TABLE I

INFRARED ABSORPTION BANDS IN 11–14 μ REGION

2,4′-Biquinolyl (nujol mull)	2,2′-Biquinolyl (nujol mull)	Quinaldine (liquid)	Lepidine (liquid)
11.35 m[a]	—	11.35 w	—
11.50 w	11.50 m	11.52 vw	—
11.59 w	—	—	11.67 s
11.96 s	11.93 s	—	11.93 vs
11.28 w	12.05 s	12.22 vs	12.32 m
12.51 w	—	—	—
12.71 m	12.71 m	12.80 s	12.78 w
13.05 w	13.08 w	13.05 vw	—
13.13 w	—	—	—
13.27 s	13.45 i	13.38 s	13.25 vs
13.53 vs	13.52 s	—	—

[a] Vs = very strong; s = strong; m = medium; w = weak; vw = very weak.

EXPERIMENTAL[6]

Methyl 4-quinolyl ketone. Ethyl cinchoninate was prepared from 14 g. of cinchoninic acid in 75 ml. of absolute ethanol and 5 ml. of concd. sulfuric acid. The ester (12 g.) was distilled at 106–107° (0.2 mm.) [lit.,[1b] b.p. 120–123 (1 mm.)], with the following infrared bands (liquid film) (μ): 5.72, (C=O), 12.50, 13.10. The picrate from the ester melted at 187–188° (lit.,[1c] m.p. 183–188°). The ester was condensed with ethyl acetate in toluene solution with sodium ethoxide and the condensation product was isolated as the sodium salt. To 6 g. of the sodio-derivative of ethyl 3-keto-3-(4-quinolyl)propanoate was added 75 ml. of water and 12 ml. of concd. sulfuric acid, and the solution was heated on the steam bath for 3 hr. The cooled solution was made weakly alkaline with sodium carbonate solution and extracted five times with ether. Evaporation of the dried ether extracts left only a small amount of a dark viscous oil that was distilled to give 0.9 g. of methyl 4-quinolyl ketone, b.p. 108–110° (0.2 mm.) (lit.,[7] b.p. 138°/2 mm.). Significant infrared bands follow (liquid film) (μ): 5.86 (ketone C=O), 6.31, 11.75, 13.05. The ketone formed a picrate, m.p. 165–167° (lit.,[7] m.p. 165–167°).

2,4′-Biquinolyl. A solution of 0.72 g. of methyl 4-quinolyl ketone in 50 ml. of ethanol was treated with 0.70 g. of freshly prepared 2-aminobenzaldehyde[8] and 0.20 g. of potassium hydroxide. On warming a solid began to form, but this redissolved in hot ethanol. The solution, which turned red, was heated on a steam bath for 1 hr., filtered from a small amount of insoluble residue, and allowed to cool. From the solution 0.8 g. of a pink voluminous solid separated. Passage of the ethanolic solution of the biquinoline through a short column of alumina gave a colorless product, m.p. 153–154°; $\lambda_{max}^{C_2H_5OH}$ (log ϵ) 3.17 (4.04), 230 mμ(4.56).

Anal. Calcd. for $C_{18}H_{12}N_2$: C, 84.35; H, 4.72; N, 10.93. Found: C, 84.40; H, 4.93; N, 10.69.

2,4′-Biquinolyl monopicrate was prepared in ethanol solution and recrystallized from acetonitrile as yellow plates, m.p. 261–262°.

Anal. Calcd. for $C_{24}H_{15}N_5O_7$: C, 59.35; H, 3.12. Found: C, 60.10; H, 3.35.

2,4′-Biquinolyl perchlorate was prepared in methanol solution and recrystallized from a mixture of methanol and water as pale yellow needles, m.p. 239–240°.

Anal. Calcd. for $C_{18}H_{13}N_2O_4Cl$: C, 60.60; H, 3.67; N, 7.85. Found: C, 60.77; H, 3.08; N, 7.99.

When 2,4′-biquinolyl or the monoperchlorate was treated with concd. perchloric acid, a salt melting at 274–276° was obtained, but recrystallization of this salt from acidic methanol gave only the salt melting at 239–240°.

