Heterocyclic Compounds XII. Quinazoline Derivatives as Potential Antifertility Agents (1)

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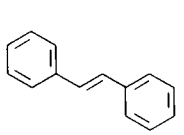
Received December 4, 1978

Several quinazoline derivatives incorporating a *trans*-stillbene moiety were synthesized as potential post-coital antifertility agents. Some of these compunds showed low level activity in rats.

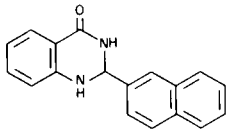
J. Heterocyclic Chem., **16**, 711 (1979).

In the course of a program on the synthesis of potential antifertility agents we planned to prepare a group of heterocycles that resemble *trans*-stilbene (**1**), a well known antifertility agent (2). We noted that a quinazolone (**1b**) has shown chemisterilant activity in rats (10). Recently we reported on the post-coital antifertility activity in rats shown by some thienopyrimidine derivatives (**1c**) (1).

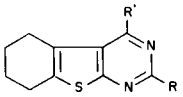
The quinazolines (**2**) are closely related to **1b** and at the same time they possess the trans stilbene type disposition of two aromatic groups (*cp.* dotted areas of **1a** *and* **2**). In view of the largely hydrocarbon nature of **2** we decided to convert it to **3** by β-aminoethanol type side chain that appears to facilitate *in vivo* transport. The target compound **3** also bears a close relationship to **1c**.



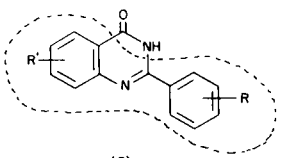
(1a)



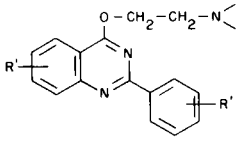
(1b)



(1c)



(2)

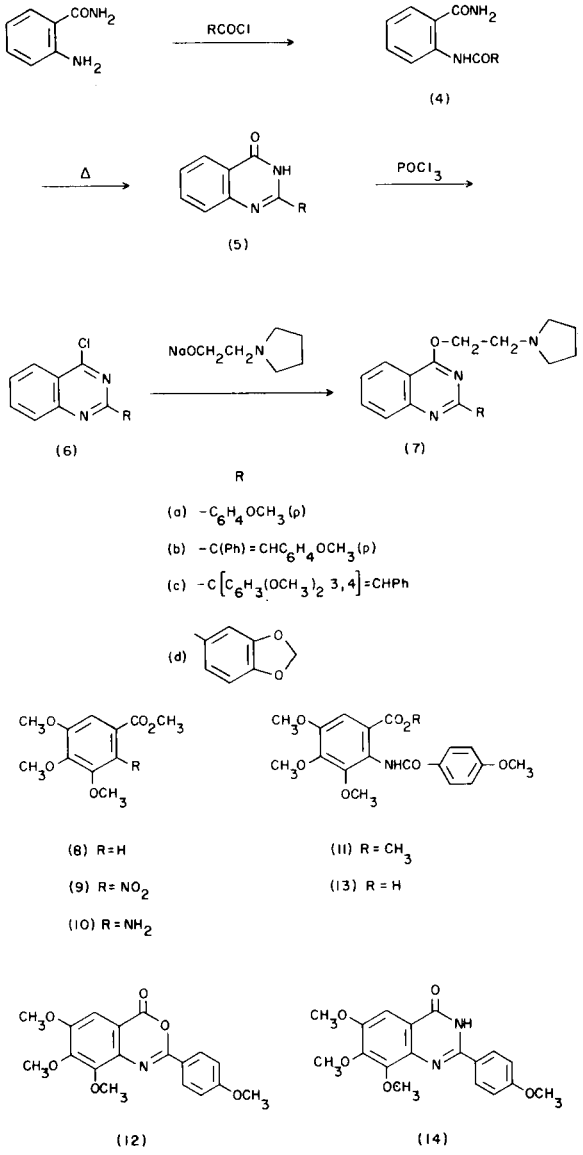


(3)

The readily available anthranilamide was selected as one of the starting materials for preparing **3**. Acylation with an appropriate aromatic acid chloride in presence of triethylamine converted anthranilamide to the diamide **4** which could be cyclized to **5** by heating in diphenyl oxide. Equally good results were obtained by just melting the diamide **4** in the absence of any solvent. In some cases a purer end product **5** was produced by melting an intimate mixture of **4** and sodium bicarbonate.

