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N-2-PYRIDYLALKANOLAMINES AND ESTERS

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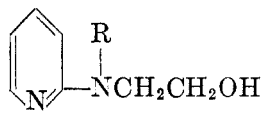
Received April 25, 1949

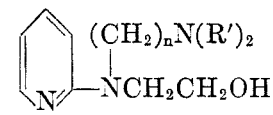
Despite the occurrence of natural compounds with pharmacological activity containing the pyridine nucleus, few attempts at the introduction of this group into the structures of synthetic drugs appear to have been reported. While the work, herein reported, was in progress, reports on the synthesis of 2-pyridyl substituted ethylene diamines as histamine antagonists (1), and longer chained 2-pyridylalkylenediamines as potential antimalarials (2) have appeared. In addition the antihistaminic activity of N,N-dimethyl-N^1-(*p*-methoxybenzyl)-N^1-(2-pyridyl)ethylenediamine has been described (3).

This work was directed to the preparation of alkanolamines containing the pyridine nucleus, so as to examine the influence of this group in various types of pharmacological agents in which the alkanolamine group is an essential contributor to the pharmacological activity, *e.g.*, esters of benzoic acid, *p*-aminobenzoic acid (local anesthetic) and diphenylacetic acid (spasmolytic). Syntheses of N-2-pyridylamino alcohols of types (I) and (II) were undertaken. In addition 2-methyl-2-(2-pyridyl)amino-1,3-propanediol (III) was prepared.



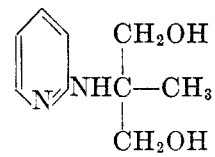
(I)

Ia R = H
Ib R = C_2H_5
Ic R = *n*-C_4H_9
Id R = $C_6H_5CH_2$
Ie R = $HOCH_2CH_2$



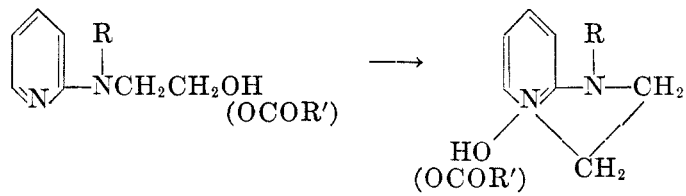
(II)

IIa n = 2, R′ = C_2H_5
IIb n = 2, R′ = *n*-C_4H_9
IIc n = 3, R′ = C_2H_5
IId n = 3, R′ = *n*-C_4H_9



(III)

Equation 1



Of the various methods available for the synthesis of compounds of these types (1, 2, 4, 5) a modification of that by which Bremer (4) prepared Ia was selected as affording the most conveniently applicable general procedure. The higher-boiling and more reactive 2-bromopyridine was used in preference to 2-chloropyridine (4), thus avoiding the need for carrying out the reaction in sealed tubes.

The amino alcohols required for the preparation of type (I) compounds and compound (III) were readily available from commercial sources or by described synthesis. The dialkylaminoalkyl ethanolamines for the preparation of type II were hitherto unknown, but were made by the interaction of the appropriate dialkylaminoalkyl chloride and excess ethanolamine in boiling dioxane. The properties and yields of these intermediates are listed in Table I. The properties

TABLE I

DIALKYLAMINOALKYLAMINOETHANOLS

$(R')_2N(CH_2)_nNHCH_2CH_2OH$

PRODUCT		REAGENTS					B.P., °C/MM.	YIELD		ANALYSIS N, %	
R'	n	$(R')_2N(CH_2)_nCl$		$NH_2CH_2CH_2OH$		Dioxane, cc.		Gms.	%	Calc'd	Found
		Gms.	Moles	Gms.	Moles						
C_2H_5	2	136.6	1.01	183	3.03	430	140–143/24	78	48	17.48	17.33
C_2H_5	3	67	0.45	82.5	1.35	260	146–147/14[a]	48.5	66	16.08	16.23
n-C_4H_9	2	256	1.34	244	4.01	700	136–137/2.5	188.5	65	16.30	16.01
n-C_4H_9	3	258	1.25	380	6.22	400	143–147/2	244	85	12.16	12.10

[a] Hydrochloride, recrystallized from n-propanol, m.p. 181–182.5°. *Anal.* N, Calc'd 11.33%; Found 11.45%.

and yields of the new pyridine derivatives (I b–e, II a–d, and III) are given in Table II.

