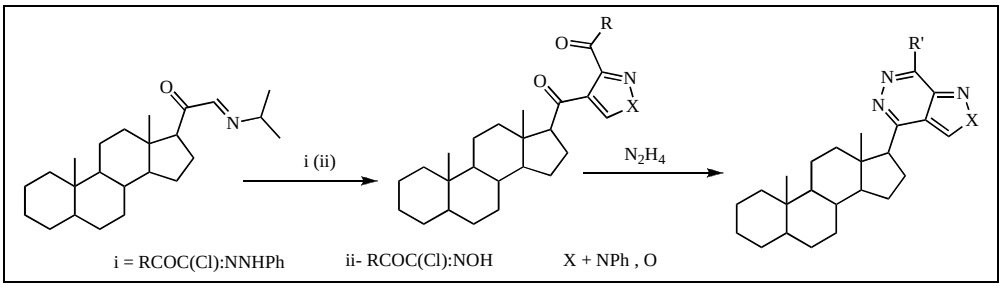
New Routes to Steroidal Heterocyclic Derivatives: Synthesis of Biologically Active Pyrazolyl- and Isoxazolylpregnene Derivatives.

Abdou O. Abdelhamid[a], Mervat M. Abdelhalim[b] and Gamal A. Elmegeed[b]

[a]Chemistry Department, Faculty of Science, Cairo University, Giza 12613, Egypt
[b]Hormone Department, National Research Centre, Dokki, Giza 12622, Egypt
Abdou_Abdelhamid@yahoo.com

Received October 19, 2005



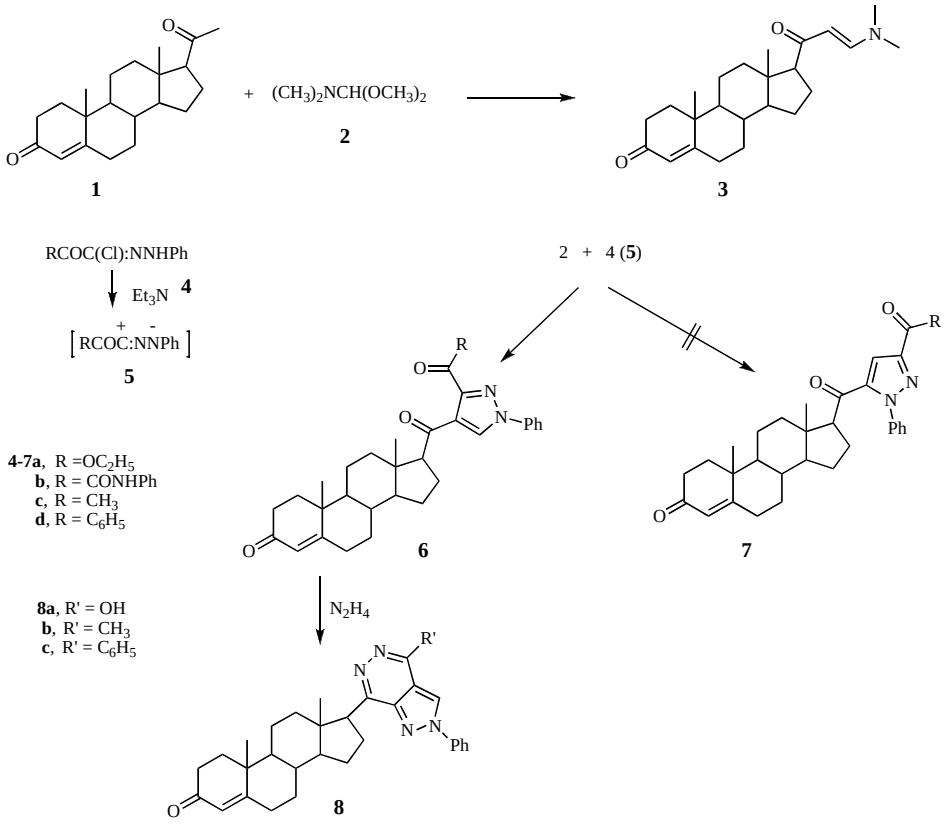
Pyrazolyl- and isoxazolylpregnene derivatives were synthesized from the appropriate hydrazonoyl chlorides and hydroximoyl chlorides with enaminoprogesterone derivative. The newly synthesized compounds were elucidated by elemental analysis, spectral data and chemical transformation. Some products were tested towards some bacteria and some Fungal-plant pathogens

