A Novel Synthesis of Methyl *cis*-(3-Thienyl)glycidate with 2-Aminothiophenol and the Synthesis of [1,5]Benzothiazepine Derivatives

Jean Charles Lancelot, Bertrand Letois, Sylvain Rault, Carmela Saturnino and Max Robba*

Laboratoire de Chimie Thérapeutique, U.F.R des Sciences Pharmaceutiques, 1 Rue Vaubénard, 14032 Caen Cedex, France

Paolo De Caprariis

Dipartimento di Chimica Farmaceutica e Tossicologia, Università degli Studi di Napoli, Facoltá di Farmacia, Via Domenico Montesano, 49 80138, Napoli, Italy

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The synthesis of *cis*-2,3-dihydro-3-hydroxy-2-(3-thienyl)[1,5]benzothiazepin-4(5*H*)-one derivatives is described starting from 2-aminothiophenol and methyl *cis*-(3-thienyl)glycidate. The structures were confirmed by ^{1}H-nmr spectroscopy.

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In previous papers, results from the reaction of 3-(4-methoxyphenyl)glycidate **1d** with 2-nitrothiophenol [1], 2-nitrophenol [2] and 2-nitroaniline [3] were described with details. It must be pointed out that according to the conditions, these stereospecific reactions led either to *threo* or *erythro* isomeric forms of intermediate opened esters **1e-1g**. The *threo* isomer was an intermediary used for the synthesis of Diltiazem **1h**, a calcium antagonist with anti-angorous activity [4]. The oxa and aza analogous *threo* derivatives **1i, 1j** were obtained from the *threo* esters intermediary [5,6]. These interesting stereospecific reactions realized from arylglycidic esters led us to synthesize a new

Chart 1

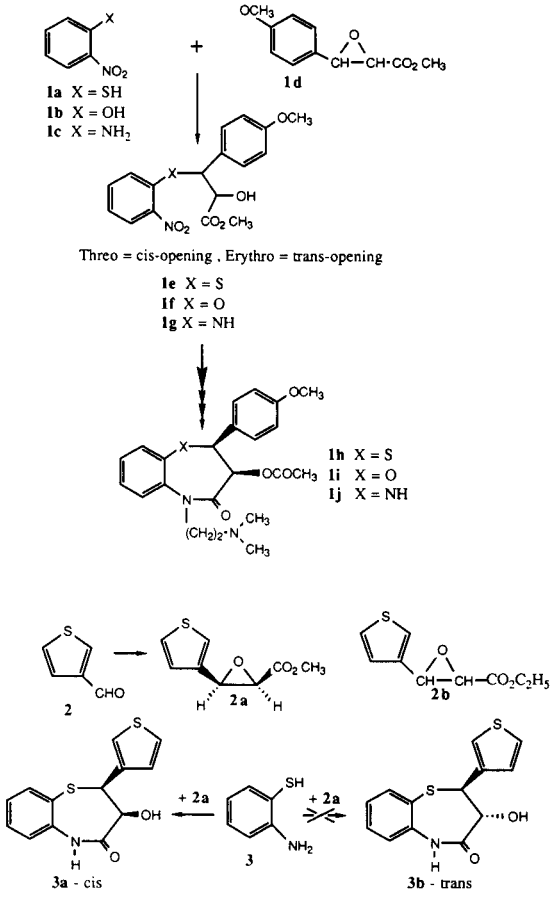
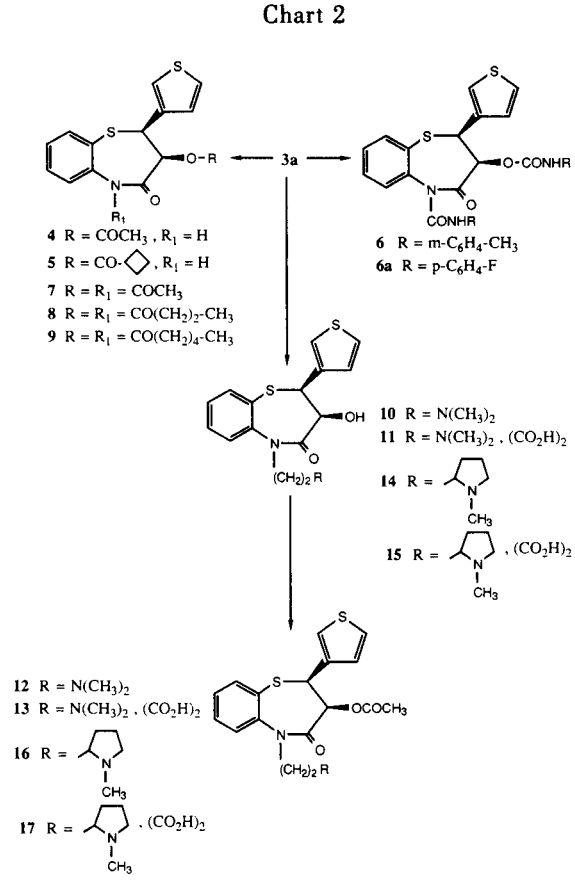


