Table II. *In Vitro* Antimicrobial Activity of 4,5-Dihalopyrrole-2-carboxylic Acid Derivatives

Compd	MIC,[a] μg/ml			
	Staph. aureus	*P. aerug*[b]	*E. coli*[c]	*P. vulg*[d]
8	7.8	250	15.6	125
10	3.9	250	31.2	62.5
12	1.95	500	31.2	250
13	3.9	>125	31.2	125
18	0.62	125	125	>125
19	0.31	62.5	7.8	250
20	0.12	>125	7.8	250
23	2.5	>125	>125	>125
24	5	>100	>100	>100
25	0.3	>100	>100	>100
36	7.8	>125	31.2	>250
38	15.6	>62.5	>125	>125
39	3.9	>125	7.8	>125
41	7.8	>62.5	>250	>125
42	0.97	>62.5	>250	>125
46	15.6	>125	125	>125
47	3.9	125	>125	>125
48	0.075	>62.5	>125	>125
52	0.8	>125	>250	>125

[a] Minimum inhibitory concentration. [b] *Pseudomonas aeruginosa*. [c] *Escherichia coli*. [d] *Proteus vulgaris*.

The crude material was crystallized from EtOH–H_2O to give 14.2 g (78% yield) of white powder, mp 227–228°.

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14α,17α-Alkylidenedioxy Steroids. 2. 19-Nor-9α,10β- and 19-Nor-9β,10α-progesterone Analogs

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In our previous publication[1] we described the synthesis of a series of 14α,17α-alkylidenedioxyprogesterone derivatives. This report deals with the synthesis of some 19-nor analogs in the same series. The starting compound for this synthesis was 11α,14α,17α-trihydroxypregn-4-ene-3,20-dione (1).[1] This was converted in two steps into 14α,17α-dihydroxypregna-4,9(11)-diene-3,20-dione (**3**) which was dehydrogenated to 14α,17α-dihydroxypregna-1,4,9(11)-triene-3,20-dione (**4**) with *Corynebacterium simplex*.[2] The A ring of **4** was aromatized according to the method of K. Tsuda, *et al.*,[3] and then the 9 double bond was hydrogenated with Pd on C.[4] This resulted in a mixture of two compounds, 3,14α,17α-trihydroxy-19-norpregna-1,3,5(10)-trien-20-one (**6a**) and its 9β isomer **6b** which were easily separated by crystallization. Both steroids were converted to alkylidenedioxy compounds by condensation with various aldehydes.[1] At this stage the 9α and 9β configurations could be conclusively identified by comparing the nmr absorptions of the ethylidenedioxy groups.

In 9α compounds (*e.g.*, **7a**) the absorptions appear at higher field than in their 9β isomers (*e.g.*, **7b**) as a result of a downfield shift in the latter case, which is to be ascribed to a diamagnetic effect of the aromatic A ring in the (bent) 9β isomer.[5]

After protection of the 20-keto and the 3-hydroxyl groups by conversion to the corresponding ethylenedioxy and methoxy groups the products were subjected to a Birch reduction[6] and hydrolyzed to 14α,17α-alkylidenedioxy-19-norprogesterone derivatives. In two cases these products were converted to 3-enol ethers. The whole reaction sequence is outlined in Scheme I and described in detail for the ethylidenedioxy compound in the Experimental Section. The end products are listed in Table I with some pharmacological data.

We assigned the 9β,10α configuration to the 9β-19-norprogesterone derivatives on the following considerations. From Dreiding models it is obvious that Δ^4-3-keto steroids with a 9β,10β configuration are only possible with ring B in the boat form which is thermodynamically unfavorable. It is known that such steroids rearrange under acidic conditions to the 9β,10α configuration *via* a $\Delta^5(10)$-3-keto system.[7] Since our 9β derivatives were formed under strongly acidic conditions from $\Delta^5(10)$ steroids their configurations must be 9β,10α.

