[CONTRIBUTION FROM THE AVERY LABORATORY OF CHEMISTRY OF THE UNIVERSITY OF NEBRASKA]

Arsenicals Containing the 1,2,5-Triazole Nucleus

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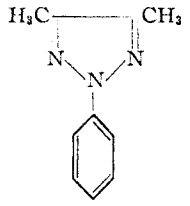
The recent advent of heterocyclic arsenicals into the field of chemotherapy[1,2] has stimulated the investigation of arsenicals containing a variety of heterocyclic nuclei. Continuing this we have prepared a number of arsenicals containing the 1,2,5-triazole nucleus. 1-Phenyl-3,4-dimethyl-1,2,5-triazole (I) was synthesized by a



I

modification of the method of von Pechmann.[3] With concentrated nitric acid (I) readily yielded 1-(4-nitrophenyl)-3,4-dimethyl-1,2,5-triazole (II) melting at 233–234° instead of 227° as reported by v. Pechmann.[3] In addition a mononitro product (III) melting at 75.3-76.1° was obtained which is presumed to be 1-(2-nitrophenyl)-3,4-dimethyl-1,-2,5-triazole (IIIA). This presumption disputes the conclusion reached by Guha and De[4] as the result of the reaction of alcoholic hydrogen chloride on diacetyl monoxime-*o*-nitrophenylhydrazone in a sealed tube. The product (IIIB) obtained by these investigators and purported to be IIIA melts at 285°.

The designation of the structure IIIA for product III is based on the following data: the compound I of known structure was subjected to nitration to give two analytically pure mononitro derivatives II and III. Ponzio[5] has satisfactorily demonstrated II to be the *para* isomer.

Consequently a second mononitration product would be expected to be the *ortho* isomer on the basis of the general rules of orientation of entering groups. Furthermore if III has the structure assigned to IIIA, the expected order of melting points for ortho and para isomers is preserved; whereas if IIIB is of structure IIIA, a contradiction to the general rule is obtained.

The procedure of Guha and De[4] when applied to diacetyl monoxime-*p*-nitrophenylhydrazone yielded a brilliant red crystalline solid (IV) m.p. 332° (dec.) which cannot be II. Although the structure of IV is unknown, the product gave an unstable amine identified as *p*-phenylenediamine on reduction with tin and hydrochloric acid. This would seem to indicate that the hydrazone type linkage was still present. The evidence for the ring closure purported by Guha and De rests entirely on analytical data; and while the carbon and hydrogen analyses of IV might possibly indicate a structure II, the value N, 23.28% obtained for IV with Hayman's catalyst does not conform with the required N, 25.68% for II.

The authors feel that this evidence is sufficient to substantiate their claim that III is 1-(2-nitrophenyl)-3,4-dimethyl-1,2,5-triazole (IIIA).

Compounds II and III have been catalytically reduced with Raney nickel and arsenation effected by the Bart[6] reaction.

1-(4-Arsonophenyl)-3,4-dimethyl-1,2,5-triazole (V) was subjected to several reactions of nitration, oxidation, reduction, and esterification to yield a number of arsenical derivatives.

Experimental

All melting points, corrected for exposed stem, were taken on a thermometer calibrated by the Bureau of Standards. The melting point of an arsonic acid is designated as that temperature range at which the solid melts or undergoes a definite change within fifteen seconds after being placed in the melting point bath.

Diacetyl Monoxime-α,α-ethylphenylhydrazone (VI).—Diacetyl monoxime (606 g., 6.0 moles) in hot water (2 liters) was treated with α,α-ethylphenylhydrazine[7] (816 g., 6.0 moles) and the mixture stirred for several hours; yield of orange oil 1.3 kg. (nearly quantitative).

1-Phenyl-3,4-dimethyl-1,2,5-triazole (I).—The hydrazone (VI) was added dropwise with stirring to hot acetic anhydride (2.4 liters) at a rate such that a steady distillation of ethyl acetate took place. The excess acetic anhydride was then removed by distillation under reduced pressure and the residual liquid fractionally distilled at atmospheric pressure to yield 856 g. (83%) of product b. p. 250–257°. The purified material boiled at 253–255° at atmospheric pressure; m. p. 34–35°.