Chart 2



ester, the methyl *cis*-(3-thienyl)glycidate **2a** on the basis of the work of Campaigne [7]. The lack of information about the ^{1}H-nmr spectrum of the known ethyl ester **2b** and its confirmation led us to carry out the study of the methyl ester **2a** synthesized from 3-thiophenecarbaldehyde and methyl chloroacetate in the presence of sodium methoxide. After distillation *in vacuo*, the assignment of the ^{1}H-nmr spectrum showed that the preferential form for this ester was the *cis-threo* stereoisomer **2a**. The 3-thienylglycidic ester **2a** was heated at 170° for 6 hours with 2-aminothiophenol **3** to afford the *cis*-2,3-dihydro-3-hydroxy-2-(3-thienyl)[1,5]benzothiazepin-4(5*H*)-one **3a**. According to the substitution reaction conditions, the benzothiazepine **3a** led either to mono of di-substituted derivatives. Thus, at ambient temperature, acetyl chloride and cyclobutyl chloride gave the *o*-substituted derivatives **4-5**. After refluxing in acetic, butyric or caproic anhydrides, the benzothiazepines **3** produced the bis-substituted derivatives **7-9**. Identically the reaction of isocyanates with **3a** in refluxing toluene afforded the carbamylurea derivatives **6** and **6a**. Alkylation of benzothiazepine **3a** in acetone with 2-(*N*,*N*-dimethylamino)ethyl chloride or with 2-(2-chloroethyl)-1-methylpyrrolidine hydrochlorides in presence of sodium carbonate led to *cis*-2,3-dihydro[1,5]benzothiazepines **10-14**, the acylation of which with acetic acid provided the corresponding 3-acetoxy derivatives **12-16**. Benzothiazepine derivatives **10**, **12**, **14** and **16** were salified by oxalic acid to the expected salts **11**, **13**, **15** and **17**. The structures of all compounds were consistent with ^{1}H-nmr spectra which were analysed at first order and allowed the assignment of all signals.

EXPERIMENTAL

Melting points were determined with a Kofler Heiz bank apparatus and are uncorrected. The ir spectra were recorded as potassium bromide pellets on a Perkin-Elmer 257G spectrometer and ^{1}H-nmr spectra were obtained on a Varian EM 90 spectrometer using DMSO-d_6 as the solvent. Chemical shifts are expressed in δ (ppm) down field from tetramethylsilane as an internal reference.

Methyl *cis*-(3-Thienyl)glycidate **2a**.

A 250 ml flask fitted with thermometer, 125 ml pressure equalizing dropping funnel, and stirrer was charged with 11.2 g (0.10 mole) of 3-thiophenecarbaldehyde **2** and 0.11 mole of methyl chloroacetate. A solution of 0.11 mole of sodium methoxide in 125 ml of dry methanol was put in the dropping funnel, and the entire system was swept with a stream of nitrogen for 15 minutes. The flask was then lowered into an ice-water bath, and the addition of the methoxide solution was begun dropwise in order to maintain the temperature of the reaction below 10°. After completion of addition, which required two hours, the slurry was stirred for an additional 1.5 hours at 10°. Most of the methanol was removed on the steam bath at reduced pressure and the residue was taken up in ether, washed with water, then with saturated sodium chloride solution, and dried over anhydrous magnesium sulfate. Ether was evaporated and the glycidic ester was distilled at reduced pressure yielding a colorless liquid, bp 191-195° (5 mm Hg), 15 g (81%) of **2a**; ir (potassium bromide): ν cm^{-1} 1710 (CO); ^{1}H-nmr (DMSO-d_6): δ 7.30 (2H, m, H_4-H_5 thienyl), 6.90 (1H, q, H_2 thienyl), 3.80 (3H, s, OCH_3), 4.13 (1H, d, J = 3.30 Hz, C*H*-CH), 3.60 (1H, d, J = 3.30 Hz, CH-C*H*).

