Fathy M. Abdelrazek[a], Peter Metz[a], Ebtehal K. Farrag[b]

[a] Institut für Organische Chemie, Technische Universität Dresden, Dresden, Germany
[b] Medicinal Chemical Department, National Research Center, Dokki, Giza, Egypt

Synthesis and Molluscicidal Activity of 5-oxo-5,6,7,8-Tetrahydro-4*H*-Chromene Derivatives

Furfurylidenemalononitriles and thienylidenemalononitriles were treated with 1,3-cyclohexanediones to afford 2-amino-4-hetaryl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile derivatives. The molluscicidal activity of these compounds was investigated.

Keywords: Furfurylidenemalononitriles; Thienylidenemalononitriles; 1,3-cyclohexanediones; 2-Amino-4-hetaryl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitriles

Received: February 25, 2004; Accepted: June 24, 2004 [FP881]
DOI 10.1002/ardp.200400881

Introduction

Schistosomiasis (bilharziasis) is one of the major national health problems in Egypt. One approach to combat this disease is to kill the water snail *Biomphalaria alexandrina* which is the intermediate host of the infective phase of *Schistosoma mansoni* in endemic areas.

Ricciocarpin A (**1**) and ricciocarpin B (**2**) (Figure 1) isolated from the liverwort *Ricciocarpos natans* were found to exhibit high molluscicidal activity against the water snail *Biomphalaria glabrata* (LC_{100} = 11 and 43 ppm, respectively) [1]. Metz et al. have reported an enantioselective synthesis of the molluscicides **1** and **2** via ring closing metathesis [2]. Previously, Abdelrazek et al. have reported the synthesis of several furo[2,3-d]pyrimidine and furo[2,3-b]pyridine derivatives. From those compounds, **3a,b** (Figure 1) showed a moderate molluscicidal activity against *Biomphalaria alexandrina* (LC_{50} = 10 ppm for both compounds) [3]. A common feature of structures **1** and **3a,b** is the presence of the furan moiety. Furthermore, we have also reported that some pyran derivatives exhibit also a moderate molluscicidal activity down to LC_{50} = 10 ppm [4]. In the light of these data, it was planned to rapidly construct structural analogs of **1** and/or **2** incorporating a furan subunit with the aim of obtaining related compounds that might possess potent molluscicidal activity.

Compounds **1** and **2** are essentially assembled from a pyran fused to a *gem*-dimethyl-substituted cyclohexane with a 3-furyl substituent (or oxidized derivative) attached to the pyran. It has been reported that

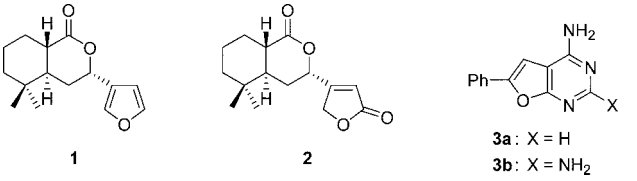


Figure 1.

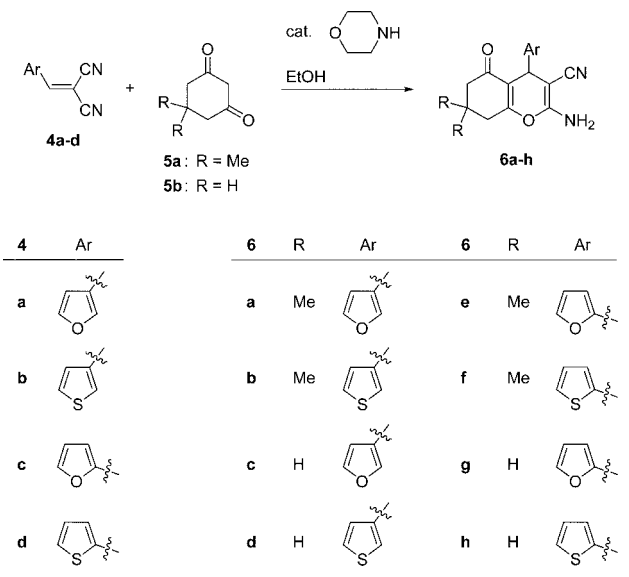
dimedone (**5a**) reacts with arylidenemalononitriles to afford tetrahydrobenzo[b]pyran (chromene) derivatives [5–7]. Therefore, it was envisioned that **5a** can serve as a suitable candidate to supply the *gem*-dimethylcyclohexane part, and ,by virtue of its active methylene and carbonyl groups, it seemed to be a good precursor for a fused pyran through its reaction with 3-furfurylidenemalononitrile as well. Furthermore, in order to verify whether the activity (if found) is attributed to the position of attachment, to the nature of the five-membered heterocyclic ring, or to the presence of the *gem*-dimethyl group at the cyclohexane, the reaction was carried out with 3- and 2-furfurylidene- as well as 3- and 2-thienylidenemalononitriles on the one hand and dimedone (**5a**) as well as 1,3-cyclohexanedione (**5b**) on the other hand.