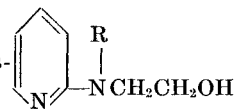
The preparation of esters of these alcohols was not unattended with difficulties inherent in the structures of these compounds. It appeared from the experience of Bremer (4, 6) that any but the mildest conditions for esterification would result in cyclization of the alcohols or their esters to the isomeric dihydroimidazo[1,2-a]-pyridine base or salt (Equation 1).

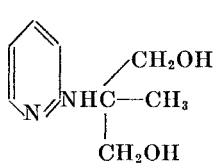
This likelihood is possibly somewhat minimized where R is not H, due to the impossibility of the existence of the tautomeric ketimine of 2-amino pyridine postulated (6) as an intermediate in such cyclizations. In order to avoid completely this complication, the alcohols were esterified at the lowest possible temperature at which reaction occurred with the acyl chlorides.

In many cases it was not possible to prepare crystalline salts of the esters. Purification by distillation was not attempted because of the instability of the compounds at elevated temperature. The crude compounds were simply dried in a high vacuum at room temperature and the resulting oils submitted for pharmacological testing.

The pyridyl ethanolamines were tested for antimalarial activity by the Survey

TABLE II

2-PYRIDYLETHANOLAMINES- 

No.	R	REAGENTS					REACTION CONDITIONS		B.P., °C/MM.	YIELD		FORMULA (SN NO.)	ANALYSIS, % N	
		α-Bromopyridine		$RNHCH_2CH_2OH$		Cumene, cc.	Time, hrs.	Bath Temp., °C.		Gms.	%		Calc'd	Found
		Gms.	Moles	Gms.	Moles									
Ia	H[a]	158	1.0	244	4.0	None	24	160	166–168/9	114.3	83	$C_7H_{10}N_2O$ (SN 2802)	20.13	19.86
Ib	C_2H_5	79	0.5	89	1.0	None	12	145	157–158/15	53.1	64	$C_9H_{14}N_2O$ (SN 2803)	16.86	16.88
Ic	n-C_4H_9	79	0.5	117	1.0	None	50	154	125–127/1	62.6	64.5	$C_{11}H_{18}N_2O$ (SN 2804)	14.42	14.49
Id	$C_6H_5CH_2$[b]	79	0.5	151	1.0	None	21	166	154–159/1	68.9	60	$C_{14}H_{16}N_2O$	[c]	[c]
Ie	$HOCH_2CH_2$	158	1.0	182	2.0	None	389	100	163/1	48.2	26.5	$C_9H_{14}N_2O_2$	15.37	15.42
IIa	$(C_2H_5)_2NCH_2CH_2$	29.7	0.19	72.5	0.47	87	14.5	170	154–158/2	20.5	46	$C_{13}H_{23}N_3O$ (SN 4229)	17.71	17.69
IIb	$(C_4H_9)_2NCH_2CH_2$	67.5	0.43	237	1.07	300	14.5	170	190–192/2	49	39	$C_{17}H_{31}N_3O$ (SN 4230)	14.32	14.27
IIc	$(C_2H_5)_2N(CH_2)_3$	16.7	0.105	43	0.26	55	16	170	160–162/1	15.5	58.5	$C_{14}H_{25}N_3O$ (SN 4227)	16.72	16.73
IId	$(C_4H_9)_2N(CH_2)_3$	31.8	0.2	116.5	0.5	163	18	170	194–200/2	31	50	$C_{19}H_{33}N_3O$ (SN 4228)	13.67	13.55
III		158	1.0	420	4.0	None	89	161–168	189–191/11	36.4	20	$C_9H_{14}N_2O_2$	15.37	15.41

[a] Bremer, *Ann.*, **521**, 286 (1936); obtained by us as a solid, m.p. 65–68° with previous softening at 57.5°.

