12-(3-DIMETHYLAMINOPROPYLIDENE)-12*H*-BENZO[*f*]NAPHTHO[1,8-*bc*] THIEPIN AND 10-CHLORO-12-(4-METHYLPIPERAZINO)-12*H*-BENZO[*f*] NAPHTHO[1,8-*bc*]THIEPIN*

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Reactions of 8-iodo-1-naphthoic acid with thiophenol and 4-chlorothiophenol yielded acids *VIIa* and *VIIb* which were cyclized with polyphosphoric acid. The primary products were benzo[*f*]-naphtho[1,8-*bc*]thiepin-12-one (*IIIa*) and its 10-chloro derivative *IIIb* which, on longer exposure to polyphosphoric acid, undergo a transacylation to the more stable benzo[*c*]thioxanthones *VIIIa* and *VIIIb*. Ketone *IIIa* reacted with 3-dimethylaminopropylmagnesium chloride and the product was dehydrated to the olefinic amine *I* which is a potential thymoleptic; in agreement with this, it displays a pronounced antireserpine and anticataleptic activity in tests in animals. The methylpiperazino derivative *IIb* was prepared from ketone *IIIb via* alcohol *Vb* and chloride *VIb*; *IIb* displays no neuroleptic activity.

In two preceding communications of this series[1,2] we dealt with the synthesis of potential neuroleptics of the 10-piperazinodibenzo[*b*,*f*]thiepin type which have another ring condensed with the tricyclic system. The present communication is a sequel to the program and deals with derivatives of the little known system of 12*H*-benzo[*f*]-naphtho[1,8-*bc*]thiepin (RRI 5308). The system is simultaneously a benzologue of dibenzo[*b*,*f*]thiepin and a benzologue of dibenzo[*b*,*e*]thiepin; using suitably constructed amines derived from it, one could thus assume both a thymoleptic and a neuroleptic activity[3-6]. Ref.[7-11] describe amines derived from the carbocyclic analogue of the present system, *i.e.* from 7,12-dihydropleiadene (RRI 5311) and from the corresponding 1,2,3,7,12,12a-hexahydro derivative, for which thymoleptic, tranquilizing and anticonvulsant activities have been reported.

The only derivative of 12*H*-benzo[*f*]naphtho[1,8-*bc*]thiepin reported in the literature is 6-methoxybenzo[*f*]naphtho[1,8-*bc*]thiepin-12-one which was obtained by Knapp[12] through cyclization of 2-(2-methoxy-1-naphthylthio)benzoic acid with the aid of phosphorus pentoxide in toluene in a 35% yield. The analogously conducted attempt at cyclization of 2-(1-naphthylthio)benzoic acid led only to the sterically more advantageous benzo[*c*]thioxanthone (*VIIIa*).

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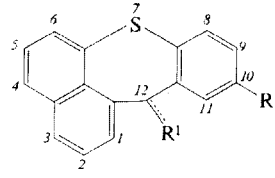
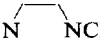
To preclude the possibility of formation of benzo[*c*]thioxanthones (*VIII*) we used as starting compounds the 8-(phenylthio)-1-naphthoic acid (*VIIa*) and its chloro derivative *VIIb* which were obtained by condensation of the known 8-iodo-1-naphthoic acid[13] with thiophenol or with 4-chlorothiophenol in a boiling solution of potassium hydroxide in the presence of copper. Acids *VII* should represent unequivocal precursors of ketones *III*. Cyclization experiments carried out at 130–150°C using polyphosphoric acid resulted in both cases in mixtures from which a combination of crystallization and chromatography succeeded to isolate two pure isomeric ketones in each case. The less polar ketones (ν(CO) 1 660 or 1 661 cm^{-1}) were identified as the desired *IIIa* and *IIIb*. The more polar ketones (ν(CO) 1 632 or 1 630 cm^{-1}) displaying a higher degree of conjugation also by its UV spectrum, represent the unexpected benzo[*c*]thioxanthones *VIIIa* and *VIIIb*. In the case of *VIIIa* the proof of identity could be supported by a comparison with an authentic sample[12,14,15]. In the case of 9-chlorobenzo[*c*]thioxanthone (*VIIIb*) the mass spectrum was recorded. It was found in further cyclization attempts that a reduction of the reaction period favours the production of practically pure ketones *III* which are apparently the primary cyclization products. On the contrary, when the reaction period is extended and a larger excess of polyphosphoric acid is used, the amount of ketones (*VIII*) formed increases so that they become in the end practically the sole products. Thus a transformation of the primarily formed ketones *III* to the more stable ketones



