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REACTION OF DIFORMYLHYDRAZINE WITH AMINOHETEROCYCLES

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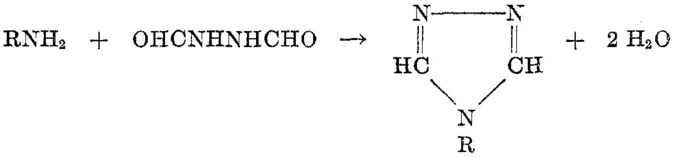
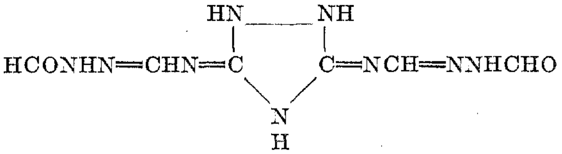
The reaction of diformylhydrazine with aromatic amines such as aniline (1), *o*- and *p*-toluidine (2), and 1- and 2-naphthylamine (3) is known to give 4-substituted-1,2,4,4*H*-triazoles.



We have studied this reaction with a variety of aminoheterocycles and have obtained 1,2,4,4*H*-triazoles from five different amines. The reaction was carried out by heating the amine and diformylhydrazine to 160–190° for 10–30 minutes. The triazoles were isolated in 13–80% yield as solids from the cooled reaction mixture. With six other aminoheterocycles under similar conditions, triazoles were not obtained.

The five aminoheterocycles which reacted according to the equation were 2-aminopyridine, 3-aminopyridine, 3-aminoquinoline, 3-amino-1,2,4,1*H*-triazole, and 2,6-diaminopyridine. The products from the first three of these amines were isolated from alcoholic solutions of the crude reaction mixture by precipitation with ether. The triazolyltriazole, obtained from the aminotriazole, was isolated by extraction with water and was recrystallized from water. This is the first description of 4,3′-bistriazole although 3,3′-bistriazole has been known since 1897 (4). Two products, a ditriazolylpyridine and a monotriazolylpyridine, were obtained from the reaction with 2,6-diaminopyridine.

The condensation of diformylhydrazine with guanazole (3,5-diamino-1,2,4-triazole) gave a product melting over 350°. Empirical analysis indicated a formula $C_6H_9N_9O_2$ having two molecules of water more than is required for the bis(triazolyltriazole). It is believed that guanazole reacts in its imino form, as it is known to do in other reactions, and that the product is 3,5-di-[N-(2-formylhydrazono)methylidine]imino-1,2,4-triazolidine (I).



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[1] Taken from a portion of the thesis submitted by Albert J. Hart in partial fulfilment of the requirements for the M.S. degree.

Two other amines, 2-aminopyrimidine and 2-aminobenzothiazole, gave low yields of products melting at 231° and 205° respectively for which the analysis indicated a 1,3-bisurea structure of the type: RNHCONHR. Formation of such products would require oxidation of the formamide to carbamide but this does not seem unlikely in view of the strenuous conditions used. Attempts to prepare bisureas from these amines using the procedure described by Sonn (5) gave products melting at 241° (with a large depression of the melting point on mixture with the product m.p. 231°) and over 350°. Both of these analyzed as monoureas: $RNHCONH_2$. 2-Benzothiazolylurea has been previously reported (6) as a compound melting over 300° and appears to be the same product we have obtained. A bis (benzothiazolylurea), m.p. 325°, has also been reported (6) and this is apparently a different product from our product which melts at 205°. The available information does not, therefore, permit a final assignment of the bisurea structure to these products. 2-Aminobenzimidazole gave good yields of an unidentified product, m.p. 200–202°. 4-Aminopyridine, guanazine, and 2-aminothiazole gave no characterizable products on reaction with diformylhydrazine.

The diformylhydrazine used in these studies was prepared by the reaction of ethyl formate and hydrazine hydrate (6) in 36% yield and also, in 31.5% yield, by a previously undescribed process in which formylhydrazine is heated with formamide.

