5-Aryl-1,3-dihydro-2H-pyrido-1,4-diazepin-2-ones

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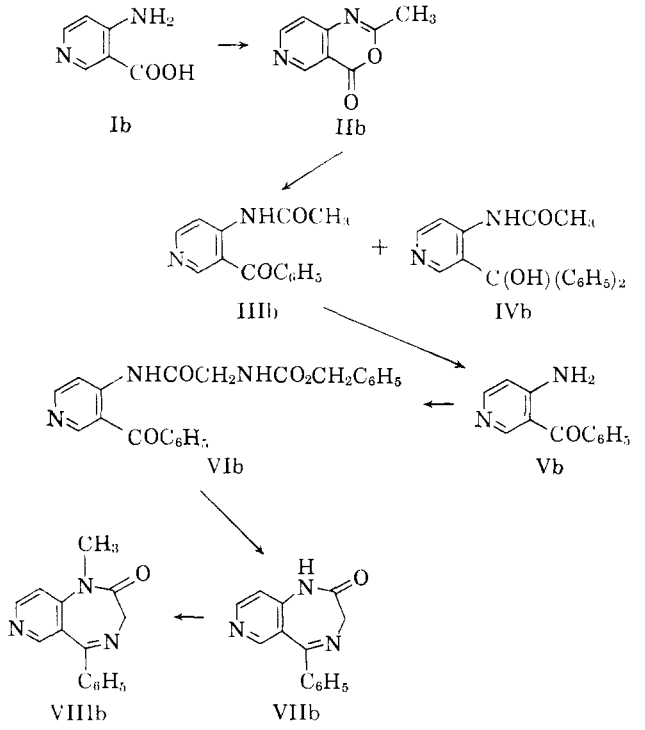
In recent years members of the 1,4-benzodiazepine class of compounds have generated considerable interest as psychotherapeutic agents.[1] Since an electronegative substituent at position 7 appears to be required for high potency,[1] it was decided to prepare certain electronically analogous pyrido[4,3-*e*]-1,4-diazepines. This note describes the preparation of these compounds (Chart I), three other isomeric pyrido-1,4-diazepin-2-ones, and the corresponding intermediates.



The most feasible route to the intermediate aminobenzoylpyridines from available starting materials appeared to be the Grignard synthesis.[2,3] Thus condensation of the appropriate aminopyridinecarboxylic acids I with acetic anhydride afforded the corresponding 2-methyl-4H-pyrido[1,3]oxazin-4-ones II (Table I). Treatment of II with arylmagnesium bromide in ether gave the desired acetamidobenzoylpyridines III (Table II) and, in three of the four isomeric series, the expected[3] acetamido-α,α-diphenylpyridinemethanol byproducts IV (Table III). In one series a third product, ethyl 3-acetamidopicolinate,[4] was isolated in low yield by adsorption chromatography as the most polar eluate. This type of abnormal reaction of a Grignard-ether complex with an oxazinone has been previously observed when, during the reaction of 6-chloroacetanthranil[5] with methylmagnesium iodide, ethyl 5-chloroanthranilate[6] was found as a minor by-product.[7] The acetamides were readily hydrolyzed with acid[3] to the primary amines V (Table II) and IVe (Table III).

Conversion of the aminobenzoylpyridines V to the pyridodiazepin-2-ones VII was first attempted by condensation with ethyl glycinate hydrochloride in refluxing pyridine.[8] This method gave discouraging results on the substituted pyridines as did acylation with chloroacetyl chloride[8] or chloroacetic anhydride. However, the carbobenzoxyglycyl derivatives VI[9] were easily formed by the method of Sheehan and Hess[10] and converted by treatment with hydrogen bromide in acetic acid to the aminoacetamidobenzoylpyridines. The latter compounds were cyclized without characterization to the corresponding pyridodiazepin-2-ones VII (Table IV). Methylation of VIIa and VIIb with iodomethane and potassium *t*-butoxide gave the desired 1-methyl compounds VIIIa and VIIIb.

