Steroids. Part X.[1] A Convenient Synthesis of Alkyl Aryl Ethers †

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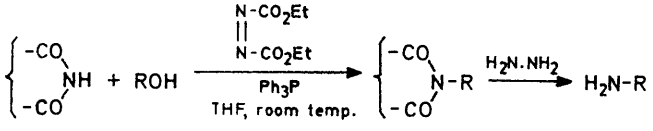
A simple synthesis of alkyl aryl ethers has been developed involving reaction between an alcohol, a phenol (or an enol), triphenylphosphine, and diethyl azodicarboxylate. By using this procedure several steroid, sugar, pyrimidine, and quinazoline ethers have been prepared.

MITSUNOBU and his co-workers [2] have described a convenient stereospecific method for the conversion of alcohols into amines. The method consists of the reaction of an alcohol with diethyl azidodicarboxylate (DEADC), triphenylphosphine (TPP), and an imide, followed by treatment of the intermediate *N*-alkylimide, which is formed in high yield, with hydrazine (Scheme). We now report our adaptation of this reaction to the synthesis of alkyl aryl ethers which are otherwise not readily accessible by conventional methods or only by multi-step reactions.



SCHEME

We have found that quinazolin-4(3*H*)-ones (1) or (2) can be substituted for the imide component in the Mitsunobu reaction; [2] obviously the 3-proton in (1) is sufficiently acidic for the reaction to occur. Thus, when 2-*p*-methoxyphenylquinazolin-4(3*H*)-one (1) [3] was treated with propan-2-ol in the presence of DEADC and TPP in tetrahydrofuran (THF), the corresponding ether (3) was obtained in 71% yield. A similar reaction of (1) with 2-(pyrrolidin-1-yl)ethanol afforded the corresponding ether (4) [4] in 85% yield. Apparently the presence of the tertiary nitrogen does not interfere with this reaction. These ethers were identified by their spectra and direct comparison with authentic samples. When 2-methylquinazolin-4(3*H*)-one (2) was employed in this reaction, the ether (5) could be isolated only in very poor yield. Use of an excess of reagents and longer reaction time did not have any noticeable effect on the yield.

The ability of 3-unsubstituted quinazolin-4(3*H*)-ones to furnish ethers suggested that they participate in their enolic form in this reaction. Phenol and *p*-bromophenol were, therefore, tested as the acidic component in place of the quinazolinones, and both reacted with ethyl alcohol in the presence of DEADC and TPP to provide ethyl phenyl (6) and ethyl *p*-bromophenyl ether (7) in *ca.* 90% yield.

This method was also extended to the synthesis of aryl ethers of steroidal alcohols. 3α-Phenoxy-5α-cholestane (9) and 3α-*p*-bromophenoxy-5α-cholestane (10) were obtained when cholestan-3β-ol (8) was allowed to react in the presence of DEADC and TPP with phenol and *p*-bromophenol, respectively. This reaction proceeds with inversion of configuration at C-3 of the steroidal alcohol as revealed by the ^{1}H n.m.r. spectra of (9) and (10), in which the 3-H signal at δ 4·5 was sharpened after ether formation which is indicative of the axial disposition of the ether group. The reaction of cholesterol with phenol and *p*-bromophenol, however,

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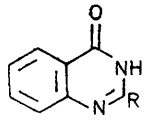
[1] Part IX, A. K. Bose, B. Lal, W. A. Hoffman, and M. S. Manhas, *Tetrahedron Letters*, 1973, 1619.

[2] O. Mitsunobu, M. Wada, and T. Sano, *J. Amer. Chem. Soc.*, 1972, **94**, 679.

[3] (*a*) H. Stephen and G. Wadge, *J. Chem. Soc.*, 1956, 4420; (*b*) T. A. K. Smith and H. Stephen, *Tetrahedron*, 1957, **1**, 38.

