[CONTRIBUTION NO. 550 FROM THE DEPARTMENT OF CHEMISTRY OF INDIANA UNIVERSITY]

THE FORMATION OF SOLID DERIVATIVES OF ALDEHYDES. I. 2-SUBSTITUTED-1,3-BIS(*p*-METHOXYBENZYL)-TETRAHYDROIMIDAZOLES

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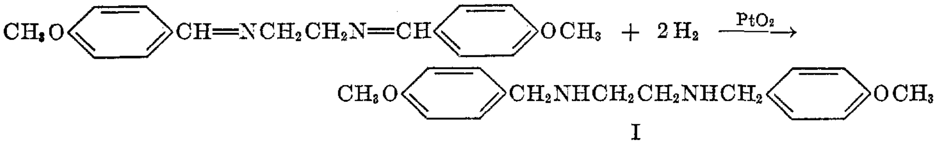
Received April 14, 1952

In general, aldehydes and ketones undergo similar chemical reactions. This is particularly true when it comes to the formation of solid derivatives for characterization purposes. Except for the methone reagent (1, 2), there appears to be no other satisfactory reagent which will permit one to form solid derivatives of aldehydes and which will not react with ketones. Because of the scarcity of such reagents any new compound which can be used for this purpose should be of real value.

In connection with some other work on di-secondary amines it was noted that 1,2-bis(benzylamino)ethane reacted with aldehydes but not with ketones to form 2-substituted-1,3-dibenzyltetrahydroimidazoles (3, 4). However, most of the products were oils and thus could not be used for the characterization of aldehydes. Rameau (5) has also prepared some tetrahydroimidazoles from 1,2-bis-(*p* - methoxybenzylamino)ethane (I), 1,2 - bis(2′ - methylpropylamino)ethane, and 1,2-bis(furfuryl-2′)methylaminoethane. Although only a few tetrahydroimidazoles were made from these reagents, there was some indication that it would be well worth investigating thd use of 1,2-bis(*p*-methoxybenzylamino)-ethane (I) as a reagent for differentiating between aldehydes and ketones as well as for forming satisfactory solid derivatives of aldehydes.

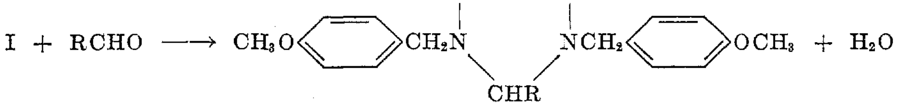
Rameau (5) reported the use of sodium and alcohol as the reducing agent of the Schiff base used in forming I. Since he did not report a yield for this preparation, it was decided that catalytic hydrogenation would be a more desirable and convenient method of reduction. By the latter method it was possible to synthesize 1,2-bis(*p*-methoxybenzylamino)ethane (I) in a 64% yield.



I

Since the diamine is a low melting solid, it was found most convenient to isolate, store, and use it in the form of its dihydrochloride.

When a large number of aldehydes were treated with 1,2-bis(*p*-methoxybenzylamino)ethane (I), it was found that it formed very satisfactory solid derivatives with almost all of the common aldehydes.

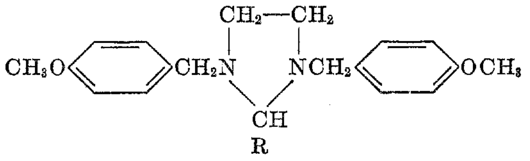


(R = alkyl or aryl group)

II

TABLE I

2-SUBSTITUTED-1,3-BIS (*p*-METHOXYBENZYL) TETRAHYDROIMIDAZOLES



(R = alkyl or aryl group)

