Absorption spectra of the compounds in ethanol all had maxima between 246 and 249 mμ except for X. The spectrum of X was expected to be somewhat different since this compound was derived from an aliphatic rather than aromatic aldehyde. Compounds containing a nitro group were yellow, as indicated by the spectra as well as observation; all others were colorless.

Experimental

Preparation of Compounds.—To 50 ml. of ethanol were added 0.02 mole of the aldehyde and 0.02 mole of amine. 8-Quinolinol (2.9 g., 0.02 mole) was then added and the mixture stoppered and left to stand at room temperature for 45 days. The compound was removed by filtration and recrystallized twice from ethanol or ethanol–acetone mixtures.

Further standing of the filtrate sometimes deposited additional product; this was not considered in calculating the yields.

Spot Tests.—The ferric chloride test was performed by adding a drop of an ethanol solution of the compound to 1% ferric chloride. Tests with concentrated sulfuric and nitric acids were performed by adding 1–5 mg. of compound to 2 ml. of concentrated acid. The colors recorded with nitric acid are the initial ones, since fading occurred after a time.

Absorption Spectra.—All measurements were made with a Beckman DU spectrophotometer with 1.00-cm. silica cells. The solvent was 95% ethanol.

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LOUISVILLE, KY.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF DARTMOUTH COLLEGE]

The Synthesis and Nitration of 2,6- and 2,7-Dimethylquinoline and of 2,5,8-Trimethylquinoline

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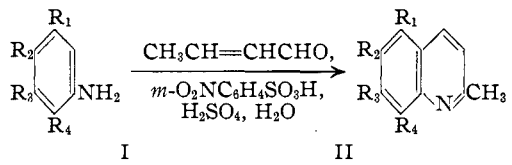
Several derivatives of quinaldine have been synthesized from aromatic amines and crotonaldehyde by Utermohlen's modification of the Skraup and Doebner–v. Miller syntheses[2]; the yield of the substituted quinoline is considerably improved by the use of a large excess of crotonaldehyde. The identity of 2,7-dimethylquinoline has been firmly established. The structures of the mononitro derivatives formed from 2,6- and 2,7-dimethylquinoline and from 2,5,8-trimethylquinoline have been determined.

Utermohlen has described a valuable modification of the Skraup and Doebner-v. Miller syntheses; an aromatic amine is treated with a suitable aldehyde or aldehyde diacetate in the presence of *m*-nitrobenzenesulfonic acid.[2] Although the reaction, as described, is quite general, the reported percentage yields, which vary in several reactions with crotonaldehyde or the corresponding diacetate from 43 to 63, are not so high as might be desired. One of the purposes of this investigation was the search, in the case of crotonaldehyde only, for reaction conditions that would lead to higher yields. A study of the course of the mononitration of 2,6- and 2,7-dimethylquinoline and of 2,5,8-trimethylquinoline was also made.



I II

All R groups = H except as otherwise specified

a, $R_2 = CH_3$
b, $R_2 = CH_3$, $R_3 = Cl$
c, $R_2 = CH_3$, $R_1 = R_4 = Cl$
d, $R_3 = CH_3$
d′, $R_1 = CH_3$
e, $R_3 = CH_3$, $R_4 = Cl$
f, $R_3 = CH_3$, $R_1 = R_4 = Cl$
g, $R_1 = R_4 = CH_3$
h, $R_1 = R_4 = CH_3$, $R_3 = Cl$
i, $R_1 = R_4 = CH_3$, $R_2 = Cl$

In the original procedure of Utermohlen equimolar amounts of amine and aldehyde were employed. At the start of the present research, *p*-toluidine (Ia) and crotonaldehyde were condensed in equimolar proportions according to the directions given previously.[2] 2,6-Dimethylquinoline (IIa) was easily isolated, but in only 48% yield, while a considerable amount of *p*-toluidine was recovered. Since a good deal of tarry matter was formed during the cyclization reaction, it appeared that much of the crotonaldehyde was destroyed before it could condense with the amine. Accordingly, the ratio of aldehyde to amine was increased to 1.67:1; no unchanged *p*-toluidine was then obtained and the yield of nearly pure 2,6-dimethylquinoline rose to 80% (based on the amine). Since further increase in the amount of aldehyde made isolation of the product more difficult without perceptibly augmenting the yield, this ratio of 1.67:1 was retained in all later applications of the synthesis. In reactions conducted with large quantities (one mole of amine) of starting materials the yields varied from 80 to 86%, while in cyclizations on a greatly reduced scale the quinoline derivative was isolated in yields of from 54 to 74%.

