[CONTRIBUTION FROM THE LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID CO.]

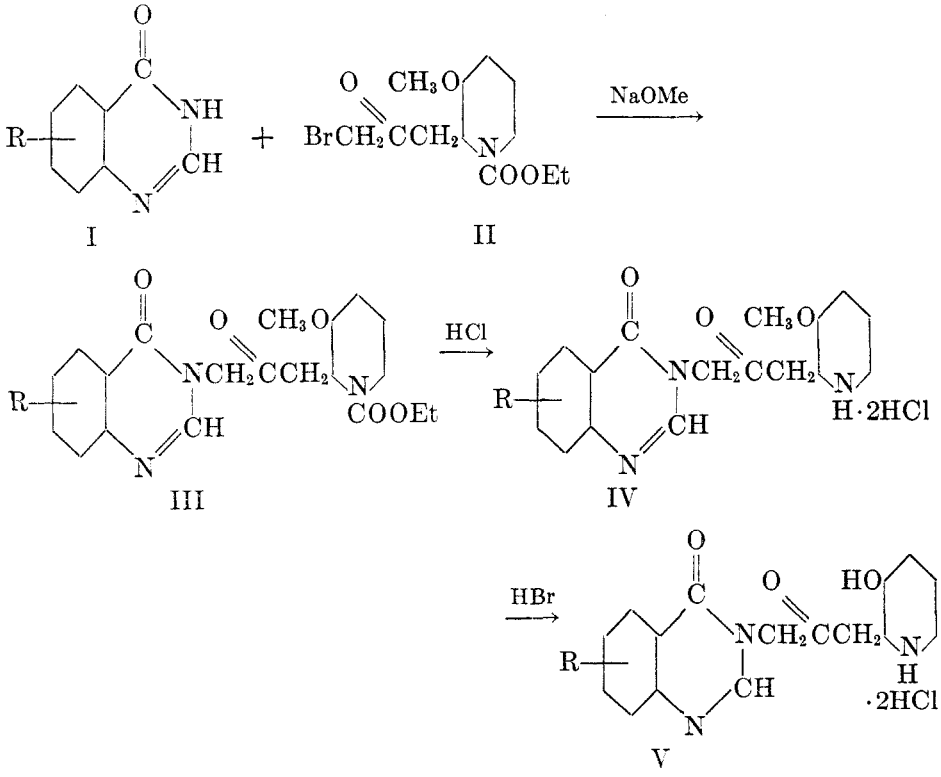
AN ANTIMALARIAL ALKALOID FROM HYDRANGEA. XIV. SYNTHESIS OF 5-, 6-, 7-, AND 8-MONOSUBSTITUTED DERIVATIVES

B. R. BAKER, ROBERT E. SCHAUB, JOSEPH P. JOSEPH, FRANCIS J. McEVOY, AND JAMES H. WILLIAMS

Received September 27, 1951

The use of the Hydrangea alkaloid as an antimalarial entails certain disadvantages, namely, the high incidence of emesis (1) and the mediocre chemotherapeutic index (2). The synthesis of the *dl*-alkaloid recently described (3) has been found to be adaptable to the preparation of derivatives containing substituents in the benzene ring (V), twenty of which are described herein.[1]

Three of the most common substituents employed on the aromatic system of antimalarials have been chloro, methoxy, and methyl. Since it was not unreasonable to suspect that there would be little or no correlation of activity of substituents placed on the aromatic system of the *dl*-alkaloid as compared to other antimalarials, a program was undertaken to synthesize all twelve derivatives with chloro, methoxy, or methyl in the 5-, 6-, 7-, or 8-positions.



[1] The biological data will be reported elsewhere by Dr. R. Hewitt and co-workers (2) as paper XIII of this series.

The key step in the preparation of these compounds involved the alkylation of the appropriately substituted 4-quinazolone, I, with the blocked side chain, II. The resultant products, III, were converted to the *dl*-alkaloid derivatives, V, by the two stage hydrolysis previously described (3).

