as plates: mp 68.0–68.6°; $[\alpha]_D$ −49.2° (*c* 3.66); ir ($CHCl_3$ 5.84 (C_6 ring or aliphatic C=O), 6.89 ($-CH_2CO-$), 7.25, 7.38 μ (CH_3CO-); nmr τ 7.83 (s, 3, CH_3CO-), 9.07 (s, 3, C-19 Me), 6.90, 7.60 (m, 1, C-20 H and C-12 H).

Anal. Calcd for $C_{24}H_{40}O_2$ (360.56): C, 79.94; H, 11.18. Found: C, 79.88; H, 10.98; M^+, 360.

Registry No.—**1**, 19534-78-2; **2**, 19594-93-5; **3**, 19594-94-6; **4**, 19654-71-8; **5**, 1251-13-4; **6**, 40429-72-9; **7**, 40429-73-0; **8**, 40429-74-1; **9**, 40429-75-2; **10**, 40429-76-3; **11**, 40429-77-4; **12**, 40429-78-5; **13**, 40429-79-6; **16**, 19654-72-9; **17**, 19594-96-8; **18**, 19594-98-0.

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Stereospecific Bromination of Methyl 3α,7α-Diacetoxy-12-oxocholanate, Catalyzed by Boron Trifluoride

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Methyl 3α,7α-diacetoxy-12-oxocholanate (1) failed to react with bromine in the presence of either hydrobromic acid or sodium acetate, but the monobromination of 1 catalyzed by BF_3 proved to be stereospecific, affording a high yield of the desired 11α-bromo ketone 2. However, the epimerization of 11β-bromo ketone 7, which was prepared by an alternative route, could only be achieved by HBr and not by BF_3. IBr, in the presence of BF_3 or HBr, was found to be very reluctant as a brominating agent for 1. Interpretation of the findings in terms of steric and stereoelectronic effects is offered. The pertinent spectroscopic data, including circular dichroism of the hitherto unknown two epimeric 11-bromo ketones, are given.

Bromination of keto steroids has been widely investigated. However, relatively few studies have been reported on 12-keto analogs.[1-3]

As part of a study we had interest in a stereoselective high-yield bromination of methyl 3α,7α-diacetoxy-12-ketocholanate (1).

Exposure of **1** to the action of bromine at 70°[1] in the presence of hydrobromic acid as a catalyst produced a complex mixture, with a low yield of bromo ketones **2** or **7**. Elimination of the catalyst[2] from the bromination reaction mixture (room temperature), or the addition of sodium acetate, did not induce much improvement in the reaction. None of the methods mentioned appears to be of any practical value, as evidenced by the nmr determinations of the reaction products.

A detailed study was undertaken to clarify the nature of the reaction and the factors determining the reactivity of the α hydrogens in **1**.

11-Bromo ketone **7** was prepared by an alternative method[2,4] (Scheme I).

The obtained 11β-bromo ketone **7** (yield 13%) was subjected to the action of hydrobromic acid in acetic acid solution.[3] The reaction was followed by tlc and nmr at various intervals. An almost complete conversion to the 11α-bromo epimer **2** was achieved after 48 hr.

To rationalize the above findings, namely the slow bromination of **1** and the facile epimerization of **7**, very low rate enolization in the parent compound **1** and enhanced enolization in its 11β-bromo derivative **7** are suggested.

To improve the reaction HBr was substituted by BF_3, a strong Lewis acid, known to be very effective as a catalyst in bromination reactions.[5]

Using bromine, in acetic acid, as the brominating agent and BF_3 as the catalyst, the desired 11α-bromo ketone **2** was obtained in a high yield of 95–97%. Only minor amounts of the 11β-bromo epimer **7** could be detected.

IBr, an effective reagent in the bromination of steroid aldehydes,[6] proved completely inactive in the presence of BF_3 or HBr. The combination, IBr and BF_3, effected a conversion of **1** to the corresponding acid (see Experimental Section).

Regarding epimerization of 11β-bromo ketone **7**, BF_3, in contrast to HBr, proved ineffective, even after long periods of time.

