34. *Tautomerism in the Solid State. Part I. Thermochromism of Heterocyclic Phenols.*

By A. G. CAIRNS-SMITH.

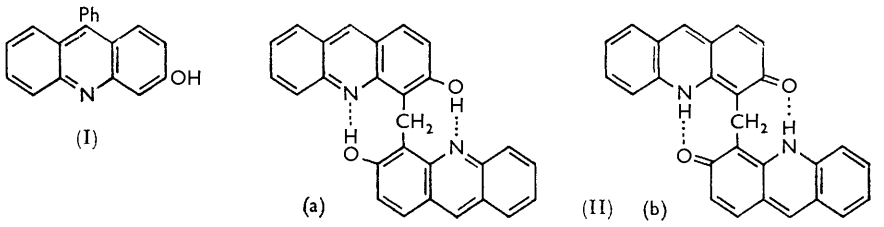
Derivatives of 2-hydroxyacridine and 2-hydroxyphenazine have been prepared which incorporate a mechanism for internal tautomeric transfer of protons. Some of these compounds are polychromic and each has at least one crystalline modification which is thermochromic. It is proposed that the thermochromism is due to a temperature-dependent disordering of protons on hydrogen bonds.

THE yellow crystals of 2-hydroxy-5-phenylacridine (I) are converted into a red powder when they are crushed. This change in colour was attributed by Kehrmann and Matusinsky [2] to a tautomeric change from a lactim to a lactam structure. A later more detailed study [1] confirmed this general explanation and it was then proposed that tautomerisation was facilitated by hydrogen bonds which were postulated to exist in the crystals between all the oxygen and nitrogen atoms. This paper is concerned with the preparation and properties of model compounds which would be expected to contain internal hydrogen bonds such that tautomerisation between differently coloured structures can occur without solvent or catalyst.

Reaction of Formaldehyde with 2-Hydroxyacridine.—When an alcoholic suspension of 2-hydroxyacridine is warmed with formaldehyde and sodium acetate, a red solution is formed from which a dark red solid is rapidly precipitated. There is no evidence of polymerisation and the product can be recrystallised from dioxan without further purification. The methylene bridged structure (II) has been assigned to this product from the following evidence.

[1] Part II, Campbell and Cairns-Smith, *J.*, 1961, in the press.
[2] Kehrmann and Matusinsky, *Ber.*, 1912, **45**, 3498.

The purity of the product suggests that there is only one reactive position in the 2-hydroxyacridine molecule. Ultraviolet absorption spectra in different solvents show that this position must be a carbon atom, since lactim–lactam tautomerism, as shown by

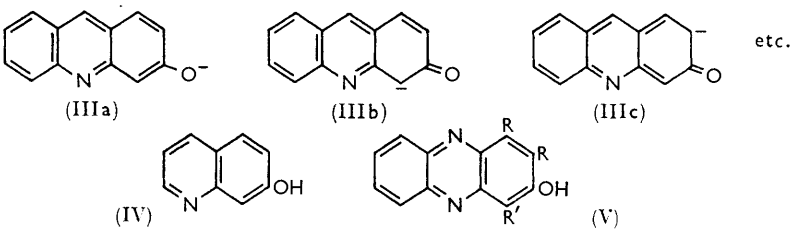


2-hydroxyacridine [3] and 2-hydroxy-5-phenylacridine,[1] is still evident. The acidic hydrogen atom has therefore not been substituted. Elemental analysis favours a methylene-bridged rather than an hydroxymethylated structure.

β-Naphthol reacts quantitatively with formaldehyde under mild conditions to give 1,1′-methylenedi-β-naphthol.[4] The greater relative reactivity of the 1-position in β-naphthol can be attributed to the possibility of localising a negative charge there without disrupting the aromaticity of the adjacent ring.[5] A similar argument applies with added force to 2-hydroxyacridine. The charge on the ion (III) may be localised at $C_{(1)}$ while leaving the aromaticity of the adjacent quinoline system intact: localisation at any other carbon atom must disrupt the aromatic nature of the whole molecule.

7-Hydroxyquinoline (IV), 2-hydroxy-5-phenylacridine (I), 2-hydroxyphenazine (V; R = R′ = H), and 2-hydroxy-3,4-dimethylphenazine (V; R′ = H, R = Me) all react with formaldehyde under the same conditions as does 2-hydroxyacridine. There is no such reaction with formaldehyde and 2-hydroxy-1,3,4-trimethylphenazine (V; R = R′ = Me).

