MALE ANTIFERTILITY COMPOUNDS: STRUCTURE AND ACTIVITY RELATIONSHIPS OF U-5897, U-15,646 AND RELATED SUBSTANCES

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Summary. U-5897 (3-chloro-1,2-propanediol), U-15,646 (1,1'-(penta-methylenedioxy) bis [3-chloro-2-propanol]), and some related compounds were found to have antifertility activity in the male rat. Oral administration for 8 days produced temporary sterility of a functional type in the male. Structural characteristics for activity were studied.

INTRODUCTION

Male antifertility research has, in the past, been dominated by scientists seeking ways to inhibit spermatogenesis. Other approaches seemed less attractive due to absence of positive information. The present approach to the problem was via the spermatozoa in the excurrent ducts. Advantages for induced sterility of post-testicular spermatozoa are: (i) almost immediate effectiveness; (ii) readily reversible; (iii) reduced chances of mutagenic damage; (iv) avoid psychological or endocrine impairment of libido; and (v) enhance knowledge of epididymal sperm maturation and fertility.

The overall objective is to find a drug(s) which when taken by the human male gives safe and effective contraception. Of immediate concern was the lack of any compound which approached this objective, even for laboratory experimentation. Empirical screening of numerous compounds resulted in the discovery that some chlorohydrins have antifertility properties in the male. This report is concerned with the relationship between chemical structure and antifertility.

COMPOUNDS AND METHODS

Compounds for test were purchased from Aldrich Chemical Co. and Distillation Products Industry, or obtained from General Tire and Rubber Co. (U-15,646), or prepared by literature procedures. All compounds were administered, at varying doses, in 0.5 ml of vehicle 122 (0.25% methylcellulose in sterile H₂O). The test animal was a 300±25 g Spartan or Upjohn male rat. Three rats per test received the compound daily for 8 days by oral intubation. Males selected to receive compounds were those which successfully mated the previous night with PMSC-primed, immature females (Uberoi & Meyer, 1966). Oestrous females were caged overnight (Day 8) with test males and then checked for evidence of mating (spermatozoa in vagina and/or vaginal plugs). Males which

did not mate were given another opportunity the following night (Ericsson & Baker, 1966). Antifertility activity was assessed in terms of implantation sites found in mated females on Day 9 or 10 of gestation.

RESULTS AND DISCUSSION

Tables 1 and 2 give the antifertility effectiveness, at 30 mg/rat dose, of U-5897 (3-chloro-1,2-propanediol), U-15,646 (1,1'-(pentamethylenedioxy) bis [3-chloro-2-propanol]) and related compounds. The relative antifertility potency

TABLE 1
MALE ANTIFERTILITY EFFECTIVENESS OF U-5897 AND
RELATED COMPOUNDS AT 30 MG/RAT FOR 8 DAYS

U-Number	$\begin{array}{c} \text{OH} \\ \\ \text{RCHCH}_2\text{X} \\ \text{R} \end{array}$		No. implants
	X	R	
27,284	Cl	H	13, —
*	Cl	CH ₃	12, 12, 13
5897	Cl	HOCH ₂	0, 0, 0
25,792	Cl	$\begin{array}{c} \text{O} \\ \\ \text{CH}_3\text{COCH}_2 \end{array}$	0, 0, 0
27,574	Cl	$\begin{array}{c} \text{O} \\ \\ \text{C}_6\text{H}_5\text{COCH}_2 \end{array}$	0, 0, 0
25,354	Cl	ClCH ₂	0, 15, —
27,970†	Cl	FCH ₂	13, 9, —
25,352	Cl	CH ₃ CHOCH ₂	0, 0, 0
25,936	Cl	CH ₃	0, 0, 0
27,967	Cl	CH ₃ (CH ₂) ₄ OCH ₂	0, 0, 0
26,554	Cl	HOCH ₂ CH ₂ OCH ₂	0, 0, 0
	Cl	HO(CH ₂) ₅ OCH ₂	0, 0, —
27,462	OH	$\begin{array}{c} \text{C}_6\text{H}_5\text{OCH}_2 \end{array}$	14, 14, 0
29,152	Br	CCl ₃	14, 14, —
29,030		HOCH ₂ ²	12, 11, 13

(—); did not mate.

* A mixture consisting of 85% 1-chloro-2-propanol and 12% 2-chloro-1-propanol.

† 5 mg/rat dose due to low LD₅₀.

of these U-numbered compounds is given in Table 3. It should not be inferred from this table, however, that some compounds not listed are incapable of activity if tested at a high enough dose. Biological properties of U-5897 and U-15,646 in reproductive processes are given in separate papers (see Ericsson & Baker, 1970; Ericsson, 1970; Kirton, Ericsson, Ray & Forbes, 1970).

