(b) 1.0 g. of VI and 1.22 g. (0.0130 mole) of chloroacetamide were refluxed together for 96 hours in 50 cc. of 95% ethanol. The suspended matter was filtered off to give 0.9 g. of a dirty white product. This was dissolved in dilute ammonia and reprecipitated with acetic acid to give 0.75 g. of IX.

Anal. Calcd. for $C_7H_8O_2N_6S$: S, 13.34. Found: S, 13.56.

Ultraviolet maxima ($c = 2.37 \times 10^{-5}$ mole/l.):

	*p*H 2.0				
mμ	220			301	
ε	19,000			17,100	
	*p*H 6.9			*p*H 9.3	
mμ	218	257	297	220	298
ε	26,400	9280	16,200	24,100	16,000

At *p*H of 2.0 there is an inflection at 241–264 mμ.

Attempts to cyclize IX by means of refluxing with phosphorus oxychloride or with dry hydrogen chloride in ethanol resulted in isolation of unreacted starting material.

2,6-Diamino-8-carbethoxymethylmercaptopurine (X).—(a) 1.0 g. of VI (0.00556 mole) was refluxed with 2.4 g. of ethyl chloroacetate (0.195 mole) for 85 hours in 50 cc. of 95% ethanol. Solution was effected and the color was a clear amber at the end of that time, so the solution was decolorized and allowed to cool. 0.85 g. of pearly white masses with a slight mercaptan odor was filtered off, X-hydrochloride, m.p. 222–224° (dec.) with rapid heating. The mother liquor gave an additional 150 mg. of product, giving a total yield of about 60%.

(b) 1.0 g. of VI was refluxed with 0.9 g. (0.0065 mole) of bromoacetic acid in 80 cc. of 95% ethanol for 43 hours and then filtered hot. The filtrate was reduced in volume to 40 cc. and on standing several hours 0.5 g. of pearly white masses deposited, X-hydrobromide, m.p. 222–224° (dec.). Esterification had obviously taken place in the course of the coupling reaction. The product is soluble in alcohol and water and insoluble in benzene.

Anal. Calcd. for $C_9H_{12}O_2N_6S \cdot HBr$; C, 30.95; H, 3.75; N, 24.07; S, 9.18. Found: C, 31.17; H, 3.85; N, 24.45; S, 9.28.

Calcd. for $C_9H_{12}O_2N_6S \cdot HCl$: C, 35.48; H, 4.27; Cl, 11.64. Found: C, 35.15; H, 4.13; Cl, 11.78.

The ultraviolet spectrum of X-hydrochloride is identical with that of IX. The spectrum of the X-hydrobromide is qualitatively also identical; the extinction coefficients of the maxima of the hydrobromide are slightly higher than those of the hydrochloride.

Attempts to cyclize these esters by the methods described under IX above were likewise unsuccessful.

2,6-Diamino[3',2'-*h*]thiazolinopurine (XI).—Reaction of chloroacetal with VI results in a yellow product whose ultraviolet spectrum is different from that of VI. Its spectrum has the double peak noted in the case of VIII, and the peak in the neighborhood of 260 mμ is much higher than that at about 325 mμ. This compound could not be purified sufficiently to give a satisfactory analysis, despite repeated attempts. No intermediate thioglycolaldehyde could be isolated.

Attempts to form thiazolinopurines by the reaction of VI with 1,2-dibromomethylene or with phenacyl chloride were unsuccessful.

Acknowledgment.—The author is grateful to Prof. Melvin Calvin for his kind encouragement and interest in this work, as well as for providing the facilities for this project. Elemental analyses were performed by the microanalytical laboratory of the Chemistry Department, University of California.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF MAY & BAKER LIMITED]

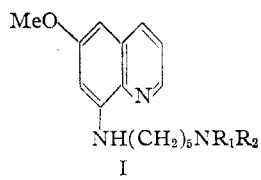
The Synthesis of 8-(5-Hydroxyamylamino)-6-methoxyquinoline: a New Method of Preparation of Pentaquin and its Analogs

BY MAURICE BERKELEY GREEN

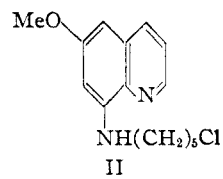
8-Amino-6-methoxyquinoline and 5-chloroamyl acetate react readily on heating, yielding 8-(5-hydroxyamylamino)-6-methoxyquinoline which is converted by treatment with thionyl chloride to 8-(5-chloroamylamino)-6-methoxyquinoline. Reaction of this latter compound with isopropylamine, *n*-butylamine and diethylamine gives the corresponding 8-(5-alkylaminoamylamino)-6-methoxyquinolines. Reduction of 8-(5-isopropylaminoamylamino)-6-methoxyquinoline with hydrogen and Raney Ni gives the tetrahydro derivative.

