[CONTRIBUTION FROM THE AVERY LABORATORY OF CHEMISTRY, UNIVERSITY OF NEBRASKA]

CONDENSATION OF HYDROXY AND METHOXY N-METHYL-BENZYLAMINES WITH HETEROCYCLIC CHLORIDES

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It had been found that one of the N-methylbenzylamines, namely, *o*-hydroxy-N-methylbenzylamine, reported in a previous communication (1), showed mild activity against avian malaria (2). It therefore seemed important to attempt to obtain more active antimalarials through a combination of such benzylamino groups with the pharmacologically important groupings, 2-amino-4-pyrimidyl and 7-chloro-4-quinolyl.

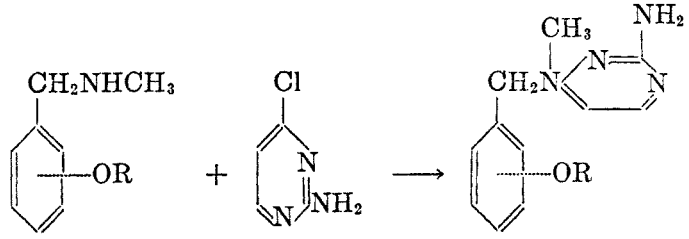
TABLE I

PHYSICAL AND ANALYTICAL DATA

2-AMINO-4-(N′-METHYLBENZYL-AMINO)PYRIMIDINES	NO.	M.P. °C.	YIELD %	FORMULA	% NITROGEN Calc'd	Found
p-Methoxy	(I)	145	70	$C_{13}H_{16}N_4O$	22.94	23.15
o-Methoxy	(II)	150	60	$C_{13}H_{16}N_4O$	22.94	22.98
p-Hydroxy	(III)	213	40	$C_{12}H_{14}N_4O$	24.33	24.32
o-Hydroxy	(IV)	208	31	$C_{12}H_{14}N_4O$	24.33	24.38
7-CHLORO-4-(BENZYLAMINO)-QUINOLINES						
N′methyl-*p*-methoxy	(V)	105–107	20	$C_{18}H_{17}ClN_2O$[a]		
p-Hydroxy	(VI)	253–255	5	$C_{16}H_{13}ClN_2O$[b]		

[a] Calc'd: C, 69.11; H, 5.48. Found: C, 69.50; H, 5.50.
[b] Calc'd: C, 67.48; H, 4.60. Found: C, 67.08; H, 4.95.

The *p*-methoxy and *o*-methoxy-N-methylbenzylamines reacted with 2-amino-4-chloropyrimidine to give good yields of the expected products (I) and (II), while the corresponding hydroxy-N-methylbenzylamines gave only fair to poor yields of compounds (III) and (IV).



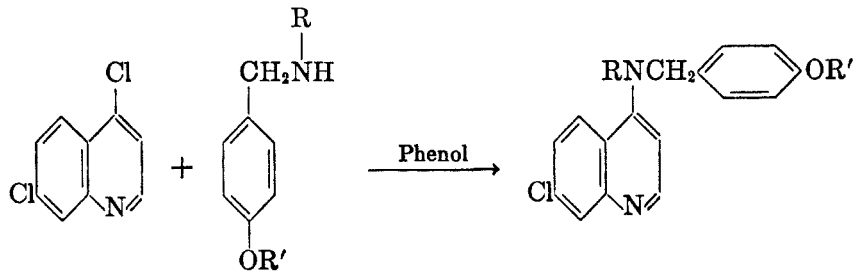
OR

(I), *p*-OCH_3
(II), *o*-OCH_3
(III), *p*-OH
(IV), *o*-OH

p-Hydroxybenzylamine (3) was too unstable under the conditions required for such condensations to give a product other than a resin.

