acetic acid. All the above developer ratios are volume for volume.

As the English humic acid reaction mixture was not quantitatively analyzed, the results of the analysis are not shown in Table II. However, all bands on the chromatograms of this mixture correspond exactly to those shown in Table II.

Spectra. In preparation for spectral measurements, the final purified eluates (from each chromatographic band described above) was half-banded on Whatman #1 paper; the band and blank cut from the other half of the paper were cut out and separately eluted with 70% ethanol. Spectral shifts in base were determined by adding three drops of 1*M* potassium hydroxide to the sample cuvette and the blank cuvette. Such shifts have been shown to be diagnostic in elucidating structural features.[30] The γ_{max} values for the nine prominent bands are summarized in Table IV.

Quantitative analysis. The concentration of each compound listed in Table I was based on the amount of humic acid hydrolysate which reacted with cupric oxide-sodium hydroxide (water-soluble products). A quantitative estimation of each compound was obtained by comparing the optical density of its eluate (obtained from a known aliquot of the aqueous reaction solution) with the optical density of a standard solution of an authentic substance at the same wave length.

The determination of 3,5-dihydroxybenzoic acid illustrates the method used in this analysis. A 1.5-ml. aliquot of the ether extract was streaked on Whatman #1 paper. After development in solvent 1, the band at R_f 0.38 was eluted; the eluate was concentrated and rechromatographed in solvent 2. The band at R_f 0.23 was eluted; the eluate was half-banded on paper and developed in acetic acid. The band appearing at R_f 0.60 in acetic acid solvent was cleanly separated from other bands, particularly vanillic and *p*-hydroxybenzoic acids. It was eluted (together with its blank) and the optical density of the eluate determined at 310 mμ in a Cary Recording Spectrophotometer. The optical density was compared to a standard curve which was derived from a solution of known concentration of 3,5-dihydroxybenzoic acid and which had been chromatographed in an identical manner to that described above.

All seven compounds obeyed Beer's Law in ethanol solution.

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TUCSON, ARIZ.

[CONTRIBUTION FROM THE ORGANIC RESEARCH LABORATORIES, U. S. VITAMIN & PHARMACEUTICAL CORP.]

Pyridylethylbarbituric Acids

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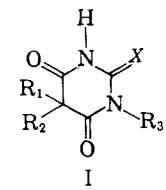
A series of 5-pyridylethylated barbituric acids has been synthesized and the effect of structure on ultraviolet absorption spectra and pK_a noted. Several of these compounds markedly increased hexobarbital sleeping time.

For only a few basic structures has the relationship between structure and physiological activity been so extensively explored as for the barbiturates. Since Doran's recent review[1] many papers and patents[2] have evaluated new structural parameters including amino-substituted derivatives.[3] The 5-pyridylalkyl derivatives have, however, received scant attention, and have been limited to 5-picolyl substituents,[4,5] and 5-monosubstituted pyridylethyl derivatives.[6]

This study explores 5-pyridylethylated barbituric acids, which were varied[7] as shown for I. (Table I).



I

R_1 = 2-, 3-, and 4-picolyl-, [2-(2-, and 4-pyridyl)etyhl]-, [2-(5-ethyl-2-pyridyl)ethyl]-
R_2 = methyl and ethyl
R_3 = hydrogen, methyl, ethyl, allyl, butyl, and phenyl
X = oxygen, sulfur, and imino

The requisite intermediates were obtained from the picolyl chloride and the substituted diethyl malonate,[4] or by pyridylethylation[8] of the malonate ester. These intermediate compounds are described in Table II.