The report by Loeb[1] of radical cure of *P. vivax* infections with pentaquin (8-(5-isopropylaminoamylamino)-6-methoxyquinoline, I, R_1 = *i*-Pr, R_2 = H) led us to undertake the preparation for biological assessment of a number of analogous 8-(5-alkylaminoamylamino)-6-methoxyquinolines (I) and, in continuation of previous work on tetrahydropamaquin,[2] also of the tetrahydro derivatives of some of these compounds.

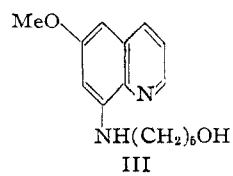
Hitherto 8-(5-alkylaminoamylamino)-6-methoxyquinolines (I) have been prepared by condensation of a 1-chloro-5-alkylaminopentane hydrochloride with 8-amino-6-methoxyquinoline,[3,4,5] by condensation of 1-bromo-5-phthalimidopentane with the same aminoquinoline and subsequent alkylation,[6] or by reductive alkylation of the appropriate



I



II



III

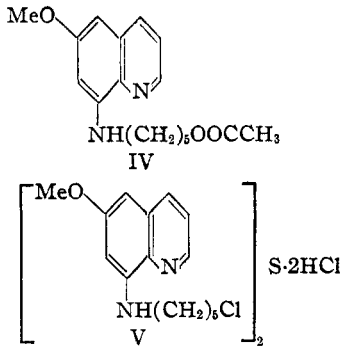
8-aminoamylaminoquinoline with the requisite aldehyde or ketone.[5]

We have now found that condensation of 8-(5-chloroamylamino)-6-methoxyquinoline (II) with a mono- or dialkylamine yields an 8-(5-alkylaminoamylamino)-6-methoxyquinoline (I). This reaction should be a worthwhile addition to previously described methods since it makes possible the prep-

(1) Loeb, *J. Am. Med. Assoc.*, **132**, 321 (1946).
(2) Barber and Wragg, *J. Chem. Soc.*, 610 (1946).
(3) Magidson and Strukov, *Arch. Pharm.*, **271**, 569 (1933); **273**, 320 (1935); *J. Gen. Chem. (U. S. S. R.)*, **8**, 899 (1938)
(4) Drake, *et al.*, THIS JOURNAL, **68**, 1529 (1946)
(5) Drake, *et al.*, *ibid.*, **71**, 455 (1949).
(6) Baldwin, *J. Chem. Soc.*, 2959 (1929).

aration of a whole range of analogous compounds from the single intermediate (II) by reaction with readily available amines.

The 8-(5-chloroamylamino)-6-methoxyquinoline (II) was prepared by chlorination of 8-(5-hydroxyamylamino)-6-methoxyquinoline (III) which was in turn obtained by condensation of 5-chloroamyl acetate with excess 8-amino-6-methoxyquinoline. 5-Chloroamyl acetate was readily obtained by reaction of tetrahydropyran with acetyl chloride in the presence of zinc dust.[7]



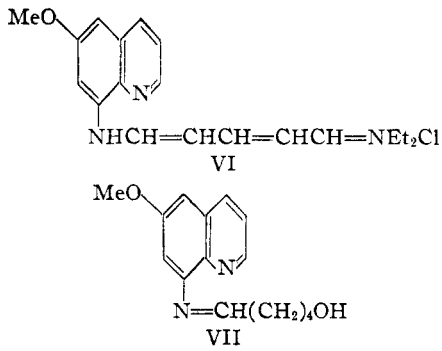
The method is an extension of that used by Crum and Robinson[8] for the preparation of the analogous 3-aminopropylaminoquinoline. In the present case the condensation of 8-amino-6-methoxyquinoline with pentamethylene chlorohydrin could not be used since the chlorohydrin cyclized to tetrahydropyran when heated with an amine. We therefore treated 8-amino-6-methoxyquinoline with 5-chloroamyl acetate in the hope of obtaining 8-(5-acetoxyamylamino)-6-methoxyquinoline (IV). The product proved to be a mixture of the acetoxy (IV) and hydroxy (III) compounds, since the 8-amino-6-methoxyquinoline not only condensed with the chlorine atom in 5-chloroamyl acetate, but also hydrolyzed the acetate group. Both these reactions proceeded under similar conditions; below 130° there was substantially no reaction, above this temperature a mixture of products was always formed. We therefore used an excess of 8-amino-6-methoxyquinoline to carry the formation of the hydroxy compound (III) to completion, heated the crude product with hydrochloric acid to hydrolyze 8-acetamido-6-methoxyquinoline and separated the 8-(5-hydroxyamylamino)-6-methoxyquinoline (III) and 8-amino-6-methoxyquinoline by fractional distillation. The hydroxy compound (III) was a crystalline solid which formed a well-defined hydrochloride, picrate and phosphate.

