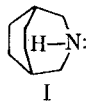
Potential Anti-Infective Agents I

Quinoline, Phenolic, and β-Aminoketone Derivatives

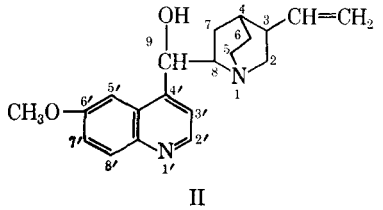
By ROBERT ARMEN MAGARIAN* and W. LEWIS NOBLES

Mannich bases were prepared from quinolinols, isoquinolinols, phenols, biphenols, and ketones in order to have their antimicrobial properties evaluated.

THE USE OF 3-azabicyclo[3.2.2]nonane (I), also known as AZBN, in the Mannich reaction was reported by Blanton and Nobles in 1962 (1). In biological screening, some of these Mannich bases were found to possess marked antimicrobial activity (2). As an extension of this study, AZBN, along with other bicyclic and heterocyclic amines, was condensed with moieties of known anti-infective agents utilizing the Mannich reaction (3) in order to study their antimicrobial properties, *i.e.*, antimalarial, antiamebic, and related effects. Quinine (II), a quinolylcarbinolamine containing a methoxy group on the quinoline nucleus linked by a secondary carbinol to a quinuclidine ring bearing a vinyl group, is an antimalarial that has been utilized since the year 1630 (4). This structure (II) served to provide the fountainhead of ideas for this work when a search of the literature revealed that many known anti-infectives have resulted from condensation of quinoline and phenolic compounds with aminomethyl moieties. Since AZBN is a bicyclic amine, it is conceivable that this amine can be useful—along with other bicyclic and heterocyclic amines—in place of the quinuclidine moiety in quinine. With this in mind, a number of substituted phenols and compounds structurally related to quinine were synthesized; more specifically, the products were prepared by the condensation of quinolinols, isoquinolinols, phenols, biphenols, and ketones with 37% aqueous formaldehyde (formalin), and cyclic amines.



I



II

Quinine (6′-methoxy-3-vinyl-9-rubanol)

DISCUSSION

The *o*- and *p*-hydrogens in phenols are sufficiently active to react in the Mannich reaction (5). From 8-quinolinol and 5-isoquinolinol (Table I), mono- and disubstituted products are expected, while only a mono-substituted product is obtainable with 5-chloro-8-quinolinol. Bruson (6), Burckhalter and associates (7), and Burke (8) have carried out Mannich reactions with phenols in which an *ortho* or *para* position was blocked by a chloro or bromo group. From the reaction of equimolar amounts of 2-phenylphenol, formaldehyde, and diethylamine, Burckhalter (9) was able to prove that the Mannich condensation takes place preferentially in the *ortho* position as compared to the *para* position.

It is interesting to note that the disubstituted Mannich product of 8-quinolinol (compound *2*, Table I) was not obtainable when 8-quinolinol was refluxed in absolute ethanol with 2 moles each of formaldehyde and AZBN. This disubstituted compound could only be obtained when equimolar amounts of formaldehyde and AZBN were reacted with the monosubstituted Mannich product III in absolute ethanol.

The solubility of aminomethylphenols in dilute alkali has served also as an aid in the confirmation of structure. Burckhalter and co-workers (7, 9), reported that 4-phenyl, 4-alkyl, or 4-halo-substituted 2-(dialkylaminomethyl) phenols are insoluble in 5% sodium hydroxide solution at room temperature, whereas the isomeric and analogous 4-(dialkylaminomethyl) phenols are soluble. The work of Julia and Tchernoff (10) is in agreement with that of Burckhalter and associates. They concluded that solubility in alkali apparently depends on the position of the amino group; the phenolic properties of the compound are possibly masked by the amino groups.

Millon's test has been utilized to identify an unsubstituted *ortho* position in phenolic derivatives (9). This test is used with monohydroxy phenols, tyrosine, tyrosine-containing proteins, phenolic acids, and other compounds that have a phenolic group with an open *ortho* position (11). The procedure involves the addition of 50 mg. of the phenolic derivative to 1 ml. of Millon's reagent. The test tube is placed in a beaker of water and heated to boiling. A red color indicates an open *ortho* position. (See Table II.)

