A NEW SYNTHETIC ROUTE TO PYROGALLOLESTROGEN DIMETHYL ETHERS BY NUCLEOPHILIC SUBSTITUTION OF 2,4-DIBROMOESTROGENS

Xu-hua Zheng, Wen-long Wang, Zhi-zheng Zhong,
Zhen-bon Xu and Hua-ming Zhao

Department of Chemistry, Sichuan University
Chengdu, Sichuan, P. R. C.

Received 12-21-81

ABSTRACT

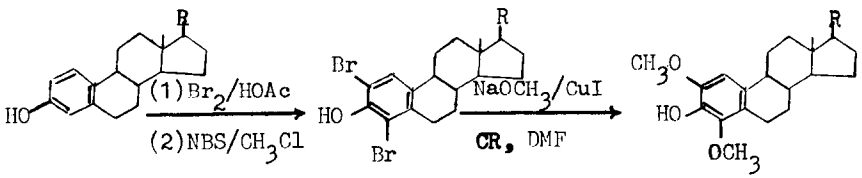
A novel synthetic route to pyrogallolestrogen dimethyl ethers was developed. Benzo-15-crown-5 with CuI catalyses the specific nucleophilic substitution of bromo atoms by methoxide ions.

INTRODUCTION

Investigations on the physiological properties and the synthetic methods of polyhydroxyl estrogenic steroids have currently aroused widespread interest; however, existing methods for the synthesis of compounds of this kind are not only few but also are not completely satisfactory. For instance, one of the synthetic routes employing the corresponding monoethers of ortho hydroxyl estrogenic steroids gave polyhydroxyl estrogens or their dimethyl ethers only in low yield (1).

With a view to developing a useful synthetic route from the easily accessible 2,4-dibromo steroidal estrogens (2), nucleophilic substitution of the bromo atoms by methoxide ions under the catalysis of CuI-crown ether in dimethyl formamide (DMF)(3,4) was investigated, with emphasis on the catalytic role of CuI and crown ether (CR) on the reaction.

The overall synthetic route is outlined in the following scheme:



I II III

a: R = OH, b: R = O=

NBS = N-Bromosuccinimide

EXPERIMENTAL

Melting points were determined with a microscope hot stage and are uncorrected. Ultraviolet spectra were determined on a SP 800 recording spectrophotometer in ethanol. IR spectra, using pressed KBr discs, were recorded on a Perkin-Elmer Infrared Spectrophotometer. Benzo-15-crown-5 and 18-crown-6 were a gift from the chemical plant of Sichuan University. High pressure liquid chromatography was performed on a Tracor-900-78S chromatograph.

2,4-Dibromoestradiol (IIa, 2,4-Dibromo-1,3,5(10)-estratriene-3,17β-diol)

Method 1: A 5% solution of Br_2 in glacial acetic acid (w/w) was added dropwise to a mixture of estradiol (1g, 3.77 mmol) and glacial acetic acid (100 ml) under vigorous stirring and at room temperature (17-20°) until the color of bromine persisted. Stirring was continued for 20 min and the reaction mixture was poured into 1000 ml of distilled water. A pale yellow solid material separated, and was filtered and washed until neutral. The crude product (1.5 g) was chromatographied through a column packed with silica gel (200 mesh). Elution with 20 % alcohol in chloroform (v/v) afforded a product with mp 214-216°(1.35g, 85%).

Method 2: NBS (1.4 g) was added to a solution of estradiol (1g, 3.77 mmol) in chloroform. The resulting light brown colored solution was stirred under reflux for 2 hours. Chloroform was removed under reduced pressure to give a solid, which was first dissolved in methanol (30 ml) and then precipitated again upon addition of water (200 ml). The solid was filtered, dried and recrystallized to give 2,4-dibromoestradiol (1.26 g, 80%) with mp 215-216°.

2,4-Dibromoestrone (IIb, 2,4-Dibromo-1,3,5(10)-estratrien-17-one)

Following the same procedure described above for the preparation of IIa by method 2, estrone (4 g, 1.48 mmol) gave IIb (5.03 g, 1.18 mmol) in 70.4% yield.

2,4-Dimethoxyestradiol (IIIa, 2,4-Dimethoxy-1,3,5(10)-estratriene-3,17β-diol

To a solution of sodium methylate (prepared from 1 g of sodium in 10 ml DMF and freed from methanol as much as possible) was added 2,4-dibromoestradiol (IIa), (1 g, 2.3 mmol) mixed with copper(I) iodide (200 mg) and benzo-15-crown-5 (620 mg). The resulting mixture was heated to about 100-105°. After stirring at this temperature for 14 hours, the reaction mixture was poured into water, neutralized with hydrochloric acid and then extracted with ether. The ether extract, after drying and evaporating, was taken up in 1,2-dichloroethane and chromatographed over silica gel (200 mesh). Elution with benzene-petroleum ether-acetone (10:1:1, v/v) gave IIa (Rf 0.93) and IIIa (Rf 0.21). Recrystallization from ethyl ether-petroleum ether (1:1, v/v) gave an analytical sample of IIIa (350 mg, 0.92 mmol) in 40% yield.

