by chromatography on silica gel (2 × 120 cm) in $CHCl_3$–ether (3:2) to give, after evaporation of the solvent, four homogeneous (TLC) fractions. The fraction (0.15 g) that was eluted first was discarded. The second fraction (0.63 g) was the 3,5-di-*O*-acetyl derivative of V: ^1H NMR ($CDCl_3$) δ 9.7 (br s, 1, NH), 7.18 (s, 1, H-6), 6.58 (t, 1, $J_{1',2'} = 7.8$ Hz, H-1′), 5.23 (q, 1, $J = 27$ and 3 Hz, $CH{=}CF_2$), 2.0 (2 s, 6, CH_3CO).

The third fraction (0.88 g) was the acetylated α-anomer VI: ^1H NMR ($CDCl_3$) δ 9.35 (br s, 1, NH), 7.60 (s, 1, H-6), 6.24 (d of d, 1, $J = 5.4$ and 8.1 Hz, H-1′), 5.31 (q, 1, $J = 3$ and 27 Hz, $CH = CF_2$), 2.05 (2 s, 6, CH_3CO). The fraction (0.02 g) that was eluted last was also discarded.

5-(2,2-Difluorovinyl)-2′-deoxyuridine (V) and Its α-Anomer VI. The acetylated V (1.1 g) was disolved in 75 mL of 0.75 N methanolic HCl and kept 4 h at room temperature. The solution was neutralized with weekly basic Amberlite IRA45 resin. The resin was filtered and washed with methanol (~50 mL). The filtrate that contained some decomposed material (base line, TLC, $CHCl_3$–MeOH, 9.1) was evaporated to a syrupy residue, which was coevaporated several times with ethanol and purified by chromatography on partially deactivated (8% H_2O) silica gel (2 × 100 cm), with ethyl acetate–acetone (1.1) as the eluant. The fraction collected from the column was free of decomposed material, but contained some partially deacetylated product. It was evaporated to a syrup, which was coevaporated with ethanol and crystallized from ethanol–acetone (9:1) to give two crops, 166 mg and 81 mg, respectively, of TLC (EtOAc) pure V. The combined filtrate was evaporated and deacetylated in 70 mL of 1 N methanolic HCl to give, after workup, 73 mg of pure V: yield 322 mg (40%); mp 152 °C; ^1H NMR (Me_2SO-d_6) δ 11.45 (br s, 1, NH), 8.04 (s, 1, H-6), 6.27 (t, $J = 6.9$ Hz, H-1′), 5.30 (q, 1, $J = 3$ and 27 Hz, $CH{=}CF_2$), 4.96 (t, 1, $J \sim 4.5$ Hz, CH_2OH). Anal. ($C_{11}H_{12}F_2N_2O_5$) C, H, N, F.

Deacetylation of the blocked α-anomer (1.58 g) in 70 mL of 0.75 M methanolic HCl for 18 h followed by neutralization with Amberlite IRA 45, chromatography, and crystallization gave 0.487 g (39%) of the α-anomer VI: mp 173–174 °C; ^1H NMR (Me_2SO-d_6) δ 11.5 (br s, 1, NH), 8.10 (s, 1, H-6), 6.13 (d of d, 1, $J = 2.8$ and 7.5 Hz, H-1′), 5.33 (q, 1, $J = 3$ and 27 Hz, $CH{=}CF_2$), 4.8 (t, 1, CH_2OH). Anal. ($C_{11}H_{12}F_2N_2O_5$) C, H, N, F.

(*E*)-2,4-Dimethoxy-5-(2-fluorovinyl)pyrimidine (VII) and 2,4-Dimethoxy-5-(2,2-difluoro-2-ethoxyethyl)pyrimidine (VIII). To a solution of III (121 mg, 0.6 mmol) in 10 mL of absolute EtOH was added $NaBH_4$ (42 mg, 1.11 mmol) and the reaction mixture was stirred for 4 h at 50–55 °C and at room temperature overnight. The solution was neutralized with a 1% ethanolic H_2SO_4 and evaporated. The residue was coevaporated with benzene, dissolved in CH_2Cl_2 (40 mL), and filtered, and the solvent was evaporated. Separation of the residue by chromatography on silica gel, using petroleum ether–ether (6:1, v/v) as the eluent, gave three fractions. In the order they were eluted from the column (1 × 100 cm): Fraction 1 (4 mg) was the starting material (III). Fraction 2 (48 mg), compound VIII: ^1H NMR ($CDCl_3$) δ 8.20 (s, 1, H-6), 4.03, 4.02 (2 s, 6, OCH_3), 3.92 (q, 2 H, $J = 7.1$ Hz, OCH_2CH_3), 3.17 (t, 2 H, $J_{HF} = 10.7$ Hz, CH_2CF_2), 1.23 (t, 3 H, $J = 7.1$ Hz, OCH_2CH_3); ^{19}F NMR ($CDCl_3$) 74.666 (t, $J_{F,H} = 10.75$ Hz). Fraction 3 (60 mg), compound VII: ^1H NMR ($CDCl_3$) δ 8.03 (s, 1, H-6), 7.26 (q, 1, $J_{F,H2'} = 85.5$ Hz, $J_{H1',2'} = 11$ Hz, H-2′), 6.15 (q, 1, $J_{F,H1'} = 21$ Hz, $J_{1',2'} = 11$ Hz, H-1′), 4.04, 3.97 (2 s, 6, OCH_3).

Biological Assays. The assay systems for measuring antiviral and antitumor activity, the source of the virus strains, and the growth characteristics of the tumor cell lines, including the FM3A cell line transformed with the HSV-1 TK gene,[16] have been described previously.[12–17]

Acknowledgment. This investigation was supported in part by Grants CA24538 and CA13038 awarded by the National Cancer Institute and by grants from the Belgian Fonds voor Geneeskundig Wetenschappelijk Onderzoek (Krediet No. 3.0040.83) and the Geconcerteerde Onderzoeksacties (Conventie No. 85/90-79). We thank D. Ayusawa, K. Shimizu, and T. Seno for the establishment of the mutant FM3A cell lines[15–17] and Anita Van Lierde and Lizette van Berckelaer for excellent technical assistance.

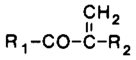
Synthesis and Antifungal Activity of a Series of Novel 1,2-Disubstituted Propenones

Masaru Ogata,*[†] Hiroshi Matsumoto,[†] Shiro Kida,[†] Sumio Shimizu,[†] Katsuya Tawara,*[‡] and Yoshimi Kawamura[‡]

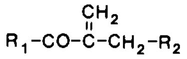
Shionogi Research Laboratories, Shionogi & Co., Ltd., Fukushima-ku, Osaka 553, Japan. *Received October 14, 1986*

To find an antifungal agent other than those of the imidazole and triazole series, a new class of 1,2-disubstituted propenones I and II was prepared and tested for antifungal activity. Comparison of the structure–activity relationships showed that the conjugated structure of carbonyl and exomethylene groups in I and II plays an important role in potent antifungal activity. However, it is noteworthy that compounds **53**, **54**, and **56**, which have a hydroxymethyl or methoxymethyl group instead of an *exo*-methylene group in I, also showed potent activity. Although many compounds exhibited strong antifungal activity in vitro, none showed activity in vivo of oral efficacy against subacute systemic candidiasis in mice.

Previous papers[1–3] from our group reported the synthesis and biological evaluation of compounds from the imidazole and triazole series as a novel type antifungal agent. In continuing our study, we found a new class of 1,2-disubstituted propenones I and II that differ from imidazole and triazole compounds. These new compounds were prepared and screened for potential antifungal activity.