Pharmacology.—Representative compounds were tested for central nervous system depressant properties.[11] Compound VIIIb had pharmacological effects in mice similar to but less pronounced than those of diazepam.[12] Compound VIIIb caused locomotor ataxia (inability to walk across a horizontal rod) and showed anticonvulsant action (corneal electroshock) at low dose levels. Higher doses were required to elicit a paralytic effect (inability to remain on an inclined screen and loss of righting reflex).

Experimental[13,14]

The procedures given in the Experimental for the preparation of IIb through VIIIb can be considered, with minor variations, as representative of the methods used for the preparation of the other members of the series.

2-Methyl-4H-pyrido[4,3-*d*][1,3]oxazin-4-one (IIb).—A solution of 2.0 g. of 4-aminonicotinic acid (Ib) in 10 ml. of acetic anhydride was heated at reflux for 2 hr. during which time 40 ml. of solvent was removed by distillation. Upon evaporation, the brown residue was dissolved in ethyl acetate and passed through a column containing 50 g. of Florisil.[15] The eluate was concentrated and, upon the addition of ether, 1.9 g. of the pyridooxazin-

(1) S. J. Childress and M. I. Gluckman, *J. Pharm. Sci.*, **53**, 577 (1964), and references cited therein.

(2) W. C. Lothrop and P. A. Goodwin, *J. Am. Chem. Soc.*, **65**, 363 (1943).

(3) L. H. Sternbach, R. I. Fryer, W. Metlesics, G. Sach, and A. Stempel, *J. Org. Chem.*, **27**, 3781 (1962).

(4) D. Harrison and A. C. B. Smith, *J. Chem. Soc.*, 2157 (1960).

(5) A. J. Tomisek and R. E. Christensen, *J. Am. Chem. Soc.*, **70**, 2423 (1948).

(6) D. Baciana, H. Sachdeo, and K. Narang, *J. Indian Chem. Soc.*, **32**, 644 (1955).

(7) Unpublished results from this laboratory.

(8) L. H. Sternbach, R. I. Fryer, W. Metlesics, E. Reeder, G. Sach, G. Saucy, and A. Stempel, *J. Org. Chem.*, **27**, 3788 (1962).

(9) Only one carbobenzoxyglycyl derivative VIb was characterized. The others were used without extensive purification for the next step.

(10) J. C. Sheehan and G. P. Hess, *J. Am. Chem. Soc.*, **77**, 1067 (1955).

(11) Dr. A. C. Osterberg, Experimental Therapeutics Research Section, Lederle Laboratories, personal communication.

(12) Valium®, 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one.

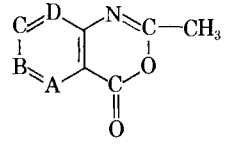
(13) All melting points are uncorrected and were determined in open soft-glass capillaries. Extracts were dried ($MgSO_4$) and evaporated under reduced pressure on a rotary evaporator. Sublimations were carried out at 0.05 mm. All compounds shown in Tables I, II, III, and IV were examined by ultraviolet, infrared, and, except for VIIf and compounds in Table I, n.m.r. spectroscopy. Ultraviolet spectra were determined in methanol using a Cary recording spectrophotometer. Infrared spectra were determined in KBr disks on a Perkin-Elmer spectrophotometer (Model 21).

(14) Thin layer chromatography on silica gel was used in all phases of this work. The plates were prepared containing 0.5% phosphor Type P-1 (U. S. Radium Corp.) and the products were detected by ultraviolet scan at 2540 Å. The solvent systems used were heptane–ethyl acetate (1:1) and benzene–acetone–water (2:1:2 and 1:2:2).

(15) A brand of synthetic magnesium silicate. That used was 60–100 mesh size.

