NEUROLEPTIC AGENTS DERIVED FROM PERATHIEPIN: 6,7-DICHLORO DERIVATIVE OF 10-(4-METHYLPIPERAZINO)-10,11-DIHYDRODIBENZO[*b*,*f*]THIEPIN AND RELATED COMPOUNDS*

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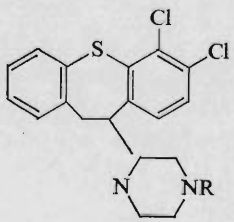
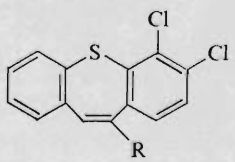
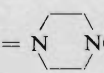
The reaction of 2,3-dichlorothiophenol with 2-iodobenzoic acid gave 2-(2,3-dichlorophenylthio)benzoic acid (*V*) which was transformed in four steps to the homological acid *IX*. Cyclization resulted in 6,7-dichlorodibenzo[*b*,*f*]thiepin-10(11*H*)-one (*X*) which was converted *via* the alcohol *XI* to the trichloro compound *XII*. Substitution reactions of *XII* with 1-methylpiperazine and 1-(2-hydroxyethyl)piperazine afforded the title compound *I* and its hydroxyethyl analogue *II*. Reaction of the ketone *X* with 1-methylpiperazine and titanium tetrachloride gave the enamine *III*. Compounds *I*—*III* exhibit mild central depressant and relatively strong cataleptic activity.

Recently, we have described the synthesis of the 2,4-dichloro derivative of 10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b*,*f*]thiepin (perathiepin) and have summarized all of the dichloro derivatives of this prototype of potent neuroleptics and tranquillizers[1]. Most of these compounds have at least one of the atoms of chlorine in positions 2 or 8 of the skeleton making of them either derivatives of the noncataleptic doclothepin (2-chloro derivative of perathiepin[2,3]) or of the cataleptic clorothepin (8-chloro derivative of perathiepin[4,5]); this relation indicates the character



I, R = CH_3
II, R = CH_2CH_2OH



III, R =  NCH_3

IV, R = H

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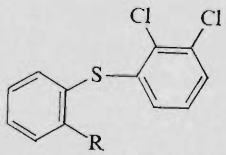
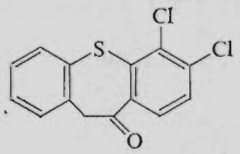
of their effects. In addition to the mentioned 8-chloro derivative, the 7-chloro derivative of perathiepin[2,6] shows also a clear cataleptic efficacy. We considered useful to modify the activity of this compound by a further substitution and in the present communication we describe the synthesis of the 6,7-dichloro derivative of perathiepin (*I*), the corresponding amino alcohol *II* and enamine *III*.

The syntheses of compounds *I*–*III* used methods described for analogous compounds in preceding communications[1–4,6]. The starting 2,3-dichlorothiophenol[7,8] was prepared from 2,3-dichloroaniline by the known procedure *via* the corresponding diazonium xanthate and aryl xanthate[9,10]. Its reaction with 2-iodobenzoic acid[11] in a boiling solution of potassium hydroxide in the presence of copper gave 2-(2,3-dichlorophenylthio)benzoic acid (*V*) which was reduced to the alcohol *VI*. The reduction was carried out with lithium aluminium hydride in a mixture of ether and tetrahydrofuran on the one hand, and with sodium dihydridobis-(2-methoxyethoxy)aluminate in benzene on the other; the first method gave a higher yield. The alcohol *VI* was transformed by treatment with thionyl chloride in boiling benzene to the benzyl chloride *VII* which was processed in crude state with potassium cyanide in dimethylformamide at 100–110°C. The nitrile *VIII* was obtained which was hydrolyzed with potassium hydroxide in aqueous ethanol and afforded [2-(2,3-dichlorophenylthio)phenyl]acetic acid (*IX*).