The behavior on nitration of derivatives of quinoline has been discussed in detail by Elderfield.[3] Since quinaldine is attacked approximately equally at the 5- and 8-positions, it is to be expected that 2,6-dimethylquinoline (IIa) will undergo substitution at the 5-position, while the 2,7 isomer (IId) will react preferably at the 8-position. After the initiation, but before the completion of this investigation, Price and co-workers reported the nitration of 2,6-dimethylquinoline.[4] A nitro compound, differing from the known 8-nitro derivative

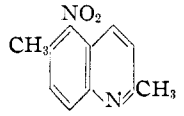
(1) Abstracted in part from the theses presented by Robert W. Belfit, Jr. (1951) and Rodney A. Walser (1948) in partial fulfillment of the requirements for the degree of Master of Arts.

(2) W. P. Utermohlen, *J. Org. Chem.*, **8**, 544 (1943).

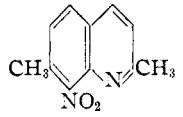
(3) R. C. Elderfield in "Heterocyclic Compounds," edited by R. C. Elderfield, Vol. 4, John Wiley and Sons, Inc., New York, N. Y., 1952, pp. 264–271.

(4) C. C. Price, B. H. Velzen and D. B. Guthrie, *J. Org. Chem.*, **12**, 203 (1947).

was obtained and was regarded as the 5-nitro isomer (III), although the structure of a 7-nitrodimethylquinoline could not be excluded. We have now established that this compound is indeed the 5-nitro derivative (III) and that *ortho* substitution also occurs in the case of 2,7-dimethylquinoline with the formation of 8-nitro-2,7-dimethylquinoline (IV).



III



IV

Attempts at oxidation and other forms of degradation were not promising, but success in establishing structures was obtained by conversion of the nitro compounds *via* amines to chlorides, followed by independent synthesis of the latter substances. Such a procedure was used by Roberts and Turner in their work on derivatives of 2,4-dimethylquinoline.[5] 2,6-Dimethylquinoline was nitrated in sulfuric acid solution with a solution of potassium nitrate in sulfuric acid. The resulting nitro compound was reduced with stannous chloride to the corresponding amine. The melting points of both compounds checked with the values reported by Price.[4] The amine was converted through the Sandmeyer reaction into a chloro-2,6-dimethylquinoline. 4-Amino-2-chlorotoluene was subjected to the cyclization process, but the product was not identical with the compound obtained from the Sandmeyer reaction; the cyclization product could, according to the then existing evidence, be either the 5- or the 7-chloro derivative.

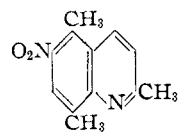
In order to elucidate these structures, the chlorodimethylquinoline obtained from the Sandmeyer reaction was nitrated and the product was converted *via* reduction and a Sandmeyer reaction into a dichlorodimethylquinoline. 4-Amino-2,5-dichlorotoluene (Ic) was cyclized with crotonaldehyde, yielding 5,8-dichloro-2,6-dimethylquinoline (IIc). The two dichlorides were identical. Since the nitrodimethylquinoline is not the 8-nitro isomer, it follows that it must be the 5-nitro derivative (III), that 5-chloro-2,6-dimethylquinoline undergoes nitration in the 8-position, and that the cyclization of 4-amino-2-chlorotoluene (Ib) yields a 7-chlorodimethylquinoline (IIb).

Some uncertainty has existed concerning the identity of 2,7-dimethylquinoline (IId) and the 2,5-dimethyl isomer (IId'), both of which are formed in cyclization processes from *m*-toluidine.[6-8] A solid dimethylquinoline (m.p. 61°) is readily isolated as the major constituent of the crude distillate, leaving an oily residue from which the isomer can be obtained as a picrate. Doebner and v. Miller assigned to the solid compound the 2,7-structure, but this choice was later reversed, largely because of the work of Decker and Remfrey on the orientation of ring closures.[9,10] Manske, after seemingly unambiguous synthetic work, maintained that 2,5-dimethylquinoline is an oil and that the original conclusions of Doebner and v. Miller are therefore correct. Spivey and Curd[8] agreed with Manske without, however, adding further proof. Since there remained some doubt[10] concerning these isomeric compounds, it was desirable to add further evidence; the results of the present investigation clearly indicate that the solid compound is 2,7-dimethylquinoline.

