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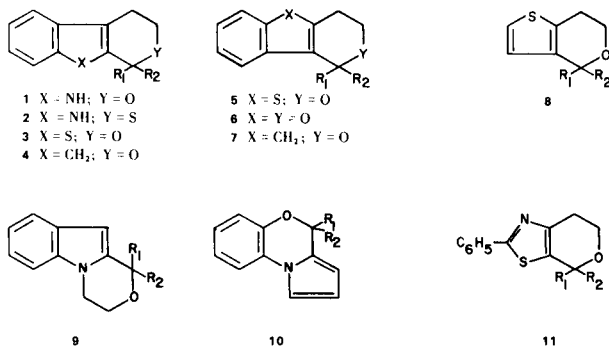
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Received September 19, 1977

A synthesis of the novel 4*H*-pyrano[4,3-*d*]thiazole ring system is described. Derivatives bearing alkylamine and alkanolic acid side chains have been prepared and tested for potential antidepressant and antiinflammatory activities, respectively; only marginal activities were found in these tests.

J. Heterocyclic Chem., **15**, 413 (1978)

We have recently described a new synthetic route which has been utilized in these Laboratories for the preparation of isochromans (1) and several novel heterocyclic systems, comprising, pyrano[3,4-*b*]indoles (1) (2-4), thiopyrano[3,4-*b*]indoles (2) (5), 1*H*-[1]benzothieno[2,3-*c*]pyrans (3) (1), indeno[2,1-*c*]pyrans (4) (6), 1*H*-[1]benzothieno[3,2-*c*]pyrans (5) (1), 1*H*-pyrano[4,3-*b*]benzofurans (6) (1), indeno[1,2-*c*]pyrans (7) (6), 4*H*-



thieno[3,2-*c*]pyrans (8) (1), 1*H*-1,4-oxazino[4,3-*a*]indoles (9) (7), and 4*H*-pyrrolo[2,1-*c*][1,4]benzoxazines (10) (8). Derivatives of some of these systems are potent antiinflammatory (2,4,9,10) and antidepressant (3,7,11-14) agents.

As a continuation of our studies on novel pyrano-fused heterocyclic systems, we describe in this report, the synthesis of a series of 4,4-disubstituted-2-phenyl-4*H*-pyrano[4,3-*d*]thiazole derivatives, 11, and their evaluation as antiinflammatory and antidepressant agents.

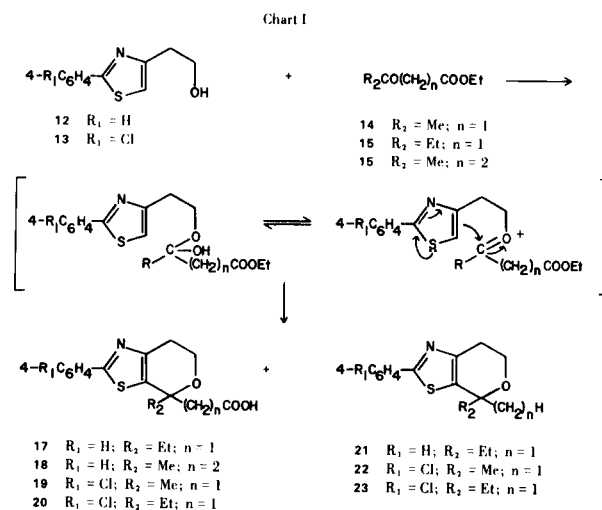
Chemistry.

