Pyridazines VIII. Some 6-Aryl-3-(basically-substituted) Pyridazines (1)

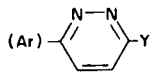
Edgar A. Steck (2a), R. Pauline Brundage, and Lynn T. Fletcher (2b)

Sterling-Winthrop Research Institute, Rensselaer, New York 12144

Received June 9, 1975

A number of years ago, work was completed (3) on a series of pyridazine derivatives intended for evaluation of chemotherapeutic and pharmacologic effects (*cf.* 1, 4 for recent publications of our studies). Among the diverse representatives readily accessible (5,6), 6-aryl pyridazines bearing a basic substitutent at position 3 were selected for this phase of investigation. Subsequent to completion of our syntheses, others (7-11) have also been attracted to such series, however there has been no obvious overlap of efforts. Certain representatives have been claimed (8-11) to exert valuable pharmacological effects, especially upon the central nervous system.

The compounds selected as targets for this work had the general structure I. As indicated below, the greater number prepared had terminal diethylamino groupings, for common denominator among the basically-substituted series of pyridazines. The functional groupings at position 6 was ordinarly an aryl function, however, the 2-thienyl type of heteraryl moiety was also employed.



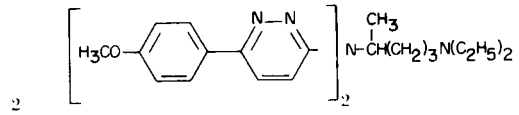
I

Ar = aryl; heteraryl

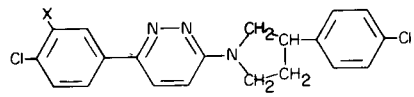
(a) Y = $OCH_2CH_2N(C_2H_5)_2$

(b) Y = amino; dialkylamino; or diethylaminoalkylamino group

A common intermediate was required for both the 6-aryl-3-(2-diethylaminoethoxy)pyridazines and those bearing an amino-derived function at position 3. This was the related 6-aryl-3-chloropyridazine. Preparation of those compounds by action of phosphorus oxychloride upon 6-substituted 3(2*H*)pyridazones is well known (5,6,12). Table I summarizes pertinent data on the intermediates used in this work. Interaction of the chloro compounds with sodium 2-diethylaminoethoxide in xylene (*cf.* 1) readily afforded the 6-aryl-3-(2-diethylaminoethoxy)-pyridazines assembled in Table II. The intermediate chloro compounds and nitrogenous bases were caused to react at elevated temperatures to give the series chiefly summarized in Table III. In certain instances, reactions of the 6-aryl-3-chloro pyridazines with N^4,N^4-diethylputrescine types in phenol melt (*cf.* 13) gave rise to products not anticipated. Thus, 3-chloro-6-(4-methoxyphenyl)pyridazine and 5-diethylamino-2-pentylamine provided both the expected compound and the *bis* type, II. In the case of 3-chloro-6-(2-thienyl)pyridazine and the same base, only the *bis* compound corresponding to II resulted in appreciable yield. Entirely unexpected, however, were the products of reactions (in phenol) of 2-(4-chlorophenyl)-4-diethylamino-butylamine with 3-chloro-6-(4-chlorophenyl)pyridazine and the related 6-(3,4-dichlorophenyl) compound. In those cases, there was loss of diethylamine, leading to isolation of appreciable yields of the 6-aryl-3-[3-(4-chlorophenyl)-1-pyrrolidinyl]pyridazines, III and IV.



II



III X = H

IV X = Cl

EXPERIMENTAL (14)

Intermediates.

Requisite 6-aryl-3(2*H*)pyridazones were prepared during the course of our previous work, as recently reported (4).

2-(4-Chlorophenyl)-4-diethylaminobutylamine was synthesized after the method of Kwartler and Lucas (15,16).

5-Diethylamino-2-pentylamine was a commercial sample, purified *via* the dithiocarbamate (17), and freshly distilled prior to use; b.p. 71-72° (6 mm.), n_D^{25} 1.4415. Similarly, 3-diethylamino-2-hydroxypropylamine was a commercial product, redistilled immediately before use; b.p. 85-87° (0.5 mm), n_D^{25} 1.4654.