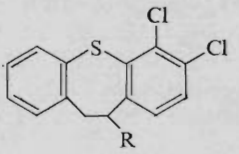


V, R = COOH *VII*, CH_2Cl
VI, R = CH_2OH *VIII*, R = CH_2CN
IX, R = CH_2COOH

Cyclization of the acid *IX* was carried out with polyphosphoric acid in boiling toluene; 6,7-dichlorodibenzo[*b*,*f*]thiepin-10(11*H*)-one (*X*) was obtained in an almost theoretical yield. Reduction with sodium borohydride in aqueous ethanol resulted in the alcohol *XI* which was treated with hydrogen chloride in benzene and gave the trichloro derivative *XII*. Substitution reactions of this compound with 1-methylpiperazine and 1-(2-hydroxyethyl)piperazine in boiling chloroform led to bases *I* and *II*, which were transformed to the maleates. The neutral by-product was characterized as 3,4-dichlorodibenzo[*b*,*f*]thiepin (*IV*) formed by the simultaneously proceeding elimination reaction. Reaction of the ketone *X* with 1-methylpiperazine and titanium tetrachloride in boiling benzene afforded in a good yield the enamine *III*, likewise transformed to the maleate.



X



XI, R = OH
XII, R = Cl

Compounds *I*–*III* were tested in the form of maleates for the expected neuroleptic activity on the one hand, and by methods of the general screening on the other (Dr M. Bartošová, affiliated unit of our institute at Rosice n/L); the doses given were calculated for the bases. The acute toxicity was determined in mice; the LD_{50} (mg/kg): *I*, 260 orally; *II*, 50 *i.v.*; *III*, 228 orally. The incoordinating effect, corresponding to the central depressant activity, has been determined in the rotarod test in mice; ED_{50} (in the interval of maximum activity, mg/kg): *I*, 2·0 *i.v.*; *II*, 5·0 *i.v.*; *III*, 3·1 *i.v.*. The cataleptic activity, corresponding to the neuroleptic action of the compounds, has been determined in rats; ED_{50} (mg/kg): *I*, >50 orally (this dose brings about catalepsy in 30% animals); *II*, 8·7 orally; *III*, 12·5 orally.

The cataleptically most active compound *II* was subjected to further tests which completed its characterization as a neuroleptic. In a dose of 10 mg/kg *s.c.* it inhibits significantly the spontaneous motility of mice in known surroundings. In doses of 5–10 mg/kg *i.v.* it prolongs the thiopental sleeping time of mice to 200% of the control values. In a dose of 10 mg/kg *i.v.* it exhibits a significant antiamphetamine effect in mice (this dose protects 100% mice from the lethal effect of a standard dose of amphetamine; for chlorpromazine, ED = 1 mg/kg *i.v.*). The compound has also an antihistamine effect; a dose of 5 mg/kg *s.c.* protects 50% guinea-pigs from the lethal effect of 5 mg/kg histamine administered intrajugularly (for mebrophenhydramine, ED = 0·25 mg/kg *s.c.*). In a dose of 10 mg/kg *i.v.* it decreases the blood pressure of normotensive rats by 20% for at least 10 min. It has a positive inotropic effect: a concentration of 50 μg/ml increases the inotropy of the isolated rabbit atrium by 25%. Finally, it showed and antiarrhythmic effect: a dose of 0·5 mg/kg *i.v.* prolongs with statistical significance the latency of ventricular extrasystoles in rats elicited with aconitine (for quinidine, ED = 5–10 mg/kg *i.v.*).

In conclusion, the tranquillizing and neuroleptic activity of compounds *I*–*III*, especially of *II* and *III*, is well comparable with that of 7-chloro derivative perathiepin[6]. In comparison with clorothepin[5] there is a clear shift in the ratio of central depressant and cataleptic activity (clorothepin is about 100 times more active than *II* in the rotarod test but only twice as active in the test of catalepsy).

Compounds *I*—*III* were also tested for antimicrobial activity *in vitro* (Dr J. Turinová, bacteriological department of this institute). The used microorganisms, numbers of compounds and the

minimum inhibitory concentration in μg/ml (unless they exceed 100 μg/ml) are given: *Streptococcus β-haemolyticus*, *I* 12·5, *II* 12·5, *III* 12·5; *Streptococcus faecalis*, *I* 25, *II* 25, *III* 25; *Staphylococcus pyogenes aureus*, *I* 6·25, *II* 12·5, *III* 6·25; *Mycobacterium tuberculosis* H37Rv, *I* 3·12, *II* 6·25, *III* 6·25; *Saccharomyces pasterianus*, *I* 12·5, *II* 12·5, *III* 6·2; *Trichophyton mentagrophytes*, *I* 25, *II* 12·5, *III* 6·2; *Candida albicans*, *I* 50, *II* 50, *III* 50; *Aspergillus niger*, *III* 50.