It appears that the action of BF_3 and HBr as catalysts is of an entirely different nature in effecting bromination and epimerization of **1** and **7**, respectively.

The configurations of the hitherto unknown epimers **2** and **7** were assigned by spectroscopic data. The nmr, ir, and uv data, given in the Experimental Section, are in full agreement with those reported on the 7-deoxy analogs. The circular dichroism curves of the two epimeric 11-bromo ketones and the mass spectra are given in Figure 1 and Table I, respectively.

Discussion

The preferential loss of an axial proton in the enolization of conformationally rigid cyclohexanones and the predominance of axial α-bromo ketone in kinetically

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SCHEME I

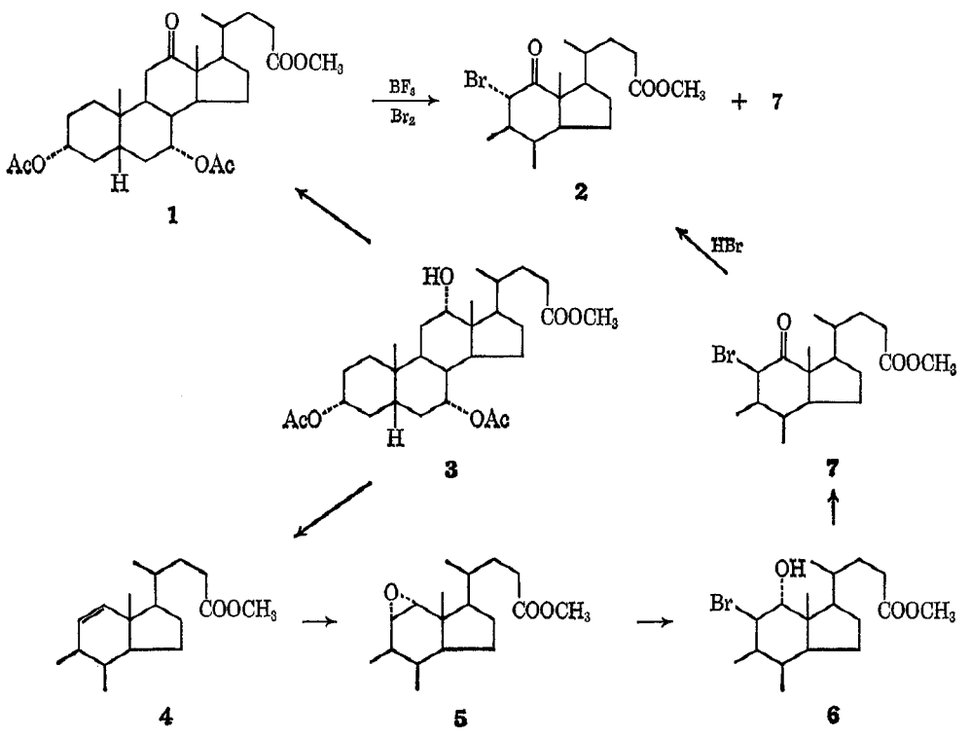


TABLE I

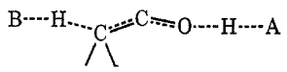
MASS SPECTRA OF COMPOUNDS 1, 2, 6, AND 7

Compd	m/e values and relative abundances (%) of characteristic ion fragments		
	M^+	Base peak	
Methyl 3α,7α-Diacetoxy-12-oxocholanate (1)	504 (27)	444	384, 311, 289, 269, 251, 243, 229, 154 (32) (21) (18) (25) (23) (32) (93) (79)
Methyl 3α,7α-Diacetoxy-11α-bromo-12-oxocholanate (2)	582, 584 (0.17) (0.10)	502	550, 442, 383, 351, 275, 231 (2) (17) (90) (20) (19) (37)
Methyl 3α,7α-Diacetoxy-11β-bromo-12α-hydroxy-cholanate (6)	584, 586 (0) (0)	251	487, 444, 427, 371, 367, 351, 311, 269 (8.8) (50) (42) (64) (78) (42) (57) (50)
Methyl 3α,7α-Diacetoxy-11β-bromo-12-oxocholanate (7)	582, 584 (0) (0)	93	502, 489, 488, 429, 369, 368, (0.17) (0.34) (0.7) (28) (42) (28) 133, 131, 121, 109, 107, 95 (32) (39) (78) (51) (78) (82)

controlled bromination were rationalized by Corey[3] in terms of stereoelectronic effects.