There is evidence that in the 2-hydroxyacridine–formaldehyde product the acidic hydrogen atoms are both involved in internal hydrogen bonds: the bridged compound is more soluble in chloroform and runs much more quickly on alumina than does 2-hydroxyacridine itself; but it is less soluble in alcohol and quite insoluble in hot sodium hydroxide solution. This last point is in marked contrast to 2-hydroxyacridine, and might by itself suggest that the acidic hydrogen atoms are no longer present in the formaldehyde product.



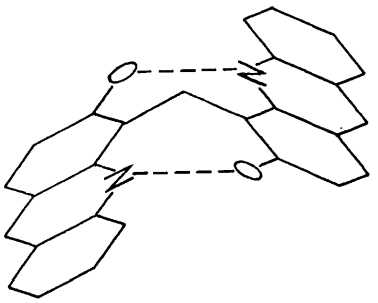
But the spectra show clearly that this is not so. The apparent contradiction can be resolved if it is assumed that the methylene bridge is formed between the carbon atoms in the 1-positions, and that both acidic hydrogen atoms are involved in hydrogen bonds which allow movement of the protons between the oxygen and nitrogen atoms while preventing their ready removal from the molecule as a whole.

The Figure illustrates the internally hydrogen-bonded arrangement envisaged. With the long axes of the acridine nuclei parallel the length of each hydrogen bond will be

[3] Albert and Short, *J.*, 1945, 760.
[4] Fries and Hubner, *Ber.*, 1906, **39**, 439.
[5] Dewar, " The Electronic Theory of Organic Chemistry," Clarendon Press, Oxford, 1949, p. 175.

2·5 Å; this is rather short for bonds of this type, but with such an arrangement each hydrogen bond will be as nearly linear as is possible. Other conformations with equivalent hydrogen bonds may be obtained by rotating each of the carbon–carbon bonds of the methlyene bridge by the same amount in the same sense; thus the length of each hydrogen bond can be increased to the more usual oxygen–nitrogen hydrogen-bond distance of about 2·8 Å,[6] although with this arrangement the hydrogen atoms are further out of the line between the oxygen and the nitrogen atoms. Probably the favoured conformation will give a pair of equivalent hydrogen bonds of between 2·5 and 2·8 Å. In any case the approximation to ideal conditions for the formation of hydrogen bonds, reviewed by Hunter,[7] is closer in this system than in most small molecules containing internal hydrogen bonds.

Dimedone–formaldehyde in the enolic form can have a similar pair of hydrogen bonds (VI); this probably accounts for the great difference in solubility in hydrogen-bonding solvents between dimedone and dimedone–formaldehyde.



Internally hydrogen-bonded conformation of 1,1′-methylenedi-2-hydroxyacridine.

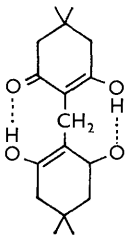
According to Chmielewska and Ciercierska [8] 3-substituted derivatives of 4-hydroxycoumarin (VII) at concentrations of about 10^{-5} mole/l. in 96% aqueous alcohol exist exclusively as anions, whereas 3,3′-methylenedi-4-hydroxycoumarin is un-ionised. Here again a pair of internal hydrogen bonds seems probable (VIII).

Since the ultraviolet spectra of 1,1′-methylenedi-2-hydroxyacridine show all the absorption bands typical of lactim and lactam structures, and since the relative contributions change with change of solvent, the solutions must contain mixtures rather than a resonance hybrid of the structures (IIa) and (IIb): there must be two positions for the hydrogen atoms on the bonds and the energies of these bonds must be mainly electrostatic. This is in line with the conclusion drawn by Burawoy, Salem, and Thompson [9] from a study of the ultraviolet spectra of derivatives of the internally hydrogen-bonded compound 1-phenylazo-2-naphthol.