J. Heterocyclic Chem., **44**, 7 (2007).

INTRODUCTION

Attention has been devoted in the literature to the synthesis of several steroidal heterocyclic derivatives that exhibit marked medicinal activities [1-3]. Heterocyclic pregnene derivatives have been found to possess a variety of interesting pharmacological and biological activities [4-7]. In continuation of the synthesis of modified steroids [8-11], we report herein new and efficient procedures for

Scheme 1



the synthesis of some pyrazolyl-, isoxazolyl-, pyrazolo[3,4-*d*]pyridazinyl- and isoxazolo[3,4-*d*]pyridazinyl-pregnene derivatives.

RESULTS AND DISCUSSION

Progesterone (**1**) was reacted with dimethylformamide dimethylacetal (**2**) to afford 17-(3-dimethylamino-acryloyl)-10,13-dimethyl-1,2,6,7,8,9,10,11,12,13,14,15,16,17-teteradecahydrocyclopenta[*a*]phen-anthren-3-one (**3**) (Scheme 1). Structure **3** was confirmed by elemental analysis, spectral data and chemical transportation. MS spectrum showed molecular ion peaks at m/z = 369. ^{1}H NMR showed signals at δ = 2.47 (s, 6H), 5.09 (d, 1H), 7.17 (d, 1H) that are characteristic signals of the cyclopentanoperhydrophenanthrene moiety [12,13]. Thus, compound **3** was reacted with *C*-ethoxycarbonyl-*N*-phenylhydrazonoyl bromide (**4a**) in the presence of triethylamine to give one isolable product, according to *tlc*, whose mass spectrum and elemental analysis indicated a molecular formula $C_{32}H_{38}N_2O_4$. The product seemed to be one of two possible isomeric structures **6** and **7** (Scheme 1). The ^{1}H NMR spectrum of the product showed, in addition to the expected signals of the pregnene moiety [12,13], the presence of signals at δ = 1.35 (t, 3H, CH_3CH_2), 4.25 (q, 2H, CH_2CH_3), 7.38-7.75 (m, 5H, ArH's) and 8.12 (s, 1H, pyrazole H-5). The product was easy to convert into pyrazolo[3,4-*d*]-pyridazine **8a** by its reaction with hydrazine hydrate, therefore structure **7** was ruled out. Formation of **6** can be explained *via* reaction of nitrilimine **5**, which formed *in situ* from hydrazonoyl chloride **4** and triethylamine, with **3** to afford cyclo adduct intermediate *via* 1,3-dipolar cycloaddition followed by elimination of dimethylamine to give pyrazole as the final product.

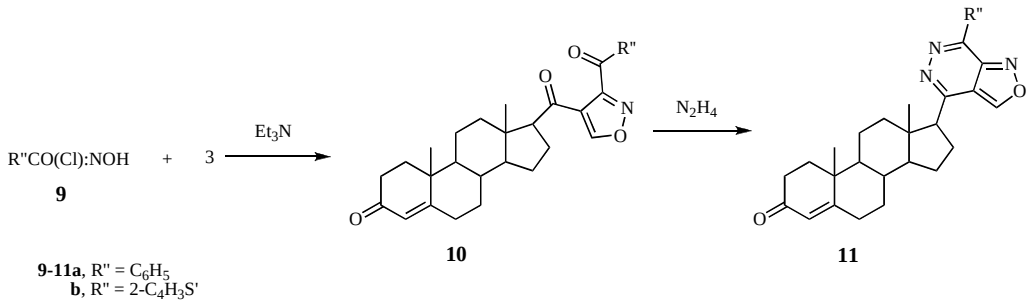
Similarly, compound **3** was reacted with the appropriate hydrazonoyl chlorides **4b-d** in boiling benzene and triethylamine afforded the corresponding pyrazolyl-pregnene derivatives **6b-d**, respectively (Scheme 1).