Results and discussion

Synthesis

Furfurylidene- and thienylidenemalononitriles **4a–d** were prepared via Knoevenagel condensation of the corresponding aldehydes with malononitrile in the presence of a basic catalyst as reported in the literature [5–10]. These arylidene compounds were allowed to react with both dimedone (**5a**) and 1,3-cyclohexanedione (**5b**) to afford a 1:1 adduct in each case

Correspondence: Fathy Mohamed Abdelrazek, Chemistry Department, Faculty of Science, Cairo University, Giza, Egypt. Phone: +20 2 330-1651 or +20 2 567-6601, e-mail: prof_fmrazek@yahoo.com



Scheme 1.

(Scheme 1). Elemental analyses and spectral data proved these reaction products to be the tetrahydro-4*H*-chromene compounds **6a**–**h**, respectively (see Experimental). The 2-furanyl and 2-thienyl derivatives are generally darker in colour than the 3-substituted analogs presumably due to the longer conjugation in the former compounds which causes a shift of the wave length to the visible region [11]. Formation of these heterocycles is assumed to proceed via Michael addition of the active methylene group in **5a** or **5b** to the electron-deficient double bond of the ylidenes **4a**–**d** followed by intramolecular addition of an enol hydroxyl group to one of the nitrile functions under the reaction conditions to give the isolated products. A support of this plausible mechanism has been recently reported [12].

Molluscicidal activity

The toxicity of compounds **6a**–**h** to *Biomphalaria alexandrina* snails, the intermediate host of *Schistosoma mansoni* in Egypt was evaluated as shown in Table 1. The half lethal dose (LC_{50} in ppm/nM) for each compound was determined and is shown in Table 2. An insight inspection of the results listed in Table 2 shows that the presence of a 3-furanyl substituent along with a *gem*-dimethyl group (**6a**) gives the relatively best results (5 ppm; 17.6 nM), while a 2-furanyl substituent with the two methyl groups present (**6e**) is lower in activity (8 ppm; 28.17 nM). 3-Furanyl and 2-furanyl substituents are associated with nearly equal, but lower, activities in the absence of methyl groups at the cyclohexane ring (**6c**, **6g**) (11 and 12 ppm; 42.97 and 46.88 nM, respectively). Thiophene derivatives are generally less active than their furan analogs. 3-Thienyl and 2-thienyl derivatives with methyl groups at the cyclohexane ring (**6b**, **6f**) show also nearly equal activities (10 and 11 ppm; 33.33 and 36.66 nM, resp.), whereas both thienyl derivatives in the absence of cyclohexane methyl groups are completely inactive even in concentrations above 17 ppm; 62.50 nM (**6d**, **6h**). In comparison with ricciocarpin A (1) having LC_{100} = 11ppm, and with our previous compounds **3a, b** having LC_{50} = 10ppm; our new compound **6a** is superior in activity. LC_{50} = 5ppm means that half the number of the snails die at this concentration and that any slight increase in the concentration (approx. 6–7 ppm, not necessarily double the value) will lead to the death of all snails, which is LC_{100}. A comparison of the molluscicidal activity of our compounds with an international standard: 2,5-dichloro-4-nitrosalicylanilide which is reported to possess LC_{100} = 1ppm [13, 14] showed that our compounds are still far inferior as molluscicidal agents. Thus, the combination of 3-furanyl substitution at the pyran and a cyclohexane bearing a *gem*-dimethyl group is the most promising

Table 1. The mean number of snails killed ±1 after an exposure time of 24 h at the given concentration.