$R_1{-}CO{-}C({=}CH_2){-}R_2$

I


$R_1{-}CO{-}C({=}CH_2){-}CH_2{-}R_2$

II

Chemistry

The general synthetic routes (methods A–F) for the preparation of I and II outlined in Scheme I. Various aryl or alkyl methyl ketones III were treated with bromine to obtain the bromo ketone IV and followed by treatment

---

[†] Division of Organic Chemistry.

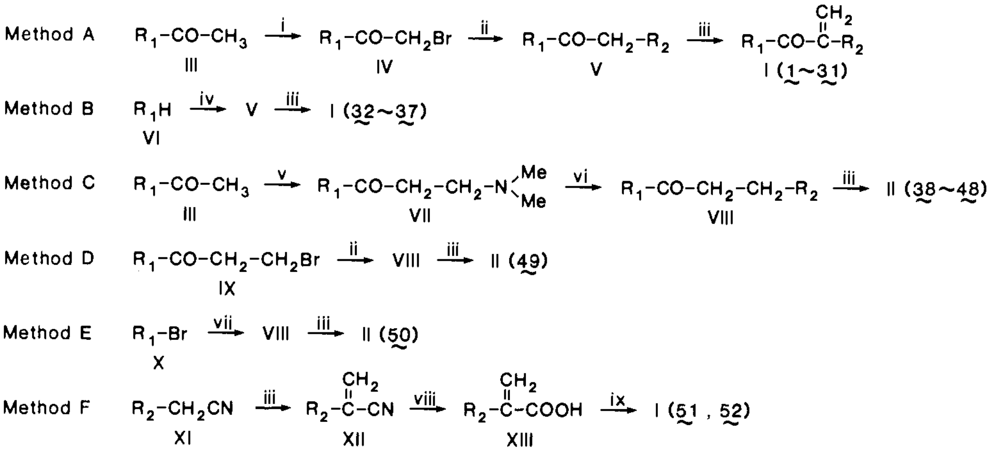
[‡] Division of Microbiology.

(1) Ogata, M.; Matsumoto, H.; Tawara, K. *Eur. J. Med. Chem.* 1981, *16*, 373.

(2) (a) Ogata, M.; Matsumoto, H.; Hamada, Y.; Takehara, M.; Tawara, K. *J. Med. Chem.* 1983, *26*, 768. (b) Ogata, M.; Tawara, K. *Drugs Future* 1985, *10*(6), 451.

(3) Ogata, M.; Matsumoto, H.; Takahashi, K.; Shimizu, S.; Kida, S.; Murabayashi, A.; Shiro, M.; Tawara, K. *J. Med. Chem.* 1987, *30*, 1054.

Scheme I



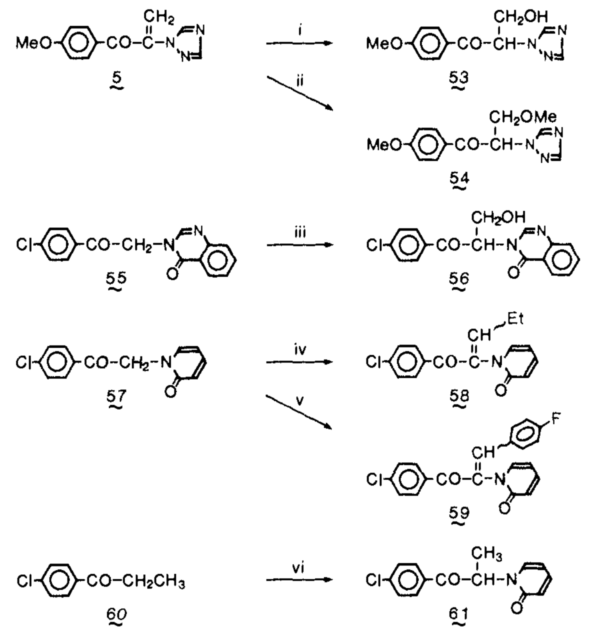
R_1=alkyl, aryl R_2=alkyl, aryl, azole, azinone, amine

i : $Br_2/CHCl_3$ ii : R_2H/NaH or KOH/DMF iii : $Me_2N\text{-}CH_2\text{-}NMe_2/Ac_2O$ iv : $R_2CH_2COCl/AlCl_3$
v : $Me_2NH{\cdot}HCl/(CHO)n/EtOH$ vi : R_2H/aq. EtOH vii : 1)Mg/Et_2O 2)$R_2CH_2CH_2CN$ 3)dil. HCl
viii : dil. H_2SO_4 ix : 1)$SOCl_2$ 2)amine/Et_3N

with various azoles or azinones in the presence of NaH in DMF to the ketone V. The desired propenones I were prepared by the reaction of *N,N,N'N'*-tetramethyldiaminomethane (TMDAM) in the presence of Ac_2O[3,4] (method A). Friedel-Craft reaction of substituted acetyl chloride with aromatic compounds VI in the presence of $AlCl_3$ also afforded the ketone V, which was converted into I with the reaction of TMDAM/Ac_2O as described above (method B). Mannich reaction of aryl methyl ketones III with dimethylamine hydrochloride and paraformaldehyde yielded the dimethylamino derivatives VII. The dimethylamino group in VII could be interchanged with azoles or azinones to give VIII (method C). This compound VIII was also obtained by the reaction of β-bromo ketone IX with azinone in the presence of sodium hydride in DMF (method D). Grignard reaction of aryl bromide X and 3-phenylpropionitrile also afforded VIII (method E). The compounds VIII obtained by methods C–E were converted into II with TMDAM/Ac_2O in a manner similar to method A. Treatment of substituted acetonitrile XI with TMDAM/Ac_2O gave the substituted acrylonitrile XII, which was hydrolyzed to the substituted acrylic acid XIII with aqueous H_2SO_4. Compound XIII was converted to acid chloride with $SOCl_2$ and then made to react with various amines in the presence of Et_3N to obtain substituted acrylamide I (method F).

Treatment of **5** with aqueous hydrochloric acid or methanol gave the hydroxymethyl derivative **53** or the methoxymethyl derivative **54**, respectively (Scheme II). Reaction of the quinazolylacetophenone derivative **55** with paraformaldehyde in the presence of $KHCO_3$ in DMF afforded the hydroxymethyl derivative **56**. The pyridinylacetophenone **57** was converted with propionaldehyde or *p*-fluorobenzaldehyde in the presence of piperidine in acetic acid to the pentenophenone derivative **58** or the chalcone derivative **59**, respectively. Treatment of propanone derivative **60** with bromine, followed by reaction with 2-hydroxypyridine in the presence of KOH in DMF, gave the pyridinylpropanone derivative **61**.

Scheme II



i : 6N-HCl/100°C
ii : MeOH reflux
iii : (HCHO)n/$KHCO_3$/DMF
iv : EtCHO/piperidine/AcOH
v : p-F-PhCHO/piperidine/AcOH
vi : 1) $Br_2/CHCl_3$
2) 2-OH-pyridine/KOH/DMF

Biological Methods

The title compounds were tested for their fungistatic activity against *Candida albicans*, *Aspergillus fumigatus*, and *Trichophyton asteroides*. MIC values were determined by a microtiter dilution system,[3] using final inocula of 1 × 10^5 cells (yeast) or 1 × 10^5 conidia (mould and dermatophyte) per milliliter of Sabouraud's glucose broth.

