

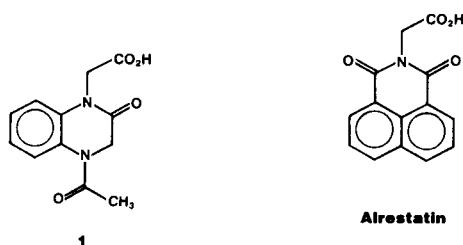
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Synthetic routes have been developed for the preparation of 4-acylated, 4-benzenesulfonylated, and 4-methylated 3,4-dihydro-2(1*H*)-quinoxalinone-1-acetic acids. One example of the corresponding propionic acid has also been made. These compounds have been evaluated for their ability to inhibit bovine lens aldose reductase *in vitro*. Some members from this series also show weak activity *in vivo*, inhibiting sorbitol formation in sciatic nerves of streptozotocin-diabetic rats.

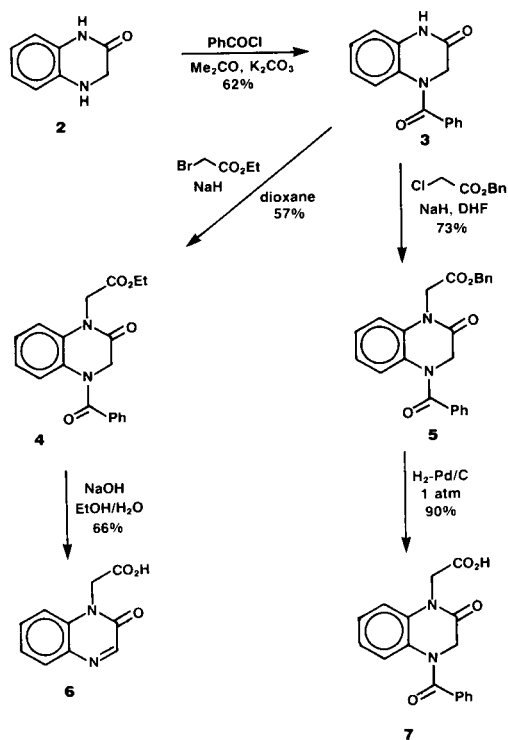
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We discovered that 4-acetyl-3,4-dihydro-2(1*H*)-quinoxalinone-1-acetic acid **1** inhibited bovine lens aldose reductase [1] ($IC_{50} = 10^{-6}M$) and prevented sorbitol accumulation in sciatic nerves of diabetic rats [2] at very



high doses ($ED_{50} = 500$ mg/kg, t.i.d., p.o.). This finding indicated that compounds of this type might be useful in the

SCHEME I



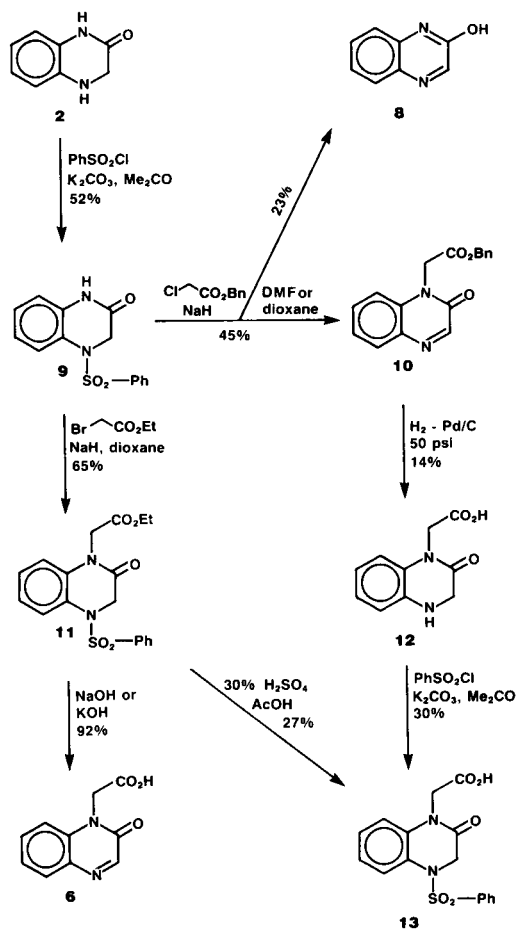
therapy of chronic complications of diabetes mellitus and prompted us to explore additional compounds in this heterocyclic class. We were particularly interested in the effect of replacing the acetyl group with more lipophilic groups, such as benzoyl and benzenesulfonyl, and with alkyl groups.