8-(5-Hydroxyamylamino)-6-methoxyquinoline (III) was chlorinated by treating in chloroform at 0° with exactly one molecular proportion of thionyl chloride added in two equal portions with a one-hour interval and afterwards refluxing for several hours with the addition of a small amount of pyridine.[9] In this way a pure product which contained no sulfur was obtained. The chloro compound (II) decomposed on attempted distillation and was purified by conversion to the phosphate. However, recrystallization of this phosphate involved considerable loss owing to its great solubility and, in general, the crude chloro compound (II) was used for further reaction without purification. If any excess of thionyl chloride was used in the chlorination a red by-product, bis-8-(5-chloroamylamino)-6-methoxyquinolyl sulfide hydrochloride (V) was obtained; this became the sole product if the hydroxy compound (III) was refluxed in chloroform with excess thionyl chloride. The sulfide hydrochloride was converted to the free base by treatment with ammonia solution. Crum and Robinson[8] noted the formation of a similar by-product in their reaction.

Reaction of the chloro compound (II) with amines was carried out by heating either the free base or the phosphate with excess amine in a sealed tube at 130°. A substantial amount of 8-piperidino-6-methoxyquinoline was formed as well as the 8-(5-alkylaminoamylamino) - 6 - methoxyquinoline (I); these could best be separated by dissolving the crude mixture of bases in hydrochloric acid, buffering the solution to *p*H 5.0 with sodium hydroxide and sodium acetate, extracting the 8-piperidino-6-methoxyquinoline with a solvent and isolating the 8-(5-alkylaminoamylamino) - 6 - methoxyquinoline (I) from the aqueous liquors either by crystallizing out the monohydrochloride or by making alkaline, extracting the base and distilling.

Reference samples of the N-isopropyl (I, R_1 = *i*-Pr, R_2 = H) and N-*n*-butyl (I, R_1 = *n*-Bu, R_2 = H) compounds were prepared both by Drake's[4] and Baldwin's[6] methods.

8-(5-Aminoamylamino)-6-methoxyquinoline (I, R_1 = R_2 = H) was prepared substantially as described by Baldwin,[6] except that the modified procedure of Barber and Wragg[10] was used in which the 1-bromo-5-phthalimidopentane was condensed with 8-amino-6-methoxyquinoline by heating in chlorobenzene and the intermediate phthalimido compound hydrolyzed by means of hydrazine hydrate in the cold, whereby the formation of unwanted by-products was reduced to a minimum.



8-(5-Diethylaminoamylamino)-6-methoxyquinoline (I, R_1 = R_2 = Et) was prepared by catalytic reduction of the condensation product (VI) of 5-diethylamino-1-pentadieneal with 8-amino-6-methoxyquinoline. The amino aldehyde was prepared by treatment of 2,4-dinitrophenylpyridinium chloride with diethylamine as described by Knunyantz and Kefeli.[11] Treatment of 2,4-dinitrophenylpyri-

(7) *Cf.* British Patent 593,913.
(8) Crum and Robinson, *J. Chem. Soc.*, 561 (1943).
(9) *Cf.* Liebermann, *Nature*, **160**, 903 (1947).
(10) Barber and Wragg, *J. Chem. Soc.*, 1331 (1947).
(11) Knunyantz and Kefeli, *J. Gen. Chem.* (*U. S. S. R.*), **15**, 628 (1945).

dinium chloride with primary amines did not give an amino aldehyde; highly colored products, probably derivatives of glutaconic aldehyde, were formed.

An attempt to prepare 8-(5-hydroxyamylamino)-6-methoxyquinoline (III) by catalytic reduction of the anil (VII) obtained by condensation of 5-hydroxy-1-pentanal with 8-amino-6-methoxyquinoline failed.

8-(5-Isopropylaminoamylamino)-6-methoxyquinoline (I, R_1 = *i*-Pr, R_2 = H) was reduced to the tetrahydro derivative by hydrogenation in dioxane in the presence of Raney nickel.

A number of the compounds described in this paper were examined for antimalarial activity and toxicity. Tetrahydropentaquin was about one-third as toxic to mice as Pentaquin; it was half as active as pentaquin toward *P. gallinaceum* in chicks and one-tenth as active toward *P. relictum* in canaries. In comparison, tetrahydropamaquin was about one-fifth as toxic to mice as Pamaquin and was one-quarter as active as Pamaquin toward both *P. gallinaceum* and *P. relictum*. In view of these results the work on tetrahydro derivatives was discontinued.

The *n*-butyl analog of Pentaquin was slightly more toxic to mice than Pentaquin; its activity toward *P. gallinaceum* was equal to, and toward *P. relictum* slightly greater than, that of Pentaquin. 8-(5-Hydroxyamylamino)-6-methoxyquinoline was effective against *P. gallinaceum* at half its lethal dose; neither 8-(5-chloroamylamino)-6-methoxyquinoline nor the condensation product of 5-diethylamino-1-pentadieneal with 8-amino-6-methoxyquinoline were effective at the lethal dose.