However, this theory has been modified[7] as a result of recent studies on the bromination of steroid ketones to account also for the opposing steric hindrance factor.

The lack of bromination of 1 in contrast to the 7-deoxy analog[1,2] clearly demonstrates the great importance of even a remote bulky substituent in determining enolization rates. Thus our findings are in agreement with the demands of the "push–pull" process suggested for the reacting complex.



The flexibility of ring C in compound 1 is probably restrained by the bulky 7-OAc, causing the shielding effect at the 11-axial hydrogen to be more pronounced than in the 7-deoxy analog. The rigidity of ring C also prevents the equatorial hydrogen from acquiring the pseudoaxial orientation suitable for enolization. The facile epimerization of the 11β-bromo ketone 7 in the presence of HBr may be accounted for by the enhanced acidity of the equatorial hydrogen in the β-bromo compound 7. Such pronounced stereoelectronic effects imply high activation energy for the bending of ring C. The steric acceleration due to the axial bromine in 7 compensates for the energy necessary for the abstraction of what appears to be equatorial hydrogen, but in fact is pseudoaxial hydrogen in the flexible or boat conformation of ring C (Scheme II).

The fact that no epimerization could be effected by BF_3 (in contrast to HBr) under the reaction conditions, and that high stereospecificity was observed in the bromination of 1, suggest that some other factors are operative in this case.

It seems that in 1, where the steric requirements are strict, BF_3 with its small volume and polar bonds adjusts itself to the substrate in proper steric relationship. Both reacting centers are connected by the catalyst molecule (Scheme II). Thus BF_3 functions simultaneously as an acid and as a base. As a result, the suitably oriented equatorial hydrogen is abstracted and the C-11 attacked by bromine synchronously, this accounting for the high stereospecificity observed.

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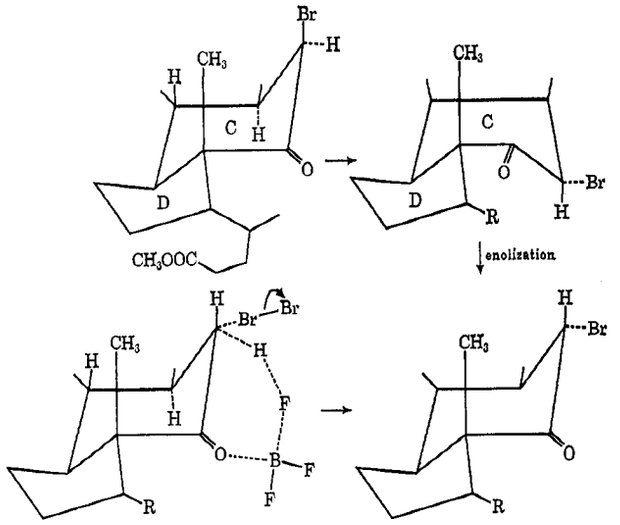
SCHEME II



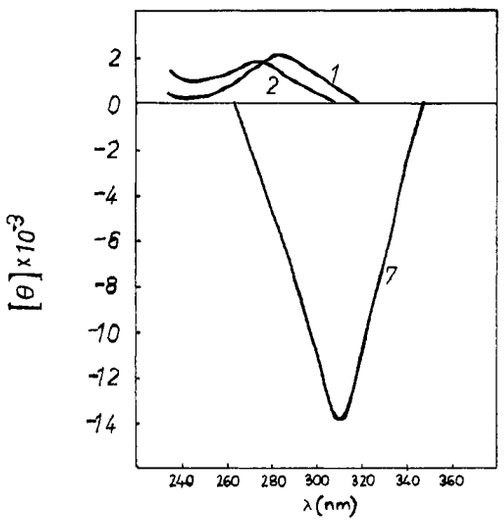


Figure 1.—Circular dichroism of compounds 1, 2, and 7.

