Summary

Six β-dialkylamino ketones, one α-dialkylamino ketone and one α-dialkylamino alcohol, were made, based on the 2,5-diphenyl-3-furyl system.

The synthetic work involved a study of (a) the Friedel–Crafts acylation of 2,5-diarylfurans and bromination of the 3-acetyl group, and (b) conversion of the 3-carboxylic acid through the acid chloride and diazomethyl ketone into the bromoketone and bromohydrin.

The α,β-dimorpholino ketone was made from the benzal derivative of the 3-acetylfuran.

Very little or no antimalarial activity was observed in the limited studies in this field.

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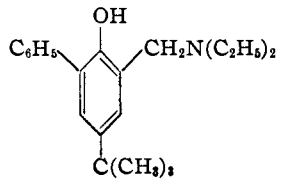
RECEIVED NOVEMBER 20, 1947

[CONTRIBUTION FROM THE RESEARCH LABORATORIES, PARKE, DAVIS & COMPANY]

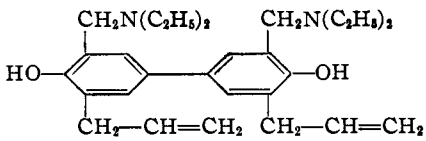
Aminoalkylphenols as Antimalarials. II.[1] (Heterocyclic-amino)-α-amino-o-cresols. The Synthesis of Camoquin[2]

BY J. H. BURCKHALTER,[3] F. H. TENDICK, ELDON M. JONES, PATRICIA A. JONES, W. F. HOLCOMB AND A. L. RAWLINS

In an earlier publication[1] we described a new class of antimalarial compounds represented by 4-*t*-butyl-α-diethylamino-6-phenyl-*o*-cresol (SN 7,744) and 6,6′-diallyl-α,α′-bis-(diethylamino)-4,4′-bi-*o*-cresol (SN 6,771). The high activity of

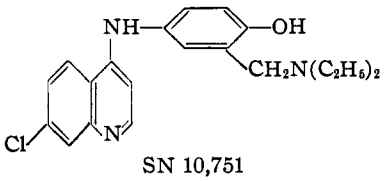


SN 7744



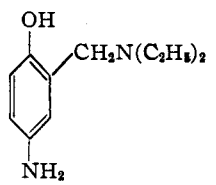
SN 6771

SN 6,771, SN 7,744 and simple analogs led, in 1943, to the synthesis of analogs containing substituent heterocyclic nuclei. This paper describes the work on quinolines, acridines and other heterocyclic compounds which has resulted in the preparation of a new antimalarial, SN 10,751.[2,4]

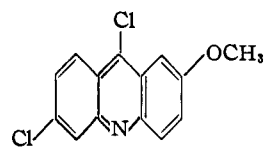


SN 10,751

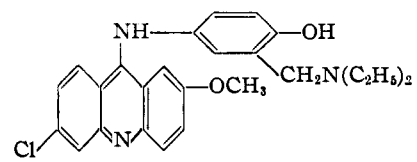
Early attempts to prepare the first member of the new heterocyclic series were unsuccessful. Treatment of 6-chloro-9-(4-hydroxyanilino)-2-methoxyacridine with formaldehyde and diethylamine in the manner of the Mannich reaction failed to yield a product.[5] A method was developed, however, through the preparation of 4-amino-α-diethylamino-*o*-cresol (SN 12,458) and its condensation with 6,9-dichloro-2-methoxyacridine (I) in phenolic solution[6] to give 4-(6-chloro-2-methoxy - 9 - acridylamino) - α - diethylamino-*o*-cresol (SN 8,617).



SN 12,458



I



SN 8,617

The intermediate 4-amino-α-diethylamino-*o*-cresol (SN 12,458) is new and has been prepared both by acid deacetylation of 4-acetamido-α-diethylamino-*o*-cresol (SN 7,767) and by reduction of 4-nitro-α-diethylamino-*o*-cresol (SN 7,292). The last two compounds were obtained from 4-

(1) For paper I see Burckhalter, Tendick, Jones, Holcomb and Rawlins, THIS JOURNAL, **68**, 1894 (1946).

(2) (a) Camoquin is the Parke, Davis name for 4-(7-chloro-4-quinolylamino)-α-diethylamino-*o*-cresol, SN 10,751. (b) The designation SN identifies a compound in the monograph *A Survey of Antimalarial Drugs*, 1941–1945, F. Y. Wiselogle, Editor, J. W. Edwards, Ann Arbor, Mich., 1946.

(3) Present address: University of Kansas, Lawrence, Kansas.

(4) This drug has been receiving extensive clinical trial in many parts of the world with promising results. Chemical data are summarized in Table VI, compound 9.

(5) F. F. Blicke, "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942, Chapter 10. Subsequently, incomplete studies have shown that the reaction can be effected with certain substituted aminophenols. *e. g.*, see compound 3, Table XII (VI).

(6) Because of the objection to the handling of phenol, this and similar condensations were later carried out in dilute mineral acid according to a procedure used by Banks, THIS JOURNAL, **66**, 1127 (1944).

TABLE I

ACETAMIDOPHENOLS[a]

No.	Compound	Yield, %	M. p., °C.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
1	4-Acetamidophenol	56[b]	168							
2	4-Acetamido-2-chlorophenol	55[c]	144	$C_8H_8ClNO_2$	51.77	51.68	4.35	4.24		
3	2-Acetamido-4-chlorophenol	52[d]	186	$C_8H_8ClNO_2$	51.77	51.81	4.35	4.39		
4	4-Acetamido-2-phenylphenol	60[e]	160	$C_{14}H_{13}NO_2$					6.16	6.01
5	2-Acetamido-4-phenylphenol	89[f]	165	$C_{14}H_{13}NO_2$					6.16	6.43
6	2-Acetamido-4-*t*-butylphenol	79[g]	170	$C_{12}H_{17}NO_2$					6.75	6.91

[a] The nitrophenols were obtained through the coöperation of Dow Chemical Co. [b] Identical with the product from Eastman Kodak. [c] Recrystallized from isopropanol as light gray crystals. [d] Recrystallized from ethanol. [e] Recrystallized from methanol. [f] Recrystallized from benzene–ethanol. [g] Recrystallized from benzene.

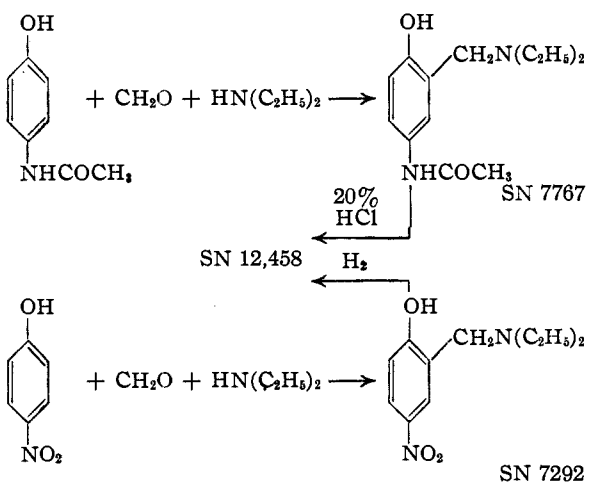
TABLE II

2-ACETAMIDO-α-ALKYLAMINO-*o*-CRESOLS

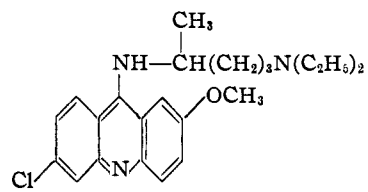
No.	Substituents: z	Alkylamino	Other	Yield, %	M. p., °C.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
1	4	Diethylamino		82[a]	135	$C_{13}H_{20}N_2O_2$	66.07	66.45	8.53	8.48	11.85	11.86
2	5	Diethylamino		33[a]	210	$C_{13}H_{20}N_2O_2 \cdot HCl$					10.27	10.19
3	4	Di-*n*-butylamino		87[b]	73	$C_{17}H_{28}N_2O_2$	69.82	70.30	9.65	9.51		
4	4	Dibenzylamino		75[c]	230	$C_{23}H_{24}N_2O_2$					7.77	7.76
5	4	2-Methyl-1-piperidyl		65[d]	175	$C_{15}H_{22}N_2O_2 \cdot HCl \cdot H_2O$	56.86	56.60	7.95	7.96	8.84	8.42
6	4	4-Morpholinyl		27[e]	133	$C_{13}H_{18}N_2O_3$	62.40	62.35	7.25	7.40		
7	4	Methyl-(2-hydroxyethyl)-amino		50[a]	198	$C_{12}H_{18}N_2O_3 \cdot HCl$					10.20	10.09
8	4	Mono-2-hydroxyethylamino		31[f]	230	$C_{11}H_{16}N_2O_3 \cdot HCl$					10.75	10.44
9	4	Mono-2-butylamino		37[g]	156	$C_{13}H_{20}N_2O_2$	66.07	66.27	8.53	8.60		
10	4	Diethylamino	6-Allyl	58[h]	86	$C_{16}H_{24}N_2O_2$	69.53	69.44	8.75	8.69		
11	6	Diethylamino	4-Chloro	66[c]	212	$C_{13}H_{19}ClN_2O_2 \cdot HCl$	50.82	50.89	6.56	6.57		
12	6	Diethylamino	4-*t*-Butyl	53[i]	158	$C_{17}H_{28}N_2O_2 \cdot HCl$	62.08	62.29	8.89	8.91		
13	6	Diethylamino	4-Phenyl	..[d]	183	$C_{19}H_{24}N_2O_2 \cdot HCl$	65.41	65.74	7.22	7.07		

[a] Recrystallized from ethanol. [b] From isopropanol–petroleum ether. A monopicrate of this compound was prepared; m. p. 183–185°. *Anal.* Calcd. for $C_{23}H_{31}N_5O_9$: C, 52.96; H, 5.99. Found: C, 53.31; H, 5.85. [c] From methanol. [d] From ethanol–acetone. [e] From isopropanol. [f] From methanol–ethanol. [g] From isopropanol–petroleum ether. [h] From dilute methanol. For intermediate 2-allyl-4-acetamidophenol see Experimental part. [i] From acetone.

acetamidophenol and 4-nitrophenol, respectively, by the Mannich reaction.[5]



SN 8,617 proved to be as active as quinacrine (SN 390) in screening tests and thus provided the impetus for the work which followed. The structural relationship of SN 8,617 to both SN 6,771 and SN 7,744, as well as to SN 390, suggested that a practical antimalarial might be found among its analogs.



