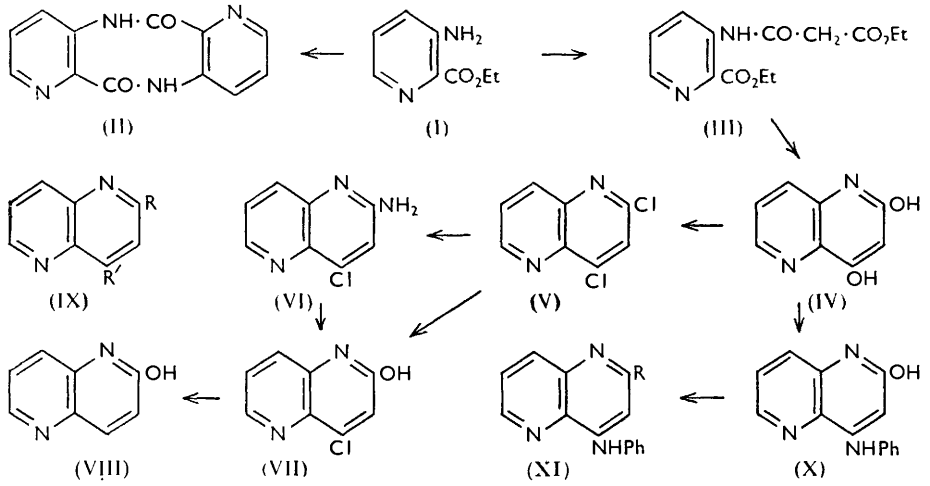
43. *Polyazanaphthalenes. Part V.* Some 2 : 4-Disubstituted 1 : 5-Naphthyridines.*

By V. Oakes and H. N. Rydon.

Several 2 : 4-disubstituted 1 : 5-naphthyridines have been synthesised by way of the 2 : 4-dihydroxy- and 2 : 4-dichloro-compounds. In agreement with the results of approximate quantum-mechanical calculations, the 2-chlorine atom in 2 : 4-dichloro-1 : 5-naphthyridine is more reactive than the 4-chlorine atom towards nucleophilic reagents, the compound resembling, in this respect, 2 : 4-dichloroquinoline rather than 2 : 4-dichloroquinazoline. In 2 : 4-dihydroxy-1 : 5-naphthyridine, however, the 4-hydroxyl group reacts with aniline in the presence of acid in preference to the 2-hydroxyl-group; an explanation of this apparent anomaly is proposed.

The chemistry of 1 : 5-naphthyridine (1 : 5-diazanaphthalene) has been but little studied [1] and no disubstitution products containing reactive groupings in both the 2- and the 4-position have been described. As a preliminary to a projected synthesis of pteroic and folic acid analogues based on this ring system it was, therefore, essential first to investigate some simpler 2 : 4-disubstituted 1 : 5-naphthyridines; the present paper is concerned with this preliminary study.

The key intermediate required for our work was 2 : 4-dihydroxy-1 : 5-naphthyridine (IV). An attempt to prepare this by Claisen condensation of ethyl 3-aminopicolinate (I)



with ethyl acetate, followed by cyclisation, failed, intermolecular amidation, with production of 1 : 7-diazadianthranilide (II), taking precedence over the Claisen condensation; similar self-amidations resulting in the formation of dianthranilide derivatives

* Part IV, Oakes and Rydon, *J.*, 1956, 4433.

[1] For a review, see Allen, *Chem. Rev.*, 1950, **47**, 275.

have previously been observed with methyl 2-aminonicotinate [2] and methyl anthranilate.[3] 2 : 4-Dihydroxy-1 : 5-naphthyridine (IV) was finally prepared, in good yield, by an adaptation of a method [4] previously used for the synthesis of 2 : 4-dihydroxy-quinolines and -1 : 8-naphthyridines. Condensation of ethyl 3-aminopicolinate (I) with malonic ester gave the substituted malonamic ester (III), which readily underwent Dieckmann cyclisation; hydrolysis and decarboxylation then gave the required dihydroxy-compound (IV), which with phosphorus oxychloride readily yielded the dichloro-compound (V).