The conversion of **5** to a 4-chloroquinazoline (**6**) was readily achieved by reaction with phosphorus oxychloride. The aminoethanol side chain was added by allowing **6** to react with the sodium salt of β-pyrrolidinoethanol (3). A series of target compounds (**7a-d**) was prepared by this method (Scheme 1).

Scheme 1



(4)

(5)

(6)

(7)

R

(a) $-C_6H_4OCH_3(p)$

(b) $-C(Ph)=CHC_6H_4OCH_3(p)$

(c) $-C[C_6H_3(OCH_3)_2\ 3,4]=CHPh$

(d)

(8) R=H

(9) R=NO_2

(10) R=NH_2

(11) R=CH_3

(13) R=H

(12)

(14)

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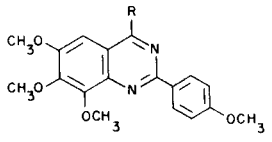
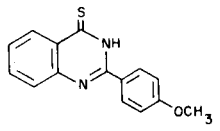
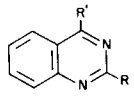


(15) R = Cl

(16) R = O-CH_2-CH_2-N



(17)



(18) R = C_6H_4OMe(p), R' = SMe

(19) R = C_6H_4OMe(p), R' = HN- 

The starting material for the compound **16** was methyl 3,4,5-trimethoxybenzoate (**8**) which was nitrated with cupric nitrate in acetic anhydride solution to give **9**. Catalytic reduction over platinum/carbon was uneventful but during acylation of **10** to **11**, a minor by-product was obtained which appeared to be the lactone of imidoester **12** on the basis of spectral data. This lactone structure **12** was confirmed by an alternative synthesis in which **11** was selectively hydrolyzed to the amido acid **13** and then refluxed with thionyl chloride to form the cyclic imido ester **12**. The amido ester **11** could be directly transformed to **12** on refluxing with sodium methoxide in benzene solution.

The most convenient method for the preparation of the quinazolone **14** was found to be reaction of the amido ester **11** with methanolic ammonia under pressure. The final product **16** was obtained in the usual manner *via* the chloro compound **15**.

Compound **19**, an analog of **7**, was prepared from the intermediate **5a** *via* the 4-methylthioquinazoline hydroiodide **18**. Reaction of **5a** with phosphorus pentasulfide led to the thione amide **7** which was refluxed with methyliodide to give **18**. The methylthio group was smoothly replaced be an amino function to produce **19** when **18** was heated with *m*-methyoxyaniline.

Post-coital Antifertility Test Data.

The compounds **7a, 7c, 7d** and **19** were tested at the Endocrine Laboratory of Madison, Inc., Madison, Wisconsin. Adult cycling female rats were selected in the proestrous phase of the cycle. Each female was caged overnight with two adult males. The finding of sperm in the vaginal smear the following morning was used as evidence of insemination. Treatment began on the day of finding sperm and continued to a total of seven days. The rats were sacrificed on the tenth day of pregnancy and the number of implantation sites, resorbing embryos, empty sites and corpora lutea were recorded for each female. A summary of the test data is given in Table I.

The compounds under test showed only low level post-coital antifertility activity. The dose-response relationship, however, was unusual. Compounds **7a** and **19** showed activity at low dose level but with increased dosage reached a peak value which was reduced to zero on further increase of the dosage. On the other hand compounds **7c** and **7d** showed activity at higher and lower levels and none at an intermediate dosage. On the basis of these data it is difficult to rationalize the difference in the antifertility results of these four compounds.