I, $R^1 = CHCH_2CH_2N(CH_3)_2$

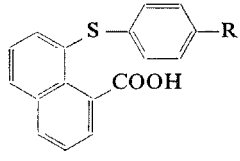
II, R^1 = 

IV, R^1 = 

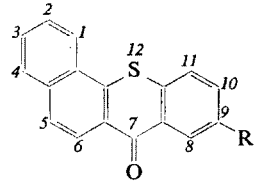
III, $R^1 = =O$

V, $R^1 = OH$

VI, $R^1 = Cl$



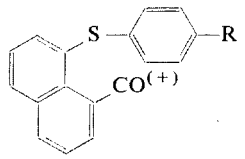
VII



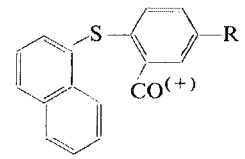
VIII

VIII takes place, as documented by longer heating of the pure ketone *IIIa* with excess polyphosphoric acid, practically pure *VIIIa* resulting from the process.

The mentioned formation of benzo[*c*]thioxanthones (*VIII*) is accounted for by a transacylation mechanism as described for asymmetric benzophenones for the first time by Fuson and coworkers[16] and studied systematically by Indian authors[17–19]. The recently described cyclization of 2-[2-(2-naphthyl)ethyl] benzoic acid with polyphosphoric acid when 7,8-dihydrobenzo[*a*]naphtho[2,1-*e*]cycloheptene-13-one is formed primarily belongs to the same category. The ketone is further transformed to the thermodynamically more stable 12,13-dihydrobenzo[*a*]-naphtho[2,3-*e*]cyclohepten-5-one[20]. In this case, the common precursor of both ketones is the same acylium cation. In the present case it must be assumed that the primary products *III* are formed from acylium cations *A* and, in the course of further exposure to polyphosphoric acid, the ketones formed are cleaved to the isomeric acylium cations *B* which are the immediate precursors of benzo[*c*]thioxanthones *VIII*. All the cases of transacylation reactions[16–20] provide experimental evidence for Gore's theory[21,22] of reversibility of the Friedel–Crafts acylation reaction; apparently one has to assume equilibrium states between the resulting ketones and the corresponding acylium cations, two different acylium cations being involved in the asymmetric diarylketones. Thus the view that the Friedel–Crafts acylation is an irreversible process when no complications with rearrangement can arise is hardly tenable[23,24] (see also the paper by Agranat and coworkers[25] which appeared during the preparation of this manuscript).



A



B

In all formulae *a*, R = H; *b*, R = Cl.

Ketone *IIIa* was exposed to 3-dimethylaminopropylmagnesium chloride[26] in tetrahydrofuran and converted to amino alcohol *IVa* which was dehydrated by heating with dilute sulfuric acid. The resulting olefinic amine *Ia* is apparently a mixture of geometric isomers; crystallization of the hydrochloride yielded two fractions, one of which may be a homogeneous substance. Ketone *IIIb* was reduced with sodium borohydride in ethanol to alcohol *Vb* which was treated with hydrogen chloride in benzene to convert it to the chloro derivative *VIb*. Its substitution reaction[27] with 1-methylpiperazine in chloroform requires a longer reaction time; however, finally the desired piperazine derivative *IIb* was obtained.