Application of the approximate quantum-mechanical treatment developed by Longuet-Higgins [5] and subsequently applied to heterocyclic chloro-compounds by Chapman [6] and ourselves [7] shows that 2 : 4-dichloro-1 : 5-naphthyridine should resemble 2 : 4-dichloro-quinoline, and differ from 2 : 4-dichloroquinazoline, in that the 2-chlorine atom should be the more reactive. The results of the calculations are tabulated, the symbolism being the same as that used in our earlier paper.[7]

2 : 4-Dichloro-derivative of	Nucleophilic substitution of	$\Delta U - \Delta U_0$	$\Delta U_{4Cl} - \Delta U_{2Cl}$
Quinazoline [7]	2-Cl	$0{\cdot}63\delta^N + 0{\cdot}08\delta^{Cl}$	$0{\cdot}10\delta^N + 0{\cdot}16\delta^{Cl} + \delta'$
	4-Cl	$0{\cdot}73\delta^N + 0{\cdot}24\delta^{Cl}$	
Quinoline	2-Cl	$0{\cdot}50\delta^N + 0{\cdot}08\delta^{Cl}$	$-0{\cdot}14\delta^N + 0{\cdot}16\delta^{Cl} + \delta'$
	4-Cl	$0{\cdot}36\delta^N + 0{\cdot}24\delta^{Cl}$	
1 : 5-Naphthyridine	2-Cl	$0{\cdot}58\delta^N + 0{\cdot}08\delta^{Cl}$	$-0{\cdot}15\delta^N + 0{\cdot}16\delta^{Cl} + \delta'$
	4-Cl	$0{\cdot}43\delta^N + 0{\cdot}24\delta^{Cl}$	

$\Delta U_{4Cl} - \Delta U_{2Cl}$ is a measure of the difference in activation energy, at 0° K, of the reactions of the 4- and the 2-chlorine atom with a given nucleophilic reagent; since δ is negative, and δ^N without doubt larger than δ^{Cl} and δ', it is clear that the 4-chlorine atom will be less reactive than the 2-chlorine atom in the 1 : 5-naphthyridine and quinoline derivatives, but more reactive in the quinazoline derivative. It is already known that the 2-chlorine atom is the more reactive of the two in 2 : 4-dichloroquinoline,[8,9,10] in agreement with the theoretical predictions, and our results now show that the same is true for 2 : 4-dichloro-1 : 5-naphthridine.*

The predicted preferential reactivity of the 2-chlorine atom in 2 : 4-dichloro-1 : 5-naphthyridine (V) towards nucleophilic reagents was exhibited in its reactions with ammonia, water, and hydrazine. With ethanolic ammonia at 170°, the sole product isolated was 2-amino-4-chloro-1 : 5-naphthyridine (VI), which was converted by nitrous acid into 4-chloro-2-hydroxy-1 : 5-naphthyridine (VII); the latter compound was also obtained directly from the dichloro-compound (V), by the action of aqueous hydrochloric acid, a reagent which similarly brings about preferential hydrolysis of the 2-chlorine atom in 2 : 4 : 7-trichloroquinoline.[12] The structures of the two monochloro-compounds (VI) and (VII) were established by conversion of the latter into 2-hydroxy-1.: 5-naphthyridine (VIII) by treatment with toluene-*p*-sulphonhydrazide, followed by alkali.[13] Hydrazine

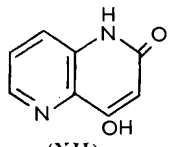
* Dornow and von Loh [11] have recently shown that the 2-chlorine atom reacts preferentially with hydrazine in a number of 2 : 4-dichloro-1 : 8-naphthyridines; this finding, too, is in agreement with calculation ($\Delta U_{4Cl} - \Delta U_{2Cl} = -0{\cdot}18\delta^N + 0{\cdot}16\delta^{Cl} + \delta'$).