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(3) (a) L. Donatelli, E. Genazzani, E. De Nito, W. Chiti, and R. Selleri, *Boll. soc. ital. biol. sper.*, **29**, 50 (1953). (b) G. S. Skinner and D. J. Lyman, *J. Am. Chem. Soc.*, **75**, 5909 (1953). (c) W. Chiti, *Il Farmaco, Ed. Sc.*, **15**, 29, (1960). (d) J. W. Clark-Lewis and M. J. Thompson, *J. Chem. Soc.*, 2401 (1959). (e) W. Chiti and R. Selleri, U. S. Patent **2,842,547** (July 8, 1958). (f) A. H. Sommers, U. S. Patent **2,953,566** (Sept. 20, 1960). (g) J. A. Stanfield and P. M. Daugherty, *J. Am. Chem. Soc.*, **81**, 5167 (1959). (h) E. A. Ferguson, Jr., U. S. Patent **2,921,072** (Jan. 12, 1960). (i) H. Goldhan, *Acta. Chim. Acad. Sci. Hung.*, **18**, 395 (1959).

(4) C. S. Kuhn and G. H. Richter, *J. Am. Chem. Soc.*, **57**, 1927 (1935).

(5) T. Kato, F. Hamaguchi, and T. Ohiwa, *Yakugaku Zasshi*, **80**, 1293 (1960).

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(8) W. E. Doering and R. A. N. Weil, *J. Am. Chem. Soc.*, **69**, 2463 (1947).

TABLE I

5-(PYRIDYLALKYL)BARBITURIC ACIDS (I)[a]