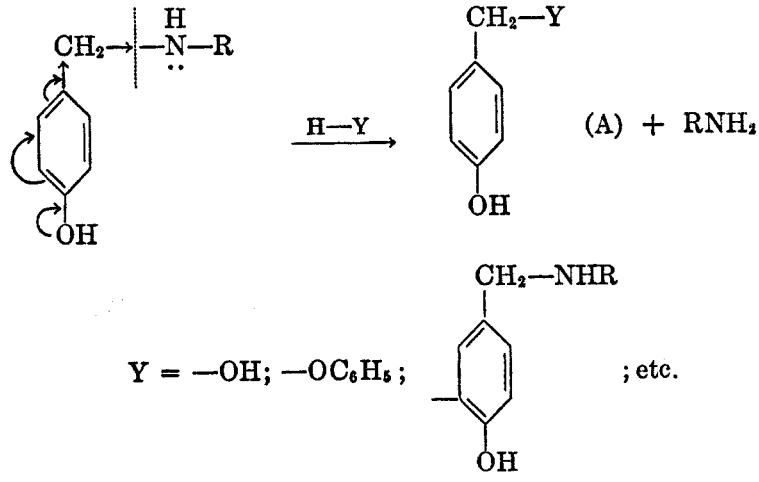
In some simple experiments designed to check the lability of the benzyl-to-nitrogen bond in these *ortho*- and *para*-hydroxybenzylamines, it was found that ammonia or methylamine is readily lost when water solutions of such compounds are heated for a short time. In the earlier communication it was observed that such decompositions are experienced when these amines are heated alone (1).

4,7-Dichloroquinoline was condensed with *p*-methoxy-N-methylbenzylamine to give a low yield of (V) and with *p*-hydroxybenzylamine to give a trace of (VI). Most of the *p*-hydroxybenzylamine decomposed to give off ammonia in this latter reaction. *p*-Hydroxy-N-methylbenzylamine formed only resins in such attempted condensations.



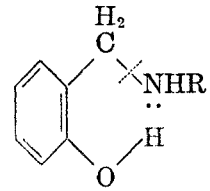
	R	OR′
(V)	CH_3	OCH_3
(IV)	H	OH

It seems evident that the *ortho*- and *para*-hydroxybenzylamines are not promising compounds for such condensations because of the ease with which they undergo the following types of decomposition,



The products (A) are insoluble resin-like substances probably of the phenol-formaldehyde type, when the *ortho*- and *para*-hydroxybenzylamines undergo

self-condensation. The presence of the hydroxyl group in the *ortho* or *para* position would of course be expected to labilize this benzyl-to-nitrogen bond through a mesomeric (resonance) effect transmitted along the side chain by an inductive effect. The fact that the *ortho*-hydroxy compounds seem to be the more unstable in this respect (1) can probably be ascribed to an additional "ortho" effect operating through chelation to aid in labilizing the benzyl-to-nitrogen bond.



Preliminary studies of the pyrimidines (I), (II), (III) and (IV) showed them to be almost devoid of activity in avian malaria.[1]

Acknowledgment. The author appreciates very much a research grant from Parke, Davis and Company of Detroit, Michigan, which aided in the completion of this investigation.

EXPERIMENTAL[2]

2-Amino-4-(N'methylbenzylamino)pyrimidines

(I) *p-Methoxy* and (II) *o-Methoxy.* The pyrimidines (I) and (II) were prepared by refluxing for three hours mixtures of 8.5 g. (0.057 mole) of *p*-methoxy-N-methylbenzylamine and *o*-methoxy-N-methylbenzylamine (1), respectively with 6.5 g. (0.05 mole) of 2-amino-4-chloropyrimidine in 100 ml. of water and 10 ml. of acetone. After the first thirty minutes of heating, all of the starting materials had dissolved. The solutions were cooled in an ice-bath and made strongly basic with 10% sodium hydroxide. The colorless precipitates were recrystallized twice from alcohol and water.

(III) *p-Hydroxy* and (IV) *o-Hydroxy.* The pyrimidines (III) and (IV) were prepared using the same conditions except that the *p*-hydroxy and *o*-hydroxy-N-methylbenzylamines were introduced as their hydrochlorides (1). To isolate the products the solutions were made strongly basic with conc'd. ammonium hydroxide to give almost colorless precipitates. The pyrimidine (III), 7 g., was recrystallized from 200 ml. of boiling 95% alcohol. It was found it could also be recrystallized from dioxane. This product was quite insoluble in cold benzene, acetone, or absolute alcohol.

Pyrimidine (IV) was insoluble in absolute alcohol, methyl alcohol, benzene, acetone, water-alcohol, chloroform, or chloroform-alcohol. It was recrystallized from boiling isopropyl alcohol (2 g. in 100 ml.) to give pale, salmon-colored needles.

