Amebicides. II. Acyl Derivatives of 2-Amino-1,4-naphthoquinone

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Buu-Hoï[2] reported that the 1-naphthylamine, *p*-phenylenediamine, 1,5-naphthylenediamine and similar derivatives of 2-chloro-1,4-naphthoquinone were capable of inhibiting the growth of the tubercle bacillus. Calandra and Adams[3] prepared amino derivatives of 2 - chloro - 1,4 - naphthoquinone by treating 2,3-dichloro-1,4-naphthoquinone with amino acids, aminoalkanes aminobenzene, sulfonamide and aminopyridines and found them active against acid-producing bacteria. Thus, it seemed feasible to prepare a number of 2-acylamino-3-chloro-1,4-naphthoquinones to test for biological activity. As these compounds were found to exhibit amebicidal activity, it was logical to replace the 3-chloro with various substituted amino groups to determine the effect of this change on amebicidal activity. This change in structure did indeed enhance the amebicidal activity.

The preparation of 2-amino-3-chloro-1,4-naphthoquinone by the action of ammonia on 2,3-dichloro-1,4-naphthoquinone has been reported by Fries and Ochwat,[4] who also found that this compound was easily acetylated. The activity of the chlorine was greatly enhanced by the acetylation

(1) Research Fellows of Parke, Davis & Co., 1950–1953.

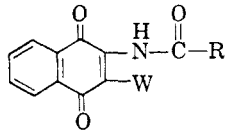
(2) Ng. Ph. Buu-Hoï, *Bull. soc. chim.*, **11**, 578 (1944).

(3) J. C. Calandra and E. C. Adams, *J. Am. Chem. Soc.*, 4804 (1950).

(4) K. Fries and P. Ochwat, *Ber.*, **56B**, 259 (1921); *Ber.*, **56**, 1291 (1923).

TABLE I

2-ACYLAMINONAPHTHOQUINONE DERIVATIVES



	R	W	Yield, %	M.P. °	Formula	Analysis Nitrogen, % Calcd.	Found
1	CH_3	Cl	60	218–219[a]			
2		—$NHC_{14}H_{29}$	95	141–142	$C_{26}H_{38}N_2O_3$	6.57	6.78
3		—NHC_6H_5	88	202–204[b]			
4	C_2H_5	Cl	85	190–192[c]	$C_{13}H_{10}NO_3Cl$		
5		—$NHC_{14}H_{29}$	80	124–125	$C_{27}H_{40}N_2O_3$	6.36	6.38
6		—NH(2-Butyl)	88	111–113	$C_{17}H_{20}N_2O_3$	9.33	9.30
7		—NHC_6H_5	85	182–183	$C_{19}H_{17}N_2O_3$	8.75	8.67
8		—NH(*p*-Tolyl)	85[d]	165–166[e]	$C_{20}H_{18}N_2O_3$	8.38	8.56
9		—NH(*o*-Tolyl)	90	165 dec.	$C_{29}H_{18}N_2O_3$	8.38	8.39
10	C_3H_7	Cl	90	164–165[f]	$C_{14}H_{12}NO_3Cl$[e]		
11		—NH(1-Butyl)	48	148–149	$C_{18}H_{22}N_2O_3$	8.91	8.83
12		—NH(1-Heptyl)	50	120–122	$C_{21}H_{28}N_2O_3$	7.86	8.07
13		—$NHC_{14}H_{29}$	85	112–114	$C_{28}H_{42}N_2O_3$	6.23	6.16
14		—NHC_6H_5	75	207–208	$C_{20}H_{18}N_2O_3$	8.38	8.29
15		—NH(*p*-Tolyl)	89	149–150	$C_{21}H_{20}N_2O_3$	8.04	8.02
16	*i*-C_4H_9	Cl	51	162–163[g]			
17		—$NHC_{14}H_{29}$	50	109–110	$C_{29}H_{44}N_2O_3$	5.98	6.10
18	$C_{11}H_{23}$	Cl	26	133–134	$C_{22}H_{28}NO_3Cl$[h]	3.59	3.51
19		—NH(1-Butyl)	60	124–127	$C_{26}H_{38}N_2O_3$	6.57	6.63
20		—NH(1-Heptyl)	64	108–110	$C_{29}H_{44}N_2O_3$	5.98	6.11
21		—NH($C_{14}H_{29}$)	61	125–126	$C_{36}H_{58}N_2O_3$	4.94	5.11
22	$C_{17}H_{35}$	Cl	54	133–134	$C_{28}H_{40}NO_3Cl$[i]	2.95	3.19
23		—NH(1-Butyl)	33	123–124	$C_{32}H_{50}N_2O_3$	5.49	5.41
24		—NH(1-Heptyl)	66	115–116	$C_{35}H_{54}N_2O_3$	5.07	5.24
25		—$NHC_{14}H_{29}$	51	129–130	$C_{42}H_{26}N_2O_3$	4.30	4.37
26		—NH(*p*-Tolyl)	83	162–163	$C_{35}H_{48}N_2O_3$	5.14	5.34
27	$CHCl_2$	Cl	50	218–219	$C_{12}H_6NO_3Cl_3$[j]	4.40	4.44
28		—NH(1-Butyl)	65	151–152	$C_{16}H_{16}N_2O_3Cl_2$	7.89	7.95
29		—NH(1-Heptyl)	37	141–142	$C_{19}H_{22}N_2O_3Cl_2$	7.05	7.09
30		—$NHC_{14}H_{29}$	54	128–130	$C_{26}H_{36}N_2O_3Cl_2$	5.65	5.97
31		—NH(*p*-Tolyl)	76	203 dec.	$C_{19}H_{14}N_2O_3Cl_2$	7.20	7.16

[a] Reported[4] m.p. 218–219°. [b] Reported m.p. 203°. [c] Reported[5] m.p. 188–189°. [d] Darkened at 94° but regained orange color as the temperature rose above 100°. [e] See ref. 2. [f] Reported[6] m.p. 162–163°. [g] Reported[6] m.p. 161°. [h] Calcd.: Cl, 9.12; found: Cl, 9.31. [i] Calcd.: Cl, 7.51; found: Cl, 7.69. [j] Calcd.: Cl, 33.38; found: Cl, 33.61.

and these workers found that the halogen readily reacted with amines.