Compd. No.	1 ppm	3 ppm	5 ppm	7 ppm	9 ppm	11 ppm	13 ppm	15 ppm	17 ppm
6a	–	2	5	8	10	10	10	10	10
6b	–	–	–	1	3	7	10	10	10
6c	–	–	–	–	2	5	8	10	10
6d	–	–	–	–	–	–	–	–	–
6e	–	–	2	3	8	10	10	10	10
6f	–	–	–	–	3	5	10	10	10
6g	–	–	–	–	1	3	8	10	10
6h	–	–	–	–	–	–	–	–	–

Full Paper

Table 2. Molluscicidal activity of compounds **6a**–**h** expressed as LC_{50} in ppm.

Compound	LC_{50} (nM)	Compound	LC_{50}
6a	5 (17.61)	**6e**	8 (28.17)
6b	10 (33.33)	**6f**	11 (36.66)
6c	11 (42.97)	**6g**	12 (46.88)
6d	>17 (62.50)	**6h**	>17 (62.50)

structural feature. Modifications on the basis of this lead scaffold might further improve molluscicidal activity, which should be taken into consideration in future studies.

Acknowledgments

We are indebted to the Alexander von Humboldt Foundation (Germany) for granting a research fellowship to F. M. Abdelrazek from July to September 2003; during this time the synthetic part of this work has been carried out.

Experimental

Melting points were measured on an Electrothermal 9100 apparatus (Kleinfeld, Gehrden, Germany) and are uncorrected. FT-IR spectra (KBr) were obtained on a Nicolet 205 spectrophotometer (Nicolet, Madison, WI, USA). ^{1}H NMR and ^{13}C NMR spectra were obtained on a Bruker AC 300 P (^{1}H: 300 MHz, ^{13}C: 75.5 MHz; Bruker, Rheinstetten, Germany) in $CDCl_3$ unless mentioned otherwise using TMS as internal reference. Chemical shifts are expressed in δ (ppm) values. ^{13}C multiplicities were determined using DEPT pulse sequences. Elemental analyses were carried out in the microanalytical laboratory of the Institut für Organische Chemie, Technische Universität Dresden. Molluscicidal activity tests were conducted in the Medicinal Chemical Department, Laboratory of Parasitology, National Research Center of Egypt.

*Furfurylidene and thienylidene derivatives **4a**–**d** (general procedure)*

To the appropriate aldehyde (10 mmol) in dry ethanol (20 mL) malononitrile (0.66 g, 10 mmol) and 2–3 drops of sodium ethoxide solution in dry ethanol were added, whereupon the content of the flask boiled vigorously. After allowing the mixture to cool to room temperature, crystalline products precipitated, which were filtered off and washed several times with cold ethanol to afford analytically pure compounds.

*1,1-Dicyano-2-furan-3-ylethylene (**4a**)*

Yield 85%; grey solid crystals, mp 119–120 °C (EtOH); IR 2232, 2222 (CN) cm^{-1}; ^{1}H NMR δ 7.19 (d, J = 2.1 Hz, 1H), 7.59 (apparent t, J = 1.4 Hz, 1H), 7.69 (s, 1H), 8.06 (s, 1H); ^{13}C NMR δ 81.65 (s), 108.08 (d), 112.66 (s), 113.42 (s), 120.99 (s), 145.96 (d), 150.02 (d), 150.14 (d). Anal. calcd. for $C_8H_4N_2O$: C, 66.67; H, 2.80; N, 19.44. Found C, 66.32; H, 2.73; N, 19.25.

