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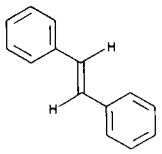
Received August 14, 1978

A series of heterocyclic analogs of diarylethylene and triarylethylene were synthesized as potential anti-implantation agents. Tested in rats as oral, post-coital antifertility agents, a few of our compounds showed some activity.

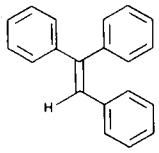
J. Heterocyclic Chem., 16, 371 (1979).

Steroid antifertility agents have proved very effective in inhibiting the ovulatory mechanism or the implantation of the fertilized ovum (2). However, adverse side effects (3) of such agents have focussed renewed attention on the search for non-steroid antifertility drugs (4). Compounds with different structural moieties have been investigated with varying degree of success in their effectiveness as orally effective non-steroidal contraceptives. Besides a few compounds with unusual structures (5) that have shown activity in rats, the main effort has been directed to variations of the diarylethylene (**1a**) and triarylethylene (**2a**) molecules (6).

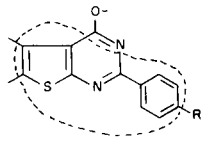
In a project concerned with a search for post-coital antifertility agents we were interested in the synthesis of heterocyclic compounds of the type **1b** and **2b**. In structure **1b** C=N is introduced in place of C=C in diarylethylene (**1a**); in **2b** an aromatic ring of **2a** is replaced by a heterocycle.



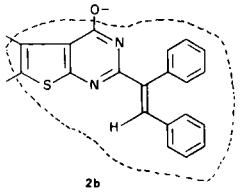
1a



2a



1b



2b

Compounds of the type **3** were synthesized by treating 2-aryl-4-chloro-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidines (7) with the sodium salt of various β-amino alcohols in refluxing benzene.

a. R = Ph, R' = $OCH_2CH_2N(C_2H_5)_2$

b. R = Ph, R' = OCH_2CH_2N

c. R = Ph, R' = OCH_2CH_2NO

d. R = p-$CH_3C_6H_4$, R' = OCH_2CH_2NO

e. R = p-$CH_3C_6H_4$, R' = OCH_2CH_2N

f. R = o-$CH_3C_6H_4$, R' = OCH_2CH_2N

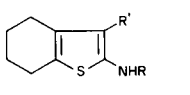
g. R = p-$CH_3OC_6H_4$, R' = OCH_2CH_2N

h. R = Ph, R' = OCH_2CH_2N(CO)$_2$C$_6$H$_4$

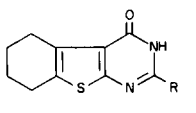
i. R = p-$CH_3C_6H_4$, R' = OCH_2CH_2N(CO)$_2$C$_6$H$_4$

The reaction of 2-amino-3-carboxamido-4,5-tetramethylenethiophene (**4**) (8) with α-phenylcinnamoyl chloride (9) afforded the amide (**6**). Attempts to cyclize this amide in the presence of phosphorus oxychloride resulted in the dehydration of the amide function, resulting in the cyano compound (**7**). However, **7** could be conveniently prepared by the direct acylation of 2-amino-3-cyanothiophene **5** (8). The cyclization of **7** to **9** was accomplished by refluxing an alcoholic solution of **7** saturated with hydrogen chloride. Similarly, the reaction of **5** with α-phenyl-*p*-methoxycinnamoyl chloride gave the amide (**8**) which on cyclization resulted in **10**.

The pyrimidones **9** and **10** were converted to the corresponding 4-chloro derivatives **11** and **12** by treatment with phosphorus oxychloride. The reaction **11** and **12** with the appropriate β-aminoethyl alcohols afforded **13**, **14** and **15**. Refluxing **12** with *N*-methylformamide (10) gave 4-methylaminothienopyrimidine (**16**).

