Phase Relationships in the Pyridine Series. Part IV. The Miscibility of the Ethylpyridines and Dimethylpyridines with Water.*

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The miscibility with water of 2-, 3-, and 4-ethylpyridine and of 2 : 3-, 3 : 4-, and 3 : 5-dimethylpyridine is examined. All six compounds are partially miscible with water and give rise to solubility curves of the closed-loop type; the lower consolute point of the 3-ethylpyridine–water system could not, however, be reached owing to separation of a solid phase. The relation between solubility in water and molecular structure in the pyridine series is discussed.

In Part I (Andon and Cox, *J.*, 1952, 4601) the solubilities in water of the three methylpyridines and of 2 : 4-, 2 : 5-, and 2 : 6-dimethylpyridine were reported. These dimethylpyridines were shown to belong to the comparatively rare group of compounds which form mixtures with water having both upper and lower consolute temperatures. The present paper deals with the solubility in water of the three ethylpyridines and of the three dimethylpyridines which were not studied previously.

EXPERIMENTAL

Materials.—As in previous work in this series, considerable care was taken to secure the compounds in an adequate state of purity. As far as is known, the compounds used were free

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* The paper entitled " The thermodynamic properties of dilute solutions of pyridine bases in water " (Andon, Cox, and Herington, *Discuss. Faraday Soc.*, 1953, **15**, 168) is regarded as Part III. Part II, *J.*, 1952, 4606.

from contaminants which were themselves much less soluble (*e.g.*, hydrocarbons) or much more soluble (*e.g.*, ammonia) in water. The amount of water present in each sample (*ca.* 0·05% by wt.) was measured by infra-red spectroscopy (Coulson, Hales, and Herington, *J.*, 1951, 2125) and due allowance made, where necessary, in calculating the compositions of the mixtures.

2-*Ethylpyridine.*—A sample, prepared by selective hydrogenation of technical-grade 2-vinylpyridine and purified by fractional distillation, had b. p. 144·5—144·8°/700 mm. No impurity, apart from water, was disclosed by infra-red spectroscopy.

3-*Ethylpyridine.*—Nicotinic acid of high purity was converted into methyl 3-pyridyl ketone hydrochloride by Strong and McElvain's method (*J. Amer. Chem. Soc.*, 1933, **55**, 816), and the ketone was reduced to 3-ethylpyridine by that of Fand and Lutomski (*ibid.*, 1949, **71**, 2931). The crude product was fractionally distilled in a Podbielniak microdistillation column (equivalent to about 30 theoretical plates) to give a main fraction, b. p. 166°/760 mm. The presence of an unidentified impurity was indicated by the infra-red spectrum, although the ultra-violet spectrum agreed well with that published (Coulson, Hales, Holt, and Ditcham, *J. Appl. Chem.*, 1952, **2**, 71). Ketones appeared to be absent.

FIG. 1. *Solubility curves for the systems* (a) 2-*ethylpyridine–water and* (b) 2 : 3-*dimethylpyridine–water.*

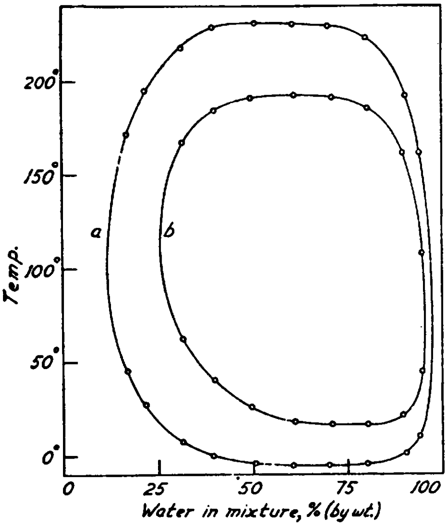
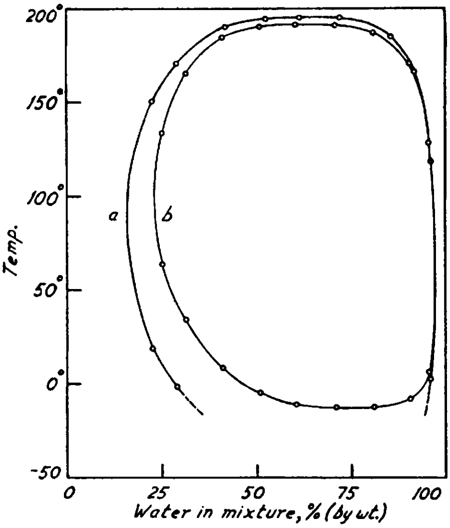


FIG. 2. *Solubility curves for the systems* (a) 3-*ethylpyridine–water and* (b) 3 : 5-*dimethylpyridine–water.*



4-*Ethylpyridine.*—A sample, prepared by Frank and Smith's method (*Org. Synth.*, 1947, **27**, 38) and purified by fractional distillation, had b. p. 165—165·5°/760 mm. The infra-red spectrum disclosed the presence of impurities, but these did not exceed 1% by weight.

