ACKNOWLEDGMENTS

We thank Mr. G. Ensell for the construction of the variable-temperature assembly. The work was supported by the National Research Council and the Research Corporation.

1. H. S. Gutowsky and C. H. Holm. J. Chem. Phys. **25**, 1228 (1956).
2. J. A. Pople, W. G. Schneider, and H. J. Bernstein. High resolution nuclear magnetic resonance. McGraw-Hill Book Co., Inc., New York, N.Y. 1959. p. 73.
3. S. W. Benson. The foundations of chemical kinetics. McGraw-Hill Book Co., Inc., New York, N.Y. 1960. p. 250.

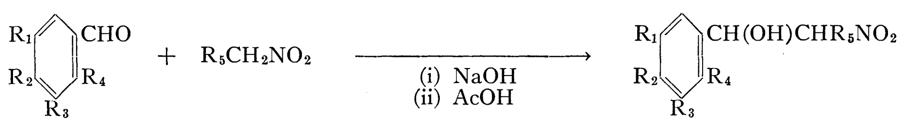
Received September 21, 1962.
Department of Chemistry,
University of Manitoba,
Winnipeg, Manitoba.

THE PREPARATION OF SOME NEW 1-PHENYL-2-NITROETHANOL DERIVATIVES

R. A. Heacock and O. Hutzinger

An improved method for the synthesis of 1-phenyl-2-nitroethanol derivatives, substituted in the 3- and 4-positions of the benzene ring (of the general type shown in formula III), has recently been described (1). The preparative procedure involved condensation of a suitable aldehyde (I) with excess nitromethane (II: $R_5 = H$) at about 5°, in the presence of sodium hydroxide in aqueous alcoholic solution, using a very short reaction time ($\not> 60$ seconds).

This communication describes the preparation of eight further examples of this class of compound containing two, three, or four substituents in the benzene ring. (In all cases, the substituents in the 3- and 4-positions of the aromatic ring were either methoxy or benzyloxy groups.) Uusally, no particular difficulties were encountered when the condensation was carried out with nitroethane (II: $R_5 = CH_3$) instead of nitromethane (II: $R_5 = H$). However, 4-benzyloxy-3,5-dimethoxybenzaldehyde, which condensed readily with nitromethane under the conditions described above, could not be induced to condense with nitroethane by this technique. The following new 1-phenyl-2-nitroethanol derivatives have been prepared: 4-benzyloxy-3,5-dimethoxy-α-nitromethylbenzyl



I II III

alcohol (III: $R_1 = R_3 = OCH_3$; $R_2 = OCH_2C_6H_5$; $R_4 = R_5 = H$); 3,4,5-trimethoxy-α-(1-nitroethyl)-benzyl alcohol (III: $R_1 = R_2 = R_3 = OCH_3$; $R_4 = H$; $R_5 = CH_3$); 3,4-dimethoxy-6-nitro-α-nitromethylbenzyl alcohol (III: $R_1 = R_2 = OCH_3$; $R_3 = R_5 = H$; $R_4 = NO_2$); 3,4-dimethoxy-6-nitro-α-(1-nitroethyl)-benzyl alcohol (III: $R_1 = R_2 = OCH_3$; $R_3 = H$; $R_4 = NO_2$; $R_5 = CH_3$); 5-iodo-3,4-dimethoxy-α-nitromethylbenzyl alcohol (III: $R_1 = R_2 = OCH_3$; $R_3 = I$; $R_4 = R_5 = H$); 5-iodo-3,4-dimethoxy-α-(1-nitroethyl)-benzyl alcohol (III: $R_1 = R_2 = OCH_3$; $R_3 = I$; $R_4 = H$; $R_5 = CH_3$);

TABLE

Preparation of nitroalcohols

Nitroalcohol prepared					Reagents used and reaction conditions						Yield of purified product	
R_1	R_2	R_3	R_4	R_5	Aldehyde (g)	CH_3NO_2 (ml)	$C_2H_5NO_2$ (ml)	Solvent	10% NaOH (ml)	2% AcOH (ml)	(g)	(%)
CH_3O	$C_6H_5CH_2O$	CH_3O	H	H	1.0	0.7	—	95% ethanol (20 ml)	1.3	11.5	0.9	74
CH_3O	CH_3O	CH_3O	H	CH_3	1.0	—	1.2	95% ethanol (20 ml)	1.84	16.0	0.4	29
CH_3O	CH_3O	H	NO_2	H	1.0	0.7	—	Ethanol (40 ml) +dioxane (5 ml)	1.72	14.2	0.9	70
CH_3O	CH_3O	H	NO_2	CH_3	1.0	—	1.0	Ethanol (40 ml) +dioxane (5 ml)	1.72	14.2	0.6	44.5
CH_3O	CH_3O	I	H	H	0.5	0.35	—	Ethanol (10 ml) +dioxane (2 ml)	0.6	5.5	0.4	66
CH_3O	CH_3O	I	H	CH_3	1.0	—	1.0	Ethanol (20 ml) +dioxane (5 ml)	1.2	11.0	0.8	63.5
CH_3O	CH_3O	I	NO_2	H	0.5	0.35	—	Ethanol (7 ml) +dioxane (7 ml)	0.55	4.6	0.4	68
CH_3O	CH_3O	I	NO_2	CH_3	0.2	—	0.18	Ethanol (2 ml) +dioxane (2 ml)	0.22	1.8	0.17	69.5

*The crude product, an oil, was stirred with concentrated sodium bisulphite solution for 20 minutes before recrystallization from benzene.
†LP = light petroleum (b.p. 60–80°); B.D.H. AnalaR grade.

