The Reaction of Azodicarboxylic Acid Esters with Aldehyde Monosubstituted Hydrazones[1]

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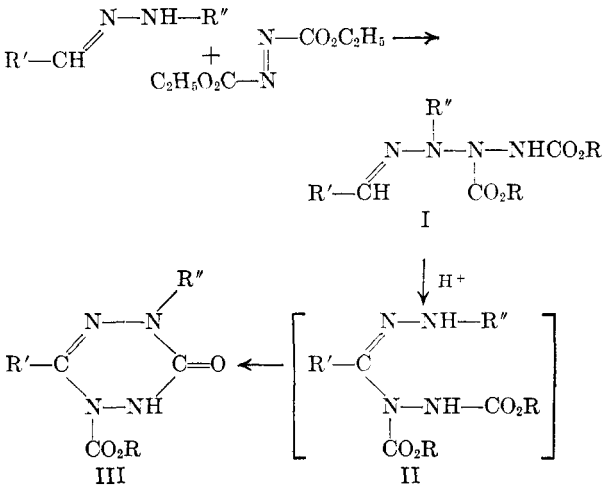
The reaction of aldehyde monosubstituted hydrazones with azodicarboxylic acid esters has been shown to yield hydrazide-hydrazones (II) of the acids corresponding to the aldehydes, rather than the reported tetrazane derivatives. The hydrazide-hydrazones cyclized under acidic, basic, or thermal conditions to furnish 4-amino-2,3-dihydro-3-oxo-1,2,4-triazole derivatives rather than the reported 1,2,3,4-tetrahydro-3-oxo-1,2,4,5-tetrazine derivatives.

Büsch, Müller, and Schwarz[3] have proposed the following sequence for the reaction of azodicarboxylic acid esters with aldehyde monoalkylhydrazones (scheme A).

Scheme A:



Further, the intermediate tetrazane (I) was reported then to rearrange in the presence of acid to the non-isolable intermediate hydrazide-hydrazone (II) which immediately cyclized to the tetrazinone (III).[3] About that time the reaction of azodicarboxylic acid esters with aldehydes was found to result in substitution of a hydrazine moiety for the aldehyde hydrogen.[4] The reaction was slow at room temperature but gave good yields of the adducts. The failure of ketone monoalkylhydrazones,[3] and aldehyde dialkylhydrazones[5] severely restricted the possible mechanisms of the addition of azodicarboxylic acid esters to aldehyde monoalkylhydrazones. Further, in view of the unusual rearrangement of the intermediate I to give II which was proposed, the reactions of scheme A were reinvestigated.

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(2) Petroleum Research Fund Scholar, 1960–1961.

(3) M. Büsch, H. Müller, and E. Schwarz, *Ber.*, **56**, 1600 (1923).

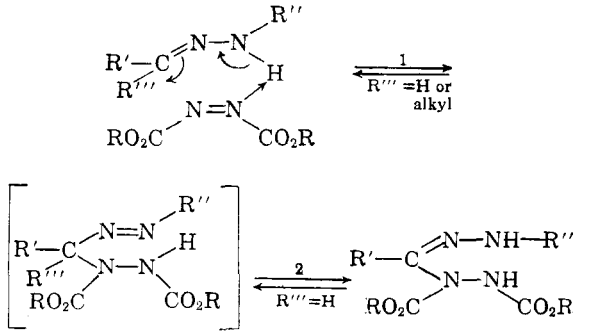
(4) K. Alder and T. Noble, *ibid.*, **76**, 54 (1923).

(5) When ethyl azodicarboxylate was mixed with benzaldehyde benzylphenylhydrazone and heated, the hydrazone was recovered in 90% yield.

When benzaldehyde phenylhydrazone was treated with ethyl azodicarboxylate, a 55% yield of yellow crystals, m.p. 104–106°, was obtained. This compound was the material which was purported to be the tetrazane derivative (I).[3] However, when this compound was treated with the standard 2,4-dinitrophenylhydrazine reagent, no benzaldehyde 2,4-dinitrophenylhydrazone was formed. This evidence was the first indication that the structure of the proposed intermediate was wrong. A subsequent infrared spectrum determination and ring closures under a variety of conditions both acidic and basic cast further doubt on structure I. An active hydrogen determination (which showed two rather than one active H) clearly indicated the structure of the intermediate as a hydrazide-hydrazone (II) in contrast to the proposed tetrazane (I). Table I shows the intermediates isolated from various aldehyde phenylhydrazones (IIa, b, and c.)