[b] Rumpf and Kwass, *Bull. soc. chim.*, **10**, 347 (1943).

[c] Purified for analysis as the picrate, m.p. 132.5–134°; *Anal.* Calc'd for $C_{20}H_{19}N_5O_8$: N, 15.31; Found: N, 15.26.

of Antimalarial Drugs under the SN numbers given in Table II. No important activity was disclosed.

EXPERIMENTAL

Preparation of dialkylaminoalkylaminoethanols (Table I). The appropriate, freshly distilled, free dialkylaminoalkyl chloride was dissolved with ethanolamine in dioxane in the quantities indicated in Table I. The mixture was boiled under reflux overnight (14–16 hours). The product usually separated in the course of the reaction as an oil. The dioxane was

TABLE III

ESTERS OF 2-PYRIDYLAMINOALCOHOLS

ALCOHOL	ESTER[g]	M.P., °C	ESTER FORMULA	ANALYSIS % N		PICRATE		ANALYSIS, % N	
				Calc'd	Found	M.P., °C	Formula	Calc'd	Found
Ia	A					171–173.5[a]	$C_{20}H_{17}N_5O_9$	14.86	14.78
Ia	B	73–74[b]	$C_{21}H_{20}N_2O_2$	8.43	8.82	131 (sinters)	$C_{27}H_{23}N_5O_9$	12.47	12.34
Ia	C	162.5–165[c]	$C_{14}H_{16}ClN_3O_2$	14.31	14.71				
Ib	A		$C_{16}H_{18}N_2O_2$	10.36	10.30	146–147[d]	$C_{22}H_{21}N_5O_9$	14.03	14.04
Ib	B	83–84[b]	$C_{23}H_{24}N_2O_2$	7.77	7.69				
Ib	C	93–93.5[b]	$C_{16}H_{19}N_3O_2$	14.73	14.73				
Ic	A		$C_{18}H_{22}N_2O_2$	9.39	8.91	120–121[e]	$C_{24}H_{25}N_5O_9$	13.28	13.24
Ic	C	76–76.5[b]	$C_{18}H_{23}N_3O_2$	13.41	13.39				
Id	A		$C_{21}H_{20}N_2O_2$	8.43	8.09	133–135[a]	$C_{27}H_{23}N_5O$	12.47	12.26
Id	B	93–94[b]	$C_{28}H_{26}N_2O_2$	6.63	6.59				
Id	C	103–103.5[a]	$C_{21}H_{21}N_3O_2$	12.10	12.09				
Ie	A[f]		$C_{23}H_{22}N_2O_4$	7.18	6.82	134–135[a]	$C_{29}H_{25}N_5O_{11}$	11.31	11.14
Ie	B		$C_{37}H_{34}N_2O_4$	4.91	4.55	116.5–117.5	$C_{43}H_{37}N_5O_{11}$	8.76	8.87
IIc	A					136–137[e] softens at 128	$C_{33}H_{35}N_9O_{16}$	15.31	15.46

[a] Recrystallized from ethanol.
[b] Recrystallized from methanol.
[c] Hydrochloride, recrystallized from acetone–ethanol.
[d] Recrystallized from acetone.
[e] Recrystallized from *n*-propanol.
[f] Dibenzoate.
[g] A is benzoate; B is diphenylacetate; C is *p*-aminobenzoate.

removed *in vacuo*. The residue was shaken with a saturated solution of potassium carbonate equal to 1.1 equivalents of the alkyl chloride. The mixture was extracted with ether, and the ether extracts, after being dried over potassium carbonate, were concentrated to a solvent-free residue. The residue was distilled *in vacuo* to yield the products tabulated in Table I.