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(6) Melting points were taken in a Drechsel melting point apparatus and are otherwise uncorrected. Analyses are by Schwarzkopf Microanalytical Laboratory. The infrared spectra were recorded on a Beckman IR-4 spectrophotometer with sodium chloride optics, and the ultraviolet spectrum was taken on a Beckman DK-1 instrument.

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2,4-Diamino-5-formylpyrimidine and 2,4-Diamino-5-hydroxymethylpyrimidine[1]

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In a study of the catalytic hydrogenation of heterocyclic nitriles,[3a,b] Huber has prepared a compound described as 2,4-diamino-5-hydroxymethylpyrimidine (I), which was formed from the hydrochloride of an amine characterized as di-(2,4-diamino-5-pyrimidylmethyl)amine (II) on treatment with aqueous sodium hydroxide. This latter amine was formed along with 2,4-diamino-5-aminomethylpyrimidine (III) on hydrogenation of 2,4-diamino-5-cyanopyrimidine.[3a]

We have hydrogenated 2,4-diamino-5-cyanopyrimidine using a W-4[4] Raney nickel catalyst. Substances were formed which gave the approximate properties of the compounds previously described as the hydrochlorides of II and III. Treatment of the compound, presumed to be II, with aqueous sodium hydroxide gave a compound with properties different from those shown by a sample of I which had been prepared by Nairn and Tieckel-

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mann.[5] The latter report a melting point of 231–234° compared with a melting point of 265° dec., previously reported.[3a] The most striking difference between the two materials was in their inhibitory effects on *Bacillus subtilis* ATCC-6051. It has been observed[6] that many 2-substituted 4-amino-5-hydroxymethylpyrimidines inhibit the growth of this organism and that this inhibition is reversed by the thiamin pyrimidine 2-methyl-4-amino-5-hydroxymethylpyrimidine. The compound prepared by the method of Huber had little effect on this organism, whereas I, prepared by Nairn and Tieckelmann, produced a strong inhibition that was specifically prevented by the thiamin pyrimidine, thiamin, or cocarboxylase.

In the present work elementary analyses indicated that the compound previously described as I was 2,4-diamino-5-formylpyrimidine (IV). The structure was confirmed by the formation of the oxime and by reduction to I with sodium borohydride. Prepared by this method, I was identical with the substance prepared by Nairn and Tieckelmann in melting points, infrared and ultraviolet absorption spectra, and specific inhibition of *Bacillus subtilis*.

Although the 5-aldimine also can be predicted to give the aldehyde IV by hydrolysis, evidence indicates that the substance formed along with III in our hydrogenation was the Schiff's base V of III and IV. We did not characterize this material. It was isolated as a hydrochloride but it was not possible to obtain consistent chlorine analyses after crystallization from aqueous alcohol. The values ranged from 25–33%, depending on conditions, and most probably were due to hydrolysis during recrystallization. A small amount of this material was hydrolyzed in 10% sodium hydroxide. Paper chromatography of the hydrolysate with water-saturated *n*-butyl alcohol containing ammonia revealed two spots, when observed under ultraviolet light, corresponding in Rf and inhibition of *B. subtilis* to III and IV (Table I). When the spots were excised and extracted with water, ultraviolet absorption spectra indicated approximately equal amounts of III and IV. In subsequent experiments, III and IV were formed in reasonable yield by hydrolysis of the crude Schiff's base.

TABLE I

PAPER CHROMATOGRAPHY OF PYRIMIDINES

	Rf[a]	λ Max. (mμ)	Inhibition by *B. subtilis*
III	0.05	284	+[b]
I	0.17	275	+
IV	0.29	299 265	−
Hydrolysate of V	0.04	284	+
	0.29	299 265	−

[a] One ml. of concd. ammonium hydroxide was added to a solution of 1 l. of *n*-butyl alcohol saturated with water. After shaking and standing overnight the butyl alcohol layer was used as the solvent. [b] The ultraviolet light absorbing spots on the paper were marked. A strip was cut and placed on solid agar medium seeded with *B. subtilis*. Following a suitable growth period, the marked spot was observed at the center of a symmetrically shaped inhibitory area.