5-iodo-3,4-dimethoxy-6-nitro-α-nitromethylbenzyl alcohol (III: $R_1 = R_2 = OCH_3$; $R_3 = I$; $R_4 = NO_2$; $R_5 = H$); 5-iodo-3,4-dimethoxy-6-nitro-α-(1-nitroethyl)-benzyl alcohol (III: $R_1 = R_2 = OCH_3$; $R_3 = I$; $R_4 = NO_2$; $R_5 = CH_3$).

Unsuccessful attempts were made to condense 3-benzyloxy-4-methoxybenzaldehyde and 3,4-dibenzyloxybenzaldehyde with nitromethane using this procedure; in both cases the starting material was essentially recovered unchanged, even when considerably longer reaction times were employed. The failure of these two aldehydes to condense with nitromethane under the conditions employed is not altogether surprising in view of the fact that veratraldehyde would not condense with nitroalkanes in similar circumstances (cf. ref. 1).

EXPERIMENTAL

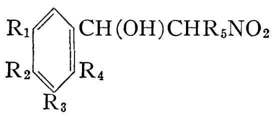
Aldehydes

4-Benzyloxy-3,5-dimethoxybenzaldehyde.—A solution of 4-hydroxy-3,5-dimethoxybenzaldehyde (12.0 g), potassium hydroxide (4 g), and benzyl chloride (9.0 g) in ethanol (60 ml) was boiled under reflux for 4 hours. The product was poured into water, and the aqueous reaction mixture repeatedly extracted with ether. The ethereal extract was washed with aqueous potassium hydroxide and water, dried (Na_2SO_4), and on evaporation to dryness, afforded a pale yellow oil, which on purification by distillation in vacuum (b.p. 190° at 0.5–1.0 mm) and recrystallization first from 95% ethanol and finally from benzene/light petroleum (b.p. 80–100°) afforded 4-benzyloxy-3,5-dimethoxybenzaldehyde as colorless prisms, m.p. 63°. Kratzl *et al.* prepared this compound by a somewhat different procedure but report the same melting point (2).

3,4,5-Trimethoxybenzaldehyde and 6-nitroveratraldehyde.—These compounds were obtained from the Aldrich Chemical Company.

5-Iodoveratraldehyde.—This compound was prepared by the methylation of 5-iodovanillin by the method of Dominguez *et al.* (3).

I



Properties of products			Analyses							
			Found				Calculated			
Crystalline form	M.p. (°C)	Empirical formula	C	H	N	I	C	H	N	I
Colorless prisms from benzene	108	$C_{17}H_{19}O_6N$	61.09	5.56	4.10	—	61.25	5.75	4.20	—
Colorless prisms* from benzene	135	$C_{12}H_{17}O_6N$	53.20	6.46	5.08	—	53.13	6.32	5.16	—
Pale yellow needles from benzene (darken in light)	142	$C_{10}H_{12}O_7N_2$	44.25	4.54	10.31	—	44.12	4.44	10.29	—
Colorless needles (yellow in light) from benzene	141–142	$C_{11}H_{14}O_7N_2$	46.26	5.06	9.80	—	46.15	4.93	9.79	—
Colorless needles from benzene/LP†	120	$C_{10}H_{12}O_5NI$	34.09	3.40	3.71	35.86	34.01	3.42	3.96	35.94
Colorless prisms from aqueous ethanol	135	$C_{11}H_{14}O_5NI$	35.91	3.97	3.73	34.40	35.98	3.85	3.82	34.57
Pale yellow prisms from benzene/ LP†	126–127	$C_{10}H_{11}O_7N_2I$	30.15	2.84	7.01	31.96	30.16	2.78	7.04	31.88
Pale yellow prisms from benzene/ LP†	162	$C_{11}H_{13}O_7N_2I$	32.36	3.30	6.80	30.84	32.05	3.18	6.79	30.79

5-Iodo-6-nitroveratraldehyde.—This compound was prepared by the nitration of 5-iodoveratraldehyde, the nitroaldehyde being purified via its bisulphite derivative (4).

1-Phenyl-2-nitroethanol Derivatives (General Procedure) (cf. Ref. 1)*

Aqueous sodium hydroxide (10%; 1.05 mole) was added with stirring to a mixture of the aldehyde and nitromethane (2–3 mole) dissolved in a suitable solvent (see Table I) at ca. 5°; the product was vigorously stirred for a further 30–45 seconds. Aqueous acetic acid (2%) was then added to halt the reaction and decompose the sodium derivative of the nitroalcohol; the crude product separated out as a yellow to colorless solid or oil. After being allowed to stand at 4° for 1 hour, the crude product was filtered and purified by repeated recrystallization from a suitable solvent.

In the previous note on this subject (1), it was reported that 95% alcohol was invariably used as a solvent for this type of reaction mixture. However, in several of the cases described above, the solubility of the aldehyde in 95% ethanol was quite low, and it was necessary to use mixtures of absolute alcohol and dioxane to ensure complete solution of all the reactants.

This investigation was supported by grants from the Department of National Health and Welfare (Ottawa) and the Government of Saskatchewan (Department of Public Health).

1. R. A. Heacock, O. Hutzinger, and C. Nerenberg. Can. J. Chem. **39**, 1143 (1961).
2. K. Kratzl, T. Horejschi, and G. Billek. Monatsh. **85**, 1154 (1954).
3. X. A. Dominguez, G. L. Diaz, and F. V. Gonzalez. Ciencia (Mex.), **15**, 208 (1955); Chem. Abstr. **50**, 12886 (1956).
4. R. A. Heacock and O. Hutzinger. In preparation.

Received September 17, 1962.
Psychiatric Research Unit,
University Hospital,
Saskatoon, Saskatchewan.

**The specific quantities of reagents used are given in Table I.*