mole of *p*-tolylsulfonylmethylnitrosoamide) was carried out as described above for other olefins.

The white needles (5.27 g., 56.3% yield, m.p. 129–131°) that separated from the cold ether were recrystallized from acetone–water to give **3-phenyl-4-benzenesulfonylpyrazoline** (VIIg m.p. 131–132°).

Anal. Calcd. for $C_{15}H_{14}N_2O_2S$: C, 62.91; H, 4.93; N, 9.78; S, 11.20. Found: C, 62.99; H, 5.06; N, 9.47; S, 11.21.

The ethereal solution was concentrated (no heat) until considerable crystallization was evident, and the solution was placed in the refrigerator. The solid (1.85 g., 19.6%, m.p. 107–110°) obtained was recrystallized from methanol–water to give **4-phenyl-3-benzenesulfonylpyrazoline** (VIg, m.p. 110–111° from methanol).

Anal. Calcd. for $C_{15}H_{14}N_2O_2S$: C, 62.91; H, 4.93; N, 9.78; S, 11.20. Found: C, 63.17; H, 4.81; N, 9.65; S, 11.39.

The ether mother liquors contained a solid (~ 1.14 g.) and an oil (0.7 g.) which were not resolved into pure components but contained some VIg.

Proofs of Structure of Pyrazolines.—The procedure used for conversion of the sulfonylpyrazolines to pyrazoles, in each case, was essentially identical.

1. 5-Benzenesulfonylpyrazoline (VIa).—Pyrazoline VIa (2.1 g., 0.01 mole) was dissolved in a solution of potassium hydroxide (1.5 g., 0.27 mole) in methanol (20 ml.). The solution was allowed to stand in the cold (~0–15°) overnight, and was then diluted with salt water. The oil which separated crystallized (0.5 g., 73.5%, m.p. 66–67°, 66.5–67° from petroleum ether (b.p. 90–100°).

Anal. Calcd. for $C_3H_4N_2$: C, 52.92; H, 5.92. Found: C, 52.67; H, 6.03.

The picrate melted at 158–160° (from methanol). These data are in agreement with the assigned structure **pyrazole** (reported,[23] m.p. 69.5–70°; picrate, m.p. 158–160°).

2. 4-Methyl-5-benzenesulfonylpyrazoline (VIb).—The combined dried ether extract, obtained after treating VIb (4.5 g., 0.02 mole) as described above, was concentrated to a colorless oil (1.22 g., 75.3%). The material was identified as **4-methylpyrazole** by its conversion into: the picrate, m.p. 140–142°, from methanol; the silver double salt, m.p. 139–142°; and pyrazole-4-carboxylic acid, m.p. 275–280° from water. Basic permanganate was used for the oxidation to the acid. The reported[24] constants for 4-methylpyrazole are: picrate, m.p. 142°; silver double salt, m.p. 142°; pyrazole-4-carboxylic acid, m.p. 275°. The data reported[25] for the isomeric 3-methylpyrazole are: picrate, m.p. 142°; silver double salt, m.p. 121°; pyrazole-3-carboxylic acid, m.p. 212°.

3. 4-Methyl-5-dodecylsulfonylpyrazoline (VIc).—The colorless liquid obtained from VIc (1.58 g., 5.0 mmoles) possessed an infrared spectrum identical to that of 4-methylpyrazole, obtained in (2) above. The picrate of this material (m.p. 141–142°) caused no depression in melting point when admixed with the picrate described in (2), above.

4. 3-Phenyl-4-butylsulfonylpyrazoline (VIId).—The solid obtained when VIId (1.33 g., 5.0 mmoles) was treated with methanolic potassium hydroxide was recrystallized from petroleum ether (b.p. 90–100°) to give **3-pyenylpyrazole** (0.6 g., 83.3%, m.p. 73°, mixture m.p. with an authentic sample,[26] m.p. 72–73°, was 72–73°).

5. 4-Phenyl-5-butylsulfonylpyrazoline (VId).—Pyrazoline VId (1.33 g., 5.0 mmoles) was converted, as described above, into 4-phenylpyrazole (0.55 g., 76.4% yield, m.p. 221–230°, m.p. 228–230 from methanol; mixture m.p. with authentic,[27] m.p. 231°, was 230–231°).