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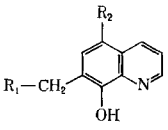
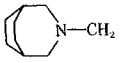
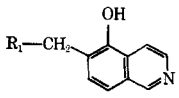
TABLE I—MANNICH BASES (QUINOLINOL AND ISOQUINOLINOL)

No.	R_1	R_2	Yield, %	M.p.,[a] °C.	Formula	Anal.[b] C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
											
1	AZBN	H	80	130–132[c]	$C_{18}H_{22}N_2O$	76.56	76.61	7.85	7.88	9.92	9.88
2	AZBN		76	156–158[d]	$C_{27}H_{37}N_3O$	77.28	77.11	8.89	8.90	10.02	10.24
3	AZBN	Cl	73	112–114[e]	$C_{18}H_{21}ClN_2O$[g]	68.24	68.05	6.68	6.61	8.84	8.64
											
4	AZBN	...	30	186.5–188[f]	$C_{18}H_{22}N_2O$	76.56	76.82	7.85	8.85	9.92	9.76

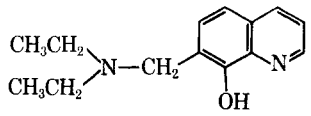
[a] Melting points are corrected. [b] Microanalyses were conducted by Alfred Bernhardt Microanalytisches Laboratorium, Max-Planck-Institut fur Kohlenforschung, Mulheim (Ruhr), Germany. [c] Recrystallized from absolute ethanol–water; [d] pyridine–water; [e] acetone; [f] absolute ethanol. [g] *Anal.*—Calcd. for Cl: 11.19. Found: 11.06.

8-Quinolinols have been found to be effective against bacteria (12, 13), and considerable evidence points to direct antiamebic activity by compounds of this type (13). One such compound is shown in structure III (14).

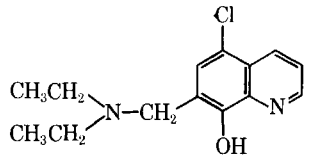
Various 7-(mono- and di-alkylaminomethyl)-8-quinolinols have also been prepared and evaluated by others as amebicides in the hope that the introduction of this solubilizing group would confer promising activity against amebic hepatitis (13–19). Although this new type of 8-quinolinol conferred only partial suppression of the hepatic lesion in hamsters (13), the activity of many of these compounds *in vitro* and in experimental intestinal amebiasis is equivalent to or exceeds that of the clinically-used iodinated 8-quinolinols (13, 18). One of the most promising members of this series is 5-chloro-7-diethylaminomethyl-8-quinolinol (IV) which was synthesized by Burckhalter and co-workers (14) and was found to be effective in human intestinal amebiasis (13).

There is a possibility that such derivatives could also be antifungal, since quinoline derivatives frequently possess such a property. This fact led to the preparation of the compounds in Table I. The effectiveness of diallylbiphenols, biphenols, and phenolic derivatives as medicinal agents was established by Burckhalter (7) when he found that certain α-dialkylamino-*o*-cresols (V, VI) possessed antimalarial activity. This work aroused interest in the synthesis of derivatives using various amine components along with the phenolic-types mentioned above in the Mannich reaction.

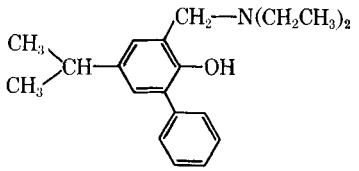
The products shown in Tables III, IV, V, and VI possibly offer the basis for a good study in structure–activity relationship, since they can be viewed as compounds that resemble 2,2′-diallyl-4,4′-biphenol (VII) with or without all the functional groups. The antibacterial activity of the Mannich bases derived from *p*-nitroacetophenone (20) led to the preparation of four β-aminoketones (Table VII) to be tested for possible anti-infective activity.