Experimental

8-(5-Hydroxyamylamino)-6-methoxyquinoline.—A mixture of 2,800 g. (16.0 moles) of finely-ground 8-amino-6-methoxyquinoline[12] and 660 g. (4.0 moles) of 5-chloroamyl acetate[13] was stirred in a 5-liter 3-necked flask and heated to 150° for 8 hours in an atmosphere of nitrogen. The black melt was poured into 4 liters of water and a solution of 400 g. of caustic soda in 1 liter of water added gradually with stirring and cooling. The mixture was extracted with three 2-liter portions of chloroform and the extract washed with three 1-liter portions of water. The small amount of tarry emulsion which appeared between the layers during separation was broken down by filtration through a bed of Hyflo supercel. The chloroform was distilled off on the steam-bath, the last traces being removed under reduced pressure.

The black oily residue was cooled in ice and a mixture of 4 liters of concentrated hydrochloric acid and 1 liter of water added. The semi-solid orange mixture was heated under reflux for one hour in a water-bath at 90°, allowed to cool and the precipitated 8-amino-6-methoxyquinoline hydrochloride filtered off, washed thoroughly with 2 *N* hydrochloric acid and dried in the steam-oven; 2,112 g. of the hydrochloride was thus recovered.

The red filtrate was made alkaline by the gradual addition of 2,500 ml. of 50% $^{w}/_{v}$. caustic soda solution and extracted with three 2-liter portions of chloroform. The extract was filtered through a bed of Hyflo supercel and washed with three 1-liter portions of water. The chloroform was distilled off on the steam-bath and the residue fractionated through an 8″ electrically-heated Vigreux column. A first fraction of 393 g. of 8-amino-6-methoxyquinoline, b. p. 120–175° (0.1 mm.), was obtained. The next fraction was 8-(5-hydroxyamylamino)-6-methoxyquinoline, b.p. 175–210° (0.1 mm.), m.p. 66–70°. The yield was 811 g. (78% based on the side-chain; 83% based on the nucleus).

The crude product was dissolved in 750 ml. of warm benzene and the solution treated with 20 g. of charcoal and filtered. The charcoal was washed with 250 ml. of warm benzene and 750 ml. of warm petroleum ether (60–80°). The filtrate was cooled in ice–salt and the solid filtered off, washed with ice-cold petroleum ether and dried *in vacuo*. The yield was 698 g. (67% based on the side-chain; 71% based on the nucleus) of a yellow-green solid, m. p. 71–72°. Further recrystallization from benzene–petrol gave a product, m.p. 73.5°. *Anal.* Calcd. for $C_{16}H_{20}N_2O_2$: C, 69.20; H, 7.74; N, 10.76; MeO, 11.92. Found: C, 69.0; H, 7.75; N, 10.75; MeO, 12.0. The hydrochloride formed deliquescent orange-red needles from ethanol–ether, m.p. 128–130°; the phosphate formed yellow prisms from ethanol, m.p. 119–120°, and the picrate formed orange-red needles from ethanol, m.p. 143–145°.

8-(5-Chloroamylamino)-6-methoxyquinoline.—A solution of 260 g. (1.0 mole) of 8-(5-hydroxyamylamino)-6-methoxyquinoline in 750 ml. of dry chloroform was stirred in a 2-liter 3-necked flask cooled in ice–salt. One 37.5-ml. (0.5 mole) portion of purified thionyl chloride was added during 30 minutes and the mixture stirred and cooled for 1 hour. A second 37.5-ml. (0.5 mole) portion of thionyl chloride was then added during 30 minutes and the mixture stirred and allowed to warm to room temperature during 1 hour. One ml. of pyridine was added and the mixture refluxed gently on the steam-bath for 5 hours. The red reaction product was poured into 500 ml. of saturated potassium carbonate solution containing crushed ice and the chloroform layer separated after shaking well. The aqueous layer was extracted with two 500-ml. portions of chloroform and the combined extracts filtered through a bed of Hyflo supercel and washed with three 500-ml. portions of water. The chloroform was distilled off on the steam-bath, the last traces being removed under reduced pressure, leaving crude 8-(5-chloroamylamino)-6-methoxyquinoline as a brown oil. The yield was 285–295 g. The base decomposed on attempted distillation at 0.1 mm. pressure.

The product was dissolved in 500 ml. of dry ethanol and the solution boiled under reflux and stirred in a 2 liter 3-necked flask. A solution of 100 g. of 89% $^{w}/_{w}$. phosphoric acid in 250 ml. of ethanol was added during 30 minutes and the solution refluxed for 1 hour. After cooling to room temperature, 1 liter of ether was added and the mixture cooled for 2 hours in a bath of ice–salt. The slightly sticky monophosphate was filtered off, washed with ether and recrystallized from ethanol–ether as an orange solid, m.p. 115–119°. The yield was 211 g. (58%). Further recrystallization from ethanol–ether gave a poor recovery of orange-yellow prisms, m.p. 124–125°. *Anal.* Calcd. for $C_{15}H_{19}N_2OCl\ H_3PO_4$: N, 7.43; MeO, 8.24. Found: N, 7.3; MeO, 8.3.

