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An improved synthesis of the 1,4-dihydropyrazine derivative, **3**, is described that involves the versatile 1,4-diketointermediate, **9**. This intermediate was converted to several heterocyclic ring-analogs of 1,4-dihydropyridine in addition to **3** including derivatives of pyrrole and furan.

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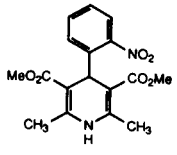
Introduction.

The potent calcium channel blocking activity of dihydropyridine derivatives such as nifedipine **1** has prompted the preparation and pharmacological evaluation of a great number of related derivatives [1,2]. The majority of these contain the 1,4-dihydropyridine nucleus. Some, however, are derivatives of other closely related heterocycles including the 1,4-dihydropyridazines [3,4], 1,4-dihydropyrazines [5,6], 1,4-dihydropyrimidines [7,8], and 4H-thiopyrans [9,10]. Detailed pharmacological data for many of these series have not been reported, although the patents claim that these modifications are consistent with maintenance of calcium antagonist activity. Recent reports of the 1,4-dihydropyridine calcium agonists, such as Bay k 8644, **2**, in which apparently minor structural modifications produce opposite biological effects, have renewed the effort in many laboratories to prepare novel dihydropyridine analogs for biological evaluation [11,12].



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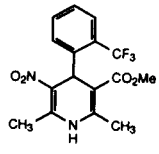

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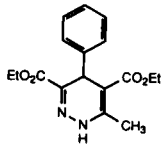
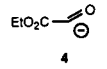


3

Recently we required diethyl 6-methyl-4-phenyl-1,4-dihydro-3,5-pyridazinedicarboxylate, **3**, as a pharmacological reference agent and as a potential intermediate to other derivatives. In the course of preparing **3** we developed a synthetic route that allowed the preparation of a variety of heterocyclic analogs from a common intermediate. Among these are five-membered ring analogs which have not been previously reported.

Results and Discussion.

A synthesis of 3,5-diester-1,4-dihydro-4-arylpyridazines was reported recently in the patent literature [3,4]. The key step is the addition of ethyl nitroacetate anion to a benzylidene derivative. Ethyl nitroacetate serves as an equivalent of the α-carbonylester carbanion synthon **4**. Treatment with base, ozonolysis, and addition of hydrazine completed the synthesis. Although this reaction worked well in the reported case, it failed at the ozonolysis step when applied to the synthesis of the closely related dihydropyridazinone, **5**. Therefore, we investigated more versatile alternatives to nitroacetate in the Michael reaction.



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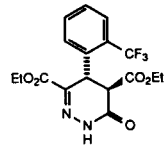

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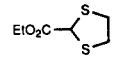

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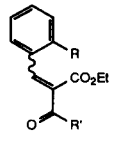
Although ethyl 1,3-dithiolane-2-carboxylate, **6**, has pre-



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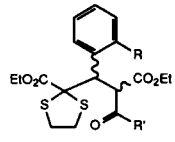

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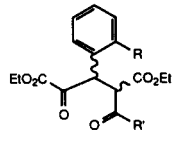
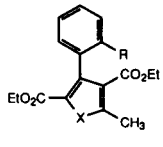
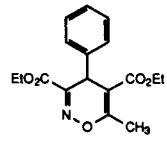


9

	R	R'
a	H	CH_3
b	CF_3	OEt
c	CF_3	CH_3



	X	R
10	O	H
11	NH	CF_3
12	S	H



13

viously been shown to add 1,4 to α,β-unsaturated carbonyl compounds, its use in this manner has been limited [13,14]. We found that the lithum salt of **6** added readily to benzylidene derivatives, **7**, to produce the dithiolane adducts **8** as mixtures of diastereoisomers. Deprotection using NBS [13] produced the tetracarbonyl intermediates, **9**, in good yield.

The oxoesters, **9**, proved to be useful intermediates to several heterocyclic analogs. Treatment of **9a** and **9b** with hydrazine produced **3** and **5**, respectively, in good overall yield. Treatment of **9a** with acid catalyst produced the furan **10**. Treatment of **9c** with ammonium chloride gave the pyrrole **11**. Reaction of **9a** with Lawesson's reagent [15] did not produce the expected thiophene **12**, but resulted in production of a poor yield of **10** along with considerable destruction of starting material. An attempt to prepare the oxazine, **13**, from **9a** and hydroxylamine instead produced a moderate yield of the corresponding pyrrole.