No.	R_3	M.P.[b]	R.S.[c,d]	Formula	Carbon, %[e] Calcd.	Carbon, %[e] Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
				R_1 = picolyl, R_2 = ethyl						
1[f]	H	230–232	A	$C_{12}H_{15}N_3O_4$	54.3[e]	54.5	5.2	5.0	15.8	15.5
2[g]	H	220	A	$C_{12}H_{13}N_3O_3$	58.3	58.0	5.3	5.5	17.0	17.3
3[h]	H	234–235	A	$C_{12}H_{13}N_3O_3$	58.3	58.4	5.3	5.4	17.0	17.1
				R_1 = [2-(2-pyridyl)ethyl], R_2 = ethyl						
4	H	205	B	$C_{13}H_{15}N_3O_3$	59.8	60.1	5.8	5.7	16.1	15.7
5[i]	H	217–219	B	$C_{13}H_{15}N_3O_2S$	—	—	—	—	15.2	15.3
6[j]	H	>300	C	$C_{13}H_{16}N_4O_2$	—	—	—	—	21.5	21.5
6[k]	H	238–240	D	$C_{25}H_{22}N_{10}O_{16}$	41.8	42.1	3.1	3.0	19.5	19.5
7	CH_3—	150–153	D	$C_{14}H_{17}N_3O_3$	61.1	61.7	6.2	6.1	15.3	14.9
8	C_2H_5—	123–124	D	$C_{15}H_{19}N_3O_3$	62.3	62.5	6.6	6.5	14.5	14.5
9	CH_2=CH—CH_2—	120	E	$C_{16}H_{19}N_3O_3$	63.8	64.0	6.4	6.3	14.0	13.8
10	n-C_4H_9—	85	D	$C_{17}H_{23}N_3O_3$	64.3	64.4	7.3	7.3	13.2	13.1
11	C_6H_5—	185–187	D	$C_{19}H_{19}N_3O_3$	67.6	67.5	5.7	5.8	12.5	12.1
				R_1 = [2-(5-ethyl-2-pyridyl)ethyl]; R_2 = ethyl						
12	H	220–222	E	$C_{15}H_{19}N_3O_3$	—	—	—	—	14.5	14.5
13[i]	H	201–202	E	$C_{15}H_{19}N_3O_2S$	59.0	59.3	6.3	6.2	13.8	14.0
14[j]	H	280 d.	F	$C_{15}H_{20}N_4O_2$	62.5	62.0	7.0	7.1	—	—
15	CH_3—	154	D	$C_{16}H_{21}N_3O_3$	63.4	63.4	7.0	6.8	—	—
16	C_2H_5—	137–138	D	$C_{17}H_{23}N_3O_3$	64.3	63.8	7.3	7.3	13.2	13.1
17	CH_2=CH—CH_2—	127–128	E	$C_{18}H_{23}N_3O_3$	65.6	65.6	7.0	7.0	12.8	12.9
18	n-C_4H_9—	80–81	G	$C_{19}H_{27}N_3O_3$	66.1	65.7	7.9	7.7	12.2	12.5
19	C_6H_5—	166–167	D	$C_{21}H_{23}N_3O_3$	69.0	69.1	6.3	6.3	11.5	11.6
				R_1 = [2-(4-pyridyl)ethyl]; R_2 = methyl						
20	H	252–254	H	$C_{12}H_{13}N_3O_3$	58.3	58.1	5.3	5.4	17.0	16.9
21[i]	H	227-230	B	$C_{12}H_{13}N_3O_2S$	54.8	55.2	5.0	5.0	—	—
22[j]	H	>300	H	$C_{12}H_{14}N_4O_2$	58.5	58.3	5.7	5.9	22.8	22.9
23	CH_3—	204–206	D	$C_{13}H_{15}N_3O_3$	—	—	—	—	16.1	16.1
24	C_2H_5—	176–177	E	$C_{14}H_{17}N_3O_3$	61.1	60.8	6.2	6.4	15.3	14.9
25	n-C_4H_9—	174–175	D	$C_{16}H_{21}N_3O_3$	63.4	63.3	7.0	6.9	13.9	14.0
26	C_6H_5—	125–126	H	$C_{18}H_{17}N_3O_3$	—	—	—	—	13.0	13.6
				R_1 = [2-(4-pyridyl)ethyl]; R_2 = ethyl						
27	H	224–226	E	$C_{13}H_{15}N_3O_3$	59.8	59.9	5.8	5.5	16.1	16.0
28[i]	H	224–226	B	$C_{13}H_{15}N_3O_2S$	56.3	56.2	5.5	5.4	15.2	15.0
29[j]	H	>300	B	$C_{13}H_{16}N_4O_2$	—	—	—	—	21.5	21.1
30[l]	H	210–212	D	$C_{13}H_{18}Cl_2N_4O_2$	46.9	46.6	5.5	5.4	—	—
31	CH_3—	148–150	D	$C_{14}H_{17}N_3O_3$	61.1	61.4	6.2	6.0	15.3	15.4
32	C_2H_5—	110	D	$C_{15}H_{19}N_3O_3$	62.3	62.5	6.6	6.9	14.5	14.3
33	CH_2=CH—CH_2—	115	E	$C_{16}H_{19}N_3O_3$	63.8	63.9	6.4	6.2	14.0	14.1
34	n-C_4H_9—	102–104	G	$C_{17}H_{23}N_3O_3$	64.3	64.5	7.3	7.5	13.2	13.2
35	C_6H_5—	177–178	D	$C_{19}H_{19}N_3O_3$	67.6	67.7	5.7	5.6	12.5	12.6

[a] X is O unless otherwise indicated. [b] Melting points were taken on a Fisher-Johns melting point block, and are not corrected. [c] R.S. = recrystallizing solvent: A = n-butyl alcohol; B = n-propyl alcohol; C = acetic acid–acetonitrile; D = ethanol; E = acetonitrile; F = acetic acid–ethanol; G = ether-hexane; H = methanol. [d] General description of yields is given in the discussion section. [e] Analyses are by Weiler and Strauss, Oxford, England. [f] R_1 = 2-picolyl, compound isolated as monohydrate. Ref. 5 reports m.p. 235°. [g] R_1 = 3-picolyl. [h] R_1 = 4-picolyl. [i] X = S. [j] X = NH. [k] Dipicrate of preceding compound. [l] Dihydrochloride of preceding compound.

In the pyridylethylation, best results were noted with R_2 = ethyl. Poor yields with R_2 = H are probably a function of depyridylethylation, whereas with R_2 = C_6H_5—, a steric factor may influence the reaction.