Compound **6a** was reacted with hydrazine hydrate to give pyrazolo[3,4-*d*]pyridazine **8a**. Structure **8a** was confirmed by elemental analysis, spectral data and alternative synthesis method. Thus, treatment of **6b** with boiling hydrazine hydrate gave product identical in all respects (mp., mixed mp., and spectra) with **8a**.

Also, pyrazolylpregnene derivatives **6c** and **6d** reacted with hydrazine hydrate in ethanol to afford the corresponding pyrazolo[3,4-*d*]pyridazinopregnene derivatives **8b** and **8c**, respectively (Scheme 1). Compound **3** was reacted with the appropriate hydroximoyl chlorides **9a** and **9b** in toluene containing triethylamine to afford the isoxazolylpregnene derivatives **10a** and **10b**, respectively (Scheme 2).

Isoxazoloylpregnene derivatives **10a,b** was reacted with hydrazine hydrate to give isoxazolo[3,4-*d*]pyridazinyl-pregnene derivatives **11a** and **11b**, respectively (Scheme 2). Structures **11a,b** and **12a,b** were elucidated based on their elemental analyses and spectral data.

Scheme 2



Antimicrobial Activity. Sensitivity of the selected microorganisms to some synthesized compounds were determined *in vitro* culture on three concentrations (1, 2.5 and 5 mg/ml) that were dissolved in *N,N*-dimethylformamide, the tests were carried out using the filter paper and hole plate method [14]. Studies on the biological activity of compounds in comparison with chloroamphenicol and terbinafin are shown in Tables 1 and 2. In general all tested compounds were capable of inhibiting the growth of gram-positive bacteria and gram-negative bacteria (Tables 1 and 2).

Table 1

Response of various microorganisms to some synthesized compounds *in vitro* (culture).

Microorganisms		Inhibition zone diamter (mm / mg sample)			
		6a	**6b**	**6c**	**St.**
Staphylococcus albus	G^+	21	00	16	18
Streptococcus facealis	G^+	20	00	15	12
Saccharomyces cervisiae	Fungus	0.0	0.0	0.0	3

Table 2

Response of various microorganisms to some synthesized compounds in vitro (culture).

Compounds	**8a**			**8b**			**8c**			**11a**			**11b**			**St.**		
	mg/ml			mg/ml			mg/ml			mg/ml			mg/ml			mg/ml		
Concentration	5	2.5	1	5	2.5	1	5	2.5	1	5	2.5	1	5	2.5	1	5	2.5	1
Aspergillus fumigatus	10	3	0	0	0	0	0	0	0	5	0	0	0	0	0	13	14	10
Penicillium italicum	4	5	4	0	0	0	5	4	0	0	0	0	0	0	0	14	15	9
Syncephalastrum racemosum	9	8	5	4	0	0	0	0	0	9	8	4	5	0	0	15	14	14
Candida albicans	5	0	5	0	0	0	0	0	0	5	0	0	0	0	0	9	10	9
Staphylococcus aureus	0	0	0	9	9	4	0	0	0	0	0	0	0	0	0	9	10	8
Pseudomonas areuginosa	0	0	0	8	5	0	3	0	0	4	3	0	0	0	0	15	14	9
Bacillus subtilis	4	0	0	0	0	0	4	0	0	0	0	0	5	3	0	12	13	10
Escherichia coli	0	0	0	5	0	0	0	5	5	0	0	0	0	0	0	8	9	10

St. Reference standerd; Chloramphenicol was used as a slandered antibacterial agent; Terbinafin was used as a slandered antifungal agent. Values show zone of inhibition in mm. Diameter of the inhibition zones were: high (11-15 mm), moderate (6-10 mm), slight (1-5 mm) and negative (0).