EXPERIMENTAL

The melting points of analytical preparations were determined in an automatic Mettler FP-5 melting point recorder. The samples were dried at about 60 Pa over P_2O_5 at room temperature or at 77°C. UV spectra (in methanol) were recorded with a Unicam SP 8000 spectrophotometer, the IR spectra (in Nujol) with a Unicam SP 200G spectrophotometer and the ^{1}H-NMR spectra (in $CDCl_3$) with a Tesla BS 487C (80 MHz) spectrometer. The homogeneity of the compounds was checked by chromatography on thin layers of silica gel.

2-(2,3-Dichlorophenylthio)benzoic Acid (*V*)

A solution of 100 g KOH in 1200 ml water was heated to 55°C and treated under stirring with 98·8 g 2,3-dichlorothiophenol[7,8] (b.p. 116—118°C/2·7 kPa). The mixture was stirred for 10 min and treated with 137 g 2-iodobenzoic acid[11] and 5 g copper catalyst. It was then stirred and refluxed for 7 h, filtered while hot and the filtrate was cooled and acidified with 100 ml hydrochloric acid. After standing overnight, the product was filtered, washed with water and dried *in vacuo*; 165 g (almost theoretical yield), m.p. 235—237°C. Analytical sample, m.p. 239—240°C (ethanol). UV spectrum: λ_{max} 252 nm (log ε 4·02), 308 nm (3·72). IR spectrum: 744, 780 (4 and 3 adjacent Ar—H), 920, 1260, 1678, 2520, 2555, 2570 (ArCOOH), 1565, 1590 cm^{-1} (Ar). For $C_{13}H_8Cl_2O_2S$ (299·2) calculated: 52·19% C, 2·69% H, 23·70% Cl, 10·72% S; found: 52·19% C, 2·76% H, 23·48% Cl, 10·77% S.

2-(2,3-Dichlorophenylthio)benzyl Alcohol (*VI*)

A) A suspension of 22·1 g $LiAlH_4$ in 300 ml ether was stirred and slowly treated with a suspension of 130 g *V* in 200 ml tetrahydrofuran and 1900 ml ether. The mixture was refluxed for 6 h. After cooling it was decomposed by addition of 500 ml wet ether, 300 ml water and finally 900 ml 1 : 3 dilute hydrochloric acid. The organic layer was separated, washed with 900 ml, 10% Na_2CO_3, dried ($MgSO_4$) and evaporated. The residue crystallized on standing; 96·1 g (78%), m.p. 54—57°C. Analytical sample, m.p. 64°C (benzene–light petroleum). IR spectrum: 752, 768 779 (4 and 3 adjacent Ar—H), 1025, 1042 (CH_2OH), 1565 (Ar), 3170 cm^{-1} (OH). For $C_{13}H_{10}Cl_2OS$ (285·2) calculated: 54·75% C, 3·53% H, 24·87% Cl, 11·24% S; found: 55·04% C, 3·57% H, 24·80% Cl, 11·40% S.

B) A suspension of 30 g *V* in 300 ml benzene was stirred and treated dropwise over 1·5 h with 80 ml 50% sodium dihydridobis(2-methoxyethoxy)aluminate in benzene. The temperature rose spontaneously to 45°C and a solution was formed which was stirred for 3 h at room temperature. After standing overnight, it was decomposed by slow addition of 160 ml 10% NaOH under cooling, stirred for 1 h, the organic layer dried with K_2CO_3 and evaporated; 15·6 g (55%) oil. Distillation gave 12·5 g (44%) product, b.p. 168—178/67 Pa, which crystallized, m.p. 53—58°C.