The cyclization to the barbituric acids proceeded best (58% yield) with R_1 = picolyl. No criticality was associated with the pyridylethyl substituents, with average yields being 26–29%. As R_2 was varied from hydrogen, methyl, ethyl, allyl, n-butyl, and phenyl (X = O) average yields of 20, 24, 41, 14, 30, and 33%, respectively, were noted. It is likely that the poorer yields with the pyridylethylated compounds relative to the picolyl derivatives are associated with reversibility of these additions.[9,10]

The attempted cyclization of diethyl phenyl-[2-(2-pyridyl)ethyl]malonate and urea under alkoxide catalysis resulted instead in the formation of α-

(9) S. L. Shapiro, I. M. Rose, E. Roskin, and L. Freedman, *J. Am. Chem. Soc.*, **80**, 1648 (1958).

(10) E. W. Maynert and E. Washburn, *J. Am. Chem. Soc.*, **75**, 700 (1953).

TABLE II

INTERMEDIATES

$Py(CH_2)_nCR_2(COOC_2H_5)_2$

No.	Py[a]	n	R_2	B.P. (Mm.)	Yield, %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
1	2	1	C_2H_5—	122–128 (0.05)	18	$C_{15}H_{21}NO_4$	64.5	64.4	7.6	7.9	5.0	4.8
2	3	1	C_2H_5—	132 (0.35)	5	$C_{15}H_{21}NO_4$	—	—	—	—	5.0	5.0
3	4	1	C_2H_5—	138–142 (0.3)	14	$C_{15}H_{21}NO_4$	—	—	—	—	5.0	4.9
4	2	2	H	130–134 (0.1)	26	$C_{14}H_{19}NO_4$	—	—	—	—	5.3	5.2
5	2	2	C_2H_5—	150–160 (0.15)	65	$C_{16}H_{23}NO_4$	—	—	—	—	4.8	
6	2	2	C_6H_5—	150–152 (0.6)	16	$C_{20}H_{23}NO_4$	70.4	70.8	6.8	6.5	—	—
7	[b]	2	C_2H_5—	160–168 (0.3)	41	$C_{18}H_{27}NO_4$	67.3	67.2	8.5	8.7	—	—
8	4	2	H	140–142 (0.3)	5	$C_{14}H_{19}NO_4$	63.4	63.2	7.2	7.2	5.3	5.1
9	4	2	CH_3—	140–150 (0.1)	37	$C_{15}H_{21}NO_4$	64.5	64.5	7.6	7.6	—	—
10[c]	4	2	C_2H_5—[d]	150–158 (0.45)	50	$C_{16}H_{23}NO_4$	—	—	—	—	4.8	4.4

[a] The number in the column indicates position of azine nitrogen. [b] 5-ethyl-2-pyridyl. [c] The picrate, m.p. 113–114° (ethanol). *Anal.* Calcd. for $C_{22}H_{26}N_4O_{11}$: N, 10.7. Found: N, 10.8. [d] The analog wherein $R_2 = C_6H_5$ was obtained impure, b.p. 176–178° (0.2 mm.), but on hydrolysis gave α-phenyl-γ-(4-pyridyl)butyric acid (see Experimental).

phenyl-γ-(2-pyridyl)butyramide[11,12] as well as the corresponding butyric acid.

In earlier work under basic catalysis, 5-ethyl-5-phenylbarbituric acid was pyridylethylated in the 1 position,[13] in relatively poor yield. As an alternative synthesis for I, it was found that 5-ethyl barbituric acid condensed with 4-vinylpyridine to pyridylethylate at the 5 position giving compound 27 in the absence of catalyst. Alternatively, under these conditions with a large excess of 4-vinylpyridine, no additional pyridylethylation at the 1 position occurs.