1-(4-Nitrophenyl)-3,4-dimethyl-1,2,5-triazole (II) and 1-(2-Nitrophenyl)-3,4-dimethyl-1,2,5-triazole (III).—To concentrated nitric acid (400 g., density, 1.42) at room temperature was added with stirring (50 g., 0.29 mole) of (I). The temperature was allowed to rise spontaneously to 75–80°. After the vigorous reaction subsided, the nearly solid mass was diluted with water (1 liter) and filtered. The crude nitration product was extracted with absolute ethanol until a white residue of nearly pure (II) remained; yield 35 g. (55%). The ethanol extract was concentrated and the concentrate diluted with water to precipitate the crude *ortho* isomer, which was purified by repeated crystallization from dilute ethanol and petroleum ether (b. p. 60–70°) as solvents. The yield of pure (III) was 6.4 g. (10%), m. p. 75.3–76.1°.

Anal. Calcd. for III $C_{10}H_{10}N_4O_2$: C, 55.04; H, 4.62. Found: C, 55.23, 54.92; H, 4.75, 4.81.

1-(2-Aminophenyl)-3,4-dimethyl-1,2,5-triazole (VII).—A solution of III (14.4 g., 0.066 mole) in hot absolute ethanol (100 ml.) was reduced at 40 lb. hydrogen pressure in the presence of Raney nickel catalyst (3 g.) for twenty-four hours. The catalyst was removed by filtration, the filtrate concentrated by reduced pressure distillation and the re-

(1) Friedheim, *Schweiz. Med. Wochschr.*, **71**, 116 (1941); *C. A.*, **36**, 1676 (1942).

(2) Banks, Gruhzit, Tillitson and Controulis, THIS JOURNAL, **66**, 1771 (1944).

(3) v. Pechmann, *Ann.*, **262**, 265 (1891).

(4) Guha and De, *Quart. J. Indian Chem. Soc.*, **3**, 41 (1926).

(5) Ponzio, *Gazz. chim. ital.*, **291**, 280 (1899).

(6) Bart, *Ann.*, **429**, 55 (1922).

(7) Audrieth, Weissiger and Carter, *J. Org. Chem.*, **6**, 417 (1941).

TABLE I

ARSENICALS

3,4-Dimethyl-1,2,5-triazole		Yield, %	M. p., °C.	Formula	As analyses, %[g] Calcd.	Found
1-(4-Arsonophenyl)-	(V)	47	>250	$C_{10}H_{12}AsN_3O_3$	25.21	25.28
1-(2-Arsonophenyl)-	(XIX)[a]	24	265–266	$C_{10}H_{12}AsN_3O_3$	25.21	25.02
1-(2-Nitro-4-arsonophenyl)-	(IX)	70	187.5–188.5	$C_{10}H_{11}AsN_4O_5$	21.90	21.84
1-(2-Amino-4-arsonophenyl)-	(X)[b,c]	77	>250	$C_{10}H_{13}AsN_4O_3$	24.00	23.92
1-(2-Amino-4-arsenosophenyl)-	(XI)	90	>250	$C_{10}H_{11}AsN_4O$	26.93	26.85
3-Carboxy-4-methyl-1,2,5-triazole						
1-(4-Arsonophenyl)-	(XIII)	86	>250	$C_{10}H_{10}AsN_3O_5$	22.90	22.72
1-(2-Nitro-4-arsonophenyl)-	(XII)	49	>250	$C_{10}H_9AsN_4O_7$	20.13	19.97
1-(2-Amino-4-arsonophenyl)-	(XVI)[c,d]	54	>250	$C_{10}H_{11}AsN_4O_5$	21.90	21.84
3-Carbethoxy-4-methyl-1,2,5-triazole						
1-(4-Arsonophenyl)-	(XVII)	70	>250	$C_{12}H_{14}AsN_3O_5$	21.09	20.96
1-(2-Nitro-4-arsonophenyl)-	(XVIII)[e]	60	[f]	$C_{12}H_{13}AsN_4O_7$	18.72	18.91
1,2,5-Triazole						
1-(4-Arsonophenyl)-3,4-dicarboxy-	(XIV)	62	>250	$C_{10}H_8AsN_3O_7$	20.98	21.15
1-(4-Arsonophenyl)-3-carboxy-	(XV)	33	>250	$C_9H_8AsN_3O_5$	23.93	23.88

