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Nonsteroidal Antiinflammatory Agents. IV.¹⁾ Syntheses of Pyridobenzoxepin, Pyridobenzothiepin and Their Acetic Acid Derivatives

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As part of a search for new antiinflammatory agents, some new tricyclic compounds and their acetic acid derivatives were prepared. Pyrido[2,3-*c*][1]benzoxepin-5(11H)-one (**4a**) and pyrido[3,2-*c*][1]benzoxepin-11(5H)-one (**10a**) and their thiepin analogs (**4b**, **10b**) were synthesized by cyclization of the corresponding pyridinecarboxylic acid derivatives (**3a**, **3b**, **9a** and **9b**) with polyphosphoric acid (PPA). The acetic acid derivatives (**12a—b**) of **4a—b** were prepared *via* methyl derivatives (**14a—b**) of **4a—b**. Their antiinflammatory activities were less potent than those of the corresponding dibenz[*b,e*]oxepin- and dibenz[*b,e*]thiepinacetic acids.

Keywords—antiinflammatory; pyrido[2,3-*c*][1]benzoxepin-5(11H)-one; pyrido[2,3-*c*][1]benzothiepin-5(11H)-one; pyrido[3,2-*c*][1]benzoxepin-11(5H)-one; pyrido[3,2-*c*][1]benzothiepin-11(5H)-one; acetic acid derivatives; cyclization

We have previously reported the preparations and high antiinflammatory activities of 6,11-dihydro-11-oxodibenz[*b,e*]oxepinacetic acids (A, Fig. 1).²⁾ Thienobenzothiepin and thienobenzoxepin analogs (B, Fig. 1),¹⁾ prepared as bioisosteric derivatives, also exhibited similar activities.³⁾

This paper describes the syntheses of some bioisosteric compounds such as the acetic acid derivatives of pyrido[2,3-*c*][1]benzoxepin-5(11H)-one (**4a**) and its thiepin analog (**4b**) (see Chart 1) and pyrido[3,2-*c*][1]benzoxepin-11(5H)-one (**10a**) and its thiepin analog (**10b**) (see Chart 2).

Protiva *et al.*⁴⁾ have reported unsuccessful attempts to synthesize the tricyclic compounds (**4b** and **4c**) from 2-(phenylthiomethyl)- and 2-[(3-methoxyphenyl)thiomethyl]pyridine-3-carboxylic acid (**3b** and **3c**) by cyclization with polyphosphoric acid (PPA) (see Chart 1). Initial studies were therefore directed toward the preparation of these ring systems.

Pyrido[2,3-*c*]benzoxepin-5(11H)-one (**4a**) and -thiepin (**4b**)

The intermediates, 2-(phenoxymethyl)pyridine-3-carboxylic acid (**3a**) and **3b**, were readily prepared by treatment of ethyl 2-(bromomethyl)pyridine-3-carboxylate (**1**)⁵⁾ with phenol and thiophenol, respectively, followed by alkaline hydrolysis.