The assay data[1] obtained with eleven of these compounds may be summarized roughly as follows:

1. Substitution in the 5-position of the 4-quinazolone nucleus doubled the chemotherapeutic index in all cases and activity was increased with the chloro and methyl.

2. Substitution in the 6-position increased activity but either decreased or did not change the chemotherapeutic index.

3. Substitution in the 7- or 8-positions decreased either activity or chemotherapeutic index or both.

The twelfth derivative, 8-methoxy, was not made in view of the above results. Derivatives containing five other groups were also synthesized. The 5-, 6-, or 7-bromo derivatives had antimalarial activity roughly the same of the corresponding chloro derivatives, whereas 6- or 7-phenyl, 6- or 7-amino, 6-carboxy, or 7-carbomethoxy were inactive at twenty times the dosage used for the alkaloid.

Of the requisite substituted 4-quinazolones (I), nos. 1–8, 10–15, 20, 23, and 25 (Table I) were obtained by fusion of the appropriate anthranilic acid (VI) with formamide (4). In the case of nos. 9 and 16 corresponding anthranilamides (VII) were more readily available than the acids. Formamide fusion of these led

VI I

VII VIII

to tars instead of I. However, treatment of 4-phenylanthranilamide with hot formic acid led directly to 7-phenyl-4-quinazolone (no. 16). In contrast the same formic acid treatment of 6-methoxyanthranilamide gave the intermediate N-formyl derivative, VIII, which could be rapidly cyclized with dilute base to the desired 5-methoxy-4-quinazolone (no. 9).

In order to prepare the 6- and 7-amino derivatives of the *dl*-alkaloid (V) with

a minimum of side-reactions, the amine group was blocked by acetylation (nos. 19, 22) prior to condensation with the side chain, II. The N-acetyl was removed simultaneously in the first stage hydrolysis. Similarly, 6- and 7-carboxy were blocked by esterification (nos. 24, 26). The 7-carboxyl group was re-esterified after the two stage hydrolysis.

Acknowledgment: The authors are indebted to Miss E. Sherman for the many literature searches, Mr. Louis Brancone and staff for the microanalyses, and Messrs. Willard McEwen and John Poletto for large scale preparation of intermediates.

EXPERIMENTAL

3-Chloroanthranilic acid. To a stirred solution of 49.5 g. of 7-chloroisatin (5) in 485 cc. of 5% sodium hydroxide was added dropwise 73 cc. of 30% hydrogen peroxide over a period of 20 minutes. The temperature rose to 68°. After being stirred an additional 20 minutes the solution was clarified with Norit, acidified to *p*H 4, and the product collected; yield, 36.3 g. (78%), m.p. 186–188°. Recrystallization from dilute methanol gave yellow crystals, m.p. 187–188°.

Anal. Calc'd for $C_7H_6ClNO_2$: C, 49.0; H, 3.49; N, 8.16.
Found: C, 49.3; H, 3.93; N, 8.33.

8-Chloro-4-quinazolone. A mixture of 35.2 g. of 3-chloroanthranilic acid and 31 cc. of formamide was heated in a bath at 130 for 45 minutes and at 175° for 75 minutes (4). The hot semi-solid mass was slurried with 50 cc. of Cellosolve and poured into 500 cc. of cold water; yield, 31.1 g. (84%), m.p. 279–281°. Additional compounds prepared in this manner are listed in Table I.

2-Amino-6-methoxybenzonitrile. A mixture of 25 g. of 2-nitro-6-methoxybenzonitrile (23), 150 cc. of Methyl Cellosolve, and 2 g. of 10% palladium-charcoal was shaken with hydrogen at 2–3 atm. until reduction was complete (30 minutes). The filtered solution was evaporated to dryness *in vacuo*. Recrystallization from alcohol afforded 14.3 g. (69%) of white crystals, m.p. 139–141°.

Friedländer (24) prepared this compound, m.p. 141°, by stannous chloride reduction but recorded no yield.