2,7-Dimethylquinoline (the solid isomer) was nitrated and the nitro derivative was converted in two steps into the corresponding chloride. 8-Chloro-2,7-dimethyl-quinoline (IIe) was prepared from 3-amino-2-chlorotoluene (Ie); the product was found to be identical with the substance obtained from the nitro compound.

The reduction of the nitrodimethylquinoline afforded pure amine when iron was used as the reducing agent, but reduction with stannous chloride yielded a mixture of amine and chloroamine containing about equal amounts of the two substances.[11] The crude product of the latter reduction was submitted to the Sandmeyer reaction; there was obtained after fractional crystallization a dichlorodimethylquinoline. This dichloride proved to be identical with the product (IIf) of the cyclization reaction applied to 3-amino-2,5-dichlorotoluene (If). From these results it can be concluded that 2,7-dimethylquinoline is the solid isomer, that it yields on nitration the 8-substituted compound (IV), and that reduction of the nitro derivative with stannous chloride causes considerable simultaneous chlorination at the 5-position.

2,5,8-Trimethylquinoline (IIg), previously unreported, was prepared from amino-*p*-xylene (Ig) in 79% yield. Nitration proceeded less smoothly than in the previous cases where the 5- and 8-positions are available. A solid nitro derivative, m.p. 123–124°, was isolated in 40–60% yield. In one reaction a small amount of a second substance, m.p. 91–93°, was isolated; this latter material was not further investigated. The nitro compound was reduced satisfactorily to the corresponding amine by either tin or stannous chloride. The chloride, obtained by the usual Sandmeyer reaction, differed from 7-chloro-2,5,8-trimethylquinoline (IIh), produced from 2-amino-6-chloro-1,4-dimethylbenzene (Ih), but was identical with the 6-chloro isomer (IIi), afforded by 2-amino-5-chloro-1,4-dimethylbenzene (Ii). The nitro compound is therefore a 6-nitro derivative (V), a fact in accord with the results obtained by Roberts and Turner in the nitration of 5,8-dichloro-2,4-dimethylquinoline.[5]



V

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(9) H. Decker and P. Remfrey, *Ber.*, **38**, 2773 (1905).

(10) Reference (5), pp. 11–13.

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TABLE I

PRODUCTS OF CYCLIZATION

Substituted quinoline	M.p., °C.	Yield, %	Formula	Chlorine, % Calcd.	Chlorine, % Found
2,6-Dimethyl (IIa)	57–58[a,b]	80[c]			
7-Chloro-2,6-dimethyl (IIb)	91.2–92.0[a]	[d]	$C_{11}H_{10}NCl$	18.50	18.18
5,8-Dichloro-2,6-dimethyl (IIc)	83.9–84.2[e]	74[f]	$C_{11}H_9NCl_2$	31.36	31.23
2,7-Dimethyl (IId)	60–61[a,g]	81–86[h]			
8-Chloro-2,7-dimethyl (IIe)	64.5–65.0[a]	54[f]	$C_{11}H_{10}NCl$	18.50	18.51
5,8-Dichloro-2,7-dimethyl (IIf)	96–97[a]	60[f]	$C_{11}H_9NCl_2$	31.36	31.02
2,5,8-Trimethyl (IIg)[i,j]	Oil[k]	78–80[k]	$C_{12}H_{13}N$[i]		
7-Chloro-2,5,8-trimethyl (IIh)[l]	108–109[a]	73[m]	$C_{12}H_{12}NCl$[l]		
6-Chloro-2,5,8-trimethyl (IIi)	93–95[n]	32–57[f]	$C_{12}H_{12}NCl$	17.24	17.27