Biological Results and Discussion

The propenone compounds I and II were tested for their fungistatic activity against three species of fungi (*Candida albicans*, *Aspergillus fumigatus*, and *Trichophyton asteroides*), by using procedures previously described.[3] Most compounds were active against the test fungi. Especially, **4**, **6**, **18**, **19**, **20**, **23**, **25**, **27**, **29**, **34**, and **55** exhibited excellent

---

(4) (a) Kunz, W.; Sturm, E. Eur. Pat. Appl. 0114567. (b) Clough, J. M.; Worthington, P. A.; Gravestock, M. B. Eur. Pat. Appl. 0114487. (c) Ogata, M.; Matsumoto, H.; Tawara, K. Japan Unexamined Pat. Publn. No. 59 155365, 1984. (d) Takahashi, K.; Ogata, M. *Synth. Commun.*, in press.

MIC values comparable to those of the known imidazole antimycotics clotrimazole,[7] miconazole,[6] econazole,[6] and croconazole[2] (Table I).

Since *C. albicans* was found to be comparatively susceptible to these effective propenones, the more active each anticandida agent **4**, **5**, **14**, **17**, **19**, **20**, **23**, **25**, **27**, **29**, **30**, **31**, **35**, **40**, **54**, and **55** were examined for their protective effects on subacute systemic infection with *C. albicans* in mice. However, none showed remarkable prolongation of survival time of the infected mice treated with 50 mg/kg oral dose once daily for 5 consecutive days.[3]

In general, comparison of the antifungal activity of I and II showed that more I compounds showed higher activity than II compounds (**1–37** vs. **38–50**). Furthermore, the antifungal activity of I decreased depending on the alkyl group in the R_1 or R_2 position (**9**, **21**, **37**), with the exception of **10** (which displayed high potency). On the other hand, introduction of an aryl group in R_1 and R_2 in I resulted in high potency. Thus, introducing a bulky R_1 and R_2 group such as an aryl or *tert*-butyl one, seems to result in high potency.

Introduction of the amide group in exchange for the carbonyl group in I resulted in loss of activity (**51**, **52**). Compounds **58** and **59**, which have ethyl and *p*-fluorophenyl groups on the double bond, showed low activity, and **61**, which has a methyl group instead of an *exo*-methylene group, showed no antifungal activity. From these results, it is clear that the conjugated structure of the carbonyl and *exo*-methylene groups plays an important role in potent antifungal activity as the pharmacophore, and Michael reaction with enzyme seems to a possible mechanism for biological action. Therefore, modification of the *exo*-methylene group in I would also contribute to the structure–activity relationships in this moiety. Thus, **53**, **54**, and **56**, which possess the hydroxymethyl or methoxymethyl group instead of the *exo*-methylene group (**5**, **29**), maintained relatively high potency in spite of the lack of an *exo*-methylene group in their structure. These facts indicate that the methoxymethyl and hydroxymethyl derivatives may be precursors to the vinyl derivatives and that there may exist more potent antifungal agents related to **53**, **54**, and **56**, which are different from I and II.

Further comparative in vitro and in vivo studies of the effective propenone compounds and imidazole antimycotics are now under study.

Experimental Section

Melting points were determined in a Büchi capillary melting point apparatus and are uncorrected. NMR spectra were obtained with a Varian T-60 or EM-390 spectrometer. A Hitachi 260-10 spectrophotometer was used to obtain IR spectra. Elemental analyses were performed by the analytical department of Shionogi Research Laboratories. Where analyses are indicated only by symbols of the elements, analytical results obtained for these elements were within ±0.4% of the theoretical values.

1-(4-Methoxyphenyl)-2-(1*H*-1,2,4-triazol-1-yl)-2-propen-1-one (5) (Method A). To a solution of *p*-methoxyacetophenone (10 g, 66.6 mmol) in $CHCl_3$ (50 mL) was added portionwise Br_2 (10.6 g, 66.3 mmol) in $CHCl_3$ (25 mL) with stirring at room temperature. After 15 min at room temperature, the mixture was diluted with ice water and aqueous $Na_2S_2O_3$ and extracted with CH_2Cl_2. The organic layer was washed with H_2O, dried over Na_2SO_4, and evaporated to give IV (R_1 = *p*-methoxyphenyl). This product was added to a mixture of dry THF (74 mL), 50% NaH (dispersion in mineral oil, 3 g, 62.5 mmol), and 1,2,4-triazole (4.3 g, 62.3 mmol) under room temperature with stirring. After 30 min, the mixture was diluted with ice water and extracted with CH_2Cl_2. The organic layer was washed with H_2O, dried over Na_2SO_4, and evaporated. The residue was chromatographed on a column of silica gel. The fractions eluted with 2% MeOH/CH_2Cl_2 were collected to obtain V (R_1 = *p*-methoxyphenyl, R_2 = 1,2,4-triazol-1-yl) (6 g, mp 118–120 °C, the overall yield from III 42%, from AcOEt/*i*-Pr_2O). Anal. ($C_{11}H_{11}N_3O_2$) C, H, N.

To a solution of the above comound V (R_1 = *p*-methoxyphenyl, R_2 = 1,2,4-triazol-1-yl, 1 g, 4.6 mmol) in acetic anhydride (540 mg, 5.3 mmol) was added portionwise *N*,*N*,*N'*,*N'*-tetramethyldiaminomethane (TMDAM) (540 mg, 5.3 mmol) with stirring at 40 °C. After 15 min, the mixture was diluted with aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was washed with H_2O, dried over Na_2SO_4, and evaporated. The residue was chromatographed on a column of silica gel. The fractions eluted with 50% benzene/AcOEt were collected to obtain **5** (460 mg, mp 88–89 °C, 44%, from AcOEt/*i*-Pr_2O): overall yield from III 18%; IR (Nujol) 1610 and 1635 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.88 (3 H, s, OMe), 5.71 (1 H, s, =CH*H*), 6.57 (1 H, s, =CH*H*), 6.9–9.6 (6 H, m, triazole and aromatics). Anal. ($C_{12}H_{11}N_3O_2$) C, H, N.

The other compounds (1–31) were prepared in a similar manner.

1-(2-Thienyl)-2-phenyl-2-propen-1-one (35) (Method B). To a solution of thiophene (5 g, 59.4 mmol) and phenylacetyl chloride (11.0 g, 71.2 mmol) in CS_2 (50 mL) was added $AlCl_3$ (7.9 g, 59.4 mmol) with stirring at room temperature. After 30 min at room temperature, the reaction mixture was mixed with ice water and extracted with AcOEt. The organic layer was washed with H_2O, dried over Na_2SO_4, and evaporated. The residue was chromatographed on a column of silica gel. The fractions eluted with 50% benzene/*n*-hexane were evaporated to obtain V (R_1 = 2-thineyl, R_2 = Ph) (4 g, mp 38–45 °C, 33%) after washing with petroelum ether.

The above compound V (R_1 = 2-thienyl, R_2 = Ph, 1.2 g, 5.9 mmol) was treated TMDAM (920 mg, 9 mmol) in Ac_2O (920 mg, 9 mmol) at 60 °C for 30 min with stirring as described in method A. Usual workup and column chromatography on silica gel with 50% benzene/*n*-hexane as the solvent afforded **35** (500 mg, mp 30–31 °C, 39%) after washing with petroleum ether: IR (Nujol) 1635 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.73 (1 H, s, =CHH), 6.97–7.67 (8 H, m, aromatics). Anal. ($C_{13}H_{10}OS$) C, H, S.

The other compounds (**32–37**) were prepared in a similar manner.

