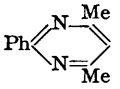
728. *The Ultra-violet Absorption Spectra of Phenylpyrimidines.*

By Allison Maggiolo and Peter B. Russell.

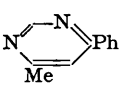
The attachment of a phenyl nucleus to a pyrimidine nucleus in any of the available positions causes shift to longer wave-length and an increase in intensity of the absorption maximum. This exaltation is diminished by the interference with the planarity of the molecule by substitution about the joining bond. The spectroscopic phenomena are analogous in some respects to those previously observed in the diphenyl series and, like them, they may be readily accounted for on the quasi-classical theory of Lewis and Calvin (*Chem. Reviews*, 1939, **25**, 273). From a study of these phenomena and their interpretation, certain conclusions are drawn as to the nature of the pyrimidine ring.

In a recent communication (Russell and Hitchings, *J. Amer. Chem. Soc.*, 1951, **73**, 3763) mention was made of some rather marked differences in the ultra-violet absorption spectra of 2 : 4-diaminopyrimidines with phenyl groups in the 5- and the 6-position. Since the former group of compounds show high antimalarial activity while the latter are inactive, an attempt has been made to gain an insight into the differences in fine structure of these compounds from a study of these spectra. The present paper deals with the spectra of the parent 2-, 4-, and 5-phenylpyrimidines. For purely practical reasons it has in some cases been necessary to utilize the spectra of methyl derivatives of these compounds. There is, however, every reason to believe that the introduction of this substituent, except possibly when placed adjacent to the ring junction, has little or no effect on the resulting spectrum.

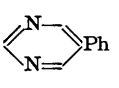
4 : 6-Dimethyl-2-phenyl- (I) (Pinner, *Ber.*, 1893, **26**, 2124), 6-methyl-4-phenyl- (II) (von Merkatz, *Ber.*, 1919, **52**, 869), and 5-phenyl-pyrimidine (III) were examined. Their spectra



(I)



(II)



(III)

are shown in Fig. 1 and listed in the table together with the spectra of diphenyl and the three phenylpyridines.

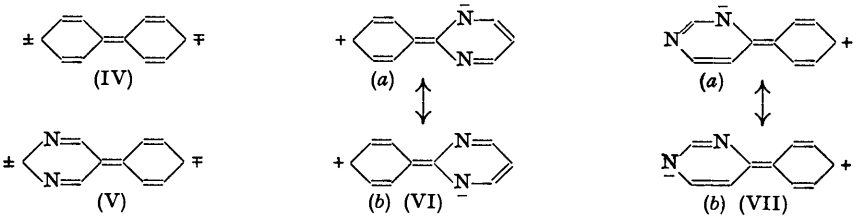
Compound	$\lambda_{max.}$, mμ	ε_{max}	Compound	$\lambda_{max.}$, mμ	$\varepsilon_{max.}$
(I)	258	20,200	3-Phenylpyridine [2]	246	17,200
(II)	273	18,000		275 infl.	10,000
(III)	256	12,100	4-Phenylpyridine [2]	257	16,000
Pyrimidine [1]	242	2,500	Pyridine [3]	253	1,820
2-Phenylpyridine [2]	245	12,700	Diphenyl [4]	246	20,300
	276	11,300	Benzene [5]	197	4,360
				255	213

[1] Uber and Winters, *J. Amer. Chem. Soc.*, 1941, **63**, 137. [2] Gillam, Hey, and Lambert, *J.*, 1941, 364. [3] International Critical Tables, Vol. V, 363. [4] Gillam and Hey, *J.*, 1939, 1170. [5] Henri, *J. Phys. Radium*, 1922, **3**, 181.

The relation between colour and chemical constitution has recently received renewed attention (Braude, *Ann. Reports*, 1945, **42**, 105; Maccoll, *Quart. Reviews*, 1947, **1**, 144; Bowen, *ibid.*, 1950, **4**, 236; Ferguson, *Chem. Reviews*, 1948, **43**, 385). Although the theoretical status of the subject is not entirely satisfactory, a qualitative interpretation of the spectra of many compounds can be based on the concept of resonance and on the theory of Lewis and Calvin (*loc. cit.*; see also Branch and Calvin, "The Theory of Organic Chemistry," Prentice-Hall Inc., New York, 1943, pp. 155 *et seq.*). These authors ascribe the absorption of light by diphenyl to electronic oscillations, the extremes of which may be represented by (IV). These are resonance forms contributing particularly to the excited state of the molecule.