Attempts to condense p-hydroxybenzylamine with 2-amino-4-chloropyrimidine. When the conditions outlined in the above syntheses were applied using the free base, *p*-hydroxybenzylamine (3), only a high-melting resin resulted and ammonia was detected in the hot residual reaction mixture when sodium hydroxide was added. The reaction was repeated under the same conditions, except that the *p*H of the solution was held between 3.5 and 6

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[1] We are indebted to Drs. L. L. Coggeshall and Richard J. Porter of the University of Michigan for the antimalarial testing of these substances.

[2] Micro-Kjeldahl analyses for nitrogen were determined by the Parke, Davis and Company Research Laboratories, Detroit, Mich.

by an initial addition of hydrochloric acid followed by periodic additions of sodium carbonate solution as the reaction mixture became more acidic on continued heating. The only products isolated were a resin and a small amount of the starting *p*-hydroxybenzylamine.

Heating water solutions of hydroxybenzylamines. One-gram samples of *p*-hydroxybenzylamine, *p*-hydroxy-N-methylbenzylamine, and *o*-hydroxy-N-methylbenzylamine were boiled for five minutes in dilute hydrochloric acid, the solutions made basic with sodium bicarbonate and boiled for an additional five minutes. In all three cases the odor of ammonia or methylamine was detected during the latter operation. Distillation gave clear distillates from which ammonium chloride and methylamine hydrochloride, respectively, were isolated after neutralization with hydrochloric acid and evaporation. When a water solution of *p*-hydroxybenzylamine was boiled for five minutes the solution became cloudy and ammonia was evolved.

Condensation of 4, 7-Dichloroquinoline with Benzylamines

(a) *With p-methoxy-N-methylbenzylamine.* A mixture of 4.5 g. of *p*-methoxy-N-methylbenzylamine, 6.34 g. of 4,7-dichloroquinoline, and 40 g. of phenol was heated at 100° for four hours. The cooled mixture was poured into 600 ml. of water containing 17 g. of sodium hydroxide. The precipitated thick oil was extracted with ether and the ether layer washed with water, dried, and evaporated. Addition of low-boiling petroleum ether followed by cooling caused slow formation of colorless crystals which were recrystallized from 90% alcohol to give (V).

Longer heating for fifteen hours using the above quantities gave about the same yield of (V). Attempts to carry out the condensation in absolute alcohol at *p*H 3.5 to 6 gave none of (V); most of the 4,7-dichloroquinoline was recovered unchanged.

(b) *With p-hydroxy-N-methylbenzylamine hydrochloride.* Attempted condensations with this amine hydrochloride in water and acetone, in pyridine, in *n*-propyl alcohol, or ethyl alcohol and water gave only resin-like products and unchanged 4,7-dichloroquinoline.

(c) *With p-hydroxybenzylamine.* A mixture of 12.3 g. of *p*-hydroxybenzylamine, 19.3 g. of 4,7-dichloroquinoline, and 50 g. of phenol was heated at 100° for four hours. A colorless solid appeared in the solution at the end of the first hour. The reaction mixture was cooled and 150 ml. of dry acetone and 70 ml. of dry ether added, and 6.0 g. of a white solid was filtered from the mixture. Ninety per cent of this was proved to be ammonium chloride. The residual phenol-ether-acetone solution was treated with an absolute alcohol solution of hydrogen chloride to give 6.4 g. of mixed amine hydrochlorides. This product was dissolved in water and neutralized with sodium bicarbonate to give a small amount of a gray material which after two recrystallizations from a mixture of absolute alcohol, benzene, and petroleum ether gave light gray crystals of (VI).

SUMMARY

1. *p*-Methoxy, *o*-methoxy, *o*-hydroxy, and *p*-hydroxy-N-methylbenzylamines have been condensed with 2-amino-4-chloropyrimidine to give the corresponding 2-amino-4-(N′-methylbenzylamino)pyrimidines.

2. *p*-Methoxy-N-methylbenzylamine was condensed with 4,7-dichloroquinoline to give 4-(N′-methyl-*p*-methoxybenzylamino)-7-chloroquinoline.

3. *p*-Hydroxybenzylamine could not be condensed with 2-amino-4-chloropyrimidine and only low yields resulted from its reaction with 4,7-dichloroquinoline. No identifiable product could be isolated from an attempted condensation of *p*-hydroxy-N-methylbenzylamine with this latter heterocyclic chloride.

4. The low yields obtained in certain of these condensations have been shown

to be the result of the lability of the benzyl-to-nitrogen bond in these *ortho* and *para* substituted benzylamines.

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