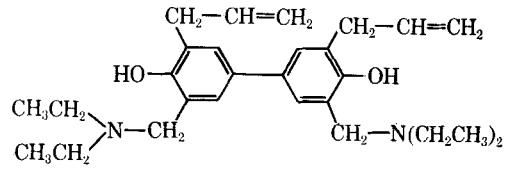
III



IV



V



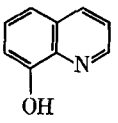
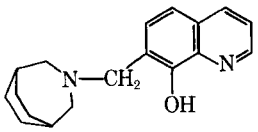
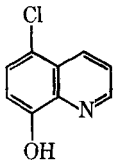
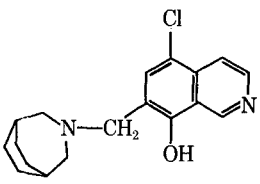
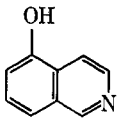
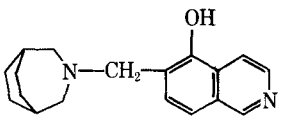
VI

Also, there was interest in seeing what activity the 3-azaspiro[5.5]undecane may possess, since Grogan (21) and co-workers have prepared a number of different azaspirane derivatives that were found to be of interest in medicinal chemistry.

EXPERIMENTAL

Experimental Results—The procedure of Blanton

TABLE II—MANNICH BASES (DIALLYLBIPHENOLS)

Compd.	Solubility in 5% Sodium Hydroxide	Millon's Test (Color)
	Soluble	Positive—blood red
	Insoluble	Negative—dark green
	Soluble	Positive—dark red
	Insoluble	Negative—light orange
	Soluble	Positive—blood red
	Insoluble	Negative—light orange

and Nobles (1) was essentially followed, except that 37% aqueous formaldehyde (formalin) was employed rather than paraformaldehyde and the amine hydrochloride was used only in the synthesis of the β-aminoketones. The starting materials were available commercially.[1]

RESULTS AND DISCUSSION

Conclusions regarding the reactants used were drawn from this study based on the reaction conditions employed. The phenolic and quinolinolic derivatives reacted with facility when the free amine was used; however, Mannich products were virtually impossible to obtain when the amine hydrochloride was used. For example, 4,4′-biphenol and 3-azabicyclo[3.2.1]octane hydrochloride were refluxed together with 37% aqueous formaldehyde; instead of isolating the Mannich product, the starting materials were obtained. The results were similar with 4-phenylphenol. Conversely, the Mannich ketones were relatively easy to obtain when the amine hydrochloride was used. If the free base were used, however, the ketonic product was not isolated; when AZBN, as the free base, was refluxed with *p*-nitroacetophenone and formalin, a novel di-substituted substance was isolated (22).

Aqueous formaldehyde (37%) was employed in all reactions and it was found to be as effective as paraformaldehyde; the latter appears more often in the literature when the Mannich reaction is discussed. The reason that paraformaldehyde is used more often may be attributed to its use with organic solvents, whereas a condensation reaction involving 37% aqueous formaldehyde is ordinarily carried out by shaking or stirring the reactants in the absence of an organic solvent (3). When aqueous formaldehyde was used with 2-allyl-4-methylphenol and 1-(*p*-chlorophenyl)-2-methylpiperazine in only 10 ml. of absolute ethanol as solvent, the desired Mannich base was not isolated in spite of shaking, stirring, and finally refluxing for 2.5 hr. Instead, a bis-amine (VIII) was isolated as the product. The white crystalline solid was thus obtained in 70% yield and had a melting point of 162–164° (corrected). Recrystallization from acetone–water resulted in a product melting at 164–166° (corrected). The conclusion that the product was a bis-amine was based on elemental analyses and infrared spectral data. The following analytical values were obtained.

Anal.—Calcd. for CHN: C, 63.79; H, 6.98; N, 12.93. Found: C, 63.94; H, 6.91; N, 12.12.