1-(4-Phenylphenyl)-2-[(1*H*-pyrazol-1-yl)methyl]-2-propen-1-one (42) (Method C). A mixture of 4-phenylacetophenone (III, R_1 = 4-phenylphenyl, 20 g, 101.9 mmol), dimethylamine hydrochloride (8.3 g, 101.8 mmol), paraformaldehyde (3.1 g, 103 mmol), 36% HCl (1.8 mL), and EtOH (120 mL) was refluxed for 15 h. The reaction mixture was evaporated and the residue was basified with aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was washed with H_2O, dried over Na_2SO_4, and evaporated. The residue was added to MeOH/HCl and Et_2O. The resulting hydrochloride was filtered to give VII (R_1 = 4-phenylphenyl, 7.6 g, 26%, mp 191–192 °C) after washing with Et_2O. Anal. ($C_{17}H_{19}NO{\cdot}HCl$) C, H, Cl, N.

A mixture of the above product (VII, R_1 = 4-phenylphenyl, 1.5 g, 5.2 mmol), pyrazole (710 mg, 10.4 mmol), EtOH (15 mL), and H_2O (7.5 mL) was refluxed for 16 h. The reaction mixture was added H_2O and extracted with CH_2Cl_2. The organic layer was washed with H_2O, dried over Na_2SO_4, and evaporated to give VIII (R_1 = 4-phenylphenyl, R_2 = pyrazol-1-yl, 1.3 g, 91%, mp 140–141 °C, from AcOEt/*i*-Pr_2O). Anal. ($C_{18}H_{16}N_2O$) C, H, N.

The above product VIII (R_1 = 4-phenylphenyl, R_2 = pyrazol-1-yl, 1 g, 3.6 mmol) was treated with TMDAM (1.11 g, 10.9 mmol) in Ac_2O (1.11 g, 10.9 mmol) at 60 °C for 1.5 h with stirring. Usual workup as described in method A and column chromatography on silica gel with 25% AcOEt/benzene as the eluent afforded **42** (450 mg, mp 96–97 °C 43%, from AcOEt/petroleum ether): overall yield 10%; IR (Nujol) 1642 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.17 (2 H, s, CH_2), 5.77 (1 H, s, =CH*H*), 5.83 (1 H, s, =CH*H*), 6.23–7.89. (12 H, m, aromatics). Anal. ($C_{19}H_{16}N_2O$) C, H, N.

The other compounds (**38–48**) were prepared in a similar manner.

1-(4-Chlorophenyl)-2-[(1*H*-2-oxo-1,2-dihydroquinolin-1-yl)methyl]-2-propen-1-one (49) (Method D). To a solution of 2-hydroxyquinoline (3.5 g, 24.1 mmol) and 50% NaH (dispersion

---

(5) Osuch, C.; Levine, *J. Org. Chem.* **1957**, *22*, 939.

(6) Godefroi, E. F.; Heeres, J.; Van Cutsem, J.; Janssen, P. A. J. *J. Med. Chem.* **1969**, *12*, 784.

(7) Büchel, K. H.; Draber, W.; Regel, E.; Plempel, M. *Arzneim.-Forsch.* **1972**, *22*, 1260.

Table I

$R_1COC(=CH_2)R_2$ I (**1-37**, **51**, **52**)

$R_1COC(=CH_2)CH_2R_2$ II (**38-50**)

