

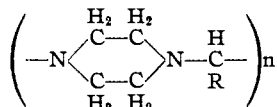
[CONTRIBUTION FROM THE ORGANIC CHEMICAL LABORATORY OF THE UNIVERSITY OF FLORIDA]

Derivatives of Piperazine. VIII. Condensation with Aldehydes

BY W. T. FORSEE, JR., AND C. B. POLLARD

The literature reveals very few data on reactions between piperazine and aldehydes and this small amount of published work is somewhat contradictory. Experimental evidence has failed to establish a basis for predicting the type of compound expected when an aldehyde is condensed with piperazine.

In this investigation piperazine was condensed with formaldehyde, acetaldehyde, butyraldehyde, benzaldehyde, salicylaldehyde, *p*-tolylaldehyde and *o*-chlorobenzaldehyde. With two exceptions, data indicate compounds of the structure



The structure of the products from acetaldehyde and butyraldehyde have not yet been determined.

benzal chloride and piperazine. These reactions and the analyses show these condensation products to be a N,N'-bis-piperazylalkylmethane type of compound. However, the molecular structure might be one of any number of polymers. Since these compounds are practically insoluble in all solvents and are unstable at temperatures near the melting points, a molecular weight determination by ordinary methods was impossible. Purification was accomplished by using highly purified reagents and washing the products repeatedly with several solvents.

In order to block the possibility of polymerization, N-monophenylpiperazine was condensed with various aldehydes. Compounds of the N-bis-(N'-phenylpiperazyl)-alkylmethane type were obtained from formaldehyde, acetaldehyde, benzaldehyde, *p*-tolylaldehyde and anisaldehyde.

TABLE I
YIELDS, PROPERTIES AND COMPOSITION OF PIPERAZINE DERIVATIVES

Compound	Formula	Yield, %	M. p., °C.	Analyses, % N	
				Found	Calcd.
1 Methylene piperazine	(—NC ₄ H ₈ N·CH ₂ —) _n	97	Not under 300	28.51	28.57
1 From methylene iodide		98	Not under 300	28.67	28.57
2 Benzylidene piperazine	(—NC ₄ H ₈ N·CH(C ₆ H ₅)—) _n	98	270 (dec.)	16.12	16.09
2 From benzal chloride		46	265 (dec.)	15.93	16.09
3 <i>o</i> -Hydroxybenzylidene piperazine	(—NC ₄ H ₈ N·CH(C ₆ H ₄ ·OH)—) _n	44	210 (dec.)	14.70	14.73
4 <i>p</i> -Methylbenzylidene piperazine	(—NC ₄ H ₈ N·CH(C ₆ H ₄ ·CH ₃)—) _n	90	275 (dec.)	15.12	14.88
5 <i>o</i> -Chlorobenzylidene piperazine	(—NC ₄ H ₈ N·CH(C ₆ H ₄ ·Cl)—) _n	95	240 (dec.)	13.37	13.42
6 <i>p</i> -Methoxybenzylidene piperazine	(—NC ₄ H ₈ N·CH(C ₆ H ₄ ·OCH ₃)—) _n	85	290 (dec.)	13.72	13.72

TABLE II
YIELDS, PROPERTIES AND COMPOSITION OF N-MONOPHENYLPIPERAZINE DERIVATIVES

Compound	Formula	Yield, %	M. p., °C.	Analyses, % N	
				Found	Calcd.
1 N-Bis-(N'-phenylpiperazyl)-methane	C ₆ H ₅ ·NC ₄ H ₈ N·CH ₂ ·NC ₄ H ₈ N·C ₆ H ₅	79	123-124	16.58	16.66
1 From methylene iodide		24	123-124	16.74	16.66
2 N-Bis-(N'-phenylpiperazyl)-ethane	C ₆ H ₅ ·NC ₄ H ₈ N·CH(CH ₃)·NC ₄ H ₈ N·C ₆ H ₅	25	121-123	15.82	16.00
3 N-Bis-(N'-phenylpiperazyl)-phenylmethane	C ₆ H ₅ ·NC ₄ H ₈ N·CH(C ₆ H ₅)·NC ₄ H ₈ N·C ₆ H ₅	90	125-126	13.54	13.59
4 N-Bis-(N'-phenylpiperazyl)- <i>o</i> -methylphenylmethane	C ₆ H ₅ ·NC ₄ H ₈ N·CH(C ₆ H ₄ ·CH ₃)·NC ₄ H ₈ N·C ₆ H ₅	83	144-144.5	13.29	13.13
5 N-Bis-(N'-phenylpiperazyl)- <i>o</i> -methoxyphenylmethane	C ₆ H ₅ ·NC ₄ H ₈ N·CH(C ₆ H ₄ ·OCH ₃)·NC ₄ H ₈ N·C ₆ H ₅	67	135-136	12.67	12.66

Formaldehyde and piperazine¹ gave the same product as was obtained from methylene iodide and piperazine. Benzaldehyde and piperazine² gave the same product as was obtained from

N-Monophenylpiperazine with formaldehyde³ gave the same compound as was obtained from N-monophenylpiperazine and methylene iodide.

