The Synthesis of Trypanocides. Part V. A Rearrangement of Some 6-Amino-1-methylpyrimidinium Salts, and the Synthesis of 4-Amino-1 : 2-dimethyl-6-(1 : 2-dimethyl-6-methylaminopyrimidinium-4-amino)-quinolinium Di-iodide.*

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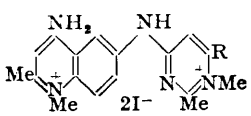
6-Amino-1-methylpyrimidinium salts which may carry hydrocarbon substituents in position 2 and arylamino-groups in position 4 are converted under alkaline conditions into the corresponding 6-methylaminopyrimidines.

4-Amino-1 : 2-dimethyl-6-(1 : 2-dimethyl-6-methylaminopyrimidinium-4-amino)quinolinium di-iodide (I; R = NHMe) was prepared by the action of methylamine on the corresponding compound with a 6-methylthio-group in the pyrimidine nucleus.

A SECOND method (cf. Part IV *) investigated for the preparation of the isomer (I; R = NH_2) of " Antrycide " was the preparation of a compound (I; R = SMe or Cl) in which R could be replaced by an amino-group on treatment with ammonia. Preliminary work was carried out on the corresponding anilinopyrimidines and this paper is chiefly concerned with the preparation and reactions of these simple compounds.

By treatment of 6-chloro-2-methyl-4-methylthiopyrimidine (II; R = Me, R′ = SMe) with methyl sulphate in nitrobenzene, and isolation of the product as the iodide, a mixture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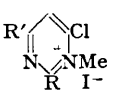
(II)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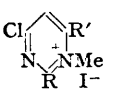
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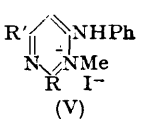
of 6-chloro-1 : 2-dimethyl-4- (III; R = Me, R′ = SMe) and 4-chloro-1 : 2-dimethyl-6-methylthiopyrimidinium iodide (IV; R = Me, R′ = SMe) was obtained. These compounds were unstable, but with aniline gave the anilino-derivatives (V and VI; R = Me, R′ = SMe). The orientation of these pairs of quaternary salts was established by treating 4-chloro-1 : 2-dimethyl-6-methylthiopyrimidinium iodide (IV; R = Me,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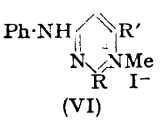
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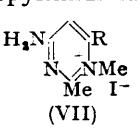
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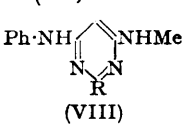
(VIII)

R′ = SMe) with aqueous ammonia, 4-amino-1 : 2-dimethyl-6-methylthiopyrimidinium iodide (VII; R = SMe) being obtained, identical with that obtained by the action of sodium methyl sulphide on 4-amino-6-chloro-1 : 2-dimethylpyrimidinium iodide (VII; R = Cl) the constitution of which was established as reported in the preceding paper.

Quaternisation of 4-anilino-6-chloro-2-methylpyrimidine (II; R = Me, R′ = NHPh)

* Part IV, preceding paper.

gave a single quaternary salt which proved to be 4-anilino-6-chloro-1 : 2-dimethylpyrimidinium iodide (VI; R = Me, R′ = Cl) since with sodium methyl sulphide it gave 4-anilino-1 : 2-dimethyl-6-methylthiopyrimidinium iodide (VI; R = Me, R′ = SMe).

The action of liquid or alcoholic ammonia on the compounds (VI; R = Me, R′ = Cl; and R = Me, R′ = SMe) was then examined. The product, crystallised from dilute hydriodic acid, was not the expected iodide (VI; R = Me, R′ = NH_2; preceding paper) but an isomer. Titration showed that it was not a quaternary salt but the hydriodide of a weaker base, namely, 4-anilino-2-methyl-6-methylaminopyrimidine (VIII; R = Me), an authentic sample of which was prepared from 4-anilino-6-chloro-2-methylpyrimidine (II; R = Me, R′ = NHPh) and alcoholic methylamine.