SN 390

Many analogs of intermediates SN 7,767 and SN 7,292 were prepared (Tables II and III). Although several others could not be readily crystallized, we found that deacetylation of the crude materials yielded the desired intermediates which, without isolation, could be successfully condensed with reactive chloroheterocycles. Certain analogs of SN 7,292, *e. g.*, α-monoisobutylamino-4-nitro-*o*-cresol (II), were best obtained by conden-

TABLE III

α-ALKYLAMINO-4-NITRO-o-CRESOLS[a]

No.	Substituent: Alkylamino	Substituent: Other	Procedure	Yield, %	M. p., °C.	Formula	Analyses, %: Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
1	Diethyl		A	40[b,c]	224 dec.	$C_{11}H_{16}N_2O_3 \cdot HCl$	50.67	50.76	6.57	6.47
2	1-Piperidyl		A	68[b]	260 dec.	$C_{12}H_{16}N_2O_3 \cdot HCl$	52.84	52.67	6.28	6.30
3	Diisopropyl		B	19[d]	193 dec.	$C_{13}H_{20}N_2O_3 \cdot HCl$	54.07	54.14	6.98	6.91
4	Di-*n*-butyl		B	75[e]	176 dec.					
5	Diisobutyl		B	43[f,g]	113	$C_{15}H_{24}N_2O_3$	64.26	64.20	8.63	8.18
6	Diisoamyl		B	32[d]	132 dec.	$C_{17}H_{28}N_2O_3 \cdot HCl$	59.20	59.42	8.48	8.67
7	Diethyl	6-Phenyl	A	21[f,g]	125	$C_{17}H_{20}N_2O_3$			9.33	9.29
8	Monoisopropyl		B	38[h]	238 dec.	$C_{10}H_{14}N_2O_3 \cdot HCl$	48.69	48.92	6.13	6.03
9	Monoisobutyl		B	29[i]	247 dec.	$C_{11}H_{16}N_2O_3 \cdot HCl$	50.67	50.81	6.57	6.67
10	Mono-*t*-butyl		B	20[h]	275 dec.	$C_{11}H_{16}N_2O_3 \cdot HCl$	50.66	50.86	6.57	6.28
11	Diethyl	4-*t*-Butyl[a]	A	50[f,g]	103	$C_{15}H_{24}N_2O_3$	64.26	64.33	8.63	8.44

[a] Note that compound 11 is a 6-nitro-*o*-cresol. [b] From methanol. [c] Off-white color. [d] From isopropanol–ether. [e] This hydrochloride was not analyzed; it was converted by a procedure similar to the one applied to compounds in Table I into compound 3, Table II. [f] From isopropanol. [g] Yellow colored. [h] From ethanol–ether. [i] From isopropanol–methanol

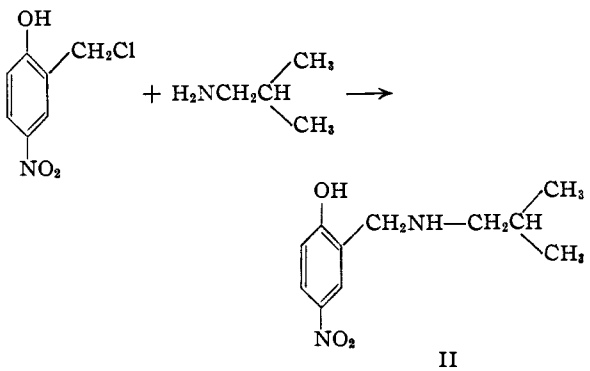
TABLE IV

NITROBENZYLAMINES

No.	Substituents: Amino	Substituents: Benzyl	Yield, %	M. p., °C.	Formula	Analyses, %: Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
1	Diethyl	3-Nitro	60[a]								
2	Diethyl	4-Nitro	45[b]	162	$C_{11}H_{16}N_2O_2 \cdot HCl$					11.45	11.12
3	Di-*n*-propyl	4-Nitro	68[c]	138 dec.	$C_{13}H_{20}N_2O_2 \cdot HCl$					10.27	10.43
4	Monoisopropyl	4-Nitro	82[d]	232 dec.	$C_{10}H_{14}N_2O_2 \cdot HCl$					12.15	12.16
5	Monoisobutyl	4-Nitro	64[d]	214 dec.	$C_{11}H_{16}N_2O_2 \cdot HCl$					11.44	11.19
6	Diethyl	5-Nitro-2-methoxy	72[e,f]	178 dec.	$C_{12}H_{18}N_2O_3 \cdot HCl$	52.46	52.38	6.97	6.67		
7	Monoisobutyl	5-Nitro-2-methoxy	63[e,f]	176 dec.	$C_{12}H_{18}N_2O_4 \cdot HCl$	52.46	52.56	6.97	6.90		
8	Diethyl	5-Nitro-2-ethoxy	56[g]	182 dec.	$C_{13}H_{20}N_2O_3 \cdot HCl$	54.07	54.31	7.33	7.36		
9	Mono-*n*-amyl	5-Nitro-2-methoxy[h]			$C_{13}H_{20}N_2O_3 \cdot HCl$						

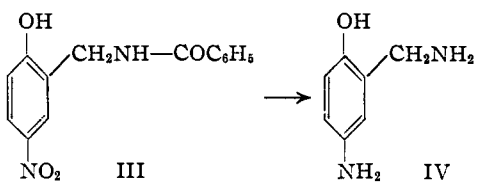
[a] Prepared by the general procedure of this table; b. p. 145–148° (6 mm.); picrate, m. p. 161°. Noelting and Kragczy, *Bull. soc. chim.*, [4], 19, 336 (1916), prepared the same compound in a pressure bottle; b. p. 206–208° (42 mm.); picrate, m. p. 161°. [b] From acetone–ethanol. [c] From acetone–ligroin. [d] From ethanol–isopropanol. [e] From isopropanol. [f] Intermediate 2-methoxy-5-nitrobenzyl chloride prepared by the method of U. S. Patent 2,278,996. [g] From ligroin–isopropanol. [h] The separation of the hydrochloride of this compound from *n*-amylamine hydrochloride was very difficult. Analytical data indicated the presence of this impurity to a considerable extent. However, compound 8, Table XIII, was readily prepared from the crude product.

sation of α-chloro-4-nitro-*o*-cresol[7] with the proper mono- and dialkylamines.



II

α,4-Diamino-*o*-cresol[8] (IV) was prepared by catalytic reduction of α-benzamido-4-nitro-*o*-cresol (III) followed by acid hydrolysis of the derived 4-amino-α-benzamido-*o*-cresol.



III IV

As a part of our studies, certain non-phenolic and O-methylated analogs of SN-8,617 and Camoquin were synthesized. These compounds listed in Table XIII were prepared prior to the appearance of another publication[9] describing 6-chloro-9-(2-diethylaminomethylanilino) - 2 - methoxyacridine, which is a position isomer of compounds 10 and 11. The two necessary types of non-phenolic inter-

(7) "Organic Syntheses," **20**, 59 (1940).

(8) Einhorn, *Ann.*, **343**, 249 (1906).

(9) Hall and Turner, *J. Chem. Soc.*, 694 (1945).

TABLE V

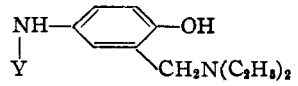
4-CHLOROQUINOLINES

No.	Substituents	Yield,[a] %	M. p., °C.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
1	7-Ethoxy	53[b]	76	$C_{11}H_{10}ClNO$					6.75	6.96
2	7-*n*-Hexyloxy	41[c,d]		$C_{15}H_{18}ClNO$						
3	5-Chloro-8-methoxy	6[c,e]	127	$C_{10}H_7Cl_2NO$						
4	6,7,8-Trichloro	39[c,e]	156	$C_9H_4Cl_4N$						
5	5-Methyl-8-methoxy	45[c,e]	78	$C_{11}H_{10}ClNO$						
6	6-Methyl	50[e]	55	$C_{10}H_8ClN$	67.61	68.18	4.54	4.58		
7	8-Methyl	71[e]	99	$C_{10}H_8ClN$					7.88	7.75
8	5,7-Dimethyl	51[e]	59	$C_{11}H_{10}ClN$	68.93	68.99	5.26	5.48		
9	5,8-Dimethyl	59[e]	51	$C_{11}H_{10}ClN$	68.93	69.03	5.26	5.40		
10	6,8-Dimethyl	82[e]	90	$C_{11}H_{10}ClN$					7.31	7.44
11	6-Anilino	6[f]	148	$C_{16}H_{11}ClN_2$	70.72	70.86	4.35	4.34		

[a] The yield of each 4-chloroquinoline is an over-all value based on the amount of substituted aniline used in the first step of the synthesis. [b] From dilute alcohol. [c] It is regrettable that analytical data are not available on every compound listed in this table. However, the compounds are tabulated because they are new and necessary intermediates in the preparation of several antimalarials which were more thoroughly characterized. [d] A high boiling liquid which was directly converted into compound 6, Table IX. [e] From ligroin. [f] From benzene–ligroin.