6-Aryl-3-chloropyridazines.

The 6-aryl-3(2*H*)pyridazones were converted into 6-aryl-3-chloropyridazines after the method of Gabriel and Colman (12).

Table I

6-Chloro-3-Substituted Pyridazines

6-Substituent	Appearance	Solvent (a)	M.p. °C	Yield, %	Formula	Analyses Calcd. C	H	N	Found C	H	N
4-Chlorophenyl	Needles	A	200-201	89	$C_{10}H_6Cl_2N_2$	53.36	2.69	12.45	53.06	2.65	12.64
3,4-Dichlorophenyl	Needles	aA	188-188.8	95	$C_{10}H_5Cl_3N_2$	42.68	1.94	10.79	42.06	1.72	10.54
4-Methoxyphenyl	Felted needles	aA	168.5-169	84.5	$C_{11}H_9ClN_2O$	59.87	4.11	16.07 (b)	59.88	3.87	15.89 (b)
3-Bromo-4-methoxyphenyl	Cottony needles	aD	195-195.5	86	$C_{11}H_8BrClN_2O$	44.10	2.69	9.35	44.04	2.52	9.41
3-Nitrophenyl	Yellowish needles	Hp	208-209	82	$C_{10}H_6ClN_3O_2$	50.97	2.57	17.83	50.71	2.59	17.70
2-Thienyl	Leaflets	aA	162-162.5	93	$C_8H_5ClN_2S$	48.84	2.56	16.30 (c)	48.58	2.43	16.30 (c)
5-Bromo-2-thienyl	Blades	aA	209.5-210	89	$C_8H_4BrClN_2S$	34.87	1.46	11.64 (c)	34.73	1.49	11.47 (c)

(a) Legend: A, ethanol; Cb, 2-methoxyethanol; Ch, cyclohexane; D, acetone; E, ether; H, hexane; Hp, heptane; iPr, propanol-2; M, methanol; Pe, pentane; a, aqueous. (b) Chlorine. Dumas values were not concordant. (c) Sulfur.

TABLE II

6-Substituted 3-(2-Diethylaminoethoxy) Pyridazines

6-Substituent	Base or Salt (a)	Appearance	M.p. °C	Solvent (b)	Yield, %	Formula	Analyses, % Calcd. N	Calcd. Ionic Halogen	Found N	Found Ionic Halogen
4-Methoxyphenyl	B	Platelets	50.5-51.5	Pe	89.7	$C_{17}H_{23}N_3O_2$	13.97	(c)	13.87	(c)
	2C	Creamy needles	138-139.5	A-E	99	$C_{17}H_{23}N_3O_2.2HCl$	11.23	18.95	11.14	18.94
	M	Needles	170-171	Me-E	91	$C_{18}H_{26}BrN_3O_2$	10.60	20.17	10.79	19.92
3,4-Dichlorophenyl	B	Nacreous plates	74-74.5	Pe	89.5	$C_{16}H_{19}Cl_2N_3O$	12.43	(d)	12.43	(d)
	C	Needles	159.5-160	iPr-E	94	$C_{16}H_{19}Cl_2N_3O.HCl$	11.95	9.41	12.06	9.46
	M	Needlets	196.5-197.5	A-E	99	$C_{17}H_{22}BrCl_2N_3O$	9.66	18.37	9.55	18.26
2-Thienyl	B	Golden oil	(e)		87.5	$C_{14}H_{19}N_3OS$	15.15	11.56 (f)	14.98	11.59 (f)
	C	Needles	143-144	A-E	91.5	$C_{14}H_{19}N_3OS.HCl$	13.39	11.30	13.64	11.25
	M	Needlets	199.5-200.5	A-E	84	$C_{15}H_{22}BrN_3OS$	11.29	21.47	11.50	21.20

(a) Legend: B, Base; C, hydrochloride; M, methobromide. (b) Legend, see Table I, footnote a. (c) *Anal.* Calcd. for $C_{17}H_{23}N_3O_2$: C, 67.75; H, 7.69. Found: C, 67.34; H, 7.89. (d) *Anal.* Calcd. for $C_{16}H_{19}Cl_2N_3O$: C, 56.48; H, 5.63. Found: C, 56.59; H, 5.39. (e) B.p. 160-162° (0.08 mm.). (f) Sulfur.