2-Formylamino-6-methoxybenzamide. A solution of 3.0 g. of 6-methoxyanthranilamide (24) in 30 cc. of 89% formic acid was heated on the steam-bath for 2½ hours, then evaporated to dryness *in vacuo*. The hot residue was crystallized from a small volume of water; yield, 2.5 g. (71%), m.p. 174–177°. Recrystallization of a similar preparation from water gave white crystals, m.p. 175–176°.

Anal. Calc'd for $C_9H_{10}N_2O_3$: C, 55.7; H, 5.25; N, 14.5.
Found: C, 55.8; H, 5.55; N, 14.6.

5-Methoxy-4-quinazolone. A mixture of 2.5 g. of 2-formylamino-6-methoxybenzamide and 39 cc. of 3% sodium hydroxide was warmed a few minutes to complete solution. Clarification with Norit, acidification with acetic acid, and ice-cooling gave 2.0 g. (88%) of white crystals, m.p. 204–206°. Recrystallization from water raised the m.p. to 208–209°.

Anal. Calc'd for $C_9H_8N_2O_2$: C, 61.4; H, 4.54; N, 15.9.
Found: C, 61.5; H, 4.60; N, 15.7.

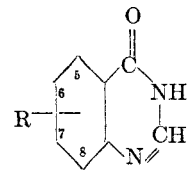
7-Phenyl-4-quinazolone. A solution of 5 g. of 4-phenylanthranilamide (25) in 50 cc. of 89% formic acid was heated on the steam-bath for two hours, filtered, and the filtrate evaporated to dryness *in vacuo*. The solid residue was triturated with 100 cc. of hot water, the mixture cooled, and the product collected; yield, 4.8 g. (94%), m.p. 259–261°. A sample was recovered unchanged when reprecipitated from dilute alkali showing that ring closure to the 4-quinazolone had taken place during the formic acid treatment. Recrystallization of a sample from xylene gave white crystals, m.p. 261–262°.

Anal. Calc'd for $C_{14}H_{10}N_2O$: C, 75.7; H, 4.50; N, 12.6.
Found: C, 76.1; H, 5.00; N, 12.3.

6-Amino-4-quinazolone. A suspension of 3 g. of 6-nitro-4-quinazolone (19) and 1 g. of 10% palladium-charcoal in 50 cc. of Methyl Cellosolve was shaken with hydrogen at 2-3

TABLE I

SUBSTITUTED 4-QUINAZOLONES



NO.	R[a]	YIELD, %	M.P., °C.	LIT. M.P., °C.	REFERENCE TO ANTHRANILIC ACID
1	5-Cl	79	210	[b]	(6)
2	6-Cl	92	259–261	263 (7)	(7)
3	7-Cl	72	242–245	254 (8)	(6)
4	8-Cl	84	299–300[c]	[d]	[e]
5	5-Me	46	210–212	224 (9)	(10)
6	6-Me	75	242–245	255 (4)	(10)
7	7-Me	33	239–240	239 (4)	(10)
8	8-Me	56	243–245	251 (11)	(10)
9	5-CH_3O	88	208–209	[e]	
10	6-CH_3O	57	242–245	255 (12)	(13)
11	7-CH_3O	21	238–240[f,g]	265 (26)	(14)
12	5-Br	78	237–238d.[f]	[h]	(15)
13	6-Br	92	261–267	273 (16)	(17)
14	7-Br	68	258–259[c]	[i]	(15)
15	6-C_6H_5	89	229–230	[k]	(18)
16	7-C_6H_5	94	261–262	[e]	
17	6-NO_2[l]	84	275–277d.	284d. (19)	
18	6-NH_2[e]	95	302–304d.	318 (19)	
19	6-AcNH[e]	82	324–326	335 (19)	
20	7-NO_2	86	263–266d.	276d. (20)	(21)
21	7-NH_2	86	306d.	[e]	
22	7-AcNH	65	302–303	[e]	
23	6-COOH	90	>300d.	>300d. (22)	(22)
24	6-$COOCH_3$	80	219	[e]	
25	7-COOH	86	>300d.	>300d. (22)	(22)
26	7-$COOCH_3$	86	252–254	[e]	