Assignment of structures for the above compounds was straightforward in most cases, however, introduction of the carbonyl of the pyridazinone in **5** imparts an element of stereochemistry at the C-4,5 positions. Only one isomer was observed. The stereochemistry of the 4,5-substituents in **5** was assigned the *trans* configuration after examination of the proton nmr spectrum. The C-4 and C-5 protons were assigned to singlets at δ 5.27 and 3.62. The lack of vicinal coupling is consistent with an orthogonal torsional angle accessible only to conformations of the *trans* isomer.

In contrast to the dihydropyridazines, which retain potent calcium antagonist activity, the dihydropyridazinone, pyrrole, and furan analogs exhibited no significant affinity for the dihydropyridine receptor [16].

EXPERIMENTAL

General.

Melting points were determined in open glass capillary tubes on a Thomas-Hoover apparatus and are uncorrected. The ^{1}H nmr spectra were obtained in deuteriochloroform solution and recorded on a Varian XL-200 (200 MHz) or EM-390 (90 MHz) spectrometer. The ir spectra, reported in cm^{-1}, were obtained on Digilab FTS-14 spectrometer. Mass spectra were recorded on a Finnegan 4500 mass spectrometer with an INCOS data system or a VG 7070 E/HR mass spectrometer with an 11/250 data system. Elemental analyses were preformed by the Warner-Lambert/Parke-Davis Analytical Chemistry Section. Silica gel 60 PF_{254} plates were used for thin-layer chromatography (tlc); spots were visualized with uv light. Flash chromatography refers to the method of Still and co-workers [17]. Preparative medium pressure liquid chromatography (mplc) employed Michel-Miller columns containing 230-400 mesh silica gel. Organic extracts were dried over magnesium sulfate. All concentrations and evaporations were performed *in vacuo*. Representative experimental procedures for the synthesis of the compounds shown are given below.

Diethyl 1,4-Dihydro-6-methyl-4-phenyl-3,5-pyridazinedicarboxylate, **3**.

To a solution of 8.1 g (25 mmoles) of **9a** in 250 ml of ethanol was added 1.4 g (28 mmoles) of hydrazine monohydrate. The resulting solution was heated at reflux for 16 hours. Concentration of the solution left 7.9 g (100%) of an amorphous tan solid. Purification of the major component by mplc (19:1 ethyl acetate:methylene chloride) gave 3.4 g (43%) of a yellow solid, mp 164-165°; ^{1}H nmr: (200 MHz) δ 8.02 (br s, 1H), 7.3-7.2 (m, 5H), 5.14 (s, 1H), 4.4-4.2 (m, 2H), 4.13 (q, J = 7.1 Hz, 2H), 2.39 (s, 3H), 1.31 (t, J = 7.2 Hz, 3H), 1.24 (t, J = 7.1 Hz, 3H); ir (potassium bromide): 3271, 2988, 1710, 1698, 1612, 1456 cm^{-1}.

Anal. Calcd. for $C_{16}H_{20}N_2O_4$: C, 64.54; H, 6.37; N, 8.85. Found: C, 64.74; H, 6.64; N, 8.96.

trans-Diethyl 1,4,5,6-Tetrahydro-6-oxo-4-[2-(trifluoromethyl)-phenyl]-3,5-pyridazinedicarboxylate, **5**.

