chloric acid to give a precipitate which was insoluble in acid and extractable with ether.

(b) **Hydrolysis.**—A solution of 1.00 g. of V was boiled under reflux for two hours with 15 cc. of 15% hydrochloric acid. The solution was evaporated to dryness *in vacuo*. A solution of the remaining oil in 10 cc. of water was treated with an excess of silver oxide, filtered, freed of silver ion by precipitation with hydrogen sulfide, and finally evaporated to dryness. Trituration of the residue in ethyl alcohol induced the formation of crystals which could be recrystallized from ethanol–methanol, ethanol–water, or methanol–ethyl acetate mixtures. In this way 0.75 g. (84%) of meroquinene was obtained, m. p. 220–221° (with decomposition even on rapid heating). When heated slowly meroquinene started to decompose at 194°; $[\alpha]^{26}D$ +28.6° (c = 0.081 g./cc. in water).

Anal. Calcd. for $C_9H_{15}O_2N$: C, 63.87; H, 8.94; N, 8.28. Found: C, 63.67; H, 9.36; N, 7.89.

Koenigs[13] reported for meroquinene, m. p. 220–222°, and $[\alpha]D$ +27.5°.

(c) **N-Acetylmeroquinene.**—A solution of 0.6 g. of the meroquinene obtained as above in 6 cc. of acetic anhydride was boiled for three hours under reflux. The residue obtained on evaporation of the solvent solidified on trituration with ethyl alcohol–ether. Recrystallization to give pure N-acetylmeroquinene was best effected by boiling the crude material in a small amount of water for a few minutes and allowing the resulting solution to remain in the ice-box. The pure material sintered at 107° and melted at 110°. Koenigs[13] reported N-acetylmeroquinene, m. p. 110°, and Dirscherl and Thron[14] reported m. p. 110–111°.

(d) **Transesterification.**—An absolute ethanolic solution of 0.17 g. of meroquinene *t*-butyl ester containing a trace of sodium ethoxide was allowed to stand for a week. Hydrogen chloride was passed in until the solution was acidic. A small amount of salt was removed and the solution was evaporated to dryness. Recrystallization of the residue from absolute ethanol gave 0.10 g. of meroquinene ethyl ester hydrochloride, m. p. 165°. Koenigs[13] and Dirscherl and Thron[14] reported m. p. 165 and 168°, respectively.

(13) Koenigs, *Ann.*, **347**, 143 (1906).

(14) Dirscherl and Thron, *ibid.*, **521**, 48 (1936).

Summary

The autoxidation of quininone, occurring with great ease in the presence of tertiary butoxide ion, gives rise to quininic acid and meroquinene *t*-butyl ester. The possible relation of the formation of the latter to the theoretical problem of bicyclic amides with a bridgehead nitrogen atom is discussed.

NEW YORK, N. Y. RECEIVED JANUARY 9, 1946

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

Derivatives of 1,2,4-Triazole and of Pyrazole

BY DEXTER B. SHARP[1] AND CLIFF S. HAMILTON

In view of the well-known uses of heterocyclic compounds in chemotherapy it was of interest to synthesize a number of 1,2,4-triazole derivatives for pharmacological studies. During the investigation an arsenic-containing intermediate gave rise to a 4-hydroxypyrazole type and several such derivatives were accordingly prepared.

Ethyl α-acetoglyoxylate-*p*-nitrophenylhydrazone (I) was synthesized by a method based on that of Bowack and Lapworth[2] and brominated according to a modification of the procedure of Chattaway and Ashworth[3] to give ethyl α-bromoglyoxylate-*p*-nitrophenylhydrazone (II). Treatment of II with potassium cyanate in the aqueous alcohol solvent as used by Fusco and Musante[4] in the synthesis of the triazole (IV) was unsatisfactory. Employing anhydrous methanol as a solvent gave better yields of the triazole but an ester interchange produced V, the corresponding methyl ester of IV. The poor quality and yields of the triazole derivative were attributed to a number of undesirable side-reactions between the basic decomposition products of the unstable potassium cyanate and the alkali-sensitive bromo compound II.