TABLE III

6-Amino-3-Substituted Pyridazine Types

6-Substituent	3-Substituent	Appearance	M.p. °C	Solvent (a)	Yield, %	Formula	Analyses, % Calcd. C	H	N	Found C	H	N
Phenyl	$NHCH(CH_3)CH_2CH_2CH_2N(C_2H_5)_2$	Leaflets		Hp	54.5	$C_{19}H_{28}N_4$	73.03	9.04	17.93	72.84	8.97	17.74
	$NHCH_2CH(OH)CH_2N(C_2H_5)_2$	Platelets		Hp	59	$C_{17}H_{24}N_4O$	67.97	8.05	18.65	68.24	7.96	18.68
4-Chlorophenyl	NH_2	Platelets	181.5-182	aA	88	$C_{10}H_8ClN_3$	58.40	3.92	20.44	58.55	3.87	20.84
	$N(CH_3)_2$	Blades	210-211	aA	82	$C_{12}ClN_3$	61.65	5.18	17.97	61.46	5.26	18.14
	$NHCH(CH_3)CH_2CH_2CH_2N(C_2H_5)_2$	Leaflets	124-125	H	64.5	$C_{19}H_{27}ClN_4$	65.80	7.85	16.16	65.98	7.75	15.98
	$NHCH_2CH(4\text{-}ClC_6H_4)CH_2N(C_2H_5)_2$	Needles	131.5-132.5	Ch	(b)	$C_{24}H_{31}Cl_2N_4$	65.01	6.36	12.64	65.05	6.28	12.67
4-Methoxyphenyl	$NHCH(CH_3)CH_2CH_2CH_2N(C_2H_5)_2$	Platelets	127.5-128.5	aD	(b)	$C_{20}H_{30}N_4O$	70.14	8.83	16.36	70.43	8.96	16.35
3-Nitrophenyl	NH_2	Yellow prisms	181-182	aCb	76.5	$C_{10}H_8N_4O_2$	55.56	3.73	6.48 (c)	55.82	3.83	6.50 (c)
2-Thienyl	$NCH(CH_3)CH_2CH_2CH_2N(C_2H_5)_2$	Platelets	104-105	Hp or H	68	$C_{17}H_{26}N_4S$	64.11	8.25	10.09 (d)	64.21	7.98	10.15 (d)

(a) Legend, see Table I, footnote a. (b) See Text. (c) Nitro nitrogen. (d) Sulfur.

In our cases, it was found expedient to take up the crude, precipitated chloro compounds in methylene chloride, wash with brine, dry the extracts (sodium sulfate), and remove the solvent.

Most of the compounds (Table I) were sufficiently volatile that sublimation was an adjunct to crystallization in obtaining analytically pure samples with minimal losses. 3-Chloro-6-phenyl pyridazine separated from heptane-ethanol as white leaflets, m.p. 162.5-163° [lit. (12), m.p. 160°].

6-Aryl-3-(2-diethylaminoethoxy)pyridazines.

The requisite 6-aryl-3-chloro pyridazines were caused to react with sodium 2-diethylaminoethoxide in xylene after the procedure described by us recently (4). The crude bases were purified either by distillation or crystallization, and then converted into hydrochlorides and methobromides. Pertinent data on the products are assembled in Table II.

3-(Amino-substituted)-6-arylpyridazines.

The 6-arylpyridazines bearing an amino or dimethylamino function at position 3- were prepared from the requisite 6-aryl-3-chloropyridazines by reaction with ammonia or dimethylamine in ethanolic solution at 150-170° for 8-10 hours. At the end of the heating, the solvent was stripped *in vacuo* and the residual solid merely crystallized from the appropriate solvent, as shown in Table III.