On one occasion there was a little complication in the reaction sequence. After Birch reduction of the benzylidenedioxy compound it appeared that the benzylidenedioxy group had been removed and the 14- and 17-hydroxyls had been formed again. We reintroduced the benzylidenedioxy group after acid removal of the protecting enol ether and ethylenedioxy groups. The latter reactions are also described in the Experimental Section.

Pharmacology. The compounds were tested as solutions or suspensions in maize oil (50 mg/ml for rats; 5 mg/ml for rabbits). The rats used in most of these experiments were the Wistar-derived Cpb strain from TNO (Zeist, Holland); in some experiments (indicated in Table I) the strain "Orga Cpb" from the same institute was used. The rabbits used were the "Bastard" strain bred by TNO.

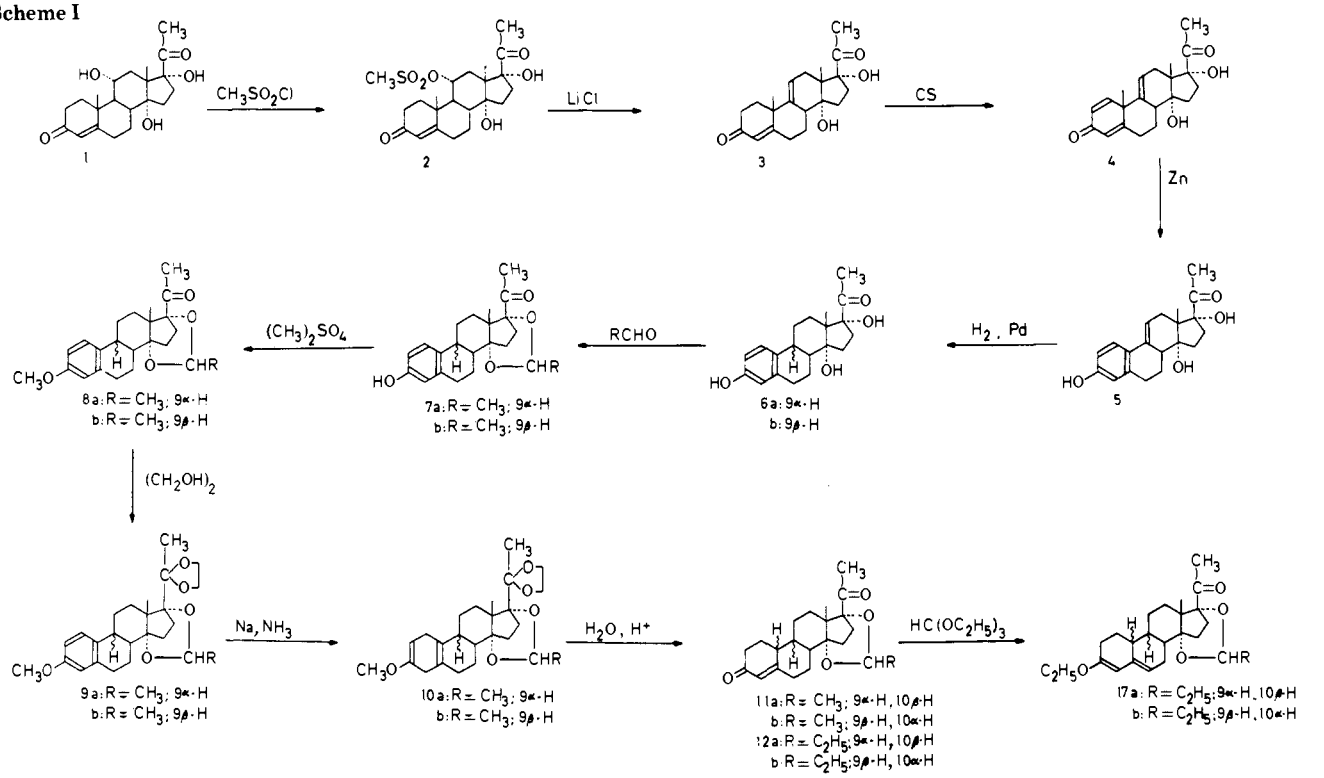
The procedures used for testing the anticonceptive and progestational activities were essentially the same as reported earlier.[1] The results are summarized in Table I.