Table I

Test Results on Substituted Quinazolones (a)

Compound	Dose-mg./kg./day	Number of Implantation Sites	Number of Resorbed Embryos	Number of Empty Sites	Number of Corpora Lutea.	Inhibition of Pregnancy (%)
7a	0.5	8/8	0	0	13	0
7a	5.0	6/8	0	0	11	25
7a	50.0	7/8	0	0	12	12.5
7c	0.5	5/8	0	0	11	37.5
7c	5.0	8/8	0.12	0	12	0
7c	50.0	7/8	0	0	11	12.5
7d	0.5	6/8	0	0	12	25
7d	5.0	8/8	0	0	12	0
7d	50.0	5/8	0	0	10	37.5
19	0.5	6/6	0	0	14.7	0
19	5.0	5/6	0	0	12.8	17
19	50.0	6/6	0	0	12.7	0

(a) For these tests carbomethoxycellusolve (CMC) was used as the diluent. In control experiments CMS produced 0% inhibition of pregnancy; ethinylestradiol produced 60% inhibition of pregnancy at the level of 0.064 mg./kg./day and 100% inhibition at 0.128 mg./kg./day.

EXPERIMENTAL

Melting points were determined on a Mel-Temp apparatus and are uncorrected. Ir spectra were recorded on a Perkin-Elmer 247 grating spectrometer. Nmr spectra in deuterated solvents containing TMS as an internal standard were recorded on a Varian A-60A spectrometer; chemical shifts are reported in δ units (ppm downfield from TMS). Mass spectra were obtained with a Hitachi RMU-7 spectrometer. Elemental analyses were performed by Bernhardt, Max-Planck Institute, Mülheim, West Germany and Central Drug Research Institute, Lucknow, India.

General Synthesis of Quinazolines (7).

a. Acylation of Anthranilamide (2).

Anthranilamide (0.208 mole), triethylamine (0.208 mole) and 300 ml. of THF were stirred and a solution of the acid chloride (0.208 mole) in 150 ml. of THF was added dropwise in the course of 20 minutes. The mixture was refluxed for 1 ½ hours, cooled and filtered. The solid was triturated with water. The insoluble portion was the desired amide **4**. The THF solution was concentrated which provided additional product. The acylated material obtained in this manner was sufficiently pure and was used as such for further work.

b. Cyclization of the Amide.

The acylated anthranilamide obtained in the previous operation was refluxed in diphenyl ether using a water separator. The 4-quinazolones (**5**) crystallized out of the ether solution on cooling and were recrystallized from 2-propanol-DMF (8:1) solution.

The cyclization could also be effected by cautiously heating an intimate mixture of the acylated anthranilamide and excess sodium bicarbonate until the frothing subsided. The cooled melt was crushed to a powder, stirred with water for ½ hour, filtered and recrystallized from 2-propanol-DMF (8:1) solution.

c. Formation of 4-Chloroquinazolines (**6**).

The quinazolone (25 g.), phosphorus oxychloride (250 ml.) and DMF (25 ml.) were refluxed for 12 hours. After concentration of the reaction mixture to 70 ml. and cooling, it was poured over crushed ice (500 g.) and exhaustively extracted with dichloromethane. The dried extract was evaporated to afford the 4-chloro derivative in about 80% yield. In most cases these compounds were used directly for further operation. They could, however, be crystallized from benzene-hexane.

d. 4-(β-Pyrrolidinoethoxy)quinazolines (**7**).

The chloroquinazoline (21 g.) in 200 ml. of anhydrous benzene was added to a 10% excess of sodium β-pyrrolidinoethoxide (prepared by adding sodium or sodium hydride to a benzene solution of β-pyrrolidinoethanol). The reaction mixture was refluxed overnight, cooled, washed with 200 ml. portions of ice-cold water, dried (magnesium sulfate) and evaporated. The residue (invariably an oily material) was chromatographed over basic alumina using benzene as the eluant. Unreacted chloroquinazoline was eluted first and this was followed by the desired product which could be recrystallized from benzene-hexane.

Methyl 2-Nitro-3,4,5-trimethoxybenzoate (**9**).

This compound was prepared from 3,4,5-trimethoxybenzoate by the method of Williams, *et al.* (4).

