Studies in Remote Functionalization (I). Synthesis and Spectroscopic Studies of 3α, 5α-Cyclosteroidal Substrates

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Various 3α,5α-cyclocholestan-6β-yl ethers were synthesized from solvolysis reactions of cholesteryl tosylate. 3α,5α-Cyclocholestan-6β-yl sulfides were the sole products when cholesteryl tosylate was solvolyzed in thiol solvents. Diol solvolysis products were derivatized to aromatic esters, and nuclear magnetic resonance spectroscopic method was used to show that aromatic rings can approach C-18 methyl group and the side chain.

1. Introduction

Remote functionalization method represents one of the most fascinating developments in organic chemistry in recent years. The reactions performed by Breslow[1] are more widely applicable compared to the well-known Barton reactions[2] and it is possible to select the precise positions to be functionalized by adjusting the length of the bridge joining the unactivated and activating sides of the substrate molecule. One example involves the removal of the alkyl side chain of steroids, (Figure 1) which suggests a novel way of synthesizing sex hormones from sterols without functionalities on the side chain.

Breslow's reactions were designed to reach unactivated tertiary hydrogens on the α-side by using 3α-derivatives of 5α-steroids. Inspection of molecular models indicates that one should have the functionalizing group approaching from the β-side to achieve direct functionalization of the alkyl side chain on ring D. It would be interesting to see whether reactive groups attached on the β-side could indeed attack hydrogens on the side chain (particularly H-20) in spite of unfavorable steric crowding from the C-18 methyl group.

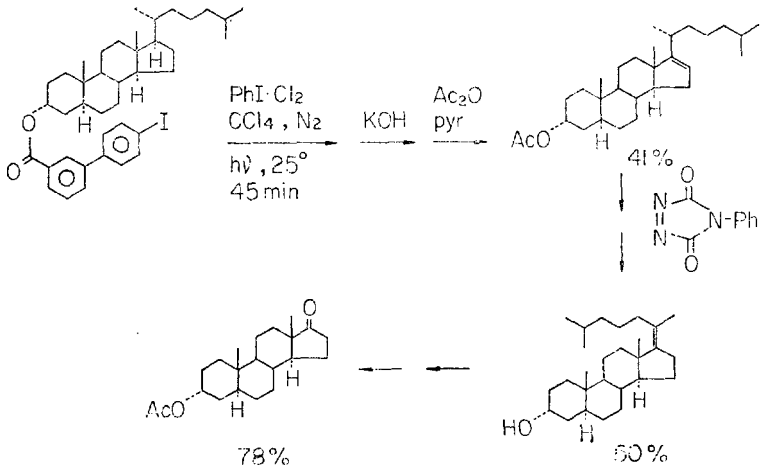


Figure 1.

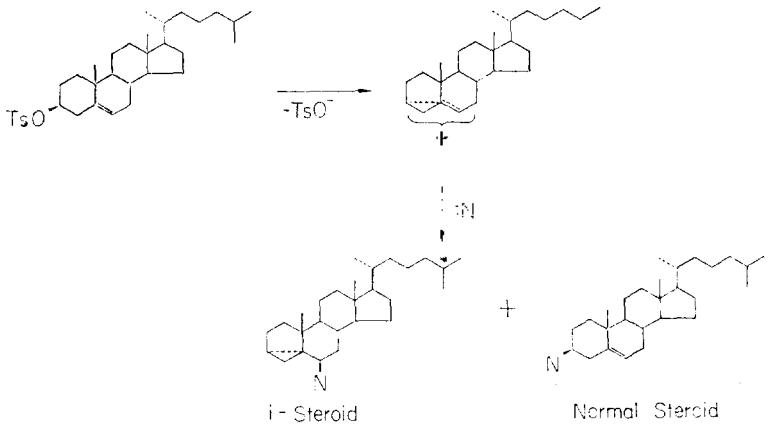


Figure 2.

3α,5α-Cyclocholestan-6β-yl derivatives (*i*-steroids) are formed in the solvolysis reactions of cholesteryl tosylate[3] and the mechanism of their formation was discussed by Winstein[4] as one of the first examples of neighboring group participation (Figure 2). They were used in limited cases in synthetic applications, *i. e.*, in ecdysone synthesis,[5] in C-19 methyl group oxidation by lead tetraacetate,[6] and, in a number of cases, for the protection of 3 β-hydroxy-5-ene functionality common in many sterols.[7] Their easy preparation and the facile conversion back to 3β-hydroxy-5-ene series suggest 3α,5α-cyclocholestan-6β-yl ethers as ideal candiates for remote functionalization on the β-side.

We wish to describe here the results of our work on the solvolysis reactions of cholesteryl tosylate in a number of solvents which resulted in the formation of various 3α,5α-cyclocholestan-6β-yl derivatives. 5α-Cholestan-6β-yl derivatives were synthesized by a standard scheme for comparison. Nuclear magnetic resonance studies on some of the derivatives were undertaken to ascertain informations regarding their solution conformations.

2. Results and Discussion

2.1 Preparation of 3α, 5α-Cyclocholestan-6β-yl Derivatives

The solution of cholesteryl tosylate in each solvent containing solid base (to quench *p*-toluenesulfonic acid) was heated until the starting material disappeared. As a rule, 3α, 5α-cyclocholestan-6β-yl ethers showed higher R_f values than those of cholesteryl ethers on silica gel TLC. The products were worked up and purified on silica gel columns and identified with ease by comparing nmr spectra of pure samples. In the nmr spectra of 3α,5α-cyclocholestan-6β-yl derivatives, the olefinic 6-H signal was absent and the cyclopropyl proton multiplet was clearly seen in the high field region. The conditions and yields are summarized in Figure 3.

Solvolysis in Simple Alcohols. 3α,5α-Cyclocholestan-6β-yl ethers (**4, 6, 8**) were major products in methanol ethanol, and 2-propanol. Bulkier alcohols with lower dielectric constants produced relatively less amounts of 3α, 5α-cyclocholestan-6β-yl ethers. In benzyl alcohol, no 6β-benzyloxy-3α, 5α-cyclocholestane (**10**) was formed, but a high yield of cholesteryl benzyl ether (**11**) was obtained. Addition of acetone prolonged the reaction period producing much lower yield of **11**, and **10** was obtained as the major product from the solvolysis in benzyl alcohol–acetone (1:2, v/v).