Chemistry.

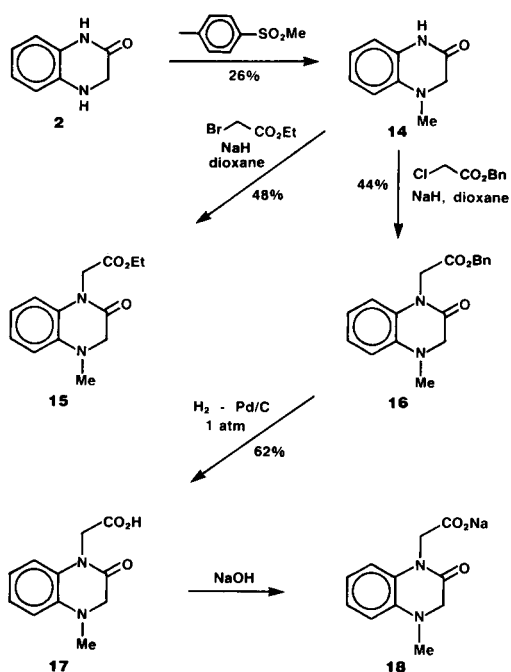
The title compounds were prepared as shown in Schemes I to IV. Reaction of 3,4-dihydro-2-hydroxyquinoxaline **2** [3] with benzoyl or benzenesulfonyl chloride gave the 4-acylated derivatives **3** and **9** in good yields. Treatment of these compounds with ethyl bromoacetate gave the 1-alkylated ester derivatives **4** and **11**. Attempts to convert these ethyl esters to the desired carboxylic acids by hydrolysis with aqueous base proved difficult; in both cases the major product was 2(1*H*)-quinoxalinone-1-acetic acid **6** [4]. The formation of **6** from **11** is reminiscent of the conversion of *N*-benzenesulfonylhydroxamic acid to benzenesulfinic acid and nitroxyl by aqueous alkali [5] and might involve a similar mechanism, *i.e.* elimination of benzenesulfinic acid from **6**. By analogy, one could then postulate the loss of benzaldehyde from **4**. Alternatively, these rather facile conversions would have to involve cleavage of the acyl residues, followed by air oxidation of a dihydro product such as **12** to **6** [4].

Substitution of the benzyl ester for the ethyl ester led to a successful route to the benzoylated target; alkylation of **3** with benzyl chloroacetate, followed by catalytic hydrogenation gave **7**. By contrast, attempts to alkylate **9** with benzyl chloroacetate and sodium hydride in dioxane or DMF gave mainly the elimination products **10** and **8**, again suggesting facile elimination of benzenesulfinic acid from **9** under these conditions. Hydrogenation of **10** gave **12** in low yield, and treatment of **12** with benzenesulfonyl chloride resulted in modest amounts of the target compound **13**. A better route to **13** proved to be acid catalyzed hydrolysis of the ethyl ester **11** with aqueous sulfuric acid in acetic acid.

SCHEME II



SCHEME III

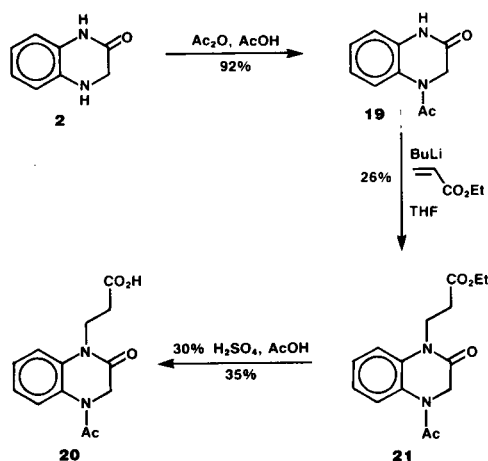


Attempts to methylate **2** with methyl iodide or with formaldehyde/formic acid resulted in poor yields of the desired product. A number of unwanted products which formed were not further investigated. However, heating of **2** in neat methyl tosylate gave the desired **14** in modest

yield. Alkylation of **14** with benzyl chloroacetate, followed by hydrogenation gave the target acid **17**, which proved rather unstable and was converted to the more stable sodium salt **18**.