Acyl groups were selected for use in this work that ranged from two to eighteen carbons. The dichloroacetyl group was included as a representative as the group is found in chloroamphenicol.[5] Hoover and Day[6] have recently reported the synthesis and use of some 2-acylamino-3-amino-1,4-naphthoquinones in the formation of two substituted 1H-naphthimidazole-4,9-diones.

Although none of the compounds reported in this paper have high amebicidal activity, certain features which correlate this activity with structure are of interest. The lauric acid and stearic acid derivatives, No. 18–26 were inactive in the amebicidal and tubercular tests. Propionic acid and butyric acid derivatives were the most active, and compound No. 9 exhibited the highest activity of any of those tried in the two tests mentioned above. This compound was amebicidal at a dilution of 1:50,000.

EXPERIMENTAL

Acylation of 2-amino-3-chloro-1,4-naphthoquinone. A mixture of 1 mole of 2-amino 3 chloro 1,4-naphthoquinone and 3 moles of the desired acyl halide in 10 parts of dioxane was refluxed for 12 to 15 hr.

A yellow solid separated when the mixture was cooled. This solid was removed and recrystallized from a 50:50 mixture of methanol and dioxane. Most of the acyl derivatives were yellow to tan in color and somewhat light sensitive. The data for these compounds are included in Table I.

2-Acylamino-3-alkyl (or aryl)amino-1,4-naphthoquinones. To a hot solution of 0.01 mole of 2-acylamino-3-chloro-1,4-naphthoquinone in 25 ml. of dioxane was added 0.02 mole of the selected amine. The solution was refluxed for 2 hr., cooled, and filtered. The red product was recrystallized from ethanol. The data for these compounds are given in Table I.

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Conversion of 1-*O*-Methyl-L-sorbose to "α"-L-Glucosaccharinic Acid by Alkali

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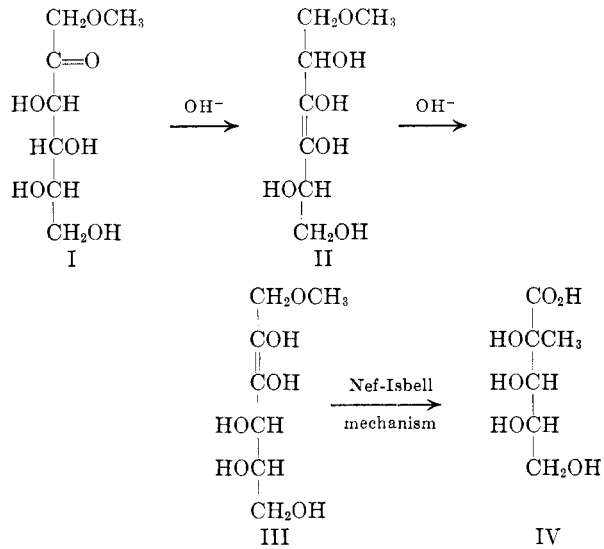
Recent studies by Kenner and his associates have indicated certain general rules, based on the Nef-Isbell mechanism,[1] relating the effects of substitution in a sugar molecule to the course of its conversion to saccharinic acids. For example, treatment of 1-*O*-methyl-D-fructose,[2] 3-*O*-methyl-D-fructose,[3] and 4-*O*-methyl-D-fructose[4] with aqueous calcium hydroxide is reported to lead, respectively, to the preferential formation of the saccharinic, metasaccharinic, and isosaccharinic acid structures.

From the above results, it was to be expected that a new acid of the saccharinic acid class, 2-*C*-methyl-L-*xylo*- or 2-*C*-methyl-L-*lyxo*-pentonic acid, would be the principal product from the treatment of 1-*O*-methyl-L-sorbose with aqueous calcium hydroxide. Accordingly, we have examined the latter reaction in an effort to obtain a reference compound for further studies of alkaline isomerization in the galactose family of sugars. 1-*O*-Methyl-L-sorbose was prepared in amorphous form by methylation of 2,3:4,6-di-*O*-isopropylidene-L-sorbose, followed by hydrolysis of the isopropylidene groups. After reaction of the methylated ketose with aqueous calcium hydroxide, paper chromatography revealed the presence of at least eight components in the product. The mixture was partially separated by column chromatography on powdered cellulose and, although we were unsuccessful in our attempts to isolate and identify either of the two new saccharinic acids indicated above, there was obtained in low yield a crystalline product that proved to be the enantiomorph of the known "α"-D-glucosaccharinic lactone (2-*C*-methyl-D-*ribo*-pentonic γ-lactone[5]).



The unexpected formation of "α"-L-glucosaccharinic acid may be explained by assuming an initial in-

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(5) J. C. Sowden and D. R. Strobach, *J. Am. Chem. Soc.*, **82**, 954 (1960).