

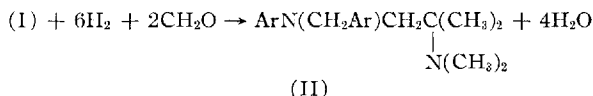
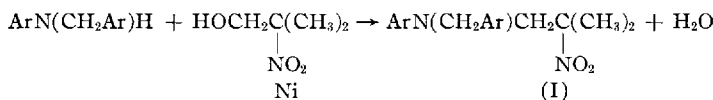
Some New Nitro Amines and Diamines*

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By the reaction of 2-nitro-2-methyl-1-propanol with some aryl aralkylamines, a series of new nitro amines was prepared. Diamines were prepared from these nitro amines by reduction and reductive methylation. Some of the ditertiary amines, prepared by reductive methylation, showed pronounced antihistaminic activity.

JOHNSON (1) has reported the preparation of nitro amines by the reaction of aromatic amines with a nitroparaffin and formaldehyde or with the corresponding nitro alcohol. In these preparations, strongly basic catalysts were used.

It seemed possible that if this reaction could be extended to amines of the type $\text{ArN}(\text{CH}_2\text{Ar})\text{H}$, where Ar represents an aryl group, the resulting nitro amines should be capable of reductive methylation to give compounds which by analogy with other known compounds might be expected to exhibit antihistaminic activity (2). The reactions are illustrated below:



When reactions of the type illustrated were tried, it was found that the amines did not react as readily as the more simple aromatic amines; but under proper conditions, fairly good yields of nitro amines were obtained. Reduction and reductive methylation of these products presented no particular difficulties. The nitro amines prepared are listed in Table I. All of these compounds except No. 6 are yellow, but the shade varies from almost orange to an "off white," depending on the substituents on the aryl groups.

The amines listed in Table II were prepared by reduction and reductive methylation of nitro amines prepared as described above.

The antihistaminic activities of these compounds, relative to diphenylhydramine hydrochloride, were determined by Dr. J. N. Spencer,

of the Pharmaceutical Research Division, Commercial Solvents Corp., by a method similar to that described by Rocha e Silva and Beraldo (3). They are recorded in the table as per cent activity. Thus, 100 means that the antihistamine activity of the compound was equal to that of diphenylhydramine hydrochloride.

EXPERIMENTAL

Nitro Amines.—The most convenient method found for preparing the nitro amines consisted in refluxing a solution of the amine and 2-nitro-2-methyl-1-propanol in *n*-butyl alcohol with a small amount of a mildly basic catalyst such as sodium carbonate or sodium acetate. Under these conditions, most of the reactions were complete in six to twelve hours, although a few took longer. The course of the reaction was followed by separating and measuring the water formed. The nitro amines generally crystallized from the *n*-butyl alcohol on cooling. The preparation of *N*-benzyl-*N*-phenyl-2-nitroisobutylamine is given as an example.

A mixture of 18.3 Gm. (0.1 mole) of *N*-benzyl-aniline, 11.9 Gm. (0.1 mole) of 2-nitro-2-methyl-1-propanol, 0.3 Gm. of sodium carbonate, and 75 ml. of *n*-butyl alcohol was refluxed for seventeen hours with a trap attached for removing the water. Then the reaction mixture was decanted, cooled, and filtered, yielding 14.8 Gm. of yellow crystals, m. p. 80–83°. Repetition of this process, using the filtrate as the reaction medium, gave 19.3 Gm. of product. Thus, the over-all yield was 60%. The product was crystallized from methanol.

Primary, Tertiary Amines.—Reduction of the nitro amines was carried out by hydrogen in the presence of Raney nickel. An example is given below.

A solution of 29.8 Gm. (0.1 mole) of *N,N*-dibenzyl-2-nitroisobutylamine in 500 ml. of methanol was reduced in the presence of 10 Gm. of Raney nickel at 1000 p. s. i. and 50°. After reduction, the mixture was concentrated on the steam bath, dissolved in ether, and made just acidic with concentrated hydrochloric acid. A white precipitate formed which was filtered, washed with ether, and dried, yielding 25.5 Gm. of product. Recrystallization from water gave 18 Gm. The product contained

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TABLE I.—NITRO AMINES OF THE FORMULA $\text{ArCH}_2\text{N}(\text{Ar}')\text{CH}_2\text{C}(\text{NO}_2)(\text{CH}_3)_2$

No.	Ar	Ar'	M. P., ^a ° C.	Yield, %	Analyses, %			
					N, Calcd.	N, Found	Cl, Calcd.	Cl, Found
1	C_6H_5	C_6H_5	83.5–84.5	60	9.85	9.61
2	$p\text{-ClC}_6\text{H}_4$	C_6H_5	93–94	50	8.79	8.53	11.12	11.08
3	C_6H_5	$p\text{-CH}_3\text{C}_6\text{H}_4$	109.5–110	69	9.36	9.22
4	$p\text{-CH}_3\text{OC}_6\text{H}_4$	C_6H_5	101.5–102.5	58	8.91	8.79
5	C_6H_5	$p\text{-CH}_3\text{OC}_6\text{H}_4$	74.5–76	63	8.91	8.73
6	C_6H_5	$\text{C}_6\text{H}_5\text{CH}_2$	46.5–47.5	53	9.39	9.15
7	$p\text{-CH}_3\text{OC}_6\text{H}_4$	$p\text{-CH}_3\text{OC}_6\text{H}_4$	77–78	68	8.15	7.91
8	$p\text{-CH}_3\text{OC}_6\text{H}_4$	$p\text{-CH}_3\text{C}_6\text{H}_4$	117.5–118	56	8.53	8.45
9	$3,4\text{-CH}_2\text{O}_2\text{C}_6\text{H}_3$	C_6H_5	86–87	51	8.53	8.45
10	$p\text{-CH}_3\text{OC}_6\text{H}_4$	$p\text{-ClC}_6\text{H}_4$	110.5–112	48	8.03	7.93	10.17	10.06
11	C_6H_5	$p\text{-C}_6\text{H}_5\text{C}_6\text{H}_4$	120.5–122	50	7.77	7.57
12	C_6H_5	$\alpha\text{-Naphthyl}$	132–134.5	61	8.38	8.29