TABLE I

2-METHYL-4H-PYRIDO[1,3]OXAZIN-4-ONES

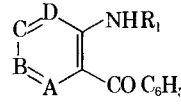


No.	A	B	C	D	M.p., °C.	Recrystn.[a] solvent	% yield	Formula	% calcd. C	% calcd. H	% calcd. N	% found C	% found H	% found N
IIa	N	CH	CH	CH	108–112	A–P[b]	50	$C_8H_6N_2O_2$	59.26	3.73	17.28	59.3	3.60	17.6
IIb	CH	N	CH	CH	156–159	A–P[b]	70	$C_8H_6N_2O_2$	59.26	3.73	17.28	58.9	3.93	17.4
IIc	CH	CH	N	CH	99–102	A–P[b]	64	$C_8H_6N_2O_2$	59.26	3.73	17.28	59.0	3.86	17.3
IId	CH	CH	CH	N	176–180	B[b]	94	$C_8H_6N_2O_2$	59.26	3.73	17.28	59.3	3.92	17.3

[a] A = ethyl acetate, B = benzene, P = heptane. [b] Specimen prepared for analysis by sublimation.

TABLE II

AMINOBENZOYLPYRIDINES

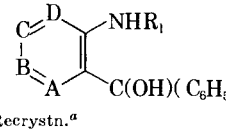


No.	A	B	C	D	R_1	M.p., °C.	Recrystn.[a] solvent	% yield	Formula	% calcd. C	% calcd. H	% calcd. N	% found C	% found H	% found N
IIIa	N	CH	CH	CH	Ac	110–112	C–P[b]	23	$C_{14}H_{12}N_2O_2$	69.99	5.03	11.66	69.9	5.17	11.9
IIIb	CH	N	CH	CH	Ac	82–83	E–H	43	$C_{14}H_{12}N_2O_2$	69.99	5.03	11.66	69.8	5.19	11.5
IIIc	CH	CH	N	CH	Ac	123–125	T–P	39	$C_{14}H_{12}N_2O_2$	69.99	5.03	11.66	70.2	5.17	11.7
IIId	CH	CH	CH	N	Ac	137–139	E	27	$C_{14}H_{12}N_2O_2$	69.99	5.03	11.66	69.8	5.19	11.4
Va	N	CH	CH	CH	H	99–101	E–H[b]	80	$C_{12}H_{10}N_2O$	72.71	5.09	14.13	72.5	5.35	13.6
Vb	CH	N	CH	CH	H	159–162	C–H	96	$C_{12}H_{10}N_2O$	72.71	5.09	14.13	72.3	4.91	13.8
Vc	CH	CH	N	CH	H	126–128	E–H	*Ca.* 100	$C_{12}H_{10}N_2O$	72.71	5.09	14.13	71.7	4.95	14.0
Vd	CH	CH	CH	N	H	145–148[c]	D–H	*Ca.* 100	$C_{12}H_{10}N_2O$	72.71	5.09	14.13	72.5	5.06	14.3
VIb	CH	N	CH	CH	$COCH_2NHCOOCH_2C_6H_5$	84–87	M–W	80	$C_{22}H_{19}N_3O_4 \cdot 0.33CH_3OH$[d]	67.04	5.12	10.51	67.0	5.24	10.3

[a] E = ether, H = hexane, T = toluene, P = heptane, C = chloroform, D = dichloromethane, W = water, M = methanol. [b] Specimen prepared for analysis by sublimation. [c] A. Kirpal, [*Monatsh.*, **27**, 371 (1906)] reported m.p. 145° from water. [d] $0.3CH_3OH$ observed on n.m.r. spectrum.

TABLE III

AMINO-α,α-DIPHENYLPYRIDINEMETHANOLS



No.	A	B	C	D	R_1	M.p., °C.	Recrystn.[a] solvent	% yield	Formula	% calcd. C	% calcd. H	% calcd. N	% found C	% found H	% found N
IVa	N	CH	CH	CH	Ac	167–169	C–P[b]	19	$C_{20}H_{18}N_2O_2$	75.45	5.70	8.80	75.0	5.76	8.76
IVb	CH	N	CH	CH	Ac	212–214	C–H	5	$C_{20}H_{18}N_2O_3$	75.45	5.70	8.80	76.0	5.87	8.88
IVd	CH	CH	CH	N	Ac	190–192	D–H	14	$C_{20}H_{18}N_2O_2$	75.45	5.70	8.80	74.7	5.12	8.40
IVe	CH	CH	CH	N	H	142–144	C–P[b]	58	$C_{18}H_{16}N_2O$	78.23	5.84	10.14	77.8	5.93	10.3

[a] C = chloroform, P = heptane, H = hexane, D = dichloromethane. [b] Specimen prepared for analysis by sublimation.