*1,1-Dicyano-2-thien-3-ylethylene (**4b**)*

Yield 90%; pale yellowish crystalline solid, mp 63–64 °C (EtOH); IR 2224 (CN) cm^{-1}; ^{1}H NMR δ 7.51 (dd, J = 2.9 Hz, J = 4.9 Hz, 1H), 7.70-7.85 (m, 2H), 8.18 (d, J = 1.5 Hz, 1H); ^{13}C NMR δ 80.74 (s), 113.03 (s), 113.77 (s), 126.88 (d), 128.45 (d), 134.02 (s), 136.72 (d), 152.20 (d). Anal. calcd. for $C_8H_4N_2S$: C, 59.98; H, 2.52; N, 17.49; S, 20.02. Found C, 60.08; H, 2.54; N, 17.41; S, 20.13.

*1,1-Dicyano-2-furan-2-ylethylene (**4c**) and 1,1-Dicyano-2-thien-2-ylethylene (**4d**)*

Yield **4c**: 87%, yield **4d**: 91%. The data of these two compounds were found to be identical to those reported in the literature [4–9].

*Reaction of arylidenemalononitriles **4a**–**d** with dimedone (**5a**) and 1,3-cyclohexanedione (**5b**) (general procedure)*

To a solution of dimedone (**5a**) (1.4 g, 10 mmol) or 1,3-cyclohexanedione (**5b**) (1.12 g, 10 mmol) in dry ethanol (20 mL) the appropriate arylidene derivative (10 mmol) was added, as well as 5 drops of morpholine as catalyst. The reaction mixture was heated gently until the contents of the flask dissolved and then stirred at room temperature until a precipitate appeared (usually 1 h). Otherwise, the reaction mixture was refluxed for 30 min, after which the products precipitated. In any case, the reaction mixture was allowed to cool to room temperature, poured on ice-cold water and neutralized by dropwise addition of conc. HCl. The precipitated solids were filtered off and recrystallized from ethanol to afford the pure products.

*2-Amino-4-furan-3-yl-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (**6a**)*

Yield 91%; yellow granules, mp 181–183 °C (EtOH); IR 3400, 3330, 3216 (NH_2), 2196 (CN), 1657 (CO) cm^{-1}; ^{1}H NMR δ 1.03 (s, 3H), 1.11 (s, 3H), 2.26 (s, 2H), 2.40 (s, 2H), 4.43 (s, 1H), 4.70 (s, 2H, D_2O exchangeable, NH_2), 6.27 (d, J = 0.8 Hz, 1H), 7.25-7.35 (m, 2H); ^{13}C NMR δ 26.07 (d), 27.52 (q), 28.88 (q), 32.12 (s), 40.73 (t), 50.75 (t), 62.08 (s), 109.58 (d), 113.88 (s), 118.62 (s), 127.52 (s), 139.71 (d), 143.06 (d), 158.28 (s), 161.61 (s), 195.80 (s). Anal. calcd. for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67; N, 9.85. Found C, 67.41; H, 5.62; N, 9.83.

*2-Amino-4-thien-3-yl-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (**6b**)*

Yield 93%; fine white needles, mp 214–215 °C (EtOH); IR 3370, 3320, 3206 (NH_2), 2196 (CN), 1656 (CO) cm^{-1}; ^{1}H NMR δ 1.03 (s, 3H), 1.11 (s, 3H), 2.25 (s, 2H), 2.42 (s, 2H), 4.56 (s, 1H), 4.58 (s, 2H), 6.95 (dd, J = 1.3 Hz, J = 5.0 Hz, 1H), 7.09 (dd, J = 1.3 Hz, J = 2.9 Hz, 1H), 7.21 (dd, J = 2.9 Hz, J = 5.0 Hz, 1H); ^{13}C NMR δ 27.63 (q), 28.87 (q), 30.36 (d), 32.16 (s), 40.69 (t), 50.68 (t), 62.93 (s), 114.13 (s), 118.68 (s), 125.88 (d), 126.74 (d), 127.75 (d), 143.84 (s), 157.86 (s), 161.44 (s), 195.84 (s). Anal. calcd. for $C_{16}H_{16}N_2O_2S$: C, 63.98; H, 5.37; N, 9.33; S, 10.67. Found C, 64.09; H, 5.32; N, 9.28; S, 10.63.

