

The Synthesis of Benzoxazole-5-acetic Acid Derivatives

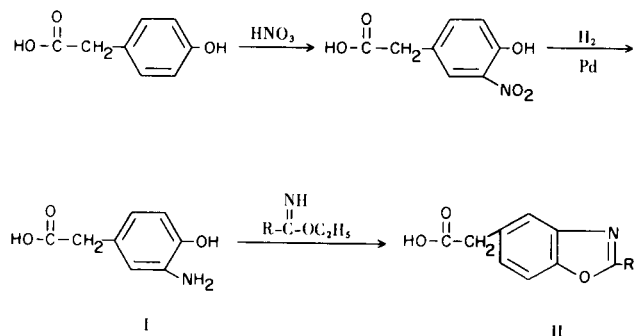
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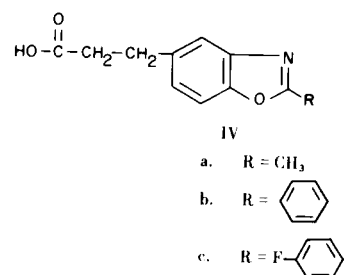
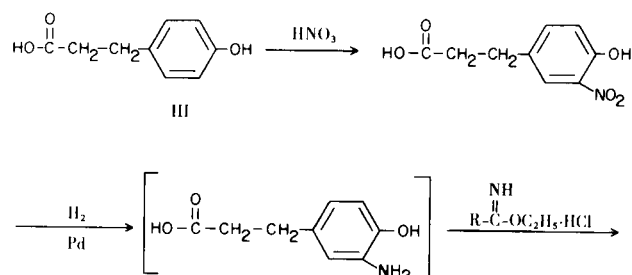
In connection with some work under way in these laboratories, we were interested in synthesizing a number of benzoxazole-5-acetic acid derivatives in order to study the biological properties of these compounds.

A review of the literature indicates that benzoxazole-5-acetic acids apparently have not been synthesized. We found that such compounds could be prepared from 3-amino-4-hydroxyphenylacetic acid (I), which is readily available by reduction of the known 4-hydroxy-3-nitrophenylacetic acid. Reaction of I with the requisite imido



ether (either as the *hydrochloride* or as the free base) in methanolic solution gave the desired benzoxazole-5-acetic acid derivatives (II). The compounds prepared are listed in Table I.

The same series of reactions was carried out also starting with 3-*p*-hydroxyphenylpropionic acid to give several benzoxazole-5-propionic acid derivatives (IV).



EXPERIMENTAL (1-2)

(3-Amino-4-hydroxyphenyl)acetic Acid (I).

A solution of 9.85 g. (0.05 mole) of (3-nitro-4-hydroxyphenyl)acetic acid (3) in 100 ml. of a saturated sodium bicarbonate solution was hydrogenated at 3 atmospheres of hydrogen using 200 mg. of 10% palladium on charcoal catalyst. The catalyst was removed by filtration and the filtrate was acidified with acetic acid. The precipitate was removed by filtration and washed with ethanol. There was obtained 8.1 g. (97%) of material melting at 227-228°. Recrystallization from water raised the melting point to 231-232.5°.

Anal. Calcd. for C₈H₉NO₃: C, 57.48; H, 5.43; N, 8.37. Found: C, 57.12; H, 5.41; N, 8.39.

2-Methyl-5-benzoxazoleacetic Acid (Procedure A).

A mixture of 8.35 g. (0.05 mole) of (3-amino-4-hydroxyphenyl)acetic acid, 6.18 g. (0.05 mole) of acetimido ethyl ether hydrochloride and 100 ml. of methanol was stirred for 3.5 hours and allowed to stand overnight. The precipitate was removed by filtration and recrystallized.


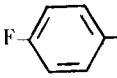
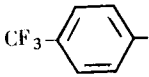
2-(2-Pyridyl)-5-benzoxazoleacetic Acid (Procedure B).

To a solution of sodium methoxide prepared by adding 0.115 g. (0.005 mole) of sodium to 45 ml. of methanol was added 5.20 g. (0.05 mole) of 2-cyanopyridine. The solution was allowed to stand overnight. To the solution was then added 300 mg. (0.005 mole) of acetic acid and 8.35 g. (0.05 mole) of (3-amino-4-hydroxyphenyl)acetic acid. The mixture was heated under reflux for 6 hours, the methanol was removed by distillation, and the residue was triturated with water, removed by filtration and recrystallized.

4-Hydroxy-3-nitrohydrocinnamic Acid.

