

Anal. Calcd. for $C_{15}H_{18}O_2N_2$: N, 10.85. Found: N, 11.02.

In contrast to the results observed with piperidine (below) only a slight difference in reaction time was noted when methanol was used as the solvent.

Compounds VI and VII.—A suspension of 5 g. of the methoxyquinone (I) in 75 ml. of methanol containing a 10% excess of the amine was stirred at room temperature for 4 hours. Slight warming occurred at the start. A trace of starting material was removed by filtration and the dark orange solution was evaporated to dryness at room temperature under reduced pressure. The residue was triturated with anhydrous ether and the brownish crystals thus obtained were recrystallized from Skellysolve (90–100°). The ethereal mother liquors yielded more of the product when treated with Darco, evaporated to a small volume and cooled. The additional crystals thus obtained were recrystallized from Skellysolve (90–100°) and combined with the main product to give the indicated yields of materials melting within 0.5–1.0° of the melting points of the analytical samples.

Compound VIII.—This product was prepared as compound VI except that the reaction time was 3 days. After the solvent was removed the residue was taken up in anhydrous ether and the ether solution decanted from a black tar. When the ether solution was evaporated to a low volume, cooled and treated gradually with small portions of high boiling Skellysolve (90–100°) the crystalline product separated. Material obtained by adding a large volume of Skellysolve to the ethereal mother liquor was recrystallized from Skellysolve (90–100°) and combined with the above giving a 55% yield of product which melted at 93–96° with preliminary sintering.

Compound IX.—In the reaction of I with piperidine, carried out as above, it was found that the reaction time was more than twice as long with ethanol as the solvent than it was with methanol. (Compound I dissolves more readily in methanol than in ethanol.) The reaction was essentially complete in 4 hours in methanol solution. After removal of a trace of starting material, the red solution was evaporated

to dryness and the residue was recrystallized from a small volume of dilute methanol. The product thus obtained (82%) melted at 148.5–150.0°.

Compound X.—Five grams of I was suspended in 50 ml. of chloroform and stirred at room temperature to dissolve as much of the quinone as possible. Upon the addition of 50 ml. of diethylamine considerable spontaneous warming occurred. After the mixture had been stirred for 2 days the resulting dark orange solution was stirred with Darco, filtered and evaporated to dryness under reduced pressure. Upon recrystallization from benzene there was obtained 4.3 g. of red crystals which melted at 143–147° with preliminary sintering. An additional 1.5 g. of dark sticky crystals was obtained by concentrating the mother liquors, but this material was difficult to purify and only 0.4 g. of acceptable product (m.p. about 149–152° with sintering at about 140°) was readily obtained by recrystallization from benzene. The total yield was 4.7 g. (77%). After repeated recrystallization from carbon tetrachloride and from benzene the product had no definite melting point.

Hydrolysis of *n*-Hexylamino-5,8-quinolinequinone (V).—One millimole of V was dissolved in 2 to 3 ml. of absolute ethanol by heating and the warm solution was treated with 2 ml. of 1 *N* potassium hydroxide solution. The odor of hexylamine was apparent almost at once. After 1 hour at room temperature much of the starting material remained so the mixture was gently warmed. Since considerable decomposition occurred after 15 minutes, the solution was cooled and extracted with benzene. About 0.06 g. of starting material was recovered from the first benzene extract. After the aqueous layer had been freed of benzene under reduced pressure, it was neutralized with 1 ml. of 2 *N* hydrochloric acid. The brownish gold crystals of II weighed 0.06 g. (34% conversion, 44% yield). This crude product was converted to the phenazine (procedure A) which was obtained as light yellow needles (0.075 g., 39%). The melting point was 254.0–255.5° and that of a mixture with an authentic sample of the phenazine XI was the same.

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[CONTRIBUTION FROM THE ORGANIC CHEMISTRY LABORATORIES OF THE UNIVERSITY OF FLORIDA]

Derivatives of Piperazine. XXVII. A Modified Strecker Synthesis Utilizing 1-Arylpiperazines¹

BY C. B. POLLARD AND L. J. HUGHES

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Thirty-seven new nitriles, amides and acids have been prepared from 1-arylpiperazines with chloroacetonitrile, lactonitrile or acetone cyanohydrin.