Solvolysis in Diols. Brief reflux of cholesteryl tosylate suspension in ethylene glycol produced cholesteryl 2-hydroxyethyl ether (**13**) and elimination products. The desired product, 6β-(2-hydroxyethoxy)-3α,5α-cyclocholestane (**12**) probably did not survive under the reaction conditions. Addition of acetone again resulted in the predominant formation of the the 3α,5α-cyclocholestan-6β-yl ether as **12** was obtained as the major product accompanied by a small amount of **13** in ethylene glycol-acetone (1:2) mixture. The completion of the reaction required longer reaction time but no elimination products were noticed. With one equivalent of ethylene glycol in acetone, no reaction occurred. 1,3-Propanediol, diethylene glycol, and triethylene glycol behaved in the same way to yield 3α,5α-cyclocholestan-6β-yl ethers (**14, 16, 18**).

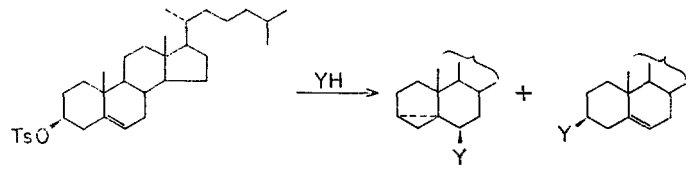
Solvolysis in Thiols. Reaction in 2-mercaptoethanol quickly yielded a single product in almost quantitative yield. The structure was identified as 6β-(2-hydroxyethylthio)-3α,5α-cyclocholestane (**20**) from the nmr data. It indicates that 3α, 5α-cyclocholestan-6β-yl sulfides are preferred products in the presence of good nucleophiles like thiols. As expected, 6β-(2-mercaptoethylthio)-3α,5α-cyclocholestane (**22**) was obtained in high yield in 1,2-ethanedithiol solvolysis.

Solvolysis in Phenols. Reaction in phenol-acetone (1:2) gave rise to a complex reaction mixture which contained cholesteryl phenyl ether (**25**), choleterol (**3**), and 6β-hydroxy-3α,5α-cyclocholestane (**2**). On the other hand, solvolysis in thiophenol-acetone (1:2) produced a single product, which was assigned as 6β-(phenylthio)-3α, 5α-cyclocholestane (**26**).

Synthesis of Aromatic and Other Esters. Esters containing *m*-iodophenyl,[1a] *p*- and *m*-benzoylphenyl,[1b] and *p*-nitrophenyl groups[8] for future functionalization were prepared from **2, 12, 14, 20,** and **22**. Acetic anhydride, benzoyl chloride, *p*-nitrobenzoyl chloride, *m*-iodobenzoyl chloride, 3, 5-dinitrobenzoyl chloride, *p*-benzoylbenzoyl chloride, *m*-benzoylbenzoyl chloride, and succinic anhydride were reacted with appropriate alcohols in pyridine to yield various esters. *p*-Nitrophenylacetates and 4-(*p*-nitrophenyl) butyrates were prepared by reacting alcohols with corresponding acids in dry pyridine in the presence of dicyclohexylcarbodiimide and 4-dimethylaminopyridine.

2.2 Preparation of 5α-Cholestan-6β-yl Derivatives

Cholesteryl tosylate in methanol was heated to reflux in the absence of base to afford cholesteryl methyl ether (**5**) in almost quantitative yield (Figure 4). Hydroboration-oxidation[9] of **5** produced 6α alcohol which was oxidized without purification to 3β-methoxy-5α-cholestan-6-one (**47**) in good yield. The corresponding ketal (**48**) was reduced in ether with mixed hydride to give 3β-methoxy-6β-(2-hydroxyethoxy)-5α-cholestane (**49**) in good yield. In the mixed hydride reduction, the α-side aproach of the attacking hydride was assumed on steric ground to yield the desired 6β-ether. Acetate (**50**) and *m*-iodobenzoate (**51**) of **49** were synthesized using acetic anhydride and *m*-iodobenzoyl chloride in pyridine.



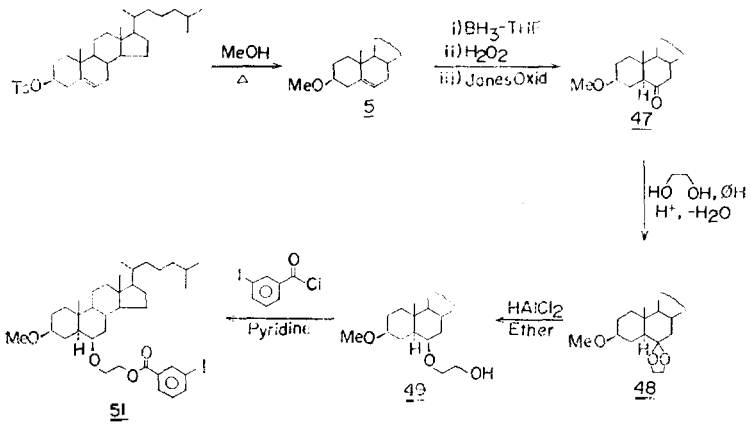
Y=HO, acetone, $NaHCO_3$, reflux, 150 min.	~90%	2	minor	3
CH_3O, KOAc, reflux, 1 h.	69%	4	12%	5
CH_3CH_2O, KOAc, reflux, 30 min.	51%	6	12%	7
$(CH_3)_2CHO$, KOAc, reflux, 1 h.	44%	8	20%	9
$PhCH_2O$, $NaHCO_3$, 100°, 30 min.	0	10	≈100%	11
$PhCH_2O$, acetone, KOAc, reflux, 8 h.	≈50%	10	minor	11
$HOCH_2CH_2O$, KOAc, reflux, 5 min.	0	12	≈30%	13
$HOCH_2CH_2O$, acetone, KOAc, reflux, 4 h.	60%	12	19%	13
$HOCH_2CH_2CH_2O$, acetone, $NaHCO_3$, reflux, 4 h.	77%	14	15%	15
$HO(CH_2CH_2O)_2$, acetone, KOAc, reflux, 7 h.	57%	16	minor	17
$HO(CH_2CH_2O)_3$, acetone, KOAc, reflux, 7 h.	41%	18	minor	19
$HOCH_2CH_2S$, $NaHCO_3$, reflux, 5 min.	≈100%	20	0	21
$HSCH_2CH_2S$, $NaHCO_3$, reflux, 5 min.	≈100%	22	0	23
PhO, acetone, $NaHCO_3$, reflux, 2 h.	0	24	minor	25
PhS, acetone, $NaHCO_3$, reflux, 15 h.	≈100%	26	0	27

Figure 3.