In view of this unexpected transformation, the behaviour of 6-amino-4-anilino-1 : 2-dimethylpyrimidinium iodide (VI; R = Me, R′ = NH_2) under alkaline conditions was investigated. Conversion into the base (VIII; R = Me) took place on treatment with alcoholic ammonia, aqueous sodium carbonate solution, or piperidine, but not with pyridine. It thus appears that in the reaction between the iodides (VI; R = Me, R′ = SMe; and R = Me, R′ = Cl) with ammonia a normal replacement first takes place and is followed by rearrangement of the quaternary compound. Similar rearrangements take place in analogous pyrimidines unsubstituted in the 2-position or with a 2-phenyl group, *i.e.*, in (VI; R = H, R′ = Cl, and R = Ph, R′ = Cl).

The rearrangement of the system ·NR·C(NH_2):· to ·N:C(NHR)· by alkali has been demonstrated in rings other than the pyrimidine. For instance, Dimroth (*Annalen*, 1909, **364**, 183) describes the rearrangement of 5-amino-1-phenyl-1 : 2 : 3-triazoles to 2-anilinotriazoles. More recently the rearrangement of 5-amino-1-aryl-1 : 2 : 3 : 4-tetrazoles to 5-anilino-1 : 2 : 3 : 4-tetrazoles has been demonstrated (Garbrecht and Herbst, *J. Org. Chem.*, 1953, **18**, 1269, 1283). In this series, however, 5-alkylaminotetrazoles rearrange in the reverse way to 5-amino-1-methyl-1 : 2 : 3 : 4-tetrazoles. Work on the metabolite of " Paludrine " has given examples of a somewhat similar change in the dihydrotriazines (Carrington, Crowther, and Stacey, *J.*, 1954, 1017) and the conversion of 5-amino-2-mercaptothiazoles by alkali into 2 : 4-dithiohydantoins (Cook, Heilbron, and Levy, *J.*, 1947, 1598) is a similar case in which hetero-atoms other than nitrogen are involved.

This pyrimidine transformation would almost certainly preclude the preparation of a compound (I; R = NH_2) by the reaction of the di-iodide (I; R = SMe or Cl) with ammonia. However, by treating the salts (VI; R = Me, R′ = Cl; and R = Me, R′ = SMe) with alcoholic methylamine the consequences of the rearrangement were avoided and the quaternary 4-anilino-1 : 2-dimethyl-6-methylaminopyrimidinium iodide (VI; R = Me, R′ = NHMe) was obtained.

A similar synthesis was therefore carried out with the corresponding pyrimidylaminoquinoline. 4-Chloro-1 : 2-dimethyl-6-methylthiopyrimidinium iodide, with 4 : 6-diamino-1 : 2-dimethylquinolinium iodide in hot water, gave the di-iodide (I; R = SMe), which with methanolic methylamine was converted into 4-amino-1 : 2-dimethyl-6-(1 : 2-dimethyl-6-methylaminopyrimidinium-4-amino)quinolinium di-iodide (I; R = NHMe).

Experimental

6-Chloro-2-methyl-4-methylthiopyrimidine (II; R = Me, R′ = SMe).—4-Chloro-6-hydroxy-2-methylpyrimidine (Basford, Curd, and Rose, *J.*, 1946, 713) (33·6 g.) and alcoholic sodium hydrogen sulphide [200 c.c.; prepared by dissolving sodium (9·6 g.) in alcohol (200 c.c.) and passing in hydrogen sulphide until gain in weight was 13·2 g.] were heated in an autoclave at 100° for 1 hr. The contents of the autoclave were diluted with water, treated with carbon, and filtered. Acidification with acetic acid precipitated 6-hydroxy-2-methyl-4-thiopyrimidine which was used without further purification. 6-Hydroxy-2-methyl-4-thiopyrimidine (25 g.) was suspended in a solution of sodium (3·68 g.) in methanol (75 c.c.), methyl iodide (16 c.c.) was added, and the mixture was heated under reflux for 1 hr. *6-Hydroxy-2-methyl-4-methylthiopyrimidine* separated on cooling and crystallised from alcohol as prisms, m. p. 222—224° (Found: C, 45·95; H, 4·85; N, 18·6. $C_6H_8ON_2S$ requires C, 46·2; H, 5·1; N, 17·9%). 6-Hydroxy-2-methyl-4-methylthiopyrimidine (31·4 g.) and phosphoryl chloride (100 c.c.) were heated under reflux for 1 hr. The excess of phosphoryl chloride was evaporated under reduced