^a Corrected.TABLE II.—DIAMINE HYDROCHLORIDES OF THE FORMULA $\text{ArCH}_2\text{N}(\text{Ar}')\text{CH}_2\text{C}(\text{CH}_3)_2\cdot\text{HCl}$

No.	Ar	Ar'	R	M. P., ^b ° C.	Yield, %	Analyses, %				Anti-histaminic Activity, % ^e
						N, Calcd.	N, Found	Cl, Calcd.	Cl, Found	
1	$p\text{-CH}_3\text{OC}_6\text{H}_4$	C_6H_5	H	172–174	89 ^d	8.73	8.72	11.05	11.14	1.0
2	C_6H_5	$\text{C}_6\text{H}_5\text{CH}_2$	H	149–153 (dec.)	79	9.19	9.01	11.63	11.61	2.0
3	$p\text{-CH}_3\text{OC}_6\text{H}_4$	$p\text{-CH}_3\text{C}_6\text{H}_4$	H	87.5–89 ^c	...	8.37	8.24	10.59	10.51	<1.0
4	$p\text{-CH}_3\text{OC}_6\text{H}_4$	$p\text{-ClC}_6\text{H}_4$	H	101–104 ^c	51	7.89	7.85	10.96	19.67	1.0
5	$p\text{-CH}_3\text{OC}_6\text{H}_4$	$\alpha\text{-Naphthyl}$	H	178–181	33 ^d	7.55	7.37	9.56	9.49	... ^a
6	C_6H_5	$p\text{-C}_6\text{H}_5\text{C}_6\text{H}_4$	H	221–225.5	...	7.64	7.45 ^a
7	C_6H_5	C_6H_5	CH_3	127.5–128.5	73 ^d	8.78	8.63	11.12	11.17	100
8	$p\text{-ClC}_6\text{H}_4$	C_6H_5	CH_3	187.5–190	55	7.93	7.58	20.07	19.57	100
9	$p\text{-CH}_3\text{OC}_6\text{H}_4$	C_6H_5	CH_3	165–166	46	8.03	7.85	10.16	10.33	50
10	$p\text{-CH}_3\text{OC}_6\text{H}_4$	$p\text{-CH}_3\text{C}_6\text{H}_4$	CH_3	196–197	74	7.72	7.54	9.77	9.86	2
11	$p\text{-CH}_3\text{OC}_6\text{H}_4$	$p\text{-CH}_3\text{OC}_6\text{H}_4$	CH_3	169.5–172	54	7.39	7.14	9.36	9.48	1
12	C_6H_5	$\text{C}_6\text{H}_5\text{CH}_2$	CH_3	104–106	88 ^d	8.42	8.25	10.65	10.38	2
13	$3,4\text{-CH}_2\text{O}_2\text{C}_6\text{H}_3$	C_6H_5	CH_3	189–191	64	7.72	7.54	9.77	9.69	10
14	$p\text{-CH}_3\text{OC}_6\text{H}_4$	$p\text{-ClC}_6\text{H}_4$	CH_3	201–202	70	7.31	7.22	18.50	17.93	10
15	C_6H_5	$p\text{-C}_6\text{H}_5\text{C}_6\text{H}_4$	CH_3	175–179	60 ^d	7.09	7.02	8.98	8.79	... ^a

^a Too insoluble to assay.^b Corrected.^c Of monohydrate.^d Of free base; other yields are for hydrochlorides.^e Relative to diphenhydramine hydrochloride.

water of crystallization which was removed by drying at 105° at about 1 mm. of mercury.

Tertiary, Tertiary Amines.—Reductive methylations of the nitro amines were carried out by two-step reductions, with the second step in the presence of formaldehyde. An illustrative example is given below.

To a quantity of 31.4 Gm. (0.1 mole) of *N*-*p*-methoxybenzyl-*N*-phenyl-2-nitroisobutylamine in 500 ml. of methanol was added 10 Gm. of Raney nickel and the mixture was reduced at 1000 p. s. i. and 50°. Then the bomb was cooled, 25 Gm. of aqueous 37% formaldehyde solution was added, and the reduction was continued under the same conditions as before. After hydrogen absorption had ceased, the catalyst was filtered out and the filtrate was concentrated to give 30 Gm. of residue. This was dissolved in 100 ml. of ether; 25 ml. of ethanol was added, and the solution was made just acid with concentrated hydrochloric acid. The mixture crystallized and was filtered to give 16 Gm.; m. p. 162–165°. Recrystallization was carried out using an ethanol-benzene mixture.

SUMMARY

1. A series of new nitro amines has been prepared by the reaction between 2-nitro-2-methyl-1-propanol and some amines of the type $\text{ArN}(\text{CH}_2\text{Ar})\text{H}$ where Ar represents an aryl group.

2. Reduction of some of the nitro amines led to a series of amines which showed weak anti-histaminic activity.

3. Reductive methylation of some of the nitro amines led to a series of amines, some of which showed moderate to strong antihistaminic activity.

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