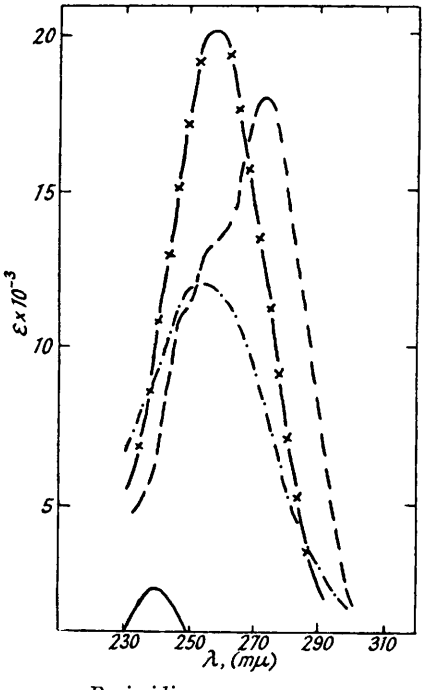
Although similar forms (V) can be written for 5-phenylpyrimidine, yet for both 2- and 4-phenylpyrimidine forms are possible where the negative charge is carried on a ring nitrogen (VI*a* and *b*, and VII*a* and *b*). In these two cases the favourable disposition of charge should lead to increased contribution of the ionoid forms (Branch and Calvin, *op. cit.*, p. 267). The effect of this is observed in the spectra of (I) and (II), the maxima here being much more intense than that shown by (III). In addition, (II), which can give rise to unsymmetrical ionoid

forms (VII*a* and *b*), shows a complicated spectrum with inflexions at 250 and 260 mμ. In the phenylpyridine series (Hey, Gillam, and Lambert, *loc. cit.*, see table) complexity of spectra is



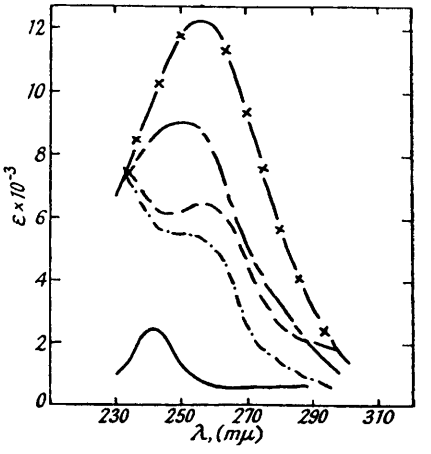
also associated with lack of symmetry, for both 2- and 3-phenylpyridine, (VIII) and (IX), show complex spectra while 4-phenylpyridine (X) shows a single sharp peak.

FIG. 1.



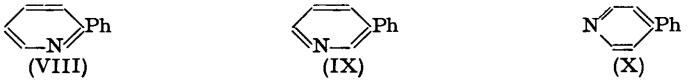
——————— *Pyrimidine.*
—×—×— 4 : 6-*Dimethyl-2-phenylpyrimidine* (I).
— — — — 6-*Methyl-4-phenylpyrimidine* (II).
— · — · — 5-*Phenylpyrimidine* (III).
[*All in ethyl alcohol* (10 *mg./l.*).]

FIG. 2.



——————— *Pyrimidine.*
—×—×— 5-*Phenylpyrimidine* (III).
— — — — 4-*Chloro-5-phenylpyrimidine* (XI).
— — — — 4 : 6-*Dichloro-2-methyl-5-phenylpyrimidine* (XII).
— · — · — 4-*Chloro-5-o-chlorophenylpyrimidine* (XIII).
[*All in ethyl alcohol* (10 *mg./l.*).]