2.3 Nuclear Magnetic Resonance Study

Nuclear magnetic resonance spectra of a number of aromatic esters are compared with those of the parent alcohols. The singlet for H-18 is easily recognized in each spectrum. Conformations with the aromatic ring sitting on top of the C-18 methyl group and the reactive group approaching the side chain should cause the H-18 signal to shift upfield.

6β-Hydroxy-3α,5α-Cyclocholestane (**2**) and its simple ethers (**4, 6, 8**) show identical chemical shifts for H-18 as well as



Figuer 4.

Chemical Shifts from TMS (Hz)

		(H-19)	(H-18)
2	R=H	61	42
4	$R=CH_3$	61	42
6	$R=CH_2CH_3$	61	42
8	$R=CH(CH_3)_2$	61	42
10	$R=CH_2C_6H_6$	65	42
28	R=p-Nitrobenzoyl	68	42
29	R=p-Nitrophenylacetyl	50	36
30	R=4-(p-Nitrophenyl)butyryl	69	42

Figure 5.

H–19 (Figure 5). 6β–Benzyloxy–3α, 5α–cyclocholestane (**10**) is the only exception in that it shows some downfield shift for H–19. 3α, 5α–Cyclocholestane–6β–yl *p*–nitrobenzoate (**28**) exhibits similar chemical shift values as in **10**. Marked tendency for upfield sift is noticed with 3α,5α–cyclocholestane–6β–yl *p*–nitrophenylacetate (**29**) for both H–18 and H–19. Apparently, the aromatic ring in **29** can favorably generate shielding environment for both C–18 and C–19 methyl groups. The aromatic ring moves away from the steroid nucleus with the longer bridge, since the H–18 and H–19 chemical shift values of 3α, 5α–cyclocholestan–6β–yl 4–(*p*–nitrophenyl)butyrate (**30**) are quite similar to those in the parent alcohol **2**.

In a number of aromatic esters (**31, 32, 33, 34, 35, 37**) of 6β–(2–hydroxyethoxy)–3α,5α–cyclocholestane (**12**), H–18 appears to experience noticeable shielding effect (2–5 Hz) compared to that in the parent alcohol **12** (Figure 6). *m*–Benzoylbenzoate (**34**) and 3,5–dinitrobenzoate (**35**) exhibit the maximum shifts. The small, but readily observable upfield shift of the H–18 signal (2 Hz) in *p*–nitrobenzoate (**37**) is particularly interesting because no such shift is observed in **30**, which has the same number of atoms in the bridge as in **37**. With longer bridge, the effect diminishes as examplified in the spectra of *p*–nitrophenylacetate (**38**) and 4–(*p*–nitrophenyl)butyrate (**39**).

Aromatic esters (**40, 41, 42, 43, 44**) of 6β–(3–hydroxy propoxy)–3α, 5α–cyclocholestane (**14**) display minimal or no shifts for H–18 (Figure 7). The effect of one carbon enlongation in the bridge is best seen when one compares the chemical shift difference of the H–18 signals in the pair **12** and **34** (5 Hz) and in the corresponding pair **14** and **41** (1 Hz).

Surprisingly, sulfur analongs of **12**, 6β–(2–hydroxyethylthio)–3α,5α–cyclocholestane (**20**) and 6β–(2–mercapto–ethylthio)–3α,5α–cyclocholestane (**22**) do not show any upfied shift for H–18 when esterified to aromatic esters **45** and **46** (Figure 8). The presence of bulkier sulfur atom in the bridge somehow causes the desired conformation less favorable.

Finally, the nmr spectra of 3β–methoxy–6β–(2–hydroxy–ethoxy)–5α–cholestane (**49**) and its *m*–iodobenzoate (**51**) are compared (Figure 9). A large upfield sift (6 Hz) is apparent and it is concluded that normal 5α–cholestan–6β–yl ethers can assume the desired conformation at least as favorably as in the cases of 3α,5α–cyclocholestane–6β–yl ethers when the spacing group is ethy lene glycol. The result is in line with the finding[10] that the distance between C–19 and 6β oxygen is shorter in 5α–steroidal derivatives compared with that in 3α,5α–cyclosteroids and also confirms the structural assignment of **49** as 6β ether rather than the isomeric 6α ether.

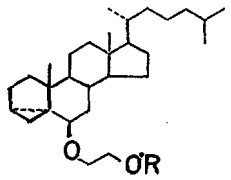
3. Experimental

Melting points were recorded on a Fisher–Johns block and are uncorrected. ^1H NMR spectra were recorded on a Varian EM–360 spectrometer in $CDCl_3$ and are reported in δ from Me_4Si.

Crude reaction mixture was always checked with thin layer chromatography (TLC). TLC plates were made by dipping microscopic slides in the chloroform–methanol (2:1, v/v) slurry of Merck 7749 Kieselgel HF_{254} and drying in the air. Spots were viewed under a UV light and/or by charring after spraying with 2% ceric ammonium sulfate solution in 1 *M* sulfuric acid. Samples were isolated by column chromatography with the aid of Merck 10184 or 7734 Kieselgel.

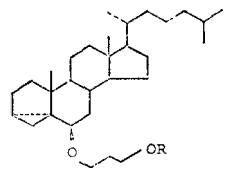
p–Benzoylbenzoic acid, *p*–nitrophenylacetic acid, *p*–nitrobutyric acid (Aldrich) and *m*–iodobenzoic acid (Wako Pure Chemical) were used without further purification. All other reagent whose preparation is not described were purchased from Merck. *m*–Benzoylbenzoic acid was prepared in this laboratory following the published procedure of White[11] from *m*–toluic acid (Tokyo Kasei Kogyo).

All the carboxylic acid chlorides were obtained from their corresponding acid by the reaction with thionyl chloride. Solvents used for reactions under anhydrous conditions



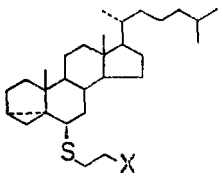
		Chemical Shifts from TMS (Hz) (H-19)	(H-18)
12	R=H	59	42
31	R=Benzoyl	60	40
32	R=m-Iodobenzoyl	60	38
33	R=p-Benzoylbenzoyl	60	39
34	R=m-Benzoylbenzoyl	58	37
35	R=3,5-Dinitrobenzoyl	60	37
36	R=Succinyl	58	42
37	R=p-Nitrobenzoyl	60	40
38	R=p-Nitrophenylacetyl	58	42
39	R=4-(p-Nitrophenyl)butyryl	58	40

Figure 6.