Properties of the compounds obtained from piperazine are shown in Table I. Table II gives

(1) Herz, *Ber.*, **30**, 1584 (1897).(2) Schmidt and Wichmann, *ibid.*, **24**, 3237 (1891).(3) Prelog and Blazik, *Coll. Czech. Chem. Comm.*, [2] **6**, 549 (1934).

the data for those obtained from N-monophenyl-piperazine.

All of the condensation products are readily decomposed by acids. In contrast to the products from piperazine those from N-monophenyl-piperazine were readily crystallized from appropriate solvents.

All of the condensation products were prepared by reacting the amine with the aldehyde either in the absence or presence of a solvent. The method recommended by Cummings, Hopper and

Wheeler⁴ was used in all reactions which involved alkyl halides.

Summary

It has been shown that when aldehydes react with piperazine or N-mono-substituted piperazines, one molecule of the aldehyde reacts with two amino groups and a molecule of water is eliminated.

(4) Cummings, Hopper and Wheeler, "Synthetic Organic Chemistry," p. 294.

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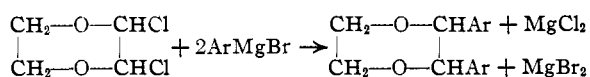
RECEIVED AUGUST 22, 1935

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

Studies in the Dioxane Series. II. Aryl Substituted Dioxanes Synthesis of *p*-Dioxene¹

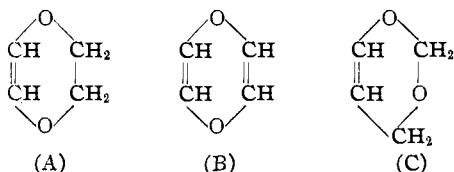
BY R. K. SUMMERBELL AND L. N. BAUER

The preparation of 2,3-diphenyl-1,4-dioxane by the reaction of 2,3-dichloro-1,4-dioxane with phenylmagnesium bromide was described by Christ and Summerbell.²



The same method of synthesis has been satisfactorily applied to a number of aryl substituted dioxanes.

(1) The name 1,4-(or *p*-)dioxene for a new compound (A) described in this paper requires explanation. It follows logically from 1,4-dioxane, the preferred name [Patterson, *THIS JOURNAL*, **55**, 3911 (1933)] of the fully hydrogenated analog. It might be called 2,3-dihydro-1,4-dioxin since dioxin has been proposed [Widman, *Ber.*, **42**, 3269 (1909)] to represent the least hydrogenated member. Unfortunately for the logic involved, dioxin turns out to be either C₄H₆O₂ or C₆H₈O₂ depending on whether 1,4-dioxin (B) or 1,3-dioxin (C) is being considered.



(See *Chem. Abs.*, **28**, 8219 (1934) for both structures.) It is incredible that two related non-isomeric substances of known structures should needlessly be assigned the same name.

The logical name for (C) is 1,3-dioxene. Instead of 1,4-dioxin, the name dioxadiene is proposed for (B). The name is simple, informative, and free from an ambiguous past.

This plan applies equally well for the sulfur analogs: dithiane, dithiene, oxathiane and oxathiene. The last two names are preferable to thioxane and thioxene since, according to the rules of numbering ring systems, the oxygen should be numbered one; thus 1,4-oxathiane, etc. We acknowledge assistance in this formulation from E. J. Crane and A. M. Patterson, members of the A. C. S. committee on nomenclature.—C. D. HURD, C. M. SUTER AND R. K. SUMMERBELL.

(2) Christ and Summerbell, *THIS JOURNAL*, **55**, 4547 (1933).

Although two 2,3-disubstituted dioxanes may be predicted from theory, only one was obtained in each case. In a repetition of the 2,3-diphenyl-1,4-dioxane synthesis, a yield of 80% of the previously described material was obtained, and attempts to isolate a second disubstituted dioxane were unsuccessful. The high yield of a single product in this case, and the failure to obtain two isomers in any of the experiments described in this paper, may be taken to indicate that the 2,3-dichloro-1,4-dioxane used was a pure compound, rather than a mixture of *cis* and *trans* isomers.

The reaction of benzylmagnesium chloride with dichlorodioxane might give an *o*-tolyl derivative.³ As only a small amount of phthalic acid was obtained on permanganate oxidation of the reaction product, there is very little, if any, of this type of rearrangement. Further work on high molecular weight residues must be carried out to explain all that takes place in this reaction.

In an attempt to extend this method of synthesis to alkyl substituted dioxanes, only small yields of dimethyl, diethyl and dibutyl-1,4-dioxanes were obtained. The yields were so small that a discussion of their properties will be withheld, pending the outcome of experiments now under way on modifications of procedure designed to increase the yield and hence the material available for investigation.

(3) Gilman and Kirby, *ibid.*, **54**, 345 (1932); John R. Johnson, *ibid.*, **55**, 3029 (1933); and earlier work to which these articles contain references.