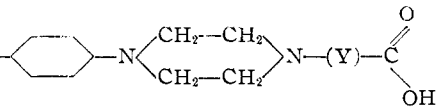
TABLE III

PHYSICAL AND ANALYTICAL DATA OF 2-[4-ARYLPIPERAZINO]-ALKANOIC ACIDS Ar— 

Ar	Y	Mol. formula	Mol. wt.	Nitrogen, % Calcd.	Nitrogen, % Found	Neut. equiv. Calcd.	Neut. equiv. Found
C_6H_5	CH_3CH	$C_{13}H_{18}N_2O_2 \cdot 2HCl \cdot H_2O$	323.20	9.12[a]	8.90	161.6	158.1
p-$CH_3C_6H_5$	CH_3CH	$C_{14}H_{20}N_2O_2 \cdot 2HCl \cdot H_2O$	339.24	8.26	8.33	168.6	171.3
o-ClC_6H_5	CH_2	$C_{12}H_{15}N_2O_2Cl \cdot HCl \cdot H_2O$	308.18	9.63[b]	9.54	308.2	305.1
o-ClC_6H_5	CH_3CH	$C_{13}H_{17}N_2O_2Cl \cdot HCl \cdot H_2O$	323.21	8.67[c]	9.17	323.2	322.2
o-ClC_6H_5	$(CH_3)_2C$	$C_{14}H_{19}N_2O_2Cl \cdot HCl$	319.24	8.78	8.92	...	...
m-ClC_6H_5	CH_3CH	$C_{13}H_{17}N_2O_2Cl$	268.74	10.42	10.50	...	...
p-ClC_6H_5	CH_3CH	$C_{13}H_{17}N_2O_2Cl \cdot 2HCl$	341.67	8.37	8.71	...	...
p-ClC_6H_5	$(CH_3)_2C$	$C_{14}H_{19}N_2O_2Cl$	282.76	9.93	10.02	...	...

[a] Calcd. for $C_{13}H_{18}N_2O_2 \cdot 2HCl \cdot H_2O$. [b] Calcd. for $C_{12}H_{15}N_2O_2Cl \cdot HCl \cdot H_2O$. [c] Calcd. for $C_{13}H_{17}N_2O_2Cl \cdot HCl \cdot H_2O$.

nitrile. The resulting mixtures were allowed to stand at room temperature for 24 hours and then were poured onto 1 kg. of cracked ice. These solutions were made basic with concentrated ammonium hydroxide, and the precipitates were filtered off. The products were extracted from the filter cake with hot 95% ethanol and recrystallized from 95% ethanol or toluene. The compounds were dried at 50° (2 mm.) before analysis. Physical and analytical data, along with purified yields, are shown in Table II.

2-(4-Phenylpiperazino)-alkanoic Acids.—The nitrile (0.175 mole) or the amide derived from this amount of nitrile was dissolved in 150 ml. of concentrated hydrochloric acid and the solution refluxed for 8–12 hours. The solution was transferred to a beaker and concentrated to one-third volume or until crystals appeared in the boiling solution. When cool the solid was filtered off and recrystallized from water. The compounds were dried at 100° (2 mm.). Physical and analytical data are shown in Table III.

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GAINESVILLE, FLORIDA

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, ALABAMA POLYTECHNIC INSTITUTE]

3(2H)-Pyridazones. I. Compounds Related to Phenacetin[1]

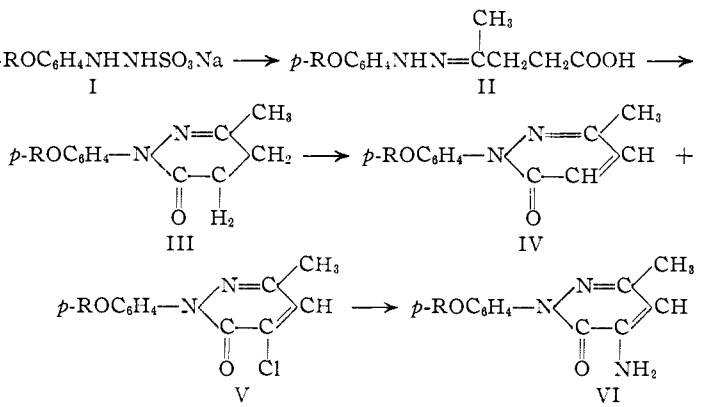
BY FRANK J. STEVENS, TOMMY D. GRIFFIN AND THOMAS L. FIELDS

RECEIVED JULY 22, 1954

The preparation of some derivatives of 2-phenyl-4,5-dihydro-6-methyl-3(2H)-pyridazone from the appropriate hydrazones of levulinic acid is described. These compounds are structurally related to phenacetin.