Anal. Calcd. for $C_8H_8O_3S$: C, 52.18; H, 4.38; S, 17.37. Found: C, 52.20; H, 4.40; S, 17.50.

cis-2,3-Dihydro-3-hydroxy-2-(3-thienyl)[1,5]benzothiazepin-4(5*H*)-one **3a**.

A mixture of **2a** 18.40 g (0.10 mole) and 2-aminothiophenol **3** 12.5 g (0.10 mole) was heated at about 180° for 3.5 hours. The solid obtained was recrystallized from ethanol to give **3a**, mp 212°, 20 g (72%); ir (potassium bromide): ν cm^{-1} 3420 (OH), 3180 (NH) and 1680 (CO); ^{1}H nmr (DMSO-d_6): δ 4.30 (1H, t, OH), 5.65 (1H, d, J = 6.60 Hz, C_2-H), 4.80 (1H, d, J = 6.60 Hz, C_3-H), 10.30 (1H, s, NHCO, deuterium oxide exchangeable), 7.50-7.10 (7H, m, ArH).

Anal. Calcd. for $C_{13}H_{11}NO_2S_2$: C, 56.30; H, 4.00; N, 5.05; S, 23.12. Found: C, 56.40; H, 4.02; N, 5.06; S, 23.03.

cis-Acetoxy-2,3-dihydro-3-hydroxy-2-(3-thienyl)[1,5]benzothiazepin-4(5*H*)-one **4**.

A mixture of the *cis*-lactam **3a** 2.77 g (0.01 mole), acetyl chloride 0.78 g (0.01 mole) and pyridine (1 ml) was stirred at room temperature for 3 hours, then neutralized with dilute hydrochloric acid and extracted with ethyl acetate. The extracts were washed with water, dried and evaporated. The residue was recrystallized from diethyl ether to give **4**, mp 78°, 2.70 g (84%); ir (potassium bromide): ν cm^{-1} 3200 (NH), 1740 and 1680 (CO); ^{1}H nmr (DMSO-d_6): δ 9.00 (1H, s, NH), 5.40 (1H, d, C_2-H), 5.20 (1H, d, C_3-H), 1.96 (3H, s, $COCH_3$), 7.63-7.20 (7H, m, ArH).

Anal. Calcd. for $C_{15}H_{13}NO_3S_2$: C, 56.41; H, 4.10; N, 4.39. Found: C, 56.50; H, 4.11; N, 4.29.

cis-3-Cyclobutyloxy-2,3-dihydro-2-(3-thienyl)[1,5]benzothiazepin-4(5*H*)-one **5**.

This *cis*-lactam **3a** 2.77 g (0.01 mole), cyclobutyl chloride 1.18 g (0.01 mole) and pyridine (1 ml) was reacted as in the reaction described for **4** (diethyl ether), mp 134°, 2.70 g (75%); ir (potassium bromide): ν cm^{-1} 3420 (OH), 3300 (NH), 1725 and 1685 (CO); ^{1}H nmr (DMSO-d_6): δ 10.33 (1H, s, NH), 5.43 (1H, d, J = 6.60 Hz, C_2-H), 5.13 (1H, d, J = 6.60 Hz, C_3-H), 2.83-1.76 (7H, m, CO-C_4H_7), 7.46-7.13 (7H, m, ArH).

Anal. Calcd. for $C_{18}H_{17}NO_3S_2$: C, 60.16; H, 4.77; N, 3.90. Found: C, 60.30; H, 4.79; N, 3.96.

cis-3-Acetoxy-5-acetyl-2,3-dihydro-2-(3-thienyl)[1,5]benzothiazepin-4(5*H*)-one **7**.

A solution of the *cis*-lactam **3a** 2.77 g (0.01 mole) was heated in acetic anhydride 15 ml at 100° for 2 hours, then poured into a mixture of ice and sodium bicarbonate. After extraction with chloroform, the extracts were washed with water, dried and evaporated to give crude **7** (hexane), mp 36°, 3 g (83%); ir (potassium bromide): ν cm^{-1} 1750, 1720 and 1690 (CO); ^{1}H nmr (DMSO-d_6): δ 5.40 (1H, d, C_2-H), 5.10 (1H, d, C_3-H), 2.76 (3H, s, N-COC*H*$_3$), 1.96 (3H, s, O-COC*H*$_3$), 7.73-7.33 (7H, m, ArH).