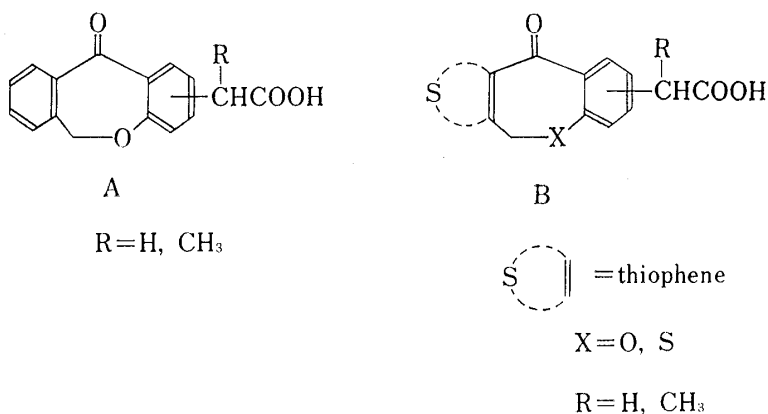


Fig. 1

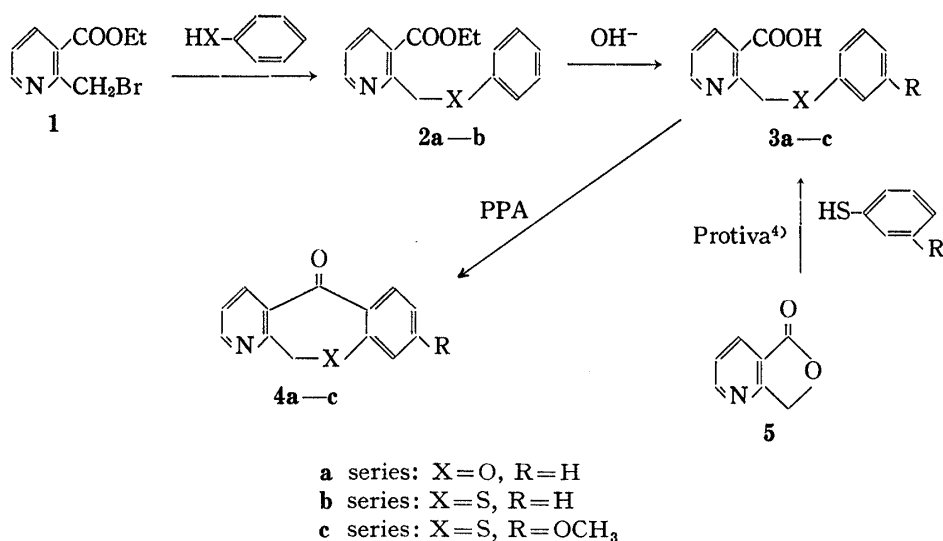


Chart 1

The carboxylic acids (**3a, b**) were heated with a large excess of PPA to give **4a, b**, respectively, in satisfactory yields. Other attempts to obtain **4a—b**, by cyclization of **3a—b** using polyphosphate ester (PPE) under various conditions, and conversion of **3a—b** to the acid chloride with SOCl_2 or PCl_5 followed by cyclization with aluminum chloride, were unsuccessful.

The structure of **4a** was confirmed by the following spectral data and elemental analysis. The infrared (IR) spectrum showed an absorption at 1644 cm^{-1} due to the C=O group between the benzene and pyridine nuclei. The nuclear magnetic resonance (NMR) spectrum (CDCl_3) exhibited signals at δ 5.37 (2H, s), 7.06—7.68 (4H, m), 8.18—8.40 (2H, m) and 8.75 (1H, dd, $J=1.5$ and 4.5 Hz) due to $\text{C}_{11}\text{-H}$, $\text{C}_{3,7-9}\text{-H}$, $\text{C}_{4,6}\text{-H}$, and $\text{C}_2\text{-H}$, respectively. The structure of **4b** was similarly confirmed.

The cyclization of **3b** with PPA, in an amount less than 5 times that of **3b**, was unsuccessful giving only resinous substances. The failure of the cyclization reaction reported by Protiva *et al.*, mentioned above, can be attributed to the use of an insufficient amount of PPA.

Pyrido[3,2-c][1]benzoxepin-11 (5H)-one (10a) and -thiepin (10b)

The reaction of 2-cyano-3-methylpyridine (**6**)⁶⁾ with N-bromosuccinimide (NBS) afforded unstable 3-(bromomethyl)-2-cyanopyridine (**7**), which, without purification, was condensed with phenol or thiophenol to give 2-cyano-3-(phenoxyethyl)- or 2-cyano-3-(phenylthioethyl)pyridine (**8a** or **8b**). Alkaline hydrolysis of **8a—b** gave 3-(phenoxyethyl)- and 3-(phenylthioethyl)pyridine-2-carboxylic acid (**9a—b**). The compound (**9a**) thus produced