R	M.P., °C. (corr.)	YIELD, %	NITROGEN	
			Calc'd	Found
H[a]	30	—		
Ethyl	48.5–49.5	44	8.24	8.29
2-Nitrophenyl	57–57.5	27	9.69	9.55
n-Propyl	65–65.5	57	7.92	7.68
3,4-Diethoxyphenyl	67.5–68.5	59.1	5.88	5.87
Benzyl[a]	68–69	—		
n-Butyl	70–70.5	51.7	7.61	7.63
4-Methoxyphenyl[a]	73	—		
Isobutyl	75.5–76.5	62.9	7.61	7.83
2-Furyl[a]	76	—		
2-Chlorophenyl	76.5–77.5	58	6.78	6.62
Methyl[a]	76–77	—		
3,4-Dimethoxyphenyl	78–78.5	58	6.24	6.14
3,4-Dichlorophenyl	87–87.5	72.1	6.12	6.15
5-Methyl-2-furfuryl[a]	84	—		
2-Naphthyl	85–86	36	6.38	6.76
4-Methylphenyl	90–91	85	6.97	7.08
Phenyl[a]	93	—		
3-Thienyl	99–100	13	7.10	7.06
4-Chlorophenyl	102–102.5	72	6.78	6.65
4-Hydroxy-5-methoxyphenyl	105–106	36	6.45	6.45
5-Hydroxymethyl-2-furyl	108	—		
2-Phenylethenyl	108.5–109	56	6.76	6.56
4-Diethylaminophenyl	110–110.5	53.7	9.15	9.38
4-Dimethylaminophenyl	111.5–112.5	57.4	9.74	9.68
3,4-Methylenedioxyphenyl[a]	120	—		
2-Hydroxyphenyl	122–123	70.8	6.94	6.80
4-Hydroxyphenyl	130.5–131.5	28.3	6.94	7.05
4-Nitrophenyl	150–150.5	56	9.69	9.47
3-Nitrophenyl	154–155	80.4	9.69	9.42
2,4-Dihydroxyphenyl	158–159 (decomp.)	67.5	6.67	7.09

[a] Prepared by Rameau (5).

Twenty-two new solid tetrahydroimidazole (II) derivatives of aldehydes (Table I) with melting points within a convenient temperature range of from 49° to 159° were prepared by this method.

The derivatives of the following aldehydes were found to produce oils or resinous substances: hydrocinnamaldehyde, *n*-caproaldehyde, *n*-enanthaldehyde, citronellal, α-amylcinnamaldehyde, α-ethyl-*n*-caproaldehyde, 2-ethyl-3-propylacrolein, 2,4-dichlorobenzaldehyde, α-ethyl-*n*-butyraldehyde, isobutyraldehyde, *m*-hydroxybenzaldehyde, pyruvic aldehyde, aldol, and acrolein.

A series of ketones (acetophenone, benzophenone, diethyl ketone, cyclohexanone, methyl propyl ketone, methyl isopropyl ketone, diisopropyl ketone, and diisobutyl ketone) were treated with 1,2-bis(*p*-methoxybenzylamino)ethane under the same conditions used for aldehydes. Of these, only acetone was found to react to produce a solid which melted at 110–110.5°. This is somewhat surprising in view of the fact that Lob (4) found that no reaction occurred between 1,2-dibenzylaminoethane and acetone or acetophenone, even when they were heated together in a sealed tube at 200–210°.

In addition to the facts that the reagent is easy to prepare, has a high molecular weight, reacts readily with aldehydes to give a large number of solid derivatives which are easily purified, and have satisfactory melting points, these derivatives are easily and quickly hydrolyzed by dilute mineral acids to regenerate the aldehydes and the diaminedihydrochloride, according to the following equation:

$$\text{II} + 2\,\text{HCl} + \text{H}_2\text{O} \rightarrow \text{I}\cdot 2\text{HCl} + \text{RCHO}$$

The tetrahydroimidazoles decomposed by this method gave the aldehyde and the diaminedihydrochloride in almost quantitative yields.

Other diamines and aspects of this problem are under investigation.

Acknowledgment: We wish to thank Eli Lilly Co. for analyzing a large number of the reported compounds.

EXPERIMENTAL

1,2-Bis(p-methoxybenzylideneamino)ethane. Dry 1,2-diaminoethane (50 ml.) was added drop by drop to 182 ml. (200 g.) of anisaldehyde in 100 ml. of absolute alcohol in a one-liter, three-necked flask set up with a dropping-funnel, a stirrer, and a reflux condenser, while the mixture was refluxed at about 120° with stirring. After an hour, the clear solution was poured into a beaker surrounded by ice. The light yellow crystals obtained were filtered and washed with 25-ml. portions of absolute ethanol; yield, 209 g. (96%); m.p. 110–111°; reported 110–111° (6).