pressure, and the residue was poured on ice and made alkaline with ammonia. The crude product was extracted with ether, and, after drying and evaporation of the ether, the residue of 6-*chloro*-2-*methyl*-4-*methylthiopyrimidine* was distilled in a vacuum; it had b. p. 126—128°/19 mm. (yield, 25·35 g.) (Found, in material dried in a vacuum at room temperature: C, 40·75; H, 4·35; N, 16·5. $C_6H_7N_2SCl$ requires C, 41·2; H, 4·0; N, 16·0%).

6-*Chloro*-1 : 2-*dimethyl*-4-*methylthiopyrimidinium Iodide* (III; R = Me, R′ = SMe).—6-Chloro-2-methyl-4-methylthiopyrimidine (25·35 g.) was dissolved in nitrobenzene (120 c.c.) at 90—95°. Methyl sulphate (72 c.c.) was added and the mixture was stirred at 90—95° for 1 hr. After cooling, the solution was extracted with water, and the aqueous extract was treated with excess of sodium iodide. The precipitated pyrimidinium iodide was collected, washed with acetone, and dried in a vacuum. The product was not sufficiently stable to be crystallised for analysis. The aqueous liquors gradually deposited the isomer, 4-chloro-1 : 2-dimethyl-6-methylthiopyrimidinium iodide (IV; R = Me, R′ = SMe).

4-*Amino*-6-*methylthio*-1 : 2-*dimethylpyrimidinium Iodide* (VII; R = SMe).—(*a*) 4-Amino-6-chloro-1 : 2-dimethylpyrimidinium iodide (2·85 g.) was dissolved in water (20 c.c.), and alcoholic 2M-sodium methyl sulphide (5 c.c.) was added. Immediate reaction took place. Methanethiol was passed through the warmed solution for 15 min. and, after cooling, the *pyrimidinium iodide* was collected and crystallised from water as prisms, m. p. 260° (decomp.) (Found: C, 28·05; H, 3·95; N, 13·55. $C_7H_{12}N_3SI$ requires C, 28·3; H, 4·0; N, 14·1%).

(*b*) 4-Chloro-1 : 2-dimethyl-6-methylthiopyrimidinium iodide (1·5 g.) was stirred with aqueous ammonia (5 c.c.; *d* 0·88). The crude product was filtered off and crystallised from water; it had m. p. and mixed m. p. 260° (decomp.).

4-*Anilino*-6-*chloro*-1 : 2-*dimethylpyrimidinium Iodide* (VI; R = Me, R′ = Cl).—4-Anilino-6-chloro-2-methylpyrimidine (Basford, Curd, and Rose, *loc. cit.*) (5·5 g.) was dissolved in nitrobenzene (50 c.c.) at 60°. Methyl sulphate (6·5 c.c.) was added and the temperature was raised to 90—95° for 4·5 hr. The crude methosulphate which crystallised on cooling was collected and dissolved in water. Addition of sodium iodide to the aqueous solution precipitated the *pyrimidinium iodide*, flat needles, m. p. 212° (decomp.) (from water) (Found: C, 40·0; H, 3·8; N, 11·5. $C_{12}H_{13}N_3ClI$ requires C, 39·8; H, 3·6; N, 11·6%).

6-*Anilino*-1 : 2-*dimethyl*-4-*methylthiopyrimidinium Iodide* (V; R = Me, R′ = SMe).—6-Chloro-1 : 2-dimethyl-4-methylthiopyrimidinium iodide (1·58 g.), aniline (0·46 g.), and water (10 c.c.) were heated under reflux for 1 hr. The *pyrimidinium iodide*, which separated on cooling, crystallised from water as thick plates, m. p. 180—181° (Found: C, 41·6; H, 4·3; N, 11·5. $C_{13}H_{16}N_3SI$ requires C, 41·8; H, 4·3; N, 11·3%).