In the course of work in these laboratories on the preparation of physiologically active compounds it seemed advisable to prepare certain 2-amino acids using piperazines as the amines.

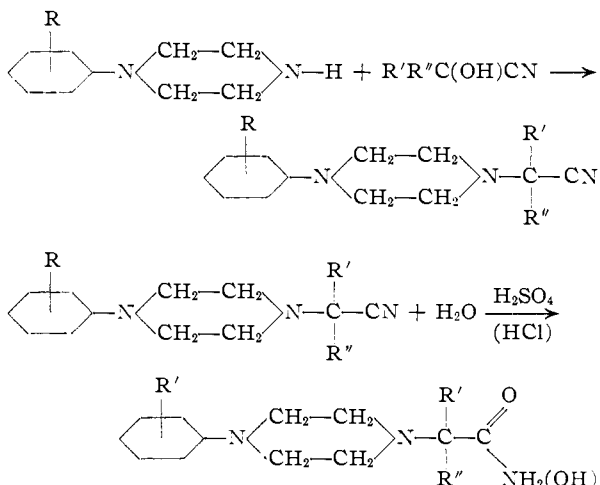
The 2-aminoalkylnitriles are best obtained by mixing the secondary amine and the cyanohydrin in the absence of a solvent.² A noticeable heat is evolved when the amine and cyanohydrin are mixed.

All the nitriles were obtained in quantitative yields of crude products. All compounds are solids.

The amides were made by dissolving the nitriles in concentrated sulfuric acid, allowing to stand 24 hours, and pouring the solution onto cracked ice. Isolation was effected by neutralization with ammonium hydroxide and filtration of the precipitated amide.

(1) This paper is abstracted from a portion of a dissertation submitted by L. J. Hughes to the Graduate Council of the University of Florida in partial fulfillment of the requirements for the degree of Doctor of Philosophy, August, 1953.

(2) R. A. Jacobson, *THIS JOURNAL*, **67**, 1996 (1945).



R = H, 2-CH₃, 3-CH₃, 4-CH₃, 2-Cl, 3-Cl, 4-Cl

R' = H, CH₃

R'' = H, CH₃

TABLE I

 PHYSICAL AND ANALYTICAL DATA OF 2-(ARYLPIPERAZINO)-ALKANONITRILES $\text{Ar}-\langle \text{C}_4\text{H}_8 \rangle-\text{N} \begin{cases} \text{CH}_2-\text{CH}_2 \\ \text{CH}_2-\text{CH}_2 \end{cases} \text{N}-(\text{Y})-\text{CN}$