[a] Crystallized from petroleum ether. [b] Reported, 60°.[7] [c] Yield of distillate, b.p. 125–127° (10 mm.). [d] Most of the material was lost by accident. [e] Crystallized from ether–petroleum ether. [f] Yield of steam distilled material. [g] Reported, 61°.[7] [h] Yield of distillate of mixed 2,5- and 2,7-dimethylquinoline, b.p. 119–121° (7 mm.); from this mixture 2,7-dimethylquinoline was obtained in 43–44% over-all yield. [i] Calcd.: C, 84.17; H, 7.67; mol. wt., 171. Found: C, 84.04, 84.14; H, 7.84, 7.88; mol. wt. (freezing point lowering in benzene), 172. [j] Picrate, m.p. 181–182°. *Anal.* Calcd. for $C_{18}H_{16}N_4O_7$: C, 54.02; H, 4.03. Found: C, 54.27; H, 4.33. Trinitro-*m*-cresolate, m.p. 196–197°. *Anal.* Calcd. for $C_{19}H_{18}N_4O_7$: C, 55.07; H, 4.38. Found: C, 55.21; H, 4.60. Styphnate, m.p. 180° (considerable prior softening). *Anal.* Calcd. for $C_{18}H_{16}N_4O_8$: C, 51.93; H, 3.96. Found: C, 51.86; H, 4.04. [k] B.p. 144–146° (15 mm.), $n^{21}D$ 1.5958. [l] Calcd.: C, 70.07; H, 5.89. Found: C, 69.76, 70.22; H, 6.14, 6.04. [m] Yield of once-crystallized material. [n] Crystallized from 95% ethanol.

TABLE II

PRODUCTS OF NITRATION

Substituted quinoline	M.p., °C.	Yield, %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
5-Nitro-2,6-dimethyl (III)	105–106[a,b]	84, 86	$C_{11}H_{10}O_2N_2$	65.33	65.23	4.99	5.17
5-Chloro-8-nitro-2,6-dimethyl[c]	140.6–141.4[a]	94	$C_{11}H_9O_2N_2Cl$[c]				
8-Nitro-2,7-dimethyl (IV)	117.0–117.5[a,d]	88, 92	$C_{11}H_{10}O_2N_2$	65.33	65.36	4.99	5.32
6-Nitro-2,5,8-trimethyl (V)	123–124[a]	40–59	$C_{12}H_{12}O_2N_2$	66.68	66.47	5.56	5.75

[a] Crystallized from ethanol–water. All the samples were pale yellow except V, which was light tan. [b] Reported, 106–107°.[4] 8-Nitro-2,6-dimethylquinoline is reported to melt at 116–117°.[4] [c] Calcd.: Cl, 14.98. Found: Cl, 14.84. [d] For polymorphic forms and behavior on fusion, refer to section on nitration.

TABLE III

PRODUCTS OF REDUCTION

Substituted quinoline	M.p. °C.	Yield, %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
5-Amino-2,6-dimethyl	190–191[a,b]	84[c]	$C_{11}H_{12}N_2$	76.70	76.40	7.03	7.21
8-Amino-5-chloro-2,6-dimethyl[d]	102.4–102.8[e]	93[c]	$C_{11}H_{11}N_2Cl$[d]				
8-Amino-2,7-dimethyl	33–34[e]	69[f,g]	$C_{11}H_{12}N_2$	76.70	76.87	7.03	7.36
6-Amino-2,5,8-trimethyl	122–123[a]	91[c,h]	$C_{12}H_{14}N_2$	77.38	77.55	7.58	7.56

[a] Crystallized from ethanol. [b] Reported, 189–189.5°.[4] [c] Reduction using stannous chloride and hydrochloric acid. [d] Calcd.: Cl, 17.16. Found: Cl, 17.17. [e] Crystallized from petroleum ether. [f] Reduction using iron and acetic acid; yield of steam distilled material. [g] For results on reduction with stannous chloride, refer to section on reduction of nitro compounds. [h] Reduction using tin and hydrochloric acid gave a yield of 73%.