Conversion of the 6-aryl-3-chloro pyridazines into the 3-NHR types assembled in Table III was accomplished in phenol melt much after the method which we (13) applied to 4-chloroquinolines. Here, the 3-chloropyridazine type was dissolved in one and one-half times its weight of phenol at 100°, then a trace of powdered potassium iodide was added to the stirred mixture prior to running in a 100% excess of the diamine. The temperature was held at 100-125° for an half-hour, then raised to 160-165° in half-hour, heated at that temperature for 10 hours, cooled, quenched in a heavy slurry of ice in water. An excess of 35% sodium hydroxide solution was added and the organic bases taken into methylene chloride, then washed free of alkali with saturated brine. The bases were extracted with hydrochloric acid, and the acidic extracts treated with charcoal, clarified, the bases then liberated. The products were extracted with methylene chloride, washed (brine), dried over sodium sulfate, and the solvent removed. It was satisfactory to crystallize the crude residual bases directly. Table III summarizes data on the various compounds of the group, with yields given for products which had melting points within 5° of that found for analytically pure samples. In the earlier runs, detailed attention was not given to oily or gummy residues obtained from mother liquors from crystallizations. Subsequent work gave indication that the 6-aryl-3-chloro pyridazines not only produced the expected compounds of structure Ib, but also (*e.g.*) *N,N-bis*-(6-aryl-3-pyridazinyl)-5-diethylamino-2-pentylamines, as II.

Certain cases gave indication that the *bis* type formed a considerable share of total products. In two instances, however, an unexpected compound was the major substance resulting from use of 2-(4-chlorophenyl)-4-diethylaminobutylamine as the base.

6-(4-Chlorophenyl)-3-[2-(4-chlorophenyl)-4-diethylaminobutylamino]pyridazine and 6-(4-Chlorophenyl)-3-[3-(4-chlorophenyl)-1-pyrrolidinyl]pyridazine.

These were the products isolated from the interaction of 3-chloro-6-(4-chlorophenyl)pyridazine and 2-(4-chlorophenyl)-4-diethylaminobutylamine in phenol melt. In the work-up, a mixture was obtained after basification which was incompletely extractable with methylene chloride. The solid was combined with the extracts, and the solvent removed. The residual material was steam-distilled, and the still foots were extracted well with methylene chloride. A tan solid (A) and a golden brown solution (B) resulted. Fraction

(A) was converted to the hydrochloride, treated with charcoal in aqueous solution, and the base liberated. The solid (m.p. *ca.* 200°) was crystallized once from butanol and twice from chlorobenzene to give lemon yellow needles, m.p. 223-224°. On the basis of analyses, this fraction was 6-(4-chlorophenyl)-3-[3-(4-chlorophenyl)-1-pyrrolidinyl]pyridazine (structure III) of *ca.* 95% purity in a yield of *ca.* 20%. Two additional crystallizations from xylene afforded the pure compound as light yellow needles, m.p. 223.5-224°.

Anal. Calcd. for $C_{20}H_{17}Cl_2N_3$: C, 64.87; H, 4.63; Cl, 19.15; N, 11.35; N (basic), 3.78; Mol. wt., 370.3. Found: C, 64.88; H, 4.84; Cl, 19.33; N, 11.59; N (basic), 3.69; Mol. wt. (Rast, in camphor), 372.3.

Liquors from the first three crystallizations of (A) were steam distilled, and the residues extracted well with methylene chloride. The extracts were united with the methylene chloride fraction (B), dried and concentrated. A brownish gum resulted. The gum was dissolved in benzene, subjected to chromatography on alumina, and eluted with 2:5 benzene-hexane. A nearly white solid was obtained, m.p. *ca.* 130°. This represented a 37% yield of 6-(4-chlorophenyl)-3-[2-(4-chlorophenyl)-4-diethylaminobutylamino]pyridazine. To obtain analytically pure compound, it was necessary to charcoal the chromatographed material in methanol solution, clarify, strip the solvent, and recrystallize the residues from cyclohexane. Pertinent data on the compound are given in Table III.