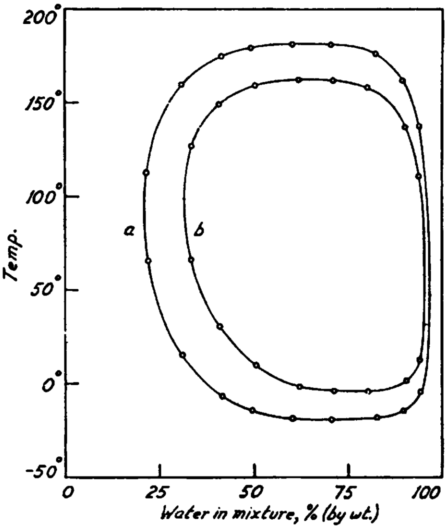
2 : 3-*Dimethylpyridine.*—A sample of this base, purchased from Kodak Ltd., was purified by a combination of fractional distillation and fractional freezing. The sample used contained *ca.* 0·2% of 2 : 4-dimethylpyridine and 0·04% of water, as measured by the infra-red spectrum, but no other impurities could be detected.

3 : 4-*Dimethylpyridine.*—A specimen prepared by Wibaut and Kooyman's method (*Rec. Trav. chim.*, 1944, **63**, 231) and purified by fractional distillation in a Podbielniak microdistillation column had b. p. 111°/98 mm. and appeared from the infra-red spectrum to be of high purity.

3 : 5-*Dimethylpyridine.*—A sample of this base, kindly supplied by Messrs. Robinson Brothers, West Bromwich, was purified by fractional distillation and fractional freezing. The sample used had b. p. 172·2—172·8°/762 mm. As several bands due to impurity were detected in the infra-red spectrum, the sample was examined by the freezing-point technique (Herington and Handley, *J.*, 1950, 199) and found to be 99·2 mole-% pure.

Solubility Measurements.—As in Part I (*loc. cit.*) Alexejeff's method was employed. Solution temperatures above room temperature were determined with the aid of an electrically-heated metal block; the sealed tube containing the specimen was fixed in a cavity in the middle of the block and could be viewed through windows, of Chance O.N.20 glass, fixed in the side of the block. Mixing of the liquid layers was effected by rotating the block and hence the specimen through an angle of 180° in a vertical plane.

FIG. 3. *Solubility curves for the systems* (a) *4-ethylpyridine–water and* (b) 3 : 4-*dimethylpyridine–water.*



Solution temperatures below room temperature were determined by the following simple technique. The tube containing the specimen was fixed in a bracket which was then lowered into an unsilvered Dewar vessel filled with methanol; manual shaking of the tube-holder gave adequate mixing of both the methanol and the contents of the tube. The temperature of the bath was lowered by addition of solid carbon dioxide until the lower solution temperature had been passed; the temperature of the bath was then allowed to rise at the rate of 0·1° per min., small pieces of solid carbon dioxide being added when necessary, until the cloud point had been reached.

The results of the solubility measurements are shown in Fig. 1, 2, and 3; the solubility–temperature relations in five of the six systems studied may be represented by closed-loop curves. In the 3-ethylpyridine–water system [curve (*a*), Fig. 2] only an upper consolute temperature was found; at every attempt to reach the lower consolute point, a solid phase separated before the two liquid phases had become completely miscible. A tendency to solidify also occurred with mixtures of 4-ethylpyridine and of 3 : 5-dimethylpyridine with water but it was possible to supercool these mixtures, so that the lower solution temperatures could be reached before the onset of freezing. In these two systems, the liquid mixtures at the lower consolute points were thus metastable with respect to a solid phase.

DISCUSSION

Critical solution data for all the nine C_7H_9N alkylpyridines are set out in the Table, the data for 2 : 4-, 2 : 5-, and 2 : 6-dimethylpyridine being taken from Part I (*loc. cit.*).