[2] Klisiecki and Sucharda, *Roczniki Chem.*, 1923, **3**, 251.
[3] Cooper and Partridge, *J.*, 1954, 3429.
[4] Koller, *Ber.*, 1927, **60**, 407, 1108; cf. Lutz, Ashburn, Freek, Jordan, Leake, Martin, Rowlett, and Wilson, *J. Amer. Chem. Soc.*, 1946, **68**, 1285.
[5] Longuet-Higgins, *J. Chem. Phys.*, 1950, **18**, 283; *Nature*, 1950, **166**, 139.
[6] Chapman, *Chem. Soc. Special Publ.* No. 3, 1955, p. 155; Chapman and Russell-Hill, *J.*, 1956, 1563.
[7] Oakes and Rydon, *J.*, 1956, 4433.
[8] Friedländer and Weinberg, *Ber.*, 1882, **15**, 2679.
[9] Buchmann and Hamilton, *J. Amer. Chem. Soc.*, 1942, **64**, 1357.
[10] Curd, Raison, and Rose, *J.*, 1947, 899.
[11] Dornow and von Loh, *Arch. Pharm.*, 1957, **290**, 136.
[12] Rowlett and Lutz, *J. Amer. Chem. Soc.*, 1946, **68**, 1288.
[13] Albert and Royer, *J.*, 1949, 1148.

likewise replaces only one of the chlorine atoms of compound (V); the product is, beyond reasonable doubt, the 4-chloro-2-hydrazino-compound (IX; R = NH·NH_2, R′ = Cl). All attempts to replace both chlorine atoms by amino-groups were unsuccessful; treatment with ammonia in boiling phenol [14] gave only the diphenoxy-compound (IX; R = R′ = OPh), also obtained by heating with phenol alone, while ammoniacal copper sulphate [15] at 200° gave the 2-amino-4-hydroxy-compound (IX; R = NH_2, R′ = OH).

The differential reactivity of the two chlorine atoms in the dichloro-compound (V) is not exhibited in its reactions with aniline and benzylamine; here both chlorine atoms are replaced, with formation of the 2 : 4-dianilino- and the 2 : 4-dibenzylamino-compound (IX; R = R′ = NHPh and NH·CH_2Ph, respectively); even if only one mol. of aniline is used, in dioxan solution, the major product is the dianilino-compound. Attempts to prepare the diamino-compound (IX; R = R′ = NH_2) from the dibenzylamino-compound, by hydrogenolysis or by the action of sodium in liquid ammonia or of hydrogen bromide in acetic acid, were unsuccessful.

Curd, Raison, and Rose [10] obtained 4-arylamino-2-hydroxyquinolines by heating 2 : 4-dihydroxyquinoline with arylamines in the presence of their hydrochlorides. We have applied this reaction to 2 : 4-dihydroxy-1 : 5-naphthyridine (IV), obtaining a good yield of 4-anilino-2-hydroxy-1 : 5-naphthyridine (X); this structure is assigned on the basis of the insolubility of the product in alkali, a property it shares with 4-anilino-2-hydroxyquinoline, whereas 2-anilino-4-hydroxyquinoline is soluble in alkali.[10,16] In both 2 : 4-dihydroxy-1 : 5-naphthyridine and 2 : 4-dihydroxyquinoline, the preferential reactivity of the 4-hydroxyl group towards aniline is anomalous, since the 2-hydroxyl group would have been expected to be the more reactive towards nucleophilic reagents. However, spectroscopic evidence [17] suggests that 4-hydroxy-groups are more phenolic than 2-hydroxy-groups in both the quinoline and the pyridine series, and it seems likely that both 2 : 4-dihydroxy-compounds exist mainly as the 2-keto-tautomerides (XII) and (XIII); this formulation as vinylogues of carboxylic acids is supported by solubility of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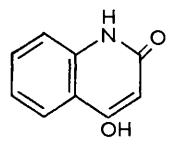
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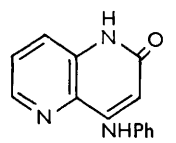
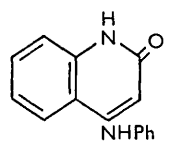

(XIV)


(XV)

these compounds in sodium hydrogen carbonate. The alkali-insolubility of 4-anilino-2-hydroxy-1 : 5-naphthyridine and -quinoline may similarly be due to the preponderance of the keto-forms (XIV) and (XV). The 4-anilino-2-hydroxy-compound, (X) or (XIV), could not be obtained by heating 4-chloro-2-hydroxy-1 : 5-naphthyridine (VII) with aniline; Buchmann and Hamilton [9] observed a similar lack of reactivity towards aniline of 4-chloro-2-hydroxyquinoline. Treatment of 4-anilino-2-hydroxy-1 : 5-naphthyridine (X) with phosphorus oxychloride gave the 4-anilino-2-chloro-compound (XI; R = Cl), which yielded 2-amino-4-anilino-1 : 5-naphthyridine (XI; R = NH_2) with ethanolic ammonia.