Finally, we prepared the propionic acid homolog (**20**) of **1** as shown in Scheme IV. Acetylation of **2** gave **19**, which after Michael addition to ethyl acrylate and acid catalyzed saponification gave the target compound **20**.

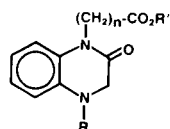
SCHEME IV



Pharmacology Results and Discussion.

The target compounds and some of the synthetic intermediates were tested for their ability to inhibit bovine lens aldose reductase (BLAR) *in vitro* according to the method of Hayman and Kinoshita [1]. These compounds were also assayed for their ability to suppress sorbitol formation in sciatic nerves of streptozotocin-diabetic rats *in vivo* according to the method of Peterson *et al.* [2]. All of the test results are summarized in Table I. It is apparent that the *in vitro* activity of compound **1** is shared by all the acidic analogs, although none showed a significant potency increase over the lead compound. The corresponding ethyl esters were all inactive *in vitro* at a concentration of

Table I



Compound No.	R	R'	n	<i>In Vitro</i> IC ₅₀ [a], M BLAR	<i>In Vivo</i> ED ₅₀ [b] (% Suppression of nerve sorbitol at dose indicated), mg/kg	
					i.p. [c]	p.o. [d]
1	Ac	H	1	~10 ⁻⁶	500 (50*)	> 250 (12)
7	PhCO	H	1	~10 ⁻⁶	> 250 (21)	
4	PhCO	Et	1	>10 ⁻⁴	>250 (33*)	
13	PhSO ₂	H	1	10 ⁻⁵ -10 ⁻⁶		> 100 (7)
11	PhSO ₂	Et	1	>10 ⁻⁴	~100 (46*)	> 100 (19*)
18	Me	H	1	10 ⁻⁵ -10 ⁻⁶		> 100 (2)
15	Me	Et	1	>10 ⁻⁴		> 15 (17)
20	Ac	H	2	10 ⁻⁴ -10 ⁻⁵		
21	Ac	Et	2	>10 ⁻⁴		> 100 (0)

alrestatin [6] 10⁻⁵ 10⁻⁶ 100 (36*) -250 (61*) 250 (40*) -500 (86*)

[a] Concentration which causes a 50% inhibition of partially bovine aldose reductase, using glyceraldehyde as substrate [1]. Single determinations; the reproducibility of the assay did not vary by more than 10%. [b] Dose, given t. i. d., which causes a 50% reduction in sorbitol levels of sciatic nerve of streptozotocinized rats [2]. The percent inhibition of sorbitol levels is given in parentheses; the asterisk * indicates statistical significance at the $p < 0.05$ level (Student's *t* test). Single determinations in groups of 5 rats. [c] Intraperitoneal dose. [d] Oral dose.

10⁻⁴ M. However, *in vivo* activity was displayed by the ethyl esters **4** and **11**, presumably because they serve as prodrugs for the corresponding acids **7** and **13**. The *in vitro* activity of these acids and the weak *in vivo* activity of compound **11** are comparable to that of the aldose reductase inhibitor alrestatin [6].

EXPERIMENTAL

Melting points were determined with a Thomas-Hoover apparatus and are uncorrected. Elemental analyses were performed by the Analytical Department of Pfizer Central Research. The ¹H nmr spectra were obtained on a Varian T-60 instrument. Mass spectra were obtained on a Hitachi-Perkin Elmer RMU-GE spectrometer.

4-Benzoyl-3,4-dihydro-2(1H)-quinoxalinone (3).

A solution of 20 g (0.135 mole) of **2** (prepared according to the procedure of Perkin and Riley [3] in 50% yield) and 18.7 g (0.135 mole) of potassium carbonate in 500 ml of acetone was stirred under nitrogen while 15.8 g (0.135 mole) of benzoyl chloride was added over 15 minutes. After stirring at room temperature for 1 hour, the mixture was poured on ice, filtered, dried and recrystallized from 2-propanol to give 21 g (62%) of a tan solid, mp 212-213°; ¹H nmr (deuteriochloroform): δ 4.6 (s, 2H), 6.7-7.4 (m, 9H), 9.65 (s, 1H).

