—CH_3), 380, 378 (M^+—NO), 338, 336 (M^+—$N(C_2H_5)_2$), 274, 272 (M^+—$SO_2(C_2H_5)_2$).

Compound **9**. (65%), m.p. 212–214°C, TLC one spot R_F 0.40. (Found: C, 50.8; H, 3.7; N, 6.6. $C_{18}H_{15}ClN_2O_6S$ requires C, 51.1; H, 3.6; N, 6.6%). IR ν_{max} 1600 (Ar C=C), 1510, 1330 (NO_2), 1320, 1180 (SO_2) cm^{-1}. ^1H NMR δ: 8.5–7.7 (7H, m, ArH), 2.7–2.2 (8H, m, alkyl H). MS m/Z 424, 422 (M^+), 338, 336 (M^+—C_4H_8NO).

Compound **10**. (65%), m.p. 195–196°C, TLC one spot R_F 0.40. (Found: C, 53.0; H, 4.2; N, 6.1. $C_{20}H_{19}ClN_2O_6S$ requires C, 53.3; H, 4.2; N, 6.2%). IR ν_{max} 1600 (Ar C=C), 1540, 1330 (NO_2), 1350, 1160 (SO_2) cm^{-1}. ^1H NMR δ: 8.4–7.7 (7H, m, ArH), 3.7–1.0 (12H, m, alkyl H).

Compound **13**. (65%), m.p. 185–187°C, TLC one spot R_F 0.50. (Found: C, 43.1; H, 3.7; N, 6.0. $C_{16}H_{17}ClN_2O_5S_3$ requires C, 42.8; H, 3.8; N, 6.2%). IR ν_{max} 1600 (Ar C=C), 1360, 1160 (SO_2) cm^{-1}. ^1H NMR δ: 8.0–7.5 (5H, m, ArH), 2.9 (6H, s, 2 × CH_3), 2.8 (6H, s, 2 × CH_3). MS m/Z 450, 448 (M^+), 342, 340 (M^+—$SO_2N(CH_3)_2$).

Compound **14**. (70%), m.p. 203–204°C, TLC one spot R_F 0.50. (Found: C, 47.3; H, 4.9; Cl, 7.2; N, 5.2; S, 18.7. $C_{20}H_{25}ClN_2O_5S_3$ requires C, 47.6; H, 5.0; Cl, 7.0; N, 5.6; S, 19.0%). IR ν_{max} 1600 (Ar C=C), 1320, 1140 (SO_2) cm^{-1}. ^1H NMR δ: 8.0–7.7 (3H, ABC, ArH), 7.75 (1H, d, thiophene-H4'), 7.58 (1H, d, thiophene-H3'), 3.4–3.2 (8H, 2 × q, 2 × CH_2), 1.4–1.3 (6H, 2 × t, 2 × CH_3). MS accurate mass measurement for M^+, found 504.0601, requires 504.0612, M^+—$N(C_2H_5)_2$, found 431.9819, requires 431.9798, M^+—$SO_2N(C_2H_5)_2$, found 368.0164, requires 368.0180.

Compound **15**. (45%), m.p. 233–235°C, TLC one spot R_F 0.30. (Found: C, 45.4; H, 4.1; N, 5.3. $C_{20}H_{21}ClN_2O_7S_3$ requires C, 45.1; H, 3.9; N, 5.3%). IR ν_{max} 1600 (Ar C=C), 1350, 1150 (SO_2) cm^{-1}. ^1H NMR δ: 8.0–7.5 (5H, m, ArH), 2.7–2.2 (16H, m, alkyl H). MS m/Z 534, 532 (M^+), 448, 446 (M^+—C_4H_8NO), 384, 382 (M^+—$SO_2C_4H_8NO$).

Compound **16**. (35%), m.p. 320–322°C, TLC one spot R_F 0.20. (Found: C, 49.2; H, 4.8; N, 5.0. $C_{24}H_{29}ClN_2O_7S_3$ requires C, 48.9; H, 4.9; N, 4.8%). IR ν_{max} 1600 (Ar C=C), 1350, 1150 (SO_2) cm^{-1}. ^1H NMR δ: 8.5–7.5 (5H, m, ArH), 4.0–1.0 (24H, m, alkyl H). MS m/Z 590, 588 (M^+).

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