A solution containing 3.8 g (7.7 mmoles) of **8b** in 25 ml of acetonitrile was added to a solution of 9.4 g (7.7 mmoles) of *N*-bromosuccinimide in 140 ml of aqueous acetonitrile (80%) at 0°. The mixture turned briefly red, then pale orange. After stirring 30 minutes, the mixture was poured into saturated sodium sulfate and 1:1 hexane:chloroform. The organic fraction was separated, washed with brine, dried, and concentrated to yield 3.7 g of an orange oil. The crude oil was dissolved in 20 ml of absolute ethanol, treated with 0.3 ml (10 mmoles) of anhydrous hydrazine, and stirred at room temperature overnight. Analysis (tlc) (3:7 ethyl acetate:hexane) indicated the starting material had been consumed. Toluenesulfonic acid hydrate (20 mg) was added and the mixture heated at reflux for 4 hours. The solution was concentrated and the residue purified by mplc (3% methanol in chloroform) to yield 1.95 g (66%) of a gum; ^{1}H nmr: (200 MHz) δ 9.12 (s, 1H), 7.75 (d, J = 7.1 Hz, 1H), 7.5-7.4 (m, 2H), 7.05 (d, J = 7.1 Hz, 1H), 5.27 (s, 1H), 4.3-4.1 (m, 4H), 3.62 (s, 1H), 1.28 (t, J = 6.2 Hz, 3H), 1.24 (t, J = 6.2 Hz, 3H).

Anal. Calcd. for $C_{17}H_{17}F_3N_2O_5$: C, 52.85; H, 4.44; N, 7.25. Found: C, 52.46; H, 4.38; N, 7.13.

Ethyl 3-Oxo-2-[[2-(trifluoromethyl)phenyl]methylene]butanoate, **7c**.

A solution containing 23.0 g (0.120 mole) of 2-(trifluoromethyl)-benzaldehyde, 17.2 g (0.132 mole) of ethyl acetoacetate, and 0.51 g (0.006 mole) of piperidine in 250 ml of toluene was heated at reflux under a Dean-Stark trap for 60 hours during which time approximately 2 ml (2.16 ml theory) of water was collected. The solution was cooled and concentrated to a yellow oil. Distillation (110°, 0.1 mm Hg) gave 30.8 g (89%) of **7c** as a 3:2 mixture of *E* and *Z* isomers; ^{1}H nmr: (90 MHz) δ 7.9-7.1 (m, 5H), 4.21 (q, J = 7 Hz, 0.8H), 4.07 (q, J = 7 Hz, 1.2H), 2.41 (s, 1.8H), 2.11 (s, 1.2H), 1.32 (t, J = 7 Hz, 1.2H), 1.03 (t, J = 7 Hz, 1.8H).

Anal. Calcd. for $C_{14}H_{13}F_3O_3$: C, 58.74; H, 4.58; F, 19.91. Found: C, 58.79; H, 4.25; F, 20.23.

Ethyl 2-Acetyl-2-(ethoxycarbonyl)-β-phenyl-1,3-dithiolane-2-propanoate, **8a**.

To a tetrahydrofuran solution of lithium diisopropylamide (48 mmoles in 250 ml of tetrahydrofuran) at 0° was added ethyl 1,3-dithiolane-2-carboxylate in tetrahydrofuran (50 ml) dropwise with vigorous magnetic stirring. After 10 minutes, **7a** (10 g, 46 mmoles) in tetrahydrofuran (50 ml) was added dropwise. When

the addition was complete, the reaction was allowed to warm to room temperature. The resulting solution was partitioned with cold 1*N* hydrochloric acid/diethyl ether (250 ml portions), the organic fractions were combined, dried, and concentrated to a yellow wax (18 g, 99%). Analysis (tlc) (5% ethyl acetate/dichloromethane) indicated the presence of a minor impurity at the origin. The yellow wax was dissolved in methylene chloride and filtered through 150 ml of 230-400 mesh silica gel, eluting with methylene chloride (2000 ml). Concentration of the eluate produced a bright yellow oil (15.9 g, 87%). The ^{1}H nmr (90 MHz) was complex due to the mixture of diastereomers, but consistent with the desired structure.

Anal. Calcd. for $C_{19}H_{24}O_5S_2$: C, 57.57; H, 6.06. Found: C, 57.55; H, 6.10.

Diethyl [[2-(Ethoxycarbonyl-1,3-dithiolan-2-yl][2-(trifluoromethyl)-phenyl]methyl]propanedioate, **8b**.