Ar	Y	Mol. formula	Mol. wt.	M.p., °C.	Yield, %	Nitrogen, %	
						Calcd.	Found
C ₆ H ₅	CH ₂	C ₁₂ H ₁₆ N ₃	201.26	75-76
C ₆ H ₅	CH ₃ CH	C ₁₃ H ₁₇ N ₃	215.29	87.3-88.1	80.5	19.52	19.16 ^a
C ₆ H ₅	(CH ₃) ₂ C	C ₁₄ H ₁₉ N ₃	229.31	111.8-112.5	87.2	18.74	18.15 ^b
<i>o</i> -CH ₃ C ₆ H ₅	CH ₃ CH	C ₁₄ H ₁₉ N ₃	229.31	105.5-106.5	48.4	18.39	18.75
<i>o</i> -CH ₃ C ₆ H ₅	(CH ₃) ₂ C	C ₁₅ H ₂₁ N ₃	243.34	122.5-124	84.2	17.27	17.22
<i>m</i> -CH ₃ C ₆ H ₅	CH ₃ CH	C ₁₄ H ₁₉ N ₃	229.31	62.8-64	51.0	18.39	18.41
<i>m</i> -CH ₃ C ₆ H ₅	(CH ₃) ₂ C	C ₁₅ H ₂₁ N ₃	243.34	81-82.1	75.0	17.27	17.20
<i>p</i> -CH ₃ C ₆ H ₅	CH ₃ CH	C ₁₄ H ₁₉ N ₃	229.31	126-127.2	80.5	18.39	18.26 ^c
<i>p</i> -CH ₃ C ₆ H ₅	(CH ₃) ₂ C	C ₁₅ H ₂₁ N ₃	243.34	136-137.5	87.2	17.27	17.09
<i>o</i> -ClC ₆ H ₅	CH ₂	C ₁₂ H ₁₄ N ₃ Cl	235.71	112.2-113.5	43.0	17.83	18.00
<i>o</i> -ClC ₆ H ₅	CH ₃ OH	C ₁₃ H ₁₆ N ₃ Cl	249.17	84-84.8	92.5	16.83	16.77
<i>o</i> -ClC ₆ H ₅	(CH ₃) ₂ C	C ₁₄ H ₁₈ N ₃ Cl	263.76	113-115.5	81.8	15.93	15.74
<i>m</i> -ClC ₆ H ₅	CH ₃ CH	C ₁₃ H ₁₆ N ₃ Cl	249.17	98.5-99.3	84.2	16.83	16.68
<i>m</i> -ClC ₆ H ₅	(CH ₃) ₂ C	C ₁₄ H ₁₈ N ₃ Cl	263.76	89-90	89.0	15.93	15.82
<i>p</i> -ClC ₆ H ₅	CH ₃ CH	C ₁₃ H ₁₆ N ₃ Cl	249.17	120-121.5	93.0	16.83	16.89
<i>p</i> -ClC ₆ H ₅	(CH ₃) ₂ C	C ₁₄ H ₁₈ N ₃ Cl	263.76	126.5-127.2	90.0	15.93	15.83

^a Calcd., neut. equiv., 215.29; found, 212.7. ^b Calcd., neut. equiv., 229.31; found, 229.8. ^c Calcd., neut. equiv., 229.31; found, 230.5.

TABLE II

 PHYSICAL AND ANALYTICAL DATA OF 2-(4-ARYLPIPERAZINO)-ALKANAMIDES $\text{Ar}-\langle \text{C}_4\text{H}_8 \rangle-\text{N} \begin{cases} \text{CH}_2-\text{CH}_2 \\ \text{CH}_2-\text{CH}_2 \end{cases} \text{N}(\text{Y})-\text{C} \begin{matrix} \text{O} \\ \text{NH}_2 \end{matrix}$