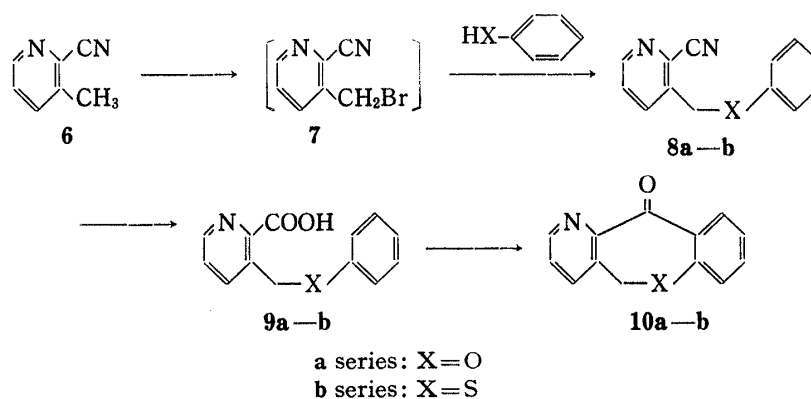


Chart 2

was heated with PPA, in an amount 50 times that of **9a**, at 180°C for 15 min giving the desired tricyclic compound (**10a**) in a poor yield (about 5%). A similar reaction of **9b** at 195°C for 1 h gave **10b**, also in a low yield (18%). The cyclization of **9a—b** under various conditions gave no better results and other attempts similar to those mentioned in connection with the cyclization of **3a—b** were also unsuccessful, giving only decomposed products. The yields of **10a—b** were lower than those of **4a—b**, probably due to greater lability of the carbonyl cations of **9a—b** in comparison with those of **3a—b**.

Syntheses of Acetic Acid Derivatives (**12a—b**)

The condensation of **1** with *p*-hydroxyphenylacetic acid followed by alkaline hydrolysis gave 2-[4-(carboxymethyl)phenoxy]methylpyridine-3-carboxylic acid (**11**). Attempted cyclization of **11** with PPA in a manner similar to that used for the preparation of **4a** was unsuccessful, giving only decomposed products. On the other hand, the synthetic route shown in Chart 3 provided satisfactory results.

The condensation of **1** with *p*-cresol or *p*-thiocresol followed by alkaline hydrolysis gave 2-[(4-methylphenoxy)methyl]- or 2-[(4-methylphenyl)thiomethyl]pyridine-3-carboxylic acid (**13a** or **13b**), which was cyclized in a manner similar to that used for the preparation of **4a—b** to give **14a—b** in satisfactory yields. Bromination of **14a—b** with NBS gave 7-(bromomethyl)-5,11-dihydro-5-oxopyrido[2,3-*c*][1]benzoxepin (**15a**, 25%) and 7-(bromomethyl)-5,11-dihydro-5-oxopyrido[2,3-*c*][1]benzothiepin (**15b**, 12%), respectively. In the latter case, 5,11-dihydro-11-hydroxy-7-methyl-5-oxopyrido[2,3-*c*][1]benzothiepine (**17**, 17%) was obtained and the