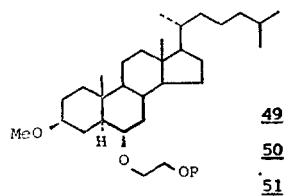
		Chemical Shifts from TMS (Hz) (H-19)	(H-18)
14	R=H	59	41
40	R=p-Benzoylbenzoyl	59	40
41	R=m-Benzoylbenzoyl	59	40
42	R=p-Nitrobenzoyl	59	40
43	R=p-Nitrophenylacetyl	58	42
44	R=4-(p-Nitrophenyl)butyryl	59	42

Figure 7.



		Chemical Shifts from TMS(Hz) (H-19)	(H-18)
20	X=OH	61	43
45	X=OBenzoyl	62	43
22	X=SH	61	43
46	X=S-p-Benzoylbenzoyl	62	44
26	S-(O)	67	45

Figure 8.



		Chemical Shifts from TMS(Hz) (H-19)	(H-18)
49	R=H	58	41
50	R=Acetyl	58	41
51	R=m-Iodobenzoyl	57	35

Figure 9.

were purified and dried as follows; pyridine:distilled from KOH, acetone:distilled from $CaCl_2$, MeOH & EtOH:distilled from Mg, benzene & toluene:distilled from Na, THF: distilled from LAH. Organic solutions were washed with saturated NaCl solution, dried over anhydrous Na_2SO_4, evaporated on a rotary evaporator, and then firmly dried on a vacuum pump.

3.1 Solvolysis of Cholesteryl Tosylate

(1) Solvolysis in Pure Alcohol

Methyl Ethers **4** & **5**. Cholesteryl tosylate(300 mg, 0.555 mmol) was suspended in 10 m*l* of dry methanol along with 300 mg of KOAc. The suspension was heated to reflux for 1 h. The reaction mixture was concentrated, diluted with water, and extracted with ether. The ether extract was washed with water, dried and evaporated. The crude product was placed on a column of 30 g of silica gel. Elution with 1% ether in petroleum ether afforded 152 mg (59 %) of *i*-ether (**4**): NMR δ3.31(*s*, 3H,-OCH_3), 2.74 (*br*, 1H, 6α-H) 1.01(*s*, 3H, 19-H), 0.70 (*s*, 3H, 18-H), and 27 mg (12%) of *n*-ether (**5**).

Ethyl Ethers (**6** & **7**). A suspension of **1** (300 mg, 0.555 mmol) and KOAc (300 mg) in 10 m*l* of dry ethanol was refluxed for 30 min. After the usual workup, the residue was chromatographed on 30 g of silica gel column. Elution with 1 % ether in petroleum ether gave 117 mg (51 %) of **6**:NMR δ 3.42 (*q*, 2H, J=7Hz, -OCH_2-), 2.85(*br*, 1H, 6α-H), 1.13(*t*, 3H, -$OCCH_3$), 1.01 (*s*, 3H, 19-H), 0.70(*s*, 3H, 18-H), and 26 mg (12 %) of **7**.

2-Propyl Ethers (**8** & **9**). The same method gave 104 mg (44 %) of **8**:NMR δ 3.72 (septet, 1H, J=6Hz, -OCH-), 2.93 (*br*, 1 H, 6α-H), 1.02 (*s*, 3H, 19-H), 0.70 (*s*, 3H, 18 -H), and 61 mg (26 %) of **9**.

Benzyl Ether (**11**). A suspension of **1** (102 mg, 0.189 mmol) and $NaHCO_3$ (100 mg) in 5 m*l* of benzyl alcohol was heated at 100°C for 30 min. After workup, the mixture was chromatographed on a silica gel column, but the benzyl alcohol was not completely removed. Then the resulting solution was evaporated to dryness under reduced pressure. Washing with petroleum ether followed by recrystallization yielded only *n*-ether (**11**) (88 mg, 98 %): m.p 113-114 °C: NMR δ7.31(*s*, 5H, aromatic), 5.32(*br*, 1H, olefinic), 4.55(*s*, 2H, benzylic), 3.23(*m*, 1H, 3α-H), 0.99(*s*, 3H, 19-H), 0.67(*s*, 3H, 18-H).

2-Hydroxyethyl Ether (**13**). A batch (110 mg, 0.185 mmol) of **1** was suspended in 7 m*l* of ethylene glycol along with 72 mg of KOAc. The suspension was heated at 140 °C for 5 min. Column chromatography gave 24 mg (30 %) of **13**: NMR δ5.33 (*m*, 1H, olefinic), 3.63 (*br*, A_2B_2, 4H, -OCH_2 CH_2OH), 0.99 (*s*, 3H, 19-H), 0. 6 (*s*, 3H, 18-H).

2-Hydroxyethyl Thioether (**20**). 1 (100 mg, 0.185 mmol) and $NaHCO_3$(90 mg) were dissolved in 5 m*l* of 2-mercaptoethanol. After 5 min reflux, the usual workup followed by column chromatography afforded 82 mg (99 %) of **20**: NMR δ3.65(*t*, 2H, J=6Hz, -CH_2-OH), 2.65(*t*, 2H, J=6H z, SCH_2-), 2.47(*br*, 6α-H), 1.02 (*s*, 3H, 19-H), 0.72 (*s*, 3H, 18-H).

2-Mercaptoethyl Thioether (**22**) **1**(156 mg, 0.288 mmol) and $NaHCO_3$ (100 mg) were dissolved in 1,2-ethanedithiol (7.5 m*l*). After 5 min reflux, was obtained 132 mg(99%) of **22**: NMR δ 2.98(*t*, 2H, J=4Hz,-SCH_2-), 2.69(*t*, 2H, J= 4Hz,-CH_2 SH), 2.46 (*br*, 1H, 6α-H), 1.02(*s*, 3H, 19-H), 0.71 (*s*, 3H, 18-H).

(2) Solvolysis in Alcohol with Acetone

i-Cholesterol (**2**). Cholesteryl tosylate (1.5 g, 2.77 mmol) and $NaHCO_3$ (700 mg) were dissolved in acetone (90 m*l*), and water (45 m*l*). The solution was heated to reflux for 150 min. The reaction mixture was concentrated, and extracted with ether. The ether extract was placed on a column of 60 g of silica gel. Elution with 33 % ether in hexane yielded 1.021 g(95%) of **2**:NMR δ3.24(*br*, 1H, 6α-H), 1.04(*s*, 3 H, 19-H), 0.70 (*s*, 3H, 18-H), and trace of **3**.