Anal. Calcd. for C₁₃H₁₂N₂O₂: C, 71.42, H, 4.79; N, 11.10. Found: C, 71.10; H, 4.88; N, 11.09.

Ethyl 4-Benzoyl-3,4-dihydro-2(1H)-quinoxalinone-1-acetate (4).

To a suspension of 720 mg (0.012 mole) of 50% sodium hydride in 45 ml of dioxane in a dry flask under nitrogen was added 3 g (0.012 mole) of **3**. To this mixture was added 2.5 g (0.015 mole) of ethyl bromoacetate over 15 minutes. After being stirred for 16 hours at room temperature, the mixture was poured into 100 ml of ice and the resulting tan solid was recrystallized from carbon tetrachloride to yield 2.3 g (57%) of **4**, mp 129-131°; ¹H nmr (deuteriochloroform): δ 1.3 (t, 3H), 4.25 (q, 2H), 4.6 (s, 2H), 4.75 (s, 2H), 6.7-7.5 (m, 9H).

Anal. Calcd. for C₁₉H₁₈N₂O₄: C, 67.45; H, 5.36; N, 8.28. Found: C, 67.06; H, 5.40; N, 8.18.

Benzyl 4-Benzoyl-3,4-dihydro-2(1H)-quinoxalinone-1-acetate (5).

A suspension of 700 mg (0.015 mole) of 50% sodium hydride in 100 ml of DMF in a flame dried flask under nitrogen was treated dropwise with a solution of 3.7 g (0.015 mole) of **3** in 50 ml of DMF. To this solution was added with stirring, 2.5 g (0.015 mole) of benzyl chloroacetate and after 24 hours at 40° the contents were poured onto 100 ml of ice. The solid was recrystallized from 2-propanol to yield 4.4 g (73%) of **5**, mp 139-141°; ¹H nmr (DMSO-d₆): δ 4.6 (s, 2H), 4.8 (s, 2H), 5.2 (s, 2H), 6.7-7.4 (m, 9H).

Anal. Calcd. for C₂₄H₂₀N₂O₄: C, 71.99; H, 5.03; N, 7.00. Found: C, 71.50; H, 4.93; N, 6.91.

4-Benzoyl-3,4-dihydro-2(1H)-quinoxalinone-1-acetic Acid (7).

A solution of 4.3 g (0.0107 mole) of **5** in 100 ml of ethyl acetate was hydrogenated at 1 atmosphere over 430 mg of 10% Pd/C. After the uptake of 245 ml of hydrogen, the mixture was filtered and concentrated to a yellow solid which was recrystallized from ethyl acetate to yield 3 g (90%) of **7**, mp 226-227°; ¹H nmr (DMSO-d₆): δ 4.55 (s, 2H), 4.7 (s, 2H), 6.7-7.4 (m, 9H).

Anal. Calcd. for C₁₇H₁₄N₂O₄: C, 65.80; H, 4.55; N, 9.03. Found: C, 65.60; H, 4.49; N, 8.67.

4-Benzenesulfonyl-3,4-dihydro-2(1H)-quinoxalinone (9).

A suspension of 10 g (0.068 mole) of **2** and 9.6 g (0.069 mole) of potassium carbonate in 250 ml of acetone was stirred under nitrogen at 40° while 11.5 g (0.07 mole) of benzenesulfonyl chloride was added over 30 minutes. The mixture was heated at reflux temperature for 4 hours, stirred at room temperature for 14 hours and then poured onto 500 ml of ice. The resulting brown solid was recrystallized from ethyl acetate to yield 10.2 g (52%) of **9**, mp 183-185°; ¹H nmr (deuteriochloroform): δ 4.3 (s, 2H), 6.6-7.8 (m, 9H), 8.5 (s, 1H).

Anal. Calcd. for C₁₄H₁₂N₂O₃S: C, 58.32; H, 4.19; N, 9.72. Found: C, 58.36; H, 4.37; N, 9.58.

Benzyl 2(1H)-quinoxalinone-1-acetate (10).