3-[3-(4-Chlorophenyl)-1-pyrrolidyl]-6-(3,4-dichlorophenyl)pyridazine (IV).

This compound was the only pure product which could be isolated from the reaction of 3-chloro-6-(3,4-dichlorophenyl)-pyridazine with 2-(4-chlorophenyl)-4-diethylaminobutylamine in phenol melt. The mixture of crude bases in methylene chloride was not readily extractable with hydrochloric acid, hence that solvent was removed. Following steam distillation, the residues were extracted with methylene chloride and dried (sodium sulfate), then the solvent removed. The residual gum was taken into the minimal amount of boiling ethanol, and allowed to cool slowly. A yellowish solid (A) deposited from the golden liquors (B), and was collected. Two crystallizations of (A) afforded a 28% yield of 3-[3-(4-chlorophenyl)-1-pyrrolidinyl]-6-(3,4-dichlorophenyl)pyridazine in the form of creamy microcrystals, m.p. 151-152°. Analytically pure compound was obtained by crystallizing it once, each, from methanol and benzene. The snowy microcrystalline base melted 151.5-152.5°.

Anal. Calcd. for $C_{20}H_{16}Cl_3N_3$: C, 95.35; H, 3.99; Cl, 26.28; N, 10.38; N (basic), 3.46; Mol. wt., 404.5. Found: C, 59.01; H, 4.19; Cl, 26.38; N, 10.19; N (basic), 3.48; Mol. wt. (cryoscopic, benzene), 414.

The liquors from crystallization of the base were re-worked, and a further amount was reclaimed from the ethanolic liquors, (B). In such way, a total yield of 38% resulted. Thereafter, all gummy residues were united, chromatographed multiply on alumina in benzene solution, then crystallized repeatedly from acetone and from methanol. Only small amounts of white solid (m.p. 124-128°) could be won. Analyses were approximately those required for the above-mentioned base.

6-(4-Diethylamino-1-methylbutylamino)-3-(4-methoxyphenyl)-pyridazine and 4-Diethylamino-*N,N-bis*-[6-(4-methoxyphenyl)-3-pyridazinyl]-2-pentylamine.

These were the products isolated from the reaction of 3-chloro-6-(4-methoxyphenyl)pyridazine in phenol. The mixture of crude bases produced was taken up in methylene chloride, concentrated, and the viscous oil subjected to steam distillation to remove volatile amine. The still residues were extracted with methylene chloride, then the basic material removed by extraction with hydrochloric acid. The acidic extracts were basified in the cold, and the products taken into methylene chloride and dried (sodium sulfate). Upon removing the solvent, a brownish tar was left; that was dissolved in hot benzene and allowed to cool slowly. A yellowish solid (A) deposited from the brown liquors (B). The solid was crystallized four times from dilute aqueous acetone (charcoal) to give 6-(4-diethylamino-1-methylbutylamino)-3-(4-methoxyphenyl)pyridazine in 30.5% yield. Data on this compound are in Table III.

The benzene liquors (B) were combined with gummy residues left after re-working of mother liquors from crystallization of (A). Repeated chromatography on alumina gave an off-white solid which melted 107-109° and had analyses approximating those required for 5-diethylamino-*N,N-bis*-[6-(4-methoxyphenyl)-3-pyridazinyl]-2-pentylamine. The yield was 11.6%. Four crystallizations from heptane failed to provide analytically pure compound. Multiple passage through chromatographic columns (alumina; benzene as solvent) afforded the pure base following crystallization of eluted material from heptane, benzene, and then benzene-heptane. It formed shimmering white platelets, m.p. 111-111.5°.

Anal. Calcd. for $C_{31}H_{38}N_6O_2$: C, 70.69; H, 7.27; N, 15.97. Found: C, 70.90; H, 6.99; N, 15.86.

N,N-bis-[6-(5-Bromo-2-thienyl)-3-pyridazinyl]-2-pentylamine.