[a] These compounds were made by fusion of the proper anthranilic acid with formamide as described for 8-chloro-4-quinazolone unless otherwise indicated. [b] *Anal.* Calc'd for $C_8H_5ClN_2O$: C, 53.2; H, 2.77; N, 15.5. Found: C, 53.3; H, 3.02; N, 15.9. [c] Recrystallized from Methyl Cellosolve. [d] *Anal.* Calc'd for $C_8H_5ClN_2O$: C, 53.2; H, 2.77; N, 15.5. Found: C, 53.1; H, 3.12; N, 14.9. [e] See experimental. [f] Recrystallized from Methyl Cellosolve—water. [g] Not pure. *Anal.* Calc'd for $C_9H_8N_2O_2$: C, 61.4; H, 4.54; N, 15.9. Found: C, 62.5; H, 4.82; N, 14.7. [h] *Anal.* Calc'd for $C_8H_5BrN_2O$: C, 42.7; H, 2.22; N, 12.4. Found: C, 42.5; H, 2.59; N, 12.7. [i] *Anal.* Calc'd for $C_8H_5BrN_2O$: C, 42.7; H, 2.22; N, 12.4. Found: C, 42.7; H, 2.47; N, 13.1. [j] Recrystallized from methanol. [k] *Anal.* Calc'd for $C_{14}H_{10}N_2O$: C, 75.7; H, 4.50; N, 12.6. Found: C, 75.6; H, 4.87; N, 12.3. [l] By nitration of 4-quinazolone (19).

atm. for 30 minutes when hydrogenation was complete. The mixture was diluted with 50 cc. of Methyl Cellosolve, heated to 95° to dissolve the separated product, and filtered hot.

Evaporation of the filtrate to dryness *in vacuo* and trituration of the residue with benzene gave 2.4 g. (95%) of product, m.p. 302–304° dec.

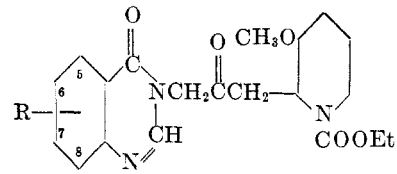
Bogert and Geiger (19) recorded m.p. 318° (corr.) when the reduction was performed with aqueous sodium sulfide. Attempts to duplicate this procedure gave infusible products.

Similarly, reduction of 4 g. of 7-nitro-4-quinazolone gave 2.9 g. (86%) of *7-amino-4-quinazolone*, m.p. 305–307° dec. Recrystallization from hot methanol by the addition of sufficient Methyl Cellosolve to cause solution afforded white crystals, m.p. 306° dec.

Anal. Calc'd for $C_8H_7N_3O$: C, 59.8; H, 4.35; N, 25.3.

Found: C, 59.8; H, 4.62; N, 25.8.

TABLE II



R[a]	YIELD, %	M.P., °C.	ANALYSIS					
			Calc'd			Found		
			C	H	N	C	H	N
6-Cl	40	124–125	57.0	5.70	9.98	57.3	5.96	10.3
7-Cl	21	125–126	57.0	5.70	9.98	56.8	5.99	10.3
8-Cl	26	153–154	57.0	5.70	9.98	57.0	5.90	10.2
6-Me	29	113–115	62.9	6.74	10.5	62.7	6.92	10.6
8-Me	24	143–145	62.9	6.74	10.5	62.9	6.96	10.2
6-CH_3O	34	102–103	60.4	6.47	10.1	60.1	6.35	10.2
6-C_6H_5	[b]	134–136	67.4	6.26	9.08	67.6	6.56	8.89
7-C_6H_5	[b]	114–116	67.4	6.26	9.08	67.5	6.51	9.08
6-$COOCH_3$	[b]	128–129	59.4	6.06	9.44	59.4	6.35	9.66

[a] These compounds were prepared by condensation of 1-carbethoxy-2-(γ-bromoacetonyl)-3-methoxypiperidine with the appropriate x-R-4-quinazolone in the presence of sodium methoxide as described for 4-quinazolone (3). Where necessary an equal volume of Methyl Cellosolve was added to dissolve the quinazolone in the 1 *N* methanolic sodium methoxide. Compounds 1, 5, 7, 9, 11–14, 17, 19, 20, 22, and 26 (Table I) failed to give crystalline products. These crude oils were hydrolyzed (See Table III).