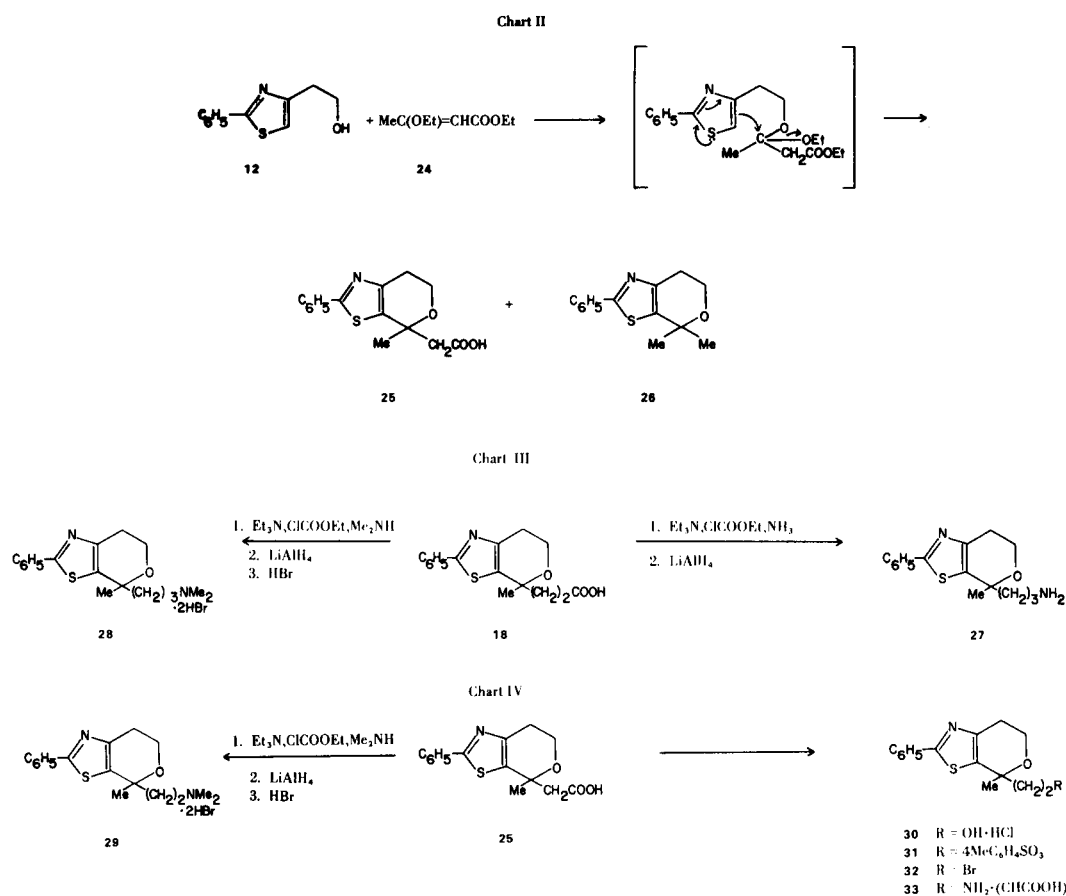
The pyrano[4,3-*d*]thiazoles were obtained as illustrated in Charts I and II. The synthesis involved, as the key step, the acid-catalyzed intramolecular Friedel-Crafts-type alkylation of the thiazole nucleus by the hemiketal or mixed ketal, or a derived oxonium ion intermediate, which is formed *in situ* by the reaction between a 2-phenyl-4-(β -hydroxyethyl)thiazole and a "carbonyl component". Thus, as illustrated in Chart I, the β -hydroxyethylthiazoles 12 and 13 (15) were condensed with the ketoesters 14-16 to afford, after hydrolysis, the pyrano[4,3-*d*]thiazole-4-alkanoic acids 17-20. For the synthesis of 25, shown in Chart II, 12 was condensed with 24, the enol

ethyl ether of ethyl acetoacetate. This type of "carbonyl component" has not previously been used in this reaction, although acetals (1) and cyclic ethyleneketals (16) have been successfully condensed. In contrast to previous reactions of this type (1-8) which were completed during 2-6 hours of refluxing in benzene in the presence of a catalytic amount of *p*-toluenesulfonic acid, the condensations shown in Charts I and II required more vigorous conditions. Thus, refluxing toluene was required, for periods of from 10-40 hours, and, because of the basic nitrogen in the thiazole nucleus, the use of more than one equivalent of *p*-toluenesulfonic acid was necessary. Under these conditions, yields of the pyrano[4,3-*d*]thiazoles were low and considerable quantities of the decarboxylation products 21-23 and 26 were obtained as by-products, although, in the condensation of 12 with ethyl levulinate, 16, no such product was observed. The propionic acid 18 was transformed into the 4-aminopropyl derivatives 27 and 28, and the acetic acid was converted to the 4-aminoethyl derivatives 29 and 33 by conventional procedures as indicated in Charts III and IV, respectively.

Compounds 17-20 and 25 were evaluated for their antiinflammatory effects in rats with established adjuvant arthritis, as described previously (2,4). Weak activity was found with 19 (ED₅₀ ca 50 mg./kg. po) while the other compounds tested were inactive at 100 mg./kg.