Ar	Y	Mol. formula	Mol. wt.	M.p., °C.	Yield, %	Nitrogen, %	
						Calcd.	Found
C ₆ H ₅	CH ₂	C ₁₂ H ₁₇ N ₃ O	219.28	169-170	31.0
C ₆ H ₅	CH ₃ CH	C ₁₃ H ₁₉ N ₃ O	233.30	143-143.8	70.0	18.01	18.03
C ₆ H ₅	(CH ₃) ₂ C	C ₁₄ H ₂₁ N ₃ O	247.33	162.8-163.5	76.0	16.99	16.74
<i>o</i> -CH ₃ C ₆ H ₅	CH ₃ CH	C ₁₄ H ₂₁ N ₃ O	247.33	122.3-123.4	23.1	16.99	17.01
<i>o</i> -CH ₃ C ₆ H ₅	(CH ₃) ₂ C	C ₁₅ H ₂₃ N ₃ O	261.35	174.5-175.5	60.0	16.08	16.12
<i>m</i> -CH ₃ C ₆ H ₅	CH ₃ CH	C ₁₄ H ₂₁ N ₃ O	247.33	126.5-127.3	48.0	16.99	16.91
<i>m</i> -CH ₃ C ₆ H ₅	(CH ₃) ₂ C	C ₁₅ H ₂₃ N ₃ O	261.35	132.5-133.3	66.0	16.08	16.06
<i>p</i> -CH ₃ C ₆ H ₅	CH ₃ CH	C ₁₄ H ₂₁ N ₃ O	247.33	152.8-154	70.0	16.99	16.83
<i>p</i> -CH ₃ C ₆ H ₅	(CH ₃) ₂ C	C ₁₅ H ₂₃ N ₃ O	261.35	170-171	76.0	16.08	16.42
<i>o</i> -ClC ₆ H ₅	CH ₂	C ₁₂ H ₁₆ N ₃ OCl	253.73	169-170	54.0	16.56	16.44
<i>o</i> -ClC ₆ H ₅	CH ₃ CH	C ₁₃ H ₁₈ N ₃ OCl	267.75	163-165	70.0	15.69	15.93
<i>o</i> -ClC ₆ H ₅	(CH ₃) ₂ C	C ₁₄ H ₂₀ N ₃ OCl	281.78	186-188	76.0	14.91	14.84
<i>m</i> -ClC ₆ H ₅	CH ₃ CH	C ₁₃ H ₁₈ N ₃ OCl	267.75	151.3-152.6	60.0	15.69	15.65
<i>m</i> -ClC ₆ H ₅	(CH ₃) ₂ C	C ₁₄ H ₂₀ N ₃ OCl	281.78	157.2-158.3	86.0	14.91	14.76
<i>p</i> -ClC ₆ H ₅	CH ₃ CH	C ₁₃ H ₁₈ N ₃ OCl	267.75	171-172.2	88.5	15.69	15.63
<i>p</i> -ClC ₆ H ₅	(CH ₃) ₂ C	C ₁₄ H ₂₀ N ₃ OCl	281.78	180.2-181.2	84.0	14.91	14.85

The acids were prepared by hydrolysis in concentrated hydrochloric acid. Hydrolysis of the amides was successful in all cases attempted, whereas the hydrolysis of the nitriles yielded ammonium chloride as the only crystalline product in the following: 2-(4-phenylpiperazino)-2-methylpropanonitrile, 2-[4-(2-methylphenyl)-piperazino]-propanonitrile, 2-[4-(2-methylphenyl)-piperazino]-2-methylpropanonitrile, 2-[4-(3-methylphenyl)-piperazino]-propanonitrile, 2-[4-(3-methylphenyl)-piperazino]-2-methylpropanonitrile, 2-[4-(methylphenyl)-piperazino]-2-methylpropanonitrile and 2-[4-(3-chlorophenyl)-piperazino]-2-methylpropanonitrile.

Experimental

Detailed directions for the preparation of the compounds reported in this paper are given for only one representative member of each class.

Cyanohydrins—Products from American Cyanamid Company or Matheson, Coleman and Bell were used without further purification.

1-Arylpiperazines.—The preparation of the phenylpiperazines utilized in these syntheses already has been described.^{3,4}

2-(4-Phenylpiperazino)-ethanonitriles.—2-(4-Phenylpiperazino)-ethanonitrile and 2-[4-(2-chlorophenyl)-piperazino]-ethanonitrile were prepared from chloroethanonitrile by the method of Adelson and Pollard.⁵

2-(4-Phenylpiperazino)-propanonitriles.—To 0.2 mole of the 1-phenylpiperazine in a glass container was added, with stirring, 0.2 mole of the cyanohydrin. Exothermic reactions set in immediately; after they subsided the mixtures were heated on a steam-bath 15-30 minutes. On cooling the mixtures solidified to give quantitative yields. Recrystallization from 95% ethanol or *n*-heptane gave pure products. The compounds were dried at 50° (2 mm.) before analysis. Physical and analytical data, along with yields of pure products, are shown in Table I.

2-(4-Phenylpiperazino)-alkanamides.—To 200 ml. of concentrated sulfuric acid was added, with cooling and stirring, 0.175 mole of the 2-(4-phenylpiperazino)-alkano-

(3) C. B. Pollard and L. G. MacDowell, *THIS JOURNAL*, **56**, 2199 (1934).

(4) C. B. Pollard and T. H. Wicker, Jr., *ibid.*, **76**, 1853 (1954).