To a stirred solution of 50 g. (0.03 mole) of 3-*p*-hydroxyphenylpropionic acid in 250 ml. of acetic acid cooled below 15° was added dropwise (over the course of 45 minutes) 19 ml. (0.03 mole) of concentrated nitric acid in 38 ml. of acetic acid. The

TABLE I
2-Substituted Benzoxazole-5-acetic Acid Derivatives

R	Procedure	Yield	M.p., °C	Formula	Analysis					
					C	Calcd. H	N	C	Found H	N
CH ₃	A	57	182-183 (a)	C ₁₀ H ₉ NO ₃	62.82	4.75	7.33	62.70	4.85	7.19
	A (g)	68	171-172 (a)	C ₁₅ H ₁₁ NO ₃	71.14	4.37	5.53	71.29	4.60	5.55
	A (g)	73	195-196 (b)	C ₁₅ H ₁₀ FNO ₃ (c)	66.47	3.72	5.16	66.82	3.46	5.09
	A (h)	54	232-233 (b)	C ₁₆ H ₁₀ F ₃ NO ₃ (d)	59.82	3.14	4.36	59.77	3.11	4.72
2-Pyridyl	B	14	221-222 (e)	C ₁₄ H ₁₀ N ₂ O ₃	66.13	3.96	11.02	66.38	3.78	11.26
3-Pyridyl	B	29	270-271 (f)	C ₁₄ H ₁₀ N ₂ O ₃	66.13	3.96	11.02	66.00	4.04	11.11
4-Pyridyl	B	54	310-312 (dec.) (e)	C ₁₄ H ₁₀ N ₂ O ₃	66.13	3.96	11.02	65.71	3.73	11.04

(a) Recrystallized from methanol. (b) Recrystallized from ethanol. (c) Calcd. for F, 7.01; Found, 6.91. (d) Calcd. for F, 17.74; Found, 17.69. (e) Recrystallized from ethanol-water. (f) Recrystallized from acetonitrile-water-ethanol. (g) The reaction mixture was heated under reflux for 3.5 hours. (h) The amount of methanol was increased to 500 ml. and the mixture was heated under reflux for 8 hours.

mixture was then stirred in an ice-bath at 10° for an additional 3.5 hours. The mixture was poured into 1 l. of ice water. The precipitate was removed by filtration and recrystallized from 50% ethanol. There was obtained 24.2 g. (38%) of material melting at 95-96°.

Anal. Calcd. for C₉H₉NO₃: C, 51.29; H, 4.30; N, 6.63. Found: C, 51.17; H, 4.48; N, 6.68.

2-Methyl-5-benzoxazolepropionic Acid (IVa).

A mixture of 22.2 g. (0.105 mole) of 4-hydroxy-3-nitrohydrocinnamic acid, 225 ml. of a saturated sodium bicarbonate solution and 450 mg. of 10% palladium on charcoal catalyst was hydrogenated at an initial pressure of 3 atmospheres of hydrogen. The catalyst was removed by filtration and the filtrate was acidified to pH 4.5 with acetic acid. The precipitate was removed by filtration and the filtrate was evaporated to dryness. The residue was combined with the precipitate obtained above, m.p. 132-134°.

A mixture of 3.62 g. (0.02 mole) of the material obtained above, 2.49 g. (0.02 mole) of acetimido ethyl ether hydrochloride and 40 ml. of absolute methanol was stirred for 1.5 hours and then heated under reflux for 3.5 hours. The mixture was filtered while hot and the filtrate was concentrated to dryness and the residue recrystallized from dilute methanol. There was obtained 1.40 g. (39%) of needles melting at 122-123°.

Anal. Calcd. for C₁₁H₁₁NO₃: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.20; H, 5.56; N, 6.90.

2-Phenyl-5-benzoxazolepropionic Acid (IVb).

The procedure described above for 2-methyl-5-benzoxazolepropionic acid was used, using an equivalent amount of benzimidazole ethyl ether hydrochloride. There was obtained 1.90 g. (36%) of clusters of tan prisms melting at 150-152°. Recrystallization from methanol gave material possessing the same melting point.

Anal. Calcd. for C₁₆H₁₃NO₃: C, 71.90; H, 4.90; N, 5.24. Found: C, 71.67; H, 4.62; N, 5.19.

2-(p-Fluorophenyl)-5-benzoxazolepropionic Acid (IVc).

The procedure described above for 2-methyl-5-benzoxazolepropionic acid was used, using an equivalent amount of p-fluorobenzimidazole ethyl ether hydrochloride. There was obtained 2.65 g. (47%) of material melting at 170-172°. Recrystallization from methanol gave colorless needles melting at 171.5-172°.

Anal. Calcd. for C₁₆H₁₂FNO₃: C, 67.36; H, 4.24; N, 4.91. Found: C, 67.16; H, 4.19; N, 4.86.

REFERENCES

- (1) All melting points are corrected.
- (2) Microanalyses were performed by Mr. N. Knight and his associates of our Department of Physical and Analytical Chemistry. The author is also indebted to Mr. Nelson Major for excellent technical assistance.
- (3) T. Yametani, *et al.*, *Yakugaku Zasshi*, **84**, 532 (1964); *Chem. Abstr.*, **61**, 13359b (1964).