EXPERIMENTAL

All melting points were determined on an Electrothermal apparatus and are uncorrected. The IR spectra are expressed in cm^{-1} and recorded in KBr pellets on a Pa-9721 IR spectrometer. ^1H NMR spectra were obtained on a Varian EM-390 (90) MHz spectrometer in DMSO-d_6 as solvent and TMS as internal reference. Chemical shifts (δ) are expressed in ppm. Mass spectra were recorded on Kratos (75eV) MS equipment. Elemental analysis ere carried out at Microanalytical Data Unit at the National Research Center, Giza, Egypt. Antimicrobial study of the new compounds were carried out at the laboratory of Micro Analytical Center, Faculty of Science, Cairo University, and the laboratory of The Regional Center for Mycology and Biotechnology, El-Azher University, Egypt. Hydrazonoyl chlorides and hydroximoyl chlorides were prepared as previously methods [15-18].

17-(3-dimethylaminoacryloyl)-10,13-dimethyl-1,2,6,7,8,9,10, 11,12,13,14,15,16,17-teteradecahydrocyclopenta[*a*]phenanthren-3-one (3). A solution of progesterone (1) (3.14 g, 0.01 mole) and DMF-DMA (1.69g, 0.01 mole) in dry xylene (30 mL) was refluxed for 20 h. the solvent was removed under vacuum and the residue triturated with petroleum ether (b.p. 40/60ºC). The resulting solid was collected and crystallized from ethanol to gave yellow crystals 3, yield 2.76 gm (75%), mp 110-112º, ir (KBr): 2976, 2860 (CH), 1698, 1715 (C=O) cm^{-1}. ^1H nmr ($CDCl_3$): 1.16 (s, 3H), 1.26 (s, 3H), 1.27-1.71 (m, 14H), 1.99-2.01 (t, 3H), 2.35 (t, 1H), 2.47 (s, 6H), 2.99 (t, 2H), 5.09 (d, 1H), 5.85 (s, 1H) and 7.17 (d, 1H). MS [m/z, (%)]: 369 (M^+, 73 %). *Anal*. Calcd. for $C_{24}H_{35}NO_2$ (369.55): C, 78.00; H, 9.55; N;3.79. Found: C, 77.92; H, 9.32; N, 3.65.

Synthesis of 17-(3-Substituted 1-phenyl-1*H*-pyrazole-4-carbonyl)-10,13-dimethyl-1,2,3,6,7,8,9,10,11,12,13,14,15,-16, 17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthrene-one 6a-c. General Procedure. To a mixture of compound **3** (3.96 g, 0.01 mole), the appropriate hydrazonoyl chlorides **4a-d** (0.01 mole) and triethylamine (1.5 mL, 0.01 mole) in dry benzene (30 mL), was heated under reflux for 2 h then the solvent was removed under vacuum and the oil was triturated with petroleum ether (40/60ºC). The resulting solid was collected and crystallized from ethanol to give **6a-d**, respectively.

Ethyl 4-(10,13-Dimethyl-3-oxo-2,3,6,7,8,9,10,11,12,13,14,15, 16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthrene-17-carbonyl-1-phenylpyrazole-3-carboxylate (6a). This compound was obtained as yellow crystals (ethanol), 2.60 g (51 %), mp 215°. ir (KBr): 3035 (CH aromatic), 2983, 2850 (CH aliphatic), 1695, 1715, 1720 (CO's), 1640 (C=N) cm^{-1}. ^1H nmr ($CDCl_3$): 1.16 (s, 3H), 1.26 (s, 3H), 1.27-1.71 (m, 14H), 1.35 (t, 3H, CH_3CH_2), 1.99-2.01 (t, 3H), 2.35 (t, 1H), 2.99 (t, 2H), 4.25 (q, 2H, CH_2CH_3), 5.85 (s, 1H), 7.38-7.75 (m, 5H, ArH's), and 8.12 (s, 1H, pyrazole H-5). ms: m/z 514 (55) (M^+). *Anal*. Calcd. for $C_{32}H_{38}N_2O_4$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.86; H, 7.23; N, 5.61.