6. Other Pyrazolines.—By the procedures described above: **3-phenyl-4-methylsulfonylpyrazoline** (VIIe) gave 3-phenylpyrazole (80% yield), **4-phenyl-5-methylsulfonylpyrazoline** (VIe,f) gave 4-phenylpyrazole (78% yield), **3-phenyl-4-methylsulfonylpyrazoline** (VIIf) gave 3-phenylpyrazole (82% yield), **4-phenyl-5-benzenesulfonylpyrazoline** (VIg) gave 4-phenylpyrazole (95% yield), **3-phenyl-4-benzenesulfonylpyrazoline** (VIIg) gave 3-phenylpyrazole (75% yield).

(23) D. L. Balbiano, *Gazz. chim. ital.*, **20**, 459 (1890).

(24) H. von Pechman and E. Burkard, *Ber.*, **33**, 3593 (1900); E. Büchner and M. Fritsch, *Ann.*, **273**, 253 (1813).

(25) R. von Rothenberg, *J. prakt. Chem.* [2], **52**, 46, 49 (1895); L. Knorr, *Ann.*, **279**, 227, 231 (1894).

(26) L. Knorr, *Ber.*, **28**, 696 (1895).

(27) H. Rupe and A. Huber, *Helv. Chim. Acta*, **10**, 848 (1927).

Reaction of 1,5-Diazacycloöctane with Aldehydes

JOHN H. BILLMAN AND LINNEAUS C. DORMAN[1]

Chemistry Department of Indiana University, Bloomington, Indiana

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1,5-Diazacycloöctane undergoes an intramolecular condensation reaction with aldehydes to form exclusively 9-substituted 1,5-diazabicyclo[3.3.1]nonanes, hitherto unknown. This is in contrast to the reaction of piperazine and aldehydes which proceeds intermolecularly to form polymers.

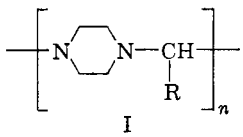
It has been shown that piperazine reacts with aliphatic and aromatic aldehydes to form polymeric condensation products. Herz[2] reported that when an excess of benzaldehyde was mixed with piperazine at room temperature or in a sealed tube at 60°, a white solid was obtained which appeared to decompose on standing in a desiccator. Herz assigned no structure for this product. However, formaldehyde was reported to react with piperazine to form a polymeric solid with an empirical formula of $C_4H_{10}N_2 \cdot 2H_2O$.

Forsee and Pollard[3] made a more thorough study of these condensation reactions. In all cases, except in the reaction of butyraldehyde and acetaldehyde, they were able to assign the polymethylene piperazine structure (I) for these polymeric condensation products.

(1) Dow Research Fellow, 1959–1960. Taken from the Ph.D. Thesis of L.C.D., Indiana University, 1961. Present address, Dow Chemical Company, Midland, Michigan.

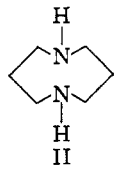
(2) Herz, W., Ber., **30**, 1584 (1897).

(3) W. F. Forsee, Jr., and C. B. Pollard, *J. Am. Chem. Soc.*, **57**, 2363 (1935).



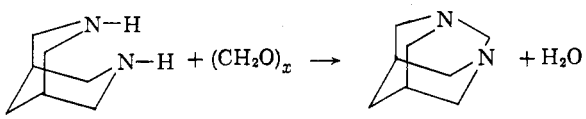
I

On the other hand, open chain 1,2-diamines react with aldehydes to produce imidazolidines[4,5] rather than polymers. In like fashion, open chain 1,3-diamines undergo intramolecular condensations to yield hexahydropyrimidines.[6-9] However, there was no concrete evidence as to how 1,5-diazacyclooctane (II) would behave when allowed to react



II

with aldehydes. The only clue to its possible action is a report by Stetter[10] that bispidine (III), which is a more rigid cyclic diamine, undergoes an intramolecular reaction with paraformaldehyde to form only 1,3-diazaademantane (IV).



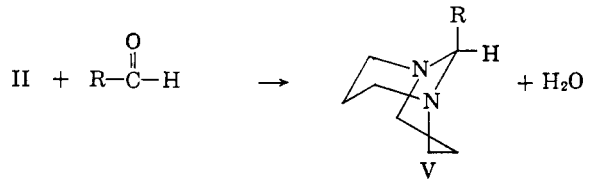
III IV

A molecular model of 1,5-diazacycloöctane reveals that some conformations may exist in which the nitrogen atoms are close together while in others they are far apart. Under these conditions then, one might expect aldehyde condensation reactions to yield cyclic products, polymers, or a mixture of both. The results would depend upon the conformation of the diamine which predominates. In view of the uncertainty of the outcome of this type of reaction the following investigation was prompted.