Examination of the tables reveals definite structural characteristics for activity. Active compounds (as defined by our test conditions) are chlorohydrins, i.e. compounds incorporating a carbon bearing a chlorine adjacent to a carbon bearing a hydroxyl group. An added characteristic is that the hydroxyl-bearing carbon is adjacent to another carbon bearing an oxygen either as a hydroxyl or

an ether group; the hydroxyls can be free or esterified. The most active compound found was the simplest one possessing these features, namely, 3-chloro-1,2-propanediol (U-5897). Incorporating two chlorohydrin groups in one compound, for example, 1,1'-(pentamethylenedioxy) bis [3-chloro-2-propanol] (U-15,646), resulted in active but less potent compounds than U-5897 (U-27,421, U-26,126, U-27,045, U-27,151). Compounds in which the hydroxyl group was esterified retained activity but were less potent than the unesterified compounds (U-25,792, U-27,574, U-26,853). Supporting these correlations are the inactivity of ethylene chlorohydrin (U-27,284), 1-chloro-2-propanol (85% pure), 1-chloro-3-fluoro-2-propanol (U-27,970) and 1,3-dichloro-2-propanol (U-25,354) which are chlorohydrins lacking additional oxygen-bearing carbon, besides the inactivity of compounds in which the chlorine is replaced by fluorine, bromine, iodine, or a trichloro group (U-29,030, U-27,214, U-25,888, U-27,971, U-29,152). However, compounds may possess all the above struc-

TABLE 2
MALE ANTIFERTILITY EFFECTIVENESS OF U-15,646 AND RELATED
COMPOUNDS AT 30 MG/RAT FOR 8 DAYS

U-Number	$\begin{array}{c} \text{OR} \qquad \qquad \text{OR} \\ \qquad \qquad \\ \text{XCH}_2\text{CHCH}_2\text{OR}_1\text{OCH}_2\text{CHCH}_2\text{X} \\ \qquad \qquad \\ \text{R} \qquad \qquad \text{R}_1 \end{array}$			No. implants
	X	R	R ₁	
27,421	Cl	H	(CH ₂) ₂	0, 0, —
26,126	Cl	H	(CH ₂) ₃	0, 0, 0
27,824	Cl	H	(CH ₂) ₄	17, 13, 12
15,646	Cl	H	(CH ₂) ₅	0, 0, 0
26,715	Cl	H	(CH ₂) ₆	12, 7, 6
27,045	Cl	H	(CH ₂) ₁₀	0, 0, 0
27,214	Br	H	(CH ₂) ₅	14, 14, —
25,888*	F	H	(CH ₂) ₅	0, 10, 15
27,971	I	H	(CH ₂) ₅	12, 12, 14
26,853	Cl	$\text{CH}_3\overset{\text{O}}{\parallel}\text{C}$	$(\text{CH}_2)_5$ CH ₃	10, 1, 0
27,874	Cl	H	CHCH ₂ CH ₃	1, 2, 4
27,963	Cl	H	CH ₂ CH ₂ $\overset{\text{CH}_3}{\parallel}\text{CCH}_2\text{CH}_2$	12, 12, 15
27,151	Cl	H	$\text{CH}_2\text{C} = \overset{\text{CH}_3}{\parallel}\text{CCH}_2$	0, 0, —
27,456	Cl	H	CH ₂ CH ₂ OCH ₂ CH ₂	9, 8, 13
27,873	Cl	H	CH ₂ — —CH ₂	1, 9, 4
26,123	Cl	H	<i>cis</i> — —CH ₂	12, 14, —
26,527	Cl	H	<i>trans</i> — —	13, 14, 0

(—), did not mate.

* 1 mg/rat dose due to low LD₅₀.

tural characteristics and be inactive (U-27,462, U-27,456, U-27,873, U-26,527, U-26,123).

TABLE 3
POTENCY OF U-NUMBERED COM-
POUNDS IN MALE ANTIFERTILITY
TEST

U-Number	Mg/rat for 8 days	
	Active dose	Inactive dose
5897	3.0	1.0
15,646	15.0	10.0
25,352	15.0	—
25,792	15.0	—
25,936	30.0	15.0
26,126	30.0	15.0
26,554	30.0	15.0
26,715	60.0	30.0
27,045	15.0	5.0
27,151	15.0	—
27,421	15.0	—
27,574	5.0	2.0
27,824	100.0	60.0
27,874	40.0	30.0
27,963	125.0	100.0
27,967	15.0	—

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