[a] Preparation similar to (V). Purified by crystallization from 75% ethanol and 90% acetic acid. [b] Crystallized from 50% acetic acid. [c] Obtained from corresponding nitro compounds by the method of Stevinson and Hamilton, THIS JOURNAL, **57**, 1298 (1935). [d] Purified by solution in dilute sodium bicarbonate and reprecipitation with dilute hydrochloric acid. [e] Preparation similar to (XVII). [f] Sinters at 135–136°; melts 189–209° (dec.) on further heating. [g] Cislak and Hamilton, THIS JOURNAL, **52**, 638 (1930).

sidual liquid poured into water (200 ml.). The yield of oil which rapidly solidified was 12 g. (97%). The product was purified by crystallization from dilute ethanol and from petroleum ether, m. p. 66.3–67.5°.

Anal. Calcd. for $C_{10}H_{12}N_4$: C, 63.80; H, 6.43. Found: C, 63.54, 63.69; H, 6.65, 6.54.

1-(4-Aminophenyl)-3,4-dimethyl-1,2,5-triazole (VIII).—The reduction of II was accomplished in a similar manner (91%) m. p. 132–133°. However, the slight solubility of II in ethanol necessitated heating at 60–70° during the reduction.

1-(4-Arsonophenyl)-3,4-dimethyl-1,2,5-triazole (V).—A solution of VIII (47.5 g., 0.25 mole) in water (670 ml.) containing hydrochloric acid (0.7 mole) was diazotized at 0–5° by the dropwise addition of sodium nitrite (17.4 g., 0.25 mole) in water (150 ml.). The stirred diazonium solution at 0–5° was treated all at once with a solution consisting of sodium hydroxide (44.5 g., 1.1 mole), arsenic trioxide (50 g., 0.25 mole), 20% copper sulfate (35 ml.) and water (350 ml.). The solution was stirred at 0–5° for four hours, heated to 65°, neutralized with hydrochloric acid, treated with charcoal and filtered. The filtrate was acidified to congo red paper with hydrochloric acid and the product removed by filtration. The yield of product crystallized from dilute acetic acid was 35 g. (47%), m. p. > 250°.

Anal. Calcd. for $C_{10}H_{12}AsN_3O_3$: As, 25.21. Found: As, 25.28.

1-(2-Nitro-4-arsonophenyl)-3,4-dimethyl-1,2,5-triazole (IX).—Powdered V (4.15 g., 0.014 mole) was added portionwise at 0–5° to sulfuric acid (40 g., d. 1.84) and fuming nitric acid (14 g., d. 1.40). The solution was allowed to stand overnight at 0°. The mixture was poured onto ice (50 g.), neutralized with 40% sodium hydroxide until no further precipitation occurred (mixture still blue to congo red paper), filtered. After crystallization from water, a yield of 3.35 g. (70%), m. p. 187.5–188.5°, was obtained.

Anal. Calcd. for $C_{10}H_{11}AsN_4O_5$: As, 21.90. Found: As, 21.84.