For a discussion of the relation between solubility and structure, it is convenient to divide these nine isomeric bases into the following groups: (i) those with an α-methyl group, *viz.*, 2 : 3-, 2 : 4, 2 : 5-, and 2 : 6-dimethylpyridine; (ii) those with a β-methyl group, *viz.*, 2 : 3-, 2 : 5-, 3 : 4-, and 3 : 5-dimethylpyridine; (iii) those with a γ-methyl group, *viz.*, 2 : 4- and 3 : 4-dimethylpyridine; (iv) those with an ethyl group, *viz.*, 2-, 3-, and

Critical solution data for nine alkylpyridine–water systems.

Alkylpyridine	Lower consolute point: Temp.	Lower consolute point: H_2O, % by wt.†	Upper consolute point Temp.	Upper consolute point H_2O, % by wt.†
2 : 3-Dimethylpyridine	16·5° ± 0·2° *	74	192·6° ± 0·4° *	61·5
2 : 4- ,, ...	23·4 ± 0·2	74·5	188·7 ± 0·3	63
2 : 5- ,, ...	13·1 ± 0·2	73	206·9 ± 0·5	62
2 : 6- ,, ...	34·0 ± 0·2	70	230·7 ± 1	59
3 : 4- ,, ...	− 3·6 ± 0·3	75·5	162·5 ± 0·3	64
3 : 5- ,, ...	−12·5 ± 0·4	74·5	192·0 ± 0·4	63
2-Ethylpyridine	− 5·0 ± 0·3	66	231·4 ± 1	58
3- ,, ...	−35 ± 3 (estimated)		195·6 ± 0·5	63
4- ,, ...	−19·0 ± 0·4	72	181·8 ± 0·3	63·5

* These standard deviations were calculated as described in Part I (*loc. cit.*). No allowance has been made for impurities, because it is impossible to calculate their effects on the solution temperatures. It is believed, however, that such effects are absent in the results reported for 2 : 4-, 2 : 5-, and 2 : 6-dimethylpyridine, as very pure samples of these bases were available. † All ±1%.

4-ethylpyridine. From examination of Figs. 1—3, and of the data of the Table, the following conclusions can be drawn.

(1) The area within the solubility loop of an ethylpyridine–water system is greater than that of a comparable dimethylpyridine–water system ("comparable" here means that the two methyl groups occupy positions in the pyridine ring which are the same distance from the nitrogen atom as is the ethyl group), *e.g.*, the area of the loop for 3-ethylpyridine is greater than that for 3 : 5′-dimethylpyridine (see Fig. 2).

(2) A pyridine homologue containing an α-alkyl group gives rise to a solubility loop slightly greater in area than that of an isomer of the same class [*i.e.*, classes (i), (ii), (iii), or (iv), defined above] containing a β-alkyl group, which, in turn, gives rise to a loop greater in area than that of an isomer of the same class containing a γ-alkyl group; *e.g.*, the areas of the loops of the dimethylpyridines of class (i) lie in the order: $2:6 > 2:5 > 2:3 > 2:4$.

(3) The temperature at which a pyridine homologue is least miscible with water (*i.e.* the temperature corresponding to the widest tie-line of a solubility curve) is higher for a homologue containing an α-alkyl group than it is for an isomer of the same class (as defined above) containing a β- or a γ-alkyl group; *e.g.*, the temperatures of least miscibility for the ethylpyridines [class (iv)] lie in the order: $2 > 3 = 4$. It is noteworthy that, although the monomethylpyridines are completely miscible with water at all temperatures, it is nevertheless possible to infer at what temperature there is a least *tendency* for these bases to mix with water, and as with the dimethylpyridines and the ethylpyridines, it is found that this temperature is highest for the α-isomer. Thus, observations of opalescence in binary mixtures and of the phase relations in ternary mixtures (Part I, *loc. cit.*) together with studies of mixtures of the methylpyridines with deuterium oxide (Cox, *J.*, 1952, 4606) all indicate that 2-methylpyridine has a least tendency to mix with water at *ca.* 110°, whereas the corresponding temperatures for 3-methylpyridine and for 4-methylpyridine are *ca.* 80° and 90°, respectively.