It is to be remarked that the introduction of a phenyl nucleus into the 5-position of the pyrimidine nucleus causes a shift and increase in intensity of the absorption which is smaller than the shift and intensity change caused by the joining of two phenyl nuclei [compare pyrimidine and 5-phenylpyrimidine with benzene (intense band at about 200 mμ) and diphenyl in the



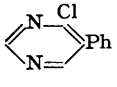
table]. This effect must again be ascribed to the fact that the C–N bond is more polar than the C–C bond, the nitrogen tending to remove some of the negative charge from the neighbouring carbon atom with a consequent reduction of the ionoid form of (V) which carries the negative charge on $C_{(2)}$ of the pyrimidine nucleus.

The hypothesis that the increase in wave-length and intensity of the band in the spectrum

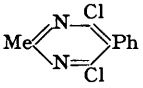
of 5-phenylpyrimidine (III) over the values for pyrimidine itself is due to contributions to the excited state of the molecule of the forms (V) may be tested directly. The concept of a non-planar coaxial structure for diphenyls substituted in the positions *ortho* to the ring junction is generally accepted (Shriner, Adams, and Marvel, in Gilman's " Organic Chemistry," Wiley and Sons, New York, 2nd edn., Vol. I, p. 352; Muller, *Fort. Chem. Forschung*, 1949, **1**, 325). Theoretically, it is to be expected that departure from a coplanar configuration of rings should reduce and ultimately prevent contributions from the ionoid structures (IV) to the excited state of the diphenyl molecule. Corresponding changes would be expected in the absorption spectrum, and these have been observed (Pickett *et al.*, *J. Amer. Chem. Soc.*, 1936, **58**, 2296; 1950, **72**, 44; Rodebush *et al.*, *ibid.*, 1940, **62**, 2906; 1941, **63**, 3018; Sherwood and Calvin, *ibid.*, 1941, **63**, 1350; Jones, *ibid.*, p. 1658).

Although diphenyl itself is planar in the solid state (Dhar, *Indian J. Physics*, 1932, **7**, 43), yet in the gaseous state the rings are inclined to one another (Karle and Brockway, *J. Amer. Chem. Soc.*, 1944, **66**, 1977). This departure from co-planarity is not great enough to inhibit the conjugation between the rings to any considerable extent; however, its effect on the absorption spectrum of diphenyl both as a gas and in solution has been observed (Merkel and Wieband, *Z. Naturforsch.*, 1948, **3** *b*, 93). For the purposes of the present discussion, however, molecules which, like that of diphenyl, have no atoms other than hydrogen in the position *ortho* to the ring junction are referred to as planar.

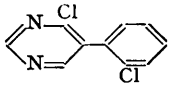
It would appear, therefore, that if the spectroscopic effects of a phenyl group in the 5-position of the pyrimidine ring are, in fact, due to contributions from ionoid forms such as (V), then the 5-phenylpyrimidine molecule must be essentially planar and destruction of this planarity should cause marked changes in the absorption spectrum. A series of 5-phenylpyrimidines in which the positions adjacent to the ring junction carry chlorine atoms was prepared, *viz.*, 4-chloro-5-phenyl- (XI) (Davies and Piggott, *J.*, 1945, 347), 4 : 6-dichloro-2-methyl-5-phenyl- (XII), and 4-chloro-5-*o*-chlorophenyl-pyrimidine (XIII). The absorption maxima of these compounds showed a marked decrease in intensity compared with that of the parent 5-phenylpyrimidine



(XI)



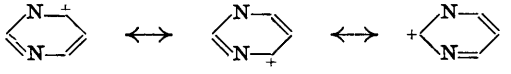
(XII)



(XIII)

(see Fig. 2). The change was least with (XI) and greatest with (XIII), (XII) being intermediate. The spectrum of (XIII) approximates to an addition curve of the two ring systems involved, indicating virtual absence of contribution from ionoid forms such as (V). It should be noticed that the effects observed here are of a higher order than, and in the opposite direction to, those resulting from the introduction of chlorine atoms into pyrimidine itself (Uber and Winters, *loc. cit.*).