[b] A sample of the crude oil crystallized after several months and the remainder was hydrolyzed directly (Table III).

6-Acetamino-4-quinazolone. A mixture of 3.4 g. of 6-amino-4-quinazolone and 75 cc. of acetic anhydride was refluxed for 40 minutes, then evaporated to dryness *in vacuo*. The residual acetate salt, m.p. 165°, was heated to boiling with 40 cc. of water during which the solid dissolved and the free base separated. The mixture was cooled in an ice-bath and the product collected; yield, 3.5 g. (82%), m.p. 324–326° dec.

Bogert and Geiger (19) recorded m.p. 335° (corr.) but gave no experimental details.

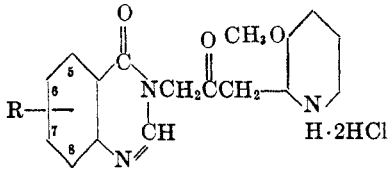
Similarly, acetylation of 2.7 g. of 7-amino-4-quinazolone resulted in 2.2 g. (65%) of white crystals of 7-acetamino-4-quinazolone, m.p. 302–303°, unchanged after recrystallization from water. It was found difficult to obtain consistent analytical values due to incomplete combustion.

7-Carbomethoxy-4-quinazolone. A mixture of 8.6 of g. 7-carboxy-4-quinazolone (22), 86 cc.

of methanol, and 8.6 cc. of 96% sulfuric acid was refluxed on the steam-bath for 17 hours, then poured into a mixture of 21 cc. of 15 *N* ammonium hydroxide and excess ice. The product was collected and washed with water; yield, 7.9 g. (86%), m.p. 244–246°. Recrystallization of a sample from methanol afforded white crystals, m.p. 252–254°.

Anal. Calc'd for $C_{10}H_8N_2O_3$: C, 58.9; H, 3.92; N, 13.7.
Found: C, 58.8; H, 4.45; N, 14.0.

TABLE III



R[a]	YIELD,[b] %	M.P., °C. DEC.	HYDRATE	ANALYSIS					
				Calc'd			Found		
				C	H	N	C	H	N
5-Cl	13	200	hemi	47.4	5.34	9.75	47.6	5.45	10.4
6-Cl	13	205–206	mono	46.3	5.45	9.54	46.1	5.36	9.85
7-Cl	7.3	209–210	hemi	47.4	5.34	9.75	47.3	5.70	9.56
8-Cl	7.5	209–211	hemi	47.4	5.34	9.74	47.2	5.65	10.2
5-Me	14	223	mono	51.5	6.43	10.0	51.9	6.22	10.5
6-Me	8.4	164–166	di	49.4	6.63	9.60	48.2	6.56	9.34
7-Me	13	229	hemi	52.6	6.33	10.2	52.7	6.58	10.2
8-Me	8.4	228–229	none	53.7	6.21	10.4	53.3	7.00	10.8
5-CH_3O	6.6	173–174	mono	49.5	6.19	9.64	49.0	6.26	10.0
6-CH_3O	7.9	165–168	di	47.7	6.40	9.28	48.1	6.70	9.70
7-CH_3O	8.0	221	mono	49.7	6.25	9.63	50.1	6.31	9.62
5-Br	8.5	211	none	43.6	4.71	8.99	43.4	4.98	9.00
6-Br	13	209	none	43.6	4.71	8.99	43.7	5.10	8.67
7-Br	18.7	216–217	mono	42.1	5.03	9.59	41.7	5.03	9.59
6-C_6H_5	15	207–208	mono	57.3	6.01	8.71	57.7	6.52	9.19
7-C_6H_5	16.4	232–233	hemi	58.4	5.92	8.89	58.7	6.16	8.97
6-NH_2[d]	12	118–120	hemi[c]	45.7	5.87	12.5	45.7	5.66	13.2
7-NH_2[d]	9	85	hemi	49.4	6.06	13.6	49.6	5.94	12.8
6-COOH[e]	8.1	180	mono	48.0	5.56	9.33	48.4	6.14	9.37
7-COOH[e]	6.7	224	none	50.0	5.32	9.72	50.7	6.05	8.94