It is of interest to speculate on the reasons underlying these correlations between structure and solubility. By analogy with the benzene series it might be expected that groups *ortho* to the nitrogen atom of the pyridine ring (*i.e.*, in positions 2 or 6) would give rise to a "proximity effect" (Hammett, "Physical Organic Chemistry," McGraw-Hill, New York, 1940, pp. 204—207), so for the moment the discussion will be confined to β- and γ-substituted pyridines. Now the molecule of a pyridine base may be considered to be made up of two parts. The first, the ═N-function, is a hydrophilic group and confers solubility in water, but the second, the remaining hydrocarbon part of the molecule, is hydrophobic in nature and gives rise to very low solubility in water. These two effects are, of course, mutually opposed and the observed solubility of a pyridine base is a resultant of the two. When one of the hydrogen atoms of the pyridine ring is substituted by an alkyl group, the hydrocarbon character of the molecule will obviously be increased and in consequence a diminution of solubility will be observed; at the same time, an increase in the electron density in the neighbourhood of the nitrogen atom will take place and this effect will in general be greater for substitition in the 4- than in the 3- or 5-position. (This statement is based on unpublished measurements made in this Laboratory of the dissociation constants of a number of pyridine bases.) If hydrogen-bonding is mainly electrostatic in origin (cf. Davies, *Ann. Reports*, 1946, **43**, 5), it would be expected that an increase in the electron density at the nitrogen atom would lead to more extensive hydrogen-bonding. It would be expected therefore that the greater basicity of γ- as compared with isomeric β-alkylpyridines would give rise to a relatively greater hydrophilic effect and, in consequence, a greater solubility in water. Reference to conclusion (2) above will show that this expectation is in fact borne out. If an ethylpyridine is now considered vis-à-vis a "comparable" dimethylpyridine [see conclusion (1)] it is possible to see how the greater solubility of the dimethylpyridine can arise. The hydrophobic effects in the two molecules will be about the same, but because an ethylpyridine is a much weaker base than a comparable dimethylpyridine, the hydrophilic effect in the latter should be greater, leading to the greater solubility observed. With regard to α-substituted pyridines, it would seem that at low temperatures they are more extensively hydrogen-bonded than isomeric γ-substituted pyridines [cf. conclusion (3) and Part V, succeeding paper] even though the base strengths of isomeric α- and γ-alkylpyridines are about the same; alternatively, the nitrogen atom in α-alkylpyridines may influence the interaction of the adjacent alkyl group with water. Further study may reveal that very bulky substituents in the 2- or 6-positions tend to reduce, by steric hindrance of the nitrogen atom, the apparently extensive hydrogen-bonding brought about by the presence of methyl or ethyl groups in these positions (cf. Brown and Kanner, *J. Amer. Chem. Soc.*, 1953, **75**, 3865).

It may be readily seen that the solubility curves of the nine systems discussed above have a number of features in common. For example, they all have relatively flat sections at the top and bottom and almost vertical sections near to the " 100% water " ordinate, while the consolute compositions are all of the same order—*ca.* 73% of water by weight (0·94 mole-fraction) at the lower consolute point and *ca.* 64% of water by weight (0·91 mole-fraction) at the upper consolute point. By comparison with the closed-loop systems described by earlier workers (Flaschner, *Z. physikal. Chem.*, 1908, **62**, 493; *J.*, 1909, **95**, 668; Flaschner and McEwen, *J.*, 1908, **93**, 1000; Hudson, *Z. physikal. Chem.*, 1904, **47**, 113; Rothmund, *ibid.*, 1898, **26**, 433; Cox and Cretcher, *J. Amer. Chem. Soc.*, 1926, **48**, 451; Cox, Nelson, and Cretcher, *ibid.*, 1927, **49**, 1080) it is found that the features noted above as being characteristic of pyridine base–water mixtures are in fact common to all systems having closed-loop solubility curves which have so far been described. Of particular interest is the fact that the lower consolute compositions of all these systems are of the order 0·9 mole-fraction of water. Those recent theories which assume the lower consolute composition to be 0·5 mole fraction (Bellemans, *J. Chem. Phys.*, 1953, **21**, 368, 369; Barker and Fock, *Discuss. Faraday Soc.*, 1953, **15**, 188) therefore need modification before direct comparisons can be made between theory and experiment. It also follows that none of the known systems having lower consolute points obeys the equation $G^E = k_T x_2(1 - x_2)$, where G^E is the excess free energy of mixing, k_T is a constant for a given temperature, and x_2 is the mole-fraction of water in the mixture. This is because the above equation requires that $x_2 = 0{\cdot}5$ at the lower consolute temperature. A similar conclusion has already been reached by Herington, using an entirely different argument (*Discuss. Faraday Soc.*, 1953, **15**, 273).

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