In 30 ml of dry tetrahydrofuran at 0° and under nitrogen, 1.6 ml (11 mmoles) of diisopropylamine was treated dropwise with 5.6 ml (11.2 mmoles) of 2.0 *M n*-butyllithium in hexane. The solution was cooled to −78° and 2.0 g (11.2 mmoles) ethyl 1,3-dithiolane-2-carboxylate in 2 ml of tetrahydrofuran was added dropwise. After 15 minutes, 3.6 g (11.2 mmoles) of **7b** in 5 ml of tetrahydrofuran was added dropwise. The mixture was stirred 1.5 hours, then quenched with 10 ml of 0.1 *N* aqueous hydrochloric acid. The mixture was extracted with ether and the combined organic extracts were washed with brine, dried, and concentrated to a pale yellow oil. Flash chromatography (200 g silica gel, 30-50% ethyl acetate in hexane) produced 4.3 g (78%) of a water white glass: the ^{1}H nmr (90 MHz) was complex due to the mixture of diastereomers, but was consistent with the desired structure.

Anal. Calcd. for $C_{21}H_{26}F_3O_6S_2$: C, 50.90; H, 5.29; S, 12.94. Found: C, 51.04; H, 5.10; S, 13.24.

Diethyl 2-Acetyl-4-oxo-3-phenylpentanedioate, **9a**.

To 400 ml of acetonitrile was added 100 ml of water and 44.5 g (0.25 mole) of *N*-bromosuccinimide. The resulting solution was cooled to 0° and a solution of **8a** (15.9 g, 35 mmoles) in acetonitrile (100 ml) was added dropwise. This mixture was allowed to warm to room temperature and then stirred for 16 hours. The reaction was quenched with 300 ml of saturated aqueous sodium sulfite solution and the resulting colloid partitioned with 1:1 dichloromethane:hexane (500 ml). The organic fraction was dried and concentrated to a cloudy yellow oil. This oil was partitioned between methylene chloride and water (250 ml each) and the organic fraction was dried and concentrated to yield 8.1 g (73%) of a bright yellow oil, which was used without further purification. The ^{1}H nmr (90 MHz) was complex due to the mixture of diastereomers, but was consistent with the expected structure.

Diethyl 5-Methyl-3-phenyl-2,4-furandicarboxylate, **10**.

A solution of 0.9 g (2.8 mmoles) of **9a** in 10 ml of benzene was treated with a solution of 2 drops concentrated sulfuric acid in 1 ml of benzene. The mixture was heated until the starting material was consumed, about 12 hours. The solution was treated with 50 mg of sodium carbonate and concentrated. The residue was dissolved in 3 ml of ether and filtered through celite. Purification was accomplished in two equal portions on a 4 mm Chromatotron disk to give 0.53 g (62%) of a white solid, mp 80-82°. An analytical sample was obtained by recrystallization from cyclohexane, mp 86-87°; ^{1}H nmr (90 MHz) δ 7.30 (m, 5H), 4.15 (q, J = 7.5 Hz, 2H), 4.08 (q, J = 7.5 Hz, 2H), 2.70 (s, 3H), 1.14 (t, J = 7.5 Hz, 3H), 1.07 (t, J = 7.5 Hz, 3H).

Anal. Calcd. for $C_{17}H_{18}O_5$: C, 67.54; H, 6.00. Found: C, 67.17; H, 5.82.

Diethyl 5-Methyl-3-[2-(trifluoromethyl)phenyl]-1*H*-pyrrole-2,4-dicarboxylate, **11**.

A mixture of 3.5 g (9.0 mmoles) of **9c** and 2.0 g (26.0 mmoles) of ammonium acetate in 60 ml of absolute ethanol was stirred at room temperature for 5 hours. The solution was diluted with two volumes of water and extracted with methylene chloride. The organic fractions were combined and washed with saturated aqueous sodium bicarbonate and dried. Concentration of the solution produced a white solid that was recrystallized from 1:3 chloroform:hexane to give 2.0 g (57%) of the corresponding 5-hydroxypyrroline, mp 110-112°; ir (potassium bromide): 3375, 1732, 1660 cm^{-1}; ms: (ei) 387 (M$^+$, 46), 369 (22), 314 (50), 294 (100); ^{1}H nmr (200 MHz) δ 7.64-7.15 (m, 4H), 5.02 (s, 1H), 4.72 (s, 1H), 3.89 (d, J = 7.1 Hz, 2H), 3.87 (s, 1H), 3.68 (q, J = 6.8, 2H), 2.44 (d, J = 1.3 Hz, 3H), 0.89 (t, J = 7.1 Hz, 3H), 0.80 (t, J = 7.1 Hz, 3H).