4-(10,13-Dimethyl-3-oxo-2,3,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthrene-17-carbonyl)-3-phenylcarbamoyl-1-phenyl-1*H*-pyrazloe (6b). This compound was obtained as yellow oil. ir (KBr): 3320 (NH), 3030 (CH-aromatic), 2975, 2825 (CH- aliphatic), 1690, 1705, 1720 (CO's), 1640 (C=N) cm^{-1}. ^1H nmr ($CDCl_3$): 1.16 (s, 3H), 1.26 (s, 3H), 1.27-1.71 (m, 14H), 1.99-2.01 (t, 3H), 2.35 (t, 1H), 2.99 (t, 2H), 5.85 (s, 1H), 7.23-7.64 (m, 10H, ArH's), 8.12 (s, 1H), pyrazole C-5) and 9.23 (s, br., 1H, NH). ms: m/z: 561 (35) (M^+). *Anal*. Calcd. for $C_{36}H_{39}N_3O_3$ (561.73): C, 76.98 ; H, 7.00 ; N, 7.48. Found : C, 76.89 ; H, 7.12 ; N, 7.53.

17-(3-Acetyl-1-phenyl-1*H*-pyrazole-4-carbonyl)-10,13-dimethyl-1,2,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-cyclopenta[*a*]phenanthren-3-one (6c). This compound was obtained as yellow oil. ir (KBr): 3035 (CH-aromatic), 2983, 2850 (CH-aliphatic), 1695, 1715, 1720 (CO's), 1640 (C=N) cm^{-1}. ^1H nmr ($CDCl_3$): 1.16 (s, 3H), 1.26 (s, 3H), 1.27-1.71 (m, 14H), 1.99-2.01 (t, 3H), 2.25 (s, 3H, CH_3), 2.35 (t, 1H), 2.99 (t, 2H), 5.85 (s, 1H), 7.32-7.54 (m, 5H, C_6H_5), 8.12 (s, 1H), pyrazole C-5). ms: m/z: 484 (55) (M^+). *Anal*. Calcd. for $C_{31}H_{36}N_2O_3$: C, 76.83; H, 7.49; N, 5.78. Found: C, 76.75; H, 6.56; N, 5.87.

17-(3-benzoyl-1-phenyl-1*H*-pyrazol-4-carbonyl)-10,13-dimethyl-1,2,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydrocyclo-penta-[*a*]phenanthren-3-one (6d). This compound was obtained as yellow crystals (EtOH), 3.40 g (63 %), mp 155-156° ir (KBr): 3030 (CH-aromatic), 2975, 2825 (CH-aliphatic), 1690, 1705, 1720 (CO's), 1640 (C=N) cm^{-1}. ^1H nmr ($CDCl_3$): 1.16 (s, 3H), 1.26 (s, 3H), 1.27-1.71 (m, 14H), 1.99-2.01 (t, 3H), 2.35 (t, 1H), 2.99 (t, 2H), 5.85 (s, 1H), 7.23-7.64 (m, 10H, ArH's), 8.12 (s, 1H), pyrazole C-5). ms: m/z: 546 (35) (M^+). *Anal*. Calcd. for $C_{36}H_{38}N_2O_3$ (546.72): C, 79.09; H, 7.01; N, 5.12. Found: C, 79.21; H, 6.85; N, 4.92.

Synthesis of 10,13-Dimethyl-17-(7-substituted 2-phenyl-2*H*-pyrazolo[3,4-*d*]pyridazin-4-yl)-1,2,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-cyclopenta[*a*]phenanthrenes 8a-c. General Procedure. To a solution of the appropriate **6a-d** (0.005 mole) in absolute ethanol (20 ml) and hydrazine hydrate (0.5 mL, 0.01 mole) was heated under reflux for 4 h and cooled. The resulting solid was collected and recrystallized from benzene to give **8a-c**, respectively.