Bis-8-(5-chloroamylamino)-6-methoxyquinolyl Sulfide.—The hydrochloride of this compound, m.p. 144–145°, was obtained as a by-product if excess thionyl chloride was used in the above chlorination or if the temperature was allowed to rise above 0° during the addition of the thionyl chloride. It was obtained in nearly theoretical yield by refluxing 8-(5-hydroxyamylamino)-6-methoxyquinoline with excess thionyl chloride in chloroform for 2 hours. On trituration with 2 *N* ammonia it gave the free base which formed a mat of fine yellow needles from petrol–benzene, m.p. 115–116°. *Anal.* Calcd. for $C_{30}H_{36}N_4O_2Cl_2S$: C, 61.32; H, 6.17; N, 9.55; Cl, 12.07; MeO, 10.54. Found: C, 61.2; H, 6.38; N, 10.0; Cl, 12.0; MeO, 10.25.

8-(5-Isopropylaminoamylamino)-6-methoxyquinoline.—A mixture of 290 g. (1.0 mole) of crude 8-(5-chloroamylamino)-6-methoxyquinoline and 295 g. (5.0 moles) of isopropylamine was heated in an autoclave for 7 hours at 120 ± 5°. The contents of the autoclave were washed out with water and chloroform and the excess isopropylamine distilled off on the steam-bath. The residue was made strongly alkaline by the addition of 20% caustic soda solution and extracted with three 500-ml. portions of chloroform. The extract was filtered through a bed of Hyflo supercel and washed with three 500-ml. portions of water. The chloroform was distilled off on the steam-bath, the last traces being removed under reduced pressure. The residual black oil (*circa* 300 g.) was stirred with water and concentrated hydrochloric acid added until the mixture was just acid to congo red paper; 50% $^{w}/_{v}$. caustic soda solution was then added until the *p*H of the mixture was 4.5 and then solid sodium acetate trihydrate until the *p*H was 5.0, determined electrometrically. The mixture was stirred and heated to 65° and extracted at that temperature with three 1-liter portions of

(12) The 8-amino-6-methoxyquinoline was almost colorless, stable in air and melted at 50–52°.

(13) Synerholm, THIS JOURNAL, **69**, 2581 (1947).

benzene, the layers being separated by suction. The benzene layer was washed with one 100-ml. portion of hot water and the washing added to the main aqueous liquors.

Evaporation of the benzene extract and distillation of the residue gave 90 g. of 8-piperidino-6-methoxyquinoline, b. p. 152–160° (0.1 mm.), m. p. 75–78°. Recrystallization from petrol–benzene gave a product of m.p. 79–80°. *Anal.* Calcd. for $C_{15}H_{18}N_2O$: C, 74.4; H, 7.5; N, 11.4; MeO, 12.8. Found: C, 74.7; H, 7.72; N, 11.2; MeO, 12.6. The hydrochloride formed yellow prisms from ethanol–ether, m.p. 140–141°. The picrate formed a mat of fine yellow needles from ethanol–acetone, m.p. 135–136°.[14]

The main aqueous liquors were allowed to stand for several days and then cooled for several hours in ice. The precipitated monohydrochloride of 8-(5-isopropylaminoamylamino)-6-methoxyquinoline was filtered off, pressed dry and dissolved in 1 liter of water at 60–70°; 100 ml. of 50% w./v. caustic soda solution was added and the mixture cooled, extracted with four 600-ml. portions of ether and the extract washed with three 200-ml. portions of water and dried over anhydrous sodium sulfate. The ether was distilled off on the steam-bath and the last traces removed under reduced pressure leaving crude 8-(5-isopropylaminoamylamino)-6-methoxyquinoline as an amber oil. The yield was 125 g. (42%).

The crude base was either distilled under reduced pressure or converted to its monophosphate. The distilled base was a yellow oil, b.p. 165–170° (0.05 mm.), $n^{24}D$ 1.5789. *Anal.* Calcd. for $C_{18}H_{27}N_3O$: C, 71.72; H, 9.03; N, 13.91. Found: C, 72.0; H, 9.0; N, 13.9.

Conversion of 125 g. of the crude base to the monophosphate by the method described by Drake[4] gave a sandy-yellow granular solid, m.p. 188–190°. The yield was 156 g. (39% over-all based on 8-(5-hydroxyamylamino)-6-methoxyquinoline). Recrystallization from three volumes of water gave a finely divided pale yellow powder, m.p. 190.5°. *Anal.* Calcd. for $C_{18}H_{27}N_3O \cdot H_3PO_4$: N, 10.52; MeO, 7.77; base, 75.46. Found: N, 10.6; MeO, 7.9; base, 75.4.