Benzyl Ethers (*10 & 11*). Cholesteryl tosylate (300 mg, 0.55 mmol) and KOAc(300 mg) were dissolved in benzyl alcohol(3 m*l*) and acetone (6 m*l*). The mixture was heated to reflux for 8 h. The TLC showed the formation of *i*-ether (*ca.* 60%), *n*-ether(10 %), and a polar product (25 %). Repeated chromatography couldn't separate the mixture completely, but *i*-ether (**10**) (37 mg, 35 %), a mixture of **10**, **11** and polar product (109 mg), and the polar product isolated (39 mg) was identified as cholesteryl acetate:NMR δ5.36 (*m*, 1H, olefinic), 4.54(*m*, 1H, 3α-H), 2.03(*s*, 3H, $-CH_3$), 1.01(*s*, 3H, 10-H), 0.66(*s*, 3H, 18-H), **10**: NMR δ7.26 (*s*, 5H, aromatic), 4.50(*d*, 2H, J=2.6Hz, benzylic), 2.92(*br*, 1H, 6α-H), 1.08 (*s*, 3H, 19-H), 0.70 (*s*, 3H, 18-H).

2-*Hydroxyethyl Ethers* (*12 & 13*). A solution of **1** (1.00 g, 1.85 mmol) and KOAc (1.00 g) in acetone (60 m*l*) and ethylene glycol (30 m*l*) was refluxed for 4 h. Separation by silica gel column chromatography afforded 151 mg (19 %) of 13 and 640 mg (80%) of 12: NMR δ 3.61 (*m*, 4H, A_2B_2, $-CH_2CH_2-$), 2.90 (*m*, 1H, 6α-H), 0.98 (*s*, 3H, 19-H), 0.70 (*s*, 3H, 18-H).

3-*Hydroxypropyl Ethers* (*14 & 15*). A solution of **1** (3.00 g, 5.55 mmol) and $NaHCO_3$ (3.00 g) in dry acetone(50 m*l*) and 1,3-propanediol (25m*l*) was refluxed for 4 h. Separation on a column of 200 g of silica gel yielded 370 mg (15 %) of 15 and 1.902 g (77 %) of **14**:NMR δ3.70 (*m*, 4H, $-OCH_2-$), 3.32(*br*, 1H, $W_{1/2}$=10Hz, -OH), 2.85(*br*, 1H, $W_{1/2}$=6Hz, 6α-H), 0.98(*s*, 3H, 19-H), 0.68 (*s*, 3H, 18-H).

Phenyl Ethers (*24 & 25*). To a solution of **1**(200 mg, 0.370 mmol) in 20 m*l* of acetone was added 10 m*l* of phenol. The solution was refluxed for 2 h. The solution was diluted with 1 *N* NaOH solution, and extracted with petroleum ether. Not being able to separate with column chromatography, the product was identified as **2**, **3**, and **25** by comparision with authentic materials on a TLC.

Phenyl Thioethers (*26 & 27*). To a solution of **1**(200 mg, 0.370 mmol) and $NaHCO_3$ (200 mg) in 10 m*l* of acetone was added 5 m*l* of thiophenol. The solution was refluxed for 15 h. Purification of reaction mixture by column chromatography gave 126 mg(71 %) of **26**: NMR δ7.32 (*dd*, 5H, J=9.6 & 3.5Hz, aromatic), 2.91(*br*, 1H, 6α-H), 1.12 (*s*, 3H, 19-H), 0.75 (*s*, 3H, 18-H).

3.2 Synthesis of Steroidal Esters

(1) Acid Chloride Method

p-Nitrobenzoate (*28*). To a stirred solution of *p*-nitrobenzoyl chloride (606 mg, 3.26 mmol) in 6 m*l* of dry pyridine, 631 mg (1.63 mmol) of **2** was added. After 5 h, several drops of 3-dimethylaminopropylamine were added to remove excess acid chloride.[12] The resulting solution was diluted with ammonium chloride solution, extracted with ether, and washed successively with water and saturated sodium bicarbonate solution. After drying over anhydrous sodium sulfate, the solvent was removed *in vacuo* and the residue was recrystallized from acetone to give 829 mg (95 %) of *p*-nitrobenzoate (**28**): m.p 141.5-142.5 °C (*lit.*[13] 140.4-141.0 °C); NMR δ 8.26 (*s*, 4H, aromatic), 4.77 (*br*, 1H, 6α-H), axial methyls at 1.14 and 0.70.

Benzoate (*31*). **12** (115 mg, 0.267 mmol) was dissolved in ether (20 m*l*) containing a slight excess of benzoyl chloride and a drop of triethylamine. The mixture was stirred at room temperature for 7 h. After the usual workup, the residue was chromatographed to give 101 mg (71 %) of **31**:NMR 8.13-7.51 (*m*, 5H, aromatic), 4.45(*t*, 2H, J=5Hz, $-CH_2OC-$), 3.76(*m*, 2H,$-OCH_2-$), 2.93 (*br*, 1H, $W_{1/2}$= 3 Hz, 6α-H), axial methyls at 1.00 and 0.66.

m-Iodobenzoate (*32*). **12**(105 mg, 0.244 mmol) was treated with *m*-iodobenzoyl chloride (76 mg, 0.308 mmol) as above. After reaction for 7 h, column chromatography afforded 150 mg (93 %) of **32**:NMR δ8.67 (*t*, 1H, J=2Hz, aromatic), 4.44(*t*, 2H, J=5 Hz, $-CH_2OC-$), 3.75 (*m*, 2H, $-OCH_2-$), 2.92(*br*, 1H, $W_{2/1}$=5 Hz, α-H), axial methyls at 1.00 and 0.63.

p-*Benzoylbenzoate* (*33*). **13** (500 mg, 1.16 mmol) was treated with *p*-benzoylbenzoyl chloride (370 mg, 1.51 mmol). After reaction for 2 h, purification by chromatography yielded 712 mg (96 %) of **33**:NMR δ8.17-7.56 (*m*, 9H, aromatic), 4.48(*t*, 2H, J=5Hz, $-CH_2OC-$), 3.78(*m*, 2H, $-OCH_2-$), 2.95(*br*, 1H, $W_{1/2}$=5 Hz, 6α-H), axial methyls at 1.00 and 0.65.

m-Benzoylbenzoate (*34*). **12**(423 mg, 0.982 mmol) was treated with *m*-benzoylbenzoyl chloride (312 mg, 1.27 mmol). After reaction for 2 h, recrystallization from methyl acetate afforded 591 mg (94 %) of **34**: m.p 84.5-85.5 °C; NMR δ8.42-7.54 (*m*, 9H, aromatic), 4.45 (*t*,2H, J=5Hz, $-CH_2OC-$), 3.76 (*m*, 2H,$-OCH_2-$), 2.92(*br*, 1H,$W_{1/2}$= 5 Hz, 6α-H), axial methyls at 0.97 and 0.62.