TABLE VI

4-(HETEROCYCLIC-AMINO)-α-DIETHYLAMINO-*o*-CRESOLS (PROCEDURE C)



No.	SN	Q Equiv.[a]	Y	Yield, %	M. p., °C.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
1	12,356	1.5	9-Acridyl	45	265 dec.	$C_{24}H_{26}N_3O\cdot 2HCl$[b,c,d]	64.86	64.48	6.13	6.14		
2	12,355	3	3-Chloro-9-acridyl	52	267 dec.	$C_{24}H_{24}ClN_3O\cdot 2HCl$[b,c,d]	60.19	60.10	5.47	5.42		
3	12,164	0.15	4-Methoxy-9-acridyl	50	245 dec.	$C_{25}H_{27}N_3O_2\cdot 2HCl$[b,c,d]	63.29	62.93	6.16	6.39		
4	8,617		6-Chloro-2-methoxy-9-acridyl	50	175	$C_{25}H_{26}ClN_3O_2$[e,f]	68.87	69.14	6.01	6.20		
					117 dec.	$C_{25}H_{26}ClN_3O_2\cdot H_2O$[e,g]	66.17	66.26	6.22	6.28		
		4		76[w]	280 dec.	$C_{25}H_{26}ClN_3O_2\cdot 2HCl$[e,h]	59.00	58.90	5.55	5.73		
					180 dec.	$C_{25}H_{26}ClN_3O_2\cdot 2HCl\cdot 2H_2O$[e,i]	54.20	53.97	5.82	5.86		
5	11,988	0.25	3-Chloro-5-methyl-9-acridyl	40	275 dec.	$C_{25}H_{26}ClN_3O\cdot 2HCl$[b,c,d]	60.92	60.99	5.73	5.91	8.52	8.30
6	9,559	0.12	2-Quinolyl	48	230 dec.	$C_{28}H_{32}N_3O\cdot 2HCl$[j,k]					10.66	10.53
7	11,537	0.7	6-Methoxy-2-quinolyl	20.5	237 dec.	$C_{21}H_{23}N_3O_2\cdot 2HCl$[j,m,n]					9.90	9.88
8	9,307	<0.07	5-Nitro-2-quinolyl	33	245 dec.	$C_{20}H_{22}N_4O_3\cdot 2HCl$[b,c,k]					12.75	12.82
9	10,751	25	7-Chloro-4-quinolyl	86	208 dec.	$C_{20}H_{22}ClN_3O$[d,f,p]	67.50	67.64	6.23	6.29		
					243 dec.	$C_{20}H_{22}ClN_3O\cdot 2HCl\cdot {}^1/_2H_2O$[h,o]	54.86	54.93	5.76	6.08		
					183 dec.	$C_{20}H_{22}ClN_3O\cdot 2HCl\cdot 1H_2O$[o,q]	53.76	54.09	5.87	6.20		
				90	160 dec.	$C_{20}H_{22}ClN_3O\cdot 2HCl\cdot 2H_2O$[n,r]	51.68	51.88	6.07	5.92		
10	9,591	1.1	2-Amino-4-pyrimidyl	41	258 dec.	$C_{14}H_{21}N_5O\cdot 2HCl$[f,s,t]	50.01	49.71	6.43	6.62		
11	10,177	0.4	2-1'-Piperidyl-4-pyrimidyl	31	156	$C_{20}H_{29}N_5O$[f,t]					19.70	19.70
12	....		2-Amino-6-methyl-4-pyrimidyl	55	245 dec.	$C_{15}H_{23}N_5O\cdot 2HCl$[b,u]					18.71	18.50
13	11,189	<0.07	4-Methoxy-2-benzothiazolyl	47	163 dec.	$C_{19}H_{23}N_3O_2S\cdot 2HCl$[b,k,v]					9.76	9.70

[a] By Dr. Porter's B-4 test; *cf.* ref. 2(b). [b] From methanol–acetone. [c] Orange crystals. [d] Heterocyclic intermediate obtained through Dr. R. C. Elderfield. [f] From absolute ethanol. [g] From 80% ethanol. Calcd. volatile loss, 3.98. Found, 4.13. [h] From methanol. [i] From 50% ethanol. [j] From isopropanol. [k] 2-Chloroquinoline obtained from Eastman Kodak Co. [l] From ethanol–acetone. [m] 2-Chloro-6-methoxyquinoline prepared by the method of Magidson, *J. Gen. Chem.* (*USSR*), **7**, 1896 (1937), and Bachman and Cooper, *J. Org. Chem.*, 9, 302 (1944). [n] Pale yellow crystals. [o] Yellow crystals. [p] See reference 11 for intermediate 4,7-dichloroquinoline. [q] From acetone–water. [r] From water. [s] Light tan crystals. [t] Intermediate 2-amino-4-chloropyrimidine from Dr. H. S. Mosher. [u] Light gray crystals. [v] Off-white crystals. [w] Also prepared in 71% yield by Procedure D.

mediates related to 4-amino-α-diethylamino-*o*-cresol (SN 12,458) were prepared by condensation of nitrobenzyl chlorides and alkoxy nitrobenzyl chlorides with aliphatic amines (Table IV). During the course of this work 2-chloromethyl-4-nitrophenetole was obtained in 75% yield by the chloromethylation of 4-nitrophenetole.

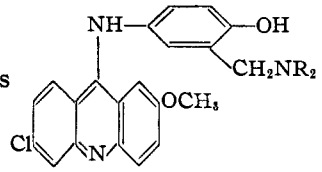
In the preparation of a group of acetamido-α-dialkylamino-*o*-cresols, several new alkyl, phenyl, and chloro acetamidophenols were obtained from the corresponding nitrophenols by catalytic reduction in the presence of acetic anhydride (Table I).

Although several of the intermediate 4-chloroquinolines were first prepared by rearrangement of the corresponding quinoline-N-oxides,[10] the ethoxymethylene malonic ester method of Price

(10) Magidson, *J. Gen. Chem.* (*U. S. S. R.*), **7**, 1896 (1937); Bachman and Cooper, *J. Org. Chem.*, **9**, 302 (1944).

TABLE VII

4-(6-CHLORO-2-METHOXY-9-ACRIDYLAMINO)-α-AMINO-*o*-CRESOLS

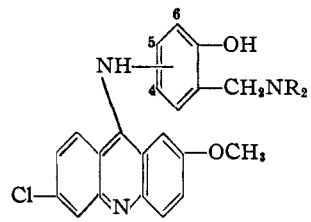


No.	SN	Q Equiv.	R_2	Procedure	Yield, %	M. p., °C.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
1	8,617	4	Diethyl[a]										
2	....	5	Ethyl (*n*-butyl)	F	36	252 dec.	$C_{27}H_{30}ClN_3O_2 \cdot 2HCl$[b,c]	60.39	60.10	6.01	6.11		
3	11,599	2.5	Di-*n*-butyl	A	69	246 dec.	$C_{30}H_{34}ClN_3O_2 \cdot 2HCl$[c,d]	61.64	61.84	6.42	6.68		
4	13,163	0.5	Diallyl	F	16	158	$C_{27}H_{26}N_2N_3Cl$[c,e]	70.49	70.11	5.69	5.99		
5	....	0.4	Di-*n*-hexyl	F	23	254 dec.	$C_{33}H_{42}O_2N_3Cl \cdot 2HCl$[c,f]	63.81	63.68	7.14	7.12		
6	....	<0.06	Di-*n*-octyl	F	20	285 dec.	$C_{37}H_{50}ClN_3O_2 \cdot 2HCl$[c,g]					6.21	6.30
7	11,536	0.6	1-Piperidyl	D	..	287 dec.	$C_{26}H_{30}ClN_3O_2 \cdot 2HCl$[c,h]	59.95	59.89	5.42	5.71		
8	....	1	Mono-*n*-hexyl	F	7	226 dec.	$C_{27}H_{30}O_2N_3Cl \cdot 2HCl \cdot H_2O$[f,i]	58.43	58.68	6.17	6.25		
9	11,233	0.2	Mono-2-hydroxyethyl	C	90	284 dec.	$C_{23}H_{22}ClN_3O_2 \cdot 2HCl \cdot H_2O$[c,h]	53.66	53.14	5.09	5.10		
10	11,589	<0.04	Benzoyl	D	95	294 dec.	$C_{23}H_{22}ClN_3O_3 \cdot HCl \cdot {}^1/_2H_2O$[c,j,k]	63.52	63.54	4.57	4.71		

[a] See compound 4, Table VI, for chemical data. [b] From methanol–isopropanol. [c] Orange crystals. [d] From ethanol–acetone. [e] From isopropanol. [f] From methanol–acetone. [g] From propylene glycol–acetone. [h] From methanol. [i] Red crystals. [j] From cellosolve–water. [k] Intermediate α-benzamido-4-nitro-*o*-cresol prepared by method of Einhorn.[8]

TABLE VIII

z-(6-CHLORO-2-METHOXY-9-ACRIDYLAMINO)-α-AMINO-*o*-CRESOLS



No.	SN	Q Equiv.	Substituents R_2	Substituents z	Substituents Other	Procedure	Yield, %	M. p., °C.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
1	9,614	1	Diethyl	5		C	50	237 dec.	$C_{23}H_{26}ClN_3O_2 \cdot 2HCl \cdot {}^1/_2H_2O$[a,b]	57.98	57.97	5.64	5.82
2	11,544	0.6	Diethyl	6	4-*t*-butyl	C	98	271 dec.	$C_{30}H_{34}N_3O_2Cl \cdot 2HCl$[a,c]	61.65	61.87	6.42	6.21
						D	53						
3	11,553	0.5	Diethyl	6	4-phenyl	C	84	274 dec.	$C_{31}H_{30}ClN_3O_2 \cdot 2HCl$[a,c]	63.64	63.74	5.52	5.79
4	11,550	2.0	Diethyl	6	4-diethylaminomethyl	F	73	257 dec.	$C_{30}H_{37}ClN_4O_2 \cdot 3HCl \cdot H_2O$[a,d]	55.56	55.87	6.53	6.53
5	11,234	3	Diethyl	4	6-Allyl	C	65	233 dec.	$C_{23}H_{30}O_2N_3Cl \cdot 2HCl$[f,e]	61.26	60.89	5.87	6.08
6	13,399	0.3	Diallyl	4	6-Allyl	F	12	188 dec.	$C_{26}H_{30}O_2N_3Cl \cdot 2HCl \cdot H_2O$[f,e]	61.92	62.11	5.72	5.67
7	12,701	2	1-Piperidyl	4	6-Allyl	F	44	164 dec.	$C_{29}H_{30}O_2N_3Cl$[f,e]	71.37	71.52	6.20	6.30

[a] Orange crystals. [b] From methanol. Calcd. volatile loss, 2.78. Found 2.77. [c] From methanol–acetone. [d] From methanol–ether. [e] Orange-red crystals. [f] From methanol.

and Roberts,[11] made available to us prior to its publication, was adopted for the preparation of all the 4-chloroquinolines originating in this Laboratory. Since the completion of these studies, many identical data have been reported by others, especially in the January, March and July, 1946, numbers of THIS JOURNAL. Table V therefore lists only a group of 4-chloroquinolines which have not yet appeared in the literature.