1-(4-Arsonophenyl)-3-carboxy-4-methyl-1,2,5-triazole (XIII).—A solution of V (4 g., 0.013 mole) and sodium hydroxide (2.7 g., 0.067 mole) in water (100 ml.) was heated on a steam-bath for three hours with potassium permanganate (5.3 g.) and then the excess oxidant destroyed by the addition of ethanol. After the removal of manganese dioxide, the solution was made acid to congo red paper with hydrochloric acid. The product was collected and an additional amount obtained by concentration of the filtrate. The arsonic acid was dissolved in dilute sodium bicarbonate and reprecipitated by the addition of dilute hydrochloric acid, yield 3.77 g. (86%), m. p. > 250°.

Anal. Calcd. for $C_{10}H_{10}AsN_3O_5$: As, 22.90. Found: As, 22.72.

1-(4-Arsonophenyl)-3,4-dicarboxy-1,2,5-triazole (XIV) and 1-(2-Nitro-4-arsonophenyl)-3-carboxy-4-methyl-1,2,5-triazole (XII).—These products were prepared in a manner similar to XIII from V and IX, respectively. (XIV) was crystallized from 12 *N* hydrochloric acid, yield 62%, m. p. > 250°; while (XII) was obtained in 49% yield, m. p. > 250° from 8 *N* hydrochloric acid.

1-(4-Arsonophenyl)-3-carboxy-1,2,5-triazole (XV).—XIV (7 g., 0.019 mole) was heated with copper oxide (1 g.) and quinoline[8,9] (30 ml.) at 190° for one hour. The mixture was extracted with 5% sodium hydroxide (50 ml.), the aqueous layer extracted with ether. The product was dissolved in dilute sodium bicarbonate and reprecipitated with dilute hydrochloric acid; yield 2 g. (33%), m. p. > 250°.

Anal. Calcd. for $C_9H_8AsN_3O_5$: As, 23.93. Found: As, 23.88.

1-(4-Arsonophenyl)-3-carbethoxy-4-methyl-1,2,5-triazole (XVII).—A solution of XIII (5 g., 0.015 mole) in absolute ethanol (50 ml.) and concentrated sulfuric acid (1 ml.) was refluxed for twenty-four hours. The mixture was concentrated to 5–10 ml. by distillation under reduced pressure and the product isolated by diluting the residual mixture with 50 ml. of water.

1-(2-Amino-4-arsenosophenyl)-3,4-dimethyl-1,2,5-triazole (XI).—A solution of (X) (see table) (3.4 g., 0.011 mole) in hot 6 *N* sulfuric acid (250 ml.) was reduced with sulfur dioxide in the presence of a trace of potassium iodide catalyst. After the reduction was complete (fifteen to twenty minutes), the mixture was cooled, filtered, and the solid dissolved in hot dilute sodium hydroxide. The solution was cooled, acidified with acetic acid, and the precipi-

(8) Shepard, Winslow and Johnson, THIS JOURNAL, **52**, 2083 (1930).

(9) Gilman and Louisinian, *Rec. trav. chim.*, **52**, 156 (1933).

tated solid collected on a filter; yield 2.5 g. (90%), and crystallized from glacial acetic acid.

Summary

1. 1-(*o*-Nitrophenyl)-3,4-dimethyl-1,2,5-triazole as well as the *p*-isomer was obtained in the nitration of 1-phenyl-3,4-dimethyl-1,2,5-triazole.

2. Arsonation by the Bart reaction has been effected from the amines obtained from the above nitro compounds.

3. Several new derivatives have been obtained by reactions of nitration, oxidation, reduction, and esterification on 1-(4-arsonophenyl)-3,4-dimethyl-1,2,5-triazole.

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A Study of Alternate Methods for the Alkylation of Acetoacetic Esters

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Evidence reported[1] earlier indicates that potassium *t*-amyloxide in *t*-amyl alcohol is superior in some cases to sodium ethoxide in ethanol as a reagent in the alkylation of acetoacetic esters. Further work has shown that *t*-butyl alcohol is a more satisfactory reagent than *t*-amyl alcohol. Inability to reproduce earlier results satisfactorily led us to discover that the method used to purify *t*-amyl alcohol (refluxing with sodium) did not give a uniform product from different batches of alcohol. Since no convenient method for obtaining reliable *t*-amyl alcohol was apparent, we investigated *t*-butyl alcohol. Practically pure *t*-butyl alcohol is available commercially and its quality can be confirmed readily by melting point. Potassium *t*-butoxide in *t*-butyl alcohol has given 5–10% higher yields of alkylation products than were obtained with potassium *t*-amyloxide in *t*-amyl alcohol.