This approach, using 5-phenylbarbituric acid also yielded the otherwise inaccessible 5-phenyl-5-[2-(4-pyridyl)ethyl]barbituric acid. The relatively low acidity (see Table III) indicated that a 5,5-disubstituted barbituric acid has been formed.

In the ultraviolet, with the exception of the imino barbituric acid, compound 6, and the thio barbituric acid, compound 28, a regularity in the noted spectra prevails. The data in methanol and 0.1*N* hydrochloric acid are fully consistent with spectral characteristics of the 2- and 4-picolyl and -pyridylethyl substituents being virtually parallel to those observed by Brown and Mihm with the alkylpyridines.[14] In these solvents no indication of barbituric acid chromophore is apparent.

While the maxima in methanol and hydrochloric acid are substantially the same, the extinction coefficients are about twice as great in hydrochloric acid.

Alternatively, in 0.1*N* sodium hydroxide, the enolic chromophore of the barbituric acid emerges and it is of interest that as the substitution at the 1 position proceeds from hydrogen through alkyl to phenyl in an otherwise similar system, that the

TABLE III

ULTRAVIOLET ABSORPTION SPECTRA AND $pK^1{}_a$[a]

No.[b]	Ultraviolet Spectra in Solvents[c] CH_3OH	0.1*N* HCl	0.1*N* NaOH	$pK^1{}_a$[d]
3	257, 2.3	254, 4.7	250, 11.7	
4	261, 3.7	261, 7.8	253, 9.0	8.82
6	259, 9.1	260, 5.4	259, 11.8	
7	260, 3.6	261, 8.0	247, 10.2	9.17
8	260, 3.7	262, 8.1	246, 9.7	9.19
10	260, 3.7	262, 8.1	247, 9.8	9.25
11	259, 3.9	262, 8.3	244, 10.7	8.61
27	255, 2.1	252, 4.7	247, 8.4	8.78
28	287, 23.4	288, 23.2	305, 27.8	8.29
34	253, 2.1	252, 4.6	245, 8.8	
[e]				8.35

[a] The authors are grateful to M. Blitz and B. Blank for supplying the data. [b] Numbers correspond to compound numbers in Table I. [c] The spectra were determined in the Beckman DK recording spectrophotometer and data for the main absorption bands are shown as λ_{max} mμ, $\epsilon \times 10^{-3}$. [d] The $pK^1{}_a$ values (acidity of the barbiturates) were established at 25°, in 50% methanol at a concentration of 0.01 mole/l. following the simplified potentiometric procedure of P. H. Grantham, E. K. Weisburger, and J. H. Weisburger, *J. Org. Chem.*, **26**, 1008 (1961); 5-ethyl-5-phenylbarbituric acid under these conditions gave $pK^1{}_a$ 8.55. [e] 5-Phenyl-5-[2-(4-pyridyl)ethyl]barbituric acid.

λ_{max} is progressively shifted to the blue with a corresponding increase in the extinction coefficient.[15] Comparison of compound 4 with compound 27 in this solvent shows a bathochromic and hyperchromic effect of the 2-pyridylethyl substituent relative to the corresponding 4-pyridylethyl substituent.

The spectral data with compounds 6 and 28 suggests that the same chromophore is being measured in all of the solvents. The high extinction with the thiobarbituric acid derivative and the considerable bathochromic shift relative to its congeners suggest that this compound exists in the enolic form under all conditions of measurement.

(11) S. L. Shapiro, I. M. Rose, and L. Freedman, *J. Am. Chem. Soc.*, **80**, 6065 (1958).

(12) A. K. Bose, *J. Indian Chem. Soc.*, **31**, 108 (1954).

(13) S. L. Shapiro, I. M. Rose, and L. Freedman, *J. Am. Chem. Soc.*, **79**, 2811 (1957).

(14) H. C. Brown and X. R. Mihm, *J. Am. Chem. Soc.*, **77**, 1723 (1955).

(15) J. J. Fox and D. Shugar, *Bull. soc. chim. Belg.*, **61**, 44 (1952).