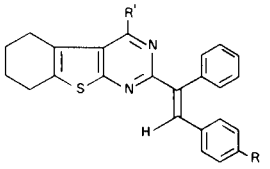


4 R = H, R' = $CONH_2$
5 R = H, R' = CN
6 R = COCPh=CHPh, R' = $CONH_2$
7 R = COCPh=CHPh, R' = CN
8 R = COCPh=$CHC_6H_4OCH_3(p)$, R' = CN



9 R = -CPh=CHPh
10 R = -CPh=$CHC_6H_4OCH_3(p)$

0022-152X/79/020371-06$02.25



11. R = H, R' = Cl

12. R=OCH_3, R' = Cl

13. R = H, R' = OCH_2CH_2N

14. R=OCH_3, R' = OCH_2CH_2N

15. R=OCH_3, R' = OCH_2CH_2N(CO, CO)

16. R=OCH_3, R' = $NHCH_3$

Biological Data.

Antifertility Tests in Rats (12).

Compounds **3g**, **14** and **15** were tested for inhibition of pregnancy in rats. 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 for insemination. Treatment began on the day of finding sperm and continued for a total of seven days. The drugs were administered as sodium carboxymethyl cellulose (CMC) solution. CMC was also used in control experiments. The rats were sacrificed on day 10 of pregnancy and the number of implantation sites, resorbing embryos, empty sites and corpora lutea were recorded for each female. These results are summarized in Table I.

The results given in Table I indicate that this category of compounds show mild inhibition of pregnancy. There, however, does not appear to be any dose-activity relationship on the basis of this limited data. The percentage of inhibition falls off to zero with increasing dose of **15** whereas it increases with the administration of **14**.

Anti-inflammatory and Other Tests.

Compounds **3d** and **3f** were tested for antiviral, antibacterial, antifungal, interferon release and antiinflammatory activity. Compound **3d** was found to be inactive in all these tests.

A comparative study of the antiinflammatory activity of **3b** and **3h** using carageenin induced edema test was undertaken (13). The results are summarized in Table II.

EXPERIMENTAL

The ir spectra were recorded on a Perkin-Elmer Infracord spectrophotometer calibrated with polystyrene film at 1603 cm^{-1}. The pmr spectra were obtained on a Varian A-60A spectrometer operating at 60 MHz using TMS as an internal standard. The mass spectra were measured on a Hitachi Perkin-Elmer RMU-7 mass spectrometer at 70 eV using an all glass heated inlet system. Thin layer chromatography (tlc) was performed on silica G plates and spots were developed with iodine vapors or aqueous potassium permanganate solution. Elemental analyses were performed by A. Bernhardt, Max Planck Institute, Mülheim, W. Germany. Melting

Table I

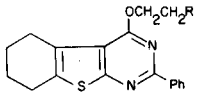
Post Coital Antifertility Data (a)

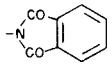
Compound	Daily Dose mg./kg./day	Average No. of Implantation Sites	Average No. of Resorbing Embryos	Average No. of Empty Sites	Average No. of Corpora Lutea	No. of Rats Pregnant	% Inhibition of Pregnancy
Controls CMC	--	12	0	0	14	8/8	0
3g	0.125	8.8	0	0	13.8	5/6	17
3g	0.250	8.2	0.3	0	13.8	4/6	33
3g	0.50	8.7	0	0	13.0	4/6	33
3g	0.5 (b)	5	0	0	12	3/8	62.5
3g	5.0 (b)	5	0	0	12	5.8	37.5
3g	50.0 (b)	11	0	0.12	13	7/8	12.5
14	0.5	11	0	0	11.7	6/6	0
14	5.0	10	0	0	11.8	5/6	17
14	50.0	3.3	3.2	0	12.3	2/6	67
15	0.5	5.8	0	0	13.5	3/6	50
15	5.0	5.2	0	0.8	11.7	3/6	50
15	50.0	12.0	0	0	12.7	6/6	0

(a) In control experiments CMC/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. (b) Results of a second experiment.

Table II

Antiinflammatory Results



Compound	R	LD_{50} mice (mg./kg.,P.O.)	Dose (mg./kg.,P.O.)	Inhibition of Carageenin Induced Edema (%) Mice	Rats	Anoraxogenic Activity (%)
3b		1200	160	31.6	23.2	14
3h		>800	200	0	0	20

points were determined in open capillary tubes and are uncorrected. Analytical and spectral data on new compounds are recorded in Table III.