The monohydrochloride formed yellow-green plates from ethanol, m.p. 152–154°, and the dihydrochloride formed orange-yellow plates from water–ethanol, m.p. 215–216°. The dipicrate formed orange prisms from acetone–ethanol, m.p. 164.5–165.5°.[15] *Anal.* Calcd. for $C_{18}H_{27}N_3O \cdot 2C_6H_3N_3O_7$: C, 47.49; H, 4.36; N, 16.59; MeO, 4.09. Found: C, 47.8; H, 4.6; N, 16.3; MeO, 4.2.

8-(5-*n*-Butylaminoamylamino)-6-methoxyquinoline.—A mixture of 37.65 g. (0.1 mole) of 8-(5-chloroamylamino)-6-methoxyquinoline monophosphate and 36.5 g. (0.5 mole) of *n*-butylamine was heated in an autoclave for 7 hours at 120 ± 5° and the product worked up as described in the previous experiment. 8.6 g. of 8-piperidino-6-methoxyquinoline was obtained. The 8-(5-*n*-butylaminoamylamino)-6-methoxyquinoline had b.p. 180–190° (0.05 mm.), m.p. 37–39°. The yield of distilled base was 16.7 g. (53%). Recrystallization of the base from two to three parts of petrol (40–60°) gave white prisms, m.p. 41°. *Anal.* Calcd. for $C_{19}H_{29}N_3O$: C, 72.34; H, 9.27; N, 13.32; MeO, 9.84. Found: C, 72.6; H, 9.2; N, 13.4; MeO, 9.85.

The monohydrochloride formed yellow-green plates from water–ethanol, m.p. 133°. The dihydrochloride formed brownish-yellow plates from ethanol, m. p. 212–216°. The phosphate formed golden-yellow prisms from ethanol, m. p. 139.0–139.5°. *Anal.* Calcd. for $C_{19}H_{29}N_3O \cdot H_3PO_4$: MeO, 7.5. Found: MeO, 7.5.[16]

8-(5-Diethylaminoamylamino)-6-methoxyquinoline.—A mixture of 37.65 g. (0.1 mole) of 8-(5-chloroamylamino)-6-methoxyquinoline monophosphate and 36.5 g. (0.5 mole) of diethylamine was heated in an autoclave for 7 hours at 120 ± 5° and the product worked up as described previously; 10.2 g. of 8-piperidino-6-methoxyquinoline was obtained. The hydrochloride of the base did not separate from water and the aqueous liquors after extraction of the 8-piperidino-6-methoxyquinoline were therefore made strongly alkaline with caustic soda and extracted with ether. The extract was washed with water, dried and distilled. The 8-(5-diethylaminoamylamino)-6-methoxyquinoline had b.p. 170–175° (0.05 mm.), $n^{24}D$ 1.5793. The yield of distilled base was 14.5 g. (46%). *Anal.* Calcd. for $C_{19}H_{29}N_3O$: C, 72.34; H, 9.27; N, 13.32; MeO, 9.84. Found: C, 72.48; H, 9.16; N, 13.4; MeO, 9.8.

The oxalate formed white prisms from ethanol–ether, m. p. 90–91°.[17]

This compound was also prepared by the following method: A solution of 3.0 g. of 1-(6-methoxyquinolyl-8-amino)-penta-1,3-diene-5-ylidene-N,N-diethylammonium chloride[11] in 200 ml. of methanol was hydrogenated at 60° and 30 atmospheres in the presence of 10% Adams catalyst. The catalyst was filtered off and 10 ml. of methanolic hydrogen chloride added to the filtrate which was then evaporated on the steam-bath. The residue was dissolved in water and the solution extracted with chloroform. The aqueous layer was made alkaline with 50% w./v. caustic soda solution and extracted with chloroform. The extract was washed with water, evaporated on the steam-bath and the residue distilled giving 8-(5-diethylaminoamylamino)-6-methoxyquinoline as a yellow oil, b. p. 150–210° (0.04 mm.), $n^{24}D$ 1.5801. The yield was 0.8 g. (25%). The oxalate had m.p. 90–91°.

8-(5-Hydroxyamylideneamino)-6-methoxyquinoline.—A mixture of 34.8 g. (0.2 mole) of 8-amino-6-methoxyquinoline, 20.4 g. (0.2 mole) of 5-hydroxy-1-pentanal[18] and 100 ml. of dry toluene was heated in an atmosphere of nitrogen in an oil-bath for 1 hour at 80° and 2 hours at 110°. The bath temperature was raised to 170° during 1.5 hours and the toluene and water distilled off. The residue was heated at 170° and 20 mm. pressure for 1 hour and then distilled, giving 8-(5-hydroxyamylideneamino)-6-methoxyquinoline as a yellow-brown oil, b.p. 175–190° (0.02 mm.), $n^{18}D$ 1.6277. The yield was 39.5 g. (77%). On long standing the oil solidified and was recrystallized from petrol (60–80°). It formed white prisms, m.p. 56.5–57.7°. *Anal.* Calcd. for $C_{15}H_{18}N_2O_2$: C, 69.74; H, 7.02; N, 10.84; MeO, 12.01. Found: C, 69.4; H, 7.1; N, 10.8; MeO, 11.9.