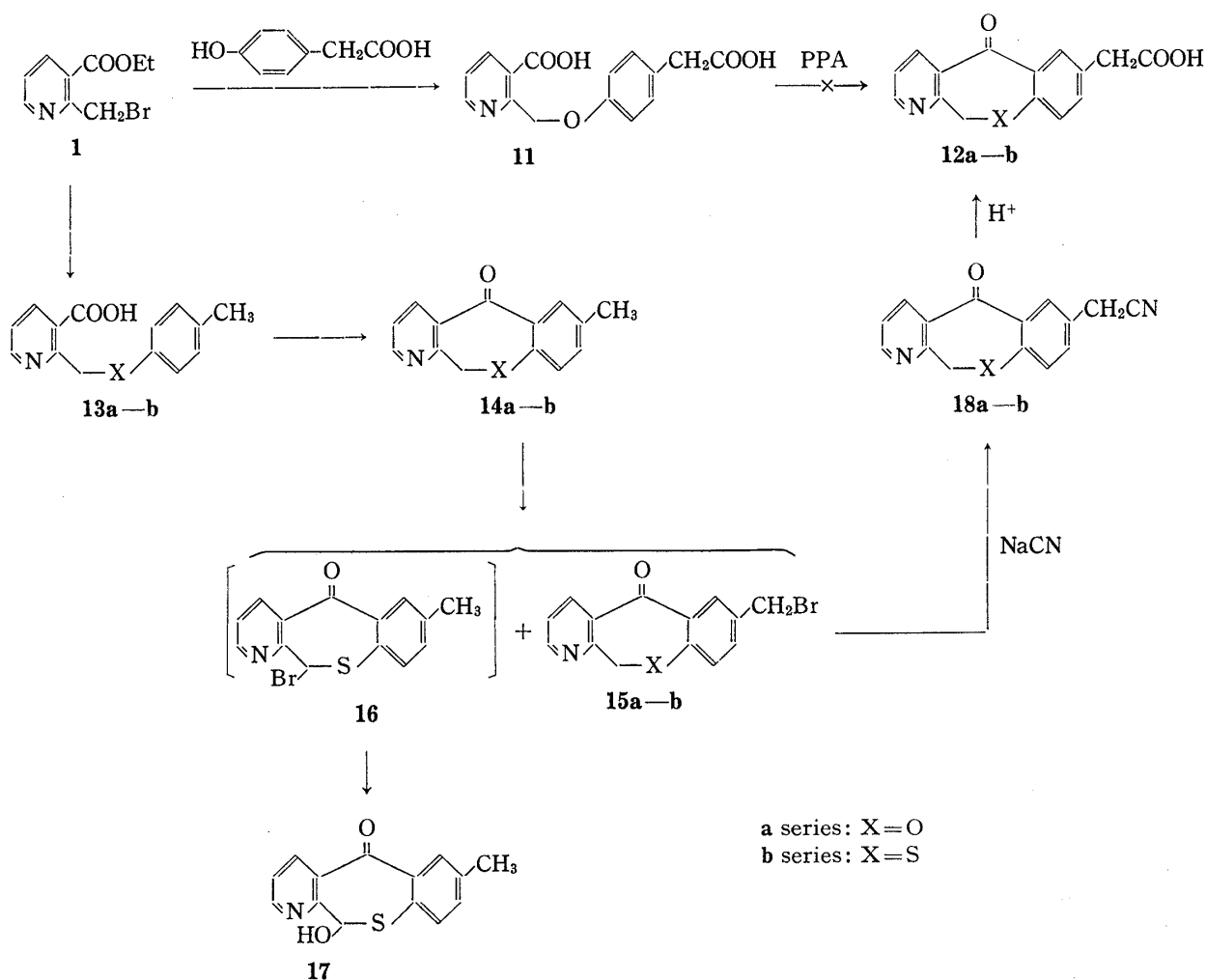


Chart 3

unchanged **14b** (60%) was recovered. Another bromination reaction of **14a** using bromine under illumination with a tungsten lamp also gave the desired **15a** in a moderate yield (42%) together with the unchanged **14a** (32%). A similar reaction of **14b** gave **17** (16%) together with the unchanged **14b** (65%), but the desired **15b** could not be isolated, although its presence in the reaction solution was detected by thin-layer chromatography (TLC).

The structure of **17** was confirmed by the following spectral data and elemental analysis. The IR spectrum showed absorptions at 3350 cm^{-1} (OH) and 1641 cm^{-1} (C=O). The NMR spectrum (CDCl_3) exhibited a signal at δ 5.93 (1H, s) due to a methine proton and no signal due to methylene protons.

The formation of **17** was assumed to be a result of bromination at the 11 position of **14b**, followed by the replacement of bromine with solvent. The oxepin compound corresponding to **17** was too unstable to be isolated.

The bromomethyl compounds (**15a—b**) were converted to the cyanomethyl compounds (**18a—b**) by reaction with NaCN. The alkaline hydrolysis of **18a—b** gave the desired acetic acid derivatives (**12a—b**).

The compounds (**12a—b**) exhibited significant antiinflammatory activities, but were less active than the corresponding dibenz[*b,e*]oxepin and -thiepinacetic acid derivatives (see Table I).

As the yields of **10a—b** from **9a—b** were poor and the antiinflammatory activities of **12a—b** were not as high as expected, no further work was done on the syntheses of acetic acid derivatives of **10a—b**.

TABLE I. Antiinflammatory Activities of Pyridobenzoxepin and Its Thiepin Analog

Compound	Antiinflam. act. ^{a)} (Carrageenan edema) ID ₅₀ , mg/kg, P.O.
12a	44
12b	>44 ^{c)}
6,11-Dihydro-11-oxodibenz[<i>b,e</i>]oxepin-2-acetic acid ^{b)}	14.3
6,11-Dihydro-11-oxodibenz[<i>b,e</i>]thiepin-2-acetic acid ^{b)}	44.4

a) Antiinflammatory activities were measured according to the method described in Part I.²⁾

b) This compound was synthesized according to Japan. Patent.⁷⁾

c) Compound **12b** showed 34% inhibition of edema at a dose of 44 mg/kg.