[2-(2,3-Dichlorophenylthio)phenyl]acetonitrile (*VIII*)

A refluxing solution of 96 g *VI* in 220 ml benzene was treated dropwise over 45 min with 60 g $SOCl_2$. The mixture was refluxed for 30 min and the volatile components were distilled off *in vacuo*. The residue (99·1 g, 97%) is homogeneous according to TLC and represents the chloride *VII*. A solution of 91 g crude *VII* in 200 ml dimethylformamide was treated with 44·5 g NaCN and the mixture was stirred and heated for 8 h to 100—110°C. Dimethylformamide was evaporated *in vacuo*, the residue was diluted with 150 ml water and extracted with benzene. The extract was washed with water, dried with $CaCl_2$ and evaporated. The residue was dissolved in benzene and the solution filtered through a column of 1 kg neutral Al_2O_3 (activity II). Evaporation of the filtrate gave 78 g (89%), m.p. 68—71°C. Analytical sample, m.p. 78°C (cyclohexane). ^{1}H-NMR spectrum: δ 7·30—7·70 (m, 4 H, Ar—H of phenylacetonitrile), 7·20 (mcd, J = 8·0; 1·5 Hz, 1 H, 4-H in dichlorophenyl), 6·92 (t, J = 8·0 Hz, 1 H, 5-H in dichlorophenyl), 6·40 (mcd, J = 8·0; 1·5 Hz, 1 H, 6-H in dichlorophenyl), 3·82 (s, 2 H, $ArCH_2CN$). For $C_{14}H_9Cl_2NS$, (294·2) calculated: 57·16% C, 3·08% H, 24·10% Cl, 4·76% N, 10·90% S; found: 57·50% C, 3·15% H, 23·85% Cl, 5·16% N, 10·78% S.

[2-(2,3-Dichlorophenylthio)phenyl]acetic Acid (*IX*)

A solution of 70·8 g *VIII* in 375 ml ethanol was treated with 68 g KOH in 300 ml water and the mixture was stirred and refluxed for 18 h. Ethanol was evaporated, the residue diluted with water and the solution washed with benzene and filtered with charcoal. The filtrate was acidified under cooling with 3M-HCl. After standing overnight the solid was filtered, washed with water and dried *in vacuo*; 60·3 g (80%), m.p. 137—141°C. Analytical sample, m.p. 144—146°C (benzene–light petroleum). IR spectrum: 755, 771 (4 and 3 adjacent Ar—H), 920, 1295, 1707, 2560, 2665 (COOH), 1470, 1566, 1588 cm^{-1} (Ar). For $C_{14}H_{10}Cl_2O_2S$ (313·2) calculated: 53·69% C, 3·22% H, 22·64% Cl, 10·23% S; found: 54·24% C, 3·24% H, 22·35% Cl, 10·13% S.

6,7-Dichlorodibenzo[*b*,*f*]thiepin-10(11*H*)-one (*X*)

A mixture of 60·3 g *IX*, 395 g polyphosphoric acid a 180 ml toluene was refluxed under vigorous stirring for 8 h (temperature of the bath 130—135°C). After partial cooling, the mixture was decomposed with 2·5 l ice-cold water and extracted with toluene. The organic layer was washed with water, 5% NaOH and water, dried with K_2CO_3 and evaporated; 56·1 g (99%), m.p. 154 to 158°C. Analytical sample, m.p. 160—161°C (ethanol). UV spectrum: λ_{max} 252 nm (log ε 4·43), 334·5 nm (3·49). IR spectrum: 741, 761, 816, 841 (4 and 2 adjacent Ar—H), 1138, 1270, 1338, 1420 (C—O and C—H in CH_2CO), 1560 (Ar), 1672 cm^{-1} (ArCO). ^{1}H-NMR spectrum: δ 7·98 (d, J = 8·0 Hz, 1 H, 9-H), 7·64 (mcd, 1 H, 4-H), 7·00—7·50 (m, 4 H, remaining Ar—H), 4·28 (s, 2 H, $ArCH_2CO$). For $C_{14}H_8Cl_2OS$ (295·2) calculated: 56·96% C, 2·73% H, 24·02% Cl, 10·86% S; found: 56·92% C, 2·62% H, 23·85% Cl, 10·76% S.