The work reported here is part of a program to evaluate the effect upon physiological activity of substituting a pyridazone ring for the amino group attached to aromatic rings in certain drugs. There are many drugs possessing such amino groups that are currently in use or which have been used in the past. The physiological activity of these drugs may require the free amino group but frequently acylation gives a derivative that is less toxic or better tolerated. In some cases the physiological activity may depend upon the action of the acylated compounds. The substitution of the pyridazone residue for the amino group might be expected to modify the action of drugs since it resembles the acylamino group in structure and yet can be reconverted to the amino group by the processes of hydrolysis and reduction. Pyridazone derivatives themselves have been reported to possess physiological action by several investigators.[2-6]

The antipyretic[3] and analgesic[6] activity noted, prompted the preparation of some pyridazone derivatives related to phenacetin. These were prepared from p-phenetidine and p-anisidine by the reactions



p-Phenetidine and p-anisidine were diazotized and converted in good yield to sodium p-alkoxyphenylhydrazine sulfonates (I) by the method of Alt-

(1) Taken in part from the Theses by T. D. Griffin and T. L. Fields presented to the Alabama Polytechnic Institute in partial fulfillment of the requirements for the M.S. degree.

(2) R. Meyer, German Patent 579,391; *C. A.*, **27**, 4631 (1933).

(3) A. Greco, *Boll. Soc. ital. biol. sper.*, **16**, 295 (1941).

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(5) R. F. Homer, H. Gregory, W. G. Overend and L. F. Wiggins, *ibid.*, 2195, 2199 (1948).

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schul.[7] Attempts to convert I to the *p*-alkoxyphenylhydrazine hydrochlorides gave low yields, as did the method of Stolz[8] for the preparation of this compound. An attempt was therefore made to convert I directly into the necessary levulinic acid *p*-alkoxyphenylhydrazones (II) without using the phenylhydrazine or the hydrochloride as an intermediate. The hydrazine sulfonates I are stable crystalline compounds that are easily recrystallized. The method of Altshul,[7] using alcoholic hydrochloric acid, was employed to hydrolyze I. Buffering with sodium acetate and addition of a slight excess of levulinic acid gave good yields of the phenylhydrazones II. The validity of the method was first checked by preparing some known *p*-alkoxyphenylhydrazones of benzaldehyde.[9,10] The hydrazones II are unstable in air and were converted to the pyridazones III as soon after formation as possible, using the technique of Overend and Wiggins.[4]

Dehydrogenation of the 4,5-dihydro-3(2H)-pyridazones increases the stability of the diazine ring to hydrolytic agents,[11] and allows the substitution of various groups into the ring, particularly in the 4-position.[2,12] The method of Ach[12] proved unsuccessful in the dehydrogenation of III. However, the use of a lower temperature and phosphorus oxychloride as solvent gave the desired products, IV and V. The 4-chloro compounds V were converted into the 4-amino derivatives VI by methanolic ammonia under pressure. In order to obtain an appreciable yield of the 2-(*p*-ethoxyphenyl)-4-amino derivative it was necessary to use cuprous oxide catalyst and a higher temperature than for the *p*-methoxyphenyl compound. Pharmacological studies are currently in progress.