Experimental

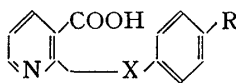
The following instruments were used. IR spectra, a Hitachi 285 spectrophotometer; NMR (tetramethylsilane as the internal standard), Hitachi R-20B spectrometer (60M Hz); melting points, a Yanagimoto melting point apparatus (all melting points are uncorrected).

For column chromatography, silica gel (Merck, 70—230 mesh) was used. TLC was carried out on Merck kieselgel GF₂₅₄ plates and spots were detected under ultraviolet light.

Polyphosphoric acid (PPA) was prepared from 85% H_3PO_4 (200 g) and P_2O_5 (290 g), and polyphosphate ester (PPE) was prepared from EtOH (246 ml) and P_2O_5 (368 g).

2-(Phenoxymethyl)pyridine-3-carboxylic Acid (3a)—A stirred solution of phenol (2.26 g, 0.024 m) and Na (0.552 g, 0.024 g-atom) in EtOH was treated with ethyl 2-(bromomethyl)pyridine-3-carboxylate (**1**), and the mixture was refluxed for 2 h. After cooling, the insoluble material (NaBr) was filtered off and the filtrate was concentrated to dryness. Et_2O and 1 N NaOH were added to the residue and, after being shaken, the Et_2O layer was concentrated to dryness. The residue was heated with KOH (4.5 g) in 60% EtOH (80 ml) under reflux for 1 h, concentrated to about 15 ml, cooled and adjusted with dil. HCl to pH 4. The resulting precipitates were collected and crystallized from EtOH– H_2O to give **3a** (3.14 g, 74.5%) as colorless crystals, mp 212—213°C. NMR ($\text{DMSO}-d_6$) δ : 5.45 (2H, s, CH_2), 6.08—7.40 (5H, m, phenyl protons), 7.50 (1H, q, $J=7.5$ and 4.5 Hz, $\text{C}_5\text{-H}$), 8.22 (1H, q, $J=7.5$ and 1.5 Hz, $\text{C}_4\text{-H}$), 8.71 (1H, q, $J=4.5$ and 1.5 Hz, $\text{C}_6\text{-H}$). Anal. Calcd for $\text{C}_{13}\text{H}_{11}\text{NO}_3$: C, 68.11; H, 4.84; N, 6.11. Found: C, 68.26; H, 4.85; N, 6.16.

TABLE II. Phenoxyethyl- and Phenylthiomethylpyridine Derivatives



Compd. No.	R	X	mp (°C)	Recrystn solvent	Yield (%)	Formula	Analysis (%)		
							Calcd (Found)	C	H N
3b	H	S	181—182 ^{a)}	EtOH-H ₂ O	66	C ₁₃ H ₁₁ NO ₂ S	63.65 (63.48)	4.52 (4.64)	5.71 (5.72)
11	CH ₂ COOH	O	207.5— 209.5(dec.)	EtOH	55	C ₁₅ H ₁₃ NO ₅	62.71 (62.78)	4.56 (4.48)	4.88 (4.94)
13a	CH ₃	O	198—200	EtOH-H ₂ O	68	C ₁₄ H ₁₃ NO ₃	69.12 (69.02)	5.39 (5.49)	5.76 (5.80)
13b	CH ₃	S	173—175	EtOH	92	C ₁₄ H ₁₃ NO ₂ S	64.84 (64.60)	5.05 (5.00)	5.40 (5.45)

a) Lit^{4a)}: 180—181°C.

The compounds **3b**, **11** and **13a—b** were prepared in a similar manner. Data are summarized in Table II.