Methyl 2-Amino-3,4,5-trimethoxybenzoate (**10**).

The nitro compound (**9**, 22.5 g.) and 3 g. of platinum on charcoal (5%) in 200 ml. of ethyl acetate were shaken in a hydrogen atmosphere (40 psi pressure) for 40 hours. The reactants were then filtered through Hi-Flo Supercel. Evaporation of the organic solvent gave the amino compound (**10**) as dark oil in 90% yield.

Reaction of **10** with *p*-Methoxybenzoyl Chloride.

To a solution of **10** (0.062 mole) and triethylamine (0.062 mole) in 200 ml. of THF was added dropwise over a period of 30 minutes a solution of *p*-methoxybenzoyl chloride in 150 ml. of THF. The reaction mixture was then refluxed for 1 ½ hours. After cooling the contents were filtered. THF was removed from the filtrate. The residue was chromatographed over neutral alumina (65 g.) column using benzene-ethyl acetate (50:50) as the eluant. The lactone (**12**) contaminated with a little **11** was eluted in the first fraction. The total yield of the lactone was 1 g., m.p. 175-176°. The subsequent fractions gave pure **11**, 93% yield, m.p. 99-100° (dichloromethane-benzene).

Synthesis of the Lactone (**12**) from **11**.

a.

Methyl 2-(*p*-ethoxybenzamido)-3,4,5-trimethoxybenzoate (**11** 5-6 g.) in methanolic sodium hydroxide (50 ml. of methanol, 10 ml. of water and 0.8 g. of sodium hydroxide) was stirred overnight at room temperature. The reaction mixture was filtered and acidified with dilute hydrochloric acid. The acid (**13**) was refluxed with thionyl chloride in benzene. The lactone (**12**) was isolated after removal of the solvent.

b.

The ester (**11**) was refluxed with one equivalent of sodium methoxide on benzene overnight. The usual work up of the reaction mixture afforded **12**.

2-(*p*-Methoxyphenyl-6,7,8-trimethoxy-4-quinazolone (**14**).

A solution of the amide **11** (0.015 mole), methanol (30 ml.), ammonium chloride (0.1 g.) and liquid ammonia (30 ml.) were placed in an autoclave and stirred overnight. It was then heated for 3 hours at 100° under 5 atmospheres pressure. The work up of the reaction mixture provided 1.8 g. of the title compound, m.p. 218-219°.

The quinazolone (**14**) was converted to the 4-chloro derivative (**15**) in 95% yield by the method described under the synthesis of **6**.

The 4-(β-pyrrolidinoethoxy)quinazoline (**16**), m.p. 110-112°, was obtained from **15** in 20% yield by a method similar to that used for the preparation of **7**.

Synthesis of 2-(*p*-Methoxyphenyl)-4(*m*-methoxyaniline)quinazoline (**19**).

a.

2-(*p*-Methoxyphenyl)-4-quinazolone (**5a**, 0.03 mole), phosphorus pentasulfide (0.012 mole) and 90 ml. of pyridine were refluxed at 140° for 2 hours. The reaction mixture was decanted into 35 ml. of warm water. The 4-thioquinazoline (7) (**17**) that separated out on cooling (70% yield) was used as such for the next separation.

b.

The 4-thioquinazolone (**17**, 0.005 mole) and excess methyl iodide (0.7 g.) were refluxed together in THF for 3 hours. 2-(*p*-Methoxyphenyl)-4-methylthioquinazoline (**18**) separated out as the hydroiodide in 82% yield, m.p. 180° dec., m.p. of the free base 120-122° (8).

c. 2-(*p*-Methoxyphenyl)-4-(*m*-methoxyaniline)quinazoline (**19**).

A solution of **18** (0.0037 mole) and *m*-methoxyaniline (0.0037 mole) in 40 ml. of 2-isopropanol was refluxed for 18 hours. On cooling the title compound separated out as the hydroiodide in 84% yield, m.p. 235-236°.

Spectral and analytical data are provided in Table II.

Acknowledgment.