4-*Anilino*-1 : 2-*dimethyl*-6-*methylthiopyrimidinium Iodide* (VI; R = Me, R′ = SMe).—(*a*) 4-Chloro-6-methylthio-1 : 2-dimethylpyrimidinium iodide (3·16 g.), aniline (0·93 g.), and water (20 c.c.) were heated under reflux for 0·5 hr. A thick precipitate was formed immediately. The *pyrimidinium iodide* was collected and crystallised from 50% aqueous alcohol as short, flat prisms, m. p. 244—246° (decomp.) (Found: C, 41·9; H, 4·4; N, 11·4%).

(*b*) 6-Chloro-4-anilino-1 : 2-dimethylpyrimidinium iodide (2·3 g.), water (10 c.c.) and sodium methyl sulphide (3·1 c.c. of alcoholic 2M-solution) were mixed. Immediate reaction ensued and, next morning the product was collected and crystallised from 50% aqueous alcohol; it had m. p. and mixed m. p. 244—246° (decomp.).

4-*Anilino*-2-*methyl*-6-*methylaminopyrimidine* (VIII; R = Me).—(*a*) 4-Anilino-6-chloro-2-methylpyrimidine (2·1 g.) and alcoholic methylamine (50 c.c. of 35% solution) were heated in a sealed tube at 150—160° for 4 hr. The clear solution was evaporated to dryness and the residue dissolved in dilute hydriodic acid. 4-*Anilino*-2-*methyl*-6-*methylaminopyrimidine hydriodide* separated, forming plates m. p. 220—222°, from water (Found: C, 42·3; H, 4·25; N, 16·5. $C_{12}H_{14}N_4,HI$ requires C, 42·1; H, 4·1; N, 16·3%). Addition of ammonia to an aqueous solution precipitated the *base* which, crystallised from benzene–light petroleum (b. p. 60—80°), had m. p. 150° (Found: C, 67·55; H, 6·55; N, 25·95. $C_{12}H_{14}N_4$ requires, 67·3; H, 6·5; N, 26·1%).

(*b*) 4-Anilino-6-chloro-1 : 2-dimethylpyrimidinium iodide (1·95 g.) was mixed with liquid ammonia (15 c.c.) and kept for 60 hr. The ammonia was evaporated and the residue dissolved in dilute hydriodic acid. The pyrimidine hydriodide which separated was crystallised from water; it had m. p. and mixed m. p. 222—224°.

4-Anilino-2-methyl-6-methylaminopyrimidine was also obtained by the action of liquid ammonia on 4-anilino-1 : 2-dimethyl-6-methylthio- and by heating 4-anilino-6-chloro-1 : 2-dimethyl-, 4-anilino-1 : 2-dimethyl-6-methylthio-, or 6-amino-4-anilino-1 : 2-dimethyl-pyrimidinium iodide with alcoholic ammonia at 100—120°.

(*c*) 6-Amino-4-anilino-1 : 2-dimethylpyrimidinium iodide (0·5 g.) was warmed in a solution of sodium carbonate (0·3 g.) in water (5 c.c.). An oil was deposited. After 4 hours' heating under reflux the mixture was cooled and the product collected and isolated as the hydriodide. Ammonia precipitated the base, m. p. and mixed m. p. 150—152° (from benzene).

(*d*) 6-Amino-4-anilino-1 : 2-dimethylpyrimidinium iodide (0·8 g.), methanol (20 c.c.), and piperidine (3 c.c.) were heated together in a sealed tube for 5 hr. at 100°. The solution was evaporated to small bulk and ethyl acetate added. Piperidine hydriodide was precipitated. The liquors were evaporated to dryness and the residue extracted with ether. Evaporation of the ether solution gave 4-anilino-2-methyl-6-methylaminopyrimidine identical with material prepared by method (*a*).