A different method of synthesis of IV was therefore devised. A mixture of II and excess ammonia in absolute alcohol was stirred for a minimum length of time and good yields of ethyl α-aminoglyoxylate-*p*-nitrophenylhydrazone (III) were obtained. Treatment of this compound with phosgene produced 1-(*p*-nitrophenyl)-3-carbethoxy-5-hydroxy-1,2,4-triazole (IV), the melting point 243–244° contrasting with the 235° reported by Fusco and Musante[4] for IV. Repeated recrystallizations of the compound obtained by their method yielded a substance identical with that prepared in this laboratory by the new method.

Reduction of IV with hydrogen and Raney nickel[5,6] resulted in good yields of VI which was readily arsonated by the Bart reaction[7] giving the arsonic acid (VII).

Saponification of IV produced the free carboxylic acid (VIII) but attempts to decarboxylate this acid gave indefinite results. Hydrazine in alcohol converted IV to the acid hydrazide (IX) and nitrous acid acted upon IX to yield the acid azide (X). Attempts to produce the corresponding amine from X by the Curtius degradation reaction were unsuccessful.

A mixture of phosphorus pentachloride and phosphorus oxychloride, followed by alcohol digestion, converted IV to the 5-chloro compound (XI) and XI reacted with morpholine to give the

(1) Parke, Davis and Company Fellow.

(2) Bowack and Lapworth, *J. Chem. Soc.*, **87**, 1854 (1905).

(3) Chattaway and Ashworth, *ibid.*, 475 (1933).

(4) Fusco and Musante, *Gass. chim. ital.*, **68**, 665 (1938).

(5) Mozingo, "Organic Syntheses," **21**, 15 (1941).

(6) Covert and Adkins, THIS JOURNAL, **54**, 4116 (1932).

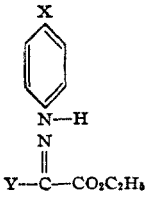
(7) Bart, *Ann.*, **429**, 55 (1922).

5-morpholinyl derivative which immediately underwent hydrolysis and decarboxylation to form 1-(*p*-nitrophenyl)-5-(N-morpholinyl) 1,2,4-triazole (XII).

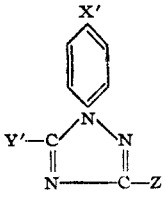
In an effort to produce the arsonic acid (VII) in better yields arsanilic acid rather than *p*-nitroaniline was used as the starting material and a series of reactions analogous to those used in the *p*-nitrophenyl series was attempted. Acetoacetic ester and *p*-arsonobenzenediazonium chloride were coupled according to a modification of the method of Bowack and Lapworth[2] to produce XIII. However, bromination of XIII resulted in the formation of ethyl α-(bromoaceto)-glyoxylate-*p*-arsonophenylhydrazone (XIV). Ring closure[3] of XIV produced 1-(*p*-arsonophenyl)-3-carbethoxy-4-hydroxypyrazole (XV). Saponification, followed by acidification, gave the carboxylic acid (XVI) but decarboxylation attempts were unsuccessful. Two moles of bromine reacted with one mole of XIII to produce directly the 5-bromopyrazole (XVII). Alternatively, XIV was produced by coupling γ-bromoacetoacetic ester with *p*-arsonobenzenediazonium chloride.

Ethyl α-chloroacetoacetic ester coupled with *p*-arsonobenzenediazonium chloride to yield ethyl α - chloroglyoxylate - *p* - arsonophenylhydrazone (XVIII) but treatment of XVIII with potassium cyanate failed to give the desired arsonic acid (VI). No attempt was made to apply the new synthetic method to this compound due to the poor yields of XVIII obtained.

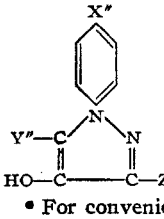
TABLE I



Comp.	X	Y
I	$-NO_2$	$-COCH_3$
II	$-NO_2$	$-Br$
III	$-NO_2$	$-NH_2$
XIII	$-AsO_3H_2$	$-COCH_3$
XIV	$-AsO_3H_2$	$-COCH_2Br$
XVIII	$-AsO_3H_2$	$-Cl$