It is not uncommon to find bis-amines as products in the Mannich reaction (3). Other bis-type Mannich products have also been reported. The isolation of a methylene-bis-indanedione (IX) involving indanedione, amine, and formaldehyde has been accomplished in this laboratory by Blanton, Magarian, and Varma with secondary amines of varying strength (23). Also, Sam and Thompson (24) isolated a methylene-bis-thiaindanone (X).

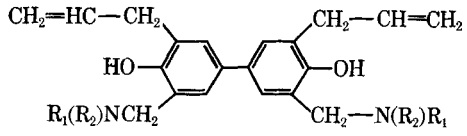
Absolute ethanol was employed in all the reactions with aqueous formaldehyde, and the latter did not appear to encumber the reaction. Also paraformaldehyde is normally used in the synthesis of ketonic Mannich bases (Table VII); however, aqueous formaldehyde was used and the yields were relatively good.

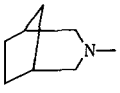
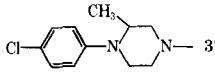
The Mannich products in most cases were easy to obtain, but, in nearly all instances exclusive of the ketonic Mannich bases, the products were difficult to recrystallize. Perhaps this could be attributed to a complex mixture of many products. In some cases, the reaction products (compounds *15* and *17*) obtained from these phenolic compounds were difficult to crystallize. They were dissolved in ethyl ether and extracted with 10% aqueous hydrochloric acid solution. The aqueous solution was neutralized with 10% sodium carbonate solution which was then extracted with ethyl ether and the extract dried over anhydrous magnesium sulfate. The drying agent was removed by filtration and anhydrous hydrogen chloride was bubbled through the anhydrous ether solution to yield a solid. In other instances (compound *19*), 20% aqueous hydrochloric acid provided the right environment to form

[1] The biphenol, 2,2′-diallyl-4,4′-biphenol, was supplied through the courtesy of Dow Chemical Co., Midland, Mich., and the amine, 3-azabicyclo[3.2.1]octane hydrochloride, was prepared by N. D. Potti of this laboratory.

a crystalline hydrochloride from a sticky residue. In another situation a viscous residue (compound *23*) was dissolved in ethyl ether and anhydrous hydrogen chloride bubbled through the solution. This precipitated an oil that crystallized from acetone when placed in the refrigerator overnight.

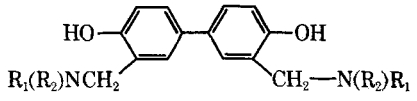
TABLE III—MANNICH BASES (DIALLYLBIPHENOLS)

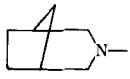
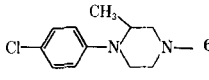
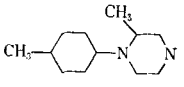


No.	R1, R2	Yield, %	M.p.,[a] °C.	Formula	Anal.[b] C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
5	AZBN	38	183–185[c]	$C_{36}H_{48}N_2O_2$	79.96	80.03	8.95	9.16	5.18	5.11
6		50	104–106[d]	$C_{32}H_{44}N_2O_2$	78.65	79.24	9.07	9.20	5.73	5.80
7		38	151–152[e]	$C_{34}H_{44}N_2O_2$	79.65	79.79	8.65	8.78	5.46	5.71
8		37	211–212.5[f]	$C_{42}H_{48}Cl_2N_4O_2$	70.87	71.62	6.80	6.92	7.87	8.03
9		39	141–142[e]	$C_{40}H_{56}N_2O_2$	80.49	80.73	9.46	9.53	4.69	4.77

[a] Melting points are corrected. [b] Microanalyses were conducted by Alfred Bernhardt Microanalytisches Laboratorium, Max-Planck-Institut fur Kohlenforschung, Mulheim (Ruhr), Germany. [c] Recrystallized from pyridine–water; [d] isopropanol; [e] absolute ethanol–water; [f] benzene–absolute ethanol.