The preparation of various intermediates analogous to both SN 12,458 and I made possible the synthesis of many new antimalarial compounds related to SN 8,617. Tables VI to XIII present chemical data, show the development of the SN 8,617 lead, and afford a study of the relationship between chemical structure and pharmacological activity. Some of the most effective compounds appear in Table XII.[12]

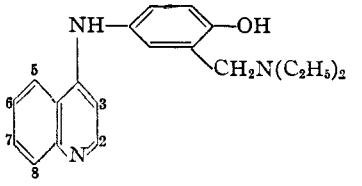
4-(7-Chloro-4-quinolylamino)-α-monoethylamino-*o*-cresol, Table XII, compound 3, (VI) could not be prepared by the usual procedures. It was finally obtained in very low yield by means of the Mannich reaction using 7-chloro-4-(4-hydroxyanilino)-quinoline (V), paraformaldehyde and monoethylamine. This application of the Mannich reaction employing heterocyclic and aromatic ami-

(11) Price and Roberts, THIS JOURNAL, **68**, 1204 (1946).

(12) Compound 25 (Camoquin) was found to be 25 times as active as quinine against *gallinaceum* malaria in chicks, while its monoisobutyl analog (compound 8) is 75 times as active—a considerable improvement over the simpler α-amino-*o*-cresols,[1] as well as over other 4-aminoquinolines heretofore reported [*cf.* tables of 4-aminoquinolines, ref. (2b), pp. 154–163].

TABLE IX

4-(SUBSTITUTED-4-QUINOLYLAMINO)-α-DIETHYLAMINO-*o*-CRESOLS



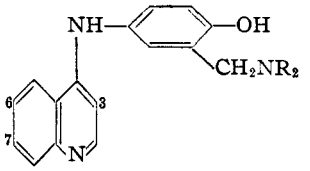
No.	SN	Q Equiv.	Substituents	Procedure	Yield, %	M. p., °C.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
1	12,452	3	None	C	48	>300	$C_{20}H_{21}N_3O \cdot 2HCl$[a,b,c]	60.91	61.02	6.39	6.75		
2	11,563	0.2	6-Hydroxy	*d*	64	262 dec.	$C_{20}H_{22}N_3O_2 \cdot 2HCl$[b,e]	58.54	58.14	6.14	6.19		
3	10,274	8	6-Methoxy	C	75	270 dec.	$C_{21}H_{25}N_3O_2 \cdot 2HCl$[b,e,f]					9.90	9.80
4	11,554	7	7-Methoxy	C	43	210 dec.	$C_{21}H_{25}N_3O_2 \cdot 2HCl \cdot {}^1/_2H_2O$[b,g,h]	58.20	58.20	6.51	6.43		
5	11,281	7	7-Ethoxy	C	44	136 dec.	$C_{22}H_{27}N_3O_2 \cdot 2HCl \cdot 2H_2O$[b,g]	57.89	58.02	6.85	6.89		
6	11,634	0.5	7-*n*-Hexyloxy-	C	35	153	$C_{28}H_{39}N_3O_2$[i]	74.07	74.20	8.37	8.09		
7	11,594	0.8	8-Methoxy	C	50	241 dec.	$C_{21}H_{25}O_2N_3 \cdot 2HCl \cdot 1{}^1/_2H_2O$[b,e,j]	55.87	55.87	6.69	6.62		
8	13,395	2.5	6,7-Dimethoxy	E	68	258 dec.	$C_{22}H_{27}N_3O_2 \cdot 2HCl$[e,k,l]	58.15	57.93	6.43	6.49		
9	12,161	0.4	5-Chloro-8-methoxy	E	80	231 dec.	$C_{21}H_{24}ClN_3O_2 \cdot 2HCl$[m,t]					9.16	8.94
10	11,986	<0.07	2-Chloro	C	30	248 dec.	$C_{20}H_{22}ClN_3O \cdot 2HCl$[b,e,n]					9.80	9.59
11	11,597	3.0	6-Chloro	C	60	220	$C_{20}H_{22}ON_3Cl \cdot 2HCl \cdot {}^1/_2H_2O$[b,e,p]	54.86	54.81	5.76	5.82		
12	10,751	25	7-Chloro[o]										
13	11,551		8-Chloro			212	$C_{20}H_{22}ClN_3O$[b,p,q]	67.50	67.17	6.23	6.50		
		0.5		C	79	253 dec.	$C_{20}H_{22}ClN_3O \cdot 2HCl \cdot {}^1/_2H_2O$[b,r]	54.90	55.25	5.76	5.91		
14	12,700	3	5,7-Dichloro	E	65	200 dec.	$C_{20}H_{21}Cl_2N_3O \cdot 2HCl$[e,t,u]					9.07	8.89
15	12,161	5	6,7-Dichloro	C	71.5	257 dec.	$C_{20}H_{21}Cl_2N_3O \cdot 2HCl$[b,e,v]	51.85	51.74	5.00	5.23		
16	11,596	0.25	5,8-Dichloro	C	60	235 dec.	$C_{20}H_{21}ON_3Cl_2 \cdot 2HCl \cdot 1H_2O$[b,e,v]	49.91	49.84	5.23	5.31		
17	11,633	<0.3	6,7,8-Trichloro	C	40	277 dec.	$C_{20}H_{20}Cl_3N_3O \cdot 2HCl$[b,e]	48.27	48.30	4.46	4.74		
18	11,559		6-Methyl			172	$C_{21}H_{25}N_3O$[b,q]	75.20	74.80	7.45	7.41		
		4		C	56	238 dec.	$C_{21}H_{25}N_3O \cdot 2HCl$[b,w]	61.76	61.61	6.67	6.80		
19	12,699	9	7-Methyl	E	93	245 dec.	$C_{21}H_{25}N_3O \cdot 2HCl$[e,f,x]					10.29	10.14
20	11,601	0.7	8-Methyl	C	66	253 dec.	$C_{21}H_{25}N_3O \cdot 2HCl \cdot H_2O$[b,e]	59.15	58.85	6.85	6.64		
21	11,561	10	5,7-Dimethyl	C	67	242 dec.	$C_{22}H_{27}N_3O \cdot 2HCl$[b,e]	62.55	62.53	6.92	6.55		
22	11,560	0.6	5,8-Dimethyl	C	80	249 dec.	$C_{22}H_{27}N_3O \cdot 2HCl$[b,e]	62.55	62.80	6.92	6.14		
23	11,990	6	6,7-Dimethyl	C	49	215 dec.	$C_{22}H_{27}ON_3$[y,z,aa]	75.61	75.90	7.78	7.87		
24	11,558	0.6	6,8-Dimethyl	C	54	264 dec.	$C_{22}H_{27}ON_3 \cdot 2HCl \cdot 1H_2O$[e,f]	59.86	59.73	7.08	7.27		
25	9,223	1.2	6,-Methoxy-2-methyl	C	45	278 dec.	$C_{22}H_{27}N_3O_2 \cdot 2HCl$[f,ab]	59.47	59.30	6.88	6.81	9.25	9.18
26	11,632	0.6	8-Methoxy-5-methyl	C	90	210 dec.	$C_{22}H_{27}O_2N_3 \cdot 2HCl$[b,e]	60.27	60.02	6.67	6.18		
27	11,985	0.3	5-Chloro-3-methyl	C	48	258 dec.	$C_{21}H_{24}ClN_3O \cdot 2HCl$[e,ac,ad]	56.96	56.94	5.92	6.21		
28	10,492	6	7-Chloro-3-methyl	C	64	260	$C_{21}H_{24}ClN_3O \cdot 2HCl$[b,e,ac]					9.49	9.59
29	11,631	0.4	3-Phenyl	C	31	155	$C_{26}H_{27}ON_3$[ac,ae]	78.56	78.31	6.85	6.68		
30	11,592	0.25	6-Methoxy-2-phenyl	C	61	198 dec.	$C_{27}H_{29}N_3O_2 \cdot 2HCl \cdot 1{}^1/_4H_2O$[b,ac,af]					7.90	7.96
31	11,232	0.3	7-Chloro-2-phenyl	C	41	260 dec.	$C_{26}H_{26}ClN_3O \cdot 2HCl$[b,ac,ag]	61.85	61.74	5.59	5.67		
32	12,228	1	7-Chloro-3-phenyl	C	..	165	$C_{26}H_{26}ClN_3O$[b,e,ac]	72.31	72.94	6.07	6.38		
33	12,361	0.2	6-Anilino	C	63	196 dec.	$C_{26}H_{28}ON_4 \cdot 2HCl \cdot H_2O$[e,ad]	62.02	61.80	6.40	6.26		
34	11,984	2.5	6-Dimethylamino	C	73	235 dec.	$C_{23}H_{28}ON_4 \cdot 3HCl \cdot {}^1/_2H_2O$[b,e,ah]	54.72	54.73	6.68	6.64		
35	....	0.8	6-Nitro	C	63	210 dec.	$C_{20}H_{22}N_4O_3 \cdot 2HCl \cdot 1{}^1/_2H_2O$[ai]					12.01	12.31