Experimental

***p*-Alkoxyphenylhydrazones of Levulinic Acid.**—Sodium *p*-ethoxyphenylhydrazine sulfonate and the methoxy analog were prepared from *p*-phenetidine and *p*-anisidine in 75 and 85% yields by the method of Altschul.[7]

A solution of sodium *p*-ethoxyphenylhydrazine sulfonate (44 g., 0.173 mole), ethanol (95%, 320 ml.), water (18 ml.) and hydrochloric acid (14.4 ml., sp. gr. 1.19) was refluxed for 15 minutes. Sodium acetate trihydrate (26 g., 0.191 mole) in water (60 ml.) was added to the above solution, followed immediately by levulinic acid (24 g., 0.206 mole). The resulting solution was allowed to cool to room temperature and was poured into water (600 ml.) cooled to 0°. The light tan crystals of levulinic acid *p*-ethoxyphenylhydrazone were collected, washed with water and dried over sulfuric acid under reduced pressure in a vacuum desiccator from which the air had been removed by flushing with nitrogen; yield 27.6 g. (70%), m.p. 103–104° dec.[13]

Anal. Calcd. for $C_{13}H_{18}O_3N_2$: N, 11.29. Found: N, 11.0.

Levulinic acid *p*-methoxyphenylhydrazone (5.6 g. (52%), m.p. 112–114° dec.) was prepared in the same way from sodium *p*-methoxyphenylhydrazine sulfonate (11 g., 0.046 mole).

Anal. Calcd. for $C_{12}H_{16}O_3N_2$: N, 11.86. Found: N, 11.6.

Benzaldehyde *p*-methoxyphenylhydrazone, m.p. 123–124° (lit. value 123°), and benzaldehyde *p*-ethoxyphenylhydrazone, m.p. 125–126° (lit. value 125°) were prepared in 85% yield by the above procedure, using 1 g. of the hydrazine sulfonate and a slight excess of benzaldehyde.

2-(*p*-Alkoxyphenyl)-4,5-dihydro-6-methyl-3(2H)-pyridazones.—Levulinic acid *p*-ethoxyphenylhydrazone (27.6 g., 0.11 mole) was cyclized in a vacuum distillation apparatus at 140° at a pressure of 30 mm. for 2.5 hours. The melt was cooled to room temperature, dissolved in benzene (150 ml.), and the benzene solution was washed successively with three portions (75 ml. each) of sodium carbonate (10%) and water (100 ml.). The benzene solution was dried with magnesium sulfate and evaporated to 40 ml. volume. The dropwise addition of petroleum ether (2 ml.) gave a brown crystalline precipitate, which was collected and washed twice with diethyl ether (50-ml. portions). Recrystallization by dissolving in ethanol and adding water yielded 20.2 g. (79%) of 2-(*p*-ethoxyphenyl)-4,5-dihydro-6-methyl-3-(2H)-pyridazone, light tan crystals, m.p. 98–99°.

Anal. Calcd. for $C_{13}H_{16}N_2O_2$: N, 12.06. Found: N, 12.1.

Levulinic acid *p*-methoxyphenylhydrazone (10.5 g., 0.044 mole) was cyclized and the crude reaction mixture purified as above except the benzene concentrate was diluted with petroleum ether (150 ml.). Recrystallization from benzene–petroleum ether yielded 6.8 g. (70%) of 2-(*p*-methoxyphenyl)-4,5-dihydro-6-methyl-3(2H)-pyridazone, light tan crystals, m.p. 59–60°.

Anal. Calcd. for $C_{12}H_{14}N_2O_2$: N, 12.80. Found: N, 12.7.

2-(*p*-Alkoxyphenyl)-4-chloro-6-methyl-3(2H)-pyridazones.—A mixture of 2-(*p*-ethoxyphenyl)-4,5-dihydro-6-methyl-3(2H)-pyridazone (20 g., 0.086 mole), phosphorus pentachloride (110 g., 0.53 mole) and phosphorus oxychloride (60 ml.) was heated slowly to 90° and maintained at that temperature with occasional shaking for one hour, at which time the evolution of hydrogen chloride had ceased. Crushed ice was slowly added to decompose the excess phosphorus chlorides. The resulting solution was poured into crushed ice (1000 g.) and allowed to stand overnight. The tan solid which deposited was separated and washed several times with water. Recrystallization from ethanol (95%) gave 10.0 g. (44%) of 2-(*p*-ethoxyphenyl)-4-chloro-6-methyl-3(2H)-pyridazone, light yellow needles, m.p. 125–126°.