The reported observations show a great similarity in behaviour between a benzene and a pyrimidine ring. The most probable explanation is the conclusion that pyrimidine possesses a highly " aromatic " character, resembling benzene in size, shape, and other properties. However, the lower degree of conjugation in a 5-phenylpyrimidine as compared with diphenyl and the large contributions of forms such as (VI) and (VII) to 2- and 4-phenylpyrimidine suggest that the ionoid forms (XIV and three equivalent forms with the negative charge on the other nitrogen atom) are more important in pyrimidine than are the corresponding Dewar forms in benzene. The importance of the Kekulé forms (XV) is correspondingly reduced.



(XIV)

(XV)

These conclusions are at variance with those of other workers (Cavalieri and Bendich, *J. Amer. Chem. Soc.*, 1950, **72**, 2587) who, from a study of the spectra of hydroxy- and amino-pyrimidines, concluded that the pyrimidine ring has a " low degree of aromaticity." However, the views expressed herein are in agreement with those reached from a study of the chemistry of pyrimidines (Lythgoe, *Quart. Review*, 1949, **3**, 194), from the results of *X*-ray studies on pyrimidines (Clews and Cochran, *Acta Cryst.*, 1949, **2**, 46), and from estimates of the resonance energy of pyrimidines which is some 30 kcals./mole (Maccoll, *J.*, 1946, 670; Dewar, " Electronic Theory of Organic Chemistry," Oxford Univ. Press, 1949, p. 36).

The removal of chlorine from 4-chloro-5-phenylpyrimidine by catalytic or chemical reduction

has been reported not to give the required 5-phenylpyrimidine (III) (Davies and Piggott, *loc. cit.*). This finding was confirmed. However, (III) was formed readily when the corresponding 4-mercapto-5-phenylpyrimidine, prepared by alkaline hydrolysis of the corresponding thiuronium salt (Polonovski and Schmitt, *Bull. Soc. chim.*, 1950, 616), was heated with Raney nickel in alcohol. This procedure for removal of sulphur was also found to be useful in the preparation of 4-methyl-6-phenylpyrimidine (II) from the corresponding 2-mercaptopyrimidine. Previously (II) had been prepared by the route 2-mercapto- ⟶ 2-hydroxy- ⟶ 2-chloropyrimidine ⟶ (II) (von Merkatz, *loc. cit.*).

Experimental.

4-Methyl-6-phenylpyrimidine.—2-Mercapto-4-methyl-6-phenylpyrimidine (4 g.) (von Merkatz, *loc. cit.*) was dissolved in ethanol (100 c.c.). Raney nickel (13 g.) was added, and the solution refluxed for 3 hours. The nickel was then filtered off, and the solvent removed under reduced pressure. The oily residue was dissolved in ether from which it crystallized on addition of light petroleum (b. p. 30—60°) and cooling. It formed almost colourless crystals, m. p. 42—43° (von Merkatz, *loc. cit.*, gives 44—45°) (Found : N, 16·3. Calc. for $C_{11}H_{10}N_2$: N, 16·5%).

4 : 6-*Dihydroxy-2-methyl-5-phenylpyrimidine.*—Ethyl phenylmalonate (11·3 g.) (Rising and Stieglitz, *J. Amer. Chem. Soc.*, 1918, **40**, 727) was added to a solution of acetamidine prepared from the hydrochloride (4·2 g.) and a solution of sodium (1·15 g.) in ethanol (50 c.c.). The solution was refluxed on a steam-bath for 20 hours, then poured into water (200 c.c.), and made acid with acetic acid. The *pyrimidine* separated and was filtered off. After recrystallization from boiling water, it formed colourless plates which did not melt below 350° (Found : C, 65·2; H, 5·0; N, 14·2. $C_{11}H_{10}O_2N_2$ requires C, 65·4; H, 5·0; N, 13·9%).

4 : 6-*Dichloro-2-methyl-5-phenylpyrimidine* (XII).—The above dihydroxypyrimidine (3·5 g.) was heated with phosphoryl chloride (20 c.c.) under reflux for 40 minutes. After removal of the excess of phosphoryl chloride, the residual oil was poured on cracked ice (200 g.), and the mixture made alkaline with ammonia. The *dichloropyrimidine* (3·2 g.) was filtered off and recrystallized from benzene. It formed white prisms, m. p. 162—163° (Found : N, 11·9. $C_{11}H_{10}N_2Cl_2$ requires N, 11·7%).