The pK_a data are of interest in that the presence of the basic pyridylethyl substituent at the 5 position has an acid weakening effect relative to the usual barbituric acid.[16,17]

The introduction of substituents on the 1 position has the anticipated acid weakening effect (about 0.3 pK_a units) noted by others. Somewhat anomalous is the acid strengthening effect with the 1-phenyl derivative. Comparison of compound 4 bearing the 2-pyridylethyl substituent with compound 27, the corresponding 4-pyridylethyl analog, shows essentially the same pK_a. However, compound 28, the thiobarbituric acid corresponding to compound 27 shows enhancement of acidity (0.5 pK_a units) consistent with the higher acidity of the thioureas relative to ureas.

The melting points of compounds described in Table I show a significant parallelism. Thus, when R_2 is ethyl and R_1 is pyridylethyl, as the group at the 1 position is varied, the melting point range is for hydrogen, 205–226°; methyl, 148–154°; ethyl, 110–138°; allyl, 115–120°; *n*-butyl, 80–104°; and phenyl, 166–187°.

With the structural change to R_2 = methyl, considerably higher melting points are noted (compounds 20–26) and, in addition, the 1-phenyl substituent emerges with a relatively low melting point.

A limited exploration of the pharmacological activity has indicated the compounds to be without substantial toxicity or central nervous system depressant effects. The most conspicuous effect noted has been enhancement of hexobarbital sleeping time, particularly with compound 31, which showed a 420% increase.[18] The (4-pyridyl)ethyl compounds showed greater effects than the 2 congeners.[9,19]

EXPERIMENTAL[20]

Diethyl ethyl (2-picolyl)malonate (Table II, compound 1). A solution of 6.6 g. (0.29 g.-atom) of sodium in 100 ml. of ethanol was treated with 26.4 g. (0.14 mole) of diethyl ethylmalonate and 22.8 g. (0.14 mole) of α-picolyl chloride hydrochloride and heated under reflux for 2.5 hr. When cool, water (100 ml.) and hydrochloric acid (10 ml.) were added, the alcohol removed, and aqueous residue washed with ether. After addition of 50 ml. of 10% sodium hydroxide, the formed oil was extracted into 150 ml. ether and washed with water. The ether was removed and the residue distilled to give 7.1 g. (18%) of product, b.p. 122–128° (0.05 mm.).

Diethyl ethyl[2-(2-pyridyl)ethyl]malonate (Table II, compound 5). A solution of 3.0 g. (0.13 g.-atom) of sodium in 100 ml. ethanol was added to a mixture of 44.0 g. (0.42 mole) of 4-vinylpyridine, 100 g. (0.53 mole) of diethyl ethylmalonate, and 0.1 g. of hydroquinone. After heating under reflux for 6 hr., the alcohol was removed and the aqueous residue diluted with water (200 ml.) and hydrochloric acid (56 ml.) and washed with ether. Addition of 100 ml. of 20% sodium hydroxide afforded the oily product which was extracted into ether and successively washed with water and aqueous sodium bisulfite solution. After removal of the ether, the residue was distilled to yield 77.4 g. (65%) of product, b.p. 150–160° (0.15 mm.).

The ester, on hydrolysis, afforded the malonic acid, m.p. 146° (acetonitrile).

Anal. Calcd. for $C_{12}H_{15}NO_4$: N, 5.9. Found: N, 6.2.

The other pyridylethylated malonates were prepared in a similar manner.

α-Phenyl-γ-(4-pyridyl)butyric acid. A mixture of 8 g. (0.023 mole) of diethyl phenyl[2-(4-pyridyl)ethyl]malonate and 1.8 g. (0.045 mole) of sodium hydroxide in 20 ml. water was refluxed for 2 hr. When cool, 50 ml. of water was added, and after addition of 4.3 ml. of hydrochloric acid, the formed oil was extracted with 50 ml. of warm chloroform. On evaporation, the residue on recrystallization (aqueous ethanol) gave 0.4 g. (7%) of product, m.p. 125–127°C.