4-(10,13-Dimethyl-3-oxo-2,3,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl)-2-phenyl-2,5-dihydropyrazolo[3,4-*d*]pyridazin-4-one (8a). This compound was obtained as yellow crystals (benzene), 3.40 g (70 %), mp 248-250°. ir This compound was obtained as yellow crystals (benzene), 3.40 g (70 %), mp 248-250°. iR (KBr): (KBr): 3030 (CH-aromatic), 2984, 2850 (CH-aliphatic), 1705, 1680 (CO), 1647 (C=N) cm-^{1}. ^{1}H nmr (DMSO-d_6): 1.16 (s, 3H), 1.26 (s, 3H), 1.27-1.71 (m, 14H), 1.99-2.01 (t, 3H), 2.35 (t, 1H), 2.99 (t, 2H), 5.85 (s, 1H), 7.50-7.68 (m, 5H, C_6H_5), 8.15 (s, 1H), pyrazole C-5), 11.21 (s, br., 1H). ms: m/z: 483 (45) (M^++1$^-$). *Anal*. Calcd. for $C_{30}H_{34}N_4O_2$: C, 74.66; H, 7.10; N, 11.61. Found: C, 74.37; H, 6.91; N, 11.72.

10,13-Dimethyl-17-(7-methyl-2-phenyl-2*H*-pyrazol[3,4-*d*]-pyridazin-2-yl)-1,2,6,7,8,9,10,11,12,13,14,15,16,17-tetradeeca-hydro-cyclopenta[*a*]phenanthren-3-one (8b). This compound was obtained as yellow crystals (benzene), 3.10 g (64 %), mp 160-162°. ir (KBr): 3025 (CH-aromatic), 2980 (CH-aliphatic), 1690 (CO), 1640 (C=N) cm^{-1}. ^{1}H nmr (DMSO-d_6): 1.16 (s, 3H), 1.26 (s, 3H), 1.27-1.71 (m, 14H), 1.99-2.01 (t, 3H), 2.35 (t, 1H), 2.38 (s, 3H, CH_3) 2.99 (t, 2H), 5.85 (s, 1H), 6.95-7.30 (m, 5H, C_6H_5), 8.12 (s, 1H), pyrazole C-5). ms: m/z: 479 (46) (M^+-1$^-$). *Anal*. Calcd. for $C_{31}H_{36}N_4O$: C, 77.47; H, 7.55; N, 11.66. Found: C, 77.65; H, 7.32; N, 11.72.

17-(2,7-Diphenyl-2*H*-pyrazolo[3,4-*d*]pyridazin-4-yl)-10,13-dimethyl-1,2,6,7,8,9,10,-11,12,13,14,15,16,17-tetradecahydro-cyclopenta[*a*]phenanthren-3-one (8c). This compound was obtained as yellow crystals (benzene), 3.20 g (59 %), mp 238-240°. ir (KBr): 3026 (CH-aromatic), 2985, 2835 (CH-aliphatic), 1690 (CO), 1645 (C=N) cm^{-1}. ^{1}H NMR (DMSO-d_6): 1.16 (s, 3H), 1.26 (s, 3H), 1.27-1.71 (m, 14H), 1.99-2.01 (t, 3H), 2.35 (t, 1H), 2.99 (t, 2H), 5.85 (s, 1H), 7.53-7.76 (m, 10H, ArH's), 8.12 (s, 1H), pyrazole C-5) and characteristic signals of cyclopenta-noperhydrophenanthrene moiety. ms: m/z: 542 (35) (M^+). *Anal*. Calcd. for $C_{36}H_{38}N_4O$: C, 79.67; H, 7.06; N, 10.32. Found: C, 79.76; H, 6.90; N, 10.05.