To a suspension of 1.7 g (0.035 mole) of 50% sodium hydride in 30 ml of dioxane in a dry flask under nitrogen was added 10 g (0.035 mole) of **9**. To the mixture was added dropwise, 5.9 g (0.035 mole) of benzyl chloroacetate. After being stirred at 40° for 1 hour and at room temperature for 16 hours the mixture was poured onto 500 ml of ice, and the solid was recrystallized from benzene to yield 4.6 g (45%) of **10**, mp 132-133.5°; ¹H nmr (deuteriochloroform): δ 5.1 (s, 2H), 5.3 (s, 2H), 6.95-8.1 (m, 9H), 8.4 (s, 1H).

Anal. Calcd. for C₁₇H₁₄N₂O₃: C, 69.38; H, 4.79; N, 9.52. Found: C, 69.09; H, 4.67; N, 9.46.

2-Hydroxyquinoxaline (8).

Chromatography of the mother liquor from the recrystallization of **10** on silica gel with ethyl acetate gave 100 mg of **8**, mp 268-270° (lit [7] mp 268-270°); ¹H nmr (DMSO-d₆): δ 7.2-7.9 (m, 4H), 8.2 (s, 1H).

Anal. Calcd. for C₈H₆N₂O: C, 65.75; H, 4.14; N, 19.17. Found: C, 65.74; H, 4.03; N, 19.41. This compound was also the major product isolated in an attempt to alkylate **9** with benzyl chloroacetate in DMF as the solvent.

Ethyl 4-benzenesulfonyl-3,4-dihydro-2(1*H*)-quinoxalinone-1-acetate (**11**).

A suspension of 192 mg (0.004 mole) of 50% sodium hydride in 15 ml of dioxane in a dry flask under nitrogen was treated with 1 g (0.0035 mole) of **9** in 20 ml of dioxane and then with 688 mg (0.004 mole) of ethyl bromoacetate over a 15 minute period. The mixture was stirred at room temperature for 7 hours, poured onto 100 ml of ice, and the precipitated solid was recrystallized from carbon tetrachloride to yield 844 mg (65%) of **11**, mp 113-115°; ¹H nmr (DMSO-*d*₆): δ 1.3 (t, 3H), 3.7 (s, 2H), 4.15 (q, 2H), 4.4 (s, 2H), 6.5-7.8 (m, 9H).

Anal. Calcd. for C₁₈H₁₈N₂O₅S: C, 57.74; H, 4.85; N, 7.48. Found: C, 57.39; H, 4.88; N, 7.42.

3,4-Dihydro-2(1*H*)-quinoxalinone-1-acetic Acid (**12**).

A solution of 1 g (0.0033 mole) of **10** in 50 ml of ethyl acetate was hydrogenated over 100 mg of 10% Pd/C at 50 psi hydrogen for 7 hours. The catalyst was filtered and the filtrate was concentrated to a solid which was recrystallized from ethanol-hexane (4:1) to yield 100 mg (14%) of **12**, mp 197-199°; ¹H nmr (DMSO-*d*₆): δ 3.8 (s, 2H), 4.6 (s, 2H), 6.0 (bs, 1H), 6.8 (m, 4H).

Anal. Calcd. for C₁₀H₁₀N₂O₃: C, 58.25; H, 4.89; N, 13.59. Found: C, 58.30; H, 4.68; N, 13.31.

2(1*H*)-quinoxalinone-1-acetic Acid (**6**).

A suspension of 500 mg (0.0013 mole) of **11** in 20 ml of 5% sodium hydroxide was heated at reflux temperature for 6 hours. After an acid-base work-up and recrystallization from ethanol-petroleum ether, 250 mg (92%) of **6** was obtained, mp 250-252° dec (lit [4] mp 225-226° dec); ¹H nmr (DMSO-*d*₆): δ 5.0 (s, 2H), 7.1-7.9 (m, 4H), 8.3 (s, 1H); ms: m/e 204.

Anal. Calcd. for C₁₀H₈N₂O₃: C, 58.82; H, 3.95; N, 13.72. Found: C, 58.48; H, 3.99; N, 13.62. This compound was also obtained in 73% yield by treatment of a solution of **11** in ethanol with 2*N* potassium hydroxide at room temperature, or in 66% yield by treating a solution of **4** in ethanol at room temperature with 2*N* sodium hydroxide.