Just as the 19-methyl derivatives,[1] the 19-noralkylidenedioxyprogesterones show an optimum of activity in the region of the propylidenedioxy compounds (R = Et; **12a** and **12b**). The very long pregnancy delay produced by **16** (R = Ph) is striking since the 19-methyl analog[1] did not possess such activity. The activities of the 9α and 9β isomers of the 19-noralkylidenedioxyprogesterones do not differ much from each other (**11a,b**, **12a,b**, and **13a,b**). Both **12a** and **12b**, when given orally, are active in the pregnancy delay test in contrast to their 19-methyl analogs. Conversion of **12a** and **12b** into their 3-ethyl enol ethers **17a** and **17b**, respectively, failed to enhance oral activity of these compounds in the pregnancy delay test.

Experimental Section

General. Melting points were determined according to Tottoli on a Büchi melting point apparatus. The ultraviolet spectra were taken in methanol with a Zeiss PMQ II spectrophotometer. The infrared spectra were taken in chloroform with a Perkin-Elmer grating/prism spectrophotometer 221. Nmr spectra (in $CDCl_3$, using TMS as internal standard) were recorded on a Varian A-60 nmr spectrometer at the Centraal Laboratorium TNO (Delft). Elemental analyses were performed at the Microanalytical section of the Organic Laboratory of the Technical University, Delft. All reactions were followed by thin-layer chromatography.

Scheme I



11α-Methylsulfonyloxy-14α,17α-dihydroxypregn-4-ene-3,20-dione (2). To a cooled solution of 1283 g (3.54 mol) of 11α,14α,17α-trihydroxypregn-4-ene-3,20-dione (1)[1] in 5 l. of pyridine was added in 0.5 hr at 5°, 290 ml (3.75 mol) of $MeSO_2Cl$ followed by a further 25 ml after 50 min. After a reaction time of 2 hr the excess of reagent was carefully destroyed with cooling by adding 25 ml of water and then the product was crystallized by adding 45 l. of water: yield 1493 g (97%); mp 160–161°; ir 3600, 3505 (OH), 1709 (20 C=O), 1665 (3 C=O), 1610 (4 C=C), 1350 (21 Me), 1333, 1170 cm^{-1} ($MeSO_2$); nmr 0.75 (3, s, 18 Me), 1.27 (3, s, 19 Me), 2.19 (3, s, 21 Me), 3.12 (3, s, SO_2Me), *ca.* 5.2 (1, br, 11 H), 5.70 ppm (1, s, 4 H).

14α,17α-Dihydroxypregna-4,9(11)-diene-3,20-dione (3). Of the mesylate **2** 1488 g was stirred for 3.5 hr at 80° with a mixture of 740 g of LiCl, 6 l. of DMF, and 600 ml of pyridine. The product was crystallized by cooling and addition of 7.5 l. of water: yield 1103 g (94.8%); mp 235–241°; nmr 5.58 ppm (1, br, 11 vinyl H).

14α,17α-Dihydroxypregna-1,4,9(11)-triene-3,20-dione (4). A slurry of 1100 g of the diene **3** in water was incubated for 21 hr with 3 kg of a paste of *Corynebacterium simplex* in 30 ml of a solution of 7 g/l. of NaCl and 1 g/l. of KH_2PO_4 in water, containing 375 ml of 40% HCOH. At the end of the conversion the enzymatic activity was stopped by the addition of 7.5 l. of 40% HCOH and the culture broth was filtered. The filter cake and the filtrate were extracted in DMF and isobutyl methyl ketone, respectively. Evaporation of the solvents and crystallization of the residue from MeOH afforded 970 g (88.7%) of **4**: mp 262–264°; uv 239 nm (ε 14,700).