3, 5-*Dinitrobenzoate* (*35*). **12**(50 mg, 0.116 mmol) in dry pyridine was treated with a small excess of 3,5-dinitrobenzoyl chloride. After reaction for 20 h, 72 mg (100 %) of **35** was obtained as clear glass: NMR δ9.20 (s, 3H, aromatic), 4.57 *t*, 2H, J=5Hz, $-CH_2OC-$), 3,75(*m*, 2H, $-OH_2-$), 2.95 (*br*, 1H, $W_{1/2}$= 6Hz, 6α-H), axial methyls at 1.00 and 0.61.

Succinate (*36*). **12** (96 mg, 0.223 mmol) in 10 m*l* of dry ether was treated with 30 mg (0.30 mmol) of succinic anhydride and 29 mg of triethylamine. The reaction mixture was heated to reflux for 3 h, then 34 mg (35 %) of **36** was obtained: NMR δ8.32 (*br*, 1H,-COOH), 4.21(*t*, 2H, J=5Hz,

$-CH_2\overset{\overset{O}{\|}}{O}C-$), 2.65(*m*, 2H, $-OCH_2-$), 2.88(*br*, 1H, $W_{1/2}$= 5 Hz:6α–H), 2.65(*br*, 4H, $W_{1/2}$=3 Hz, $-\overset{\overset{O}{\|}}{C}CH_2CH_2\overset{\overset{O}{\|}}{C}-$), axial methyls at 0.97 and 0.70.

p–Nitrobenzoate (*37*). A solution of **12**(729 mg, 1.88 mmol) and *p*-nitrobenzoyl chloride (408 mg, 2.20 mmol) in 9 m*l* of dry pyridine was stirred at room temperature for 1 h. After workup, recrystallization from chloroform/methanol gave 0.981 g(91 %) of 37: m.p 72.5–73.5 °C; NMR δ8.17 (*s*, 4H, aromatic), 4.45 (*t*, 2H, *J*=6Hz, $-CH_2\overset{\overset{O}{\|}}{O}C-$), 3.55(*m*, 2H, OCH_2-), 2.83(br, 1H, $W_{1/2}$=6Hz, 6α–H), axial methyls at 1.00 and 0.66.

p–Benzoylbenzoate (*40*) A solution of **14**(1.025 g, 2.31 mmol) and *p*-benzoylbenzoyl chloride (677 mg, 2.77 mmol) in dry pyridine (15 m*l*) was stirred at room temperature for 1.5 h. After the usual workup, 1.38 g (92 %) of **40** was obtained: NMR δ8.14–7.56(*m*, 9H, aromatic), 4.48(*t*, 2H, *J*= 5Hz, $-CH_2-\overset{\overset{O}{\|}}{O}C-$), 3.59 (*m*, 2H, $-OCH_2-$), 2.86 (*br*, 1H, $W_{1/2}$= 5Hz, 6α–H), axial methyls at 0.99 and 0.66.

m–Benzoylbenzoate (*41*). A solution of **14**(1.58 g, 3.55 mmol) and *m*–benzoylbenzoyl chloride (1.04g, 4.26 mmol) in dry pyridine (20 m*l*) was stirred for 1.5 h. 2.07 g (89%) of 41 was obtained: NMR δ8.41–7.54 (*m*, 9H, aromatic), 4.45 (*t*,, 2H, *J*=6Hz, $-CH_2\overset{\overset{O}{\|}}{O}C-$), 3.55 (*m*, 2H, $-OCH_2-$), 2.84 (*br*, 1H, $W_{1/2}$=5Hz, 6α–H), axial methyls at 0.98 and 0.66.

p–Nitrobenzoate (*42*). **14**(1.050 g, 2.36 mmol) and *p*-nitrobenzoyl chloride (561 mg, 3.02 mmol) in dry pryidine (15 m*l*) was stirred for 2.5 h. Recrystallization from chloroform/methanol gave 1.11 g (79 %) of **42**: m.p 78–79 °C; NMR δ8.20(*s*, 4H, aromatic), 4.50 (*t*, 2H, *J*= 6 Hz, $-HC_2\overset{\overset{O}{\|}}{O}C-$), 3.59 (*m*, 2H, $-CH_2O-$), 2.87 (*br*, 1H, $W_{1/2}$ =5 Hz, 6α–H), axial methylas at 0.98 and 0.66.

Benzoate (*45*). To a solution of **20** in dry ether containing a drop of benzoyl chloride, a drop of triethylamine was added. The mixture was stirred at room temperature for 4 h. After the usual workup, 60 mg of **45** was obtained: NMR δ8.06–7.34(*m*, 5H, aromatic), 4.39(*t*, 2H, *J*=7 Hz, $-COH_2-$), 2.78 (*t*, 2H, *J*=7Hz, $-SCH_2-$), 2.58(*br*, 1H, 6α–H), axial methyls at 1.03 and 0.72.

(2) Carbodiimide Method

p-Nitrophenylacetate (*29*). To a solution of **2**(600 mg, 1.55 mmol), *p*-nitrophenylacetic acid (400 mg, 2.21 mmol) and 4–dimethylaminopyridine (DAP) (200 mg) in 30 m*l* of dry pyridine, N,N′-dicyclohexylcarbodiimide (DCC) (700 mg, 3.39 mmol) was added. After stirring for several minutes, dicyclohexylurea began to crystallize. Stirring was continued for 4.5 h and dicyclohexylurea was filtered off. The filtrate was diluted with 2 *N* hydrochloric acid solution, extracted with ether. The ether extract was washed successively with 2 *N* hydrochloric acid solution, water, saturated brine, then dried over anhydrous sodium sulfate. The solvent was removed and the residue was chromatographed on silica gel. Elution with 20 % ether in hexane afforded 725 mg of **29**:NMR δ8.17(*d*, 2H, *J*=9Hz, aromatic). 7.45(*d*, 2H, *J*=9 Hz, aromatic), 4.51(*br*, 1H, $W_{1/2}$=5Hz, 6α–H), 3.73(*s*, 2H, benzylic), axial methyls at 0.83 and 0.60.