[a] Intermediate 4-chloroquinoline was identical with that prepared by Riegel, *et al.*, THIS JOURNAL, 68, 1264 (1946). [b] Yellow crystals. [c] From ethanol. [d] See Experimental part. [e] From methanol–acetone. [f] Same reference as footnote (*m*), Table VI, for preparation of 4-chloro-6-methoxyquinoline. [g] From water–alcohol. [h] 7-Methoxy-4-chloroquinoline melts at 83–85°; Lauer, *et al.*, THIS JOURNAL, 68, 1268 (1946), found 82–83°. [i] From methanol–ethanol. [j] 8-Methoxy-4-chloroquinoline melts at 83°; Lauer, *et al.*, *ibid.*, found 79–80°. [k] Light greenish tan color. [l] Intermediate 4-chloro-6,7-dimethoxyquinoline, independently prepared, was found to be identical with that of Riegel, *et al.*, *ibid.* [m] From ethanol–ethyl acetate. [n] The structure of this compound has not been definitely established. However, a formula has been assigned based on the fact that 4-chloroquinoline was found to condense much more readily than 2-chloroquinoline with aromatic amines. Intermediate, 4,7-dichloroquinoline prepared by the method of Brooker and Smith, THIS JOURNAL, 64, 1357 (1942). [o] For chemical data, see compound 9, Table VI. [p] Intermediate dichloroquinoline was independently prepared by the same procedure of Tarbell, THIS JOURNAL, 68, 1278 (1946). [q] From chloroform–ether. [r] From acetone. [s] From ethanol–acetone. [t] Greenish yellow crystals. [u] Intermediate 4,5,7-trichloroquinoline prepared by the general method of Price[11]; m. p. 108°. *Anal.* Calcd. for $C_9H_4Cl_3N$: C, 46.50; H, 1.73. Found: C, 46.90; H, 1.80. Surrey and Hammer, THIS JOURNAL, 68, 1244 (1946), employed a different procedure. [v] Surrey and Hammer, *ibid.*, also prepared the intermediate trichloroquinoline by a different procedure. [w] From acetone. [x] Intermediate 4-chloro-6-methylquinoline, b. p. 139–140 (10 mm.). *Anal.* Calcd. for $C_{10}H_8ClN$: C, 67.61; H, 4.54. Found: C, 67.23; H, 4.55. Breslow, *et al.*, THIS JOURNAL, 68, 1236 (1946), reported b. p. 140–142 (9 mm.). [y] Pale tan crystals. [z] From methanol. [aa] Independent preparation of intermediate 4-chloro-6,7-dimethylquinoline gave identical results of Price and Roberts.[11] [ab] From methanol–ether; analysis corresponds to the presence of a half

mole of methanol: Calcd. volatile loss, 3.53. Found: 3.30. [ae] Intermediate 4-chloroquinoline obtained through Dr. R. C. Elderfield. [ad] Bright orange crystals. [ae] From ligroin. [af] From water; calcd. volatile loss 5.93. Found: 5.71. [ag] From 20% ethanol. [ah] Intermediate 4-chloro-6-dimethylaminoquinoline hydrochloride obtained as a bright orange powder; m. p. 249° d. *Anal.* Calcd. for $C_{11}H_{11}ClN_2 \cdot HCl$: C, 54.37; H, 4.97. Found: C, 54.12; H, 4.75. Riegel, *et al.*, *ibid.*, p. 1265, reported m. p. 225–230°. [ai] Intermediate 6-nitro-4-chloroquinoline prepared in low yield by the general method of Price and Roberts,[11] but see a better method for this compound by Baker, *et al.*, THIS JOURNAL, **68**, 1267 (1946). Orange-red crystals. Calcd. volatile loss, 6.01. Found: 5.79. From methanol–ether.

TABLE X

4-(SUBSTITUTED-4-QUINOLYLAMINO)-α-DIALKYLAMINO-*o*-CRESOLS

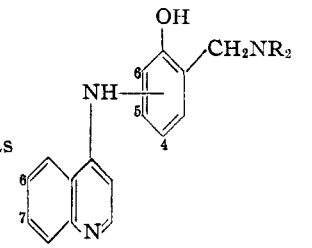


No.	SN	Q Equiv.	R_2	Substituents	Procedure	Yield, %	M. p., °C.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
1	10,274	8	Diethyl	6-Methoxy[a]								
2	....	9	Di-*n*-butyl	6-Methoxy	C	10	193 dec.	$C_{25}H_{33}O_2N_3 \cdot 2HCl \cdot 1.25H_2O$[b,c]	59.69	59.90	7.51	7.64
3	12,038	8	1-Piperidyl	6-Methoxy	C	80	270 dec.	$C_{22}H_{25}N_3O_2 \cdot 2HCl \cdot 0.5H_2O$[d]	59.32	59.15	6.33	6.25
4	11,989	1	4-Morpholinyl	6-Methoxy	C	57	265 dec.	$C_{21}H_{23}N_3O_3 \cdot 2HCl$[e,f]	57.54	57.48	5.75	5.84
5	13,395	2.5	Diethyl	6,7-Dimethoxy[g]								
6	13,413	4	1-Piperidyl	6,7-Dimethoxy	E	40	230 dec.	$C_{23}H_{27}N_3O_2 \cdot 2HCl$[b,h]				
7	10,492	6	Diethyl	7-Chloro-3-methyl[i]								
8	....	10	Di-*n*-butyl	7-Chloro-3-methyl	C	43	177 dec.	$C_{25}H_{32}ON_3Cl \cdot 2HCl \cdot 1.5H_2O$[b,j]	57.08	57.33	7.09	6.77
9	12,360	2	1-Piperidyl	7-Chloro-3-methyl	C	47	270 dec.	$C_{22}H_{24}ClN_3O \cdot 2HCl$[b,k]	58.09	58.20	5.76	5.67
10	12,362	0.15	4-Morpholinyl	7-Chloro-3-methyl	C	33	242 dec.	$C_{21}H_{22}ClN_3O_2 \cdot 2HCl$[f,k]	55.21	54.92	5.30	5.60
11	11,559	4	Diethyl	6-Methyl[l]								
12	12,456	2.5	1-Piperidyl	6-Methyl	E	41	240 dec.	$C_{22}H_{25}N_3O \cdot 2HCl$[m]				
13	12,457	0.8	4-Morpholinyl	6-Methyl	C	50	239	$C_{21}H_{23}N_3O_2$[n]				

[a] See compound 3, Table IX, for chemical data. [b] From methanol–acetone. [c] Pale greenish-yellow crystals. [d] Light green crystals from ethanol–ethyl acetate. See reference 12 for intermediate 4-acetamido-α-piperidyl-*o*-cresol. [e] Yellowish tan crystals. [f] From methanol–ethyl acetate. [g] See compound 8, Table IX, for chemical data. [h] Off-white crystals. *Anal.* for N: Calcd. 9.01. Found 9.03. [i] See compound 28, Table IX, for chemical data. [j] Yellow crystals. [k] Dark orange crystals. [l] See compound 18, Table IX, for chemical data. [m] Off-white crystals from ethanol. *Anal.* for N: Calcd. 10.00. Found: 10.22. [n] From ethanol. *Anal.* Calcd.: N, 12.02. Found: N, 12.14.

TABLE XI

z-(SUBSTITUTED-4-QUINOLYLAMINO)-α-DIALKYLAMINO-*o*-CRESOLS

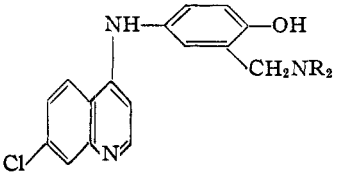


No.	SN	Q Equiv.	R_2	Cresol substituents	z	Quinoline substituents	Procedure	Yield, %	M. p., °C.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
1	13,730	9	Diethyl	None	5	7-Chloro	C	..	173	$C_{20}H_{22}ClN_3O$[a,b]	67.49	67.80	6.23	6.22
2	....	5	Diethyl	4-Diethylaminomethyl	6	7-Chloro	F	..	145	$C_{26}H_{33}ClN_4O \cdot 1\frac{1}{2}H_2O$[c,d]	64.16	64.06	7.75	7.59
3	12,885	0.5	Diethyl	4-Chloro	6	6-Methoxy	C	50	205 dec.	$C_{21}H_{24}ClN_3O_2 \cdot 2HCl$[c,e]	54.97	54.55	5.71	5.88
4	13,729	12	Diethyl	6-Chloro	4	7-Chloro	F	..	225 dec.	$C_{20}H_{21}Cl_2N_3O$[a,f]	61.54	61.50	5.42	5.38
5	....	[g]	Diethyl	6-Phenyl	4	7-Chloro	D	25	235 dec.	$C_{26}H_{26}ClN_3O \cdot \frac{1}{2}H_2O$[c,e]	70.81	70.50	6.17	5.95
6	12,039	7	Diethyl	6-Allyl	4	6-Methoxy	C	33	161	$C_{24}H_{29}O_2N_3$[h]	73.63	73.11	7.47	7.33
7	11,991	10	Diethyl	6-Allyl	4	7-Chloro	C	44	148	$C_{23}H_{26}ON_3Cl$[a,i]	69.77	69.51	6.62	6.82
8	12,697	4	1-Piperidyl	6-Allyl	4	7-Chloro	F	32	190	$C_{24}H_{26}ON_3Cl$[a,j]	70.65	70.93	6.42	6.59
9	13,394	0.7	Diallyl	6-Allyl	4	7-Chloro	F	25	131	$C_{26}H_{26}ON_3Cl$[a,k]	71.49	71.77	6.24	6.23

[a] Yellow crystals. [b] From methanol–benzene. [c] Light tan crystals. [d] From acetone–ligroin. [e] From ethanol. [f] From dioxane. [g] Sample inadequate for test. [h] Pale greenish-yellow crystals from dilute methanol. [i] From ligroin. [j] From dilute ethanol. [k] From isopropanol–ligroin.