3,14α,17α-Trihydroxy-19-norpregna-1,3,5(10),9(11)-tetraen-20-one (5). A mixture of 425 g of the triene **4**, 4.25 kg of zinc powder, 4.25 l. of pyridine, and 56.5 ml of water was refluxed with stirring for 2 hr. The mixture was cooled and filtered. The filter cake was washed with 2 l. of isobutyl methyl ketone and the combined filtrates were evaporated *in vacuo*. The residue (538 g) was dissolved in 10 l. of isobutyl methyl ketone. The solution was washed with 3 *N* HCl, saturated $NaHCO_3$, and water and evapo-

Table I. Homologs of Compounds **11a** and **11b**

No.	R	Further structural data	Mp, °C	Formula[a]	Pregnancy delay[b] sc	Pregnancy delay[b] Oral	Clauberg test[c] sc	Clauberg test[c] Oral
11a	Me	9α,10β	152–155	$C_{22}H_{30}O_4$	22 (10)	8 (50)	3.8 (0.01)	
11b	Me	9β,10α	140	$C_{22}H_{30}O_4$	16 (10)	13 (50)	3.7 (0.01)	
12a	Et	9α,10β	100–102	$C_{23}H_{32}O_4$	46 (10), 30 (10)[d] 25 (1), 34 (1)[d] 10 (0.1), 28 (0.01)[d]	4 (10), 19 (10)[d]	1.8 (0.01)	
12b	Et	9β,10α	173–177	$C_{23}H_{32}O_4$	47 (10)[d]	15 (10)[d]	3.3 (0.01)	
13a	*n*-Pentyl	9α,10β	72–77	$C_{26}H_{38}O_4$	42 (10)	9 (50)	3.5 (0.1) 0 (0.01)	
13b	*n*-Pentyl	9β,10α	79–81	$C_{26}H_{38}O_4$	16 (10)	13 (50)	1.4 (0.1)	
14	*t*-Bu	9α,10β	134–135	$C_{25}H_{36}O_4$	24 (10)	10 (50)	0.1 (0.1)	
15	Et_2CH	9α,10β	90–92	$C_{26}H_{38}O_4$	37 (10)	11 (50)	2.2 (0.1)	
16	Ph	9α,10β	152–154	$C_{27}H_{32}O_4$	51 (10)	9 (50)	3.5 (0.1) 2.8 (0.01)	
17a	Et	9α,10β; 3-enol ethyl ether	121–123	$C_{25}H_{36}O_4$		27 (10), 5 (10)[d]		4.0 (10) 3.8 (10)
17b	Et	9β,10α; 3-enol ethyl ether	111–113	$C_{25}H_{36}O_4$		17 (10), 18 (10)[d]		3.5 (10) 0.1 (1)
Progesterone (for comparison)					12 (10)		3.0 (0.1)	
Ethynylnortestosterone (for comparison)					18 (10), 24 (10)[d]	15 (10)[d]	0.7 (0.1)	

[a] Analytical results were within 0.4% of the theoretical values. (In all cases C and H were determined.) [b] The pregnancy delay is given in days following a single sc injection (or oral administration) of the doses mentioned in parentheses in mg/rat. [c] The McPhail score was determined after daily sc injection (or oral administration), for 5 days, of the doses mentioned in parentheses in mg/rabbit. [d] "Orga rats" were used instead of "Wistar rats."

rated *in vacuo*. The residue (450 g) was crystallized from 1.25 l. of MeOH to yield 316 g (77.5%) of **5**: mp 230–235°; uv 264 nm (ε 11,000); ir 1620 (9 C=C), 1605, 1575, 1490 cm^{-1} (C=C arom); nmr 6.23 (1, br, 11 H), 6.55 (1, s, 4 H), 6.6–7.5 ppm (2, A-B, 1 and 2 H).