Amine *Ia* which was evaluated pharmacologically in the form of hydrochloride, is a benzologue of the antidepressant agent "dosulepin" (prothiadene)[28-30]; its evaluation was thus oriented accordingly. Acute toxicity was determined in mice; LD_{50} on *i.v.* application is 43 mg/kg, on oral application it is between 100 and 500 mg/kg (the first dose is not lethal for any animal out of ten, the second dose is lethal for 9 out of ten). The substance has a very low central depressant action; in the rotating rod test in mice an *i.v.* dose of 20 mg/kg brings about ataxia in at most 40% animals, an oral dose of 100 mg/kg in at most 30% animals. In the catalepsy test in rats (a dose of 10 mg/kg *i.p.*) the substance is inactive. More interesting are the results of evaluating the antagonism of *Ia* toward the effects of reserpine. Intraperitoneal doses of 10 and 40 mg/kg antagonize with statistical significance the reserpine-induced eyelid ptosis in mice. Dosulepin[28-30] and imipramine[31] used for reference have analogous effects in these doses. In rats, a subcutaneous dose of 50 mg/kg *Ia* antagonizes insignificantly the ulcerogenic effect of reserpine (for method see ref.[29]). Dosulepin[28-30] has a statistically significant effect in the same dose. An oral dose of *Ia* (100 mg/kg) antagonizes the prochlorperazine or perphenazine catalepsy in rats somewhat less pronouncedly than equal doses of dosulepin or imipramine. In general, it may be concluded that *Ia* displays the assumed character of a thymoleptic even if apparently weaker than the standard preparations (dosulepin, imipramine) used as antidepressants therapeutically.

Amine *IIb* which is a benzologue of the neuroleptic "clorotepin" (octoclothepin)[27,32] was evaluated as maleate from the point of view of this structural similarity. It is very little toxic; an oral dose of 500 mg/kg is not lethal for any mouse out of ten. It has practically no central depressant activity; an oral dose of 100 mg/kg brings about ataxia in at most 20% animals in the rotating rod test in mice. Finally, at an oral dose of 50 mg/kg it is cataleptically inactive in rats. In spite of its structural similarity with clorotepin it thus lacks the character of a neuroleptic.

EXPERIMENTAL

The melting points of analytical preparations were determined in Kofler's block and are not corrected; the samples were dried *in vacuo* at about 0·5 Torr over phosphorus pentoxide at a suitable temperature (maximum 100°C). The UV spectra (in methanol) were recorded in a Unicam SP 700 spectrophotometer, IR spectra (in Nujol unless stated otherwise) in a Unicam SP 200G or in an Infrascan (Hilger and Watts) spectrophotometer; NMR spectra (in $CDCl_3$ unless stated otherwise) in a ZKR 60 (Zeiss, Jena) spectrometer; the mass spectrum in a MS 902 (AEI) spectrometer. The homogeneity of the compounds was tested by thin-layer chromatography on alumina or silica gel.

8-(Phenylthio)-1-naphthoic Acid (*VIIa*)

Copper (1·5 g) and 40 g 8-iodo-1-naphthoic acid[13] (m.p. 164—165°C) were added to a solution of 15·5 g KOH in 250 ml water with 15 g thiophenol and the mixture was refluxed for 2·5 h. The hot solution was filtered and the filtrate acidified with hydrochloric acid. The precipitated product crystallized on standing; 21 g (56%), m.p. 134—136°C (aqueous ethanol). UV spectrum: λ_{max} 220 nm (log ε 4·54), 247 nm (4·15), 273 nm (3·88), 317 nm (3·69). IR spectrum: 695, 705, 750, 765 (5 and 3 adjacent Ar—H), 917, 1285, 1685 cm^{-1} (COOH). NMR spectrum: δ 11·71 (bs, disappears after D_2O, 1 H, COOH), 7·20—8·00 (m, 6 H, aromatic protons of naphthalene), 7·04 (s, 5 H, C_6H_5). For $C_{17}H_{12}O_2S$ (280·3) calculated: 72·83% C, 4·32% H, 11·44% S; found: 72·90% C, 4·34% H, 11·70% S.

8-(4-Chlorophenylthio)-1-naphthoic Acid (*VIIb*)

Like in the preceding case, 6·0 g 8-iodo-1-naphthoic acid reacted with 2·9 g 4-chlorothiophenol to 3·9 g (62%) product, m.p. 179–180 °C (ethanol). UV spectrum: λ_{max} 225 nm (log ε 4·59), inflexion 249 nm (4·18), inflexion 282 nm (3·96), inflexion 314 nm (3·74). IR spectrum: 765 and 820 (3 and 2 adjacent Ar—H), 930, 1270 (COOH), 1500 (Ar), 1683 (ArCOOH), 2530 and 2670 cm^{-1} (COOH). For $C_{17}H_{11}ClO_2S$ (314·8) calculated: 64·86% C, 3·52% H, 11·26% Cl, 10·19% S; found: 65·31% C, 3·64% H, 11·40% Cl, 10·25% S.