Preparation of substituted 2-pyridylamino ethanols (Table II). The indicated quantities of 2-bromopyridine and the appropriate aminoalcohol were heated in an oil-bath, kept at the noted temperature or, when carried out in cumene, at the reflux temperature of the mixture for the indicated number of hours. After being allowed to cool, the mixture was dissolved in chloroform. The chloroform solution was shaken with sufficient saturated potassium carbonate solution to neutralize the hydrogen bromide formed in the reaction. The chloroform solution was dried over potassium carbonate, and evaporated to dryness. The residue was distilled *in vacuo* to yield the products listed in Table II.

Preparation of esters of the amino alcohols (*Table III*). Five grams of the amino alcohol was mixed with 5 ml. of benzoyl chloride (added in portions of 1 ml. with adequate stirring and chilling), 8 g. of *p*-nitrobenzoyl chloride, or 6.5–8 grams of diphenylacetyl chloride (7) in a heavy-walled test-tube with a stout stirring rod. The mixture was heated very gently on a steam-bath to start the reaction if it was not spontaneous. As soon as the vigorous exothermic reaction occurred, the test tube was immersed in an ice-bath and stirred vigorously. When the reaction was complete, the contents of the test-tube were transferred, with the aid of hot water, to a separatory funnel, made alkaline with strong squeous sodium hydroxide solution, and extracted with ether [In the case of N-(2-pyridyl)-diethanolamine and 2-methyl-2-(2¹-pyridyl)amino-1,3-propanediol, the *p*-nitrobenzoates were insoluble in ether, so chloroform was used as the extracting agent]. The combined ether extracts were dried over potassium carbonate and the ether removed *in vacuo*. If the residue solidified, the product was recrystallized from the solvent indicated. If the product did not crystallize, it was purified through the picrate. The latter was prepared in anhydrous ether, recrystallized to constant melting point and the picrate decomposed with aqueous ethanolamine. This was accomplished by shaking the finely-powdered picrate with a mixture of ether and a concentrated ethanolamine solution in water. The ether solution was drawn off and the aqueous layer extracted 3 times more with ether. The ether extracts were combined and washed with aqueous ethanolamine solution till the latter was no longer colored yellow, then dried over potassium carbonate and the ether removed *in vacuo*. Some of the esters gave no solid salts, including picrates, and were analyzed and tested in the crude form after removal of the ether.

The *p*-nitrobenzoates were not purified but were reduced directly to the *p*-aminobenzoates. The residue left after removal of the ether was transferred to a hydrogenation bottle and suspended in 75–100 ml. of 95% ethanol. Two grams of 10% palladium-charcoal catalyst was added and the compound hydrogenated at 50–60 lbs. When the hydrogen uptake was complete, the catalyst was filtered off and the solvent removed *in vacuo*. The products were then worked up in the same manner as the other esters.

In order to favor esterification over amide formation, in the case of the secondary amino alcohols, the latter were converted to their hydrochlorides before esterification (8).

SUMMARY

The synthesis of a series of N-2-pyridylalkanolamines, and some esters derived from these alcohols is described. The synthesis of four new dialkylaminoalkylalkanolamines as intermediates in the above syntheses is described.

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REFERENCES

(1) HUTTRER, *et al.*, *J. Am. Chem. Soc.*, **68**, 1999 (1946).
(2) WHITMORE, *et al.*, *J. Am. Chem. Soc.*, **67**, 303 (1945).
(3) BOVET, HORCHLOIS, AND WALTHER, *Compt. rend. soc. biol.*, **138**, 99 (1944).
(4) BREMER, *Ann.*, **521**, 286 (1936).
(5) SHARP, *J. Chem. Soc.*, 1191 (1938).
(6) *cf.* ALLEN, VAN ALLAN, AND WILSON, *J. Am. Chem. Soc.*, **66**, 1805 (1944) for an analogous cyclization.
(7) KLINGEMANN, *Ann.*, **275**, 84 (1893).
(8) COPE AND HANCOCK, *J. Am. Chem. Soc.*, **66**, 1448 (1944).