2,4-Dimethoxyestrone(IIIb, 2,4-Dimethoxy-1,3,5(10)-estratrien-17-one)

Following the same procedure described above for IIIa, but with a 7 hour reaction period, IIb (851 mg, 1.99 mmol) gave IIIb (70 mg, 0.212 mmol, 10%).

Effect of Reaction Conditions on the Transformation of IIa to IIIa

In a set of experiments described in the following table. mix-

tures were heated to about 105° with vigorous stirring. Portions of each batch were taken at four hour intervals, and then at three hour intervals after the first eight hours, and quenched by pouring into water. High pressure chromatography in conjunction with thin layer chromatography were employed to monitor the reactions. The results are listed in the Table 1.

Table 1. Effect of Reaction Conditions on the Transformation 2,4-Dibromoestradiol (IIa) to 2,4-Dimethoxyestradiol

Expt. No.	Mole Equivalents IIa	NaOMe	CuI	CR	Reaction Time (hours)	Relative Yield*
1	1	25			29	0
2	1	20	0.18		17	50
3	1	20	0.36		20	60
4	1	20		1	14	25
5	1	20	0.36	1	14	100
6	1	5	0.36	1	20	trace
7	1	20	0.36	1**	14	55

* The optimum yield was designated as 100 for comparison.
** 18-Crown-6 was employed instead of benzo-15-crown-5.

RESULTS AND DISCUSSION

The IR, UV and other physical properties and relevant data of the compounds IIa, IIIa, IIb and IIIb are listed in Table 2.

Table 2. Physical Constants and Relevant Data for 2,4-Dibromo- and 2,4-Dimethoxy Steroidal Estrogens

Cpds	mp found (C°) (lit)	Analysis found (calc.) C	H	Br	Rf	UV λmax nm (lit)	IR cm^{-1}
IIa	214-216 (215.5-216.5)(5)	50.30 (50.20)	5.44 (5.16)	37.50 (37.15)	0.39	292 (291)(2)	625
IIb	229-231 (225-226)(2)	50.52 (50.49)	4.77 (4.76)	37.51 (37.22)	0.64	286 (285)(2)	625
IIIa	159-161 (156-157)(1)	72.18 (72.25)	8.94 (8.48)		0.21	279	3240,3460(-OH) (3250,3460) 2850,1240 (=C-OCH_3)
IIIb	160-163 (149-151)(1)	72.69 (72.71)	7.92 (7.93)		0.46	276	3390(OH),1726 (-C=C) (3400)(1720)(1) 2860,1246 (=C-OCH_3)

* Absorbent: Silica gel (200 mesh).

To sum up, with the mole ratio of the reagent to catalyst main-

tained in benzo-15-crown-5:nucleophile:CuI = 1:20:0.36, reaction of 2,4-dibromoestradiol with sodium methoxide in DMF at 105° for about 14 hours leads to the formation of 2,4-dimethoxy estradiol in fair yield.

The present findings suggest strongly that bimolecular nucleophilic substitution is implicated in the reaction of 2,4-dibromoestrogens with sodium methoxide. The concordant action of benzo-15-crown-5 with sodium ion and of copper(I) iodide with the aryl halide may be responsible for the catalytic effect of the catalyst system. Thus, the nucleophilicity of the methoxide ion is strengthened and the carbon-halogen bond weakened. Moreover, in the aprotic solvent DMF the nucleophility of the methoxide ion should be enhanced, since solvation of anion is greatly reduced. The ineffectiveness of 18-crown-6 in such reactions may be attributed to its poorer affinity for sodium ions.

We suggest that this new route to polymethoxyl estrogens under mild conditions may have general applicability. Unfortunately, this expectation was not realized in the preparation of IIIb. The poor yield might be attributed to the presence of 17-keto function which under the conditions of the reaction may undergo intramolecular condensation of the aldol type. Experimental investigation of this is under way in our laboratory.

ACKNOWLEDGEMENTS

The materisls contained herein were written up as an article at Michigan State University. The authors wish to express their gratitude to the Chemistry Department MSU for providing the facilities. Thanks are also due particularly to Dr. W. Reusch and Dr. C. K. Chang of MSU and Dr. L. E. Lee of the USDA poultry Research Laboratory for reading the manuscript.

REFERENCES

1. G. Stubenrauch, O. Haupt and R. Knuppen, Steroids, 29, 849 (1977).
2. W. R. Slaunwhite and L. Needy, J. Org. Chem., 27, 1749 (1962).
3. D. G. Sam and H. E. Simmons, J. Am. Chem. Soc., 96, 2252 (1974).
4. C. J. Pedersen, J. Am. Chem. Soc., 92, 391 (1970).
5. R. B. Woodward, J. Am. Chem. Soc., 62, 1625 (1940).