Anal. Calcd. for $C_{13}H_{13}O_2N_2Cl$: N, 10.59; Cl, 13.40. Found: N, 10.5; Cl, 13.4.

In the same manner, 2-(*p*-methoxyphenyl)-4,5-dihydro-6-methyl-3(2H)-pyridazone (8.5 g., 0.049 mole) yielded 2-(*p*-methoxyphenyl)-4-chloro-6-methyl-3(2H)-pyridazone, yellow needles, 3.1 g. (32%), m.p. 129–130°.

Anal. Calcd. for $C_{12}H_{11}N_2O_2Cl$: N, 11.17; Cl, 14.14. Found: N, 11.3, Cl, 14.2.

2-(*p*-Alkoxyphenyl)-6-methyl-3(2H)-pyridazones.—The mother liquors obtained from the filtration of the crude 4-chloropyridazones above were cooled in an ice-bath while sodium hydroxide pellets were slowly added until the solutions were basic to litmus. The solids which precipitated were collected, dried and recrystallized from a benzene–petroleum ether mixture. The yield of 2-(*p*-ethoxyphenyl)-6-methyl-3(2H)-pyridazone was 4.2 g. (20%), m.p. 100–101°.

Anal. Calcd. for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13. Found: C, 67.4; H, 6.30.

The yield of 2-(*p*-methoxyphenyl)-6-methyl-3(2H)-pyridazone was 0.5 g. (6%), m.p. 93–94°.

Anal. Calcd. for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.6. Found: C, 66.2; H, 5.7.

2-(*p*-Alkoxyphenyl)-4-amino-3(2H)-pyridazones.—2-(*p*-Methoxyphenyl)-4-chloro-6-methyl-3(2H)-pyridazone (4.5 g., 0.018 mole) was converted to 2-(*p*-methoxyphenyl)-4-amino-6-methyl-3(2H)-pyridazone by the method of Overend and Wiggins.[4] The yield was 2.0 g. (48%), m.p. 161–162°.

Anal. Calcd. for $C_{12}H_{13}N_3O_2$: C, 62.32; H, 5.66. Found: C, 62.8; H, 5.9.

Attempts to convert the *p*-ethoxy derivative by the above procedure gave yields of less than 5% and a recovery of most of the starting material. The following modification proved successful. 2-(*p*-Ethoxyphenyl)-4-chloro-6-methyl-3(2H)-pyridazone (5 g., 0.019 mole), cuprous oxide (1 g.

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(10) H. Franzen and M. Schmidt, *J. prakt. Chem.*, [2] **96**, 9 (1917).

(11) T. Ajello and S. Cusmano, *Gazz. chim. ital.*, **70**, 765 (1940).

(12) F. Ach, *Ann.*, **253**, 44 (1889).

(13) All melting points were taken in capillary tubes and are uncorrected.

prepared from Fehling solution and glucose), and methanol (200 ml.) which had been saturated with ammonia at 0°, were heated in a stainless steel high pressure reactor at 200° for 18 hours. The contents were cooled to room temperature, transferred to a beaker, and the solvent was evaporated. The residue was thoroughly agitated with sodium hydroxide (0.5 *N*, 100 ml.) and allowed to stand overnight. The solid was separated from the basic solution by filtration and dissolved in boiling ethanol (95%, 100 ml.). This solution was decolorized with carbon and filtered. A small quantity of light green precipitate appeared, after the solution had stood overnight, and was removed. The nature of this precipitate has not been determined. The filtrate was evaporated to half volume and water was added to the hot solution to permanent cloudiness. The precipitate which formed was collected and recrystallized from benzene to give small white needles, of 2-(*p*-ethoxyphenyl)-4-amino-6-methyl-3(2H)-pyridazone, 1.5 g. (32%), m.p. 156–157°.

Anal. Calcd. for $C_{13}H_{15}N_3O_2$: C, 63.65; H, 6.16. Found: C, 63.52; H, 6.27.