6,7-Dichloro-10,11-dihydrodibenzo[*b*,*f*]thiepin-10-ol (*XI*)

A solution of 35·5 g *X* in a mixture of 150 ml benzene and 1000 ml ethanol was stirred and slowly treated at 70°C with a solution of 13·5 g $NaBH_4$ in 150 ml water, containing 1 ml 10% NaOH. The mixture was refluxed for 4 h. Ethanol was evaporated, the residue diluted with water and extracted with benzene. The extract was washed with water, dried with Na_2SO_4 and evaporated; 34 g (95%), m.p. 117—120°C. Analytical sample, m.p. 127°C (aqueous ethanol). IR spectrum: 741, 813 (4 and 2 adjacent Ar—H), 1041, 1059, 1149 (CHOH in a cycle), 1370, 3330 cm^{-1} (OH).

For $C_{14}H_{10}Cl_2OS$ (297·2) calculated: 56·58% C, 3·39% H, 23·86% Cl, 10·79% S; found: 56·55% C, 3·33% H, 23·74% Cl, 10·91% S.

3,4,11-Trichloro-10,11-dihydrodibenzo[*b*,*f*]thiepin (*XII*)

A solution of 26·5 g *XI* in 300 ml benzene was treated with 25 g $CaCl_2$ (powder) and the stirred suspension was saturated for 30 min with anhydrous HCl. After standing for 2 h the mixture was filtered with charcoal and the filtrate evaporated; 27·0 g (96%), m.p. 100—101°C. Analytical sample, m.p. 106·5°C (cyclohexane). ^{1}H-NMR spectrum: δ 6·80—7·60 (m, 6 H, Ar—H), 5·82 (dd, J = 8·0; 4·0 Hz, 1 H, Ar—CH—Cl), 3·80 and 3·56 (2 dd, J = 14·0; 4·0 and 14·0; 8·0 Hz, 2 H, $ArCH_2$). For $C_{14}H_9Cl_3S$ (315·6) calculated: 53·27% C, 2·87% H, 33·70% Cl, 10·16% S; found: 53·38% C, 2·84% H, 33·59% Cl, 9·92% S.

3,4-Dichloro-11-(4-methylpiperazino)-10,11-dihydrodibenzo[*b*,*f*]thiepin (*I*)

A mixture of 10·0 g *XII*, 12 g 1-methylpiperazine and 15 ml chloroform was refluxed for 8 h. Chloroform was evaporated under reduced pressure, the residue diluted with 170 ml water and extracted with benzene. The benzene layer was washed with water and then shaken with 75 ml 3M-HCl. The solid hydrochloride was filtered with suction, washed with benzene and decomposed with NH_4OH. The base was extracted with benzene, the extract was dried and evaporated; 7·3 g (61%) crystallizing from light petroleum. Analytical sample, m.p. 126°C (90% aqueous ethanol). ^{1}H-NMR spectrum: δ 7·50 (m, 1 Hz, 6-H), 7·40 (d, J = 8·0 Hz, 1-H), 7·18 (d, J = 8·0 Hz, 1 H, 2-H), 6·90—7·30 (m, 3 H, 7,8,9-H_3), 4·05 and 3·75 (2 dd, J = 12·0; 4·0 and 12·0; 8·0 Hz, 2 H, $ArCH_2$), 3·17 (dd, J = 8·0; 4·0 Hz, 1 H, Ar—CH—N), 2·60 (t, 4 H, $CH_2N^1CH_2$ of piperazine), 2·38 (t, 4 H, $CH_2N^4CH_2$ of piperazine), 2·21 (s, 3 H, NCH_3). For $C_{19}H_{20}Cl_2N_2S$ (379·3) calculated: 60·16% C, 5·31% H, 18·69% Cl, 7·38% N, 8·45% S; found: 60·75% C, 5·18% H, 18·70% Cl, 7·27% N, 8·53% S.

Maleate, m.p. 178—179°C (ethanol). For $C_{23}H_{24}Cl_2N_2O_4S$ (495·4) calculated: 55·76% C, 4·88% H, 14·31% Cl, 5·66% N, 6·47% S; found: 55·34% C, 4·98% H, 14·23% Cl, 5·38% N, 6·52% S.

The benzene solution, from which the basic compound was removed by shaking with 3M-HCl, was washed with water, dried and evaporated; 2·4 g 3,4-dichlorodibenzo[*b*,*f*]thiepin (*IV*), m.p. 136°C (ethanol). UV spectrum: λ_{max} 268 nm (log ε 4·34), 300 nm (3·78). For $C_{14}H_8Cl_2S$ (279·2) calculated: 60·23% C, 2·89% H, 25·40% Cl, 11·48% S; found: 60·60% C, 2·96% H, 25·30% Cl, 11·30% S.