The formation of II together with the lack of reaction with ketone monoalkylhydrazones and aldehyde dialkylhydrazones can be most easily explained by a cyclic mechanism, which necessitates an N—H bond in the hydrazone as well as an aldehydic hydrogen as shown in scheme B. A direct analogy exists in the reaction of certain conjugated and unconjugated olefins with ethyl azodicarboxylate.[6]

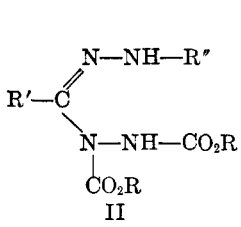
Scheme B:



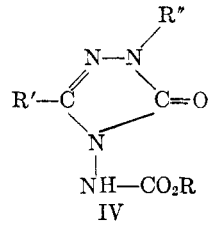
The ketone monoalkylhydrazones do not result in adduct formation because the proton shift in step 2 necessary for stabilization is impossible, and

(6) Bernard T. Gillis and Paul E. Beck, *J. Org. Chem.*, **27**, 1947 1962); Boris Franzus and John H. Surridge, *ibid.*, **27**, 1951 (1962).

TABLE I



II



IV

No.	R	R′	R″	M.p., °C.	λ_{max} mμ (EtOH)	log ε
IIa	C_2H_5—	C_6H_5—	C_6H_5—	104–106	274	4.03
IIb	C_2H_5—	CH_3—	C_6H_5—	67–68	269	4.4
IIc	$C_6H_5CH_2$—	C_6H_5—	C_6H_5—	130–131	274	4.0
IVa	C_2H_5—	C_6H_5—	C_6H_5—	148–149	268	4.25
IVb	C_2H_5	CH_3—	C_6H_5—	111–112	247	4.1
IVc	$C_6H_5CH_2$—	C_6H_5—	C_6H_5—	129–130	269	4.1
IVd	C_2H_5—	C_6H_5—	CH_3—	135–136	267	4.45

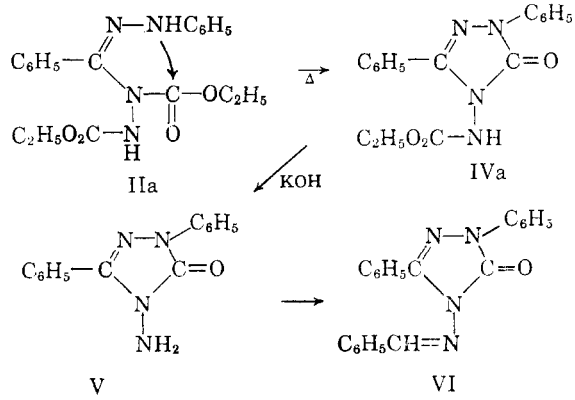
the equilibrium for step 1 where R‴ = alkyl undoubtedly lies far to the left.

When aliphatic aldehyde monoalkylhydrazones reacted with ethyl azodicarboxylate, the latter was reduced to ethyl hydrazodicarboxylate. Such hydrazones are capable of easy azine formation by the azodicarboxylic acid esters which are reasonably strong oxidants.

The intermediates of type II could be cyclized by thermal, acidic, or basic conditions. Table I lists the cyclized compounds, IVa, b, c, and d. The benzaldehyde methylhydrazone reacted with ethyl azodicarboxylate to form the cyclized compound IVd directly. No intermediate was detected. The increased nucleophilicity of the nitrogen adjacent to the alkyl group apparently increased the ease of an already facile ring closure.

Büsch, *et al.*,[3] had formulated the cyclic compounds as substituted 1,2,3,4-tetrahydro-3-oxo-1,2,4,5-tetrazine-1-carboxylates. However, treatment of IVa with potassium hydroxide in ethylene glycol for four and a half hours yielded a compound, m.p. 156–157°, whose infrared spectrum exhibited absorption characteristic of an —NH_2 group and the compound was thus formulated as 4-amino-2,5-diphenyl-2,3,-dihydro-3-oxo-1,2,4-triazole (V). Upon condensation of V with benzaldehyde a derivative (VI), m.p. 119–120°, was obtained with correct analysis for the benzylidene derivative and whose infrared spectrum was devoid of —NH— absorption. These facts indicate that the cyclic compounds of Büsch[3] and those in Table I are triazole derivatives rather than tetrazine derivatives. In view of the past literature,[7] all those cases where 1,2,4,5-tetrazines were postulated by a cyclization where 4-aminotriazole derivatives are also possible are probably the latter (see scheme C).

Scheme C:



IIa IVa V VI

Experimental[8]

Preparation of Starting Materials.—*Ethyl azodicarboxylate* was prepared by the method of Rabjohn[9] in 78% yield, b.p. 107–111° (15 mm.). *Benzyl hydrazodicarboxylate* was prepared by a modification of the method used for preparation of ethyl hydrazodicarboxylate.[9] The compound was obtained as white flakes from benzene in 72% yield, m.p. 105–105.5° (lit., m.p. 106–106.5°[10]). *Benzyl azodicarboxylate* was prepared by the method of Kenner and Stedman[10] in 69% yield, m.p. 45–46°. *Benzaldehyde methylhydrazone* was prepared according to the method of Wiley and Irick,[11] in 85% yield, b.p. 123–125° (9 mm.).