1,2-Bis(p-methoxybenzylamino)ethane (I) *dihydrochloride.* 1,2-Bis(*p*-methoxybenzylideneamino)ethane (30 g.) partially dissolved in 100 ml. of purified ethyl acetate was hydrogenated with 0.3 g. of platinum oxide at an initial hydrogen pressure of 45 p.s.i. The hydrogenation was complete in 1½ hours. The solution was filtered and acidified with 20% hydrochloric acid. The *dihydrochloride* which precipitated was recrystallized from approximately 300 ml. of boiling water. The colorless, crystalline dihydrochloride of the diamine did not melt below 270°; Yield, 24.5 g. (64.8%). It has been reported (5) that this hydrochloride begins to decompose at about 150°.

Anal. Calc'd for $C_{18}H_{26}Cl_2N_2O_2$: N, 7.51. Found: N, 7.49.

2-Substituted-1,3-bis(p-methoxybenzyl)tetrahydroimidazoles. (II) (*a*) *General procedure for identification of aldehydes.* To 2.5 g. of 1,2-bis(*p*-methoxybenzylamino)ethane (I) dihydrochloride in a test tube was added 10 ml. of 10% NaOH solution. The mixture was warmed on a steam-bath for 15 minutes after the appearance of an oil. The mixture was cooled to room temperature or below so as to solidify the diamine, and the aqueous layer was rejected. The residue was washed with two 15-ml. portions of water to remove the excess alkali and as much of the water as possible was decanted The free amine was dissolved in the minimum absolute alcohol at room temperature and to this alcoholic solution the calculated amount of aldehyde was added. (If the aldehyde was a solid, it was first dissolved in the minimum of absolute alcohol at room temperature.) The test tube was stoppered and shaken for 10 to 15 minutes. If the solid derivative did not form in this time, the stopper was removed and the mixture was heated to about 65° for ten minutes and then allowed to cool to room temperature. Occasionally it was necessary to cool this solution in ice in order to cause the derivative to precipitate or solidify. The solid was removed and recrystallized from the minimum of absolute alcohol.

(*b*) *1,3-Bis(p-methoxybenzyl)-2,2-dimethyltetrahydroimidazole.* The same experiment as (*a*) was run using 2 g. of I dihydrochloride and 0.6 ml. of acetone; yield, 0.2 g.; m.p. 110–110.5° (corr.).

Anal. Calc'd for $C_{21}H_{28}N_2O_2$: N, 8.25. Found: N, 8.38.

Decomposition of the tetrahydroimidazole derivative. 1,3-Bis(*p*-methoxybenzyl)-2-(3′,4′-methylenedioxyphenyl)tetrahydroimidazole (3 g.) was placed in a 150-ml. separatory-funnel and shaken first with 50 ml. of 10% hydrochloric acid for about ten minutes and then with 50 ml. of ether, after which the mixture was allowed to stand. The ether layer was transferred with a pipette to a 200-ml. beaker. This process of extraction of piperonal was repeated four or five times with 30-ml. portions of ether. The combined ether solution was filtered and evaporated under reduced pressure. The solid residue was dried in a vacuum desiccator and weighed approximately 1.00 g. The calculated weight is 1.04 g. The residue had m.p. 33–35° which is very close to that of piperonal (35°). Recovered I dihydrochloride weighed 2.60 g.; the calculated weight is 2.59 g.

SUMMARY

1. 1,2-Bis(*p*-methoxybenzylamino)ethane has been found to be a very satisfactory reagent for the characterization of aldehydes. Acetone is the only ketone found to react with this diamine.

2. Twenty-two new solid derivatives of 1,2-bis(*p*-methoxybenzylamino)ethane have been prepared. These compounds are 2-substituted-1,3-bis(*p*-methoxybenzyl) tetrahydroimidazoles.

3. 1,2-Bis(*p*-methoxybenzylamino)ethane dihydrochloride has been synthesized by a new method.

4. The aldehydes were regenerated in approximately quantitative yields by treatment of the tetrahydroimidazole with dilute hydrochloric acid.

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