A review of the literature revealed that 1,5-diazacycloöctane (II) had been prepared by a number of different methods.[11-13] Of these, it was found that the procedure of Buhle, Moore, and Wiselogle[13] was most convenient to use. Although the best yield of 1,5-diazacycloöctane, in the form of its hydrobromide, was only 16% the reaction was easy to conduct and required considerably less time than any of the other preparative procedures.

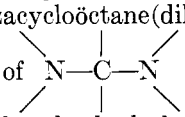
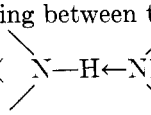
(4) J. H. Billman, J. Y. C. Ho, and L. R. Caswell, *J. Org. Chem.*, **17**, 1375 (1952).
(5) J. H. Billman, J. Y. C. Ho, and L. R. Caswell, *ibid.*, **22**, 538 (1957).
(6) E. Bergmann, U. S. Patent 2,525,855, October 17, 1950.
(7) G. H. Morey, U. S. Patent 2,535,745, December 26, 1950.
(8) H. Zahn, H. Wilhelm, and A. Rauchle, *Ann.*, **579**, 14 (1953).
(9) W. L. C. Veer, *Rec. trav. chem.*, **57**, 989 (1958).
(10) H. Stetter and H. Hennig, *Ber.*, **88**, 789 (1955).
(11) A. N. Kost and C. A. Chursing, *Chem. Abstr.*, **45**, 7008 (1951).
(12) C. C. Howard and W. Marckwald, *Ber.*, **32**, 2038 (1899).
(13) E. L. Buhle, A. M. Moore, and F. G. Wiselogle, *J. Am. Chem. Soc.*, **65**, 29 (1943).

The reactions of 1,5-diazacycloöctane with aromatic aldehydes were generally carried out by first preparing an aqueous methanol solution of the free amine from its dihydrobromide salt and sodium hydroxide. The aldehyde or its methanol solution was then added to the amine solution. Generally, the reactions proceeded fairly rapidly, according to the equation below, to form 9-substituted-1,5-diazabicyclo [3.3.1]nonanes (V), which were hitherto unknown.



V

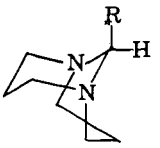
Anisaldehyde and benzaldehyde reacted exothermically at room temperature. However, other reactions were generally warmed on a steam bath for short periods of time. The products were easy to isolate and conveniently purified by recrystallization for overall yields of 54–83%. The reaction products are summarized in Table I.

In order to confirm the formation of a ring closed compound the following tests were performed. Elementary analysis showed the reactions to proceed equimolecularly with respect to both reactants. Infrared spectra showed the absence of any N—H groups (of course, phenolic aldehyde derivatives showed —OH absorption) thus demonstrating that both —NH groups of 1,5-diazacycloöctane participated in the condensation reactions. The condensation products may be hydrolysed by dilute mineral acids. Under these conditions the *p*-nitrobenzaldehyde condensation product gave an 87% yield of *p*-nitrobenzaldehyde and a 98% yield of 1,5-diazacycloöctane(dihydrobromide salt). The presence of  linkages was thus established by the hydrolysis reactions. Finally, a molecular weight determination of the *p*-dimethylaminobenzaldehyde derivative was in agreement with the theoretical value based on the bicyclononane structure. The molecular weight found was 245, calculated, 251. The molecular weight data ruled out the formation of large cyclic compounds and thereby unequivocally established the structure of the 9-substituted 1,5-diazabicyclo[3.3.1] nonane derivatives. Of interest to the present study was the observation by Kilinski, Pistrowska, and Urbanski[14] that 3,7-dialkyl-3,7-dinitro-1,5-diazacycloöctanes form only monohydrochlorides and mononitroso derivatives which they explained was due to internal hydrogen bonding between the two secondary nitrogen atoms (), or

(14) R. Kolinski, H. Pistrowska, and T. Urbanski, *J. Chem. Soc.*, 2319 (1958).