Benzoic Acid, N,N′-Dicarbethoxyhydrazide-phenylhydrazone (IIa).—The compound was prepared by the method of Büsch, Müller, and Schwarz.[3] Upon recrystallization from ethanol, IIa was obtained in 55% yield, m.p. 104–106° (lit., m.p. 106°[3]).

Acetic Acid, N,N′-Dicarbethoxyhydrazide-phenylhydrazone (IIb).—Ethyl azodicarboxylate (8.0 g., 0.046 mole) was added dropwise to acetaldehyde phenylhydrazone (6.2 g., 0.046 mole). An exothermic reaction ensued and a dark red oil was formed. The oil was taken up in 15 ml. of methanol and placed in the refrigerator to crystallize. After 2 weeks at 0° a yellow material crystallized. The material was filtered and recrystallized from petroleum ether to give 5.0 g. (35%) of IIb, m.p. 67–68°.

(7) John G. Erickson, Paul F. Wiley, and V. P. Wystrach, "The 1,2,3- and 1,2,4-Triazines, Tetrazines and Pentazines," Interscience Publishers, Inc., New York, N. Y., 1956, Chap. V and references therein.

(8) Melting points and boiling points are uncorrected. Spectra were determined on a Perkin-Elmer Model 137 double beam infrared spectrophotometer and a Beckman Model DU ultraviolet spectrophotometer. Analyses were performed by Alfred Bernhardt, Mülheim, Germany.

(9) N. Rabjohn, "Organic Syntheses," Vol. XXVIII, John Wiley & Sons, Inc., New York, N. Y., 1948, p. 58.

(10) G. W. Kenner and R. J. Stedman, *J. Chem. Soc.*, 2089 (1952).

(11) R. H. Wiley and G. Irick, *J. Org. Chem.*, **24**, 1925 (1959).

Anal. Calcd. for $C_{14}H_{20}N_4O_4$: C, 54.53; H, 6.54; N, 18.17. Found: C, 54.80; H, 6.65; N, 18.30.

Benzoic Acid, N,N'-Dicarbobenzoxyhydrazide-phenylhydrazone (IIc).—Benzyl azodicarboxylate (2.0 g., 0.0067 mole) was dissolved in 15 ml. of refluxing ether. To this solution was added slowly through the condenser in approximately one-third portions 1.7 g. (0.0086 mole) of benzaldehyde phenylhydrazone. The condenser was washed with 5-ml. portions of ether after each addition. Reflux of the ether solution was continued until the solution turned a brilliant yellow. The ether was then removed on an aspirator and a yellow solid melting at 124–128° was obtained. The solid was recrystallized from methanol to furnish 2.45 g. (77%) of IIc, m.p. 130–131°.

Anal. Calcd. for $C_{29}H_{26}N_4O_4$: C, 70.41; H, 5.35; N, 11.33; active H, 0.40. Found: C, 70.18; H, 5.30; N, 11.20; active H, 0.48.

4-Carbethoxyamino-2,5-diphenyl-2,3-dihydro-3-oxo-1,2,4-triazole (IVa). Procedure A.—The treatment of IIa by the method of Büsch, *et al.*,[3] utilizing acid resulted in a white solid from methanol, m.p. 148–149° (lit., m.p. 149–150°[3]).

Procedure B.—One gram of IIa was placed in a solution of 40 ml. of methanol and 3 g. of potassium hydroxide and refluxed for 24 hr., whereupon the solution became clear. Upon cooling and acidification with sulfuric acid, a white solid precipitated which was filtered and dissolved in benzene. The benzene solution was then filtered to remove any potassium sulfate. Upon cooling the filtrant, 0.77 g. (88%) of IVa, m.p. 146–147°, was obtained. A mixed melting point determination with an authentic sample of IVa was undepressed and infrared spectra of the two samples were superimposable.

Procedure C.—The reflux of 0.5 g. of IIa in 30 ml. of benzene for 3.5 days resulted in a color change from bright yellow to a very light yellow. Concentration of the benzene solution and cooling resulted in crystallization of 0.39 g. (90%) of IVa, m.p. 147–148°. A mixed melting point with authentic material showed no depression.

4-Carbethoxyamino-5-methyl-2-phenyl-2,3-dihydro-3-oxo-1,2,4-triazole (IVb).—Treatment of IIb according to the method of Büsch, *et al.*,[3] resulted in the formation of IVb, m.p. 110–112° from benzene (lit., m.p. 112°[3]).