TABLE IV

PRODUCTS OF THE SANDMEYER REACTION

Substituted quinoline	M.p., °C.	Yield, %	Formula	Chlorine, % Calcd.	Chlorine, % Found
5-Chloro-2,6-dimethyl	44.8–45.7[a]	75–89[b]	$C_{11}H_{10}NCl$	18.50	18.26
5,8-Dichloro-2,6-dimethyl	83.7–84.1[a,c]	64, 76[b]	$C_{11}H_9NCl_2$	31.36	31.18
8-Chloro-2,7-dimethyl	65.0–65.5[a,d]	88[b]	$C_{11}H_{10}NCl$	18.50	18.67
5,8-Dichloro-2,7-dimethyl	96–97[a,e]	[f]	$C_{11}H_9NCl_2$	31.36	31.20
6-Chloro-2,5,8-trimethyl[g]	93–94[h,i]	72, 88[b]	$C_{12}H_{12}NCl$[g]		

[a] Crystallized from petroleum ether. [b] Yield of steam-distilled product. [c] Mixed melting point with cyclization product IIc, 83.8–84.2°. [d] Mixed melting point with cyclization product IIe, 64.5–65.0°. [e] Mixed melting point with cyclization product IIf, 96–97°. [f] Since this substance was obtained from a mixture of amino- and aminochlorodimethylquinoline, no percentage yield can be calculated. [g] Calcd.: C, 70.07; H, 5.89. Found: C, 70.36; H, 6.05. [h] Crystallized from ethanol–water. [i] Mixed melting point with cyclization product IIh, 71–75° (with some prior softening); with IIi, 93–94°.

The compounds prepared by cyclization are listed in Table I, those by subsequent reactions in Tables II–IV. In all of the tables the substances are entered in accordance with the structures required by the cyclization processes or established by later experimentation.

Acknowledgment.—We should like to thank Mr. Charles J. Eby for his aid in the preparation by cyclization of 6-chloro-2,5,8-trimethylquinoline.

Experimental[12]

Preparation of Starting Materials.—"Sulfo mix" (a solution of *m*-nitrobenzenesulfonic acid in sulfuric acid) was prepared as described by Utermohlen.[2] Crotonaldehyde was distilled before use. The substituted toluidines and the xylidines were prepared almost entirely by known methods. Since in much of the previous work percentage yields were not reported, the values obtained in the present investigation are indicated: unless specified, the physical constants

(12) All melting points are corrected.

of the substances agreed with those previously reported.

4-Amino-2-chlorotoluene (Ib) was prepared from *o*-toluidine[13] [nitration (62%), Sandmeyer reaction (94%), reduction (60%)]. *o*-Toluidine was also converted into 4-amino-2,5-dichlorotoluene (Ic) [acetylation[14] (95%), N-chlorination and rearrangement[15] (50–70%), hydrolysis, followed directly by the Sandmeyer reaction[15] (66%), nitration[15,16] (56%), reduction[13] (65%)]. 3-Amino-2-chlorotoluene (Ie), b.p. 114–116° (16 mm.), was obtained from 2-acetylaminotoluene[15] [nitration and hydrolysis (50%), Sandmeyer reaction (60–73%), reduction (83%)]. 2-Acetylamino-5-chlorotoluene was converted into 3-amino-2,5-dichlorotoluene (If)[13] [nitration (62%), hydrolysis, followed directly by the Sandmeyer reaction (84%), reduction (71%)].

Satisfactory directions could not be found for the preparation of amino-*p*-xylene. Accordingly, the following procedure was developed. *p*-Xylene (106 g., 1.00 mole) was stirred mechanically at 25–30° while a mixture of 133 g. of concentrated nitric acid and 212 g. of concentrated sulfuric acid was added dropwise. The organic layer was separated and steam distilled, after neutralization with sodium hydroxide solution, until solid material appeared in the condenser. The distillate was shaken with benzene, and the organic layer was separated. After removal of the benzene and traces of water by distillation at atmospheric pressure, nitro-*p*-xylene (78–87%) was collected between 107 and 109° at 10 mm.

Amino-*p*-xylene (Ig) was first prepared from the nitro compound by reduction with tin and hydrochloric acid, but the product was contaminated with chlorine-containing material. As a consequence, all of the material used in the work reported was obtained by reduction with iron and acetic acid,[4] the yield of amine, b.p. 97–101° (10 mm.), in one-mole or larger runs varying from 81 to 83%. Because of the vigor of the reduction, it was essential to add the powdered iron in very small portions.