The product rapidly formed 8-amino-6-methoxyquinoline hydrochloride and 5-hydroxy-1-pentanal on treatment with 2 *N* hydrochloric acid at room temperature.

A number of attempts were made to reduce this compound to 8-(5-hydroxyamylamino)-6-methoxyquinoline, but the required product was in no case isolated.

8-(5-Isopropylaminoamylamino)-6-methoxy-1,2,3,4-tetrahydroquinoline.—Ninety-three grams (0.31 mole) of 8-(5-isopropylaminoamylamino)-6-methoxyquinoline was hydrogenated in dioxane in the presence of 20% Raney nickel at 100 atmospheres and 130° until the oil obtained by distillation of the small aliquot showed no further decrease in refractive index. The catalyst was filtered off and the dioxane distilled from the filtrate. The residue was fractionally distilled through an 8″ electrically-heated Vigreux column. 8-(5-Isopropylaminoamylamino)-6-methoxy-1,2,3,4-tetrahydroquinoline was obtained as a yellow-brown oil, b.p. 170–183° (0.1 mm.), $n^{19}D$ 1.5508. The yield was 65.4 g. (70%).

A solution of 50 g. of the product in 450 ml. of dry ethanol was stirred and heated to boiling in an atmosphere of hydrogen and a solution of 38.0 g. of 85% w./w. phosphoric acid in 50 ml. of dry ethanol added dropwise during 30 minutes. The mixture was refluxed for 30 minutes more, then cooled for 2 hours at room temperature and 2 hours in an ice–salt-bath. The solid was filtered off, washed with 100 ml. of ice-cold ethanol and dried in a vacuum desiccator giving the diphosphate as white plates, m.p. 141–144°. The yield was 82.0 g. (99%). The product was recrystallized from ethanol as white plates, m.p. 142–144°. *Anal.* Calcd. for $C_{18}H_{31}N_3O \cdot 2H_3PO_4$: N, 8.38; MeO, 6.18. Found: N, 8.4; MeO, 6.2.

The base regenerated from the diphosphate had b.p. 185–187° (0.15 mm.), $n^{20}D$ 1.5497. *Anal.* Calcd. for $C_{18}H_{31}N_3O$: C, 70.77; H, 10.23; N, 13.76; MeO, 10.16. Found: C, 70.6; H, 10.2; N, 13.8; MeO, 10.2.

The dihydrochloride was a very hygroscopic yellow solid.

Acknowledgment.—The author wishes to ex-

(14) Cerkovnikov, Prelog and Stern, *Helv. Chim. Acta*, **26**, 1180 (1943), reported base, m.p. 57–58°; hydrochloride, m.p. 141–142°.

(15) Drake, *et al.*, ref. 4, reported: base, b.p. 165–170° (0.02 mm.), $n^{25}D$ 1.5785; monohydrochloride, m. p. 152–153°; dihydrochloride, m.p. 218–219°; monophosphate, m.p. 189.0–189.5°.

(16) Drake, ref. 5, prepared the monohydrobromide of this compound.

(17) Elderfield, *et al.*, THIS JOURNAL, **68**, 1524 (1946), reported the melting point of the oxalate as 90–91°.

(18) Paul, *Bull. soc. chim.*, [4] **53**, 1489 (1933); [5] **1**, 971 (1934); [5] **2**, 745 (1935).

press his sincere thanks to Dr. H. J. Barber for constant help and advice. He is also indebted to Mr. S. Bance for the semimicroanalyses, to the Biological Division, May and Baker Limited for the biological results, and to the Directors of Messrs. May and Baker Limited for permission to publish the results.

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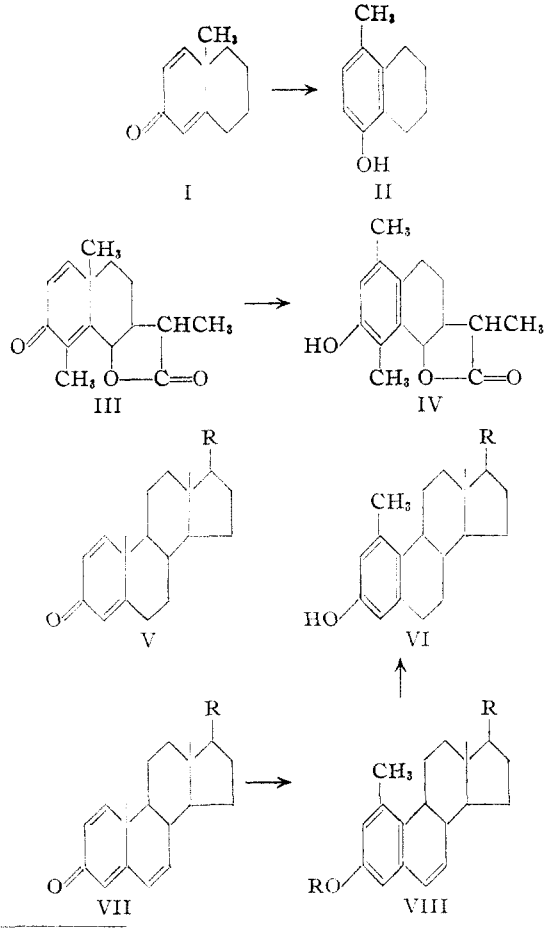
The Dienone–Phenol Rearrangement