[a] These compounds were prepared by 6 *N* hydrochloric acid hydrolysis of the compounds of Table II as described for 3-[β-keto-γ-(3-methoxy-2-piperidyl)propyl]-4-quinazolone dihydrochloride (3). [b] Yields based on original x-R-4-quinazolone. [c] Trihydrochloride. [d] N-Acetyl group removed during hydrolysis. [e] Carbomethoxy converted to carboxy during hydrolysis.

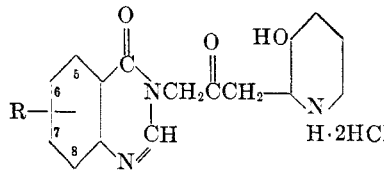
Similarly, *6-carbomethoxy-4-quinazolone* was obtained in 80% yield, m.p. 208–210° from the corresponding acid (22) except it was necessary to acidify the ammonia solution to *p*H 8 for crystallization of the product. Recrystallization from methanol with the aid of Norit gave white crystals, m.p. 219°.

Anal. Calc'd for $C_{10}H_8N_2O_3$: C, 58.9; H, 3.92; N, 13.7.
Found: C, 58.8; H, 4.20; N, 13.7.

3-[β-Keto-γ-(3-hydroxy-2-piperidyl)propyl]-7-carbomethoxy-4-quinazolone dihydrochloride. A solution of 315 mg. of 3-[β-keto-γ-(3-methoxy-2-piperidyl)propyl]-7-carboxy-4-quinazo-

lone dihydrochloride (Table III) in 4 cc. of 48% hydrobromic acid was refluxed ten minutes, then worked up in the usual manner (3). The residue left after evaporation of the absolute alcohol was dissolved in 10 cc. of methanol and treated with 0.6 cc. of acetyl chloride. After being refluxed for one hour, the solution was evaporated to dryness *in vacuo*. Trituration of the residue with 5 cc. of absolute alcoholic hydrogen chloride gave the product (see Table IV).

TABLE IV



R[a]	YIELD, %	M.P., °C. DEC.	HYDRATE	ANALYSIS					
				Calc'd			Found		
				C	H	N	C	H	N
5-Cl	56	223	hemi	45.9	5.02	10.0	46.0	5.35	10.1
6-Cl	46	255	mono	45.1	4.70	9.86	44.7	4.62	10.5
7-Cl	59	191–192	di	43.2	5.40	9.45	43.5	5.08	10.0
8-Cl	51	214–217	di	43.2	5.40	9.45	43.3	5.12	9.12
5-Me	31	225	mono	50.3	6.16	10.3	49.9	6.30	10.1
6-Me	43	165–167	di	48.1	6.37	9.90	47.0	6.35	9.80
7-Me	62	212–213	mono	50.3	6.16	10.3	49.7	6.13	10.5
8-Me	48	222–223	mono	50.3	6.16	10.3	50.6	5.87	10.7
5-CH_3O[b]	64	224	di	46.4	6.14	9.55	46.4	6.03	9.56
6-CH_3O[b]	73	196–198	di			9.55			9.20
7-CH_3O[b]	58	174	sesqui	47.4	6.08	9.75	47.7	5.89	9.47
5-Br	68	217	mono	40.8	4.67	8.92	40.6	4.57	8.93
6-Br	63	226	hemi	41.5	4.54	9.08	41.4	4.70	9.41
							35.6	4.26	
7-Br[c]	77	215–216	none	35.4	3.70	7.80	35.8	4.29	7.73
6-C_6H_5	66	75[d]	sesqui	55.3	5.86	8.80	55.0	6.08	8.57
7-C_6H_5	78	188–189[c]	none	49.0	4.64	7.79	49.5	5.66	7.73
6-NH_2	72	90	tetra[e]	38.7	6.27	11.2	38.7	5.59	11.1
7-NH_2	74	85	sesqui	46.2	6.07	13.4	46.6	6.27	12.9
6-COOH	87	[d]							
7-$COOCH_3$[f]	49	178–179	sesqui	47.1	5.66	9.16	47.4	5.70	9.15