Anal. Calcd. for $C_{17}H_{15}NO_4S_2$: C, 56.49; H, 4.18; N, 3.88. Found: C, 56.41; H, 4.20; N, 3.88.

cis-3-Butyryloxy-5-butyryl-2,3-dihydro-2-(3-thienyl)[1,5]benzothiazepin-4(5*H*)-one **8**.

The *cis*-lactam **3a** 2.77 g (0.01 mole) and 4 ml of butyric anhydride were reacted as in the reaction described for **7**, oil, bp 120° (0.5 mm Hg), 2.90 g (70%); ir (potassium bromide): ν cm^{-1} 1750, 1725 and 1680 (CO); ^1H nmr (DMSO-d_6): δ 5.40 (1H, d, J = 6.60 Hz, C_2-H), 5.20 (1H, d, J = 6.60 Hz, C_3-H), 3.43, 2.50, 1.86 (8H, m, $[(CH_2)_2]_2$), 1.23 (6H, m, $2CH_3$), 7.96-7.56 (7H, m, ArH).

Anal. Calcd. for $C_{21}H_{23}NO_4S_2$: C, 60.41; H, 5.55; N, 3.35; S, 15.36. Found: C, 60.37; H, 5.57; N, 3.14; S, 15.46.

cis-3-Caproyloxy-5-caproyl-2,3-dihydro-2-(3-thienyl)[1,5]-benzothiazepin-4(5*H*)-one **9**.

This *cis*-lactam **3a** 2.77 g (0.01 mole) and 4 ml of caproic anhydride were reacted as in the reaction described for **7**, oil, bp 135° (0.5 mm Hg), 3.10 g (65%); ir (potassium bromide): ν cm^{-1} 1755, 1720 and 1685 (CO); ^1H nmr (DMSO-d_6): δ 5.23 (1H, d, C_2-H), 4.73 (1H, d, C_3-H), 2.20, 1.43 (16H, m, $[(CH_2)_4]_2$), 0.76 (6H, m, $2CH_3$), 7.40-7.06 (7H, m, ArH).

Anal. Calcd. for $C_{25}H_{31}NO_4S_2$: C, 63.40; H, 6.60; N, 2.96. Found: C, 63.45; H, 6.69; N, 2.94.

cis-3-Amino-*m*-tolylcarbonyloxy-5-amino-*m*-tolylcarbonyl-2,3-dihydro-2-(3-thienyl)[1,5]benzothiazepin-4(5*H*)-one **6**.

A mixture of 2.77 g (0.01 mole) of compound **3a** and *m*-tolylisocyanate 2.66 g (0.02 mole) in toluene was heated at reflux for 3 hours. The reaction mixture was concentrated *in vacuo* and the solid product was collected by filtration and recrystallized from acetonitrile, mp 118°, 4.30 g (79%); ir (potassium bromide): ν cm^{-1} 3320, 3200 (NH), 1730, 1710 and 1685 (CO); ^1H nmr (DMSO-d_6): δ 9.70 (1H, s, NH), 10.90 (1H, s, NH), 5.42 (1H, d, J = 6.60 Hz, C_2-H), 5.18 (1H, d, J = 6.60 Hz, C_3-H), 7.60-7.15 (15H, m, ArH), 2.33 (6H, s, $2CH_3$).

Anal. Calcd. for $C_{29}H_{25}N_3O_4S_2$: C, 63.95; H, 4.81; N, 7.71; S, 11.77. Found: C, 64.00; H, 4.74; N, 7.73; S, 11.82.

cis-3-Amino-*p*-fluorophenylcarbonyloxy-5-amino-*p*-fluorophenylcarbonyl-2,3-dihydro-2-(3-thienyl)[1,5]benzothiazepin-4(5*H*)-one **6a**.