Comp.	X′	Y′	Z
IV[a]	$-NO_2$	$-OH$	$-CO_2C_2H_5$
V	$-NO_2$	$-OH$	$-CO_2CH_3$
VI	$-NH_2$	$-OH$	$-CO_2C_2H_5$
VII	$-AsO_3H_2$	$-OH$	$-CO_2C_2H_5$
VIII	$-NO_2$	$-OH$	$-CO_2H$
IX	$-NO_2$	$-OH$	$-CONHNH_2$
X	$-NO_2$	$-OH$	$-CON_3$
XI	$-NO_2$	$-Cl$	$-CO_2C_2H_5$
XII	$-NO_2$	$-N(C_2H_4)_2O$	$-H$



Comp.	X″	Y″	Z′
XV	$-AsO_3H_2$	$-H$	$-CO_2C_2H_5$
XVI	$-AsO_3H_2$	$-H$	$-CO_2H$
XVII	$-AsO_3H_2$	$-Br$	$-CO_2C_2H_5$

[a] For convenience in structural representation this and ensuing compounds are given as the enol form of the triazolone-5.

Experimental

Ethyl α-Acetoglyoxylate-*p*-nitrophenylhydrazone (I).—*p*-Nitroaniline (54 g., 0.4 mole) was dissolved by heating in 200 ml. of water containing 100 ml. of concentrated hydrochloric acid. The resulting hot solution was poured onto ice and the amine hydrochloride precipitated. A solution of sodium nitrite (28.0 g., 0.4 mole) in 50 ml. of water was added to this mixture and the resulting diazonium solution was added rapidly to a solution of ethyl acetoacetate (52.0 g., 0.4 mole) in 300 ml. of ethyl alcohol and 2 liters of ice water containing sodium acetate (100 g., 1.34 mole). The reaction mixture immediately thickened as the product precipitated out of solution. After stirring for four hours the yellow solid was removed by filtration, washed thoroughly, and dried at 60°. Recrystallization from 1.5 liters of ethyl alcohol yielded 101 g. (90%); m. p. 124–125°, lit. m. p. 123–124°.[2] Carefully washed crude product was found to be of sufficient purity to be used in the next step.

Ethyl α-Bromoglyoxylate-*p*-nitrophenylhydrazone (II).—Compound I (344 g., 1.23 mole) was added to a mixture of 1650 ml. of glacial acetic acid and 900 ml. of acetic anhydride containing sodium acetate (246 g., 3.0 mole) and the temperature was lowered to 0° by means of an ice–salt-bath. To this was added, over a two-hour period, bromine (199 g., 1.23 mole) dissolved in 300 ml. of glacial acetic acid. The product was precipitated by pouring the reaction mixture into 7 liters of water. After filtration and thorough washing the yield was 382 g. (97.5%); m. p. 201–203°, lit. m. p. 202–203°.[3]

1-(*p*-Nitrophenyl)-3-carbomethoxy-5-hydroxy-1,2,4-triazole (V).—Compound II (10 g., 0.03 mole) was refluxed with potassium cyanate (6.5 g., 0.08 mole) in 400 ml. of methyl alcohol for three hours. Concentrated hydrochloric acid (10 ml.) was added and the solution was refluxed for an additional thirty minutes. The excess alcohol was removed by reduced pressure distillation and the solid product collected by filtration and recrystallized from acetone; yield 6.0 g. (70%) of white product; m. p. 254–255°.

Anal. Calcd. for $C_{10}H_8N_4O_5$: C, 45.46; H, 3.05. Found: C, 45.70, 45.50; H, 3.18, 3.23.

Ethyl α-Aminoglyoxylate-*p*-nitrophenylhydrazone (III).—A portion of II (79.2 g., 0.25 mole) was added to a liter of absolute alcohol containing 1.0 mole of ammonia and the reaction mixture shaken for thirty minutes. By pouring into a liter of 2 *N* hydrochloric acid followed by addition of solid sodium bicarbonate until effervescence ceased the product was isolated. Recrystallization from ethyl alcohol yielded 53.7 g. (91%); m. p. 190–191°, lit. m. p. 181°.[3]

Anal. Calcd. for $C_{10}H_{12}N_4O_4$: C, 47.61; H, 4.80. Found: C, 47.74, 47.88; H, 4.75, 4.89.