4–(*p–Nitrophenyl*)*butyrate* (*30*). To a solution of **2**(109 mg, 0.28 mmol), 4–(*p*-nitrophenyl)butyric acid (176 mg, 0.841 mmol) and a catalytic amount of DAP in 5 m*l* of dry pyridine, 175 mg(0.848 mmol) of DCC was added. After reaction for 45 h, 53 mg (32 %) of **30** was obtained as clear glass: NMR δ8.15(*d*, 2H, *J*=9Hz, aromatic)., 7.34(*t*, 2H, *J*=9Hz, aromaic), 4.55(*br*, 1H, $W_{1/2}$=5 Hz, 6α–H), 2.78 (*t*, 2H, *J*=7 Hz, $-CH_2-$), axial methyls at 1.00 and 0.70.

p–Nitrophenylacetate (*38*). To a solution of **12**(500 mg, 1.16 mmol), *p*–nitrophenylacetic acid (700 mg, 3.86 mmol) and DAP in pyridine (20 m*l*) 900 mg(4.36 mmol) of DCC was added. After 5 h, chromatography followed by recrystallization from chlololform/methanol gave needle-like crystals melting at 66.5–67.0 °C: NMR δ8.15 (*d*, 2H, *J*= 9 Hz, aromatic), 7.44(*d*, 2H, *J*=9 Hz, aromatic), 4.23(*t*,2H, *J*=5Hz, $-CH_2OC-$), 3.75(*s*, 2H, benzylic), 2.86(*br*, 1H, $W_{1/2}$=4Hz, 6α–H), axial methyls at 0.97 and 0.70.

4–(*p–Nitrophenyl*)*butyrate* (*39*). **12** (60 mg, 0.192 mmol), 4–(*p*–nitrophenyl)butyric acid (40 mg, 0.192 mmol), DCC (100 mg, 0.485 mmol) and DAP were stirred in 5 m*l* of dry pyridine for 6 h. 85 mg (98%) of yellow glass was obtained: NMR δ8.17 (*d*, 2H, *J*=9 Hz, aromatic), 7.35(*d*, 2H, *J*= 9 Hz, aromatic), 4.23(*t*, 2H, *J*=5 Hz, $-CH_2\overset{\overset{O}{\|}}{O}C-$), 3. 67, 2.88(*br*, 1H, 6α–H), 2.80 (*t*, 2H, *J*=7 Hz, benzylic), 2.38 (*t*, 2H, *J*=6 Hz, $-OCCH_2-$), axial methyls at 0.97 and 0.67.

p–Nitrophenylacetate (*43*). After a solution of 14(560 mg, 1.259 mmol), *p*–nitrophenylacetic acid (400 mg, 2.208 mmol), DCC (600 mg, 2.908 mmol) and DAP in dry pyridine was stirred for 7 h, 662 mg (87 %) of **43** was obtained:NMR δ8.14 (*d*, 2H, *J*=9 Hz, aromatic), 7.41(*d*, 2H, *J*=9 Hz, aromatic), 4.22(*t*, 2H, *J*=6 Hz, $-CH_2\overset{\overset{O}{\|}}{O}C-$),3.71 (*s*, 2H, benzylic), 3.43 (*m*, 2H, $-OCH_2-$), 2.77 (*br*, 1H, $W_{1/2}$= 5HZ, 6α–H), axial methyls at 0.96 and 0.70.

4–(*p–Nitrophenyl*)*butyrate* (*44*). To a solution of **14**(1.04 g, 2.33 mmol), 4–(*p*–nitrophenyl)butyric acid (2 g, 9.56 mmol), and DAP in 25 m*l* of pyridine, 3 g (14.5 mmol) of DCC was added. After 5 h, column chromatography afforded 1.042 g; (70 %) of **44**: NMR δ8.17 (*d*, 2H, *J*=9Hz, aromatic), 7.35 (*d*, 2H, *J*=9 Hz, aromatic), 4.21(*t*, 2H, *J*=7 Hz,$-CH_2\overset{\overset{O}{\|}}{O}C-$), 3.49(*m*, 2H, $-OCH_2-$), 2.83(*br*, 1H, 6α–H), 2.80(*t*, 2H, *J*=7 Hz, benzylic), 2.35(*t*, 2H, *J*= 6Hz, $-OCCH_2-$), axial methyls at 0.98 and 070.

S–p–Benzoylbenzoate (*46*). Benzoylbenzoic acid (29 mg, 0.130 mmol) was added to a soluiion of **22**(56 mg, 0.121

mmol) in dry acetone (4 m*l*) containing DCC (27 mg, 0.131 mmol). The mixture was stirred for 40 h. 48 mg (59%) of 46 was obtained: NMR δ 7.94–7.57 (*m*, 9H, aromatic), 3.25 (*m*, 2H, $-CH_2SC-$), 2.81 (*br*, 1H, $W_{1/2}$=5 Hz, 6α–H), 2.65 (*m*, 2H, $-SCH_2-$), axial methyls at 1.03 and 0.73.

3.3 Preparation of 5α-Cholestan-6β-yl Derivatives

Cholesteryl Methyl Ether (**5**). A solution of clesteryl tosylate (7.5 g, 13.9 mmol) in dry methanol was heated to reflux with stirring for 16 h. On cooling, the product was crystallized. The crude product was filtered and recrystallized from methanol to give 5.3 g (95 %) of **5**: m.p 81–82 °C: NMR 5.32 (*m*, 1H, olefinic), 3.34 (*s*, 3H, $-OCH_3$), 3.05(*br*, 1H, 3–H), 0.99 (*s*, 3H, 19–H), 0.67 (*s*, 3H, 18–H).

3β-Methoxy-5α-cholestan-6-one (**47**). A solution of cholesteryl methyl ether (1 g, 2.50 mmol) in 25 m*l* of dry THF was cooled in an ice bath. To this 3.5 m*l* of 1 *M* diborane in THF was added slowly and the mixture was stirred under nitrogen at room temperature for 14 h. After decomposition of excess hydride by addition of water, 1 m*l* of 3 *M* sodium hydroxide solution was added. The solution was cooled to 0°C and maintained at this temperature during the addition of 1m*l* of 30 % hydrogen peroxide. The mixture was stirred for another 30 min, and worked up with water and ether. The ethereal solution was washed twice with water, dried and concentrated to give a oily residue. The oily residue was dissolved in 6 m*l* of acetone and 16 m*l* of THF and oxidized with 2 m*l* of 8 *N* Jone's reagent. After stirring the mixture for 1 h at 0°C, excess oxidant was decomposed by addition of sodium bisulfite solution. The crude product was extracted with ether and separated by column chromatography. Elution with 20% ether in hexane yielded 0.705 g (68 %) of **47**: NMR δ3.31(*s*, 3H,$-OCH_3$), 3.05(*br*, 1H, 3α–H), 0.72 (*s*, 3H, 19–H), 0.65 (*s*, 3H, 18–H).