Compounds 27-29 and 33 were examined for their





capacity to prevent reserpine-induced ptosis in mice, according to a procedure used previously (7). Compound **27** had an ED₅₀ of 22 ± 5 mg./kg. while the other compounds tested were inactive.

EXPERIMENTAL

Nmr spectra were determined in deuteriochloroform or DMSO using a Varian A-60A spectrometer and the chemical shifts (δ) are reported as parts per million downfield from TMS. All compounds were homogeneous by tlc and melting points were taken on a Thomas-Hoover apparatus and need no correction. Microanalyses were done by the Ayerst Analytical Chemistry Section under the direction of Dr. G. Schilling.

2-Phenyl-4-(β -hydroxyethyl)thiazole (**12**).

Ethyl 2-phenylthiazole-4-acetate (**17**) (159 g., 0.64 mole) was reduced in tetrahydrofuran (1.25 l.) with lithium aluminum hydride (50 g., 1.34 mole) during 1.5 hours. The reaction was exothermic and no external heating was required. A conventional work-up afforded the product as a light yellow oil (130 g., 98.5%) which was used without any further purification; nmr (deuteriochloroform): δ 3.05 (2, t, J = 6.75 Hz, =CCH₂), 3.45 (1, broad, OH), 4.0 (2, t, J = 6.75 Hz, CH₂O), 6.95 (1, s, =CHS), 7.25-8.0 (5, m, benzene H's).

Condensation of β -Hydroxyethylthiazoles with "Carbonyl Components",

A. 2-(4-Chlorophenyl)-6,7-dihydro-4-methyl-4H-pyrano[4,3-d]-thiazole-4-acetic Acid (**19**).

A mixture of the 4-(β -hydroxyethyl)thiazole (**13**) (15) (24.0 g., 0.1 mole), toluene (1 l.), ethyl acetoacetate, **14**, (19.5 g., 0.15 mole) and *p*-toluenesulfonic acid (38.0 g., 0.2 mole) was stirred and heated at reflux during 20 hours in an apparatus fitted with a Dean-Stark trap. The toluene was evaporated *in vacuo*, and the residue was distributed between ether and aqueous sodium bicarbonate solution. After drying, the ether phase was concentrated, dissolved in methanol and refluxed with sodium hydroxide for 5 hours. The methanol was distilled off and the residue was separated into neutral and acidic fractions by distributing between ether and aqueous sodium bicarbonate solution. The aqueous phase was acidified with hydrochloric acid and extracted with ether to give a residue. Crystallization from ether-chloroform gave the product (9.7 g., 29.6%), m.p. 161-163°; nmr (DMSO): δ 1.65 (3, s, CH₃), 2.8 (4, m, CH₂O and =CCH₂), 4.0 (2, t, J = 5.5 Hz, OCH₂), 7.5 (2, d, J = 9 Hz, benzene H's), 7.9 (2, d, J = 9 Hz, benzene H's), 12.3 (1, broad COOH).

Anal. Calcd. for C₁₅H₁₄ClNO₃: C, 55.64; H, 4.36; N, 4.32. Found: C, 55.69; H, 4.37; N, 4.05.

The neutral ethereal fraction from above was chromatographed on silica gel. Elution with benzene: ethyl acetate (9:1) gave 2-(4-chlorophenyl)-6,7-dihydro-4,4-dimethyl-4H-pyrano[4,3-d]-thiazole (**22**), m.p. 78-80° (*n*-pentane), (9.0 g., 32%); nmr (deuteriochloroform): δ 1.58 (6, s, (CH₃)₂), 2.9 (2, t, J = 5.5 Hz, =CCH₂), 4.1 (2, t, J = 5 Hz, OCH₂).

Anal. Calcd. for C₁₄H₁₄ClNO₃: C, 60.10; H, 5.04; N, 5.01. Found: C, 60.19; H, 5.00; N, 4.91.

B.

The reaction of **13** with ethyl propionylacetate (**15**) using conditions described for the preparation of **19**, afforded 2-(4-

chlorophenyl)-6,7-dihydro-4-ethyl-4*H*-pyrano[4,3-*d*]thiazole-4-acetic acid, **20**, [m.p. 190-191° (methanol), 13.9% yield].

Anal. Calcd. for C₁₆H₁₆ClNO₃: C, 56.88; H, 4.78; N, 4.15. Found: C, 57.18; H, 4.75; N, 4.21.