1-(*p*-Nitrophenyl)-3-carbethoxy-5-hydroxy-1,2,4-triazole (IV).—The amino compound (III) (45.4 g., 0.18 mole) was added to 500 ml. of benzene (dried by distillation) containing dry pyridine (43 g., 0.54 mole) and the mixture was stirred mechanically. A benzene solution of phosgene (0.27 mole) was added dropwise and the stirring continued for one hour. Water (25 ml.) was then added and the mixture was refluxed on a steam-bath to destroy the excess phosgene. The excess benzene was removed by distillation and the solid was removed by filtration and recrystallized from acetone; yield 43.5 g. (87%) of pale yellow needle-like crystals; m. p. 243–244°, lit. m. p. 235°.[4]

Anal. Calcd. for $C_{11}H_{10}N_4O_5$: C, 47.48; H, 3.62; N, 20.14. Found: C, 47.48; H, 3.71; N, 20.24.

Recrystallization of the product obtained by the method of Fusco and Musante[4] gave a product identical with IV as shown by a melting point of a mixture of the two products.

1-(*p*-Aminophenyl)-3-carbethoxy-5-hydroxy-1,2,4-triazole (VI).—A portion of IV (10 g., 0.036 mole) was added to 200 ml. of ethyl alcohol containing 2.0 g. of Raney nickel catalyst and the mixture was shaken for twenty-four hours in hydrogen at 3 atmospheres pressure. The catalyst was

removed by filtration, the volume of the filtrate was reduced by evaporation and the product weighing 5.0 g. (60%) was filtered off; m. p. 211–212°.

Anal. Calcd. for $C_{11}H_{12}N_4O_3$: C, 53.22; H, 4.87. Found: C, 53.09, 52.97; H, 4.78, 4.91.

A similar reduction of V gave **1-(*p*-aminophenyl)-3-carbomethoxy-5-hydroxy-1,2,4-triazole** with a m. p. of 212–214°.

Anal. Calcd. for $C_{10}H_{10}N_4O_3$: C, 51.28; H, 4.30. Found: C, 51.20; H, 4.64.

1-(*p*-Arsonophenyl)-3-carbethoxy-5-hydroxy-1,2,4-triazole (VII).—The amine (VI) (3.6 g., 0.0145 mole) was dissolved by warming in 150 ml. of water containing 2.6 ml. of concentrated hydrochloric acid. This solution was chilled in an ice–salt-bath, stirred mechanically and diazotized by adding sodium nitrite (1.03 g., 0.0145 mole) dissolved in 50 ml. of water. A 10% solution of sodium hydroxide was added dropwise to a point just at the first precipitation of a yellow solid. Arsenic trioxide (2.9 g., 0.0145 mole) was dissolved in 15 ml. of water containing sodium hydroxide (3.5 g., 0.087 mole) and 3 ml. of 20% copper sulfate. This chilled arsenite solution was added to the diazonium solution, a violent evolution of nitrogen resulting, and the reaction mixture was stirred for two hours. The solution was neutralized to litmus paper, filtered, and the volume reduced by evaporation. Acidification to congo red paper precipitated the product which was recrystallized by acidification of its solution in dilute sodium bicarbonate; yield, 2.4 g. (45%).

Anal. Calcd. for $C_{11}H_{12}AsN_3O_6$: As, 20.98. Found: As, 20.94, 21.03.

1-(*p*-Nitrophenyl)-3-carboxy-5-hydroxy-1,2,4-triazole (VIII).—The nitro derivative (IV) (10 g., 0.036 mole) was added to a liter of water containing potassium hydroxide (5.0 g., 0.09 mole) and the solution was boiled for three hours. Concentrated hydrochloric acid (50 ml.) was added and the boiling was continued for an additional three hours. The white crystalline solid separated on cooling; yield, 6.0 g. (61%); m. p. 316–319°, lit. m. p. 315°.[4]

Anal. Calcd. for $C_9H_6N_4O_5$: C, 43.21; H, 2.42. Found: C, 42.99; H, 2.53.