EXPERIMENTAL[2]

4-(2-Pyridyl)-1,2,4,4H-triazole. 2-Aminopyridine (2.2 g., 0.023 mole) and 2.0 g. (0.023 mole) of diformylhydrazine were mixed, heated slowly to 165°, and held at 165–170° for 0.5 hour. The reaction mixture, which solidified on cooling to room temperature, was dissolved in 20 ml. of hot ethanol with Norit, and filtered hot. Diethyl ether (100 ml.) was added to the cooled solution. The solid which separated from this mixture after standing overnight in a cold box deposited 1.3 g. (40% of the theoretical amount) of 4-(2-pyridyl)-1,2,4,*4H*-triazole. After a second recrystallization from alcohol-ether and a final recrystallization from toluene the product was obtained as water-soluble, white needles, m.p. 169°.

Anal. Calc'd for $C_7H_6N_4$: N, 38.32. Found: N, 38.51.

4-(3-Pyridyl)-1,2,4,4H-triazole. This compound was prepared by the procedure described for the 2-pyridyl isomer. The crude product, obtained in 42% yield, was recrystallized from toluene to give water-soluble, white needles, m.p. 162°.

Anal. Calc'd for $C_7H_6N_4$: C, 57.5; H, 4.14.
Found: C, 57.68; H, 4.13.

4-(3-Quinolyl)-1,2,4,4H-triazole. This compound was prepared by the procedure described for the 2-pyridyl isomer. The crude product, obtained in 80% yield, was recrystallized from alcohol-ether solutions to give water-soluble, white needles, m.p. 202–203°.

Anal. Calc'd for $C_{11}H_8N_4$: C, 67.33; H, 4.11.
Found: C, 67.32; H, 4.10.

4-[3-(1,2,4,1H-Triazolyl)]-1,2,4H-triazole. A mixture of 3.9 g. (0.046 mole) of 3-amino-1,2,4,*1H*-triazole and 4.0 g. (0.046 mole) of diformylhydrazine was heated slowly to 155° at which temperature the mixture liquefied. After ten minutes continued heating at 155–165° the mixture solidified. The cooled reaction mixture was dissolved in 13 ml. of boiling water and filtered. On cooling, 2.7 g. (44%), of the product separated. Recrystallization from hot water gave large, white crystals, m.p. 300–302° with decomposition. The compound is soluble in dilute, aqueous sodium hydroxide.

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[2] Analyses by Mirco Tech Laboratories, Skokie, Illinois.

Anal. Calc'd for $C_4H_4N_6$: C, 35.3; H, 2.96; Neut. equiv., 136.

Found: C, 35.46; H, 3.11; Neut. equiv., 135.

2,6-Di-(4-triazolyl)pyridine. A mixture of 1.3 g. (0.012 mole) of 2,6-diaminopyridine and 2.0 g. (0.023 mole) of diformylhydrazine was heated slowly to 160° and held at 160–170° for one-half hour. The crystals, which separated on cooling, were collected and recrystallized from water (Norit) to give 0.70 g. (13%), of 2,6-di-(4-triazolyl)pyridine. After several recrystallizations from water and from alcohol, the air-dried product was obtained as white needles, m.p. 325–327° (placed in hot block at 320°). Vacuum-dried samples were hygroscopic and did not analyze in accord with theory. The analysis was obtained on the air-dried sample.

Anal. Calc'd for $C_9H_7N_7 \cdot H_2O$: C, 46.75; H, 3.92.

Found: C, 46.55; H, 3.96.

2-Amino-6-(4-triazolyl)pyridine. This compound was prepared by a procedure similar to that described for the preceding compound using 4.5 g. (0.041 mole) of 2,6-diaminopyridine and 3.6 g. (0.041 mole) of diformylhydrazine. The crude solid product was dissolved in the minimum amount of alcohol and cooled to precipitate the ditriazolylpyridine which was separated by filtration. The filtrate on evaporation gave 0.8 g. (10%), of 2-amino-6-(4-triazolyl)pyridine; recrystallized from ethanol, m.p. 193–196°.

Anal. Calc'd for $C_7H_7N_5$: C, 52.2; H, 4.38.