The authors are thankful to Stevens Institute of Technology for financial support of this work.

REFERENCES AND NOTES

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(2) D. Lednicer in "Contraception: The Chemical Control of Fertility", Marcel Dekker, Inc., New York, N.Y., 1969, Chapter 5.

(3) Compounds **7a** was also prepared directly from the corresponding quinazolone **5** by treating it with β-pyrrolidinoethanol, triphenylphosphine and diethylazidodicarboxylate. For details see M. S. Manhas, W. A. Hoffman, B. Lal and A. K. Bose, *J. Chem. Soc., Perkin Trans. I*, 461 (1975).

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Table II

Analytical and Spectral Data

Compound	M.p. °C	Yield %	Molecular Formula	Analysis C	H	N	Spectral Data
4a	208-210	98	$C_{15}H_{14}N_2O_3$				Ir (nujol): 3450, 3250, 1680, 1670, 1600, 1290, 1185, 780 cm^{-1}; ms: M^+ at m/e 270.
4b	198-200	85	$C_{23}H_{20}N_2O_3$	74.17 (74.17)	5.64 (5.41)	7.37 (7.52)	Ir (nujol): 3390, 3200, 1675, 760 cm^{-1}; nmr (DMSO-d_6) δ: 3.73 (s, 3H), 6.91 (m, 5H), 7.5 (m, 11H), 8.83 (d, 1H)
4c	203-204	89	$C_{24}H_{22}N_2O_4$	71.65 (71.62)	5.82 (5.51)	6.94 (6.96)	Ir (nujol): 3290, 1670, 1500, 760 cm^{-1}; nmr (DMSO-d_6) δ: 3.73 (s, 3H), 3.84 (s, 3H) 7.2 (m, 15H), 8.82 (d, 1H).
4d	229-230	80	$C_{15}H_{12}N_2O_4$	63.59 (63.37)	4.39 (4.26)	9.81 (9.86)	Ir (nujol): 3390, 3180, 1650, 1640, 1590, 921, 751 cm^{-1}
5a(5)	246-248	60					
5b	234-235	65	$C_{23}H_{16}N_2O_2$	77.70 (77.95)	5.11 (5.12)	7.82 (7.91)	Ir (nujol): 3180, 1675, 1570, 1275, 775 cm^{-1} nmr (DMSO-d_6) δ: 3.74 (s, 3H), 6.92 (m, 5H) 7.32 (m, 9H), 9.1 (m, 1H).
5c	203-205	56	$C_{24}H_{20}N_2O_3$	74.58 (74.98)	5.11 (5.24)	7.53 (7.29)	Ir (nujol): 1670, 1605, 1575, 680 cm^{-1}; nmr (DMSO-d_6) δ: 3.6 (s, 3H), 3.81 (s, 3H), 6.8-8.3 (m, 14H).
5d(6)	279-280	49					
6a(9)	123-125	80					
6b	197-199	65	$C_{23}H_{17}ClN_2O$	73.74 (74.09)	4.73 (4.60) Cl 9.37 (9.51)	7.51 (7.52)	Ir (nujol): 1580, 1550, 1260, 705 cm^{-1}.
6c	oily liquid	70					Ir (nujol): 1565, 1545, 1325, 920, 690 cm^{-1}.
6d	oily liquid	90					Ir (nujol): 1612, 1572, 1245, 935 cm^{-1}.
7a	80-81	25	$C_{21}H_{23}N_3O_2$	72.05 (72.18)	6.53 (6.68)	11.47 (12.03)	Ir (nujol): 1608 cm^{-1} nmr (carbon tetrachloride) δ: 1.76 (m, 4H), 2.61 (m, 4H), 2.93 (t, 2H), 3.81 (s, 3H), 4.75 (t, 2H), 7.68 (q, 4H, 7.70 (m, 4H).