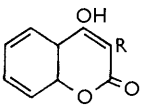
Colour Effects shown by 1,1′-Methylenedi-2-hydroxyacridine in the Solid State.—As a model for the behaviour of 2-hydroxy-5-phenylacridine in the solid, 1,1′-methylenedi-2-hydroxyacridine is not entirely successful. It crystallises from chlorobenzene in red prisms and from chloroform in orange needles: these have the same crystal structure and give similar red powders on profound grinding, but heating does not greatly affect the colours of the crystals or of the powders. It was not possible to prepare very satisfactory films of the ground forms for ultraviolet spectroscopy in this case, but the results suggested that both the lactim and the lactam form are present. Infrared spectra were complex and difficult to interpret, but the absence of bands in the normal OH and NH regions suggests strong hydrogen-bonding. From *X*-ray powder photographs it seems that lattice disintegration, if it occurs on grinding, is not so extensive as in 2-hydroxy-5-phenylacridine.[1]

[6] Robertson, " Organic Crystals and Molecules," Cornell Univ. Press, New York, 1953, p. 243.
[7] Hunter, *Progr. Stereochem.*, 1954, **1**, 224.
[8] Chmielewska and Ciercierska, *Przemysl. Chem.*, 1952, **31** (8), 253 (*Chem. Abs.*, 1953, **47**, 9773d).
[9] Burawoy, Salem, and Thompson, *J.*, 1952, 4793.

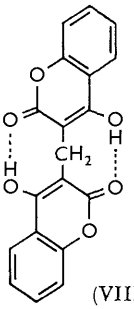
The absorption spectra of 1,1′-methylenedi-2-hydroxyacridine are similar to those of other 2-hydroxyacridine derivatives: the pure lactim form should be yellow and the pure lactam form red. In fact crystals of various intermediate shades are obtained. This suggests that in these crystals both forms of the molecule may be present: that, as in



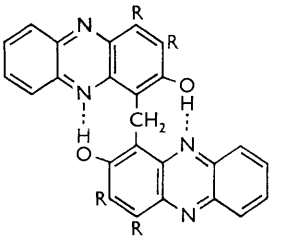
(VI)



(VII)



(VIII)



(IX)

2-phenylazo-1-naphthol [10] and some hydroxy-anils,[11] the protons may become disordered on hydrogen bonds between the oxygen and nitrogen atoms. This view is strengthened by the observation that crystals of 1,1′-methylenedi-2-hydroxyacridine become much paler on cooling: the red crystals become orange and the orange ones yellow at the temperature of liquid nitrogen. Disordered hydrogen bonds which become more ordered on cooling are known in ice [12] and in potassium dihydrogen phosphate.[13]

The thermochromism of 1,1′-methylenedi-2-hydroxyacridine is continuous and immediately reversible. That it occurs without major change in crystal structure can be seen by examining the crystals under the microscope during cooling.

There are variations in the strength of the thermochromism shown by different samples which, like the variations in the initial colours, seem to depend on the state of perfection of the crystal lattice; generally, well-crystallised samples are paler and show thermochromism more strongly than rapidly crystallised samples or ones which have been heavily ground. Such poor samples may be improved by heating them at 100° for a few hours.

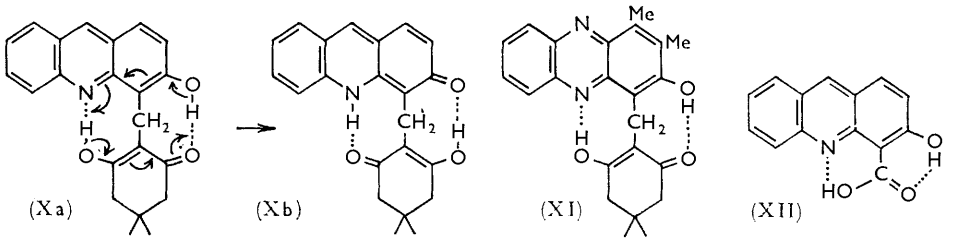
Other Related Compounds showing Thermochromism in the Solid State.—1,1′-Methylenedi-(2-hydroxy-5-phenylacridine) crystallises in orange needles from benzene and in red prisms from dioxan. The behaviour of this compound is closely similar to that of 1,1′-methylenedi-2-hydroxyacridine.