TABLE XII

4-(7-CHLORO-4-QUINOLYLAMINO)-α-AMINO-*o*-CRESOLS



No.	SN	Q Equiv.	R_2	Procedure	Yield, %	M. p., °C.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
1	1,603	6	None	E	80	325 dec.	$C_{16}H_{14}ClN_3O\ 2HCl\cdot0.5H_2O$[a,b,c]	50.35	50.42	4.88	4.49		
2	11,557	0.15	Benzoyl	D	80	289 dec.	$C_{23}H_{18}ClN_4O_2\ HCl$[a,b,d]	62.60	62.82	4.34	4.41		
			α-Monoalkyl										
3	....	40	Ethyl	f		280 dec.	$C_{18}H_{18}ClN_3O\ 2HCl$[a,e]	53.95	53.93	5.03	5.42		
4	....	30	*n*-Propyl	F	24	244 dec.	$C_{19}H_{20}ClN_3O\ 2HCl.0.5H_2O$[a,g]	53.85	54.10	5.47	5.52		
5	....	40	Isopropyl	D	50	287 dec.	$C_{19}H_{20}ClN_3O\ 2HCl$[a,h]	55.02	54.84	5.35	5.36		
6	....	30	*n*-Butyl	F	6	254 dec.	$C_{20}H_{22}ON_3Cl\cdot2HCl$[a,h]	56.02	55.68	5.64	5.58		
7	....	50	2-Butyl	C	3	252 dec.	$C_{20}H_{22}ON_3Cl\cdot2HCl\cdot H_2O$[a,i]	53.76	53.75	5.86	5.57		
8	....	75	Isobutyl	C	33	256 dec.	$C_{20}H_{22}ON_3Cl\cdot2HCl$[a,i]	56.02	56.03	5.64	5.76		
				D	65								
9	....	40	*t*-Butyl	D	36	285 dec.	$C_{20}H_{22}ClN_3O\cdot2HCl$[a,h]	56.02	56.17	5.63	5.80		
10	....	50	*n*-Amyl	C	15	266 dec.	$C_{21}H_{24}ON_3Cl\cdot2HCl$[a,j]	56.95	56.90	5.92	5.50		
11	....	40	2-Amyl	C	22	231 dec.	$C_{21}H_{24}ClN_3O\cdot2HCl$[a,i]	56.96	57.11	5.92	5.99		
12	....	50	Isoamyl	F	20	279 dec.	$C_{21}H_{24}ON_3Cl\cdot2CHl$[a,h]	56.95	57.41	5.92	6.31		
13	....	25	*n*-Hexyl	F	56	280 dec.	$C_{22}H_{26}ClN_3O\cdot2HCl$[a,k]	57.84	57.81	6.18	6.18		
14	....	50	2-Ethylbutyl	F	15	263 dec.	$C_{23}H_{28}ClN_3O\cdot2HCl$[a,i]	57.84	57.73	6.18	6.04		
15	....	15	*n*-Heptyl	F	29	278 dec.	$C_{23}H_{28}ClN_3O\cdot2HCl$[a,e]					8.92	8.64
16	....	2.5	*n*-Octyl	F	15	150	$C_{24}H_{30}ON_3Cl$[l]	69.96	70.05	7.34	7.61		
17	....	20	Allyl	F	3	257 dec.	$C_{19}H_{18}ON_3Cl\cdot2HCl$[a,i]	55.28	55.12	4.88	5.05		
18	....		1-Methallyl	F	..	95	$C_{20}H_{20}ClN_3O\cdot2HCl\cdot1.75H_2O$[a,m]	52.41	52.68	5.63	6.03		
19	....	30	Cyclohexyl	F	30	252 dec.	$C_{22}H_{24}ClN_3O\cdot2HCl\cdot0.25H_2O$[a,e]	57.52	57.52	5.82	5.98		
20	....	3	2-Hydroxyethyl	C	15	182 dec.	$C_{18}H_{18}ClN_3O_2\cdot2HCl\cdot H_2O$[a,n]	49.72	50.18	5.10	5.50		
21	....	25	2-Methoxyethyl	F	..	271 dec.	$C_{19}H_{20}ClN_3O_2\cdot2HCl$[a,h]					9.76	9.79
22	....	16	Benzyl	F	..	270 dec.	$C_{23}H_{20}ClN_3O\cdot2HCl$[a,i]					9.09	9.11
23	....	25	1-Methyl-2-phenylethyl	F	31	243	$C_{25}H_{24}ClN_3O\cdot2HCl\cdot0.25H_2O$[a,h]	60.61	60.66	5.65	5.67		
			α-Disubstituted										
24	....	6	Dimethyl	C	85	290 dec.	$C_{18}H_{18}ClN_3O_2\cdot2HCl$[a,e,o]	53.95	53.83	5.03	5.18		
25	10,751	25	Diethyl[p]										
26	....	30	Ethyl-(*n*-butyl)	F	65	240 dec.	$C_{22}H_{26}ClN_3O\cdot2HCl$[a,h]	57.84	57.70	6.18	5.81		
27	13,835	25	Di-*n*-propyl	F	11	181	$C_{22}H_{26}ON_3Cl$[a,q]	68.82	69.20	6.83	6.76		
28	14,105	35	Di-*n*-butyl	C	20	164	$C_{24}H_{30}OH_3Cl$[a,r]	69.96	69.81	7.34	7.50		
29	....	..	Diisobutyl	D	38	166	$C_{24}H_{30}ClN_3O\cdot0.5H_2O$[s]	68.47	68.86	7.42	7.88		
30	....	..	Diisoamyl	D	..	135	$C_{26}H_{34}ClN_3O\cdot0.5H_2O$[t]	69.52	69.95	7.85	8.17		
31	....	0.5	Di-*n*-hexyl	F	40	220	$C_{28}H_{38}ON_3Cl\cdot2HCl$[a,i]	62.16	62.00	7.45	7.78		
32	....	1	Di-*n*-heptyl	F	52	203	$C_{30}H_{42}ON_3Cl\cdot2HCl$[a,h]	63.32	63.26	7.79	8.04		
33	....	0.2	Di-*n*-octyl	F	46	192	$C_{32}H_{46}ON_3Cl\cdot2HCl$[a,h]	64.36	64.29	8.10	7.85		
34	....	3	Di-2-ethylhexyl	F	1	154	$C_{32}H_{46}ON_3Cl\cdot2HCl\cdot H_2O$[a,h]	62.48	62.10	8.19	8.05		
35	11,636	25	1-Piperidyl	C	77.5	302 dec.	$C_{21}H_{22}ClN_3O\cdot2HCl\cdot2.5H_2O$[a,n,u]						
36	12,357	20	2-Methyl-1-piperidyl	C	66	288 dec.	$C_{22}H_{24}ClN_3O\cdot2HCl$[d,h]	58.09	58.22	5.76	5.81		
37	11,987	4	4-Morpholinyl	C	60	292 dec.	$C_{20}H_{20}ClN_3O_2\cdot2HCl$[a,v]	54.25	54.44	5.01	5.33		
				E	65								
38	12,363	3	Methyl-(2-hydroxyethyl)	C	63	250 dec.	$C_{19}H_{20}ClN_3O_3\cdot2HCl$[a,e]	52.97	52.96	5.15	5.38		
39	14,824	12	*n*-Butyl-(2-hydroxyethyl)	F	22	149	$C_{22}H_{26}O_2N_3Cl$[r]	66.07	65.94	6.55	6.94		
40	....	0.6	Di-2-hydroxyethyl	F	25	193	$C_{20}H_{22}ClN_3O_3$[w]	62.00	61.90	5.73	6.09		
41	....	2.5	Dibenzyl	C	74	235 dec.	$C_{30}H_{26}ClN_3O\cdot2HCl$[k,x]	65.16	64.92	5.10	5.40		
42	....	0.07	Methyl-(phenyl)	F	39	140	$C_{22}H_{20}ClN_3O\cdot H_2O$[a,i]					10.77	10.72
43	....	< 0.05	Ethyl-(phenyl)	F	54	131 dec.	$C_{24}H_{22}ClN_3O$[a,i]					10.40	10.19

[a] Yellow crystals. [b] From methanol. [c] Intermediate α,4-diamino-*o*-cresol prepared by the method of Einhorn.[8] [d] See ref. (8) for intermediate. [e] From ethanol. [f] See Experimental part. [g] From ethanol–isopropanol. [h] From methanol–acetone. [i] From ethanol–acetone. [j] From dilute hydrochloric acid. [k] From methanol–ethanol. [l] From alcohol–ether. [m] From isopropanol. Calcd. for volatile loss, 6.87. Found, 7.00. [n] From methanol–ethyl acetate. [o] For intermediate 4-acetamido-α-dimethylamino-*o*-cresol, see ref. (15). [p] See compound 9, Table VI. [q] From ethyl acetate [r] From ethyl acetate–petroleum ether. [s] From dilute methanol. [t] From dilute ethanol. [u] Calcd. volatile loss, 9.27. Found: 8.95. Calcd. ionic chlorine, 14.60. Found, 14.58. [v] From methanol–ethyl acetate. [w] Pale yellowish green crystals from dilute isopropanol. [x] Ivory crystals.