AUBURN, ALABAMA

[CONTRIBUTION FROM THE OHIO STATE UNIVERSITY RESEARCH FOUNDATION]

Triazines. XI. Some Reactions of 1,3,5-Triazine[1,2]

BY CHRISTOPH GRUNDMANN AND ALFRED KREUTZBERGER

RECEIVED JULY 19, 1954

Chlorination of *s*-triazine yields cyanuric chloride and minor amounts of dichlorotriazine. Bromination gives at first a perbromide; at higher temperatures probably dibromotriazine hydrobromide is the main product, as its reaction with aniline yields dianilido-*s*-triazine. Sodium amide decomposes *s*-triazine to sodium cyanide and disodium cyanamide. *s*-Triazine is a powerful poison for noble metal hydrogenation catalysts; therefore catalytic hydrogenation was not possible. The constitution of the known double compounds of hydrocyanic acid and aluminum chloride and their behavior in the Friedel–Crafts reaction are discussed in view of their suggested triazine structure.

In previous papers[2,3] we have established that iminoformylcarbylamine ("dimeric hydrocyanic acid") is really 1,3,5-triazine (III) and furthermore suggested formulation of the dichloromethylformamidine hydrochloride ("sesquihydrochloride of hydrocyanic acid") as sesquihydrochloride of 2,4,6-trichloro-hexahydro-1,3,5-triazine (I) and the chloromethyleneformamidine as sesquihydrochloride of 1,3,5-triazine (II), mainly on the basis of their generic relationship with *s*-triazine itself, shown in the scheme below.

We present now further chemical evidence for the identity of the trimer of hydrocyanic acid with *s*-triazine by its conversion into *s*-triazine derivatives of known or established structure. With this purpose in mind we first studied the halogenation of *s*-triazine.

Chlorination of *s*-Triazine.—*s*-Triazine is not easily substituted by chlorine. At room temperature and in solution in carbon tetrachloride or chloroform a sluggish reaction takes place forming an insoluble precipitate. Application of ultraviolet light apparently increases the reaction to some extent. But the primary product is so extremely hygroscopic and also sensitive against elevated temperatures that all attempts to isolate a uniform compound failed so far. It is not improbable that the primary products of the chlorination are similar in structure to those obtained in the bromination of *s*-triazine which are described below, and that they decompose thermally in a similar manner. Chlorination in the vapor phase just above the boiling point of *s*-triazine or in CCl_4 at 100–110° in a sealed tube led only to the isolation of triazine sesquihydrochloride (II), which was identified by its known conversion with aniline into N,N'-diphenylformamidine.[4] The formation of II indicates that there must be a substitution reaction too, but also in this case we were unable to identify the other reaction products because of their instability.

At temperatures between 140 and 200° the chlorination of *s*-triazine in CCl_4 in a sealed tube yields about 25% of 2,4,6-trichloro-1,3,5-triazine, or cyanuric chloride (IV), which was further identified by its conversion with aniline into 2,4,6-trianilido-1,3,5-triazine (V). As a by-product (about 4%) 2,4-dichloro-1,3,5-triazine (VI) is formed, which could not be isolated as such but was identified after reaction of the mixture of the chlorination products with aniline as 2,4-dianilido-1,3,5-triazine (VII)[3a,6] No evidence for the presence of a monochlorotriazine could be found.

The 2,4-dianilido-1,3,5-triazine (VII) was synthesized for comparison by the following route: 2,4-Dianilido-6-chloro-1,3,5-triazine[5] (VIII) was converted with sodium hydrosulfide into 2,4-dianilido-6-mercapto-1,3,5-triazine (IX), which was then methylated with methyl iodide to 2,4-dianilido-6-methyl-mercapto-1,3,5-triazine (X). The latter was converted into VII by treatment with Raney nickel in dioxane, a method recently developed for the replacement of halogen by hydrogen in the triazine series.[7]

Bromination of *s*-Triazine.—Bromine with *s*-triazine at 0° in carbon tetrachloride readily forms an orange-colored well-crystallized addition compound, $C_3H_3N_3.3Br$, or possibly an analog to the triazine sesquihydrochloride, $2C_3H_3N_3.3Br_2$. The compound has the properties of a perbromide of *s*-triazine. Dissolved in water or in aqueous ethanol, the compound dissociates completely. The total bromine content can then be titrated as free

(1) This article is based on work performed under Project 116-B of The Ohio State University Research Foundation sponsored by the Mathieson Chemical Corporation, Baltimore, Md.

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