2-(4-Chlorophenyl)-4-ethyl-6,7-dihydro-4-methyl-4*H*-pyrano[4,3-*d*]thiazole (**23**).

This compound had nmr (deuteriochloroform): δ 0.9 (3, t, J = 7 Hz, CH₂CH₃), 1.51 (3, s, CH₃), 1.90 (2, q, J = 7 Hz, CH₂CH₃), 2.92 (2, t, J = 5.5 Hz, =CCH₂) 4.12 (2, t, J = 5.5 Hz, OCH₂) and was isolated as an oil in 25% yield.

C.

Condensation of **12** with ethyl propionylacetate (**15**) gave 2-phenyl-6,7-dihydro-4-ethyl-4*H*-pyrano[4,3-*d*]thiazole-4-acetic acid (**17**) m.p. 106-108° (chloroform-ether-*n*-pentane), 20.9% yield.

Anal. Calcd. for C₁₆H₁₇NO₃S: C, 63.34; H, 5.65; N, 4.62. Found: C, 63.28; H, 5.83; N, 4.47.

2-Phenyl-6,7-dihydro-4-ethyl-4-methyl-4*H*-pyrano[4,3-*d*]thiazole (**21**).

This compound was also obtained as an oil in 23% yield; nmr (deuteriochloroform): δ 0.9 (3, t, J = 7 Hz, CH₂CH₃), 1.5 (3, s, CH₃), 1.8 (2, q, J = 7 Hz, CH₂CH₃), 2.92 (2, t, J = 5.5 Hz, =CCH₂), 4.08 (2, t, J = 5.5 Hz, OCH₂).

D.

The reaction between **12** and ethyl β-ethoxypropionate (**24**) gave 2-phenyl-6,7-dihydro-4-methyl-4*H*-pyrano[4,3-*d*]thiazole-4-acetic acid (**25**) m.p. 143-145° (ether-hexane), 25%.

Anal. Calcd. for C₁₅H₁₅NO₃S: C, 62.19; H, 5.25. Found: C, 62.07; H, 5.18.

2-Phenyl-6,7-dihydro-4,4-dimethyl-4*H*-pyrano[4,3-*d*]thiazole (**26**).

This compound had m.p. 65-66°, (*n*-pentane), and was also isolated in 22.1% yield.

Anal. Calcd. for C₁₅H₁₅NO₃: C, 68.51; H, 6.19; N, 5.71. Found: C, 68.56; H, 6.13; N, 5.94.

E.

Condensation of **12** with ethyl levulinate (**16**) afforded 2-phenyl-6,7-dihydro-4-methyl-4*H*-pyrano[4,3-*d*]thiazole-4-propionic acid (**18**) m.p. 148-150°, (chloroform-ether), 62.1% yield.

Anal. Calcd. for C₁₆H₁₇NO₃S: C, 63.34; H, 5.65; N, 4.62. Found: C, 63.52; H, 5.74; N, 4.36.

4-Dimethylaminoethyl-6,7-dihydro-4-methyl-2-phenyl-4*H*-pyrano[4,3-*d*]thiazole Dihydrobromide (**29**).

To a solution of the acid **25** (10.0 g., 0.35 mole) in tetrahydrofuran (300 ml.) was added triethylamine (10 ml.) and ethyl chloroformate (4.2 ml.). After stirring at 0° for 2.5 hours, 40% aqueous dimethylamine (50 ml.) was added. The mixture was stirred at 22° for 1 hour, the solvent was removed *in vacuo* and the residue was distributed between water and chloroform. The organic phase was washed with aqueous sodium bicarbonate, dried and evaporated to afford 8.5 g. (78%) of *N,N*-dimethyl-6,7-dihydro-4-methyl-2-phenyl-4*H*-pyrano[4,3-*d*]thiazole-4-acetamide as an oil; ir (chloroform): 1640 cm⁻¹ (CONH). The acetamide was stirred at 22° for 1.5 hours with lithium aluminum hydride (2.5 g.) in tetrahydrofuran (500 ml.). A conventional work-up procedure afforded an oil which was chromatographed on silica gel. Elution with chloroform:methanol (9:1) gave a semi-solid which was converted to the dihydrobromide salt (5.1 g., 41%). It had m.p. 237-238° (methanol-ether).