3,14α,17α-Trihydroxy-19-norpregna-1,3,5(10)-trien-20-one (6a). A mixture of 714 g of the tetraene **5**, 14 l. of CH_2Cl_2, 7 l. of MeOH, and 180 g of 10% Pd on C was hydrogenated at atmospheric pressure. After 3 hr at room temperature the steroid was completely hydrogenated to an approximately 2:1 mixture of the isomers **6a** and **6b**. After removal of the catalyst by filtration the solution was evaporated *in vacuo*. The residue was crystallized from 3 l. of MeOH. The bulk of the 9β isomer **6b** was obtained in practically pure crystalline form (136.5 g). The mother liquor was evaporated *in vacuo* and the crystalline residue was treated with 3.3 l. of boiling C_6H_6. After cooling the bulk of the 9α isomer **6a** was obtained in nearly pure form (307 g). The latter product was recrystallized from C_6H_6 and from Me_2CO to yield 234 g (32.6%) of pure **6a** (From mother liquors a second crop of 13.5% was obtained.): mp 244–248°; uv 216 nm (ε 8750), 281 (2300), 285 (2100).

3,14α,17α-Trihydroxy-19-nor-9β-pregna-1,3,5(10)-trien-20-one (6b). The first crop from the preceding experiment (136.5 g) was recrystallized from CH_2Cl_2–MeOH to yield 125 g (17.8%) of pure **6b** (From the mother liquor, combined with those from the preceding experiment, a second crop of 3.8% was obtained.): mp 167–169°; uv 217 nm (ε 6700), 224 (6000), 281 (1800), 285 (1600).

3-Hydroxy-14α,17α-ethylidenedioxy-19-norpregna-1,3,5(10)-trien-20-one (7a). A mixture of 58.5 g (0.18 mol) of the trihydroxy compound **6a**, 360 ml of dioxane, 360 ml (2.7 mol) of paraldehyde, and 3 ml of 70% $HClO_4$ was stirred for 15 min at room temperature. The reaction was stopped by the addition of 100 ml of saturated $NaHCO_3$ solution and the product was crystallized by the addition of 2 l. of water to yield 59.5 g (94.3%) of **7a**: mp 200–201°; nmr 1.39 (3, d, J = 5 cps, Me acetal), 5.23 ppm (1, q, J = 5 cps, H acetal).

3-Hydroxy-14α,17α-ethylidenedioxy-19-nor-9β-pregna-1,3,5(10)-trien-20-one (7b). A mixture of 32 g (0.097 mol) of **6b**, 200 ml of dioxane, 200 ml (1.5 mol) of paraldehyde, and 1.7 ml of 70% $HClO_4$ was stirred for 15 min at room temperature. After treatment of the mixture with $NaHCO_3$ solution the product was crystallized by the addition of 2 l. of water to yield 28.9 g of crude **7b**. Crystallization from a 1:1 mixture of MeOH and water yielded pure **7b** (24.7 g, 71%): mp 177–180°; nmr 0.88 (3, d, J = 5 cps, Me acetal), 4.93 ppm (1, q, J = 5 cps, H acetal).

3-Methoxy-14α,17α-ethylidenedioxy-19-norpregna-1,3,5(10)-trien-20-one (8a). To a stirred mixture of 50.68 g (0.14 mol) of the 3-hydroxy compound **7a**, 900 ml of $CHCl_3$, and 250 ml of 5.36 *N* KOH solution was added at 20° in 5 min 50 ml (0.53 mol) of Me_2SO_4 and the mixture was stirred at *ca.* 15°. After 40 min a further 80 ml of the KOH solution and 16 ml of Me_2SO_4 were added and the stirring was continued for 1.5 hr. The organic layer was separated, washed with water, and evaporated *in vacuo*. The residue was crystallized from 800 ml of 50% MeOH to yield 50.9 g (96.6%) of **8a**. An analytical sample was obtained by recrystallization from EtOH: mp 163–164°.