This was the only discrete product isolated from the reaction (in phenol melt) of 6-(5-bromo-2-thienyl)-3-chloropyridazine with 4-diethylamino-1-methylbutylamine. The mixture of crude bases was freed of volatiles by steam distillation, the residual material taken into methylene chloride, and extracted well with concentrated hydrochloric acid. The acidic liquors were charcoaled well, chilled, basified, and extracted with methylene chloride afresh. Solvent was removed from the dried (sodium sulfate) extracts and the oily product triturated with pentane at -20° to obtain workable solid, which was then dissolved in benzene and chromatographed on alumina. Multiple crystallizations of the eluate from heptane gave the above-named base in 28.5% yield. It formed pale yellow, warty aggregates of fine needles which melted 131.5-132°. Careful re-working of the tailings afforded small additional amounts of the same compound, only.

Anal. Calcd. for $C_{25}H_{28}Br_2N_6S_2$: C, 47.17; H, 4.43; S, 10.08. Found: C, 47.38; H, 4.59; S, 10.02.

Acknowledgment.

The authors are pleased to have had the advantages which accrued from the patience and skill of the staff of the Analytical Laboratories of this Institute (under the direction of Mr. M. E. Auerbach and Mr. K. D. Fleischer), who performed all determinations here reported.

REFERENCES

(1) Prior contribution: E. A. Steck and L. T. Fletcher, *J. Heterocyclic Chem.*, 11, 1077 (1974).

(2) Present addresses: a) Division of Medicinal Chemistry, Walter Reed Army Institute of Research, Walter Reed Army Medical Center, Washington, D. C. 20012; b) Hilton-Davis Division of Sterling Drug, Inc., Cincinnati, Ohio 45237.

(3) This contribution is based upon investigations done during 1955-1957, and originally reduced to writing in 1957. A variety of circumstances precluded release of the manuscript and its revision until now. The entire has been modified to include more recently published studies (1,4-11).

(4) E. A. Steck, R. P. Brundage, and L. T. Fletcher, *J. Hetero-*

cyclic Chem., **11**, 755 (1974).

(5) M. Tišler and B. Stanovik, "Advances in Heterocyclic Chemistry" (A. R. Katritzky and A. J. Moulton, editors), Vol. 9, Academic Press, Inc., New York, 1968, p. 211.

(6) R. N. Castle, Ed., "Pyridazines", Wiley-Interscience Publishers, Inc., New York, 1973.

(7) N. B. Chapman, K. Clarke, and K. Wilson, *J. Chem. Soc.*, 2256 (1963).

(8) I. Zugravescu, M. Petrovanu, and E. Rucinschi, *Rev. Chim. Acad. Rep. Populaire Roumaine*, 7, 1405 (1962); [*Chem. Abstr.*, 61, 70093 (1964)].

(9) H. Laborit, German Patent, 1954 838 (23 July 1970); [*Chem. Abstr.*, 73, 77266 (1970)].

(10) Centre d' Études Experimentales et Clinique de Physio-Biologie de Pharmacologie et d' Eutonologie, Belgian Patent, 784 727 (2 October 1972); [*Derwent Belgian Patents Report*, 1972, week T-51, section B, page 6. Derwent Publications, Ltd., London].

(11) H. Laborit, S. African Patent 73/00671 (19 September 1973); [*Chem. Abstr.*, **81**, 13 541 (1974)].

(12) S. Gabriel and J. Colman, *Ber.*, **32**, 400 (1899).

(13) E. A. Steck, L. L. Hallock, and A. J. Holland, *J. Am. Chem. Soc.*, **68**, 129 (1946).

(14) All melting points were determined in Pyrex capillary tubes, in an electrically heated bath. They were immersed 10° below the apparent melting point, and heated at 1° per minute thereafter. Melting points so determined were corrected values, while boiling points were those observed during distillations.

(15) C. E. Kwartler and P. Lucas, *J. Am. Chem. Soc.*, **68**, 2395 (1946).

(16) C. E. Kwartler and P. Lucas, U. S. Patent, 2,530,126 (14 November 1950).

(17) R. G. Jones, U.S. Patent, 2,400,934 (28 May 1946).