7b	204-206d	37	$C_{29}H_{29}N_3O_2$ .2HBr	57.00 (56.78)	4.99 (5.09) Br 26.28 (26.05)	6.72 (6.85)	Ir (nujol): 1600, 1560, 1340, 1250, 685 cm^{-1} nmr (deuteriochloroform) δ: 1.95 (m, 4H), 3.5 (m, 6H), 3.7 (s, 3H), 4.9 (t, 2H), 6.4-8.4 (m, 16H).
7c	151-153	71	$C_{30}H_{31}N_3O_3 \cdot 0.5\ C_4H_6O_6 \cdot H_2O$	66.75 (66.88)	6.40 (6.31)	7.61 (7.31)	
7d	84-88	50	$C_{21}H_{21}N_3O_3$	69.24 (69.40)	5.73 (5.83)	11.38 (11.56)	Ir (neat): 2975, 1619, 1579, 1655, 675 cm^{-1} nmr (deuteriochloroform) δ: 1.79 (m, 2H), 2.67 (m, 2H), 3.0 (t, 2H), 4.8 (t, 2H), 5.93 (s, 2H), 6.7-8.2 (m, 7H).
10	oily liquid	90					Ir (neat): 3500, 3375, 2950, 1685, 750 cm^{-1} nmr (deuteriochloroform) δ: 3.47 (s, 3H) 3.59 (s, 3H), 3.64 (s, 3H), 3.78 (s, 3H), 6.25 (s, 2H), 7.25 (s, 1H).
11	99-100	93	$C_{19}H_{21}NO_7$	60.43 (60.79)	5.60 (5.64)	3.51 (3.73)	Ir (nujol): 3360, 3000, 1720, 1700, 1670, 760 cm^{-1}; nmr (deuteriochloroform) δ: 3.81 (s, 3H), 3.83 (s, 3H), 3.88 (s, 3H), 3.91 (s, 3H), 3.95 (s, 3H), 7.26 (s, 1H), 7.45 (q, 4H), 9.03 (s, 1H).
12	175-176		$C_{16}H_{17}NO_6$	63.00 (62.97)	5.18 (4.99)	3.69 (4.08)	Ir (nujol): 1752, 1610, 1515, 760 cm^{-1}; nmr (deuteriochloroform) δ: 3.84 (s, 3H), 3.92 (s, 3H), 4.01 (s, 3H), 4.14 (s, 3H), 7.32 (s, 1H), 7.55 (q, 4H).
13	178-179	74	$C_{16}H_{19}NO_7$	59.78 (59.83)	5.28 (5.30)	3.89 (3.88)	Ir (nujol): 3350, 2950, 1680, 1605, 690 cm^{-1}.
14	218-219	17	$C_{16}H_{16}N_2O_5$	63.5 (63.15)	5.47 (5.30)	8.33 (8.18)	Ir (nujol): 3175, 3090, 1670, 1655, 725 cm^{-1}; nmr (deuteriochloroform) δ: 3.81 (s, 3H), 3.85 (s, 3H), 4.05 (s, 3H), 7.3 (s, 1H), 5.75 (q, 4H), 11.7 (s, 1H).
16	110-112	20	$C_{16}H_{17}NO_6$	63.00 (62.97)	5.18 (4.99)	3.69 (4.08)	Ir (nujol): 1605, 1585, 1570, 795 cm^{-1} nmr (deuteriochloroform) δ: 1.80 (m, 4H), 2.70 (m, 4H), 3.05 (t, 2H), 3.89 (s, 3H), 4.05 (s, 3H), 4.28 (s, 3H), 4.84 (t, 2H), 7.20 (s, 1H), 7.88 (q, 4H).

Table II continued

Analytical and Spectral Data

Compound	M.p. °C	Yield %	Molecular Formula	Analysis C	H	N	Spectral Data
17(7)	186-188	70					
18(8)	120-122	82					
19	235-236	84	$C_{22}H_{19}N_3O_2 \cdot HI$	54.40 (54.43)	4.12 (3.92)	8.76 (8.66)	Ir (potassium bromide): 1625, 1600, 1570, 760 cm^{-1}; nmr (DMSO-d_6) δ: 3.8 (s, 3H), 3.9 (s, 3H), 6.9-7.8 (m, 12H). ms: m/e 357 (M^+ -HI)

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