2-Hydroxyphenazine derivatives generally show tautomerism in solution. None of these has been reported as showing thermochromism in the solid state although several examples of polychromism among them have been found by John.[14] In these cases the polychromism is between the extreme lactim and lactam colours of yellow and violet. (The ultraviolet spectrum of the violet form of 2-hydroxy-1,3,4-trimethylphenazine shows that here the molecule is entirely in the lactam state.) From the spectra in solution, the relative stability of the lactam form appears to be smaller with 2-hydroxyphenazine derivatives [15] than with the corresponding acridines,[3] but the introduction of methyl groups seems to increase it.

1,1′-Methylenedi-2-hydroxyphenazine (IX; R = H) and its tetramethyl derivative (IX; R = Me) were prepared and both were found to be thermochromic in the solid state. 1,1′-Methylenedi-2-hydroxyphenazine shows only slight thermochromism, the yellow form obtained from chlorobenzene becoming reversibly dull orange between 200° and

[10] Hadzi, *J.*, 1956, 2143.
[11] Cohen, Hirshberg, and Schmidt in "Hydrogen Bonding," ed. Hadzi, Pergamon Press, London, 1959, p. 293.
[12] Pauling, *J. Amer. Chem. Soc.*, 1935, **57**, 2680.
[13] Bacon and Pease, *Proc. Roy. Soc.*, 1955, *A*, **230**, 359.
[14] John, *Angew. Chem.*, 1947, **59**, 188.
[15] Badger, Pearce, and Pettit, *J.*, 1951, 3204.

300°. 1,1′-Methylenedi-(2-hydroxy-3,4-dimethylphenazine) is both polychromic and thermochromic. Rapid crystallisation from toluene gives yellow needles which show no thermochromism; however, when these are left in contact with toluene for several hours, or



crystallise slowly, compact brick-orange crystals are obtained which are thermochromic both above and below room temperature. At −180° these crystals are yellow. Heating changes the colour, through dull orange and brick-red, to chocolate-brown at about 280°. These colour changes are immediately reversible. That they should be towards brown rather than red is to be expected on the proton-transfer theory: as the temperature rises, more and more of the deep violet lactam structures contribute to the colour of the crystals.

It seems that to produce a compound showing thermochromism in the solid from a 2-hydroxyacridine or 2-hydroxyphenazine derivative it is necessary to provide a mechanism whereby the proton may be transferred from the oxygen to the nitrogen atom by an internal rearrangement. This requirement should be fulfilled in compounds such as (X) and (XI).

The reaction which normally leads to the formation of 1,1′-methylenedi-2-hydroxyacridine gives, when carried out in the presence of a large excess of dimedone, not only a large amount of dimedone–formaldehyde and a small amount of the normal product, but also a good yield of the unsymmetrical compound (X). In its ultraviolet and visible absorption spectra in different solvents this compound (X) again shows the lactim–lactam tautomerism typical of the 2-hydroxyacridine nucleus.

The compound (X) is quite strongly thermochromic, the bright red crystals becoming reversibly pale orange at the temperature of liquid nitrogen.

The compound (XI) was prepared similarly from 2-hydroxy-3,4-dimethylphenazine. The crude product was slightly thermochromic at low temperatures. Recrystallisation from toluene gave dull yellow crystals which were still only slightly thermochromic, but a very pure sample of these changed during a few weeks into dark reddish-brown crystals which were strongly thermochromic, becoming bright yellow at the temperature of liquid nitrogen.

Unsuccessful attempts were made to prepare the simplest possible derivative of 2-hydroxyacridine incorporating a potential proton-transfer mechanism, namely, 2-hydroxyacridine-1-carboxylic acid (XII).

2-Hydroxyacridine and 2-hydroxyphenazine derivatives generally show a very slight thermochromism in solution. There is probably no particular significance in this since one would expect an equilibrium between tautomers to be influenced by temperature: in all the cases studied these colour changes were in the opposite direction to those shown by the bridged compounds in the solid.

The existence of 1,1′-methylenedi-(2-hydroxy-3,4-dimethylphenazine) in both a thermochromic and a non-thermochromic modification emphasises that the crystal structure as well as the molecular structure is important in determining the thermochromism. Even the state of perfection of the lattice seems to be significant. The thermochromism is evidently not a simple function of the isolated molecule, and an explanation of it must take into account the special conditions which exist in the solid.