*2-Amino-4-furan-3-yl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (**6c**)*

Yield 73%; fine yellow crystals, mp 187–189°C (EtOH); IR 3460, 3337 (NH_2), 2199 (CN), 1651 (CO) cm^{-1}; ^1H NMR δ 1.90–2.10 (m, 2H), 2.30-2.60 (m, 4H), 4.45 (s, 1H), 4.57 (s, 2H, D_2O exchangeable, NH_2), 6.29 (s, 1H), 7.27-7.33 (m, 2H). Anal. calcd. for $C_{14}H_{12}N_2O_3$: C, 65.62; H, 4.72; N, 10.93. Found C, 65.62; H, 4.67; N, 10.85.

*2-Amino-4-thien-3-yl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (**6d**)*

Yield 75%; cotton white hairy needles, mp 213–215°C (EtOH); IR 3307, 3165 (NH_2), 2188 (CN), 1647 (CO) cm^{-1}; ^1H NMR δ 1.90-2.10 (m, 2H), 2.30-2.50 (m, 2H), 2.53-2.60 (m, 2H), 4.56 (s, 1H), 4.60 (s, 2H, D_2O exchangeable, NH_2), 6.97 (dd, J = 1.3 Hz, J = 5.0 Hz, 1H), 7.09 (dd, J = 1.3 Hz, J = 3.0 Hz, 1H), 7.21 (dd, J = 3.0 Hz, J = 5.0 Hz, 1H); ^{13}C NMR δ 20.09 (t), 27.01 (t), 30.30 (d), 36.77 (t), 62.75 (s), 115.33 (s), 118.68 (s), 121.78 (d), 125.85 (d), 126.88 (d), 143.92 (s), 157.83 (s), 163.13 (s), 195.92 (s). Anal. calcd. for $C_{14}H_{12}N_2O_2S$: C, 61.75; H, 4.44; N, 10.29; S, 11.77. Found C, 61.79; H, 4.34; N, 10.11; S, 11.49.

*2-Amino-4-furan-2-yl-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (**6e**)*

Yield 74%; fine brownish needles, mp 210–211°C (EtOH) (Ref. [5] 209–210°C, Ref. [6] 200–202°C).

*2-Amino-4-thien-2-yl-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (**6f**)*

Yield 76%; dark buff fine needles, mp 214–215°C (EtOH) (ref [6] 214–216°C).

*2-Amino-4-furan-2-yl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (**6g**)*

Yield 70%; reddish brown powder, mp 232–233°C (EtOH); IR 3462, 3224 (NH_2), 2197 (CN), 1675 (CO) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.90-2.07 (m, 2H), 2.32-2.58 (m, 4H), 4.50 (s, 1H), 7.10 (s, 2H, D_2O exchangeable, NH_2), 6.25-7.35(m, 3H). Anal. calcd. for $C_{14}H_{12}N_2O_3$: C, 65.62; H, 4.72; N, 10.93. Found C, 65.48; H, 4.54; N, 10.71.

*2-Amino-4-thien-2-yl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (**6h**)*

Yield 72%; brownish needles, mp 204–205°C (EtOH); IR 3327, 3265 (NH_2), 2198 (CN), 1670 (CO) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.90–2.05 (m, 2H), 2.32–2.40 (m, 2H), 2.51–2.58 (m, 2H), 4.53 (s, 1H), 6.85 (apparent dt, J_d = 3.4 Hz, J_t = 0.8 Hz, 1H), 6.91 (dd, J = 3.4 Hz, J = 5.0 Hz, 1H), 7.09 (s, 2H, D_2O exchangeable, NH_2), 7.31 (dd, J = 1.4 Hz, J = 5.0 Hz, 1H). Anal. calcd. for $C_{14}H_{12}N_2O_2S$: C, 61.75; H, 4.44; N, 10.29; S, 11.77. Found C, 61.68; H, 4.34; N, 10.41; S, 11.72.