EXPERIMENTAL[7,8]

2,4-Diamino-5-formylpyrimidine (IV). Seven grams of 2,4-diamino-5-cyanopyrimidine was hydrogenated according to the method previously described[3a] employing a W-4[4] Raney nickel catalyst. The resulting mixture gave 2.3 g. of the dihydrochloride of III and 5.6 g. of the hydrochloride of V. Crude V was dissolved in 100 ml. water and the solution made basic to litmus with 10% sodium hydroxide. The precipitate was collected and washed with water to give 1.6 g. (85%) of IV. The analytical sample was recrystallized from water; m.p. 263–264° dec. Ultraviolet absorption was as follows: *p*H 1.0 λ_{max} 279 mμ ($\epsilon = 7.5 \times 10^3$). *p*H 6.2, 300 ($1.6 \times 10^4$), 264 ($1.2 \times 10^4$).

Anal. Calcd. for $C_5H_6N_4O$: C, 43.37; H, 4.38; N, 40.56. Found: C, 43.70; H, 4.51; N, 40.40.

2,4-Diamino-5-aminomethylpyrimidine (III) *from V*. The filtrate from the previous experiment was treated with 6 ml. of concd. hydrochloric acid and evaporated to dryness at reduced pressure. The residue, consisting of the dihydrochloride of III and sodium chloride, was treated with 30 ml. of absolute alcohol and filtered. The 5.5 g. of solid collected was recrystallized from water-alcohol to give 2.24 g. of the dihydrochloride of III, dec., 278–281°, (lit.,[3a] dec. 278–280°). The ultraviolet spectra showed the following bands: *p*H 1.0 λ_{max} 269 mμ ($\epsilon = 4.7 \times 10^3$), *p*H 6.1 273 ($4.3 \times 10^3$), *p*H 11.4 285 ($6.8 \times 10^3$).

2,4-Diamino-5-hydroxymethylpyrimidine (I). A solution of 0.1 g. of sodium borohydride in 10 ml. of water was added to a suspension of 0.5 g. of 2,4-diamino-5-formylpyrimidine in 20 ml. of water. After standing for 15 min. with occasional shaking, the mixture was heated to 50–55° until the solid dissolved. After cooling and standing overnight 0.35 g. (69%) of 2,4-diamino-5-hydroxymethylpyrimidine had precipitated; m.p. 231–233° dec. The analytical sample, m.p. 234–236° dec., was recrystallized from water. Ultraviolet absorption was as follows: *p*H 0.9, λ_{max} 269 mμ ($\epsilon = 5.1 \times 10^3$), *p*H 7.7 283 ($6.7 \times 10^3$), *p*H 11.2 233 ($1.1 \times 10^4$), 284 ($7.0 \times 10^3$).

Anal. Calcd. for $C_5H_8N_4O$: C, 42.85; H, 5.75; N, 39.98. Found: C, 43.02; H, 5.79; N, 40.11.

2,4-Diamino-5-pyrimidylaldoxime. A solution of 0.3 g. of 2,4-diamino-5-formylpyrimidine in 10 ml. of hot ethyl alcohol was added to a solution of 5 g. of hydroxylamine hydrochloride in 10 ml. of water made basic with 20 ml. of 10% sodium hydroxide. The solution was heated on a steam bath for 30 min., concentrated to one half the original volume, and allowed to cool. The precipitate was crystallized four times from water. The oxime melted at 290–291° dec. and was soluble in dilute sodium hydroxide.

Anal. Calcd. for $C_5H_7N_5O$: C, 39.21; H, 4.61; N, 45.73. Found: C, 39.36; H, 4.99; N, 45.92.

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(7) Melting points were taken on a Fisher-Johns melting point apparatus and are uncorrected.