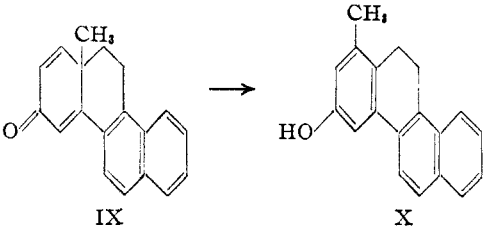
BY A. SANDOVAL, L. MIRAMONTES, G. ROSENKRANZ AND CARL DJERASSI

9-Methyl-3-keto-$\Delta^{1,2;4,10}$-hexahydronaphthalene (I) can be converted into the corresponding $\Delta^{1,2;4,10;5,6}$-tetrahydro derivative (XI) by N-bromosuccinimide bromination followed by collidine dehydrobromination. Acid-catalyzed rearrangement of this trienone and catalytic hydrogenation of the product yielded 1-methyl-3-hydroxy-5,6,7,8-tetrahydronaphthalene (XIII). This sequence of reactions not only proves the course of the acid-catalyzed rearrangement of steroidal 1,4,6-trien-3-ones but also demonstrates that the presence of a double bond in conjugation to the 1,4-dien-3-one system causes the dienone–phenol rearrangement to proceed by migration of the angular methyl group rather than the secondary alkyl group.

Recently, Woodward and Singh[1] have shown that the dienone–phenol rearrangement of the naphthalenic dienone I leads to the 1-methyl-4-hydroxyphenol(II) rather than the 3-hydroxy isomer XIII, which would have been expected by analogy to the santonin–desmotroposantonin (III →IV) rearrangement.[2] This in turn has thrown open to question the 1-methyl-3-hydroxy structure VI assigned to a considerable number of dienone–phenol rearrangement products of steroidal 1,4-dien-3-ones (V).[3]



Subsequently, it was demonstrated[4,5] that steroidal 1,4,6-trien-3-ones (VII)[6] on rearrangement, followed by hydrogenation of the 6–7 double bond (of VIII) yield phenols, different from those obtained on rearrangement[3] of 1,4-dien-3-ones (V), and which are believed to be the authentic 1-methyl-3-hydroxyphenols (VI) of the steroid series on the basis of: (a) formal analogy to the proved rearrangement in the chrysene series (IX→ X)[7]; (b) consideration of the reaction mechanism[1,4]; and (c) the physical and biological properties of the new steroidal phenols (alkali-solubility, estrogenic activity). It has now been possible to prove this supposition by studying the reaction in the naphthalene series.



As has already been illustrated in the steroid series,[8] N-bromosuccinimide bromination of a 1,4-dien-3-one (V) leads to the corresponding 6-bromo derivative, which can be dehydrobrominated with collidine to yield the corresponding 1,4,6-trien-3-one (VII), characterized by the typical ultraviolet absorption maxima at 222, 256 and 298 mμ. Application of this method to 9-methyl-$\Delta^{1,2;4,10}$-hexahydronaphthalene (I)[1] (ultraviolet maximum[1] at 240 mμ) afforded in 65% yield 9-methyl-3-keto-

(1) Woodward and Singh, THIS JOURNAL, **72**, 494 (1950).

(2) *Cf.* Huang-Minlon, Lo and Chu, *ibid.*, **65**, 1780 (1943), and references cited therein.

(3) *Cf.* Inhoffen, *Angew. Chem.*, **59**, 207 (1947), and Djerassi and Scholz, *J. Org. Chem.*, **13**, 697 (1948), for leading references.

(4) Djerassi, Rosenkranz, Romo, Pataki and Kaufmann, THIS JOURNAL, **72**, 4540 (1950).

(5) Romo, Djerassi and Rosenkranz, *J. Org. Chem.*, **15**, 896 (1950).

(6) Djerassi, Rosenkranz, Romo, Kaufmann and Pataki, THIS JOURNAL, **72**, 4534 (1950).

(7) Wilds and Djerassi, *ibid.*, **68**, 1715 (1946).

(8) Kaufmann, Pataki, Rosenkranz, Romo and Djerassi, *ibid.*, **72**, 4531 (1950).