2-Amino-6-chloro-1,4-dimethylbenzene (Ih)[17] was prepared from amino-*p*-xylene [acetylation[14] (82–90%), chlorination,[18] using exactly one equivalent of chlorine (82%), nitration[17] (78–82%), hydrolysis, followed directly by deamination[17] (57%), reduction[4] (73%)]. 2-Amino-5-chloro-1,4-dimethylbenzene (Ii) was obtained by hydrolysis of the corresponding acetyl derivative,[18] but without isolation of the intermediate salt, in 70% yield.

Cyclization Reactions.—Since preliminary attempts showed that the equimolar proportions of aldehyde and amine used by Utermohlen[2] led to the recovery of about one third of the aromatic amine employed in the reaction, the ratio of aldehyde to amine was increased to 1.67:1. Compounds Ia, Id and Ig were employed in one-mole or larger amounts. The other amines were used on a much reduced scale (0.02–0.10 mole); the lower yields obtained with these substances are attributed primarily to the difficulty of adequately stirring the mixtures, which were contained in large test-tubes. The results of the cyclization reactions are listed in Table I. The procedure for the preparation of 2,7-dimethylquinoline (IId) is given in detail; the relative proportions of the reagents in the other cyclization reactions were not varied except in those on a very small scale, where somewhat more "sulfo-mix" and water were used (in order to facilitate stirring).

To a 1-l. three-necked flask equipped with a mercury-sealed stirrer, dropping funnel, thermometer and outlet tube were added in order 100 ml. of water, 404 g. of "sulfo mix" and 107 g. (1.00 mole) of *m*-toluidine. The mixture was heated in an oil-bath to 105°, and crotonaldehyde (117 g., 1.67 moles) was added dropwise with vigorous stirring over a period of 35 minutes while the mixture was held by intermittent cooling in the range 105–110°. The temperature was then raised over the course of 20 minutes to 125°; very vigorous stirring was required to prevent loss of material through foaming. (In most of the other cyclization reactions the temperature was gradually increased to the point, between 120 and 130°, at which foaming approached becoming uncontrollable.) Under these conditions, unlike those previously described,[2] no water was distilled. The reaction mixture was poured, before it could stiffen, onto 1.5 kg. of ice in a 5-l. flask and was then basified with sodium hydroxide. The flask was arranged for steam distillation; a total of 10 l. of distillate was collected. The oily organic material was taken up in carbon tetrachloride; after separation, the aqueous layer was extracted once with the same solvent. The solvent was removed from the combined organic material, and the residue was distilled at a pressure of 7 mm. Not more than 0.5 ml. distilled below 119°; the main fraction was collected between 119 and 121°, leaving almost no residue. The mixture of 2,5-dimethylquinoline (IId′) and 2,7-dimethylquinoline (IId) (135.5 g., 86% yield) largely solidified on cooling. Crystallization from 400 ml. of petroleum ether (b.p. 35–60°) gave 68 g. (43% over-all yield) of 2,7-dimethylquinoline, m.p. 58.5–59.5°.

Nitration Reactions.—The use of potassium nitrate dissolved in concentrated sulfuric acid was found to be very convenient for the nitration of the substituted quinolines. The results of the several nitrations are listed in Table II. The procedure may be illustrated by the nitration of 2,6-dimethylquinoline (IIa).

2,6-Dimethylquinoline (25.0 g., 0.159 mole) was dissolved in 40 ml. of concentrated sulfuric acid. The mixture was stirred mechanically at 0–5° while a solution of 18.2 g. of potassium nitrate in 48 ml. of concentrated sulfuric acid was added dropwise. When the addition had been completed, the thick mixture was stirred at 0° for 15 minutes and then poured onto ice. The cold solution was made basic with aqueous ammonia, and the precipitated nitro compound, m.p. 104–106°, was collected and washed. On crystallization from alcohol there was obtained 27.6 g. (86%) of pure 5-nitro-2,6-dimethylquinoline (III) in the form of pale yellow needles, m.p. 105–106°.[4]