3β-Methoxy-6-ethylenedioxy-5α-cholestane (**48**). A solution of **47** (610 mg, 1.46 mmol), ethylene glycol (800 mg) and *p*-toluenesulfonic acid (1 mg) in benzene was placed in a 250 m*l* round-bottomed flask equipped with a Dean-Stark trap. The mixture was heated to reflux with stirring for 8 h. After cooling the benzene solution was washed twice with 10% sodium hydroxide solution and once with water. Removal of the solvent gave 616 mg (92 %) of **48**: NMR δ3.91 (*m*, 4H, A_2B_2, $-OCH_2CH_2O-$), 3.33(*s*, 3H–OCH_3), 3.07(*br*, 1H, 3α–H), 0.91(*s*, 3H, 19–H), 0.66(*s*, 3H, 18–H).

3β-Methoxy-6β- (2-hydroxyethoxy) 5α-cholestane (**49**). Aluminum chloride (2.4 g, 18 mmol) was dissolved in 5 m*l* of dry ether, and then 175 mg(4.6 mmol) of LAH emulsionized in dry ether was added. After 1 h stirring at room temperature, 616 mg (1.34 mmol) of **48** dissolved in dry ether was added. The mixture was heated to reflux fo 3.5 h under nitrogen atmosphere. Excess hydride was decomposed by addition of water. The ethereal solution was washed twice with water and dried. After removal of the solvent, purification of the product by column chromatography gave 563 mg (91 %) of **49**: NMR δ3.72 (*m*, 4H, A_2B_2,$-CH_2CH_2-$), 3.29(*s*, 3H, $-OCH_3$), 0.89(*s*, 3H, 19–H), 0.65(*s*, 3H, 18–H).

Acetate of **49**:(**50**). A solution of **49**(50 mg, 0.11 mmol) and 100 mg of acetic anhydride in 10 m*l* of dry pyridine was stirred at room temperature for a day. After workup, removal of the solvent gave 49 mg (88%) of **50**: NMR δ4.14 (*t*, 2H, *J*=4Hz. $-CH_2OC-$), 3.32(*s*, 3H, $-OCH_3$), 2.03(*s*, 3H, CH_3C-), 0.97 (*s*, 3H, 19–H), 0.68(*s*, 3H, 18–H).

m-Iodobenzoate of **49**:(**51**). A solution of **49**(450 mg, 1.0 mmol) and *m*-iodobenzoyl chloride (309 mg, 1.1 mmol) in dry pyridine was stirred at room temperature for 2 h. After workup removal of the solvent gave 673 mg (98 %) of **51**: NMR δ8.33–7.11(*m*, 4H, aromatic), 4.39(*t*, 2H, *J*=4 Hz, $-CH_2OC-$), 3.63 (*t*, 2H, *J*=4 Hz, $-OCH_2-$), 3.30 (*s*, 3H, $-OCH_3$), 0.95 (*s*, 3H, 19–H), 0.58(*s*, 3H, 18–H).

Conclusion

Aromatic esters of 6β–(2–hydroxyethoxy)–3α,5α–cyclocholestane (**12**) and 3β–methoxy–6β–(2–hydroxyethoxy)–5α–cholestane (**49**) show noticeable upfield shift for H–18 signal in the nmr spectra compared to that of parent alcohols. Close examination of molecular models reveals that they can indeed assume conformations in which the aromatic ring approaches C–18 methyl group and the side chain. Further experiments are in due order to establish the correlationship between the reactivity of H–20 and the nmr shielding effect on H–18, which will be the subject of future communications.

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Theoretical Studies on the Photo-Skinsensitizing Psoralens (II)

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The photocycloaddition reaction of 8-methoxypsoralen with purine and/or pyrimidine bases is studied as a model for the charge transfer interactions of psoralens with DNA bases by the FMO method. The results indicate that, in the case of the molecular complex formation between psoralens and purine and/or pyrimidine bases, the most probable photocycloaddition should occur in the following order: Thy (5,6)〈〉(3,4) 8-MOP, Cyt(5,6)〈〉(3,4)8-MOP, Ade (7,8)〈〉(3,4)8-MOP, Gua(7,8)〈〉(3,4)8-MOP. The theoretical results for the photocycloaddition reaction are also correlated with the experimental results. The photoadducts between 8-methoxypsoralen and adenine are likely to be C_4-cycloadducts through the cycloaddition of 3,4-pyrone double bond of 8-methoxypsoralen to 7,8-double bond of adenine.

Introduction

The photobiological reactivities of psoralens as skin-sensitizers can be described in terms of the localized $(\pi, \pi^*)^3$ state, which is supposed to be the reactive state for the cycloaddition reaction of psoralens with pyrimidine bases in DNA.[1-4]

In our previous reports,[5-6] it has been shown that the optimum value of indices is closely correlated with photo-skinsensitizing carcinogenic activity and the formation of molecular complexes between DNA and photo-skinsensitizing carcinogens is discussed in terms of charge transfer interactions.

Although several photo-products of purine bases from direct and photosensitized irradiation of purines are known,[7] the photoaddition reactions between the excited psoralens and purine bases are not well understood. In view of the fact that the photoaddition of psoralens to poly A is quite efficient and one adenine base in *E. coli* tRNA is involved in photoaddition of 8-methoxypsoralen,[8] it is important to elucidate the nature of photobinding reactions between psoralens and adenine base.

In the present paper, we report that the charge trnaster interaction in the hypothetic molecular complexes between the psoralens and the base components of nucleic acids are the first step of the photo-skinensitizing carcinogenesis and the most probable photocycloaddition reaction between psoralens and purine and/or pyrimidine bases is derived from FMO methods.

Calculations

In the hypothetic molecular complexes, the chemical reactivity index and frontier electron density[9,10] can be used as a measure of the relative reactivity index of the various positions of the photocycloaddition. The increase in the frontier electron densities in the intermolecular region originates from the overlapping of the occupied molecular orbitals of purine and pyrimidine bases.

The parameters[11] as descibed in the previous papers were obtained from Pullman's value and frontier molecular orbitals and charge transfer quantity were calculated for both the psoralens and purine and/or pyrimidine bases for their complexed forms with HEWLETT PACKARD-3000 computer.

It is postulated that the photocycloaddition of adenine to the excited psoralens may yield the following adducts. The numbering scheme for nonhydrogen atoms is given below for the psoralens and purine bases.