Found: C, 52.46; H, 4.43.

3,5-Di-[N-(2-formylhydrazono)methylidine]imino-1,2,4-triazolidine (I). A mixture of 1.0 g. (0.01 mole) of guanazole and 1.8 g. (0.02 mole) of diformylhydrazine was heated slowly to 180° for one hour. The cooled reaction mixture was extracted with eight 25-ml. portions of boiling water. These extracts, on cooling, deposited 1.4 g. (49%) of the product (I), melting over 350°. The analytical sample was carefully dried prior to analysis and gave no indication of being a hydrate.

Anal. Calc'd for $C_6H_9N_4O_2$: C, 30.12; H, 3.79.

Found: C, 30.30; H, 3.86.

Reaction of diformylhydrazine with 2-aminopyrimidine. A mixture of 1.2 g. (0.013 mole) of 2-aminopyrimidine and 1.0 g. (0.011 mole) of diformylhydrazine heated at 180–190° for one hour and cooled precipitated a solid which was recrystallized from toluene to give 0.6 g. of a crude product, m.p. 240–248°. Repeated recrystallization gave a solid, m.p. 231–233°. A substance melting at 240–255° has also been isolated from the mother liquors. The product, m.p. 231–233°, is perhaps the 1,3-bisurea on the basis of the following analysis.

Anal. Calc'd for $C_9H_8N_6O$: C, 50.0; H, 3.7.

Found: C, 49.6; H, 3.86.

Reaction of diformylhydrazine with 2-aminobenzothiazole. A mixture of 2.0 g. (0.013 mole) of 2-aminobenzothiazole and 1.2 g. (0.014 mole) of diformylhydrazine heated at 165–170° for one hour and cooled, precipitated a solid which was recrystallized from alcohol to give 0.5 g. of a solid, m.p. 205–206° and an impure solid, m.p. 240–260°. The product, m.p. 205–206°, is perhaps the 1,3-bisurea on the basis of the following analysis.

Anal. Calc'd for $C_{15}H_{10}N_4OS_2$: C, 55.2; H, 3.07.

Found: C, 55.24; H, 3.11.

Reaction of diformylhydrazine with 2-aminobenzimidazole. Following the procedure described in preceding examples, 2-aminobenzimidazole (6.2 g.) heated with diformylhydrazine (4.0 g.) gave 4.5 g. of a solid, m.p. 200–202°, recrystallized from alcohol.

Anal. Found: C, 53.62, 53.70; H, 5.14, 5.08.

(2-Benzothiazolyl)urea. A mixture of 3.0 g. (0.02 mole) of 2-aminobenzothiazole, 0.60 g. (0.010 mole) of urea, and 1.5 ml. of glacial acetic acid was heated in an open flask over a bare flame for about one minute. During this time the solids dissolved and the product precipitated. After recrystallization from alcohol, the (2-benzothiazolyl)urea was obtained as white needles, m.p. over 350°.

Anal. Calc'd for $C_8H_7N_3OS$: N, 21.75. Found: N, 21.76.

(2-Pyrimidyl)urea. A mixture of 3.0 g. (0.032 mole) of 2-aminopyrimidine, 1.0 g. (0.017

mole) of urea, and 2 ml. of glacial acetic acid was heated to 180° for one-half hour. The solid which separated on cooling was recrystallized from water to give 0.7 g. (30%) of (2-pyrimidyl)urea. Recrystallized from toluene or ethanol, m.p. 241–243°.

Anal. Calc'd for $C_5H_6N_4O$: C, 43.48; H, 4.38.

Found: C, 43.72; H, 4.57.

SUMMARY

The reaction of diformylhydrazine with 2- and 3-aminopyridine, 3-amino-1,2,4,4*H*-triazole, 2,6-diaminopyridine, and 3-aminoquinoline has given 13–80% yields of 4-substituted-1,2,4,4*H*-triazoles. With guanazole, 2-aminobenzothiazole, and 2-aminopyrimidine other products, whose possible structures are discussed, have been obtained.

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