compd						yield,[c]		MIC,[e] μg/mL		
no.	R_1	R_2[a]	method	recrystn[b] solvent	mp, °C	%	formula[d]	*C.a.*	*A.f.*	*T.a.*
1	4-ClC_6H_4	T	A	AcOEt/(*i*-Pr)$_2$O	110–111.5	44	$C_{11}H_8ClN_3O$	0.2	6.3	1.6
2	4-FC_6H_4	T	A	AcOEt/(*i*-Pr)$_2$O	73–75	26	$C_{11}H_8FN_3O$	0.4	6.3	0.8
3	4-CNC_6H_4	T	A	AcOEt/(*i*-Pr)$_2$O	111–113	2	$C_{12}H_8N_4O$	1.6	25	6.3
4	4-MeC_6H_4	T	A	(*i*-Pr)$_2$O	65–66	8	$C_{12}H_{11}N_3O$	0.2	6.3	0.8
5	4-$MeOC_6H_4$	T	A	AcOEt/(*i*-Pr)$_2$O	88–89	6	$C_{12}H_{11}N_3O_2$	0.8	12.5	0.8
6	4-PhC_6H_4	T	A	AcOEt/(*i*-Pr)$_2$O	138–139	27	$C_{17}H_{13}N_3O$	0.4	3.1	0.2
7	2-furyl	T	A	Et_2O	96.5–98.5	1	$C_9H_7N_3O_2$	0.8	6.3	3.1
8	2-thienyl	T	A	Et_2O	89.5–91	6	$C_9H_7N_3OS$	0.4	6.3	1.6
9	Me	T	A		liquid	3	$C_6H_7N_3O\cdot{}^1/_{15}H_2O$	12.5	25	3.1
10	*t*-Bu	T	A		liquid	2	$C_9H_{13}N_3O\cdot{}^1/_{10}H_2O$	0.4	6.3	6.3
11	2,4-$Cl_2C_6H_3$	PA	A		liquid	2	$C_{12}H_8Cl_2N_2O\cdot{}^1/_{20}CH_2Cl_2$	0.8	25	1.6
12	Ph	P	A	AcOEt	146–147 dec	27	$C_{14}H_{11}NO_2$	6.3	50	1.6
13	4-ClC_6H_4	P	A	AcOEt/(*i*-Pr)$_2$O	145–146	36	$C_{14}H_{10}ClNO_2$	1.6	2.5	0.8
14	4-PhC_6H_4	P	A	AcOEt	155–156	21	$C_{20}H_{15}NO_2$	0.8	12.5	0.4
15	2-$MeOC_6H_4$	P	A	AcOEt	142–143	9	$C_{15}H_{13}NO_3$	3.1	>100	1.6
16	4-$COOMeC_6H_4$	P	A	AcOEt	189–190	26	$C_{16}H_{13}NO_4$	3.1	50	3.1
17	2,4-ClC_6H_4	P	A	AcOEt/(*i*-Pr)$_2$O	159–160	9	$C_{14}H_9Cl_2NO_2$	0.8	25	0.8
18	4-ClC_6H_4	PC	A	AcOEt/(*i*-Pr)$_2$O	107–108	23	$C_{16}H_{12}ClNO_4$	0.8	3.1	0.8
19	4-ClC_6H_4	PM	A	AcOEt/(*i*-Pr)$_2$O	146–147	47	$C_{15}H_{12}ClNO_2$	0.8	3.1	0.8
20	4-ClC_6H_4	PL	A	AcOEt/(*i*-Pr)$_2$O	175–176	29	$C_{14}H_9Cl_2NO_2$	0.8	3.1	0.8
21	*t*-Bu	P	A	AcOEt/(*i*-Pr)$_2$O	114–115	3	$C_{12}H_{15}NO_2$	50	>100	6.3
22	4-ClC_6H_4	PD	A	MeOH/AcOEt	165–166	5	$C_{13}H_9ClN_2O_3$	12.5	>100	12.5
23	4-ClC_6H_4	PY	A	AcOEt	153–154	24	$C_{13}H_9ClN_2O_2$	0.4	3.1	1.6
24	4-ClC_6H_4	PE	A	AcOEt/(*i*-Pr)$_2$O	96–97	19	$C_{14}H_{11}ClN_2O_3$	6.3	6.3	3.1
25	4-ClC_6H_4	Q	A	AcOEt	181–182	17	$C_{18}H_{12}ClNO_2$	3.1	1.6	0.2
26	4-PhC_6H_4	QA	A	MeOH/AcOEt	226–228	57	$C_{23}H_{16}N_2O_2\cdot{}^1/_2H_2O$	>100	>100	25
27	4-ClC_6H_4	BZ	A	AcOEt	160–161	5	$C_{17}H_{13}ClN_2O_2$	1.6	1.6	0.4
28	4-ClC_6H_4	BH	A	AcOEt	198–200	3	$C_{16}H_{11}ClN_2O_2$	6.3	12.5	3.1
29	4-ClC_6H_4	QA	A	AcOEt/(*i*-Pr)$_2$O	135–136	60	$C_{17}H_{11}ClN_2O_2$	0.1	0.4	0.1
30	4-$MeOC_6H_4$	QA	A	AcOEt	143–144	19	$C_{18}H_{14}N_2O_3$	1.6	6.3	0.4
31	4-ClC_6H_4	PH	A	AcOEt/(*i*-Pr)$_2$O	143–144	20	$C_{17}H_{11}ClN_2O_2$	0.8	6.3	1.6
32	4-FC_6H_4	2,4-$Cl_2C_6H_3$	B	(*i*-Pr)$_2$O/petr ether	81–83	69	$C_{15}H_9Cl_2FO$	3.1	12.5	0.4
33	2,4-$Cl_2C_6H_3$	2,4-$Cl_2C_6H_3$		petr ether	61–62	66[f]	$C_{15}H_8Cl_4O$	6.3	>100	0.4
34	2-thienyl	4-ClC_6H_4	B	AcOEt/petr ether	49–50	6	$C_{13}H_{19}ClOS$	3.1	3.1	0.1
35	2-thienyl	Ph	B		liquid	9	$C_{13}H_{10}OS$	1.6	1.6	0.2
36	Ph	PL			liquid	48[g]	$C_{14}H_{11}NO$	6.3	25	3.1
37	2-furyl	Me	B		liquid	6	$C_8H_8O_2\cdot{}^1/_5H_2O$	25	25	1.6
38	4-ClC_6H_4	T	C	Et_2O/(*i*-Pr)$_2$O	77–78.5	8	$C_{12}H_{10}ClN_3O$	0.4	12.5	1.6
39	4-$MeOC_6H_4$	T	C	MeOH/(Et)$_2$O	76–78	4	$C_{13}H_{13}N_3O_2\cdot C_2H_2O_4\cdot{}^1/_3H_2O$	12.5	>100	6.3
40	4-PhC_6H_4	T	C	AcOEt/(*i*-Pr)$_2$O	121–122	14	$C_{18}H_{15}N_3O$	1.6	12.5	0.4
41	3-thienyl	T	C	MeOH/(Et)$_2$O	86–87	4	$C_{10}H_9N_3OS\cdot{}^1/_3CH_3OH\cdot C_2H_2O_4$	12.5	100	6.3
42	4-PhC_6H_4	PA	C	AcOEt/petr ether	96–97	10	$C_{19}H_{16}N_2O$	6.3	12.5	0.8
43	4-ClC_6H_4	P	C		liquid	9	$C_{15}H_{12}ClNO_2\cdot{}^1/_3H_2O$	1.6	25	0.8
44	4-$MeOC_6H_4$	P	C		liquid	11	$C_{16}H_{15}NO_3\cdot{}^1/_3H_2O$	25	100	6.3
45	4-PhC_6H_4	P	C	AcOEt/(*i*-Pr)$_2$O	107–108	22	$C_{21}H_{17}NO_2$	6.3	50	0.8
46	3-thienyl	P	C		liquid	13	$C_{13}H_{11}NO_2S\cdot{}^1/_2CH_3OH$	50	50	6.3
47	4-ClC_6H_4	QA	C	AcOEt/(*i*-Pr)$_2$O	141–142	4	$C_{18}H_{13}ClN_2O_2\cdot C_2H_2O_4$	3.1	6.3	3.1
48	4-ClC_6H_4	N(Me)$_2$	C	MeOH/(Et)$_2$O	156–158 dec	9	$C_{12}H_{14}ClNO\cdot C_2H_2O_4$	12.5	12.5	6.3
49	4-ClC_6H_4	Q	D	AcOEt/(*i*-Pr)$_2$O	95.5–96.5	6	$C_{19}H_{14}ClNO_2$	25	100	3.1
50	3-thienyl	Ph	E	petr ether	65–66	4	$C_{14}H_{12}OS$	>100	100	6.3
51	4-ClC_6H_4NH	2,4-$Cl_2C_6H_3$	F	AcOEt/(*i*-Pr)$_2$O	165–166	17	$C_{15}H_{10}Cl_3NO$	>100	>100	>100
52	4-MO	2,4-$Cl_2C_6H_3$	F	(*i*-Pr)$_2$O	82–83	17	$C_{13}H_{13}Cl_2NO_2$	>100	>100	>100
53								3.1	100	3.1
54								3.1	100	3.1
56								0.8	6.3	0.8
58								>100	>100	25
59								>100	>100	12.5
61								>100	>100	>100
clotrimazole[7]								1.6	1.6	0.1
miconazole[6]								3.1	6.3	0.1
econazole[6]								3.1	3.1	0.1
croconazole[2]								3.1	3.1	0.1

[a] T: 1-(1,2,4-triazolyl). PA: 1-pyrazolyl. P: 1-(2-oxo-1,2-dihydropyridyl). PC: 1-(2-oxo-5-(methoxycarbonyl)-1,2-dihydropyridinyl). PM: 1-(2-oxo-5-methyl-1,2-dihydropyridinyl). PL: 1-(2-oxo-5-chloro-1,2-dihydropyridinyl). PD: 1-(2,5-dioxo-1,2,5,6-tetrahydropyrazinyl). PY: 1-(6-oxo-1,6-dihydropyrimidinyl). PE: 1-(2,5-dioxo-6-methyl-1,2,5,6-tetrahydropyrazinyl). Q: 1-(2-oxo-1,2-dihydroquinolinyl). QA: 3-(4-oxo-3,4-dihydroquinazolinyl). BZ: 1-(2-oxo-3-methyl-1,2-dihydrobenzimidazolinyl). BH: 1-(2-oxo-1,2-dihydrobenzimidazolinyl). PH: 2-(1-oxo-1,2-dihydrophthalazinyl). PL: 4-(pyridinyl). MO: morpholine. [b] AcOEt: Ac. (*i*-Pr)$_2$O: I. Et_2O: E. MeOH: M. petr ether: ER. [c] Yield indicates overall yield in Scheme I or II. [d] All compounds were analyzed for C, H, and N and where present Cl, F, and S, and results were within 0.4% of the calculated values. [e] Lowest value in the in vitro tests duplicated. *C.a.*: *Candida albicans*. *A.f.*: *Aspergillus fumigatus*. *T.a.*: *Trichophyton asteroides*. [f] Yield from V to I (see ref 3). [g] Yield from V to I (starting V was prepared according to the procedure of Osuch[5]).

in mineral oil, 1.14 g, 23.8 mmol) in DMF (25 mL) was added IX (R_1 = 4-chlorophenyl, 4.9 g, 19.8 mmol) at room temperature with stirring. After 15 min, the reaction mixture was poured into ice water in 10% NaOH and extracted with Et_2O. The organic layer was washed with H_2O, dried over Na_2SO_4, and evaporated. The residue was chromatographed on a column of silica gel. The fractions eluted with 3% $MeOH/CH_2Cl_2$ were collected to obtain VIII [R_1 = 4-chlorophenyl, R_2 = (2-oxo-1,2-dihydroquinolin-1-yl)methyl, 650 mg, mp 102–103 °C, 10%, from AcOEt/*i*-Pr_iO]. Anal. ($C_{18}H_{14}ClNO$) C, H, Cl, N.