TABLE IV—MANNICH BASES (BIPHENOLS)

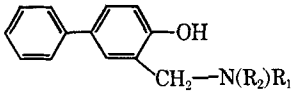
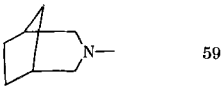
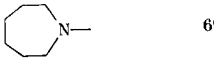
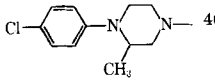
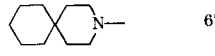


No.	R1, R2	Yield, %	M.p.,[a] °C.	Formula	Anal.[b] C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
10	AZBN	63	241–242[c]	$C_{30}H_{40}N_2O_2$	78.22	78.05	8.75	8.84	6.08	6.22
11		86	198.5–200.5[d]	$C_{28}H_{36}N_2O_2$	77.74	77.59	8.39	8.41	6.48	6.72
12		63	116–118[e]	$C_{26}H_{36}N_2O_2$	76.43	76.72	8.88	9.05	6.86	7.16
13		56	132–134[f]	$C_{22}H_{28}N_2O_2$	74.97	75.15	8.01	7.92	7.95	8.26
14		66	275–277[d]	$C_{36}H_{40}Cl_2N_2O_2$	68.45	68.38	6.38	6.46	8.87	8.75
15		98	271.5–273.5[f]	$C_{38}H_{46}N_4O_2$	77.25	77.53	7.85	8.00	9.48	9.70
16		86	220–222[d]	$C_{34}H_{48}N_2O_2$	79.02	78.88	9.36	9.21	5.42	5.62

[a] Melting points are corrected. [b] Microanalyses were conducted by Alfred Bernhardt Microanalytisches Laboratorium, Max-Planck-Institut fur Kohlenforschung, Mulheim (Ruhr), Germany. [c] Recrystallized from pyridine; [d] pyridine–absolute ethanol; [e] isopropanol; [f] pyridine–water.

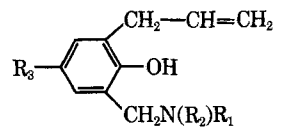
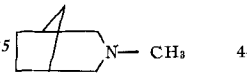
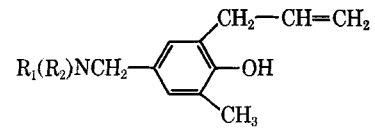
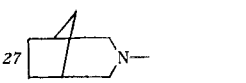
The β-amino ketones were, in general, prepared by refluxing the appropriate ketone, 37% aqueous formaldehyde, and amine hydrochloride in absolute ethanol. The solvent was removed on a rotary

TABLE V—MANNICH BASES (PHENYLPHENOLS)

No.	R_1, R_2	Yield, %	M.p.,[a] °C.	Formula	Anal. C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
										
17	AZBN	65	133–134.5[c]	$C_{21}H_{25}NO$	82.04	82.09	8.20	8.19	4.56	4.61
18		59	102–104[c]	$C_{20}H_{23}NO$	81.87	81.65	7.90	7.86	4.77	5.03
19		69	182.5–184.5[d,f]	$C_{19}H_{24}ClNO$	71.77	71.60	7.61	7.91	4.40	3.79
20		46	147.5–149.0[e]	$C_{24}H_{25}ClN_2O$	73.36	73.25	6.41	6.38	7.13	7.48
21		67	99–101	$C_{23}H_{29}NO$	82.34	82.15	8.71	8.56	4.17	4.18
										
22	AZBN	33	120–122[c]	$C_{21}H_{25}NO$	82.05	82.08	8.20	8.18	4.56	4.61

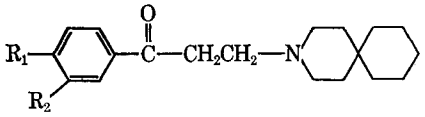
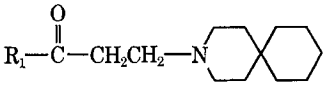
[a] Melting points are corrected. [b] Microanalyses were conducted by Alfred Bernhardt Microanalytisches Laboratorium, Max-Planck-Institut fur Kohlenforschung, Mulheim (Ruhr), Germany. [c] Recrystallized from absolute ethanol; [d] isopropanol, [e] absolute ethanol–water. [f] Hydrochloride.