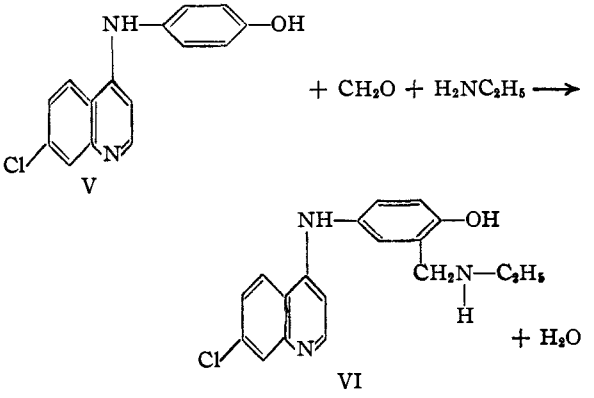
TABLE XIII

2-(HETEROCYCLIC-AMINO)-BENZYLAMINES (PROCEDURE D)

No.	SN	Q Equiv.	Substituents R₂	2	z	Yield, %	M. p., °C.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
					Y = 7-Chloro-4-quinolyl							
1	11,590	1	Diethyl		3	85	128 dec.	$C_{20}H_{22}ClN_3 \cdot 2HCl \cdot 2H_2O$[a,b]	53.52	53.26	6.29	6.36
2	12,455	4	Diethyl		4	..	261 dec.	$C_{20}H_{22}ClN_3 \cdot 2HCl$[c,d]	58.19	58.39	5.86	6.02
3	....	4	Di-*n*-propyl		4	60	255 dec.	$C_{22}H_{26}ClN_3 \cdot 2HCl$[c,d]	59.94	59.90	6.40	6.81
4	....	10	Monoisopropyl		4	23	303 dec.	$C_{19}H_{20}ClN_3 \cdot 2HCl$[d,e]	54.75	55.05	5.80	5.53
5	....	..	Monoisobutyl		4	76	288 dec.	$C_{20}H_{22}ClN_3 \cdot 2HCl \cdot H_2O$[d,e]	55.76	55.79	6.08	6.40
6	....	25	Diethyl	Methoxy	5	64	203	$C_{21}H_{24}ClN_3O$[a]	68.19	68.03	6.54	6.64
7	....	17	Monoisobutyl	Methoxy	5	76	194 dec.	$C_{21}H_{24}ClN_3O \cdot 2HCl \cdot {}^1/_4H_2O$[d,f]	55.15	55.27	5.84	6.11
8	....	15	Mono-*n*-amyl	Methoxy	5	42	288 dec.	$C_{23}H_{28}ClN_3O \cdot 2HCl$[d,e]	57.84	57.92	6.18	6.44
9	....	8	Diethyl	Ethoxy	5	73	247	$C_{22}H_{26}ClN_3O \cdot 2HCl \cdot 2H_2O$[a,d]	53.61	53.43	6.55	6.54
					Y = 6-Chloro-2-methoxy-9-acridyl							
10	10,984	0.5	Diethyl		3	55	278	$C_{24}H_{26}ClN_3O \cdot 2HCl \cdot {}^3/_4H_2O$[c,g]	59.29	59.25	5.87	5.98
11	10,028	0.4	Diethyl		4	92	260 dec.	$C_{24}H_{26}ClN_3O \cdot 2HCl \cdot {}^1/_2H_2O$[c,h]	59.82	60.06	5.82	6.28
12	....	3	Diethyl	Methoxy	5	67	212 dec.	$C_{25}H_{28}ClN_3O_2 \cdot 2HCl \cdot {}^1/_2H_2O$[c,g]	58.72	58.75	5.88	6.01

[a] From isopropanol. [b] Calcd. volatile loss, 8.03. Found: 8.85. [c] From methanol. [d] Yellow crystals. [e] From methanol–isopropanol. [f] From ethanol–isopropanol. [g] Orange crystals. [h] Red crystals.

nophenols is being continued with the prospect of obtaining better yields.



4-(6-Hydroxy-4-quinolylamino)-α-diethylamino-*o*-cresol (Table IX, compound 2) was prepared from the corresponding 6-methoxy analog (compound 3) by demethylation with hydrobromic acid.

Acknowledgments.—The authors are greatly indebted to Drs. R. J. Porter of the University of Michigan, A. L. Tatum of the University of Wisconsin and E. K. Marshall of the Johns Hopkins University for their pharmacological study of the compounds presented in this publication.[13] For the sake of simplicity, only the quinine equivalents of Dr. Porter have been reproduced. Dr. Robert C. Elderfield, who represented the O.S.R.D., kindly supplied several 4-chloroquinolines, 9-chloroacridines and dialkylamines of high molecular weight. We are grateful to Dr. C. K. Banks, Messrs. H. J. Nicholas, D. F. Walker, L. M. Montibeller, M. H. Darwish, M. L. Black and H. A. DeWald, of this Laboratory, who contributed several of the compounds reported, and to Dr. L. A. Sweet, Director of Chemical Research, for his keen interest during the course of the studies. Mr. A. W. Spang and Miss Patricia Keller supplied the microanalytical data.

(13) The facilities for testing the compounds described were provided by the Office of Scientific Research and Development through the Committee on Medical Research and by Dr. A. L. Tatum of the Department of Pharmacology in the University of Wisconsin.

Experimental

Acetamidophenols (Table I).—One-tenth of a mole each of the nitrophenol and acetic anhydride were dissolved in 50 cc. of acetic acid. After the addition of 0.2 g. of platinum oxide catalyst, the mixture was shaken in the customary manner under a pressure of about three atmospheres of hydrogen gas until three molecular equivalents had been absorbed. The catalyst was removed by filtration and the acetic acid removed by distillation under reduced pressure. Usually the crude acetamidophenol separated as a white or light gray crystalline solid pure enough for further syntheses.

2-Allyl-4-acetamidophenol.[14]—A solution of 96 g. (1.1 moles) of the allyl ether of 4-acetamidophenol in 70 g. of diethylaniline was heated at boiling temperature for forty minutes. The solution was cooled and diluted with chloroform prior to thorough extraction with 10% sodium hydroxide solution. Enough ether was added to form a distinct upper layer. The combined alkaline extracts were washed twice with ether, and then treated with a slight excess of acetic acid. Extraction of the product with ether, drying and evaporation of the extracts left an oil which was crystallized from a benzene and petroleum ether mixture; m. p. 91–93°. Recrystallization from the same mixture with charcoal treatment yielded 80 g. (83%) of pure product; m. p. 93–94°.

Acetamido-α-alkylamino-*o*-cresols[15] (Table II).—A mixture of equivalent amounts of the acetamidophenol, formaldehyde and aliphatic amine, suspended in about 250 cc. of alcohol per mole of the phenol, was heated in a steam-bath for one to three hours. Upon cooling a crystalline mass usually formed readily, and the product was washed with acetone, alcohol or dilute alcohol. After drying, the product was ordinarily white and of high enough purity to be used in further syntheses.

In certain cases when a crystalline product could not

(14) Claisen, *Ann.*, **418**, 97 (1919).

(15) German Patent 92,309; *Frdl.*, **4**, 103 (1897).

be readily obtained by the foregoing procedure, the volatile materials were removed under reduced pressure and the residue taken into ether and treated with excess alcoholic hydrogen chloride. The monohydrochloride of the desired acetamido-α-alkylamino-*o*-cresol precipitated as an oil, but after treatment with acetone or ether, it crystallized as a white solid.

4-Amino-α-diethylamino-*o*-cresol Dihydrochloride (SN 12,458).—A mixture of 500 g. (2.12 mole) of 4-acetamido-α-diethylamino-*o*-cresol and one liter of 20% hydrochloric acid was heated at refluxing temperature for an hour. The solution was evaporated under reduced pressure to a thick sirup. A liter of benzene was stirred well into the sirup, and the evaporation repeated. Once again the process was repeated using a liter of denatured absolute alcohol. Finally, the sirup was dissolved in two liters of alcohol. The desired salt was then precipitated by the addition of a liter and a half of ether. A total of 541 g. (96% yield) of off-white product was obtained; m. p. 218–220° (dec.).

For analysis a sample was recrystallized from a mixture of alcohol and ethyl acetate; the melting point of the white product did not change.

Anal. Calcd. for $C_{11}H_{18}N_2O \cdot 2HCl$: C, 49.44; H, 7.54. Found: C, 49.70; H, 7.60.

4-Amino-α-1-piperidyl-*o*-cresol Dihydrochloride.—In the same manner, this analog was obtained in a yield of 91% from 4-acetamido-α-1-piperidyl-*o*-cresol[15]; m. p. 153–155° (dec.). Recrystallized from alcohol for analysis, there was no change in the melting point.

Anal. Calcd. for $C_{12}H_{18}N_2O \cdot 2HCl \cdot H_2O$: C, 48.49; H, 7.46; N, 9.43. Found: C, 48.63; H, 7.43; N, 9.10.

4-Amino-α-4-morpholinyl-*o*-cresol Dihydrochloride.—Similarly this compound was obtained in a yield of 45% from 4-acetamido-α-4-morpholinyl-*o*-cresol; m. p. 259–260° (dec.).

Anal. Calcd. for $C_{11}H_{16}N_2O_2 \cdot 2HCl$: N, 9.97. Found: N, 9.93.

α-Alkylamino-4-nitro-*o*-cresols (Table III).—The two synthetic methods used in obtaining these compounds are described in the following procedures.

Procedure A.—One-tenth of a molecular equivalent each of the nitrophenol, paraformaldehyde and aliphatic amine were dissolved in 25 cc. of alcohol. The solution was heated in a steam-bath for at least two hours or until the alcohol had evaporated. The residue was treated with an excess of dilute hydrochloric acid to precipitate an insoluble white hydrochloride.

The yellow crystalline free base could be obtained by trituration of the hydrochloride with ammonia.

Procedure B.—A mixture of one-tenth of a mole of α-chloro-4-nitro-*o*-cresol[7] and two-tenths of a mole of aliphatic amine in 150 cc. of absolute ethanol was heated at refluxing temperature for three hours. The volatile materials were removed by distillation under reduced pressure, and the residue was washed with water for the removal of recovered aliphatic amine hydrochloride. The washed residue was dissolved in acetone and the solution dried over potassium carbonate. An equal volume of ether was added, and an excess of alcoholic hydrogen chloride precipitated the desired product as a white crystalline hydrochloride.

2-Ethoxy-5-nitrobenzyl Chloride.—A mixture of 33.4 g. (0.2 mole) of 4-nitrophenetole, 19.8 cc. (0.26 mole) of 37% formalin, and 16.5 g. of zinc chloride was stirred well at 95 to 100° while a rapid stream of hydrogen chloride gas was allowed to pass through it. After five hours, the mixture was allowed to cool overnight. The temperature was raised to 90°, and 35 cc. of water was added. The mixture was cooled, while stirring in an ice-bath, to precipitate the product in small lumps. The solid was collected on a filter and washed with water. A yield of 32.4 g. (75%) of white material was obtained; m. p. 72–75°. A sample was recrystallized from methanol for analysis, with no change in melting point.