2-Cyano-3-(phenoxyethyl)pyridine (8a)—NBS (18.7 g, 0.015 M) and perbenzoic acid (BPO, 1.5 g) were added to a solution of **6** (8.8 g, 0.075 M) in CHCl₃ (300 ml), and the mixture was refluxed for 2 h. After cooling, the reaction mixture was washed with NaHCO₃-H₂O and H₂O, then extracted with conc. HCl (75 ml). The extract was diluted with H₂O (68 ml) and the sedimented oil was extracted with CHCl₃. The extract was evaporated to dryness. The residue (6.8 g) was added to a solution of phenol (3.3 g, 0.035 M) and Na (0.805 g, 0.035 g-atom) in EtOH and the mixture was refluxed for 2 h. After evaporation, 1 N NaOH was added to the residue and the solution was extracted with CHCl₃. The extract was washed with H₂O, dried (Na₂SO₄) and evaporated to give an oil. Distillation of the oil gave **8a** (4.9 g, 31.3%), bp 154°C (1 mmHg), mp 44—46°C (Et₂O—petr. ether). IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 2250 ($\nu_{\text{C}\equiv\text{N}}$). NMR (CDCl₃) δ : 5.53 (2H, s, CH₂), 6.80—7.50 (5H, m, phenyl protons), 7.49 (1H, q, $J=7.5$ and 4.5 Hz, C₅-H), 8.07 (1H, q, $J=7.5$ and 1.5 Hz, C₄-H), 8.67 (1H, q, $J=4.5$ and 1.5 Hz, C₆-H). Anal. Calcd for C₁₃H₁₀N₂O: C, 74.27; H, 4.80; N, 13.32. Found: C, 74.37; H, 4.60; N, 13.11.

The compound **8b** was prepared in a similar manner (35.0% yield). bp 174—176°C (2 mmHg). IR $\nu_{\text{max}}^{\text{neat}}$ cm⁻¹: 2250 ($\text{C}\equiv\text{N}$). Anal. Calcd for C₁₃H₁₀N₂S: C, 69.00; H, 4.45; N, 12.38. Found: C, 69.12; H, 4.41; N, 12.22.

3-(Phenoxyethyl)pyridine-2-carboxylic Acid (9a)—**8a** (4.9 g, 0.023 M) was added to a solution of NaOH (7.5 g) in 40% EtOH (50 ml), and the mixture was refluxed for 3 h. The reaction mixture was cooled and treated with conc. HCl to pH 3—4. The resulting precipitates were collected and crystallized from H₂O to give **9a** (4.7 g, 92.0%), mp 131—132°C. Anal. Calcd for C₁₃H₁₁NO₃: C, 68.11; H, 4.84; N, 6.11. Found: C, 68.28; H, 4.70; N, 6.05.

Compound **9b** was prepared from **8b** in a similar manner (85.6% yield). mp 101—102°C (MeOH-H₂O). Anal. Calcd for C₁₃H₁₁NO₂S: C, 63.65; H, 4.52; N, 5.71. Found: C, 63.35; H, 4.61; N, 5.75.

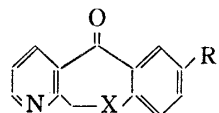
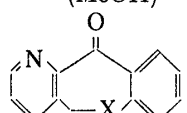
Pyrido[2,3-*c*][1]benzoxepin-5(11H)-one (4a)—A mixture of **3a** (1.0 g, 4.36 mm) and PPA (20 g) was stirred at 165° for 3 h. The reaction mixture was carefully poured into ice-water, basified with satd. NaHCO₃ solution, and extracted with Et₂O. The extract was washed with H₂O, dried (Na₂SO₄) and concentrated. The residue was crystallized from EtOH-H₂O to give **4a** (489 mg, 53.1%) as colorless needles, mp 58—59°C. Anal. Calcd for C₁₃H₉NO₂: C, 73.92; H, 4.30; N, 6.63. Found: C, 73.88; H, 4.35; N, 6.71.

The compounds **4b**, **14a—b** and **10a—b** were prepared in a similar manner. The reaction conditions and physical data are summarized in Table III.