4-Benzenesulfonyl-3,4-dihydro-2(1*H*)-quinoxalinone-1-acetic Acid (**13**).

A suspension of 3 g (0.008 mole) of **11** in 30 ml of 30% aqueous sulfuric acid and 20 ml of 98% acetic acid was heated to 80° for 15 minutes, 60° for 5 hours, and then kept at room temperature for 16 hours. The solution was concentrated to an oil, which was dissolved in saturated sodium bicarbonate and precipitated with 3*N* hydrochloric acid. The solid was recrystallized from ethanol-petroleum ether, after activated charcoal treatment, to yield 750 mg (27%) of **13**, mp 122° dec; ¹H nmr (DMSO-*d*₆): δ 3.7 (s, 2H), 4.5 (s, 2H), 6.5-7.8 (m, 9H).

Anal. Calcd. for C₁₈H₁₄N₂O₅S·½ H₂O: C, 54.77; H, 4.17; N, 7.98. Found: C, 54.83; H, 4.44; N, 7.97. Alternatively, this compound was obtained in 30% yield by treatment of **12** with benzenesulfonyl chloride.

3,4-Dihydro-4-methyl-2(1*H*)-quinoxalinone (**14**).

In a dry flask under nitrogen was combined 40 g (0.27 mole) of **2** and 55 g (0.3 mole) of methyl *p*-toluenesulfonate. The pasty mixture was heated to 100° for 2 hours with good stirring. After 30 minutes the slurry became deep purple and viscous. The mixture was diluted with 100 ml of 4*N* hydrochloric acid, poured into 200 ml of 4*N* sodium hydroxide and chilled. The precipitated solid was recrystallized from chloroform after treatment with charcoal to yield 11.5 g (26%) of **14**, mp 144-144.5°; ¹H nmr (deuteriochloroform): δ 2.8 (s, 3H), 3.75 (s, 2H), 6.45-7.1 (m, 4H), 9.95 (s, 1H).

Anal. Calcd. for C₉H₁₀N₂O: C, 66.65; H, 6.21; N, 17.27. Found: C, 66.44; H, 6.17; N, 17.29.

Ethyl 3,4-Dihydro-4-methyl-2(1*H*)-quinoxalinone-1-acetate (**15**).

To a suspension of 300 mg (0.0063 mole) of 50% sodium hydride in 25 ml of dioxane in a dry flask under nitrogen was added 1 g (0.0062 mole) of **14**. To this was added dropwise 1 ml (0.008 mole) of ethyl bromoacetate, then the mixture was stirred at room temperature for 4 hours and then poured onto 100 ml of ice. The solid was recrystallized from

2-propanol to yield 730 mg (48%) of **15**, mp 102-103.5°; ¹H nmr (deuteriochloroform): δ 1.25 (t, 3H), 2.8 (s, 3H), 3.8 (s, 2H), 4.2 (q, 2H), 4.7 (s, 2H), 6.8-7.1 (m, 4H).

Anal. Calcd. for C₁₅H₁₆N₂O₃: C, 62.89; H, 6.50; N, 11.28. Found: C, 62.60; H, 6.44; N, 11.21.

Benzyl 3,4-dihydro-4-methyl-2(1*H*)-quinoxalinone-1-acetate (**16**).

To a suspension of 300 mg (0.0063 mole) of 50% sodium hydride in 20 ml of dioxane in a dry flask under nitrogen was added 1 g (0.0062 mole) of **14**. The mixture was stirred while 1 g (0.006 mole) of benzyl chloroacetate was added dropwise. The reaction was kept at room temperature for 3 hours, poured onto 100 ml of ice, and the solid was recrystallized from benzene-petroleum ether to yield 807 mg (44%) of **16**, mp 108-110.5°; ¹H nmr (deuteriochloroform): δ 2.85 (s, 3H), 3.8 (s, 2H), 4.75 (s, 2H), 5.2 (s, 2H), 6.6-7.6 (m, 9H).

Anal. Calcd. for C₁₈H₁₈N₂O₃: C, 69.66; H, 5.85; N, 9.03. Found: C, 69.63; H, 5.77; N, 8.82.

Sodium 3,4-dihydro-4-methyl-2(1*H*)-quinoxalinone-1-acetate (**18**).