The high activation energy required for abstraction of the axial hydrogen is the main reason for the low yield of the 11β-bromo epimer 7. At higher temperatures the percentage of 7 rises.

The behavior of IBr as a brominating agent is under further investigation in keto steroid systems.

The ir values of the 11-bromo epimers 2 and 7 (see Experimental Section) are consistent with those reported previously for the 7-deoxy analogs.[8,9] In addition, the expected bathochromic shift[10] in the uv spectrum of the 11β epimer 7 was observed.

The C-18 and C-19 methyl protons resonated at lower field in the 11β-bromo epimer 7. This is attributed to the anisotropic effect[11] of the axial bromine of 7.

In Figure 1 the curves for the two bromo ketones 2 and 7 are compared with that of the parent 12 ketone 1. The axial nature of the bromine atom in 7 is clearly evident from its strong negative Cotton effect, indicating a very high degree of asymmetry in this epimer.

The similarity of the circular dichroism absorption (positive sign) of the epimeric ketone 2 and the parent compound is characteristic of the equatorial bromine substituent. These findings are consistent with the octant rule.

The following main differences in the mass spectra of 11α-bromo (2) and 11β-bromo (7) epimers were observed. In the 11α compound spectrum the molecular ion was represented (0.17), while the M^+ of the 11β-bromo derivative did not appear. The base peak of the α isomer corresponded to the loss of a hydrogen bromide molecule: 502, M − HBr; *m/e* 442 resulted from the loss of HBr + AcOH. In the β compound the loss of either the CH_2Br or CH_3Br fragment was characteristic: 489, M − CH_2Br; 429, M − (CH_2Br + AcOH); 369, M − (CH_2Br + 2AcOH); 488, M − CH_3Br; and 368, M − (CH_3Br + 2AcOH). $CH_2{=}Br^+$ represented the base peak (*m/e* 93) and *m/e* 95 corresponded to $CH_2{=}^{81}Br$ (Table I).

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Experimental Section

Ultraviolet spectra were determined with a Unicam ultraviolet spectrophotometer (Model Sp 800A). Infrared spectra were measured in potassium bromide disks using a Perkin-Elmer spectrophotometer (Model 337). Nmr spectra were recorded on a Jeol C-60-H high-resolution nmr spectrometer with tetramethylsilane as internal standard. Mass spectra were recorded on a CH5 Varian MAT mass spectrometer. CD spectra were obtained using a Cary 60 recording spectropolarimeter. Optical rotations were determined with a Perkin-Elmer 141 polarimeter.

Methyl 3α,7α-Diacetoxy-11α-bromo-12-oxocholanate (2).—To a solution of 1 (5 g) in acetic acid (50 ml) in a glass-stoppered flask, bromine (0.8 ml) and boron trifluoride etherate (5 drops) were added. After standing for 5 days at room temperature the reaction mixture was diluted with water (200 ml) and sufficient sodium bisulfite was added. The precipitate was filtered, washed with water, and dissolved in chloroform. To the concentrated solution excess diazomethane in ether was added and the reaction mixture was stirred for 2 hr, during which period solid material began to precipitate out. After an additional 1 hr the solid was filtered. Recrystallization from isopropyl alcohol gave pure 11α-bromo ketone 2 (4.7 g): mp 223–224°; $[\alpha]_D$ ($CHCl_3$) +40.7°; ir 1729 (C=O), 1250 and 1237 (CO), 753 cm^{-1} (CBr); uv (ethanol) 274 nm (ε 100); nmr (CCl_4) δ 1.02 (s, 3, 18-CH_3), 1.20 (s, 3, 19-CH_3), 1.91 (s, -OCOCH_3), 2.00 (s, -OCOCH_3), 3.57 (s, 3, 24-OCH_3), 4.80 (m, 1, HCBr); nmr ($CDCl_3$) δ 1.50 (s, 3, 18-CH_3), 1.21 (s, 3, 19-CH_3), 2.00 (s, -OCOCH_3), 3.63 (s, 3, 24-OCH_3), 4.97 (m, 1, HCBr).