7-(Bromomethyl)-5,11-dihydro-5-oxopyrido[2,3-*c*][1]benzoxepin (15a)—Method A: A solution of Br₂ (2.5 g, 15.6 mm) in 1,2-dibromoethane (10 ml) was added dropwise to a stirred and irradiated (tungsten lamp) solution of **14a** (2.25 g, 10 mm) in 1,2-dibromoethane (20 ml) at reflux temperature, and the mixture was refluxed for an additional 0.5 h. After cooling, the reaction mixture was poured into ice-water, then extracted with CHCl₃ and the washed, dried (Na₂SO₄) extract was concentrated. The residue was chromatographed using *n*-C₆H₁₄: AcOEt=3:1 as a solvent. The starting material (**14a**) (0.71 g, 31.6%) was recovered from the earlier eluate. Later eluate fractions gave **15a** (1.27 g, 41.8%), mp 111—112°C (Et₂O). IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 1635 ($\nu_{\text{C}=\text{O}}$). NMR (CDCl₃) δ : 4.53 (2H, s, CH₂Br), 5.35 (2H, s, C₁₁-H). Anal. Calcd for C₁₄H₁₀BrNO₂: C, 55.29; H, 3.31; N, 4.61. Found: C, 55.40; H, 3.35; N, 4.38.

Method B: A solution of **14a** (1.13 g, 5 mm), NBS (1.07 g, 6 mm) and BPO (20 mg) in CCl₄ was refluxed for 5 h. After cooling, insoluble material was filtered off and the filtrate was washed, dried (Na₂SO₄) and

TABLE III. Pyridobenzoxepin and -thiepin Derivatives

Compd. No.	R	X	Starting material (g)	PPA (g)	Reaction temp., °C	Reaction time, h	mp, °C (Recryst. solv.)	Yield (%)	Formula	Analysis (%)			
										Calcd (Found)	C	H	N
													
4b	H	S	3b (0.2)	6	155	1.5	105—106 (MeOH-H ₂ O)	58.4	C ₁₃ H ₉ NOS	68.70 3.99 6.16 (68.44 4.05 6.11)			
14a	CH ₃	O	13a (0.5)	15	175	0.75	79—80.5 (EtOH-H ₂ O)	74.9	C ₁₄ H ₁₁ NO ₂	74.65 4.92 6.22 (74.65 5.06 6.27)			
14b	CH ₃	S	13b (3.5)	105	160	0.67	84—85 ^a (MeOH)	67.5	C ₁₄ H ₁₁ NOS	69.68 4.59 5.80 (69.49 4.61 5.81)			
													
10a	H	O	9a (1.0)	50	180	0.25	132—133 (Et ₂ O-petr. ether)	5.0	C ₁₃ H ₉ NO ₂	73.92 4.30 6.63 (74.03 4.29 6.58)			
10b	H	O	9b (0.5)	25	195	1.0	155—156 ^a (Et ₂ O-petr. ether)	18.4	C ₁₃ H ₉ NOS	68.70 3.99 6.16 (68.41 3.99 6.00)			

a) The compounds were purified by column chromatography and then crystallized.

concentrated. The residue was chromatographed using *n*-C₆H₁₄: AcOEt=3:1 as a solvent to give **15a** (380 mg, 25.0%).

7-(Bromomethyl)-5,11-dihydro-5-oxopyrido[2,3-*c*][1]benzothiepin (15b)—Method B: NBS (2.03 g, 11.4 mm) and BPO (20 mg) were added to a solution of **14b** (1.69 g, 7 mm) in CCl₄ (100 ml), and the mixture was refluxed for 5 h. The reaction mixture was treated in a manner similar to that described in the synthesis of **15a** by Method B to give crude product, which was chromatographed using *n*-C₆H₁₄: EtOAc=3:1 as a solvent. The starting material (**14b**) (1.02 g, 60.2%) was recovered from the earlier eluate. Later eluate fractions gave **15b** (262 mg, 11.7%) as pale yellow crystals, mp 161—163°C (dec.) (Et₂O). IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 1632 (C=O). NMR (CDCl₃) δ : 4.26 (2H, s, C₁₁-H), 4.53 (2H, s, CH₂Br), 8.08 (1H, q, *J*=7.5 and 1.5 Hz, C₄-H), 8.34 (1H, d, *J*=2 Hz, C₆-H), 8.73 (1H, q, *J*=4.5 and 1.5 Hz, C₂-H). Anal. Calcd for C₁₄H₁₀BrNOS: C, 52.51; H, 3.15; N, 4.37. Found: C, 52.84; H, 3.27; N, 4.30. The residue from the final eluates was crystallized from Et₂O to give **17** (300 mg, 16.7%) as pale yellow crystals, mp 171—173°C. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3350 (OH), 1641 (C=O). NMR (CDCl₃) δ : 2.39 (3H, s, CH₃), 5.93 (1H, s, C₁₁-H), 7.22—7.55 (3H, m, C₃-H and C₈₋₉-H), 8.03—8.25 (2H, m, C₄-H and C₆-H), 8.62 (1H, q, *J*=4.5 and 1.5 Hz, C₂-H). Anal. Calcd for C₁₄H₁₁NO₂S: C, 65.33; H, 4.32; N, 5.45. Found: C, 65.61; H, 4.27; N, 5.52.