The above product VIII [R_1 = 4-chlorophenyl, R_2 = (2-oxo-1,2-dihydroquinolin-1-yl)methyl, 600 mg, 1.92 mmol] was treated with TMDAM (590 mg, 5.8 mmol) in Ac_2O (590 mg, 5.8 mmol) at 80 °C for 1 h. Usual workup as described in method A and column chromatography on silica gel with 25% AcOEt/benzene as the eluent afforded **49** (350 mg, mp 95.5–96.5 °C, 56%, from AcOEt/*i*-Pr_2O): overall yield 6%; IR (Nujol) 1645 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.33 (2 H, s, CH_2), 5.50 (1 H, s, =CH*H*), 5.77 (1 H, s, =CH*H*), 6.72–7.83 (10 H, m, aromatics). Anal. ($C_{19}H_{14}ClNO_2$) C, H, Cl, N.

1-(2-Thienyl)-2-benzyl-2-propen-1-one (50) (Method E). 3-Phenylpropionitrile (4 g, 30.5 mmol) in dry Et_2O (15 mL) was added to 2-thienylmagnesium bromide in Et_2O (75 mL) prepared from magnesium (1.11 g, 46 mmol), 2-bromothiophene (7.5 g, 46 mmol), and a catalytic amount of iodine, and the mixture was refluxed for 15 min. The reaction mixture was poured on ice water and added 6 N HCl with stirring at room temperature. After 5 min, the mixture was extracted with Et_2O and the organic layer was washed with H_2O and dried over Na_2SO_4. After evaporation of organic solvent, the residue was chromatographed on a silica gel column. The fraction eluted with 50% benzene/*n*-hexane were collected to obtain VIII (R_1 = 2-thienyl, R_2 = benzyl, 1.5 g as an oil, 15%), which was used without further purification for the next step.

The above product VIII (R_1 = 2-thienyl, R_2 = benzyl, 1.5 g, 6.9 mmol) was treated with TMDAM (4.4 g, 43.1 mmol) in Ac_2O (4.4 g, 43.1 mmol) at 80 °C for 3 h. Usual workup as described in method A and column chromatography on silica gel with 50% benzene/*n*-hexane as the eluent afforded **50** (900 mg, mp 65–66 °C, 57%, from petroleum ether): IR (Nujol) 1628 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.78 (2 H, s, CH_2), 5.63 (1 H, s, =CH*H*), 5.87 (1 H, s, =CH*H*), 7.02–7.67 (8 H, m, aromatics). Anal. ($C_{14}H_{12}OS$) C, H, S.

2-(2,4-Dichlorophenyl)-4′-chloroacrylanilide (51) (Method F). 2,4-Dichlorophenylacetonitrile (20 g, 107.5 mmol) was treated with TMDAM (32.8 g, 321 mmol) in Ac_2O (32.8 g, 321 mmol) at 70 °C for 2.5 h with stirring. Usual workup and column chromatography on silica gel with 50% benzene/*n*-hexane as the eluent afforded XII R_2 = 2,4-dichlorophenyl, 13.7 g, 64%, from petroleum ether), which was used without further purification for the next step.

The above product XII (R_2 = 2,4-dichlorophenyl, 7 g, 35.3 mmol) was treated with 98% H_2SO_4 (21 g) and H_2O (9 mL) at 130 °C for 15 h. After cooling, the reaction mixture was extracted with Et_2O. The organic layer washed with H_2O, dried over Na_2SO_4, and evaporated. The residue was chromatographed on silica gel. The fractions eluted with 3% $MeOH/CH_2Cl_2$ were collected to obtain XIII (R_2i = 2,4-dichlorophenyl, 6.5 g, 85%, after washing with *i*-Pr_2O), which was used without further purification for the next step.

The above product XIII (R_2 = 2,4-dichlorophenyl, 500 mg, 2.3 mmol) was treated with $SOCl_2$ (2.5 mL) at 50 °C for 30 min. After evaporation of $SOCl_2$, the residue was dissolved in CH_2Cl_2 (3 mL) and to this was added 4-chloroaniline (330 mg, 2.6 mmol) and Et_3N (470 mg, 4.7 mmol) in CH_2Cl_2 (10 mL) with ice cooling. After 15 min at room temperature, with stirring, the reaction mixture was evaporated, acidified with 6 N HCl, and extracted with Et_2O. The organic layer was washed with H_2O, dried over Na_2SO_4, and evaporated. The residue was chromatographed on silica gel. The fractions eluted with 2% $MeOH/CH_2Cl_2$ were collected to obtain **51** (230 mg, mp 165–166 °C, 31%, from AcOEt/*i*-Pr_2O): overall yield from the 2,4-dichlorophenylacetonitrile was 17%; IR (Nujol) 3250, 1655, 1620, and 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.67 (1 H, s, =CH*H*), 6.48 (1 H, s, =CH*H*), 7.17–7.47 (8 H, m, aromatics and NH). anal. ($C_{15}H_{10}Cl_3NO$) C, H, Cl, N.

Compound **52** was prepared in a similar manner.

3-Hydroxy-2-(1*H*-1,2,4-triazol-1-yl)-4′-methoxypropiophenone (53). Compound **5** (500 mg, 2.2 mmol) was treated with 6 N HCl (5 mL) at 100 °C for 4 h. The reaction mixture was added aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was washed with H_2O, dried over Na_2SO_4, and evaporated. The residue was chromatographed on silica gel. The fractions eluted with 5% $MeOH/CH_2Cl_2$ were collected to obtain **53** (310 mg, mp 123–125 °C, 58%, from AcOEt/*i*-Pr_2O): IR (Nujol) 3100 and 1670 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.87 (3 H, s, OMe), 4.08 (2 H, t, *J* = 4.5 Hz, CH_2OH), 5.28 (1 H, t, *J* = 4.5 Hz, CH_2O*H*), 6.35 (1 H, t, *J* = 4.5 Hz, COC*H*), 7.07–8.70 (6 H, m, aromatics). Anal. ($C_{12}H_{13}N_3O_3$) C, H, N.

3-Methoxy-2-(1*H*-1,2,4-triazol-1-yl)-4′-methoxypropiophenone (54). Compound **5** (1 g, 4.4 mmol) in MeOH (10 mL) was refluxed for 4 h. The reaction mixture was evaporated and the residue was chromatographed on a column of silica gel. The fractions eluted with AcOEt were collected to obtain **54** (650 mg, mp 114–115.5 °C, 57%, from AcOEt/*i*-Pr_2O): IR (Nujol) 1675 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.30 (3 H, s, CH_2O*Me*), 3.85 (3 H, s, PhO*Me*), 4.00 (2 H, d, *J* = 4.5 Hz, CH_2O), 6.18 (1 H, t, *J* = 4.5 Hz, COC*H*), 6.93–8.43 (6 H, m, aromatics). Anal. ($C_{13}H_{15}N_3O_3$) C, H, N.

3-Hydroxy-2-(4-oxo-3,4-dihydroquinazolin-3-yl)-4′-chloropropiophenone (56). A mixture of 2-(4-oxo-3,4-dihydroquinazolin-3-yl)-4′-chloropropiophenone (**55**, 50 mg, 17 mmol), paraformaldehyde 165 mg, 1.8 mmol), and $KHCO_3$ (250 mg, 2.5 mmol) in 80% DMF (12.5 mL) was stirred at room temperature for 1 h. The reaction mixture was added to H_2O and extracted with AcOEt. The organic layer was washed with H_2O and dried over Na_2SO_4 and evaporated. The residue was chromatographed on a silica gel. The fractions eluted with 50% benzene/AcOEt were collected to obtain **56** (216 mg, mp 172–174 °C, 39%, from MeOH/AcOEt): IR (Nujol) 3400, 1700, 1648 cm^{-1}; ^1H NMR (Me_2SO-d_6) υ 4.20 (2 H, t, *J* = 4.5 Hz, CH_2O), 5.33 (1 H, t, *J* = 4.5 Hz, OH), 6.23 (1 H, t, *J* = 4.5 Hz, COCH), 7.43–8.57 (9 H, m, aromatics. Anal. ($C_{17}H_{13}ClN_2O_3$) C, H, Cl, N.