5-Chloro-2,6-dimethylquinoline and 2,7-dimethylquinoline were nitrated by exactly the same procedure. 8-Nitro-2,7-dimethylquinoline (IV) possesses the property of enantiotropy. When the compound is crystallized from ethanol, it first separates in the form of fine needles which change on standing into small cubes. When the form which is stable at room temperature is heated in the usual capillary tube, the material begins to melt about 108–109°, but then resolidifies and finally melts at 117–117.5°. If a packed capillary tube is immersed quickly in a bath at 112°, the contents liquefies completely, resolidifies, and then remelts at 117–117.5°. When the solid compound in the form of needles is heated in contact with its saturated solution in *n*-propyl alcohol at 80.1°, it remains in the form of needles, while at 78.1° the material slowly changes to the cubic form. Seemingly, there is a transition point at about 79°, above which the two forms of the compound melt, at about 109 and at 117.5°, respectively. The system rather closely resembles that of rhombic and monoclinic sulfur.

2,5,8-Trimethylquinoline (V) could not be nitrated nearly so satisfactorily as the other compounds. When the compound was nitrated by the procedure used elsewhere, the yield of purified product was only 32% of the theoretical. When 17.0 g. of the trimethylquinoline, dissolved in 20 ml. of concentrated sulfuric acid, was treated with a solution of 17.1 g. of potassium nitrate in 50 ml. of concentrated sulfuric acid, the temperature being held between −10° and 0°, and the crude product was crystallized from alcohol with repeated decolorization, it was possible to obtain pure (although light tan) 6-nitro-2,5,8-trimethylquinoline in 50–59% yield. In one reaction a very small amount of a substance melting at 91–93° was isolated, but not further investigated. It was not possible to recover more of the principal product from the mother liquor.

Reduction of Nitro Compounds.—5-Nitro-2,6-dimethyl-, 8-nitro-5-chloro-2,6-dimethyl- and 6-nitro-2,5,8-trimethylquinoline were successfully reduced by stannous chloride and hydrochloric acid. The procedure used was similar to that employed by Dufton for the reduction of 5-nitroquinoline but for the use of mechanical stirring.[19] The results of the reductions are given in Table III. Reduction of 8-

(13) J. B. Cohen and H. D. Dakin, *J. Chem. Soc.*, **81**, 1324 (1902).

(14) As adapted for the preparation of acetanilide in "Experiments in Organic Chemistry," by L. F. Fieser, 2nd edition, D. C. Heath and Co., Boston, Mass., 1941, p. 163.

(15) J. B. Cohen and H. D. Dakin, *J. Chem. Soc.*, **79**, 1111 (1901).

(16) As applied to the nitration of 2,6-dichlorotoluene, J. B. Cohen and H. D. Dakin, *ibid.*, **81**, 1344 (1902).

(17) H. Wahl, *Chem. Centr.*, **107**[1], 4150 (1936).

(18) A. S. Wheeler and M. Morse, THIS JOURNAL, **46**, 2572 (1924).

(19) S. F. Dufton, *J. Chem. Soc.*, **61**, 782(1892).

nitro-2,7-dimethylquinoline with stannous chloride and hydrochloric acid led to the formation of what proved to be 8-amino-5-chloro-2,7-dimethylquinoline in addition to the expected amine.[11] Analysis of the crude reaction product indicated a chlorine content of 8.14%, about one-half that calculated (18.50%) for an aminochlorodimethylquinoline. The structure of the by-product (which was not isolated) was established as described in the section on the Sandmeyer reactions. The nitro compound was reduced successfully by the use of iron and acetic acid,[4] with the results indicated in Table III.

Sandmeyer Reactions.—The amines were converted by the Sandmeyer reaction into the corresponding chlorides. The procedure used was similar to that employed by Dikshoorn in the preparation of 5-bromoquinoline.[20] The results of the several Sandmeyer processes are listed in Table IV.

The mixture of amino- and aminochlorodimethylquinoline obtained in the stannous chloride reduction of 8-nitro-2,7-dimethylquinoline was subjected to the Sandmeyer reaction. The steam distilled product melted between 50 and 60° with much prior softening. Six successive crystallizations from petroleum ether gave a colorless substance with the constant melting point 96–97°, which was found to be identical with 5,8-dichloro-2,7-dimethylquinoline.

(20) R. P. Dikshoorn, *Rec. trav. chim.*, **48**, 550 (1929).