Anal. Calcd. for $C_{15}H_{15}NO_2$: C, 74.7; H, 6.3; N, 5.8. Found: C, 75.2; H, 6.3; N, 6.0.

5-Ethyl-5-(α-picolyl)barbituric acid monohydrate (Table I, compound 1). A solution of 1.0 g. (0.043 g.-atom) of sodium in 20 ml. ethanol was treated with 6.0 g. (0.021 mole) of diethyl (α-picolyl)ethylmalonate and 1.6 g. (0.026 mole) of urea in 10 ml. of hot ethanol and refluxed for 6 hr. When cool, water (100 ml.) was added and the alcohol removed. The residue was washed with ether and on neutralization, (*p*H, 7) the product, 2.5 g. (48%) separated, m.p. 230–232°.

Compounds 2 and 3, Table I, were prepared in a similar manner.

5-Methyl-5-[2-(4-pyridyl)ethyl]-2-thiobarbituric acid (Table I, compound 21). A solution of 1.0 g. of sodium (0.043 g.-atom) in 20 ml. of ethanol was treated with 7 g. (0.025 mole) of diethyl methyl [2-(4-pyridyl)ethyl]malonate, and 1.9 g. (0.025 mole) of thiourea in 20 ml. of hot ethanol and refluxed for 9 hr. When cool, water (100 ml.) was added and the alcohol removed. The aqueous residue was washed with ether and on neutralization (*p*H, 7) the product 4.0 g. (61%) separated, m.p. 220–230°.

Compounds 4–35 were prepared in a similar manner employing the appropriately substituted malonate, and urea, or allied substances. For the 2-iminobarbituric acids, an additional equivalent of sodium alkoxide liberated guanidine from its hydrochloride.

α-Phenyl-γ-(2-pyridyl)butyramide. A solution of 1.2 g. (0.052 g.-atom) of sodium in 50 ml. of ethanol was added to a mixture of 2.6 g. (0.043 mole) of urea in 20 ml. of ethanol and 17.6 g. (0.052 mole) of diethyl phenyl[2-(2-pyridyl)-ethyl]malonate and refluxed for 7 hr. When cool, water (100 ml.) was added and the alcohol removed. The aqueous residue was extracted with 100 ml. of ether and neutralized to *p*H, 7 to give 1.2 g. (11%) of the amide, m.p. 121–123° (ethanol).

Anal. Calcd. for $C_{15}H_{16}N_2O$: C, 75.0; H, 6.7; N, 11.7. Found: C, 75.2; H, 6.3; N, 11.5.

The ether extract on evaporation gave 0.5 g. (5%) of α-phenyl-γ-(2-pyridyl)butyric acid, m.p. 159–161°; recrystallized (ethanol), m.p. 161–162°.

Anal. Calcd. for $C_{15}H_{15}NO_2$: C, 74.7; H, 6.3; N, 5.8. Found: C, 74.5; H, 6.5; N, 6.0.

5-Ethyl-5-[2-(4-pyridyl)ethyl]barbituric acid (pyridylethylation of 5-ethylbarbituric acid). A mixture of 3.9 g. (0.025 mole) of 5-ethylbarbituric acid and 5.2 g. (0.05 mole) of 4-vinylpyridine in 100 ml. of ethanol reacted exothermically and on standing gave the product which was recrystallized (acetonitrile) to give 2.5 g. (40%), m.p. 224–226°, not depressing the melting point of compound 27, mixed m.p., 224–226°.