2-(2-Oxo-1,2-dihydropyridin-1-yl)-4′-chloro-2-pentenophenone (58). A mixture of 4′-chlorophenacyl bromide (2.7 g, 11.6 mmol), 2-hydroxypyridine (1 g, 10.5 mmol), and KOH and 86% purity, 650 mg, 10.0 mmol) in DMF (10 mL) was stirred at room temperature for 30 min. The reaction mixture was diluted with H_2O and extracted with AcOEt. The organic layer was washed with H_O, dried over Na_iSO_4, and evaporated. The residue was chromatographed on silica gel. The fractions eluted with 2% $MeOH/CH_2Cl_2$ were collected to obtain 2-(2-oxo-1,2-dihydropyridin-1-yl)-4′-chloroacetophenone (**57**) (1.2 g, mp 147–148 °C, 46%, from AcOEt/*i*-Pr_2O). Anal. ($C_{13}H_{10}ClNO_2$) C, H, Cl, N.

A mixture of **57** (500 mg, 2 mmol), propionaldehyde (1.18 g, 20.3 mmol), dry toluene (20 mL), and traces of piperidine and AcOH was refluxed for 5 h. The reaction mixture was evaporated and the residue was chromatographed on a column of silica gel. The fractions eluted with 50% AcOEt/benzene were collected to obtain **58** (2.75 mg as an oil, 47%): overall yield 22%; IR (Nujol) 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.07 (3 H, t, *J* = 6 Hz, CH_2C*H_3*), 2.20 (2 H, m, C*H_2*CH_3), 6.13–7.83 (9 H, m, CH=C, aromatics). Anal. ($C_{16}H_{14}ClNO_2 \cdot {}^1/_3H_2O$) C, H, Cl, N.

4′-Chloro-4-fluoro-α-(2-oxo-1,2-dihydropyridin-1-yl)chalcone (59). A mixture of **57** (500 mg, 2 mmol), *p*-fluorobenzaldehyde (375 mg, 3 mmol), dry toluene (20 mL), and traces of piperidine and AcOH was refluxed for 2 h. The reaction mixture was evaporated and the residue was chromatographed on silica gel. The fractions eluted with 50% AcOEt/benzene were collected to obtain **59** (520 mg, mp 168–169 °C, 73%, from AcOEt/*i*-Pr_2O): IR (Nujol) 1665, 1639 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.10–7.97 (13 H, m, =CHC, aromatics. Anal. ($C_{20}H_{13}ClFNO_2$) C, H, Cl, F, N.

2-(2-Oxo-1,2-dihydropyridin-1-yl)-4′-chloropropiophenone (61). To 4′-chloropropiophenone (**60**; 5 g, 29.7 mmol) in $CHCl_3$ (50 mL) was added bromine (4.74 g, 29.7 mmol) in $CHCl_3$ (15 mL) with stirring at room temperature. After 15 min, H_2O was added and the reaction mixture neutralized with aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was washed with H_2O, dried over Na_2SO_4, and evaporated. The residue was dissolved in DMF (30 mL) and 2-hydroxypyridine (1.33 g, 14 mmol) and KOH (purity 86/%, 920 mg, 14 mmol) added with stirring at room temperature. After 30 min, the reaction mixture was poured into ice water and extracted with Et_2O. The organic layer was washed with H_2O, dried over Na_2SO_4, and evaporated. The residue was chromatographed on a column of silica gel. The fractions eluted with 50% AcOEt/benzene and 2% MeOH/CH_2Cl_2 were collected to obtain **61** (700 mg, mp 76–77 °C, from AcOEt/*i*-Pr_2O, overall yield 9%): IR (Nujol) 1690, 1655 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.58 (3 H, d, J = 7.5 Hz, CH_3), 6.10–8.00 (9 H, m, =CHC, aromatics). Anal. ($C_{14}H_{12}ClNO_2$) C, H, Cl, N.

Acknowledgment. We thank K. Kanazawa and K. Ito for their excellent technical assistances.