3-Methoxy-14α,17α-ethylidenedioxy-20,20-ethylenedioxy-19-norpregna-1,3,5(10)-triene (9a). A mixture of 1.5 l. of C_6H_6, 375 ml of $(CH_2OH)_2$, and 3 g of *p*-toluenesulfonic acid was refluxed with energetic stirring for 1 hr under N_2 *via* a water-absorbing trap (filled with $CaCl_2$ and a molecular sieve); 59.9 g of the 20-keto compound **8a** was added and the mixture was refluxed in the same way for 28 hr. After cooling the layers were separated, the glycol layer was extracted with 250 ml of C_6H_6, and the combined extracts were washed with $NaHCO_3$ solution and water. The C_6H_6 solution was concentrated *in vacuo* (with a drop of pyridine) to 250 ml and the product was crystallized by addition of heptane: yield 31.30 g (47.0%). For analysis a sample was prepared by crystallization from Me_2CO: mp 182–184°.

3-Methoxy-14α,17α-ethylidenedioxy-20,20-ethylenedioxy-19-norpregna-2,5(10)-diene (10a). Into a reaction vessel with gas inlet, stirrer, dropping funnel, and reflux condensor (with CO_2–acetone), closed with drying tubes, NH_3 gas, dried over CaO, was introduced, until *ca.* 350 ml was condensed in the vessel; 200 ml of dry THF and 4.6 g (0.2 ml) of Na cuttings were added. After some minutes stirring of the intense blue solution, a solution of 5 g (0.012 mol) of the aromatic compound **9a** in 4 ml (0.068 mol) of absolute EtOH and 150 ml of dry THF was added *via* the dropping funnel in 1 hr. The mixture was stirred for 0.5 hr and then a mixture of 8 ml (0.135 mol) of EtOH and 20 ml of THF was added in 15 min. The blue color disappeared and the mixture was maintained at the distillation temperature of NH_3 for 1 hr. Then 11 g (*ca.* 0.2 mol) of powdered NH_4Cl was added and the NH_3 was allowed to distil off. The mixture was diluted with 75 ml of water and the product was filtered and washed with water to yield 5.0 g (100%) of **10a**. From uv measurement at 287 nm it appeared that this product contained *ca.* 15% of the aromatic compound **9a**: ir 1694, 1668 cm^{-1} (2 and 3 C=C); nmr 1.00 (3, s, 18 Me), 1.31 (3, s, 21 Me), 1.35 (3, d, J = 5 cps, Me acetal), 3.58 (3, s, OMe), 3.95 (4, m, $-CH_2CH_2-$), 4.67 (1, s, 2 H), 5.2 ppm (1, q, J = 5 cps, H acetal, together with small absorptions due to **9a**).

14α,17α-Ethylidenedioxy-19-norpregn-4-ene-3,20-dione (11a). Product **10a** was hydrolyzed by refluxing 5 g of the steroid in a mixture of 200 ml of MeOH and 60 ml of 6 *N* HCl during 15 min. The solution was cooled and neutralized with 59 g of NaOAc and water. The MeOH was removed by distillation *in vacuo* and the concentrate extracted with isobutyl methyl ketone. The extract was washed with water and evaporated *in vacuo*. The residue was chromatographed on silica gel with C_6H_6–Me_2CO (100:1). From the appropriate fractions the pure product was obtained by evaporation *in vacuo* and crystallization from MeOH–H_2O: yield 2.13 g (49.5%); mp 152–155°; uv 240 nm (ε 17,400); ir 1711 (20 C=O), 1669 (3 C=O), 1620 cm^{-1} (4 C=C).

3-Ethoxy-14α,17α-propylidenedioxy-19-norpregna-3,5-dien-20-one (17a). A mixture of 20 ml of dioxane, 2 ml (0.00125 mol) of triethyl orthoformate, and 100 mg of *p*-toluenesulfonic acid was stirred for 1 hr at room temperature; 2.5 g (0.0067 mol) of 14α,17α-propylidenedioxy-19-norpregn-4-ene-3,20-dione (**12a**) and 1 ml of triethyl orthoformate were added and the mixture was stirred for 1.5 hr at room temperature. The mixture was neutralized with 0.1 ml of pyridine and the product was crystallized by addition of 100 ml of water: yield 2.65 g (98.6%); mp 121–123°.