Benzo[*f*]naphtho[1,8-*bc*]thiepin-12-one (*IIIa*)

A. Acid *VIIa* (1·7 g) was added at 130°C to polyphosphoric acid prepared from 6·0 P_2O_5 and 4 ml 85% H_3PO_4 and the mixture was heated under stirring for 1 h to 130°C. After cooling, it was decomposed with water and the product was extracted with chloroform. The extract was washed with 5% NaOH, dried with K_2CO_3 and evaporated. The crystalline residue obtained (1·35 g) is (according to chromatography on silica gel) a mixture of two compounds with similar R_F values. It was dissolved in 17 ml boiling benzene; on slow cooling, 0·75 g homogenous, less polar component of the mixture precipitated: m.p. 147–149°C, apparently ketone *IIIa*. UV spectrum: λ_{max} 222 nm (log ε 4·53), inflexion 247 nm (4·12), 297 nm (3·83), 335 nm (3·81). IR spectrum: 750, 760, 785 (4 and 3 adjacent Ar—H), 1558, 1588, 1610 (Ar), 1660 cm^{-1} (Ar_2CO in a seven-membered ring). NMR spectrum: δ 7·20–8·20 (m, aromatic protons). According to analysis, the compound obtained by crystallization from benzene retains some benzene. On recrystallization from ethanol the m.p. does not change but the compound is free of the solvent. For $C_{17}H_{10}OS$ (262·3) calculated: 77·83% C, 3·84% H, 12·23% S; found: 78·53% C, 3·78% H, 12·20% S.

Evaporation of the benzene mother liquor yielded 0·5 g mixture which was chromatographed on a column of 50 g Al_2O_3 (activity II). Elution with benzene removed first the less polar fractions and then 0·15 g of the more polar component of the original mixture was eluted: m.p. 196–197°C (benzene). The compound was identified as benzo[*c*]thioxanthone (*VIIIa*) for which ref.[12,14,15] report m.p. from 193 to 199°C. The identity was indicated by a direct comparison with a sample prepared differently[15]. UV spectrum: λ_{max} 221·5 nm (log ε 4·58), 255 nm (4·37), 266 nm (4·37), inflexion 277 nm (4·44), 287 nm (4·59), inflexion 307·5 nm (4·02), inflexion 316 nm (3·95), inflexion 370 nm (3·77), 387·5 nm (3·88). IR spectrum: 745 and 829 (4 and 2 adjacent Ar—H), 1600 (Ar), 1632 cm^{-1} (Ar_2CO). For $C_{17}H_{10}OS$ (262·3) calculated: 77·83% C, 3·84% H, 12·23% S; found: 77·63% C, 3·84% H, 12·07% S.

B. A mixture of polyphosphoric acid (10 ml 85% H_3PO_4 and 15 g P_2O_5) and 4·0 g *VIIa* was heated for 30 min to 130–140°C. Processing of the product yielded 3·6 g of an almost homogeneous product which was once crystallized from 27 ml benzene to 3·2 g (85%) pure ketone *IIIa* with a m.p. of 147–149°C.

Benzo[*c*]thioxanthone (*VIIIa*)

A. A mixture of 20 g polyphosphoric acid (solid, stored for some time in the laboratory) and 1·7 g *VIIa* was heated under stirring for 20 min to 150°C. Processing as before yielded 1·3 g crude product which is chromatographically almost homogeneous ketone *VIIIa*. After a single crystallization from benzene it melts at 196–197°C and comparison with an authentic sample[15] reveals their identity.

B. A mixture of 0·1 g ketone *IIIa* and 5 g polyphosphoric acid was heated for 30 min to 160°C. Processing as before yielded a crude preparation which is practically pure ketone *VIIIa* (comparison with chromatography on a thin layer of silica gel).