Registry No. 1, 104940-90-1; **2**, 104940-89-8; **3**, 104940-93-4; 4, 104940-91-2; **5**, 104940-92-3; **6**, 104940-86-5; **7**, 104940-94-5; **8**, 104940-95-6; **9**, 104940-87-6; **10**, 104940-88-7; 11, 104941-07-3; **12**, 108664-23-9; **13**, 104940-96-7; 14, 108664-24-0; **15**, 108664-25-1; **16**, 108664-26-2; **17**, 104940-99-0; **18**, 104941-01-7; **19**, 108664-27-3; **20**, 104940-98-9; **21**, 104940-97-8; **22**, 108664-28-4; **23**, 108664-29-5; **24**, 108664-30-8; **25**, 104941-04-0; **26**, 108664-31-9; **27**, 108664-32-0; **28**, 108664-33-1; **29**, 108664-34-2; **30**, 108664-35-3; **31**, 108664-36-4; **32**, 98617-94-8; **33**, 104941-05-1; **34**, 104941-08-4; **35**, 13191-28-1; **36**, 108664-37-5; **37**, 24229-73-0; **38**, 104941-10-8; **39**·$C_2H_2O_4$, 108664-38-6; **40**, 108664-39-7; 41·$C_2H_2O_4$, 108664-41-1; **42**, 108664-42-2; **43**, 104941-12-0; 44, 104941-13-1; **45**, 108664-43-3; **46**, 108664-44-4; **47**·$C_2H_2O_4$, 108664-46-6; **48**·$C_2H_2O_4$, 108664-47-7; 49, 108664-48-8; **50**, 108664-49-9; **51**, 108664-50-2; **52**, 108664-51-3; **53**, 108664-52-4; **54**, 108664-53-5; **55**, 90059-70-4; **56**, 108664-54-6; **57**, 108664-55-7; **58**, 104941-03-9; **59**, 104941-02-8; **60**, 6285-05-8; **61**, 108664-56-8; III (R_1 = 4-$MeOC_6H_4$), 100-06-1; III (R_1 = 4-MeC_6H_4), 92-91-1; IV (R_1 = 4-$MeOC_6H_4$), 2632-13-5; IV (R_1 = 4-ClC_6H_4), 536-38-9; V (R_1 = 4-ClC_6H_4, R_2 = T), 58905-19-4; V (R_1 = 4-FC_6H_4, R_2 = T), 58905-21-8; V (R_1 = 4-CNC_6H_4, R_2 = T), 103962-24-9; V (R_1 = 4-MeC_6H_4, R_2 = T), 58905-20-7; V (R_1 = 4-$MeOC_6H_4$, R_2 = T), 89082-07-5; V (R_1 = 4-PhC_6H_4, R_2 = T), 89082-08-6; V (R_1 = 2-furyl, R_2 = T), 108674-95-9; V (R_1 = 2-thienyl, R_2 = T), 108664-57-9; V (R_1 = Me, R_2 = T), 64882-52-6; V (R_1 = *t*-Bu, R_2 = T), 58905-32-1; V (R_1 = 2,4-$Cl_2C_6H_3$, R_2 = PA), 108664-58-0; V (R_1 = Ph, R_2 = P), 952-75-0; V (R_1 = 4-PhC_6H_4, R_2 = P), 13576-81-3; V (R_1 = 2-$MeOC_6H_4$, R_2 = P), 108664-59-1; V (R_1 = 4-$COOMeC_6H_4$, R_2 = P), 108664-60-4; V (R_1 = 2,4-$Cl_2C_6H_3$, R_2 = P), 108664-61-5; V (R_1 = 4-ClC_6H_4, R_2 = PC), 108664-62-6; V (R_1 = 4-ClC_6H_4, R_2 = PM), 108664-63-7; V (R_1 = 4-ClC_6H_4, R_2 = PL), 108664-64-8; V (R_1 = *t*-Bu, R_2 = P), 108664-65-9; V (R_1 = 4-ClC_6H_4, R_2 = PD), 108664-66-0; V (R_1 = 4-ClC_6H_4, R_2 = PY), 108664-67-1; V (R_1 = 4-ClC_6H_4, R_2 = PE), 108664-68-2; V (R_1 = 4-ClC_6H_4, R_2 = Q), 108664-69-3; V (R_1 = 4-PhC_6H_4, R_2 = QA), 108664-70-6; V (R_1 = 4-ClC_6H_4, R_2 = BZ), 108664-71-7; V (R_1 = 4-ClC_6H_4, R_2 = BH), 108664-72-8; V (R_1 = 4-ClC_6H_4, R_2 = QA), 90059-70-4; V (R_1 = 4-MeC_6H_4, R_2 = QA), 90059-68-0; V (R_1 = 4-ClC_6H_4, R_2 = PH), 108664-73-9; V (R_1 = 4-FC_6H_4, R_2 = 2,4-$Cl_2C_6H_3$), 98617-95-9; V (R_1 = 2,4-$Cl_2C_6H_3$, R_2 = 2,4-$Cl_2C_6H_3$), 107680-34-2; V (R_1 = 2-thienyl, R_2 = 4-ClC_6H_4), 67947-51-7; V (R_1 = 2-thienyl, R_2 = Ph), 13196-28-6; V (R_1 = Ph, R_2 = PL), 108674-96-0; V (R_1 = 2-furyl, R_2 = Me), 3194-15-8; VII (R_1 = 4-MeC_6H_4), 5409-63-2; VIII (R_1 = 4-ClC_6H_4, R_2 = T), 81234-31-3; VIII (R_1 = 4-$MeOC_6H_4$, R_2 = T), 108664-74-0; VIII (R_1 = 4-PhC_6H_4, R_2 = T), 81234-79-9; VIII (R_1 = 3-thienyl, R_2 = T), 108664-75-1; VIII (R_1 = 4-PhC_6H_4, R_2 = PA), 108664-76-2; VIII (R_1 = 4-ClC_6H_4, R_2 = P), 108664-77-3; VIII (R_1 = 4-$MeOC_6H_4$, R_2 = P), 108664-78-4; VIII (R_1 = 4-PhC_6H_4, R_2 = P), 108664-79-5; VIII (R_1 = 3-thienyl, R_2 = P), 108664-80-8; VIII (R_1 = 4-ClC_6H_4, R_2 = QA), 108664-81-9; VIII (R_1 = 4-ClC_6H_4, R_2 = NMe_2), 2138-38-7; VIII (R_1 = 4-ClC_6H_4, R_2 = Q), 108664-82-0; VIII (R_1 = 3-thienyl, R_2 = Ph), 108664-83-1; IX (R_1 = 4-ClC_6H_4), 33994-12-6; XI (R_2 = $PhCH_2$), 645-59-0; XI (R_2 = 2,4-$Cl_2C_6H_3$), 6306-60-1; XII (R_2 = 2,4-$Cl_2C_6H_3$), 26923-38-6; XIII (R_2 = 2,4-$Cl_2C_6H_3$), 108664-84-2; TMDAM, 51-80-9; $PhCH_2COCl$, 103-80-0; 2,4-$Cl_2C_6H_3C(=CH_2)COCl$, 108664-85-3; 4-$ClC_6H_4NH_2$, 106-47-8; CH_3CH_2CHO, 123-38-6; 4-FC_6H_4CHO, 459-57-4; 4-$ClC_6H_4COCHBrCH_3$, 877-37-2; morpholine, 110-91-8; 1*H*-1,2,4-triazole, 288-88-0; thiophene, 110-02-1; 1*H*-pyrazole, 288-13-1; 2(1*H*)-quinolinone, 59-31-4; 2-thienylmagnesium bromide, 5713-61-1; 2(1*H*)-pyridinone, 142-08-5.

Progesterone Derivatives That Bind to the Digitalis Receptor: Synthesis of 14β-Hydroxyprogesterone. A Novel Steroid with Positive Inotropic Activity

J. F. Templeton,*† V. P. Sashi Kumar,† D. Cote,⊥ D. Bose,‡,§ D. Elliott,‡ R. S. Kim,‡ and F. S. LaBella*‡

Faculty of Pharmacy, Department of Pharmacology and Therapeutics and Department of Internal Medicine, Faculty of Medicine, University of Manitoba, and St. Boniface Hospital, Winnipeg, Manitoba, Canada. Received December 22, 1986

The synthesis of 14-hydroxy-14β-pregn-4-ene-3,20-dione (14β-hydroxyprogesterone) is described. This novel steroid is about 10 times more potent than progesterone and one-tenth as potent as ouabagenin in an [^{3}H]ouabain radioligand binding assay and is the first in a series of progesterone congeners that interact at the cardiac glycoside receptor both to possess the C/D cis ring junction and to enhance contractility of isolated cardiac tissue.

The high-affinity binding of the cardiac glycosides to their biological receptor, i.e., Na^+,K^+-ATPase, is noted, also, for its high degree of structural specificity.[1] In previous studies from our laboratory,[2-6] it was demonstrated that certain derivatives of progesterone are inhibitors of [^{3}H]ouabain binding to cell membrane preparations. The most active congener identified thus far is chlormadinone acetate (17α-acetoxy-6-chloropregna-4,6-diene-3,20-dione), having 3–4 times the potency of ouabagenin. These mammalian steroid derivatives interact at the cardiac glycoside binding site and inhibit Na^+,K^+-ATPase and the sodium pump, and crystallographic studies show important spatial relationships between the C-20 ketone of the progesterone derivatives and the C-23 carboxyl oxygen of the lactone moiety in the cardiac glycoside.[5] However, progesterone and the receptor-active semisynthetic derivatives elicit cardiode-

---

† Faculty of Pharmacy.

⊥ St. Boniface Hospital.

‡ Department of Pharmacology and Therapeutics.

§ Department of Internal Medicine.

(1) Guntert, T. W.; Linde, H. H. A. in *Cardiac Glycosides*; Greef, K., Ed.; Springer-Verlag: Berlin, 1981; Part 1, Chapter 2, pp 13–24.

(2) Chow, E.; Kim, R. S.; LaBella, F. S.; Queen, G. *Br. J. Pharmacol.* **1979**, *67*, 345.

(3) Kim, R. S.; LaBella, F. S.; Zunza, H.; Zunza, F.; Templeton, J. F. *Mol. Pharmacol.* **1980**, *18*, 402.

(4) LaBella, F. S.; Bihler, I.; Kim, R. S. *Can. J. Physiol. Pharmacol.* **1984**, *62*, 1057.

(5) LaBella, F. S.; Bihler, I.; Templeton, J.; Kim, R. S.; Hnatowich, M.; Rohrer, D. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **1985**, *44*, 2806.

(6) LaBella, F. S.; Bihler, I.; Kim, R. S.; *Nature (London)* **1979**, *28*, 571.