1-(*p*-Nitrophenyl)-3-carbonylhydrazide-5-hydroxy-1,2,4-triazole (IX).—Compound IV (27.8 g., 0.1 mole) was added to 500 ml. of absolute alcohol, the mixture was refluxed, and hydrazine hydrate (40 g. of an 85% solution, 0.8 mole) was added slowly. The reaction mixture was refluxed for two days, after which the yellow solid was removed by filtration. After drying, the compound was added to 1.0 liter of hot *N* hydrochloric acid, the solution was filtered, made basic to litmus paper with ammonium hydroxide, then acid to litmus with acetic acid, and the white crystalline solid separated; yield 23.8 g. (90%); m. p. 290–291°.

Anal. Calcd. for $C_9H_8N_6O_4$: C, 40.91; H, 3.05. Found: C, 41.15, 40.94; H, 3.24, 2.96.

1-(*p*-Nitrophenyl)-3-carbonylazide-5-hydroxyl-1,2,4-triazole (X).—A portion of IX (15.5 g., 0.06 mole) was added to 1.5 liters of 2 *N* hydrochloric acid and, at room temperature, a solution of sodium nitrite (4.2 g., 0.06 mole) in 100 ml. of water was introduced slowly below the surface of the liquid. The reaction mixture was allowed to stand for twelve hours after which the product was filtered off, washed, and dried at 60°; yield 15.6 g. (96%); explodes at 163–164°. The compound was too unstable to analyze.

1-(*p*-Nitrophenyl)-3-carbethoxy-5-chloro-1,2,4-triazole (XI).—The nitro compound IV (10 g., 0.036 mole) was placed in a flask containing 50 ml. of phosphorus oxychloride and 25 g. of phosphorus pentachloride and the reaction mixture was refluxed for two days. The excess phosphorus oxychloride was removed under diminished pressure and the residue was refluxed for two days in 300 ml. of ethyl alcohol to destroy excess phosphorus chlorides and convert the acyl chloride back to the ethyl ester. The product was recrystallized from ethyl alcohol, yield 9.0 g. (83%) of white needle-like crystals; m. p. 160–162°.

Anal. Calcd. for $C_{11}H_9ClN_4O_4$: C, 44.53; H, 3.06. Found; C, 44.45, 44.33; H, 3.30, 2.93.

1-(*p*-Nitrophenyl)-5-(N-morpholinyl)-1,2,4-triazole (XII).—Compound XI (5.0 g., 0.017 mole) was refluxed for seventy-two hours in 25 ml. of morpholine. The reaction mixture was poured into water and the solid that separated was removed by filtration. Unreacted chloro compound was removed by treatment with dilute hydrochloric acid, the desired compound dissolving and reprecipitating, after filtration, by the addition of ammonium hydroxide. Recrystallization from ethyl alcohol–water mixtures yielded 2.0 g. (34%) of a white solid; m. p. 165–166°.

Anal. Calcd. for $C_{12}H_{13}N_5O_3$: C, 52.36; H, 4.76; N, 25.46. Found: C, 51.90, 52.24; H, 4.82, 4.80; N, 25.62, 25.58.

Ethyl α-Acetoglyoxylate-*p*-arsonophenylhydrazone (XIII).—*p*-Arsanilic acid (50 g., 0.23 mole) was dissolved in 150 ml. of water containing sodium hydroxide (10 g., 0.25 mole). The cooled solution was diazotized by adding sodium nitrite (17 g., 0.23 mole) in 50 ml. of water, and pouring the resulting solution into a mixture of ice and 100 ml. of concentrated hydrochloric acid. The diazonium solution was added rapidly to a liter of ice and water containing 300 ml. of ethyl alcohol, ethyl acetoacetate (30 g., 0.23 mole), and sodium acetate (82 g., 1.0 mole). The reaction mixture was stirred for five hours, periodic additions of ice maintaining a minimum temperature. The solution was acidified to congo red paper with hydrochloric acid, allowed to stand for twelve hours, and the product removed by filtration. After thorough washing and drying at 60° for two days the product weighed 73 g. (92%).

Anal. Calcd. for $C_{12}H_{15}AsN_2O_6$: As, 20.91. Found: As, 20.94, 21.02.