10-Chlorobenzo[*f*]naphtho[1,8-*bc*]thiepin-12-one (*IIIb*)

A. A mixture of polyphosphoric acid (from 2 ml 85% H_3PO_4 and 3 g P_2O_5) with 1·0 g *VIIb* was heated under stirring for 1 h to 150°C. Processing as in the preceding cases yielded 0·75 g (80%) nonhomogeneous neutral product. It was chromatographed on a column of alumina (activity II) eluting with benzene. In the first fractions, 0·15 g ketone *IIIb* was eluted which melts on recrystallization from ethanol at 174—176°C. UV spectrum: λ_{max} 221 nm (log ε 4·57), inflexion 247 nm (4·09), 279 nm (3·84), 301 nm (3·80), 333 nm (3·76). IR spectrum (KBr): 769, 780, 832, 893 (3 and 2 adjacent and solitary Ar—H), 1099, 1219, 1273 (C—O), 1502, 1560, 1610 (Ar), 1661 cm^{-1} (Ar_2CO in a seven-membered ring); NMR spectrum: δ 7·20—8·40 (m, aromatic protons). For $C_{17}H_9ClOS$ (296·8) calculated: 68·80% C, 3·06% H, 11·95% Cl, 10·80% S; found: 68·60% C, 3·25% H, 11·73% Cl, 10·58% S.

On continuing the chromatography, the more polar fractions yielded 0·1 g 9-chlorobenzo[*c*]-thioxanthone (*VIIIb*), m.p. 244—246°C (benzene). Mass spectrum: the molecular ion has the composition $C_{17}H_9ClOS$ (*m/e* 296·0079 ± 0·0018, theoretically 296·0063). UV spectrum: λ_{max} 224·5 nm (log ε 4·59), inflexion 263 nm (4·28), 290 nm (4·55), inflexion 375 nm (3·65), 392 nm (3·77). IR spectrum (KBr): 770, 827, 867 (4 and 2 adjacent and solitary Ar—H), 1589 (Ar), 1630 cm^{-1} (Ar_2CO of thioxanthone). For $C_{17}H_9ClOS$ (296·8) calculated: 68·80% C, 3·06% H, 11·95% Cl, 10·80% S; found: 68·80% C, 2·86% H, 11·89% Cl, 10·77% S.

B. A mixture of 50 g polyphosphoric acid and 7·0 g *VIIb* was stirred and heated for 20 min at 140°C. Processing as in the preceding cases yielded 5·9 g (90%) chromatographically homogeneous *IIIb* melting at 172—174°C.

12-(3-Dimethylaminopropyl)-12*H*-benzo[*f*]naphtho[1,8-*bc*]thiepin-12-ol (*IVa*)

Reaction of 2·8 g 3-dimethylaminopropyl chloride with 0·6 g Mg in 10 ml tetrahydrofuran gave rise to a Grignard reagent [26] which was cooled and then a solution of 3·0 g ketone *IIIa* in 15 ml tetrahydrofuran was added dropwise. The mixture was stirred for 1 h at room temperature, decomposed with 40 ml 20% solution of NH_4Cl and the crude product (3·9 g) was isolated by extraction with chloroform. After recrystallization from a mixture of benzene and light petroleum it is pure and melts at 160—162°C. UV spectrum: λ_{max} 216·5 nm (log ε 4·51), 227 nm (4·48), 246 nm (4·17), 317 nm (3·93). IR spectrum: 760, 775 (4 and 3 adjacent Ar—H), 1093 (C—OH), 1500, 1550 (Ar), 2700 cm^{-1} (OH···N). NMR spectrum: δ 8·45 and 8·16 (2 dd, J = 7·0; 2·0 and 7·0; 2·5 Hz, 2 H, aromatic 1,11-H_2), 7·05—7·80 (m, 8 H, remaining aromatic protons), For $C_{22}H_{23}NOS$ (349·5) calculated: 75·60% C, 6·63% H, 4·01% N, 9·18% S; found: 75·50% C, 6·75% H, 3·87% N, 8·97% S.

12-(3-Dimethylaminopropylidene)-12*H*-benzo[*f*]naphtho[1,8-*bc*]thiepin (*Ia*)

A mixture of 3·9 g alcohol *IVa*, 24 ml water and 2·5 ml H_2SO_4 was refluxed for 40 min, cooled and made alkaline with NH_4OH and the product was isolated by extraction with chloroform: 3·65 g (98%) nonhomogeneous oily base. A hydrochloride was prepared from the ethanolic solution of this base with an ether solution of HCl. The hydrochloride was repeatedly crystallized from ethanol. Finally, 0·3 g substance was obtained, melting at 239—240°C which is considered as a homogeneous geometric isomer. For $C_{22}H_{22}ClNS$ (367·9) calculated: 71·81% C, 6·03% H, 9·63% Cl, 3·81% N, 8·72% S; found: 71·50% C, 6·09% H, 9·49% Cl, 3·57% N, 8·89% S.