Synthesis of Isoxazoles 10a,b. **General Procedure**. A mixture of **3** (3.96 g, 0.01 mol), the appropriate hydroximoyl chloride **9a,b** (0.01 mol) and triethylamine (1.5 mL, 0.01 mole) in dry toluene (20 mL) was stirred at 0ºC. The stirring was continued for 3 h. The reaction mixture was concentrated under *vacuum* to give the oily products **10a,b** respectively.

17-(3-Benzoylisoxazole-3-carbonyl)-10,13-dimethyl-1,2,6,7,8,9,10,11,12,13,14,15,16,-17-tetradecahydrocyclopenta[*a*]phenanthreen-3-one (10a). This compound was obtained as oil, 2.8 g (59 %). ir (KBr): 3026 (CH-aromatic), 2985, 2835 (CH-aliphatic), 1690 (CO), 1645 (C=N) cm^{-1}. ^{1}H nmr ($CDCl_3$): 1.16 (s, 3H), 1.26 (s, 3H), 1.27-1.71 (m, 14H), 1.99-2.01 (t, 3H), 2.35 (t, 1H), 2.99 (t, 2H), 5.85 (s, 1H), 7.53-7.76 (m, 5H, ArH's), (s, 1H), oxazole C-5). ms: m/z: 471 (28) (M^+). *Anal*. Calcd. for $C_{30}H_{33}NO_4$: C, 76.41; H, 7.05; N, 2.97. Found: C, 76.30; H, 6.82; N, 3.12.

10,13-Dimethyl-(3-(2-thienyl)-2-carbonyl)isoxazole-4-carbonyl-1,2,6,7,8,9,10,11,-12,13,14,15,16,17-tetradecahydrocyclo-penta[*a*]phenanthreen-3-one (10b). This compound was obtained as oil, 2.5 g (53 %). ir (KBr): 3020 (CH-aromatic), 2985, 2835 (CH-aliphatic), 1685 (CO), 1625 (C=N) cm^{-1}. ^{1}H nmr ($CDCl_3$): 1.16 (s, 3H), 1.26 (s, 3H), 1.27-1.71 (m, 14H), 1.99-2.01 (t, 3H), 2.35 (t, 1H), 2.99 (t, 2H), 5.85 (s, 1H), 7.13-7.76 (m, 3H, ArH's), 8.12 (s, 1H), oxazole C-5). ms: m/z: 471 (28) (M^+). *Anal*. Calcd. for $C_{28}H_{31}NO_4S$: C, 70.41; H, 6.54; N, 2.93; S, 6.71. Found: C, 70.30; H, 6.32; N, 2.80; S, 6.82.

Synthesis of Isoxazolo[3,4-*d*]pyradiazines 11a,b. **General Procedure**. Equimolar amounts of **10a,b** and hydrazine hydrate (0.01 mole) and absolute ethanol (20 mL) were heated under reflux for 3 h. The resulting solid was collected by filtration and crystallized from benzene to afford **11a** and **11b**, respectively.

10,13-Dimethyl-17-(7-phenylisoxazolo[3,4-*d*]pyridazin-4-yl)-1,2,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydrocyclo-penta[*a*]phenanthren-3-one (11a). This compound was obtained as yellow crystals (benzene), 2.60 g (60 %), mp 180-182°. ir (KBr): 3030 (CH-aromatic), 2960, 2830 (CH-aliphatic), 1710 (CO), 1640 (C=N) cm^{-1} ^{1}H nmr (DMSO-d_6): 1.16 (s, 3H), 1.26 (s, 3H), 1.27-1.71 (m, 14H), 1.99-2.01 (t, 3H), 2.35 (t, 1H), 2.99 (t, 2H), 5.85 (s, 1H), 7.13-7.76 (m, 5H, ArH's), 8.12 (s, 1H), oxazole C-5). *Anal*. Calcd. for $C_{30}H_{33}N_3O_2$: C, 77.06; H, 7.11; N, 8.99. Found: C, 76.90; H, 7.20; N, 8.78.