5-Phenyl-5-[2-(4-pyridyl)ethyl]barbituric acid. A mixture of 1 g. (0.005 mole) of 5-phenylbarbituric acid and 0.5 g. (0.005 mole) of 4-vinylpyridine was dissolved in 25 ml. of hot 1:1 ethanol-water. After evaporation of the ethanol on the steam bath, 1.0 g. of product precipitated and on

(16) Ref. 1, p. 41.
(17) A. I. Biggs, *J. Chem. Soc.*, 2485 (1956).
(18) See Ref. 9 for method of testing.
(19) S. L. Shapiro, I. M. Rose, F. C. Testa, and L. Freedman, *J. Org. Chem.*, **26**, 1323 (1961) and references therein.
(20) Data shown in tables are not reproduced in this section.

recrystallization (30 ml. of water and 5 ml. of ethanol) gave 0.7 g. (47%), m.p. 248–249°. A negative permanganate test indicated that the product was not a salt of 4-vinylpyridine and 5-phenylbarbituric acid.

Anal. Calcd. for $C_{17}H_{15}N_3O_3$: C, 66.0; H, 4.9; N, 13.6. Found: C, 66.5; H, 6.3; N, 13.7.

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Pyrazolidines. I. 1,2-Diarylpyrazolidines[1]

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1,2-Diarylpyrazolidines have been prepared by the oxidative cyclization of the related *N,N'*-diaryl-1,3-propanediamines using manganese dioxide. The analogous reaction with two representative *N,N'*-dialkyl-1,3-propanediamines afforded only unchanged diamine.

Although general methods have been developed for the synthesis of pyrazoles, pyrazolines, and pyrazolones,[2] methods for the preparation of the pyrazolidine ring system have not been investigated to any significant extent. Upon occasion, the synthesis of a substituted pyrazolidine has been described, but the scope of the reaction employed was not examined in any detail. In these syntheses, the approach invariably involved hydrazine, or a derivative thereof, and a 1,3-dihalopropane. In this way pyrazolidine,[3,4] 1,5-diazabicyclo[3,3,0]-octane,[3] 1-phenyl-4-allylpyrazolidine,[5] 1,2-diphenylpyrazolidine,[6,7] and 1-phenylpyrazolidine[6,8] have been prepared.

A novel approach to the formation of the pyrazolidine ring system involves closure of a 1,3-propanediamine. Thus Lüttringhaus[9] was able to transform 1,3-propanediamine into pyrazolidine by treating *N*-chloro-1,3-propanediamine with sodium hydroxide and Wittig[10] prepared 1,2-diphenylpyrazolidine from *N,N'*-diphenyl-1,3-propanediamine either by oxidation with manganese dioxide or by treatment with methyllithium followed by iodine.

The 1,2-diarylpyrazolidines described in this paper were prepared by manganese dioxide oxidation of the corresponding *N,N'*-diaryl-1,3-propanediamine. In turn, these diamines were obtained by treating 1,3-dibromopropane with an excess of a primary amine.[11] The latter reaction requires no further comment; the general procedure is given in the experimental section and some specific data are recorded in Table I.

On the other hand, the manganese dioxide oxidation of these diamines provided several noteworthy observations. In common with the experience of other workers, it was found that the oxidation was strongly influenced by the method employed to prepare the manganese dioxide.[12] Material obtained by combining stoichiometric quantities of manganese sulfate and potassium permanganate was *inactive* for ring closure, whereas manganese dioxide[13] like that used by Wittig proved to be satisfactory. Moreover, yields could be increased markedly by using the more active catalyst described by Henbest.[14]

All the *N,N'*-diaryl-1,3-propanediamines were transformed into the corresponding 1,2-diarylpyrazolidines with two exceptions. Firstly, *N,N'*-di-*p*-methoxyphenyl-1,3-propanediamine afforded 4,4'-azoanisole. This type of reaction has been

(1) This paper represents part of a thesis submitted by Bruce D. Martin to the Graduate College of the University of Illinois, 1959, in partial fulfillment of the requirements for the degree of Master of Science. This work was supported in part by a grant from the Research Board of the Graduate College of the University of Illinois, Grant No. 55-92-32.

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