TABLE IV
1,3-DIHYDRO-5-ARYL-2H-PYRIDO-1,4-DIAZEPIN-2-ONES

No.	A	B	C	D	R_1	R_2	M.p., °C.	Recrystn.[a] solvent	% yield	Formula	% calcd. C	% calcd. H	% calcd. N	% found C	% found H	% found N
VIIa	N	CH	CH	CH	H	H	207–209	M–T[b]	58[c]	$C_{14}H_{11}N_3O$	70.87	4.67	17.71	71.0	5.16	17.6
VIIb	CH	N	CH	CH	H	H	195–197	C–H	50[c]	$C_{14}H_{11}N_3O$	70.87	4.67	17.71	70.6	4.68	17.6
VIIc	CH	CH	N	CH	H	H	258–260	M–B	64[c]	$C_{14}H_{11}N_3O$	70.87	4.67	17.71	70.5	4.69	17.7
VIId	CH	CH	CH	N	H	H	203–205	C–H[b]	26[c] (45)[d]	$C_{14}H_{11}N_3O$	70.87	4.67	17.71	71.0	4.72	17.7
VIIe	CH	N	CH	CH	H	CF_3	233–235	M–B	32[c]	$C_{15}H_{10}F_3N_3O$[f]	59.02	3.30	13.77	59.0	3.80	14.4
VIIIa	N	CH	CH	CH	CH_3	H	182–184	C–H	69	$C_{15}H_{13}N_3O$	71.69	5.21	16.72	71.6	5.52	16.3
VIIIb	CH	N	CH	CH	CH_3	H	142–143	E–H[b]	54	$C_{15}H_{13}N_3O$	71.69	5.21	16.72	71.4	5.26	17.2

[a] M = methanol, T = toluene, C = chloroform, H = hexane, B = benzene, E = ether. [b] Specimen prepared for analysis by sublimation. [c] From the aminobenzoylpyridine V. [d] Based on recovered starting material. [e] The intermediates IIIf and Vf were not characterized. [f] *Anal.* Calcd.: F, 18.67. Found: F, 19.4.

4-one IIb was obtained as pale orange crystals, m.p. 157–159°. The sample for analysis was prepared by sublimation to give colorless crystals: m.p. 156–159°; λ_{max} 215, 222, 245, and 288 mμ (ε 29,000, 28,200, 6800, and 2400) and 5.67 μ.

4-Acetamido-3-benzoylpyridine (IIIb).—To a suspension of 2.2 g. (13.6 mmoles) of 2-methyl-4H-pyrido[4,3-*d*][1,3]oxazin-4-one (IIb) in 30 ml. of dry benzene and 15 ml. of ether at 0° was added 5.0 ml. (15 mmoles) of phenylmagnesium bromide (3 *M* in ether) dropwise over 1.5 hr. The mixture was allowed to warm to room temperature and was stirred overnight. Upon cooling to 0° again, 15 ml. of 2 *N* HCl was added dropwise with stirring. The mixture was diluted with ethyl acetate and neutralized with saturated $NaHCO_3$, and the organic layer was washed with 2 *N* NaOH and with saturated saline. Upon evaporation, 2.2 g. of a yellow oil was obtained which was chromatographed on 250 g. of silica gel. Elution with ether–dichloromethane (2:3) gave 1.4 g. of solid which, upon crystallization from ether–hexane, gave 1.02 g. of pure IIIb: m.p. 82–83°; λ_{max} 229 and 257 mμ (ε 21,200 and 15,800), 5.79 and 6.12 μ.