Experimental

1 : 7-*Diazadianthranilide* (II).—Ethyl 3-aminopicolinate [18] (3 g.), ethyl acetate (2·1 g.), and sodium ethoxide (1·8 g.) were heated together under reflux for 6 hr. The product was extracted with boiling water (2 × 50 ml.); the cooled extract deposited crystals, a further crop being

[14] Backeberg and Marais, *J.*, 1942, 381; Albert, Brown, and Duewell, *J.*, 1948, 1284; Brown, *J. Soc. Chem. Ind.*, 1950, **69**, 353.
[15] Hertog and Wibaut, *Rec. Trav. chim.*, 1936, **55**, 122.
[16] Dziewonski and Dymek, *Bull. int. Acad. polon. Sci. Lettres, Ser. A*, 1936, 413; *Chem. Zentr.*, 1937, I, 1153.
[17] Ewing and Steck, *J. Amer. Chem. Soc.*, 1946, **68**, 2181; Hertog and Buurman, *Rec. Trav. chim.*, 1956, **75**, 257.
[18] Oakes, Pascoe, and Rydon, *J.*, 1956, 1045.

obtained by adjusting the pH to 5·5. The *compound* (700 mg., 32%) crystallised from hot water or from formamide in needles, m. p. 382° (Found: C, 59·5; H, 3·4; N, 23·6. $C_{12}H_8O_2N_4$ requires C, 60·0; H, 3·3; N, 23·3%).

2 : 4-*Dihydroxy*-1 : 5-*naphthyridine* (IV).—Ethyl 3-aminopicolinate [18] (20 g.) was added in portions, under reflux, to malonic ester (150 ml.) at 100°, the alcohol formed being allowed to distil. When no more alcohol distilled, the excess of malonic ester was removed under reduced pressure and the cooled residue treated with anhydrous ether (100 ml.) and filtered. Addition of more ether (350 ml.) precipitated a pale yellow solid (1 g.), which was filtered off after 2 hr. and recrystallised from water; *NN'-di-(2-ethoxycarbonyl-3-pyridyl)malonamide* formed needles, m. p. 155° (Found: C, 57·3; H, 5·4; N, 13·9. $C_{19}H_{20}O_6N_4$ requires C, 57·0; H, 5·0; N, 14·0%). The ethereal filtrate was treated with ethanolic sodium ethoxide (from sodium, 3·5 g., and absolute ethanol, 100 ml.), and the mixture refluxed for 5 hr. Next day, the precipitated solid was filtered off, suspended in water (30 ml.), and refluxed with 40% sodium hydroxide solution (70 ml.) until effervescence ceased. Boiling water was added until an almost clear solution was obtained; this was filtered and acidified with acetic acid; the *dihydroxy-compound* (13·5 g., 69%) was thus obtained as a yellow solid, m. p. >360° (Found: C, 59·0; H, 3·7; N, 16·8. $C_8H_6O_2N_2$ requires C, 59·2; H, 3·7; N, 17·3%), soluble in 2N-sodium carbonate.

2 : 4-*Dichloro*-1 : 5-*naphthyridine* (V).—The dihydroxy-compound (5 g.) was refluxed for 6 hr. with phosphorus oxychloride (60 ml.). Excess of oxychloride was removed under reduced pressure and the residue treated with an excess of dilute aqueous ammonia. Filtration and sublimation at 160°/0·001 mm. afforded the *dichloro-compound* (5 g., 81%) as needles, m. p. 140° (Found: C, 48·4; H, 2·1; N, 13·8. $C_8H_4N_2Cl_2$ requires C, 48·2; H, 2·0; N, 14·1%).

2-*Amino*-4-*ch'oro*-1 : 5-*naphthyridine* (VI).—The dichloro-compound (400 mg.) was heated in a sealed tube with saturated ethanolic ammonia (10 ml.) for 20 hr. at 170°. Evaporation to dryness under reduced pressure, repeated washing with water, and drying at 100° afforded the *amino-chloro-compound* (170 mg., 47%), m. p. 184° (Found: N, 23·1. $C_8H_6N_3Cl$ requires N, 23·4%).