Method A: Reaction of **14b** (121 mg, 0.5 mm) with bromine (128 mg, 0.8 mm) in a manner similar to that described in the synthesis of **15a** by Method A gave **17** (21 mg, 16.3%), which was identical with the authentic sample mentioned above, together with the starting material (**14b**) (78 mg, 64.5%).

5,11-Dihydro-5-oxopyrido[2,3-*c*][1]benzoxepin-7-acetonitril (18a)—A solution of **15a** and NaCN (0.75 g, 15.3 mm) in H₂O (2 ml), DMF (2 ml) and dioxane (9 ml) was stirred at 80°C for 1.5 h and then evaporated to dryness. H₂O was added to the residue and the solution was extracted with AcOEt. The washed and dried extract was concentrated to dryness and the residue was purified by column chromatography using CHCl₃ as a solvent. Crystallization from AcOEt-*n*-C₆H₁₄ gave **18a** (0.62 g, 24.7%) as pale yellow needles, mp 163.5—164.5°C. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 2230 (C≡N), 1630 (C=O). NMR (CDCl₃) δ : 3.79 (2H, s, CH₂CN), 5.35 (2H, s, C₁₁-H). Anal. Calcd for C₁₅H₁₀N₂O₂: C, 71.99; H, 4.03; N, 11.20. Found: C, 72.14; H, 4.15; N, 11.52.

The compound **18b** was also prepared from **15b** in a similar manner (40.7% yield). mp 138—140°C (EtOAc-Et₂O). IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 2250 (C≡N). NMR (CDCl₃) δ : 3.83 (2H, s, CH₂CN), 4.27 (2H, s, C₁₁-H). Anal. Calcd for C₁₅H₁₀N₂OS: C, 67.65; H, 3.78; N, 10.52. Found: C, 67.34; H, 3.97; N, 10.24.

5,11-Dihydro-5-oxopyrido[2,3-*c*][1]benzoxepin-7-acetic Acid (12a)—A solution of **18a** (0.62 g) in H₂O (8 ml) and conc. H₂SO₄ (4.5 ml) was heated at 120—130°C for 1.5 h. After cooling, the reaction mixture was adjusted with dil. NaOH to pH 4 and the resulting precipitates were crystallized from AcOH-H₂O to give **12a** (0.62 g, 93.2%) as colorless needles, mp 247—248°C (dec.). IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 1710 (C=O), 1645 (C=O). NMR (DMSO-*d*₆) δ : 3.67 (2H, s, CH₂COOH), 5.29 (2H, s, C₁₁-H), 7.13 (1H, d, *J*=8.5 Hz, C₆-H), 8.02 (1H, d, *J*=2.5 Hz, C₆-H), 8.27 (1H, q, *J*=7.5 and 1.5 Hz, C₄-H), 8.80 (1H, q, *J*=4.5 and 1.5 Hz, C₂-H). Anal.

Calcd for $C_{15}H_{11}NO_4$: C, 66.91; H, 4.12; N, 5.20. Found: C, 67.05; H, 4.35; N, 5.44.

The compound **12b** was also prepared from **18b** in a similar manner (71.1% yield). mp 249–251°C (AcOH–H₂O). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 1710 (C=O), 1660 (C=O). NMR (DMSO- d_6) δ : 3.72 (2H, s, CH₂COOH), 4.40 (2H, s, C₁₁–H), 7.40–7.70 (3H, m, C₃–H and C_{8–9}–H), 7.97–8.20 (2H, m, C₄–H and C₆–H), 8.74 (1H, q, $J=4.5$ and 1.5 Hz, C₂–H). Anal. Calcd for $C_{15}H_{11}NO_3S$: C, 63.14; H, 3.89; N, 4.91. Found: C, 62.93; H, 4.03; N, 4.76.

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