Anal. Calcd: C, 59.1; H, 7.3; Br, 13.6. Found: C, 58.9; H, 7.3; Br, 13.4.

An additional 0.5 g of pure 11α-bromo ketone was obtained from the mother liquors. The residue (0.6 g) consisted of 2 and minor amounts of the 11β-bromo epimer 7, as was evident from nmr and tlc.

Methyl 3α,7α-Diacetoxy-11α,12α-epoxycholanate (5).—A mixture consisting of 3 (1.1 g), pyridine (25 ml), and phosphoroxy chloride (10 ml) in a glass-stoppered flask was stirred at 37° for 24 hr.[4] The reaction mixture was added slowly to a large volume of ice water; the precipitate so obtained was filtered and extracted with chloroform. The chloroform layer was washed with a saturated solution of sodium bicarbonate and water, dried over sodium sulfate, and filtered. Excess perbenzoic acid in chloroform was added, and the mixture was kept overnight at room temperature. The chloroformic solution was washed with aqueous sodium carbonate and water, dried, and evaporated at reduced pressure. The residue was recrystallized from methanol to give pure 5 (0.2 g): mp 154°; nmr ($CDCl_3$) δ 0.82 (s, 3, 18-CH_3), 1.02 (s, 3, 19-CH_3), 2.02 (s, -OCOCH_3), 3.06 (m, 2, 11β and 12β H), 3.65 (s, 3, 24 OCH_3).

Anal. Calcd: C, 69.0; H, 8.7. Found: C, 68.8; H, 8.6.

Methyl 3α,7α-Diacetoxy-11β-bromo-12-oxocholanate (7).—11α,12α-Epoxide 5 (400 mg) in acetone (40 ml) was subjected to the action of 48% HBr (1 ml). The crude bromohydrin 6 (400 mg) was recrystallized from methanol to give a crystalline material: mp 176°; nmr ($CDCl_3$) δ 1.00 (s, 3, 18-CH_3), 1.18 (s, 3, 19-CH_3), 1.88 and 1.91 (-$OCOCH_3$), 3.50 (s, 3, 24-OCH_3), 4.21 (m, 1, HCBr).

A 200-mg portion of the unpurified bromohydrin was oxidized (CrO_3).[9] The crude product was recrystallized from methanol to give 160 mg of 11β-bromo ketone **7**: mp 190–191°; $[\alpha]_D$ ($CHCl_3$) +15.9°; ir 1738 (C=O), 1710 (C=O), 1245 (OC), 660 cm^{-1} (axial CBr); uv (ethanol) 310 nm (ε 110); nmr ($CDCl_3$) δ 1.37 (s, 18- and 19-CH_3), 2.02 (s, 3 and 7 -$OCOCH_3$), 3.66 (s, 3, 24-OCH_3), 4.42 (m, 1, HCBr); nmr (CCl_4) δ 1.37 (s, 18- and 19-CH_3), 1.90 and 1.98 ($OCOCH_3$), 3.60 (s, 3, 24-OCH_3), 4.42 (m, 1, HCBr).

Anal. Calcd: C, 59.1; H, 7.3; Br, 13.6. Found: C, 59.4; H, 7.3; Br, 13.3.

Epimerization of 11β-Bromo Ketone 7 to 11α-Bromo Ketone 2 with HBr.—To a solution of 7 (250 mg) in acetic acid (10 ml) 10% HBr in acetic acid (3 ml) was added. The reaction mixture was kept at room temperature for 2 days. Water was added and the precipitate was extracted with chloroform. The solvent was removed and diazomethane in ether was added to the residue. Recrystallization of the solid material from isopropyl alcohol afforded pure crystals identical in all respects with 11α-bromo ketone **2**. The 11β-bromo epimer was detected in the mother liquor.

An Unsuccessful Attempt to Epimerize 11β-Bromo Ketone 7 with BF_3.—To a solution of 7 (200 mg) in acetic acid (10 ml) 10 drops of BF_3 etherate were added and the solution was kept at room temperature for 5 days. The isolated material was identical with **7**; the 11α-bromo epimer was by no means present.