4-*Anilino*-6-*chloro*-1-*methylpyrimidinium Iodide* (VI; R = H, R′ = Cl).—4 : 6-Dichloropyrimidine (Kenner, Lythgoe, Todd, and Topham *J.*, 1943, 575) (10·5 g.), aniline (6·9 c.c.), water (45 c.c.), acetone (30 c.c.), and concentrated hydrochloric acid (0·75 c.c.) were heated under reflux for 1·5 hr. The solid, which separated on cooling, was collected and dissolved in methanol; the methanol solution was made alkaline with ammonia and diluted with water. 4-*Anilino*-6-*chloropyrimidine* was precipitated and crystallised from aqueous methanol as prisms, m. p. 154—156° (8·8 g.) (Found: C, 58·4; H, 3·7; N, 20·3. $C_{10}H_8N_3Cl$ requires C, 58·4; H, 3·8. N, 20·5%). 4-Anilino-6-chloropyrimidine (5·16 g.) was dissolved in nitrobenzene (50 c.c.) at 90—95° and methyl sulphate (6·5 c.c.) was added. After being stirred for 4·5 hr. at 90—95°, the nitrobenzene solution was cooled and extracted with water (3 × 50 c.c.). Addition of sodium iodide to the combined aqueous extracts precipitated 4-*anilino*-6-*chloro*-1-*methylpyrimidinium iodide* (3·75 g.), plates, m. p. 196—197° (decomp.) (from water) (Found: C, 38·3; H, 3·3; N, 11·9. $C_{11}H_{11}N_3ClI$ requires C, 38·0; H, 3·2; N, 12·1%).

4-*Anilino*-6-*methylaminopyrimidine* (VIII; R = H).—(*a*) 4-Anilino-6-chloropyrimidine (2·0 g.) and methanolic methylamine (50 c.c.) were heated in a sealed tube at 150—160° for 5 hr. The contents of the tube were evaporated to dryness and the residue was dissolved in hot dilute hydriodic acid. Ammonia then precipitated 4-*anilino*-6-*methylaminopyrimidine* which crystallised from aqueous methanol as plates, m. p. 206—207° (Found: C, 66·6; H, 5·95; N, 27·8. $C_{11}H_{12}N_4$ requires C, 66·0; H, 6·0; N, 28·0%).

(*b*) 4-Anilino-6-chloro-1-methylpyrimidinium iodide (1·0 g.) and alcoholic ammonia (20 c.c. of saturated solution) were heated for 5 hr. in a sealed tube at 115—125°. The mixture was then filtered and the filtrate evaporated to dryness. The combined solids were dissolved in dilute hydrochloric acid and the acid solution was basified with ammonia. The precipitated 4-anilino-6-methylaminopyrimidine crystallised from aqueous methanol; it had m. p. and mixed m. p. 206—207°.

4-*Anilino*-6-*chloro*-1-*methyl*-2-*phenylpyrimidinium Iodide* (VI; R = Ph, R′ = Cl).—4-Chloro-6-hydroxy-2-phenylpyrimidine (prepared from 4 : 6-dichloro-2-phenylpyrimidine by hydrolysis with hydrochloric acid in butanol) (67·1 g.), aniline (30·8 g.), and concentrated hydrochloric acid (5·5 c.c.) were heated together for 6 hr. at 145—155°. The melt was cooled, ground, and stirred with 10% aqueous acetic acid (550 c.c.) and filtered. The solid was then treated with hot dilute aqueous ammonia (3%), filtered, and dried. 4-*Anilino*-6-*hydroxy*-2-*phenylpyrimidine* thus obtained crystallised from 2-ethoxyethanol (yield, 50 g.). An analytical sample crystallised from alcohol as prisms, m. p. 209° (Found: C, 73·45; H, 5·2; N, 16·5. $C_6H_{13}ON_3$ requires C, 73·0; H, 4·9; N, 16·0%).

4-Anilino-6-hydroxy-2-phenylpyrimidine (50 g.) and phosphoryl chloride (100 c.c.) were heated under reflux for 1 hr. The excess of phosphoryl chloride was evaporated under reduced pressure and the residue poured on ice. After basification with ammonia, the crude product was extracted with ether and the ethereal solution was shaken with dilute ammonia. After drying (Na_2SO_4), the ether was evaporated and the 4-*anilino*-6-*chloro*-2-*phenylpyrimidine* crystallised from aqueous methanol as prisms, m. p. 132—134° (Found: C, 68·0; H, 3·85; N, 14·7. $C_{16}H_{12}N_3ClI$ requires C, 68·2; H, 4·3; N, 14·9%).