4-*Chloro*-2-*hydroxy*-1 : 5-*naphthyridine* (VII).—(*a*) A solution of the amino-chloro-compound (70 mg.) in water (3·5 ml.) containing sulphuric acid (0·7 ml.) was slowly treated, at 0°, with sodium nitrite (1 g.). After being heated at 100° for 30 min., the solution was made alkaline with sodium carbonate and evaporated to dryness under reduced pressure; sublimation at 170°/10^{-4} mm. afforded the chloro-hydroxy-compound, m. p. and mixed m. p. 263°.

(*b*) The dichloro-compound (500 mg.) was refluxed for 3 hr. with 5N-hydrochloric acid (6 ml.) and dioxan (4·5 ml.). The cooled mixture was poured into water (50 ml.) and made alkaline with sodium carbonate. After being kept overnight at 0°, the *chloro-hydroxy-compound* (300 mg., 66%) was collected and recrystallised from ethyl acetate, forming needles, m. p. 263° (Found: C, 53·2; H, 3·0; N, 16·2. $C_8H_5ON_2Cl$ requires C, 53·2; H, 2·8; N, 15·5%).

2-*Hydroxy*-1 : 5-*naphthyridine* (VIII).—The chloro-hydroxy-compound (100 mg.) was dissolved in a little chloroform and treated with a concentrated solution of toluene-*p*-sulphonhydrazide (300 mg.) in the same solvent. Dry hydrogen chloride was passed through the solution until precipitation was complete. After an hour the precipitate was collected and heated for 3 hr. with 10% sodium hydroxide solution (10 ml.). The cooled solution was saturated with carbon dioxide and evaporated to dryness under reduced pressure. Vacuum-sublimation afforded the hydroxy-compound, m. p. 258° (Found: N, 19·6. Calc. for $C_8H_6ON_2$: N, 19·2%) (lit.,[19, 20] m. p. 259°; lit.,[2, 20] m. p. of 4-hydroxy-1 : 5-naphthyridine, 340°).

4-*Chloro*-2-*hydrazino*-1 : 5-*naphthyridine* (IX; R = NH·NH_2, R' = Cl).—The dichloro-compound (500 mg.) was refluxed for 16 hr. with hydrazine hydrate (1 ml.) in dioxan (20 ml.). Evaporation to dryness under reduced pressure and treatment of the residue with water afforded the *compound* (330 mg., 68%), which crystallised from water in needles, m. p. 162° (Found: C, 49·5; H, 3·6; N, 28·6. $C_8H_7N_4Cl$ requires C, 49·3; H, 3·6; N, 28·8%).

2 : 4-*Diphenoxy*-1 : 5-*naphthyridine* (IX; R = R' = OPh).—The dichloro-compound (100 mg.) was refluxed with phenol (3 g.) for 6 hr. Treatment of the cooled product with 10% sodium hydroxide solution, followed by filtration, afforded the *diphenoxy-compound* (140 mg., 89%), which crystallised from light petroleum (b. p. 60—80°) in needles, m. p. 170° (Found: C, 76·7; H, 4·9; N, 9·0. $C_{20}H_{14}O_2N_2$ requires C, 76·5; H, 4·5; N, 8·9%). The same product was obtained when gaseous ammonia was passed through the refluxing mixture.

[19] Petrow and Sturgeon, *J.*, 1949, 1157.
[20] Hart, *J.*, 1954, 1879.

2-*Amino*-4-*hydroxy*-1 : 5-*naphthyridine* (IX; R = NH_2, R′ = OH).—The dichloro-compound (450 mg.) was suspended in aqueous ammonia (*d* 0·880; 6 ml.) containing copper sulphate (100 mg.), and the mixture heated in a sealed tube at 200° for 90 hr. The cooled product was filtered and the dark green precipitate (370 mg.) extracted with hot water. Recrystallisation from hot water of the extracted material, which was soluble in both 2N-hydrochloric acid and 2N-sodium hydroxide but was precipitated from the latter with acetic acid, afforded the *amino-hydroxy-compound* (300 mg., 83%) as pale yellow prisms, m. p. 320° (Found: C, 59·6; H, 4·6; N, 26·3. $C_8H_7ON_3$ requires C, 59·6; H, 4·3; N, 26·1%).