3,4-Dichloro-11-[4-(2-hydroxyethyl)piperazino]-10,11-dihydrodibenzo[*b*,*f*]thiepin (*II*)

A mixture of 20 g *XII*, 20 g 1-(2-hydroxyethyl)piperazine and 40 ml chloroform was refluxed for 8 h and processed similarly like in the preceding case; 18·8 g (73%) oily base. It crystallized from cyclohexane as a solvate with 1/2 molecule of this solvent, m.p. 87—88°C. IR spectrum: 759, 800, 826 (4 and 2 adjacent Ar—H), 1010, 3390 (CH_2OH), 1523, 1571, 1604 cm^{-1} (Ar). ^{1}H-NMR spectrum: δ 7·50 (m, 1 H, 6-H), 7·38 (d, J = 8·0 Hz, 1 H, 1-H), 7·15 (d, J = 8·0 Hz, 1 H, 2-H), *c.* 7·10 (m, 3 H, 7,8,9-H_3), *c.* 3·90 (m, 2 H, $ArCH_2$), 3·52 (t, 2 H, CH_2O), 3·10 (dd, J = 8·0; 4·0 Hz, 1 H, Ar—CH—N), *c.* 2·60 (m, 7 H, $CH_2N^1CH_2$ of piperazine, NCH_2 in hydroxyethyl and OH), 2·38 (def. t, 4 H, $CH_2N^4CH_2$ of piperazine), 1·38 (s, 6 H, 3 CH_2 of cyclohexane). For $C_{20}H_{22}Cl_2N_2OS + 0{\cdot}5\ C_6H_{12}$ (451·4) calculated: 61·19% C, 6·25% H, 15·71% Cl, 6·20% N, 7·10% S; found: 61·28% C, 6·41% H, 15·62% Cl, 6·22% N, 7·26% S.

Maleate, m.p. 145—146°C (acetone). For $C_{24}H_{26}Cl_2N_2O_5S$ (525·4) calculated: 54·86% C, 4·99% H, 13·50% Cl, 5·33% N, 6·10% S; found: 55·06% C, 5·12% H, 13·61% Cl, 5·64% N, 6·42% S.

3,4-Dichloro-11-(4-methylpiperazino)dibenzo[*b*,*f*]thiepin (*III*)

A solution of 12·4 g *X* and 21 g 1-methylpiperazine in 100 ml benzene was stirred and treated over 5 min with a solution of 4·0 g $TiCl_4$ in 25 ml benzene. The mixture was stirred and refluxed for 24 h, cooled and treated dropwise with 125 ml water. After 40 min stirring, the solid was filtered off and washed with benzene. The filtrate was separated, the benzene layer washed with water, dried ($MgSO_4$) and evaporated. The residue crystallized after mixing with light petroleum; 12·0 g (76%), m.p. 135—139°C. Analytical sample, m.p. 143—144°C (ethanol). UV spectrum: λ_{max} 271 nm (log ε 4·01), 314 nm (3·86). ^{1}H-NMR spectrum: δ 7·50 (m, 1 H, 6-H), 7·45 (d, J = 8·0 Hz, 1 H, 1-H), 7·25 (d, J = 8·0 Hz, 1 H, 2-H), 6·90—7·40 (m, 3 H, 7,8,9-H_3), 6·32 (s, 1 H, ArCH=), 2·98 (t, 4 H, $CH_2N^1CH_2$ of piperazine), 2·50 (t, 4 H, $CH_2N^4CH_2$ of piperazine), 2·26 (s, 3 H, NCH_3). For $C_{19}H_{18}Cl_2N_2S$ (377·3) calculated: 60·48% C, 4·81% H, 18·79% Cl, 7·42% N, 8·50% S; found: 60·74% C, 5·01% H, 18·72% Cl, 7·23% N, 8·66% S.

Maleate, m.p. 224°C (90% aqueous ethanol). For $C_{23}H_{22}Cl_2N_2O_4S$ (493·4) calculated: 55·99% C, 4·49% H, 14·37% Cl, 5·68% N, 6·50% S; found: 55·70% C, 4·52% H, 14·62% Cl, 5·84% N, 6·66% S.

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