Ethyl α-(Bromoaceto)-glyoxylate-*p*-arsonophenylhydrazone (XIV).—A. Compound XIII (73 g., 0.21 mole) was added to 800 ml. of glacial acetic acid containing sodium acetate (19 g., 0.23 mole) and the mixture was stirred mechanically and cooled to 20°. Bromine (34.2 g., 0.21 mole) in 50 ml. of acetic acid was added dropwise to this solution over a period of thirty minutes, after which the reaction mixture was stirred for two hours. The solution was poured into 2 liters of water and the solid was recrystallized from glacial acetic acid; yield 65 g. (71%).

Anal. Calcd. for $C_{12}H_{14}AsBrN_2O_6$: As, 17.14. Found: As, 17.38, 16.88.

B. Ethyl α-bromoacetoacetate was prepared by the method of Schönbrodt[8] and allowed to stand for several weeks to facilitate complete rearrangement to ethyl γ-bromoacetoacetate.[9] *p*-Arsanilic acid (33.5 g., 0.15 mole) was dissolved by heating in 100 ml. of water containing sodium hydroxide (6.8 g., 0.15 mole). The solution was cooled and sodium nitrite (11.6 g., 0.15 mole) was added and the resulting mixture poured into a mixture of ice and concentrated hydrochloric acid (37 ml.). This diazonium solution was added rapidly to a solution of ethyl γ-bromoacetoacetate (32 g., 0.15 mole) and sodium acetate (41 g., 0.5 mole) in a mixture of 300 ml. of ethyl alcohol and 300 g. of ice. The stirring was continued until the reaction mixture reached room temperature, the solid was removed by filtration and recrystallized with charcoal treatment from ethyl alcohol; yield 6.0 g. (9%).

Anal. Calcd. for $C_{12}H_{14}AsBrN_2O_6$: As, 17.14. Found: As, 17.27, 17.02.

1-(*p*-Arsonophenyl)-3-carbethoxy-4-hydroxypyrazole (XV).—Compound XIV (5.4 g., 0.015 mole) was added to 75 ml. of boiling ethyl alcohol and anhydrous potassium acetate (1.5 g., 0.015 mole) was added in small amounts during a period of one hour. The alcohol was evaporated and water was added. The solid that separated on cooling was filtered off and recrystallized by acidification of its solution in dilute sodium bicarbonate; yield 2.3 g. (57%).

(8) Schönbrodt, *Ann.*, **253**, 168 (1889).

(9) Kharasch, Sternfeld and Mayo, THIS JOURNAL, **59**, 1655 (1937).

Anal. Calcd. for $C_{12}H_{13}AsN_2O_6$: As, 21.03. Found: As, 21.08, 21.01.

1-(*p*-Arsonophenyl)-3-carboxy-4-hydroxypyrazole (XVI).—A portion of XV (2.3 g., 0.0065 mole) was refluxed for four hours in 25 ml. of water containing sodium hydroxide (0.8 g., 0.02 mole). The solution was treated with charcoal, filtered and acidified to congo red paper. The yellow solid that separated was filtered off and dried at 80°; yield 1.7 g. (80%). Attempted decarboxylations were unsuccessful.

Anal. Calcd. for $C_{10}H_9AsN_2O_6$: As, 22.83. Found: As, 22.72, 22.87.

1-(*p*-Arsonophenyl)-3-carbethoxy-4-hydroxy-5-bromopyrazole (XVII).—Compound XIII (10.0 g., 0.028 mole) was dissolved by warming in 100 ml. of glacial acetic acid containing sodium acetate (7.0 g., 0.09 mole). While the solution was stirred mechanically, bromine (9.0 g., 0.056 mole) in 10 ml. of acetic acid was added over a period of fifteen minutes, the temperature ranging from 30–40°. The reaction mixture was poured into water and the yellow product that separated was filtered off and recrystallized from an acetone–water mixed solvent. The analysis indicated that the pyrazole had been formed completely in the reaction mixture.

Anal. Calcd. for $C_{12}H_{12}AsBrN_2O_6$: As, 17.22. Found: As, 17.00, 17.12.