TABLE VI—MANNICH BASE (2-ALLYLPHENOL DERIVATIVES)

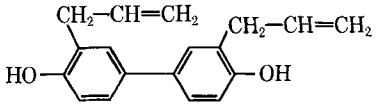
No.	R_1, R_2	R_3	Yield, %	M.p.,[a] °C.	Formula	Anal.[b] C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
											
23	AZBN	H	34	218–220[c,f]	$C_{18}H_{26}ClNO^g$	68.21	68.56	8.58	8.68	4.49	4.25
24	AZBN	CH_3	64	92–94[d]	$C_{19}H_{27}NO$	79.95	79.89	9.54	9.52	4.91	4.93
25		CH_3	44	188–188.5[e,f]	$C_{18}H_{26}ClNO$	70.22	70.49	8.51	8.61	4.55	5.20
											
26	AZBN		40	236.5–237[d,f]	$C_{19}H_{28}ClNO$	70.89	71.20	8.77	8.64	4.35	4.26
27			38	220.5–221.5[e,f]	$C_{19}H_{26}ClNO$	70.22	70.19	8.51	8.52	4.55	4.59

[a] Melting points are corrected. [b] Microanalyses were conducted by Alfred Bernhardt Microanalytisches Laboratorium, Max-Planck-Institut fur Kohlenforschung, Mulheim (Ruhr), Germany. [c] Recrystallized from methanol–ether; [d] absolute ethanol; [e] absolute ethanol–ether. [f] Hydrochloride. [g] Calculated for 0.5 mole of water.

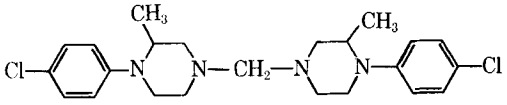
TABLE VII—MANNICH BASES (β-AMINO KETONES)

No.	R_1	R_2	Yield, %	M.p.,[a] °C.	Formula	Anal.[b] C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
											
28	NO_2	H	59	222.5–224.5	$C_{19}H_{27}ClN_2O_3$	62.18	62.11	7.42	7.42	7.63	7.49
29	F	H	97	216.5–218.5	$C_{19}H_{27}FClNO$	67.13	67.32	8.00	8.30	4.12	4.15
30	H	NO_2	41	220.5–222	$C_{19}H_{27}ClN_2O_3$	62.18	62.33	7.42	7.45	7.63	7.80
											
31			93	220.5–222.5	$C_{17}H_{26}ClNOS$	62.25	62.54	7.99	8.06	4.27	4.13

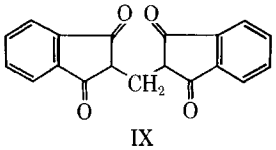
[a] Melting points are corrected. Mannich bases in this table were recrystallized from absolute ethanol. All compounds exist as the hydrochloride. [b] Microanalyses were conducted by Alfred Bernhardt Microanalytisches Laboratorium, Max Planck-Institut fur Kohlenforschung, Mulheim (Ruhr), Germany.



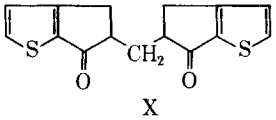
VII



VIII



IX



X

evaporator and the product was recrystallized from absolute ethanol. The reactions proceeded smoothly and the yields were consistently good. These Mannich products were easy to recrystallize in comparison with the phenolic derivatives.

Although the condensations in the Mannich reaction proceed much faster in the higher-boiling solvents, and the formation of certain by-products, obtained by prolonged heating in ethanol, is avoided (3), it is believed that the condensation in ethanol is less subject to side reactions associated with the instability of the aminoketone salts at the higher temperatures (25). The time required for a Mannich reaction depends, among other things, upon the nature of the starting materials and upon the boiling point of the solvent (3); it was found that these reactions in absolute ethanolic solution yielded the desired products after the mixtures had been refluxed for 2–3 hr. An increase in reflux time was of no avail in producing better yields.

Biological Evaluation—When the results of the antibacterial screening tests are available, they will be presented in connection with a subsequent article in this series.

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