A solution of 1 g (0.0032 mole) of **16** in 50 ml of ethyl acetate was hydrogenated at 1 atmosphere hydrogen over 100 mg of 10% Pd/C. After the absorption of 84 ml of hydrogen the solution was filtered and concentrated to give crude **17**, which was then treated with 2*N* sodium hydroxide. The resulting solution was concentrated and the solid was recrystallized from ethanol to yield 500 mg (62%) of **18**, mp above 300°; ¹H nmr (DMSO-*d*₆): δ 2.8 (s, 3H), 3.75 (s, 2H), 4.6 (s, 2H), 6.8-7.1 (m, 4H).

Anal. Calcd. for C₁₁H₁₁N₂NaO₃·½ H₂O: C, 52.59; H, 4.81; N, 11.15. Found: C, 52.94; H, 4.74; N, 10.84.

4-Acetyl-3,4-dihydro-2(1*H*)-quinoxalinone (**19**).

A solution of 15 g (0.1 mole) of **2** in 75 ml of acetic acid was stirred while 11.2 g (0.11 mole) of acetic anhydride was added dropwise. The solution was heated on a steam bath for 2 hours and then poured into 250 ml of ice, followed by the addition of 10 ml of 20% sodium hydroxide. The mixture was chilled and the solid that formed was recrystallized from ethanol to yield 17.7 g (92%) of **19**, mp 166.5-168.5°; ¹H nmr (deuteriochloroform): δ 2.3 (s, 3H), 4.5 (s, 2H), 6.9-7.3 (m, 4H), 10.1 (s, 1H).

Anal. Calcd. for C₁₀H₁₀N₂O₃: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.33; H, 5.34; N, 14.77.

Ethyl 2-(4-Acetyl-3,4-dihydro-2(1*H*)-quinoxalinone-1-yl)-propionate (**21**).

A solution of 9.5 g (0.05 mole) of **19** in 120 ml of THF was cooled to -70° while 28 ml of 2.2*M* butyllithium was added dropwise. The mixture was allowed to warm to room temperature while 5.5 g (0.055 mole) of ethyl acrylate was added dropwise. The mixture was stirred for 16 hours at room temperature, quenched with 20 ml of acetic acid and then concentrated. The resulting solid was dissolved in chloroform, washed with 2 x 150 ml of water, dried over anhydrous potassium carbonate, treated with charcoal and concentrated to a solid. The solid was recrystallized 3 x from 2-propanol to yield 3.7 g (26%) of **21**, mp 104.5-105.5°; ¹H nmr (deuteriochloroform): δ 1.15 (t, 3H), 2.25 (s, 3H), 2.7 (t, 2H), 3.95-4.25 (m, 4H), 4.45 (s, 2H), 7.1-7.5 (m, 4H).

Anal. Calcd. for C₁₅H₁₆N₂O₄: C, 62.06; H, 6.25; N, 9.65. Found: C, 61.91; H, 6.20; N, 9.60.

2-(4-Acetyl-3,4-dihydro-2(1*H*)-quinoxalinone-1-yl)-propionic Acid (**20**).

A suspension of 1.7 g (0.006 mole) of **21** in 20 ml of 10% sulfuric acid and 10 ml of 98% acetic acid was stirred at room temperature for 16 hours and then extracted with 3 x 100 ml of ethyl acetate. The combined extracts were dried over anhydrous magnesium sulfate, treated with charcoal and concentrated. The resulting solid was recrystallized from ethyl acetate-petroleum ether to yield 550 mg (35%) of **20**, mp 166-167°; ¹H nmr (DMSO-*d*₆): δ 2.2 (s, 3H), 2.4-2.6 (m, 4H), 4.5 (s, 2H), 7.1-7.9 (m, 4H), 8.5 (bs, 1H).

Anal. Calcd. for C₁₃H₁₄N₂O₄·¼ H₂O: C, 58.52; H, 5.29; N, 10.49. Found: C, 58.73; H, 5.25; N, 10.65.

Acknowledgments.

The biological testing was carried out by Messrs. D. P. MacDonald and C. E. Aldinger in the laboratory of Dr. M. J. Peterson of Pfizer Central Research. Compound **1** was originally prepared by Dr. J. M. McManus of Pfizer Central Research.

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