Anal. Calcd. for C₁₇H₂₄Br₂N₂O₅S: C, 43.97; H, 5.21; N, 6.03. Found: C, 43.79; H, 5.10; N, 5.95.

4-Dimethylaminopropyl-6,7-dihydro-4-methyl-2-phenyl-4*H*-pyrano[4,3-*d*]thiazole Dihydrobromide (**28**).

The acid **18** was reacted with triethylamine, ethyl chloroformate and dimethylamine, in tetrahydrofuran, using the procedure described above, to give, in 77% yield, *N,N*-dimethyl-6,7-dihydro-4-methyl-2-phenyl-4*H*-pyrano[4,3-*d*]thiazole-4-propionamide, as an oil; ir (chloroform): 1640 cm⁻¹ (CONH). It was reduced with lithium aluminum hydride in tetrahydrofuran during 2 hours at 22°. After the usual work-up procedure, the oily residue was chromatographed on silica gel. Elution with chloroform:methanol (9:1) gave the free base which was converted to the dihydrobromide salt, (3.1 g., 49%), m.p. 212-213° (ethanol-ether).

Anal. Calcd. for C₁₈H₂₆Br₂N₂O₅S: C, 45.20; H, 5.45; N, 5.86. Found: C, 44.98; H, 5.41; N, 5.57.

4-Aminopropyl-6,7-dihydro-4-methyl-2-phenyl-4*H*-pyrano[4,3-*d*]thiazole Dihydrobromide (**27**).

By using the procedure described above but replacing dimethylamine by ammonia, the acid **18** afforded an intermediate carboxamide. It was reduced with lithium aluminum hydride to give a free base which was converted to the dihydrobromide salt, m.p. 193-195° (methanol-ether) in 43% yield.

Anal. Calcd. for C₁₆H₂₄Br₂N₂O₅S: C, 42.68; H, 4.93; N, 6.22. Found: C, 42.83; H, 4.93; N, 5.97.

6,7-Dihydro-4-methyl-2-phenyl-4*H*-pyrano[4,3-*d*]thiazole-4-ethanol Hydrochloride (**30**).

The acid **25** (15 g.) was stirred at 22° for 15 hours with lithium aluminum hydride (3 g.) in tetrahydrofuran (250 ml.). The usual work-up procedure afforded an oil which was treated with hydrogen chloride to give the product (15.5 g., 96%), m.p. 161-162° (methanol-ether).

Anal. Calcd. for C₁₅H₁₈ClNO₂S: C, 57.78; H, 5.82; N, 4.49. Found: C, 57.91; H, 5.29; N, 4.19.

6,7-Dihydro-4-methyl-2-phenyl-4*H*-pyrano[4,3-*d*]thiazole-4-ethanol Tosylate (**31**).

The ethanol **30** (15.5 g., 0.05 mole), *p*-toluenesulfonyl chloride (10.3 g., 0.054 mole) and pyridine (50 ml.) were stirred at 22° for 4 hours. Water (150 ml.) was added and the mixture was extracted with chloroform to afford the product (16.0 g., 75%) m.p. 86-87° (hexane-ether); nmr (deuteriochloroform): δ 1.5 (3, s, CH₃), 2.2 (2, t, J = 7 Hz, CH₂), 2.35 (3, s, CH₃), 2.8 (2, t, J = 5.5 Hz, CH₂), 4.0 (4, m, CH₂O), 7.15-7.95 (9, m, aromatic H's).

4-Aminoethyl-6,7-dihydro-4-methyl-2-phenyl-4*H*-pyrano[4,3-*d*]thiazole Maleate (**33**).

The tosylate **31** (3.7 g.) was refluxed for 2 hours in acetone (25 ml.) with lithium bromide (3.7 g.). The solvent was removed *in vacuo* and the residue was distributed between ether and water. The ether phase afforded 3.3 g. of the bromide **32**, as an oil. It was dissolved in ethanol (30 ml.), combined with liquid ammonia (30 ml.) in an autoclave and heated at 90° for 11 hours. The solution was concentrated and the residue was chromatographed on silica gel. Elution with benzene:methanol (4:1) gave the free base of **33** (1.2 g., 45%). The maleate salt was prepared in acetone. It had m.p. 144-147° (acetone-ether).

Anal. Calcd. for C₁₉H₂₂N₂O₅S: C, 58.44; H, 5.68; N, 7.18. Found: C, 58.30; H, 5.85; N, 7.08.

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