Evaporation of the mother liquors led to a fraction which was repeatedly recrystallized from a mixture of ethanol and ether and finally from ethanol; it melts unsharply at 195—203°C and its analysis indicates that it is a monohydrate. For $C_{22}H_{24}ClNOS$ (385·9) calculated: 68·43% C, 6·27% H, 9·19% Cl, 3·63% N, 8·31% S; found: 68·65% C, 6·09% H, 9·38% Cl, 3·60% N, 8·64% S.

10-Chloro-12*H*-benzo[*f*]naphtho[1,8-*bc*]thiepin-12-ol (*Vb*)

$NaBH_4$ (1·0 g) was added slowly under stirring at 60°C to a mixture of 5·9 g ketone *IIIb* and 200 ml ethanol and the mixture was heated for 1 h to 60°C. After standing overnight at room temperature it was filtered and the mother liquor processed to 5·65 g (95%) crude product, which was purified by crystallization from benzene, m.p. 216—218°C. IR spectrum (KBr): 765, 790, 800, 820, 828, 880 (3 and 2 adjacent and solitary Ar—H), 1090 (CHOH), 1500, 1570, 1580 (Ar), 3360 cm^{-1} (OH). NMR spectrum (CD_3SOCD_3): δ 7·00—8·20 (m, 10 H, aromatic protons and Ar_2CH—O), 6·62 (s, disappears after D_2O, 1 H, OH), For $C_{17}H_{11}ClOS$ (298·8) calculated: 68·33% C, 3·71% H, 11·87% Cl, 10·73% S; found: 67·77% C, 3·62% H, 11·90% Cl, 11·00% S.

10,12-Dichloro-12*H*-benzo[*f*]naphtho[1,8-*bc*]thiepin (*VIb*)

Suspension of 4·6 g *Vb* in 400 ml benzene was saturated with anhydrous hydrogen chloride until a clear solution formed. After adding 5 g anhydrous powdery $CaCl_2$, hydrogen chloride was applied again briefly, the mixture was left to stand overnight at room temperature, filtered and the filtrate was evaporated. A total of 4·6 g (94%) practically pure product was obtained, a sample having been recrystallized from benzene; m.p. 161—163°C. For $C_{17}H_{10}Cl_2S$ (317·2) calculated: 64·36% C, 3·18% H, 22·35% Cl, 10·11% S; found: 65·54% C, 3·30% H, 22·02% Cl, 10·33% S

10-Chloro-12-(4-methylpiperazino)-12*H*-benzo[*f*]naphtho[1,8-*bc*]thiepin (*IIb*)

A mixture of 4·0 g *VIb*, 20 ml chloroform and 5 ml 1-methylpiperazine was heated until a clear solution formed and left to stand for two weeks at room temperature. After dilution with chloroform, it was washed with water, the basic product was extracted with dilute hydrochloric acid (50 ml, 1 : 4) liberated again with NH_4OH and isolated by extraction with benzene; 2·7 g (56%) oil which crystallizes from a mixture of benzene and light petroleum or cyclohexane and light petroleum, m.p. 127—130°C. NMR spectrum: δ 7·00—7·80 (m, 9 H, aromatic protons), 6·40 (s, 1 H, Ar_2CH—N), c. 2·50 (m, 8 H, 4 NCH_2 of piperazine), 2·25 (s, 3 H, NCH_3). For $C_{22}H_{21}ClN_2S$ (380·9) calculated: 69·36% C, 5·55% H, 9·31% Cl, 7·36% N, 8·42% S; found: 69·36% C, 5·62% H, 9·34% Cl, 7·56% N, 8·40% S.

Maleate, m.p. 197°C with decomposition (aqueous ethanol). For $C_{26}H_{25}ClN_2O_4S$ (497·0) calculated: 62·83% C, 5·07% H, 7·13% Cl, 5·64% N, 6·45% S; found: 62·71% C, 5·29% H, 7·33% Cl, 5·46% N, 6·68% S.

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