α-Phenyl-*p*-methoxycinnamic Acid.

This compound was prepared by the method of Ketcham and Jambotkar (11).

α-Phenyl-*p*-methoxycinnamoyl Chloride.

α-Phenyl-*p*-methoxycinnamic acid (25.4 g., 0.1 mole) and 100 ml. of benzene were placed in a 500 ml. round bottom flask. Thionyl chloride (250 ml.) was added dropwise and the reaction mixture was refluxed for 2 hours. Excess benzene and thionyl chloride were removed under reduced pressure. The yield of crude α-phenyl-*p*-methoxycinnamoyl chloride was 20 g., m.p. 81-82°. The crude product was used as such for further reaction; ir (nujol): 1738, 1600 cm^{-1}.

2-*N*-(α-Phenyl-*p*-methoxycinnamoyl)-3-cyano-4,5-tetramethylenethiophene (**8**).

To a cooled solution of the aminonitrile (**5**, 17.8 g., 0.1 mole) in benzene containing a molar equivalent of pyridine was added dropwise a solution of α-phenyl-*p*-methoxycinnamoyl chloride (25.4 g., 0.1 mole) in benzene. The reaction mixture was refluxed for 2 hours and then filtered. The filtrate was washed with dilute hydrochloric acid, water and dried (magnesium sulfate). Evaporation of the solvent provided (32.2 g., 78%) of the acylated product **8**, m.p. 141-142° (ethanol); ir (nujol): 2200 (-C≡N), 1778 (C=O) cm^{-1} (NH).

Amides **6** and **7** were also prepared by the acylation of **4** and **5**, respectively.

2-*N*-(α-Phenylcinnamoyl)-3-cyano-4,5-tetramethylenethiophene(**7**).

The amide **6** (2 g., 0.05 mole) and phosphorus oxychloride (14 ml.) were refluxed together for 1 hour. The reaction mixture, after cooling, was poured over crushed ice when a white solid separated out. It was filtered and recyrstallized from methylene chloride-hexane, m.p. 168-170° (60% yield). This product was identical with the compound obtained by the acylation of **5** with α-phenyl-*p*-methoxycinnamoyl chloride.

2-(α-Phenyl-*p*-methoxycinnamyl)-4-oxo-[5,6]tetraethylenethieno-[2,3-*d*]pyrimidine (**10**).

A moderately homogenous solution of **8** (8.2 g., 0.02 mole) in absolute ethanol was saturated with dry hydrogen chloride gas, heated under reflux for 0.5 hour and allowed to stand in a refrigerator overnight, when 6.9 g. (71%) of **10** separated out. After recrystallization from DMF, a pure sample of **10**, m.p. 265-267°, was obtained.

Similarly, the amide **7** was cyclized to **9**.

2-(α-Phenyl-*p*-methoxycinnamyl)-4-chloro[5,6]tetramethylenethieno[2,3-*d*]pyrimidine (**12**).

To 4.3 g. (0.01 mole) of **10** was added phosphorus oxychloride (40 ml.) at room temperature. The mixture was refluxed for 1.5 hours. After cooling it was poured into an excess of ice and stirred vigorously when **12** separated out as a solid. It was filtered and recrystallized from methylene chloride-hexane, 2.8 g., m.p. 168-170° (65%).

The 4-chloro compound **11** was similarly obtained from **9**.

2-(α-Phenyl-*p*-methoxycinnamyl)-4-(β-pyrrolidinoethoxy)-5,6-tetramethylenethieno[2,3-*d*]pyrimidine (**14**).

To a stirred solution of β-pyrrolidinoethanol (1.15 g. 0.01 mole) in anhydrous benzene (50 ml.) was added sodium hydride (500 mg., 50% dispersion in oil). The contents were maintained at 40° for about 3 hours, 4.4 g. (0.01 mole) of **12** was then added to this solution. The reaction mixture was then refluxed for 12 hours. After cooling the solvent was removed and the residue dissolved in methylene chloride. This solution was washed with water and dried (magnesium sulfate). The removal of the solvent under reduced pressure afforded 3.6 g. (70%) of **14**, m.p. 113-114° (benzene-hexane).