4-Carbobenzoxyamino-2,5-diphenyl-2,3-dihydro-3-oxo-1,2,4-triazole (IVc).—A 0.5-g. sample of IIc was dissolved in 25 ml. of refluxing methanol to which 3 ml. of 20% hydrochloric acid had been added. The solution was refluxed until clear. The methanol solution was concentrated and cooled in the refrigerator. A white solid IVc (0.33 g.; 88%) m.p. 127.5–129° crystallized. An analytical sample was recrystallized from a mixture of hexane and ether, m.p. 129–130°.

Anal. Calcd. for $C_{22}H_{18}N_4O_3$: C, 68.36; H, 4.70; N, 14.50. Found: C, 68.27; H, 4.76; N, 14.42.

4-Carbethoxyamino-2-methyl-5-phenyl-2,3-dihydro-3-oxo-1,2,4-triazole (IVd).—Ethyl azodicarboxylate (5.0 g.; 0.028 mole) was added dropwise to freshly distilled benzaldehyde methylhydrazone (3.8 g.; 0.028 mole) dissolved in 25 ml. of anhydrous ether. An exothermic reaction with decolorization of the solution resulted. The solution was allowed to stand for 4 days and a white solid melting at 132–134° crystallized. Recrystallization of this material from ether gave 4.0 g. (55%) of IVd, m.p. 135–136°.

Anal. Calcd. for $C_{12}H_{14}N_4O_3$: C, 54.93; H, 5.38; N, 21.37. Found: C, 55.00; H, 5.43; N, 21.42.

4-Amino-2,5-diphenyl-2,3-dihydro-3-oxo-1,2,4-triazole (V).—Five grams of IVa was mixed with 5 g. of potassium hydroxide in 50 ml. of ethylene glycol and the mixture was refluxed under nitrogen for 4.5 hr. The mixture was then poured into 300 ml. of water, and the total solution was extracted with two 200-ml. portions of ether. The combined ether extracts were concentrated on a steam bath, 100 ml. of methanol added, and the residual ether was driven off by heat. Upon cooling the alcoholic solution, 2.8 g. (77%) of white solid V, m.p. 154.5–156°, crystallized. An analytical sample prepared by recrystallization from ethanol melted 156–157°, and exhibited λ_{max} (EtOH) 271 mμ, log ε 4.2.

Anal. Calcd. for $C_{14}H_{12}N_4O$: C, 66.63; H, 4.79; N, 22.22. Found: C, 66.52; H, 4.94; N, 22.05.

4-Benzylideneamino-2,5-diphenyl 2,3-dihydro-3-oxo-1,2,4-triazole (VI).—In 10 ml. of boiling methanol was dissolved 0.1 g. of V. Benzaldehyde (1 ml.) was slowly added to the solution and a white precipitate formed. The solid was filtered and recrystallized from methanol to yield 0.11 g. (81%) of VI, which melted at 119–120° and exhibited λ_{max} (EtOH) 266 mμ, log ε 4.5.

Anal. Calcd. for $C_{21}H_{16}N_4O$: C, 74.08; H, 4.74; N, 16.47. Found: C, 73.89; H, 4.58; N, 16.59.

Direct Synthesis of Poly(morpholinomethyl)hydroquinones[1]

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High yields of tris- (III) and tetrakis(morpholinomethyl)hydroquinone (IV) were obtained directly from the condensation of hydroquinone with formaldehyde and morpholine. Factors influencing the condensation were studied and IV was hydrogenated to tetramethylhydroquinone (VI) and to 2,3,5,6-tetramethylcyclohexane-1,4-diol (VII).

It was recently shown that *p*-benzyloxyphenol is an attractive starting material for the synthesis of trimethylhydroquinone.[2] In further related studies it was found that reaction of 2,6-bis(morpholinomethyl)hydroquinone with morpholine and formaldehyde under certain conditions led to both tris- and tetrakis(morpholinomethyl)hydroquinone.

The formation of the latter was unexpected in view of the fact that Caldwell and Thompson[3] found that 2,5-bis(dimethylaminomethyl)hydroquinone was obtained when hydroquinone was condensed with the stoichiometric quantities required for the desired corresponding tris compound. They pointed out that hydrogenation of tris(dimethylaminomethyl)hydroquinone would provide a convenient route to trimethylhydroquinone,

(1) This investigation was supported in part by a research grant CY-5211 from the National Cancer Institute of the Public Health Service.

(2) W. J. Burke, J. A. Warburton, J. L. Bishop, and J. L. Bills, *J. Org. Chem.*, **26**, 4669 (1961).

(3) W. T. Caldwell and T. R. Thompson, *J. Am. Chem. Soc.*, **61**, 765 (1939).