The *cis*-lactam **3a** 2.77 g (0.01 mole) and *p*-fluorophenyl isocyanate 2.74 g (0.02 mole) were reacted as in the reaction described for **6**, mp 113°, 4.30 g (78%); ir (potassium bromide): ν cm^{-1} 3280, 3220 (NH), 1720, 1700 and 1680 (CO); ^1H nmr (DMSO-d_6): δ 9.73 (1H, s, NH), 10.99 (1H, s, NH), 5.40 (1H, d, J = 6.60 Hz, C_2-H), 5.20 (1H, d, J = 6.60 Hz, C_3-H), 7.56-7.10 (15H, m, ArH).

Anal. Calcd. for $C_{27}H_{19}F_2N_3O_4S_2$: C, 58.80; H, 3.44; N, 7.62; F, 6.89. Found: C, 59.00; H, 3.50; N, 7.70; F, 6.85.

cis-2,3-Dihydro-5-[2-(dimethylamino)ethyl]-3-hydroxy-2-(3-thienyl)-[1,5]benzothiazepin-4(5*H*)-one **11** (Oxalate).

A mixture of the *cis*-lactam **3a** 2.77 g (0.01 mole), 2-(dimethylamino)ethyl chloride hydrochloride 2.88 g (0.02 mole), powdered sodium carbonate 6.36 g (0.06 mole), acetone (150 ml) and water (1.5 ml) was heated under reflux for 20 hours. After cooling, inorganic compounds were filtered off and the solvent was evaporated. The residue was dissolved in diethyl ether and the solution was washed with water, dried and concentrated. The residual oil **10** was dissolved in acetone and converted to the oxalate salt **11** which was recrystallized from acetonitrile, mp 254°, 2.60 g (59%); ir (potassium bromide): ν cm^{-1} 3380 (OH), 2700 $(COOH)_2$, 1670 and 1630 (CO); ^1H nmr (DMSO-d_6): δ 4.40 (1H, t, OH), 5.66 (2H, s, $(CO_2H)_2$), 4.93 (1H, d, C_2-H), 4.16 (1H, d, C_3-H), 7.41-7.00 (7H, m, ArH), 3.73-2.66 [4H, m, $CH_2)_2$], 2.43 (6H, s, $2CH_3$).

Anal. Calcd. for $C_{19}H_{22}N_2O_6S_2$: C, 52.04; H, 5.06; N, 6.39; S, 14.62. Found: C, 52.10; H, 5.06; N, 6.42; S, 14.66.

cis-2,3-Dihydro-5-[2-(ethyl-1-methyl)pyrrolidinyl]-3-hydroxy-2-(3-thienyl)[1,5]benzothiazepin-4(5*H*)-one **15** (Oxalate).

The *cis*-lactam **3a** 2.77 g (0.01 mole) and 2-(2-chloroethyl)-1-methyl)pyrrolidine hydrochloride 3.68 g (0.02 mole) in powdered sodium carbonate were reacted as in the reaction described for **11**, mp 127°, 2.20 g (47%); ir (potassium bromide): ν cm^{-1} 3400 (OH), 2700 $(COOH)_2$, 1720 and 1645 (CO); ^1H nmr (DMSO-d_6): δ 3.90 (1H, t, OH), 7.76 (2H, s, $(CO_2H)_2$), 4.83 (1H, d, J = 7.20 Hz, C_2-H), 4.06 (1H, d, J = 7.20 Hz, C_3-H), 7.23-6.83 (7H, m, ArH), 3.46, 3.00, 1.66 [11H, m, $(CH_2)_2$ and $CH(CH_2)_3$], 2.33 (3H, d, CH_3).

Anal. Calcd. for $C_{22}H_{26}N_2O_6S_2$: C, 55.23; H, 5.48; N, 5.86. Found: C, 55.31; H, 5.46; N, 5.90.

cis-3-Acetoxy-2,3-dihydro-5-[2-(dimethylamino)ethyl]-2-(3-thienyl)-[1,5]benzothiazepin-4(5*H*)-one **13** (Oxalate).

A mixture of **10**, 3.48 g (0.01 mole), acetic anhydride (5 ml) and pyridine (0.1 ml) was heated at 80° for 2 hours. After removal of the acetic acid and pyridine. The residue was converted into the oxalate, which was recrystallized from ethanol to give oxalate **13**, mp 176°, 2.90 g (60%); ir (potassium bromide): ν cm^{-1} 3420 (OH), 2700 $(COOH)_2$, 1725 and 1660 (CO); ^1H nmr (DMSO-d_6): δ 6.93 [(2H, s, $(CO_2H)_2$)], 5.33 (1H, d, J = 7.20 Hz, C_2-H), 5.00 (1H, d, J = 7.20 Hz, C_3-H), 7.56-7.16 (7H, m, ArH), 4.20-3.16 [4H, m, $(CH_2)_2$], 2.75 [6H, s, $N(CH_2)_3$], 1.93 (3H, d, $COCH_3$).