[a] Prepared by 48% hydrobromic acid hydrolysis of the compounds in Table III as described for the *dl*-alkaloid (3). [b] Methoxyl analysis showed one methoxyl still present. 6-Methoxy-4-quinazolone is recovered unchanged by these hydrolysis conditions. [c] Dihydrobromide. [d] Amorphous. [e] Trihydrochloride: Calc'd: Cl, 21.4. Found: Cl, 21.5. [f] See experimental.

SUMMARY

The syntheses of twenty derivatives of the *dl*-form of the Hydrangea alkaloid containing one substituent on the benzene ring are described, fourteen of which are active antimalarials.

PEARL RIVER, N. Y.

REFERENCES

(1) COATNEY, COOPER, CULWELL, WHITE, AND IMBODEN, *J. Nat. Malaria Soc.*, **9**, 183 (1950).
(2) HEWITT, GILL, WALLACE, AND WILLIAMS, *Am. J. Trop. Med.*, in press.
(3) BAKER, SCHAUB, McEVOY, AND WILLIAMS, *J. Org. Chem.*, **17**, paper XII of this series.
(4) NIEMENTOWSKI, *J. prakt. Chem.*, [2] **51**, 564 (1895).
(5) BUCHMAN, SARGENT, MYERS, AND SENEKER, *J. Am. Chem. Soc.*, **68**, 2692 (1946).
(6) SENEAR, SARGENT, MEAD, AND KOEPFLI, *J. Am. Chem. Soc.*, **68**, 2695 (1946).
(7) ENDICOTT, ALDEN, AND SHERRILL, *J. Am. Chem. Soc.*, **68**, 1303 (1946).
(8) PRICE, LEONARD, AND CURTIN, *J. Am. Chem. Soc.*, **68**, 1305 (1946).
(9) GABRIEL AND THIEME, *Ber.*, **52**, 1079 (1919).
(10) MAYER, SCHÄFER, AND ROSENBACH, *Arch. Pharm.*, **267**, 571 (1929).
(11) FINDEKLEE, *Ber.*, **38**, 3542 (1905).
(12) SMITH, ELISBERG, AND SHERRILL, *J. Am. Chem. Soc.*, **68**, 1301 (1946).
(13) BACHMAN AND PICHA, *J. Am. Chem. Soc.*, **68**, 1601 (1946).
(14) STEPHENS, *J. Chem. Soc.*, 1034 (1947).
(15) INAGAKI, *J. Pharm. Soc. Japan*, **58**, 961 (1938).
(16) BOGERT AND HAND, *J. Am. Chem. Soc.*, **28**, 94 (1906).
(17) WHEELER AND OATES, *J. Am. Chem. Soc.*, **32**, 770 (1910).
(18) KRANZLEIN, U. S. Patent 2,012,569; *Chem. Abstr.*, **29**, 6905 (1935).
(19) BOGERT AND GEIGER, *J. Am. Chem. Soc.*, **34**, 524 (1912).
(20) BOGERT AND KLABER, *J. Am. Chem. Soc.*, **30**, 807 (1908).
(21) BLANKSMA AND HOEGEN, *Rec. trav. chim.*, **65**, 333 (1946).
(22) BOGERT, WIGGIN, AND SINCLAIR, *J. Am. Chem. Soc.*, **29**, 82 (1907).
(23) RUSSELL AND TEBBENS, *Org. Syntheses*, **22**, 35 (1942).
(24) FRIEDLÄNDER, BRUCKNER, AND DEUTSCH, *Ann.*, **388**, 23 (1912).
(25) JONES, *J. Org. Chem.*, **10**, 537 (1945).
(26) TSUDA, ISHII, FUKUSHIMA, AND KAGAYA, *J. Pharm. Soc. Japan*, **63**, 445 (1943); *Chem. Abstr.*, **45**, 5156 (1951).