The Use of IBr as a Brominating Agent. A. With HBr as Catalyst.—To a solution of 1 (1 g) in acetic acid (30 ml), IBr (0.22 ml of bromine and 0.92 g of iodine) in acetic acid and 5 drops of 10% HBr in acetic acid were added. The reaction mixture was kept at room temperature for 7 days. The material which was isolated after the usual work-up proved to be identical with 1, mp 181°; the nmr spectrum was consistent with that previously reported;[12] for CD in ethanol, see Figure 1; for mass spectrum, see Table I.

B. With BF_3 as Catalyst.—The procedure was the same as above except that BF_3 etherate (5 drops) was used instead of HBr. The reaction mixture was kept at room temperature for 2 days and for 3 additional days at 35–40°. The only compound isolated was 3α,7α-diacetoxycholanic acid, nmr ($CDCl_3$) δ 8.75 (1, -COOH). The peak disappeared on addition of D_2O. Reaction with diazomethane gave 1. Note: the 12-keto group in **1**, **2**, and **7** was found to be unreactive to diazomethane.

Registry No.—**1**, 28535-81-1; **2**, 40488-36-6; **3**, 3749-87-9; **5**, 40488-38-8; **6**, 40488-39-9; **7**, 40488-40-2; borontrifluoride etherate, 109-63-7.

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Conformations of Substituted Arylureas in Solution

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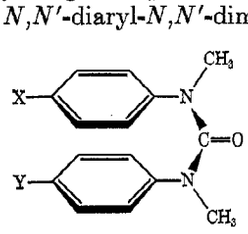
The conformation of *N,N'*-diarylureas in solution is investigated to obtain information about "stacking" interactions between aromatic rings. The only isomer which appears to exist has both aromatic rings in an anti relationship to the oxygen of the urea. Analysis of nmr and uv spectra suggests that there is a charge transfer interaction between the two rings, especially when they are substituted with electron-withdrawing and electron-donating groups.

During the past several years, a number of investigations[4] have suggested that, in aqueous solutions, parallel stacking of purine and pyrimidine bases is a major stabilizing force in oligo- and polynucleotides and in the binding of smaller aromatic compounds to nucleic acids. However, little is known about the specific factors which are responsible for this stacking. Theoretical studies have stressed the possible importance of dipole–dipole, dipole-induced dipole, London dispersion, and monopole–monopole interactions.

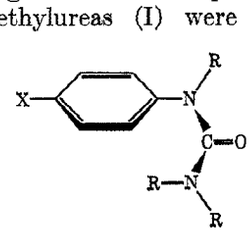
The crystal structure of *N,N'*-diethyl-*N,N'*-diphenylurea[5] has been shown to contain two phenyl rings aligned parallel to each other with their faces partially overlapping as shown in Figure 1. The preference for the conformation with the two bulky phenyl groups anti to the oxygen but in a "stacked" position near one another suggests that the same forces may be at work here.

In order to determine the conformation of diphenylureas in solution and to study the nature of the forces leading to the stacking of aromatic rings, we have studied the nuclear magnetic resonance and ultraviolet spectra of several substituted diphenylureas along with appropriate model compounds.

In order to establish the relative positions of the two phenyl rings, the proton magnetic resonance spectra of the *N,N'*-diaryl-*N,N'*-dimethylureas (I) were compared to those of the corresponding *N*-aryl-*N,N',N'*-trialkylureas (II). The results are shown in Table I.



Ia, X = Y = H
b, X = Y = = OCH_3
c, X = Y = NO_2
d, X = NO_2; Y = OCH_3



IIa, X = H; R = CH_3
b, X = OCH_3; R = CH_2CH_3
c, X = NO_2; R = CH_2CH_3

As may be seen, the aromatic protons of the diphenyl- (Ia) and dianisylureas (Ib) are uniformly shifted upfield in the presence of an aryl ring on the opposing nitrogen. This result suggests that the two rings are located near each other and are oriented so that the protons of each lie above the aromatic ring of the other so that a ring current induced upfield shift results.

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(2) Postdoctoral Fellow at the Polytechnic Institute of Brooklyn, 1970–1971.

(3) Postdoctoral Fellow at the University of California, San Diego, 1972–present.

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