Using the appropriate chloro compound and the amino alcohol, the ethers **3a-i**, **13** and **15** were also obtained.

Refluxing **12** with excess of *N*-methylformamide for 10 hours, the 4-amino compound **16** was formed in 75% yield.

Acknowledgment.

We thank the Center for Population Research, NICHD for partial support of this work through their contract No. NIH-71-2461, and Stevens Institute of Technology for providing research facilities. We also thank the Central Drug Research Institute, Lucknow (India) and Lederle Laboratories for biological test data other than the data on antifertility activity and Endocrine Laboratories for the antifertility test data.

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Table III

Analytical and Spectral Data

Compound No.	M.p.	Yield	Formula	Analysis C	Analysis H	Analysis N	Spectral Data
3a	92	80	$C_{22}H_{27}N_3OS$	69.49 (69.27)	7.08 (7.13)	10.94 (11.02)	ir: 1600 cm^{-1}
3b	103	70	$C_{22}H_{25}N_3OS$	69.77 (69.65)	6.51 (6.64)	11.23 (11.08)	ir: 1600 cm^{-1}
3c	115-116	68	$C_{22}H_{25}N_3O_2S$	66.67 (66.83)	6.44 (6.33)	10.51 (10.65)	ir: 1600 cm^{-1}; nmr: δ 1.8-2.0 (b, 4H), 2.8-3.0 (b, 4H), 3.2-3.6 (b, 4H), 3.8-4.0 (b, 4H), 7.35-7.6 (b, 3H), 8.5-8.7 (b, 2H)
3d	123-125	63	$C_{23}H_{27}N_3O_2S$	67.90 (67.46)	6.73 (6.65)	10.25 (10.26)	ir: 1600 cm^{-1}; nmr: δ 1.8-2.0 (b, 4H), 3.8-4.0 (b, 4H), 2.2-3.0 (b, 11H), 4.5-5.0 (b, 4H), 7.1 (d, 2H, J = 7 Hz), 8.5 (d, 2H, J = 7 Hz); M^+ at m/e 397
3e	131	75	$C_{23}H_{27}N_3OS$	70.02 (70.21)	7.12 (6.92)	10.53 (10.26)	ir: 1600 cm^{-1}; nmr: δ 1.8-2.0 (b, 8H), 2.4 (S, 3H), 2.5-3.0 (b, 10H), 4.6 (t, 2H), J = 7 Hz), 7.2 (d, 1H, J = 7 Hz), 8.4 (d, 2H, J = 7 Hz); M^+ at m/e 381
3f	69-70	70	$C_{23}H_{27}N_3OS$	70.43 (70.20)	6.56 (6.92)	10.68 (10.68)	ir: 1600 cm^{-1}; nmr: δ 1.8-2.0 (b, 4H), 2.2-2.4 (b, 4H), 2.75 (S, 3H), 2.8-3.2 (b, 10H), 4.7 (t, 2H, J = 7 Hz), 7.3-7.5 (b, 3H), 7.8-8.0 (b, 1H)
3g	96	60	$C_{23}H_{27}N_3O_2S$	67.26 (67.46)	6.74 (6.65)	10.28 (10.26)	ir: 1600 cm^{-1}; nmr: δ 1.75 (b, 8H), 2.8 (b, 10H), 3.85 (S, 3H), 4.85 (t, 2H), 7.6 (d, 4H, J = 8 Hz)
3h	176	72	$C_{26}H_{21}N_3O_3S$	68.50 (68.56)	4.62 (4.65)	9.32 (9.23)	ir: 1600 cm^{-1}; nmr: δ 1.8-2.0 (b, 4H), 2.8-3.0 (b, 4H), 4.2 (t, 2H, J = 7 Hz), 4.9 (t, 2H, J = 2 Hz), 7.2-7.8 (b, 7H), 8.4-8.6 (b, 2H); M^+ at m/e 455
3i	184-186	70	$C_{27}H_{23}N_3O_3S$	68.83 (69.07)	5.17 (4.94)	9.01 (8.95)	ir: 1680, 1700, 1600 cm^{-1}; nmr: δ 1.8-2.0 (b, 4H), 2.4 (S, 3H), 2.8-3.0 (b, 4H), 4.1 (t, 2H, J = 7 Hz), 4.8 (t, 3H, J = 7 Hz), 7.2 (d, 2H, J = 7 Hz), 8.4 (q, 2H, J = 7 Hz), 7.5-7.8 (b, 4H); M^+ at m/e 469
6	254-255	65	$C_{24}H_{22}N_2O_2S$	--	--	--	ir: 1667 cm^{-1}; nmr: δ 1.66-2.0 (m, 4H), 2.33-2.83 (m, 4H), 6.83-7.66 (m, 13H), 7.97 (S, 1H); M^+ at m/e 402
7	168-170	70	$C_{24}H_{20}N_2OS$	--	--	--	ir: 1667, 2222 cm^{-1}; M^+ at m/e 400
8	191-192	78	$C_{25}H_{22}N_2O_2S$	--	--	--	ir: 1778, 2200 cm^{-1}; M^+ at m/e 414
9	284-286	65	$C_{24}H_{20}N_2OS$	74.74 (74.98)	5.53 (5.24)	6.57 (7.29)	ir: 1680, 3500 cm^{-1}; M^+ at m/e 384