TABLE I

9-SUBSTITUTED 1,5-DIAZABICYCLO[3.3.1]NONANES (V)

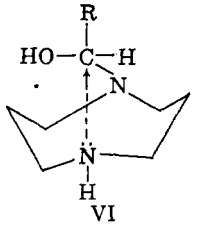


	Crude product		Purified product							
					Calculated			Found		
R	M.p., °C.	% yield	M.p., °C.	% yield	C	H	N	C	H	N
p-Nitrophenyl[a]	113.8–114.2	74	114.2–114.7	59	63.13	6.93	16.99	63.16	6.78	17.15
3-Indoyl[b]	207–212 dec.	91	211–215 dec.	74	74.68	7.94	17.42	75.09	8.23	17.57
p-Methoxyphenyl[c]	76.5–79.5	70	78.5–79.5	83[d]	72.38	8.68	12.06	72.62	8.71	12.02
Phenyl[c]	64–66	74	78.5–79.5	63[e]	77.18	8.97	...	77.01	8.91	...
p-Hydroxyphenyl[a]	165–167 dec.	79	179–181 dec.	54	71.52	8.31	12.83	71.00	8.67	13.00
o-Hydroxyphenyl[a]	...	..	109.5–110.2	67	71.52	8.31	12.83	71.42	8.41	12.87
p-Sulfamoylphenyl[a]	200–202 dec.	89	204–204 dec.	71	55.49	6.81	14.94	55.49	6.84	15.08
p-Dimethylaminophenyl[a]	145.3–146	86	147.2–148	62	73.42	9.45	17.13	73.18	9.20	17.10[f]
3,4-Methylenedioxyphenyl[c]	81–82	88	81.5–82.5	63[d]	68.27	7.37	11.37	68.67	7.33	11.38

[a] Procedure A. [b] Procedure C. [c] Procedure B. [d] Per cent recovery from petroleum ether (b.p. 40–60). [e] Per cent recovery from 40% methanol. [f] Mol. wt.: calcd., 245; found, 251.

between one of the amino and one of the nitro groups. Such internal hydrogen association is also used to explain the anamolous amine behavior of 1,5,8,12-tetrazatetradecane such as low water solubility and inertness to carbon dioxide.[15] Since 1,5-diazacycloöctane essentially does not possess these properties, which would clearly and definitely show that its two nitrogen atoms bear a close proximity to each other, therefore there is no ready explanation for its intramolecular condensation with aromatic aldehydes.

An alternate explanation for the condensation reaction would be that the *N*-methylol intermediate (VI) reacts internally with the amine group across the ring because an amino group of another, 1,5-diazacycloöctane molecule is shielded from the outside by hydrogen atoms of the polymethylene chain.[16] Probably, the proximity and shielding effects are both important in determining the course of the reaction.



VI

Experimental

Melting points were taken in open capillaries and are corrected.

Infrared spectra of the nonane derivatives were taken on a Perkin Elmer Infracord as their potassium bromide mulls.

Microanalyses were performed by Midwest Microlab, Inc., Indianapolis, Indiana.

Aldehydes.—Either reagent grades of aldehydes were used or they were purified by distillation or by recrystallization from appropriate solvents. *p*-Sulfamoylbenzaldehyde was prepared, essentially, by the procedure of Sycheva and Schuking.[17]

1,5-Diazacycloöctane Dihydrobromide.—The crude product was prepared according to the method of Buhle, Moore, and Wiselogle.[13] From 3 moles of 85% hydrazine hydrate (practical grade) and 1 mole of 1,4-dibromopropane (b.p. 151–154°)[18] was obtained 19.7 g., 14% yield, of product of m.p. 237–239°, dec. Recrystallization from 200 ml. of absolute ethanol, 30 ml. of 20% hydrobromic acid, and 10 ml. of water provided 14.1 g., m.p. 259–260°, dec., of white needles. Addition of 220 ml. of ether to the mother liquor provided a second recrystallization crop of 1.7 g., m.p. 255–256°, dec.; lit., 240–250°, dec., the range depending on the rate of heating.[13] The total recovery was 80%. An analytical sample was obtained by recrystallization of the first crop.

Anal. Calcd. for $C_6H_{16}Br_2N_2$: Br, 57.90. Found: Br, 58.09.

A picrate derivative of the free amine (generated *in situ* with base) melted at 221.5–223.5°, dec.; lit., 220–230°, dec.[13]; 226°, dec.[11] The dibenzoyl derivative (Schotten-Baumann conditions) melted at 184–185°; lit., 185–186°[12]; 184°.[13]

9-Substituted 1,5-Diazabicyclo[3.3.1]nonanes (V). Procedure A. 9-(*p*-Dimethylaminophenyl) Derivative.—A warmed, agitated suspension of 293 mg. (7.33 mmoles) of sodium hydroxide (USP) and 1.00 g. (3.62 mmoles) of purified II dihydrobromide in 4 ml. of methanol was treated with several drops of water until the neutralization reaction was complete. A small amount of water was added to dissolve completely residual sodium bromide. This warm solution was filtered into a warm solution of 542 mg. (3.62 mmoles) of *p*-dimethylaminobenzaldehyde in 3 ml. of

(15) H. Stetter, K. H. Mayer, and W. Wirth, *Angew. Chem.*, **72**, 580 (1960).