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3-Amino-4-phenylpyrazole as an Intermediate

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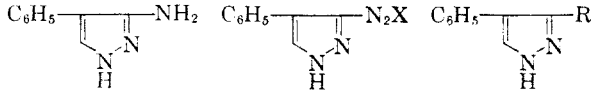
The displacement of the amine group in 3-amino-4-phenylpyrazole (I) by other groups,



I

II a. R = H
b. R = Br
c. R = NO_2
d. R = N=N—S—C_2H_5
e. R = S—C_2H_5

through the intermediate diazonium salt, has been found to be a useful preparative scheme for 3-substituted pyrazoles. The amine was diazotized in aqueous mineral acid by reaction with sodium nitrite, and the intermediate diazonium salt was converted into 4-phenylpyrazole (IIa, 93% yield) by reaction with hypophosphorous acid, and into 3-bromo-4-phenylpyrazole (IIb, 85.6% yield) by reaction with cuprous bromide: Pyrolysis of the corresponding diazofluoroborate in the presence of sodium nitrite and copper bronze afforded 3-nitro-4-phenylpyrazole in 22.4% yield.

Reaction of diazotized 3-amino-4-phenylpyrazole with ethyl mercaptan proceeded abnormally,[3] giving the diazonium sulfide (IId, 72.5% yield) instead of the expected 3-ethylmercapto-4-phenylpyrazole (IIe). The diazonium sulfide (IId) was relatively stable and was recrystallized from hot ethanol; however, prolonged boiling in methanol resulted in its reduction to 4-phenylpyrazole (52% yield). The diazonium sulfide gave colored products by reaction with phenol, β-naphthol, and dimethylaniline.

It is of interest to note that 3-amino-4-phenylpyrazole (I) can be diazotized in aqueous solution. This behavior is in contrast to the special conditions[4] required for the diazotization of 2-aminopyridine, which also contains the amidine function (—N=C—NH_2).

It has been known for some time that 3- and 5-aminopyrazoles form diazonium salts; however, most of the cases studied have involved derivatives bearing a substituent on the pyrazole nitrogen atom, and relatively little attention has been directed to replacement reactions.[5a] 4-Aminopyrazoles from typical diazonium salts which undergo the usual coupling[5a,6] and replacement[3] reactions.

Electrophilic substitution of the pyrazole ring in other than the 4-position is rare.[5b] If a phenyl group is at C_4, nitration will occur in the benzene ring.[7] The availability of certain 3-aminopyrazoles[8] and their subsequent conversion to 3-substituted pyrazole by the procedure described appears to be an attractive synthetic procedure in this series.

EXPERIMENTAL

4-Phenylpyrazole from I. 3-Amino-4-phenylpyrazole[8] (2.3 g., 0.0414 ml.) was added to boiling concd. hydrochloric acid (4.5 ml.) and, when solution was complete, an additional portion of concd. hydrochloric acid (5 ml.) was added. The mixture was cooled (0–5°) and sodium nitrite (1.5 g.) in water (3.5 ml.) was added dropwise over a 5-min. period. The resulting solution was stirred and hypophosphorous acid (15 ml., 50% aqueous) was added dropwise (5 min.) while the temperature was maintained at 0°. The resulting solution was stirred for an additional 10 min. at 0°, and then placed in a refrigerator (24 hr.). Crude IIa (1.78 g., 93% yield, m.p. 225–227°) was collected and recrystallized from methanol-water. Pure IIa melted at 227–228° and did not depress the melting point of an authentic sample (m.p. 228°).[9]

3-Bromo-4-phenylpyrazole from I. 3-Amino-4-phenylpyrazole 1.5 g., 0.0095 ml.) was dissolved in hot hydrobromic acid (10%, 5 ml.) and an excess of sodium nitrite (2.5 g.) in water (5 ml.) was added. Excess urea (~2 g.) was added to destroy excess sodium nitrite; the solution was filtered, and concd. hydrobromic acid (48%, 5 ml.) and cuprous bromide (~0.5 g.) were added. The solution was boiled to complete the reaction and then allowed to stand in an ice bath. The product weighed 2.0 g. (94.8% yield, m.p. 142–144°) and melted at 146–146.5 (1.8 g., 85.6% yield) after recrystallization from methanol. This product caused no depression in melting point when mixed with authentic IIb.[8]

3-Nitro-4-phenylpyrazole from I. 3-Amino-4-phenylpyrazole (1.8 g., 0.0113 ml.) was dissolved in fluoboric acid solution (10 ml.) in a 250-ml. beaker. The mixture was kept

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