In order to evaluate the potassium *t*-butoxide method for alkylating acetoacetic esters, we have compared it with the following alternative procedures[2]: sodium ethoxide[3] or potassium ethoxide in ethanol, sodium[4] or potassium metals in dioxane, sodium metal in toluene,[5] sodium amide in dioxane and sodium hydride in dioxane.

The butyl halides were selected as alkylating reagents because they are representative of the main types of alkyl halides and produce alkylation products of convenient boiling range. All runs were made with 120 ml. of solvent and 0.200 g.-equiv. of sodium, potassium, sodium amide, or sodium hydride. Equivalent amounts[6] (0.200 mole) of β-keto esters were used in all runs except those with sodium or potassium metals in dioxane or toluene. A 10% excess of ester (0.22 mole) was used in the latter cases to facilitate reaction with the metal. An excess of alkyl halide (0.22 mole) was used in all cases.

Whenever feasible, the times required for one-half of the alkalinity to disappear were determined at the temperatures of the refluxing solutions. The primary reason for obtaining the data on reaction rates was to determine how long the solutions should be refluxed and not to study the kinetics of the reactions. Values for reaction half-times could be satisfactorily reproduced for the reactions which yielded 70% or better of alkylation products, and these reactions appeared to follow the second-order rate of reaction equation. For those reactions that gave less than about 60% yields of alkylation products, duplicate values for the reaction half-times varied considerably.

Reaction mixtures were generally refluxed for a period equalling ten times the half-time or until 95% of the alkalinity had disappeared. When the alkylation was very slow, however, better yields were sometimes obtained by terminating the reactions earlier. For example, the alkylation of acetoacetic ester with sodium ethoxide and *i*-butyl bromide gave a 19% yield of alkylation product if the reaction was stopped after 70% of the alkalinity had reacted, but only a 7% yield after 95% of the alkalinity had reacted.

The data are listed in Table I.

Alkyl iodides are generally recognized as superior to bromides for the alkylation of acetoacetic esters[7] but the degree of superiority is difficult to estimate from data in the literature. We have found that iodides react from two to six times faster than bromides (compare experiments 2–7,

(1) Renfrow, THIS JOURNAL, **66**, 144 (1944).

(2) To facilitate presentation, names of metallating reagents or of metallating reagents and solvents will be used to refer to the entire alkylation process using the specified reagents. See equation at top of Table I.

(3) "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 248.

(4) Finkelstein and Elderfield, *J. Org. Chem.*, **4**, 370 (1939), used relatively more dioxane than we have used, and isolated the reaction product by a somewhat different method.

(5) Hope and Perkin, *J. Chem. Soc.*, **95**, 2046 (1909).

(6) Preliminary experiments on the alkylation of ethyl *n*-butylacetoacetate with sodium ethoxide and *n*-butyl iodide demonstrated that the use of 0.204 g.-atom of sodium to 0.200 mole of ester and 0.22 mole of iodide gave consistently about 3% lower yields of alkylation product than were obtained when equivalent amounts of sodium and ester were employed. Runs using 0.200 g.-atom of sodium and 0.208 mole of ester gave the same yields of alkylation product as were obtained when equivalent amounts of sodium and ester were used. Decreasing the volume of ethanol from 120 to 50 ml. did not affect the yield of alkylation product from ethyl *n*-butylacetoacetate (0.200 mole), potassium ethoxide (0.200 mole) and *n*-butyl bromide (0.22 mole). The optimum amount of ethanol for runs with potassium is about two-thirds of the quantity used in our standard procedure.

(7) Locquin, *Bull. soc. chim.*, **31**, 758 (1904).