Further elution with ether–dichloromethane (1:1) gave 200 mg. of solid which was recrystallized from chloroform–hexane to give **4-acetamido-α,α-diphenyl-3-pyridinemethanol (IVb)**, m.p. 212–214°, λ_{max} 250 mμ (ε 15,000) and 5.85 μ.

4-Amino-3-benzoylpyridine (Vb).—A solution of 700 mg. of 4-acetamido-3-benzoylpyridine (IIIb) in 10 ml. of ethanol and 10 ml. of 6 *N* HCl was heated at reflux for 2 hr., cooled, diluted with water, and neutralized with NH_4OH. Filtration gave 560 mg. of Vb, m.p. 157–160°. Crystallization from chloroform–hexane gave colorless needles: m.p. 159–162°; λ_{max} 228, 244, and 312 mμ (ε 24,000, 13,100, and 5500) and 6.14 μ.

4-[α-Carbobenzoxamidoacetamido)-3-benzoylpyridine (VIb).—A solution of 460 mg. (2.2 mmoles) of N,N′-dicyclohexylcarbodiimide in 1 ml. of dichloromethane was added to a solution of 460 mg. (2.2 mmoles) of carbobenzoxyglycine and 396 mg. (2.0 mmoles) of 4-amino-3-benzoylpyridine (Vb) in 3 ml. of tetrahydrofuran. The mixture was stirred at room temperature for 5 hr., then filtered to remove 450 mg. of N,N′-dicyclohexylurea. The filtrate was evaporated and the oily residue was chromatographed on 20 g. of silica gel. Elution with ether–dichloromethane (1:4) gave 625 mg. of VIb as colorless crystals, m.p. 84–86°. The analytical specimen, m.p. 84–87°, was obtained by crystallization from methanol–water; λ_{max} 5.85 and 6.10 μ.

1,3-Dihydro-5-phenyl-2H-pyrido[4,3-*e*]-1,4-diazepin-2-one (VIIb).—To a flask containing 525 mg. of 4-[α-carbobenzoxamidoacetamido)-3-benzoylpyridine (VIb) was added 6 ml. of a saturated solution of HBr in acetic acid. The mixture was warmed to 50° to effect solution, then stirred at room temperature for 1 hr. and concentrated under reduced pressure. Addition of ether gave a pasty solid which was filtered, dissolved in 10 ml. of 75% aqueous methanol, and neutralized with NH_4OH. The solvents were evaporated and the residue was heated in refluxing toluene for 3 hr. Upon evaporation of the solvent, 300 mg. of a green oil was obtained which was chromatographed on 20 g. of silica gel. Elution with ether gave 160 mg. of VIIb, m.p. 194–196°. Crystallization from chloroform–heptane gave the analytical specimen: m.p. 195–197°; λ_{max} 222 and 248 mμ (sh) (ε 31,200 and 18,000) and 5.90 μ.

1,3-Dihydro-1-methyl-5-phenyl-2H-pyrido[4,3-*e*]-1,4-diazepin-2-one (VIIIb).—A solution of 5.0 mmoles of potassium *t*-butoxide in 50 ml. of *t*-butyl alcohol was added to a suspension of 1.1 g. (4.7 mmoles) of 1,3-dihydro-5-phenyl-2H-pyrido[4,3-*e*]-1,4-diazepin-2-one (VIIb) in 20 ml. of *t*-butyl alcohol, and the mixture was stirred for 15 min. Complete solution occurred upon addition of the base. Methyl iodide (3 ml.) was added, and the mixture was stirred for an additional 3 hr. and filtered, and the filtrate was evaporated. The oily residue was dissolved in dichloromethane and chromatographed on 100 g. of silica gel. Elution with ethyl acetate–ether (1:3) gave, after crystallization from ether–hexane, 635 mg. of colorless crystals, m.p. 141–144°. The sample for analysis was prepared by sublimation at 110° to give m.p. 142–143°; λ_{max} 228 and 250 mμ (sh) (ε 25,100 and 17,000) and 5.97 μ.

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