(16) This shielding effect has been used by Ruzicka, *et al.* [L. Ruzicka, M. Kolbelt, O. Haffiger, and V. Prelog, *Helv. Chim. Acta.*, **32**, 544 (1949)] to explain the diminished basicities of medium-sized cyclic imines.

(17) T. P. Sycheva and M. N. Schuking, *Chem. Abstr.*, **49**, 932 (1955).

(18) Essentially the same results were obtained using a reagent grade (b.p. 165–167°).

methanol and the solution were thoroughly mixed. When cooled the reaction mixture was warmed just below the boiling point of methanol for about 10 min., whereupon the product began to crystallize as long needles. After cooling slowly to room temperature and in a refrigerator overnight, the reaction mixture was filtered, and the product was washed with 50% methanol and dried yielding 765 mg., 86%, m.p. 145.3–146°. Recrystallization from 75% methanol provided 552 mg. (62%) of white needles, m.p. 147.2–148°.

Anal. Calcd. for $C_{15}H_{23}N_3$: C, 73.42; H, 9.45; N, 17.13; mol. wt., 245. Found: C, 73.18; H, 9.20; N, 17.10; mol. wt., 251.[19]

Procedure B. 9-(*p*-Methoxyphenyl) Derivative.—To a solution of 1.2 g. (0.03 mole) of sodium hydroxide (USP) in 2 ml. of water were added 10 ml. of methanol and 4.0 g. (0.015 mole) of purified II dihydrobromide. This mixture was swirled and when solution was effected 2.0 g. (0.015 mole) of anisaldehyde was added with swirling. When the reaction mixture had cooled to room temperature, it was warmed on a steam bath for 10 min., cooled, then poured into an equal volume of water containing seed crystals of the product (obtained by cooling and scratching a similar mixture). The turbid mixture was cooled in a refrigerator overnight and the crude product was removed by filtration, washed with 50% methanol, and dried, 1.8 g., m.p. 76.5–79.5°. Two extractions of the mother liquor with 20-ml. portions of ether followed by evaporation and treatment of the residue with a little water and seed crystals, provided a second crop of 0.6 g., m.p. 79–90.5°, making the total yield 70%. Recrystallization of the combined crops from petroleum ether (b.p. 40–60°) (Darco) provided 1.3 g. of the purified product, white prisms, m.p. 78.5–79.5°; concentration of the mother liquor provided a second recrystallization crop of 0.2 g., m.p. 78.5–79.5°, making the total recovery 83%.

Anal. Calcd. for $C_{14}H_{20}N_2O$: C, 72.38; H, 8.68; N, 12.06. Found: C, 72.62; H, 8.71; N, 12.02.

Procedure C. 9-(3-Indolyl) Derivative.—This procedure is similar to Procedure A except that the reaction temperature was maintained at 40–45°. The product formed within 15 min. and was recrystallized from absolute alcohol, m.p. 211–215°, dec., yield 74%.

Anal. Calcd. for $C_{15}H_{19}N_3$: C, 74.68; H, 7.94; N, 17.42. Found: C, 75.09; H, 8.23; N, 17.57.

Hydrolysis of 9-(*p*-Nitrophenyl)-1,5-diazacyclo[3.3.1]nonane.—An 88-mg. sample of the 9-(*p*-nitrophenyl) derivative was swirled in 8 ml. of 10% hydrobromic acid for 10 min. *p*-Nitrobenzaldehyde, which precipitated, was collected on a filter, washed with water, and dried, m.p. 104–105°; the mixed melting point with authentic *p*-nitrobenzaldehyde was not depressed, yield 47 mg., 87%. Concentration of the mother liquor to dryness followed by digestion with absolute alcohol gave 96 mg., 98% yield, of 1,5-diazacycloöctane dihydrobromide, m.p. 250–252° dec.; a mixed melting point with authentic dihydrobromide was not depressed.

(19) Spang Microanalytical Laboratory, Ann Arbor, Michigan.