4-Anilino-6-chloro-2-phenylpyrimidine (5·0 g.) was dissolved in nitrobenzene (40 c.c.) at 90—95°. Methyl sulphate was added and the mixture was stirred at 90—95° for 4·5 hr. After cooling, the nitrobenzene was extracted with water (3 × 50 c.c.) and excess of sodium iodide was added to the combined aqueous extracts. 4-*Anilino*-6-*chloro*-1-*methyl*-2-*phenylpyrimidinium iodide* was precipitated, forming needles (from 50% aqueous methanol), m .p. 164—166° (decomp.) (Found: C, 47·75; H, 3·85; N, 9·8. $C_{17}H_{15}N_3ClI$ requires C, 48·1; H, 3·54; N, 9·9%).

4-*Anilino*-6-*methylamino*-2-*phenylpyrimidine* (VIII; R = Ph).—(*a*) 4-Anilino-6-chloro-2-phenylpyrimidine (1·5 g.) and methanolic methylamine (25 c.c.) were heated in a sealed tube at

140—150° for 5 hr. The solution was evaporated to dryness, and the residue was dissolved in methanol and made acid with hydrochloric acid. The precipitated solid was collected, dissolved in 50% aqueous methanol, and made alkaline with ammonia. *4-Anilino-6-methylamino-2-phenylpyrimidine* was extracted with ether; crystallised from light petroleum (b. p. 100—120°), it had m. p. 126—128° (Found: C, 73·95; H, 5·8, N, 20·2. $C_{17}H_{16}N_4$ requires C, 73·9; H, 5·8; N, 20·2%).

(*b*) 4-Anilino-6-chloro-1-methyl-2-phenylpyrimidinium iodide (0·8 g.) and alcoholic ammonia (20 c.c. of saturated solution) were heated in a sealed tube for 5 hr. at 100°. The methanol solution was evaporated to dryness and the residue worked up as in (*a*) above. The pyrimidine had m. p. and mixed m. p. 126—128°.

4-Anilino-1 : 2-dimethyl-6-methylaminopyrimidinium iodide (VI; R = Me, R′ = NHMe).—4-Anilino-1 : 2-dimethyl-6-methylthiopyrimidinium iodide (1·0 g.) and methanolic methylamine (25 c.c. of 35% solution) were heated in a sealed tube at 100° for 5 hr. The solid which separated on cooling crystallised from water as needles, m. p. 240° (Found: C, 43·75; H, 4·75; N, 15·6. $C_{13}H_{17}N_4I$ requires C, 43·5; H, 4·7; N, 15·7%). The same compound was obtained from 4-anilino-6-chloro-1 : 2-dimethylpyrimidinium iodide and alcoholic methylamine.

4-Amino-1 : 2-dimethyl-6-(1 : 2-dimethyl-6-methylthiopyrimidinium-4-amino)quinolinium Di-iodide (I; R = SMe).—4-Chloro-1 : 2-dimethyl-6-methylthiopyrimidinium iodide (3·16 g.), 4 : 6-diamino-1 : 2-dimethylquinolinium iodide (3·16 g.), and water (15 c.c.) were heated under reflux for 30 min. After cooling, the solid was filtered off and dissolved in aqueous ethanol and the quaternary *di-iodide* was precipitated by the addition of sodium iodide. It crystallised from water, in which it was approximately 10% soluble at 100°, and when pure had m. p. 300—302° (decomp.) (Found: C, 36·35; H, 4·15; N, 11·4. $C_{18}H_{23}N_5SI_2$ requires C, 36·3; H, 3·9; N, 11·8%).

4-Amino-1 : 2-dimethyl-6-(6-methylamino-1 : 2-dimethylpyrimidinium-4-amino)quinolinium Di-iodide (I; R = NHMe).—4-Amino-1 : 2-dimethyl-6-(1 : 2-dimethyl-6-methylthiopyrimidinium-4-amino)quinolinium di-iodide (1·0 g.) and methanolic methylamine (20 c.c. of 21% solution) were heated for 7 hr. in a sealed tube at 100°. The quaternary *salt* was collected and, crystallised from water, had m. p. 312° (decomp.) (Found: C, 26·3; H, 4·6; N, 13·8. $C_{18}H_{24}N_6I_2,H_2O$ requires C, 36·2; H, 4·4; N, 14·1%).

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