Ethyl α-Chloroglyoxylate-*p*-arsonophenylhydrazone (XVIII).—Ethyl α-chloroacetoacetate was prepared by the method of Michael and Carlson.[10] *p*-Arsanilic acid (13.7 g., 0.06 mole) was dissolved in 100 ml. of water containing sodium hydroxide (2.6 g., 0.06 mole). The solution was cooled and a solution of sodium nitrite (4.5 g., 0.06 mole) in 50 ml. of water was added. This solution was poured into a mixture of ice and 14.4 ml. of concentrated hydrochloric acid and the resulting diazonium solution was added rapidly to a solution of ethyl α-chloroacetoacetate (10. g., 0.06 mole) in 200 ml. of ethyl alcohol containing sodium acetate (5.0 g., 0.06 mole). The mixture was stirred mechanically and cooled in an ice–salt-bath for two hours, then allowed to stand for twelve hours at room temperature. The yellow product was filtered off and recrystallized from ethyl alcohol; yield 7.1 g. (34%).

Anal. Calcd. for $C_{10}H_{12}AsClN_2O_5$: C, 34.26; H, 3.45; As, 21.37. Found: C, 34.41, 34.53; H, 3.71, 3.68; As, 21.42, 21.32.

(10) Michael and Carlson, THIS JOURNAL, **58**, 353 (1936).

Summary

A new method of synthesis for phenyl-1,2,4-triazole derivatives has been developed and a number of arsenic-containing and arsenic-free heterocyclic compounds of this type have been prepared.

A number of glyoxylic acid *p*-arsonophenylhydrazone derivatives have been synthesized and from several of these some *p*-arsonophenyl-4-hydroxypyrazole compounds have been made.

LINCOLN, NEBRASKA RECEIVED DECEMBER 14, 1945

[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

Amines Related to 2,5-Dimethoxyphenethylamine. III[1] 2-Hydroxy and 2-Methoxy-5-methylphenylalkanolamines

BY ALAN E. ARDIS,[2] RICHARD BALTZLY AND WILLIAM SCHOEN

Pharmacological studies of the substances reported in the earlier papers of this series[3] having shown that considerable value as pressors is exhibited by the primary and secondary β-hydroxy-β-(2,5-dimethoxy)-phenylethyl and phenylisopropylamines, it was of interest to compare these with the analogous substances in which the 5-methoxyl group was exchanged for a methyl group. At the same time the preparation of 2-hydroxy-5-methyl analogs by using the benzyl group for protection proved to be feasible although offering some experimental difficulties in the earlier part of the work.

The general course of the reactions is indicated in the chart. The primary isopropylamines were prepared from the corresponding oximino ketones. The synthesis of the other members of the series was through the α-bromoketones; the primary amines being made by the hexamethylenetetramine method, the secondary by the benzylmethylamine procedure.

Certain difficulties, in part unanticipated, were encountered. The chief of these was dealkylation in the preparation of the necessary α-bromoketones. Whereas 2,5-dimethoxyacetophenone on bromination in chloroform solution yields readily the desired 2,5-dimethoxy-α-bromoacetophenone, and 2,5-dimethoxy-α-bromopropiophenone is easily obtained in usable form,[4] the 2-methoxy ketones of the present series by the chloroform bromination gave the α-bromoketones in poor yield or not at all. This was probably due to unfavorable physical properties. When the 2-benzyloxyketones were brominated, dealkylation was extensive and accompanied by ring bromination. The crude preparations so obtained sufficed in certain cases for the preparation of secondary amines, but could not be used with the hexamethylenetetramine method. Bromination in

(1) This work is part of a joint research being carried out in collaboration with a pharmacological group in the same laboratories.

(2) Present address: Research Laboratory, The B. F. Goodrich Company, Akron, Ohio.

(3) Baltzly and Buck, THIS JOURNAL, **62**, 161, 164 (1940). The pharmacological reports on these substances are now in the process of preparation and should appear soon. Briefly, the primary and secondary bases of the phenylethyl and phenylisopropylamine types have been found to possess potency rather surprising in pressors with methoxyl rather than hydroxyl groups on the rings. The activity of the phenylalkanolamines is considerably greater than that of the bases with no hydroxyl beta to the nitrogen atom.

(4) The second paper of this series describes the preparation and synthetic use of this substance. Sometime after the date of publication, an oily sample in the refrigerator solidified. Opportunity is taken in the experimental section to characterize it further.