10,13-Dimethyl-17-(7-(4-thien-2yl)isoxazolo[3,4-*d*]pyrida-zin-4-yl)-1,2,6,7,8,9,10,11,-12,13,14,15,16,17-tetradecahydro-cyclopenta[*a*]phenanthren-3-one (11b). This compound was obtained as yellow crystals from (benzene), 3.21 g (68 %), mp 165-167°. ir (KBr): 2984, 2850 (CH_3, CH_2), 1705, (CO), 1647 (C=N). ^{1}H NMR (δ ppm): 1.16 (s, 3H), 1.26 (s, 3H), 1.27-1.71 (m, 14H), 1.99-2.01 (t, 3H), 2.35 (t, 1H), 2.99 (t, 2H), 5.85 (s, 1H), 6.92-7.31 (m, 3H), 9.25 (s, 1H, isoxazole C-5). *Anal*. Calcd. for $C_{28}H_{31}N_3O_2S$: C, 71.01; H, 6.60; N, 8.87; S, 6.77. Found: C, 70.85; H, 6.40; N, 8.78; S, 6.54.

REFERENCES AND NOTES

[1] T. Kwon, A. S. Heiman, E. T. Oriaku, K. Yoon, H. J. Lee, *J. Med. Chem*. **38**(6), 1048 (1995).

[2] D. P. Jindal, P. Piplani, H. Fajrak, C. Prior, I. G. Marshall, *Eur. J. Med. Chem*. **36**, 195 (2001).

[3] R. M. Hoyte, J. Zhong, R. Lerum, A. Oluyemi, P. Persaud, C. O'Connor, D. C., Labaree, R. B. Hochberg, *J. Med. Chem.*, **45** (24), 5397 (2002).

[4] E. J. Jacobsen, M. McCall, D. E. Ayer, F. J. Van Doorink, J. R. Palmer, K. L. Belonga, M. Broughler, E. D. Hall, D. J. Houser, M. A. Krook, T. A. Runge, *J. Med. Chem.*, **33**, 1145 (1990).

[5] Y. Zhengqing, A. S. Heiman, C. E. Hudson, H. J. Lee, *Steroids*, **67**, 353 (2002).

[6] D. KO, A. S. Heiman, M. Chen, H. J. Lee, *Steroids*, **65**, 210 (2000).

[7] H. J. Lee, J. S. Cooperwood, Z. You, D. Ko, *Arch. Pharm. Res*., **25** (2), 111 (2002).

[8] S. H. Doss, N. A. Louca, G. A. Elmegeed, R. M. Mohareb, *Arch Pharm Res*, **22**, 495 (1999).

[9] G. Hajos, *Tetrahedron, Asymetry,* **4** (3), 393 (1993).

[10] R. Gupta, D. Pathak, D. P. Jindal, *Eur. J. Med. Chem.,* **34**, 659 (1999).

[11] G. A. Elmegeed, W. W. Wardakhan, M. Younis, N. A. Louca, *Arch. Pharm. Med. Chem*., **337**, 140 (2004).

[12] W. B. Smith, *Mag. Reson. Chem.* **37**(2), 103 (1999).

[13] N. S. Bhacca, D. H. William, "Application of NMR spectroscopy

in organic chemistry", **1964**, Holden Day, San Francisco.

[14] W. E. Solomons, N. J. Doorenbos, J. Pharma. Sci., **63**, 19 (1974).

[15] G. Fravel, *Bull. Soc. Chim. Fr.*, **31**, 150 (1904).

[16] N. F. Eweiss, A. Osman, *Tetrahederon Lett*., 1179 (1979).

[17] C. Parkanyi, A. O. Abdelhamid, J. C. S. Cheng, A. S. Shawali, *J. Heterocycl. Chem*., **21**, 1029 (1984).

[18] A. O. Abdelhamid, F. A. Khalifa, S. S. Ghabrial, *Phosphorus, Sulfur and Silicon*, **40**, 41 (1988).