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IMPROVED SYNTHESIS OF BENZYLIDENEBISACETAMIDE AND RELATED COMPOUNDS

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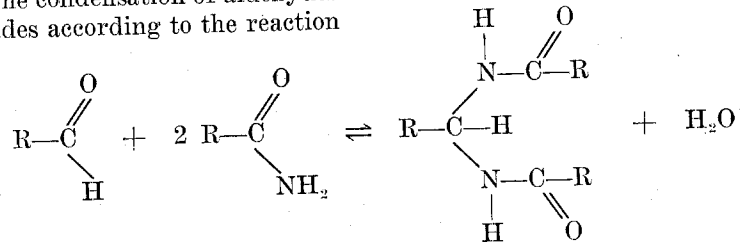
The condensation of aldehydes and amides according to the reaction



has been known for many years (15), and appears to be quite general for either alipatic or aromatic aldehydes and amides. However, with the exception of the work of Noyes and Forman (10), information on yields in this type of synthesis has been meagre (2, 8, 9, 11, 12, 13, 14, 15).

Work in progress in our laboratory has shown that very satisfactory yields can be obtained by removing the water formed by an azeotropic distillation with solvents like benzene, toluene, or xylene, the water being taken out of the refluxing solvent by a Sohxlet extractor containing a drying agent. This procedure eliminates the need for a catalyst, such as acetic acid, which was used by Noyes and Forman, and circumvents the darkening of the reaction mixture which was noted by these authors. Our preparations are summarized in table 1, and our general method is described below.

The reaction was not successful with the aldehydes containing phenolic groups. Pandya, who had reported a number of hydroxybenzylidenebisamides (6), found that salicylaldehyde and amides condense to compounds of the type o-HO-C_6H_4—CH=N-COR (7).

Our interest in the bisamide condensation stemmed from a study of the Leuckart reaction, in which formamide is reacted with an aldehyde or ketone, generally in the presence of formic acid, as follows:

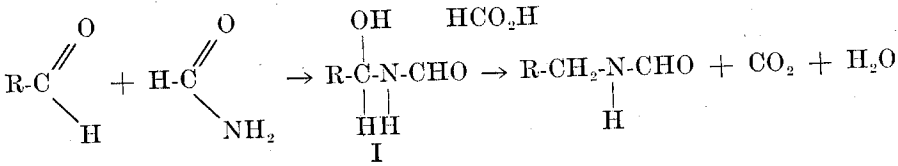
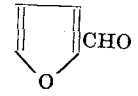
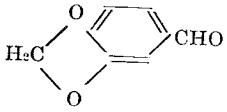
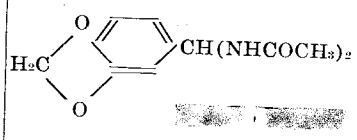


TABLE 1.—CONDENSATION OF ALDEHYDES WITH ACETAMIDE.

Aldehyde	Condensation Product	m. p. °C.	Yield %	Literature Yield %	Remarks
C_2H_5CHO	C_2H_5-CH(NHCOCH$_3$)$_2$	183	48	7.5(10)	Anal.Calcd.N, 17.74 Found, 17.72, 17.64
n-C_3H_7CHO	C_3H_7-CH(NHCOCH$_3$)$_2$	189.5	49	11.5(10)	Anal.Calcd.N, 16.30 Found, 16.31, 16.33
C_6H_5CHO	C_6H_5-CH(NHCOCH$_3$)$_2$	239.5	72	48(10)	Anal.Calcd.N, 13.61 Found, 13.62, 13.62
p-CH_3O-C_6H_4CHO	p-CH_3O-C_6H_4CH(NHCOCH$_3$)$_2$	224	84.5		Anal.Calcd.N, 11.86 Found, 11.71, 11.76
		206d. (197 lit)	67	40(1)	Anal.Calcd.N, 14.30 Found, 14.38, 14.44
		227-228 d.	43	.....	Anal.Calcd.N, 11.19 Found, 11.14, 11.04
C_6H_5CH=CHCHO	C_6H_5CH=CHCH(NHCOCH$_3$)$_2$	234	33.6	15.5(6)[a]	Anal.Calcd.N, 12.09 Found, 11.93
m-$NO_2C_6H_4CHO$	m-$NO_2C_6H_4$CH(NHCOCH$_3$)$_2$	236-8	43.7	.....	Anal.Calcd.N, 16.74 Found, 16.33, 16.28
Vanillin	.....	.....	0	.....	Resinification
Salicylaldehyde	.....	175-180	very low	.....	Resinification
Glucose	.....	.....	0	.....	Resinification

a) These authors reported a 51.7% yield with a 4:1 ratio of amide to aldehyde.

It appears likely that the mechanism for the first step in both the bisamide and Leuckart reactions is the same. The intermediate I can react with more formamide by a split-out of water to form the bisformamide (10, 2), or can undergo reduction by formic acid to form an alkyl formamide. Since the bisformamides undergo decomposition at high temperatures to form very high-melting cyclic nitrogen compounds (12, 2), we suspect that small amounts of very high-melting compounds obtained as side-reaction products in some Leuckart reactions in our laboratory may have been formed by this route.

Experimental

The general method used for the preparation of alkylidene or benzylidenebisamides was as follows:

The aldehyde (0.1 mole) and acetamide (0.2 mole) were placed with 100 ml. of benzene in a 250 ml. round-bottomed flask, to which a Sohxlet extractor containing approximately 50 g. of freshly dehydrated $MgSO_4$ was attached, along with a condenser. The reaction flask was maintained at refluxing temperature for 48 hours by means of an oil bath heated by an electric hot plate. By that time, much solid was generally apparent in the reaction mixture, which was removed by filtration after the flask was cooled. The precipitate was washed with small portions of acetone to remove traces of starting materials, allowed to dry, and then weighed. The products were all white, usually fibrous-appearing crystalline solids. The analysis samples shown in table 1 were recrystallized once from ethanol and dried under vacuum at 100°C.

Substitution of calcium chloride or calcium sulfate for magnesium sulfate as the drying agent in the Sohxlet permits condensation, but the yields with these other agents have not yet been examined. Reaction time is shortened (as judged by appearance of solid in the reaction mixture) by using toluene or xylene in place of benzene, but a comparison of yields with the different solvents has not been made.

Summary

An azeotropic distillation method for the removal of water formed in the condensation of certain aldehydes with acetamide has resulted in yields of alkylidene- and benzylidene- bisacetamides which appear generally improved over those reported in the literature. Some hydroxylated compounds failed to react satisfactorily.

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