3-Methoxy-14α,17α-dihydroxy-20,20-ethylenedioxy-19-norpregna-2,5(10)-diene (19). 3-Methoxy-14α,17α-benzylidenedioxy-20,20-ethylenedioxy-19-norpregnatriene (**18**, 10 g) (mp 124–128°; prepared analogously to **9a**) was subjected to a Birch reduction as used for the preparation of **10a**. The product obtained amounted to 7.62 g but its spectra showed that the reduction had been incomplete and that the benzylidenedioxy group had been completely removed. A second treatment in the same manner afforded 7.61 g (92.9%) of **19**: mp 194–200°.

14α,17α-Dihydroxy-19-norpregn-4-ene-3,20-dione (20). A solution of 6.8 g of 3-methoxy-14α,17α-dihydroxy-20-ethylenedioxy-19-norpregna-2,5(10)-diene (**19**) in a mixture of 300 ml of Me_2CO and 120 ml of 1 *N* HCl was maintained at room temperature for 7 hr. The mixture was neutralized with 19.7 g of NaOAc and the product was crystallized by evaporation of the Me_2CO *in vacuo* and addition of water. The product (5.43 g) was recrystallized from Me_2CO–heptane to yield 3.30 g (57.0%) of **20** (A second crop of 19% was obtained from the mother liquor.): mp 220–223°; ir 1665 (3 C=O), 1618 cm^{-1} (4 C=C).

14α,17α-Benzylidenedioxy-19-norpregn-4-ene-3,20-dione (16). A mixture of 3.73 g (0.0112 mol) of the dihydroxy compound **20**, 50 ml of dioxane, 10 ml (*ca.* 0.1 mol) of benzaldehyde, and 0.2 ml of 70% $HClO_4$ was stirred at room temperature for 1.5 hr. The mixture was neutralized, diluted with EtOAc, and washed with $NaHSO_3$ solution, $NaHCO_3$ solution, and water. The solvents were evaporated *in vacuo* and the residue was chromatographed on silica gel with C_6H_6–Me_2CO (10:1). From the appropriate fractions the pure product was isolated by evaporation *in vacuo* and crystallization from Me_2CO–heptane: yield 1.27 g (26.9%); mp 152–154°.

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Bis(dimethylamino)-*s*-triazinyl Antiinflammatory Agents

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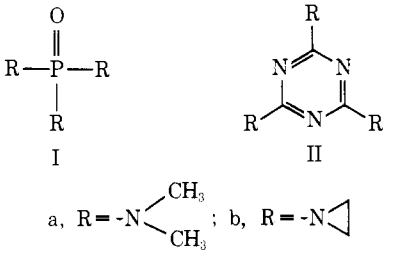
In 1964, Chang, Terry, and Borkovec[1] reported their remarkable discovery that dimethylamino analogs Ia and IIa of two cytotoxic aziridinyl compounds, tepa (Ib) and tretamine (IIb), retained the insect sterilizing properties of the latter but possessed greatly lowered toxicity to mammals. Because certain cytotoxic agents had been reported to have a beneficial effect on patients with rheumatoid arthritis,[2] we undertook the evaluation of Ia and IIa as antiinflammatory agents. Hexamethylphosphoramide (Ia) was completely without effect in a rat paw edema assay.[3] However, the significant reduction in paw volume produced by hexamethylmelamine (IIa) led us to synthesize the titled compounds in an effort to extend this activity to novel triazines.



I II

a, R = -N(CH3)2; b, R = -N(aziridinyl)

The new 6-alkyl- and 6-aryltriazines were obtained in fair to good yields by reacting 1,1,5,5-tetramethylbiguanide with the appropriate acid chlorides. Physical properties and pharmacological data for the compounds of most interest are presented in Table I. Antiinflammatory activity was evaluated using a kaolin-induced paw edema assay in rats.[3] The 48-hr LD_{50} was determined in mice after a single intraperitoneal injection.