Table III Continued

Compound No.	M.p.	Yield	Formula	Analysis C	Analysis H	Analysis N	Spectral Data
10	235-236	80	$C_{25}H_{22}N_2O_2S$	72.64 (72.45)	5.67 (5.35)	7.01 (6.76)	ir: 1580, 1600, 3500 cm^{-1}; M^+ at m/e 414
11	170-171	70	$C_{24}H_{19}ClN_2S$	71.77 (71.55)	5.14 (4.72)	6.78 (6.96)	ir: 1600 cm^{-1}; nmr: δ 1.8-2.0 (b, 4H) 2.8-3.0 (b, 4H), 7.1 (S, 5H), 7.3 (S, 5H), 8.2 (6, 1H)
12	168-170	85	$C_{25}H_{21}ClN_2OS$	--	--	--	ir: 1600 cm^{-1}; nmr: δ 1.85 (b, 4H), 2.85 (b, 4H), 3.7 (S, 3H), 6.85 (d, 4H, J = 7 Hz), 7.35 (S, 5H), 8.19 (S, 1H)
13	105-106	80	$C_{30}H_{31}N_2O_2$	74.65 (74.83)	6.70 (6.49)	8.52 (8.73)	ir: 1600 cm^{-1} nmr: δ 1.8-2.0 (b, 8H), 2.5-3.0 (b, 10H) 4.4 (t, 2H, J = 7 Hz), 7.1 (S, 5H); M^+ at m/e 481
14	113-114	60	$C_{31}H_{33}N_3O_2S$	72.42 (72.77)	6.43 (6.50)	8.11 (8.21)	ir: 1600 cm^{-1}; nmr: δ 1.9 (b, 6H), 2.0-2.75 (b, 12H), 3.7 (S, 3H), 4.52 (t, 2H, J = 7 Hz), 7.39 (S, 5H), 8.2 (S, 1H)
15	159-161	75	$C_{35}H_{29}N_3O_4S$	71.30 (71.54)	5.17 (4.97)	7.51 (7.15)	ir: 1600 cm^{-1}; nmr: δ 1.8 (b, 4H), 2.75 (b, 4H), 3.7 (S, 3H), 4.05 (t, 2H), 4.7 (t, 2H), 6.85 (d, 4H), 7.35 (S, 5H), 7.7 (d, 4H), 8.1 (S, 1H)
16	280-281	70	$C_{26}H_{25}N_3OS$	73.31 (73.05)	6.02 (5.89)	9.52 (9.83)	ir: 1600 cm^{-1}; nmr: δ 1.8-2.1 (b, 4H), 2.8-3.0 (b, 4H), 3.05 (d, 3H, J = 5 Hz), 3.8 (S, 3H), 5.2 (b, 1H), 6.95 (q, 4H), J = 7 Hz), 7.5 (S, 5H), 8.2 (S, 1H); M^+ at m/e 427

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