Anal. Calcd. for $C_9H_{10}ClNO_3$: C, 50.13; H, 4.67. Found: C, 50.54; H, 4.84.

Nitrobenzylamines (Table IV).—The synthetic method is essentially the same as that of Procedure B, Table III. However, benzene was found more desirable here than alcohol as a solvent since the nitrobenzyl chlorides and the 2-alkoxy-5-nitrobenzyl chlorides, in contrast with α-chloro-4-nitro-*o*-cresol, dissolved quite readily in it. Furthermore, the excess alkylamine hydrochlorides were removed almost quantitatively by their insolubility in benzene, giving an indication of the expected yield of crude product.

In practice, the reaction mixture was cooled and the separated alkylamine salt collected. The filtrate was evaporated under reduced pressure, and the residue was dissolved in ether. After thorough washing of the ether solution with water and finally with saturated salt solution, drying was effected over potassium carbonate. The desired product could be obtained as the hydrochloride by the addition of alcoholic hydrogen chloride to the filtered solution.

4-Chloroquinolines (Table V).—The method of Price and Roberts[11] was employed. Ethoxymethylene malonic ester was condensed with the appropriate aromatic amine by heating them in diphenyl oxide. Ring closure to the 3-carbethoxy-4-hydroxyquinoline was effected in the same medium. The corresponding acid was obtained by alkaline hydrolysis and decarboxylated by heating in diphenyl oxide. The final step was accomplished by treatment of the 4-hydroxyquinoline with phosphorus oxychloride.

Heterocyclic-amino-α-amino-*o*-cresols (Tables VI to XIII, inclusive).—The preparative methods for these compounds, together with the heterocyclic-amino-benzylamines, are described in the following procedures.

Procedure C.—For each mole of acetamido-α-alkylamino-*o*-cresol (Table II), 500 cc. of 20% hydrochloric acid was added, and the mixture was heated at refluxing temperature for an hour. The solution was cooled and treated with concd. sodium hydroxide solution until just acid to congo red. An equivalent amount of chloroheterocyclic was added, and the resulting mixture was then heated in a steam-bath for about two hours. In many cases, a crystalline hydrochloride formed after cooling, and the product was purified by recrystallization. At other times, the reaction mixture was made basic with ammonia or alkali solution and the free base either crystallized or it was extracted with chloroform. In the latter case, the extract was washed with water and dried over potassium carbonate. The filtered solution was then treated with excess alcoholic hydrogen chloride and diluted with ether or acetone for the precipitation of the desired salt. The product was then recrystallized from the solvent indicated in the table.

Procedure D.—The α-alkylamino-4-nitro-*o*-cresol, base or hydrochloride, (Table III) or the nitrobenzylamine (Table IV) was suspended in absolute alcohol and reduced catalytically using platinum oxide catalyst. The solution was treated with a slight excess of alcoholic hydrogen chloride and filtered to remove the catalyst. An equivalent amount of chloroheterocyclic was added to the filtrate, and the directions in Procedure C were followed thereafter.

Procedure E.—In a manner similar to Procedure D, the crystalline 4-amino-α-substituted-amino-*o*-cresol dihydrochloride was simply heated with the desired chloroheterocycle in water or alcohol.

Procedure F.—This method is the same as Procedure C, except that the intermediate acetamido-α-alkylamino-*o*-cresol was not isolated as a pure compound. After the Mannich reaction had been carried out, the volatile materials were removed under reduced pressure. The crude residue was treated thenceforth as the crystalline intermediate in Procedure C. Yields are based on the amount of acetamidophenol used. A by-product of this reaction is the usually relatively insoluble 4-hydroxyanilinoheterocycle; when 4,7-dichloroquinoline is employed, the by-product has been shown to be 7-chloro-4-(4-hydroxyanilino)-quinoline.

7-Chloro-4-(4-hydroxyanilino)-quinoline Monohydrochloride.—To a solution of 72.8 g. (0.5 mole) of 4-amino-

phenol hydrochloride in 500 cc. of water, 99 g. (0.5 mole) of 4,7-dichloroquinoline[16] was added. The mixture was heated in a steam-bath for two hours. After standing for two days, the yellow product was collected on a filter, washed with water and dried at 110°; yield 145 g. (94%); m. p. over 320°. A small sample was recrystallized from methanol for analysis.[17]

Anal. Calcd. for $C_{16}H_{11}ClN_2O \cdot HCl$: C, 58.64; H, 3.94. Found: C, 59.17; H, 4.11.

6-Chloro-9-(4-hydroxyanilino)-2-methoxyacridine.—This compound was obtained as the orange monohydrochloride by the foregoing procedure in 98% yield; m. p. over 300°. Trituration of a small sample with excess ammonia gave the free base. Recrystallized from dioxane, it melted at 266° (dec.).

Anal. Calcd. for $C_{20}H_{15}ClN_2O_2 \cdot H_2O$: C, 65.13; H, 4.65. Found: C, 65.54; H, 4.62.

4-(7-Chloro-4-quinolylamino)-α-monoethylamino-o-cresol Dihydrochloride (Table XII, Compound 3).—A mixture of 30.7 g. (0.1 mole) of 7-chloro-4-(4-hydroxyanilino)-quinoline monohydrochloride, 6.3 g. (0.2 mole) of 95% paraformaldehyde, 27.2 cc. (0.2 mole) of alcoholic ethylamine, and 125 cc. of alcohol was heated at refluxing temperature for sixteen hours. Upon cooling, 9 g. of starting material was recovered unchanged. The filtrate was evaporated to dryness and the residue triturated with acetone to yield a solid which was collected on a filter. Treatment of this solid with 100 cc. of warm water left a total of 23.2 g. of unchanged starting material. The aqueous filtrate was made basic with ammonia, and the precipitated free base was extracted with chloroform. After being washed with water, the extract was dried over potassium carbonate. The filtered solution was evaporated to dryness, and the residue taken up in acetone. The addition of excess alcoholic hydrogen chloride precipitated a crude yellow salt. Recrystallized first from alcohol and then from alcohol–methanol, only 1.5 g. (4% yield) of the desired product was obtained; m. p. 280° (dec.).

4-(6-Hydroxy-4-quinolylamino)-α-diethylamino-o-cresol Dihydrochloride (Table IX, Compound 2).—A mixture of 10 g. of 4-(6-methoxy-4-quinolylamino)-α-diethylamino-o-cresol dihydrochloride (Table IX, compound 3) and 100 cc. of 48% hydrobromic acid was heated at boiling temperature for two hours. The mixture was made basic with ammonia, precipitating a yellow solid base. This was collected on a filter, washed with water, converted to the dihydrochloride by treatment with alcoholic hydrogen chloride.

(16) Obtained through Dr. R. C. Elderfield from the University of Illinois.

(17) Microanalysis by Arlington Laboratories.

Summary

A group of 122 heterocyclic-amino α-amino-o-cresols and a related group of 12 heterocyclic-amino benzylamines have been synthesized with the object of finding the most effective antimalarial compounds in the general class. All these compounds are new. For the purpose of studying the relationship of chemical structure to antimalarial effectiveness, they have been classified in seven tables. Preparation of the intermediate acetamidophenols, acetamido-α-alkylamino-o-cresols, α-alkylamino-4-nitro-o-cresols, nitrobenzylamines, and 4-chloroquinolines is also described.

This general class includes the most active 4-aminoquinolines heretofore reported in trophozoite-induced *P. gallinaceum* infection in the chick. Recent clinical reports on one member of the series (Camoquin) are promising.

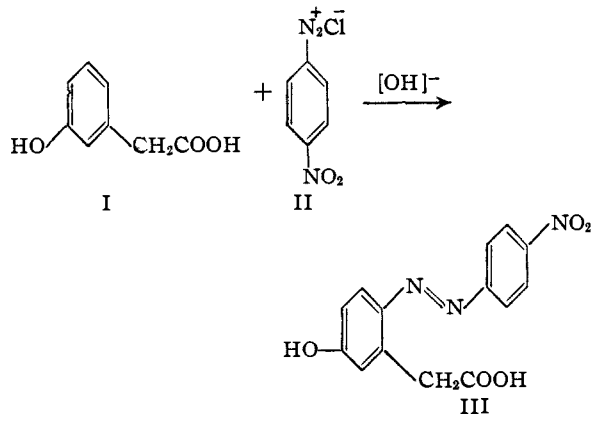
DETROIT 32, MICHIGAN RECEIVED OCTOBER 14, 1947

[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

A New Synthesis of Cinnoline Derivatives: Heterocyclic Steroid Analogs

BY EDMUND C. KORNFELD

In connection with another synthetic problem in progress in these laboratories *m*-hydroxyphenylacetic acid (I) was coupled in alkaline solution with diazotized *p*-nitroaniline (II) to form the azo dye (III) in the normal fashion. It was planned to carry out reactions on the carboxyl group of this product, and in order to effect these changes it was necessary to protect the free hydroxyl function. The azo compound was, therefore, subjected to the action of acetic anhydride in the presence of a trace of sulfuric acid as catalyst, and from the resulting reaction mixture was isolated in good yield a non-acidic, yellow, crystalline product. The analyses indicated that one acetyl group had been introduced, but they showed also that one molecule of water had been eliminated under the acetylating conditions. From the properties and reactions of the product it was evident that cyclization to a cinnoline derivative (V) had taken place. The steps in the process involved first a cyclization of the azo compound in its tautomeric form (IIIa) to 2-*p*-nitrophenyl - 3,6 - diketo - 2,3,4,6 - tetrahydrocinnoline (IV) and then acetylation of the enol form of IV to yield 2-*p*-nitrophenyl-3-acetoxy-6-keto-2,6-dihydrocinnoline (V).



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