2 : 4-*Dianilino*-1 : 5-*naphthyridine* (IX; R = R′ = NHPh).—(*a*) The dichloro-compound (500 mg.) was heated at 180° with aniline (3 ml.) for 5 hr. The cooled product was treated with benzene, and the precipitated solid washed with benzene and then with water; recrystallisation from water afforded the *monohydrochloride* (750 mg., 86%), m. p. 253° (Found: C, 68·8; H, 5·1; N, 16·5. $C_{20}H_{17}N_4Cl$ requires C, 68·9; H, 4·9; N, 16·1%). Treatment of a hot aqueous solution with excess sodium hydroxide liberated the *base*, m. p. 153° (Found: C, 76·6; H, 5·2; N, 17·9. $C_{20}H_{16}N_4$ requires C, 77·0; H, 5·1; N, 17·9%).

(*b*) The dichloro-compound (500 mg.) and aniline (233 mg., 0·5 mol.) were refluxed together in dioxan (25 ml.) for 48 hr. A yellow hydrochloride (250 mg., 57%) separated from the cooled mixture; basification of an aqueous solution afforded the dianilino-compound, m. p. and mixed m. p. 152°.

2 : 4-*Dibenzylamino*-1 : 5-*naphthyridine* (IX; R = R′ = CH_2Ph).—The dichloro-compound (500 mg.) was heated at 190° with benzylamine (5 ml.) for 4 hr. The product was evaporated to dryness under reduced pressure and the residue treated with benzene (10 ml.). Benzylamine hydrochloride was filtered off; addition of light petroleum (b. p. 60—80°) to the filtrate afforded the *dibenzylamino-compound* (750 mg., 88%), m. p. 147° (Found: C, 77·6; H, 6·2. $C_{22}H_{20}N_4$ requires C, 77·7; H, 5·9%). Treatment with hydrogen bromide in acetic acid, followed by precipitation with ether, afforded the *monohydrobromide*, which crystallised from water in prisms, m. p. 216° (Found: C, 62·5; H, 4·8; N, 13·8; Br, 18·6. $C_{22}H_{21}N_4Br$ requires C, 62·8; N, 5·0; N, 13·3; Br, 19·0%).

4-*Anilino*-2-*hydroxy*-1 : 5-*naphthyridine* (X).—2 : 4-Dihydroxy-1 : 5-naphthyridine (1·6 g.) was refluxed for 12 hr. with aniline (4·6 g.) and aniline hydrochloride (1·3 g.). The cooled product was treated with a little ethanol, and the solid washed with ethanol until colourless and then with water until free from chloride ions. The residual *base* (2·05 g., 88%) crystallised from ethanol in leaflets, m. p. 251° (Found: N, 17·8. $C_{14}H_{11}ON_3$ requires N, 17·7%); it is insoluble in 10% sodium hydroxide solution.

4-*Anilino*-2-*chloro*-1 : 5-*naphthyridine* (XI; R = Cl).—The anilino-hydroxy-compound (1 g.) was refluxed for 2 hr. with phosphorus oxychloride (30 ml.). Excess of oxychloride was removed under reduced pressure and the oily residue dissolved in ethanol (5 ml.); addition of aqueous ammonia precipitated the *base* (920 mg., 85%) which, purified by sublimation at 150°/0·01 mm., had m. p. 146° (Found: C, 65·8; H, 4·5; N, 16·7. $C_{14}H_{10}N_3Cl$ requires C, 65·8; H, 3·9; N, 16·4%).

2-*Amino*-4-*anilino*-1 : 5-*naphthyridine* (XI; R = NH_2).—The anilino-chloro-compound (500 mg.) was heated in a sealed tube at 170° with saturated ethanolic ammonia (10 ml.) for 80 hr. The cooled product was evaporated to dryness under reduced pressure, the residue treated with water and filtered, and the filtrate basified with sodium hydroxide. The precipitated *base* (280 mg., 61%) crystallised from benzene–light petroleum (b. p. 60—80°) in long needles, m. p. 152° (Found: C, 70·8; H, 5·1; N, 23·7. $C_{14}H_{12}N_4$ requires C, 71·2; H, 5·1; N, 23·7%).

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