Anal. Calcd. for $C_{18}H_{19}F_3NO_5$: C, 55.81; H, 5.20; N, 3.62. Found: C, 55.85; H, 5.22; N, 3.55.

A solution of 1.6 g of the hydroxypyrroline isolated above in 50 ml toluene was heated at reflux for 1 hour. The residue left after evaporation of the solvent was crystallized from 3:2 ether:pentane to give 1.5 g (100%), mp 142-143.5°; ir (potassium bromide): 3280, 1715, 1668 cm^{-1}; ms: (ei) 369 (M$^+$, 100), 324 (12.8), 276 (56); ^{1}H nmr (200 MHz) δ 9.94 (br, 1H), 7.71-7.23 (m, 4H), 4.10-3.90 (m, 4H), 2.62 (s, 3H), 0.88 (t, J = 7.0 Hz, 3H), 0.85 (t, J = 7.0 Hz, 3H).

Anal. Calcd. for $C_{17}H_{17}F_3NO_4$: C, 58.84; H, 4.91; N, 3.79. Found: C, 58.86; H, 4.98; N, 3.88.

REFERENCES AND NOTES

[1] D. J. Triggle, in "Calcium Regulation by Calcium Antagonists", R. G. Rahwan and D. T. Witiak, eds, ACS Symposium Series 201, American Chemical Society, Washington, DC, 1981, p 22.

[2] H. Meyer, in "Calcium Antagonists and Cardiovascular Disease', L. H. Opie, ed, Raven, New York, 1984, p 165.

[3] G. Franckowiak, F. Bossert, A. Heise and R. Towart, German Offen. DE 2,834,624, 28 Feb (1980); *Chem. Abstr.*, **93**, 46704f (1980).

[4] A. Vogel, German Offen. DE 3,239,789, 11 May (1983); *Chem. Abstr.*, **99**, 105266p (1983).

[5] E. Wehinger and S. Kazda, German Offen. DE 3,400,765, 18 Jul (1985); See *Chem. Abstr.*, **104**, 5894v (1986).

[6] R. J. Chorvat and K. J. Rorig, *J. Org. Chem.*, **53**, 5779 (1988).

[7] J. Stoltefuss, H. Boeshagen, M. Schramm and G. Thomas, German Offen. DE 3,234,684, 22 Mar (1984); *Chem. Abstr.*, **101**, 55110v (1984).

[8] H. Cho, A. Mizuno, K. Shima, M. Ueda, Y. Takeuchi, M. Hamaguchi and N. Taniguchi, *Heterocycles*, **27**, 769 (1988).

[9] E. Wehinger, H. Meyer and A. Knorr, German Offen. DE 3,208,628, 22 Sep (1983); See *Chem. Abstr.*, **100**, 22581a (1984).

[10] S. Goldmann, G. Thomas and M. Schramm, German Offen. DE 3,212,737, 6 Oct (1983); See *Chem. Abstr.*, **100**, 6342t (1984).

[11] X. Y. Wei, E. M. Luchowski, A. Rutledge, C. M. Su and D. J. Triggle, *J. Pharmacol. Exp. Ther.*, **239**, 144 (1986).

[12] M. Schramm, G. Thomas, R. Towart and G. Franckowiak, *Nature (London)*, **303**, 535 (1983).

[13] J. L. Herrmann, J. E. Richman and R. H. Schlessinger,

Tetrahedron Letters, 2599 (1973).
[14] M. Kato, H. Saito and A. Yoshikoshi, *Chem. Letters*, 213 (1984).
[15] S. Scheibye, B. S. Pedersen, S. O. Lawesson, *Bull. Soc. Chem. Belg.*, **87**, 229, (1978).
[16] Y. Shih and T. Pugsley, unpublished data.
[17] W. C. Still, M. Kahn and A. Mitra, *J. Org. Chem.*, **43**, 2923 (1978).