(5) D. E. Adelson and C. B. Pollard, *ibid.*, **57**, 1430 (1935).

TABLE III

PHYSICAL AND ANALYTICAL DATA OF 2-[4-ARYLPYPERAZINO]-ALKANOIC ACIDS

Ar	Y	Mol. formula	Mol. wt.	Nitrogen, %		Neut. equiv.	
				Calcd.	Found	Calcd.	Found
C ₆ H ₅	CH ₃ CH	C ₁₃ H ₁₈ N ₂ O ₂ ·2HCl·H ₂ O	323.20	9.12 ^a	8.90	161.6	158.1
<i>p</i> -CH ₃ C ₆ H ₅	CH ₃ CH	C ₁₄ H ₂₀ N ₂ O ₂ ·2HCl·H ₂ O	339.24	8.26	8.33	168.6	171.3
<i>o</i> -ClC ₆ H ₅	CH ₂	C ₁₂ H ₁₆ N ₂ O ₂ Cl·HCl·H ₂ O	308.18	9.63 ^b	9.54	308.2	305.1
<i>o</i> -ClC ₆ H ₅	CH ₃ CH	C ₁₃ H ₁₇ N ₂ O ₂ Cl·HCl·H ₂ O	323.21	8.67 ^c	9.17	323.2	322.2
<i>o</i> -ClC ₆ H ₅	(CH ₃) ₂ C	C ₁₄ H ₁₉ N ₂ O ₂ Cl·HCl	319.24	8.78	8.92
<i>m</i> -ClC ₆ H ₅	CH ₃ CH	C ₁₃ H ₁₇ N ₂ O ₂ Cl	268.74	10.42	10.50
<i>p</i> -ClC ₆ H ₅	CH ₃ CH	C ₁₃ H ₁₇ N ₂ O ₂ Cl·2HCl	341.67	8.37	8.71
<i>p</i> -ClC ₆ H ₅	(CH ₃) ₂ C	C ₁₄ H ₁₉ N ₂ O ₂ Cl	282.76	9.93	10.02

^a Calcd. for C₁₃H₁₈N₂O₂·2HCl·H₂O. ^b Calcd. for C₁₂H₁₆N₂O₂Cl·HCl·H₂O. ^c Calcd. for C₁₃H₁₇N₂O₂Cl·HCl·H₂O.

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.

Acknowledgment.—During the period in which this research was conducted L. J. Hughes held a Parke, Davis and Company research fellowship. The authors wish to express their appreciation for this research grant.

GAINESVILLE, FLORIDA

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

3(2H)-Pyridazones. I. Compounds Related to Phenacetin¹

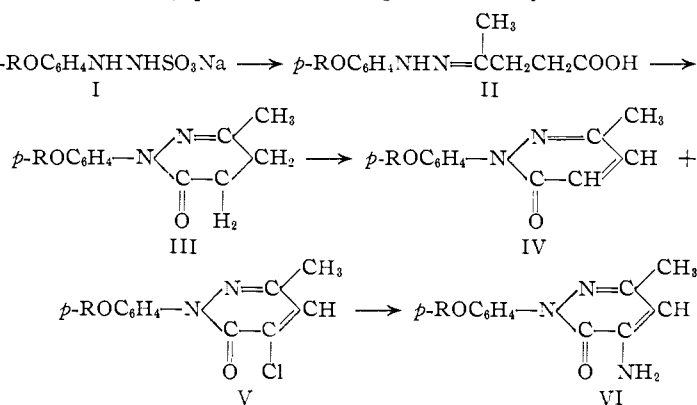
BY FRANK J. STEVENS, TOMMY D. GRIFFIN AND THOMAS L. FIELDS

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 acyl-amino 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 antipyretic³ and analgesic⁶ 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).

(4) W. G. Overend and L. F. Wiggins, *J. Chem. Soc.*, 239, 549 (1947).

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

(6) H. Gregory and L. F. Wiggins, *ibid.*, 2066, 2546 (1949).