Ubbelohde and Gallagher [16] have discussed hydrogen bonds in crystals from the point of view of the modern theory of acids and bases. These authors conclude that " proton-transfer defect sites "—sites where the protons are in the " wrong " positions on hydrogen bonds—should occur quite generally in such crystals, the extent depending on the relative energies of the normal and the defect positions, and on the temperature. The thermochromism of the methylene-bridged compounds which have been considered here can be discussed along similar lines. At absolute zero all the molecules in the crystals are in the lactim state; as the temperature rises, " defects " appear in the crystals in the form of lactam molecules resulting from the co-operative transfer of pairs of protons across the internal hydrogen bonds; since the lactam form absorbs light at a longer wavelength, the crystals become more deeply coloured. The tautomeric nature of the methylene-bridged compounds provides them with an additional means of absorbing energy, which is effective in the solid because it does not require any substantial movement or change in the overall shape of the molecules.

Experimental

Symmetrical Thermochromic Compounds from Heterocyclic Phenols and Formaldehyde.—2-Hydroxyacridine (3 g.) and anhydrous sodium acetate (2 g.) were added to alcohol (50 ml.), and the mixture warmed to the b. p. 40% Aqueous formaldehyde (25 ml.) was added and the mixture refluxed for 10 min. The resulting red precipitate of *1,1'-methylenedi-2-hydroxyacridine* was separated by filtration, washed with water, and dried (2·8 g.). Recrystallisation gave orange needles from chloroform or red prisms from dioxan; both forms had m. p. 350° (decomp.) (Found: C, 80·8; H, 4·7; N, 7·0. $C_{27}H_{18}N_2O_2$ requires C, 80·6; H, 4·5; N, 7·0%). The *diacetyl derivative*, formed by refluxing acetic anhydride and sodium acetate, was pale yellow (from dioxan) with m. p. 263—265° (Found: C, 76·7; H, 4·45; N, 5·85. $C_{31}H_{22}N_2O_4$ requires C, 76·5; H, 4·6; N, 5·8%).

2-Hydroxy-5-phenylacridine reacted with formaldehyde under the above conditions, to give *1,1'-methylenedi-(2-hydroxy-5-phenylacridine)*, pale orange needles (from benzene) or red prisms (from dioxan), m. p. (both forms) 333—335° (decomp.) (Found: C, 84·8; H, 4·8; N, 4·6. $C_{39}H_{26}N_2O_2$ requires C, 84·5; H, 4·7; N, 5·1%).

2-Hydroxyphenazine gave *1,1'-methylenedi-2-hydroxyphenazine*, yellow needles (from chlorobenzene), m. p. 331—334° (decomp.) (Found: C, 74·6; H, 4·1; N, 13·3. $C_{25}H_{16}N_4O_2$ requires C, 74·2; H, 4·0; N, 13·9%).

2-Hydroxy-3,4-dimethylphenazine gave *1,1'-methylene-di-(2-hydroxy-3,4-dimethylphenazine)*, yellow needles (rapid crystallisation from toluene) or brick-orange prisms (slow crystallisation from toluene), m. p. (both forms) 350° (decomp.) (Found: C, 75·4; H, 5·2; N, 12·3. $C_{29}H_{24}N_4O_2$ requires C, 75·6; H, 5·25; N, 12·2%). The general procedure of John [14] for the preparation of 2-hydroxy-1,3,4-trimethylphenazine was followed in preparing the 3,4-dimethyl compound except that Thiele's original conditions [17] were used to form 1,2,4-triacetoxy-5,6-dimethylbenzene from *o*-xyloquinone. The final condensation of hydroxyxyloquinone with *o*-phenylenediamine was carried out under the conditions described by Kehrmann and Cherpillod [18] for the preparation of 2-hydroxyphenazine: yields were improved with an excess of the diamine.

Unsymmetrical Thermochromic Compounds.—2-Hydroxyacridine (5 g.), dimedone (10 g.), and sodium acetate (5 g.) were warmed in alcohol (250 ml.) on a water-bath. 40% Aqueous formaldehyde (50 ml.) was then added. After a minute the 2-hydroxyacridine had dissolved and a deep red colour had developed. The solution was heated under reflux for 10 min., then poured into cold water (2 l.) and left for 15 min. The red solid was separated, washed with water, dried, dissolved in benzene (200 ml.) and placed on a short alumina column. A solution of 1 : 99 alcohol–benzene was used for elution and the first deep red band taken. The volume of this fraction was reduced to 30 ml. and the solution left to crystallise. This gave *1-(4,4-dimethyl-2,6-dioxocyclohexylmethyl)-2-hydroxyacridine* (4·5 g., 50%), m. p. 200—202°. Recrystallisation from benzene gave large red prisms (3·4 g.), m. p. 202—203° (Found: C, 76·0; H, 5·8; N, 4·2. $C_{22}H_{21}NO_3$ requires C, 76·1; H, 6·1; N, 4·0%).