Molluscicidal activity tests

The molluscicidal activity tests were carried out by determination of the half lethal dose LC_{50} of each compound under investigation. *Biomphalaria alexandrina* snails were collected from the field (water canals) and maintained under laboratory conditions for a period of 45 days before the test and fed daily with lettuce leaves. Then, the snails were examined to ensure that they were free from parasitic infection. A series of concentrations (nine) ranging from 1 ppm to 17 ppm of each compound under investigation was prepared. The required amount of the compound under investigation was mixed thoroughly with few drops of Tween 20 followed by addition of the appropriate volume of untreated raw water (taken direcly from the River Nile or its subsidary branches/canals) to get a homogeneous suspension with the necessary concentration; it was poured in glass jar vessels 15 × 25 × 20 cm dimensions fitted with air bubblers. Ten snails having the same size and diameter (ca. 7 mm) were used in each experiment and maintained in the test solution under laboratory conditions at ambient temperature for 24 h. Each experiment was repeated three times and the mean number of killed snails was taken for each concentration as shown in Table 1. A control group was taken by placing 10 snails in water containing few drops of Tween 20. These bioassays are in accordance with the W.H.O. guidelines [15].

References

[1] G. Wurzel, H. Becker, *Phytochemistry* **1990**, *29*, 2565–2568; G. Wurzel, H. Becker, T. Eicher, K. Tiefensee; *Planta Med.* **1990,** *56,* 444-445; H. D. Zinsmeister, H. Becker, T. Eicher; *Angew. Chem.* **1991**, *103*, 134–151; *Angew. Chem. Int. Ed.* **1991**, *30*, 130–147.

[2] C. Held, R. Fröhlich, P. Metz, *Angew. Chem.* **2001**, *113*, 1091–1093; C. Held, R. Fröhlich, P. Metz, *Angew. Chem. Int. Ed.* **2001**, *40*, 1058–1060; C. Held, R. Fröhlich, P. Metz, *Adv. Synth. Catal.* **2002**, *344*, 720–727.

[3] F. M. Abdelrazek, G. A. M. Nawwar, *Egypt. J. Chem.* **1991**, *34*, 559–564.

[4] G. A. M. Nawwar, F. M. Abdelrazek, R. H. Swellam; *Arch. Pharm. (Weinheim)* **1991**, *324*, 875–877.

[5] X. S. Wang, D. Q. Shi, S. J. Tu, C. S. Yao, *Synth. Commun.* **2003,** *33(1),* 119–126.

[6] Y. A. Sharanin, L. N. Shcherbina, L. G. Sharanina, V. V. Puzanova, *J. Org. Chem. USSR (Engl. Transl.)* **1983**, *19*, 150–158; *Zh. Org. Khim.* **1983**, *19*, 164–173.

[7] F. F. Abdel-Latif, M. M. Mashaly, E. H. El-Gawish, *J. Chem. Res. Miniprint* **1995**, *5*, 1220–1228.

[8] P. H. H. Hermkens, J. H. Van Maarseveen, C. G. Kruse, H. W. Scheeren, *Tetrahedron* **1988**, *44*, 6491–6504.

[9] S. Balalaie, N. Nemati, *Synth. Commun.* **2000**, *30*, 869–876.

[10] M. Matsouka, M. Takao, T. Kitao, T. Fujiwara, K. Nakatsu, *Mol. Cryst. Liq. Cryst.* **1990**, *182*, 71–79.

[11] J. R. Dyer *Application of absorption spectroscopy of organic compounds*, Prentice-Hall International, Inc., London, **1965**, pp. 11–16; D. L. Pavia, G. M. Lampman, G. S. Kris, Jr. *Introduction to spectroscopy*, W. S. Saunders Company, Philadelphia, London, Toronto, **1979**, pp. 192–198.

[12] T.-S. Jin, A.-Q. Wang, X. Wang, J.-S. Zhang, T.-S. Li, *Synlett* **2004**, *No.5*, 871–873.

[13] R. Gonnert, *Bull. Wld. Hlth Org.* **1961,** *25,* 483–487.

[14] R. Gonnert, R. Strufe; *Ciba Found. Symp. Bilharziasis* **1962**, pp. 326–338; *Chem. Abstr.* **1963**, *59*, 5714f.

[15] K. Memoranda; *Bull. Wld. Hlth. Org.* **1965,** *33*, 567–581.