5-Phenylpyrimidine.—4-Chloro-5-phenylpyrimidine (XI) (Davies and Piggott, *loc. cit.*) (10 g.) and thiourea (4·5 g.) were dissolved in alcohol (20 c.c.), and the solution refluxed for 5 hours. After cooling, the crystalline thiuronium compound (cf. Polonovski and Schmitt, *loc. cit.*) (6 g.) was collected and refluxed with 2N-sodium hydroxide solution for 1 hour, the solution was acidified, and the gummy thiol heated with Raney nickel (8 g.) in alcohol (50 c.c.). After 3 hours, the nickel was filtered off, and the alcohol evaporated under reduced pressure. The *5-phenylpyrimidine* formed an oil which solidified and remelted at about 25°. It boiled at 120—140° (bath-temp.)/0·01 mm., to give a clear yellow oil which crystallized at about 23—27° (Found : N, 17·8. $C_{10}H_8N_2$ requires N, 17·9%).

The base (0·5 g.) was converted into the nitrate by dissolving it in 25% aqueous nitric acid (1·0 c.c.) and adding a saturated solution of potassium nitrate (0·5 c.c.). On cooling, the *nitrate hemihydrate* separated as colourless prisms, m. p. 181—183° (Found : C, 52·3; H, 4·4. $C_{10}H_8N_2,HNO_3,\frac{1}{2}H_2O$ requires C, 52·6; H, 4·4%).

4-Amino-5-o-chlorophenylpyrimidine (cf. Davies, Johnson, and Piggott, *J.*, 1945, 352).—Formamide (50 g.) and *o*-chlorophenylacetonitrile (30 g.) were heated at 180° for 14 hours under reflux. The cooled mixture was poured into water (500 c.c.), acidified with 3N-hydrochloric acid (200 c.c.), and the whole was warmed on a steam-bath and stirred for 1 hour; the insoluble oil was separated with ether, and the aqueous solution was basified with 3N-sodium hydroxide and cooled; the resulting *base* (20 g.) was collected and crystallized from benzene, forming colourless crystals, m. p. 180° (Found : C, 58·3; H, 3·7; N, 20·2. $C_{10}H_8N_3Cl$ requires, C, 58·5; H, 3·9; N, 20·4%).

5-o-Chlorophenyl-4-hydroxypyrimidine.—The above aminopyrimidine (8 g.) was heated under reflux with concentrated hydrochloric acid (30 c.c.) for 16 hours. The whole reaction mixture was then brought to pH 11 with 6N-sodium hydroxide, treated with charcoal, and filtered. On acidification with acetic acid the *pyrimidine* separated as colourless crystals (7·5 g.), which recrystallized from benzene–alcohol in needles, m. p. 136—137° (Found : N, 13·4. $C_{10}H_7ON_2Cl$ requires N, 13·5%).

4-Chloro-5-o-chlorophenylpyrimidine (XIII).—The above hydroxy-pyrimidine (7 g.) was heated with phosphoryl chloride (30 c.c.) under reflux for ½ hour. After removal of the excess of phosphoryl chloride, the residue was dissolved in chloroform (50 c.c.) and poured on cracked ice (200 g.) and made alkaline with ammonia. The mixture was stirred violently for 10 minutes and then the organic layer was separated and dried (Na_2SO_4). After removal of the chloroform the residue was distilled. The colourless *chloropyrimidine* boiled at 150—160° (bath-temp.)/0·01 mm. (5·5 g.). It solidified to a colourless crystalline mass, m. p. 20—21° (Found : C, 53·1; H, 2·5; N, 12·1. $C_{10}H_6N_2Cl_2$ requires C, 53·4; H, 2·7; N, 12·4%).

Absorption Spectra.—These were determined by using a Beckman model D.U. quartz spectrophotometer (cell length, 1 cm.). The solutions were made in purified alcohol at a concentration of 10 mg./l.

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