[16] Ubbelohde and Gallagher, *Acta Cryst.*, 1955, **8**, 71.
[17] Thiele, *Ber.*, 1898, **31**, 1247.
[18] Kehrmann and Cherpillod, *Helv. Chim. Acta*, 1924, **7**, 973.

Under similar conditions 2-hydroxy-3,4-dimethylphenazine gave 1-(4,4-*dimethyl*-2,6-*dioxocyclohexylmethyl*)-2-*hydroxy*-3,4-*dimethylphenazine*. This crystallised from toluene as yellow needles, m. p. 219°, which changed slowly into dark brown prisms. Brown crystals, m. p. 219°, were obtained directly from benzene (Found: C, 73·6; H, 6·3; N, 7·5. $C_{23}H_{24}N_2O_3$ requires C, 73·4; H, 6·4; N, 7·4%).

1-*Formyl*-2-*hydroxyacridine*.—Aqueous sodium hydroxide (4 g. in 10 ml. of water) was added to a suspension of 2-hydroxyacridine (2 g.) in alcohol (20 ml.). Chloroform (2 ml.) was added during 10 min., the temperature being kept just below the b. p. during the addition and for a further hour. The mixture was then heated under reflux for 1½ hr. and the excess of chloroform and most of the alcohol were removed under reduced pressure. The solid was separated, suspended in water, and acidified with hydrochloric acid. The mixture was warmed slightly and filtered to remove tar. The filtrate was neutralised with sodium hydrogen carbonate, and the resulting yellow precipitate of 1-*formyl*-2-*hydroxyacridine* recrystallised twice from water, giving yellow needles (0·4 g., 20%), m. p. 232—233° (Found: C, 75·1; H, 4·0; N, 6·1. $C_{14}H_9NO_2$ requires C, 75·3; H, 4·1; N, 6·3%). Attempts to oxidise the aldehyde to the acid were unsuccessful: with boiling nitric acid there was little effect on the aldehyde; on aerial oxidation of a hot alkaline solution a complex mixture was formed (paper chromatography with ethyl methyl ketone–water as solvent was used to detect oxidation products).

Spectra.—Ultraviolet and visible absorption spectra (see Tables) were determined with a Unicam quartz spectrophotometer (S.P. 500).

Maxima and shoulders (sh) (mμ) *in ultraviolet and visible absorption spectra of* 1,1′-*methylenedi*-2-*hydroxyacridine*.

				In 9 : 1 *cyclohexane–chloroform*						
λ	236	264	298sh	324sh	337	355	402	—	490sh	—
log ε	4·72	5·12	3·94	3·74	4·04	4·32	3·88	—	2·68	—
				In chloroform						
λ	—	265	299	—	338	355	398	434sh	490	530sh
log ε	—	5·04	4·34	—	4·06	4·32	3·82	3·64	3·50	3·16
				In absolute alcohol						
λ	235	262	290	—	348sh	355	400sh	—	472	515sh

Maxima and shoulders (sh) (mμ) *in ultraviolet and visible absorption spectra of* 1-(4,4-*dimethyl*-2,6-*dioxocyclohexylmethyl*)-2-*hydroxyacridine*.

				In cyclohexane					
λ	236	260	292sh	322sh	338	355	406	518	545sh
log ε ...	4·50	4·86	3·78	3·38	3·72	3·92	3·60	2·58	2·44
				In absolute alcohol					
λ	235	260	—	—	352sh	364	420sh	480	—
log ε ...	4·46	4·74	—	—	3·98	4·10	3·40	3·54	—
				In 10% *aqueous alcohol*					
λ	236	265	298sh	—	352sh	364	—	445	—
log ε ...	4·32	4·80	3·94	—	4·04	4·20	—	3·56	—

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Department of Chemistry, The University,
Edinburgh, 9.

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