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[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

Studies on Condensed Pyrimidine Systems. XI. Some 8-Alkyl-7-pteridones[1]

BY GERTRUDE B. ELION AND GEORGE H. HITCHINGS

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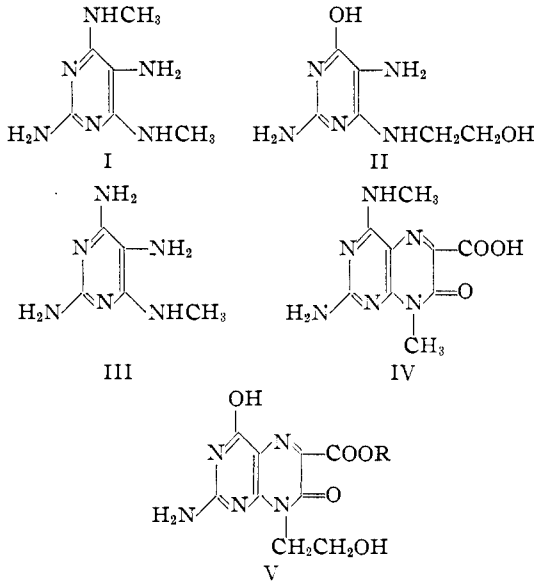
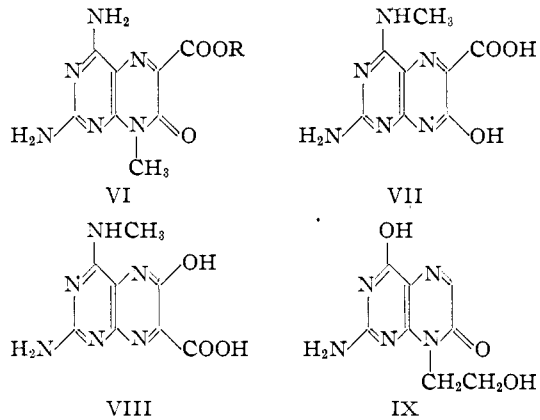
The preparation is described of several 8-alkyl-7-oxo-7,8-dihydro-6-pteridine-carboxylic acids by the condensation of the 2-amino derivatives of 4,5-diamino-6-methylamino-, 5-amino-4,6-bis-(methylamino), and 5-amino-6-hydroxy-4-β-hydroxyethylaminopyrimidine with ethyl oxomalonate. 6-Methylamino-2,4,5-triaminopyrimidine gave two products, for which are proposed the structures ethyl 2,4-diamino-8-methyl-7-oxo-7,8-dihydro-6-pteridinecarboxylate and 2-amino-4-methylamino-7-hydroxy-6-pteridinecarboxylic acid. On heating, 2-amino-4-hydroxy-8-β-hydroxyethyl-7-oxo-7,8-dihydro-6-pteridinecarboxylic acid loses carbon doxide and is converted to the corresponding 7-pteridone.

Pteridines with a substituent in the 8-position are of interest because the analogous position is the site of attachment of a sugar moiety in the purine nucleosides, riboflavin and vitamin B_{12}. During the course of these experiments, the synthesis of some 8-substituted pteridines was reported[2,3] in which ethyl oxalate, benzoin and chloroacetic acid were the carbonyl reagents used. The present report deals with the condensation of ethyl oxomalonate with the three types of pyrimidine exemplified by structures I, II and III. With pyrimidine I, the substituents at positions 4 and 6 are the same so that when ring closure occurs, only one product is possible, namely, IV. With pyrimidine II ring closure with ethyl oxomalonate likewise gives only one product, V (R = C_2H_5), since there is an hydroxyl group in the 4-position. Because the nitrogen on the 6-position of I and II has a substituent, it is not possible in either case to form the isomeric 6-hydroxy-7-pteridinecarboxylic acid, such as is formed when 6-hydroxy-2,4,5-triaminopyrimidine is condensed with ethyl oxomalonate.[4] Compound III is however, theoretically capable of reacting with this ester to give three products VI, VII and VIII, only one of which VI is an 8-substituted pteridine. Since 4-alkylamino-6-amino-5-thioformamidopyrimidines give 9-substituted purines exclusively on ring closure,[5] it was expected that the primary product would be the 8-substituted pteridine. Furthermore, 2,4,5,6-tetraaminopyrimidine with ethyl oxomalonate gives exclusively the 7-hydroxypteridine rather than a mixture of the





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