Anal. Calcd. for $C_{21}H_{24}N_2O_7S_2$: C, 52.49; H, 5.03; N, 5.83; S, 13.34. Found: C, 52.31; H, 4.99; N, 5.79; S, 13.24.

cis-3-Acetoxy-2,3-dihydro-5-[2-(ethyl-1-methyl)pyrrolidino]-2-(3-thienyl)[1,5]benzothiazepin-4(5*H*)-one **17** (Oxalate).

A mixture of **14**, 3.88 g (0.01 mole), acetic anhydride (5 ml) and pyridine (0.1 ml) was reacted as in the reaction described for **13**, mp 100°, 2 g (38%); ir (potassium bromide): ν cm^{-1} 3400 (OH), 2700 $(COOH)_2$, 1720 and 1670 (CO); ^1H nmr (DMSO-d_6): δ 8.46 [(2H, s, $(CO_2H)_2$)], 5.40 (1H, d, J = 7.20 Hz, C_2-H), 5.06 (1H, d, J = 7.20 Hz, C_3-H), 7.60-7.20 (7H, m, ArH), 4.63, 3.83, 2.03 [11H, m, $(CH_2)_2$ and $CH(CH_2)_3$], 2.70 (3H, s, N-CH_3), 1.93 (3H, s, $COCH_3$).

Anal. Calcd. for $C_{24}H_{28}N_2O_7S_2$: C, 55.38; H, 5.44; N, 5.37; S, 12.29. Found: C, 55.42; H, 5.45; N, 5.40; S, 12.31.

REFERENCES AND NOTES

[1a] T. Hashiyama, H. Inoue, M. Konda and M. Takeda, *J. Chem. Soc., Perkin Trans. I*, 1725 (1984); [b] T. Hashiyama, H. Inoue and M. Takeda, *ibid.*, 421 (1985); [c] T. Hashiyama, H. Inoue, M. Konda and M. Takeda, *Chem. Pharm. Bull.*, **33**, 1256 (1985).

[2] T. Hashiyama, A. Watanabe, H. Inoue, M. Konda, M. Takeda, S. Murata and T. Nagao, *Chem. Pharm. Bull.*, **33**, 634 (1985).

[3] T. Hashiyama, H. Inoue, M. Takeda, S. Murata and T. Nagao, *Chem. Pharm. Bull.*, **33**, 2348 (1985).

[4a] H. Kugita, H. Inoue, M. Ikezaki and S. Takeo, *Chem. Pharm. Bull.*, **18**, 2028 (1970); [b] H. Kugita, H. Inoue, M. Ikezaki, M. Konda and S. Takeo, *ibid.*, **18**, 2284 (1970); [c] T. Nagao, M. Sato, H. Nakajima and A. Kijomoto, *Chem. Pharm. Bull.*, **21**, 92 (1973).

[5a] A. Elker, J. Lehmann and F. Zymalkowski, *Arch. Pharm.*, **312**, 26 (1979); [b] E. Kamandi, A. W. Frahm and F. Zymalkowski, *ibid.*, **307**, 871 (1974); [c] *Idem., ibid.*, **308**, 135 (1975).

[6a] S. Ohno, K. Mizukoshi, K. Izumi, K. Kato and M. Hori, *Chem. Pharm. Bull.*, **36**, 551 (1988); [b] H. Kugita, H. Inoue, M. Ikezaki, M. Konda and S. Takeo, *ibid.*, **19**, 595 (1971); [c] J. Krapcho, E. R. Spitzmiller and C. F. Turk, *J. Med. Chem.*, **6**, 544 (1963); [d] *Idem., ibid.*, **9**, 191 (1966); [e] *Idem., ibid.*, **11**, 361 (1968).

[7a] E. Campaigne and O. E. Yokley, *J. Org. Chem.*, **28**, 914 (1963); [b] E. Campaigne and W. M. Lesuer, *J. Am. Chem. Soc.*, **71**, 333 (1949); [c] *Idem., ibid.*, **76**, 2445 (1954).