During the course of this work several reports appeared in the patent literature describing the synthesis and antiinflammatory activity of 6-cycloalkyl- and 6-aryl-2,4-diamino-*s*-triazines.[4,5] At least one compound of this type, 6-phenyl-2,4-diamino-*s*-triazine, has been studied in human subjects and found to cause an acute rise in plasma corticosteroids without inducing other evidence of stress.[6] Because N-methylated congeners of drugs containing amino groups have sometimes exhibited decreased toxicity and/or modified biological activity,[7] we obtained and tested the analog of most interest in each of the reported diaminotriazine series (Table I, 6 and 7) for comparison with our tetramethyl derivatives.

As expected, the methylated aminotriazines 1–5 were less toxic than the corresponding primary amino derivatives 6 and 7. The effect of methylation on antiinflammatory activity was variable but generally resulted in enhanced activity in the 6-cycloalkyltriazine series and unaltered or slightly reduced activity with 6-aryltriazines.

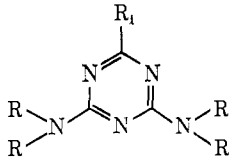
Compound 4, the most effective analog in the present study, was also tested for its ability to inhibit inflammation using the granuloma pouch technique.[8] It provided 16, 46, and 100% inhibition of inflammation at dose levels of 7.5, 30, and 75 mg/kg, suggesting a potency of at least 2.5 times indomethacin in this assay.

Experimental Section

Melting points were determined with a Thomas-Hoover apparatus equipped with a corrected thermometer. Analyses indicated by elemental symbols agree with calculated values within ±0.4%.

General Procedure for Preparation of Bis(dimethylamino)-*s*-triazines. A solution of the acid chloride (10.5 mmol) in 10 ml of acetone was added dropwise with cooling (ice–water bath) and vigorous stirring to a solution of 1,1,5,5-tetramethylbiguanide[9] in 10 ml of 5% aqueous sodium hydroxide. The resulting slurry was allowed to warm to room temperature with continued stirring over a period of 2 hr. The acetone was removed *in vacuo* and the product was isolated by filtration, washed with ice water, dried, and recrystallized from aqueous methanol. All of the triazines exhibited a moderately strong characteristic absorption at 795–810 cm^{-1} in the ir spectra (KBr). Yields and melting points of the triazines thus prepared are presented in Table I.

Table I. 2,4-Diamino-*s*-triazines



Compd no.	R_1	R	Mp, °C	Yield, %	Formula	Analyses	Anti-inflammatory activity[a]	LD_{50}, mg/kg
1	Cyclopropyl	CH_3	70–71	50	$C_{10}H_{17}N_5$	C, H, N	40	730
2	Cyclohexyl	CH_3	50–51	64	$C_{13}H_{23}N_5$	C, H, N	33	>1000
3	C_6H_5	CH_3	103–104	81	$C_{13}H_{17}N_5$	C, H, N	24	>1000
4	*p*-FC_6H_4	CH_3	121.5–122.5	83	$C_{13}H_{16}FN_5$	C, H, N	51	575
5	2-Furyl	CH_3	110–112	88	$C_{11}H_{15}N_5O$	C, H, N	27	575
6[b]	Cyclopropyl	H	294–297				22	333
7[c]	C_6H_5	H	226–228				33	545

[a] Except for 3 and 6, compounds were tested at multiple dose levels between 12 and 150 mg/kg using seven animals per dose level. The figures given are per cent inhibition following a single po administration of the compound at 150 mg/kg. In our hands, indomethacin caused a 50% reduction in inflammatory response at 20–30 mg/kg in this rat paw edema assay.[3] [b] Lit.[1] 296–298°. [c] Purchased from Aldrich Chemical Co.