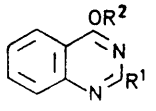
[4] M. S. Manhas, W. A. Hoffman, and A. K. Bose, unpublished results.

resulted in the formation of the 3β-ethers (11) [5] and (12), respectively. The formation of (11) from cholesterol with retention of configuration is unexceptional



(1) R = C_6H_4OMe-*p*

(2) R = Me



(3) $R^1 = C_6H_4OMe$-*p*, $R^2 = Pr^i$

(4) $R^1 = C_6H_4OMe$-*p*, $R^2 = CH_2CH_2N$⟨⟩

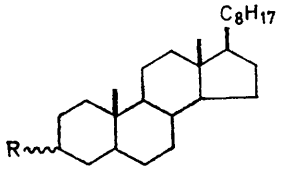
(5) R^1 = Me, $R^2 = CH_2CH_2N$⟨⟩

p-R C_6H_4·OEt

(6) R = H

(7) R = Br

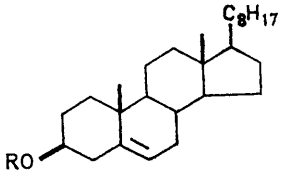
because of the well known intervention of *i*-steroid intermediates through double-bond participation.[6]



(8) R = β-OH

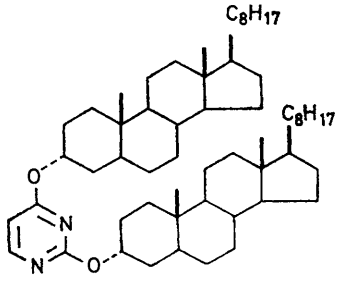
(9) R = α-OPh

(10) R = α-OC_6H_4Br-*p*



(11) R = Ph

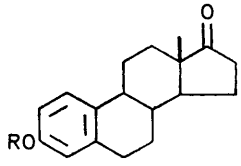
(12) R = C_6H_4Br-*p*



(13)

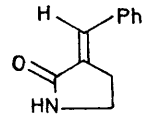
In order to prepare ethers involving sterols and pyrimidines, the reaction of uracil with (8) was studied. No ether formation was observed even after 30 days reaction when THF was employed as the reaction medium, probably because uracil is sparingly soluble in THF. However, in hexamethylphosphoramide triamide, 2,4-bis(cholestan-3α-yloxy)pyrimidine (13) was formed in 50% yield in a few hours.

Estra-1,3,5(10)-trien-17-one (14) could also function as the phenolic component in these reactions. It was readily converted into its methyl ether (15) on reaction with methanol, TPP, and DEADC. When 1,2:3,4-di-*O*-isopropylidenegalactopyranose was treated with the estratrienone, a novel ether (16) was obtained in 43% yield. In the reaction of an alcohol with the estratrienone an extra equivalent of TPP was needed to compensate for the TPP that is reversibly bound to the carbonyl function during the reaction. In the absence of the extra TPP the yield is sharply reduced.



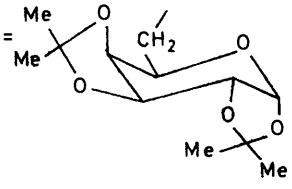
(14) R = H

(15) R = Me



(17)

(16) R =



Tertiary alcohols do not provide the corresponding ethers by this method. Nitrophenols undergo side-reactions with TPP and are not suitable reagents for ether formation. Attempts to prepare enolic ethers from conjugated amides, such as (17),[7] were unsuccessful.

EXPERIMENTAL

M.p.s were taken with open capillary tubes in a Mel-Temp apparatus. I.r. spectra were recorded on a Perkin-Elmer IR 247 spectrometer either neat or as Nujol mulls. N.m.r. spectra were obtained on a Varian A-60A or a Perkin-Elmer R-12 spectrometer with tetramethylsilane as an internal standard. Mass spectra were obtained on a Perkin-Elmer RMU-7 mass spectrometer. Elemental analyses were performed by Alfred Bernhardt, West Germany.

General Method for the Synthesis of Ethers.—A solution of the quinazoline or phenol (1 mmol), triphenylphosphine (1 mmol), alcohol (1 mmol), and diethylazadicarboxylate (1 mmol) in tetrahydrofuran (25 ml) was stirred at room

[5] Y. Kashman, *J. Org. Chem.*, 1972, **37**, 912.

[6] (*a*) S. Winstein and R. Adams, *J. Amer. Chem. Soc.*, 1948, **70**, 838; (*b*) S. Winstein and A. H. Schlesinger, *ibid.*, p. 3528.

[7] A. K. Bose, J. L. Fahey, and M. S. Manhas, *Tetrahedron*, 1974, **30**, 3.

Analytical and spectroscopic data of ethers

Compound	M.p. (°C)	Yield (%)	Molecular formula	Analysis (%) [a] C	H	N	Spectroscopic data
(3)	Oil	71	$C_{18}H_{18}N_2O$				$\nu_{max.}$ (neat) 2975, 1605sh, 1595, 1565, and 1020 cm^{-1}; δ ($CDCl_3$) 7·7 (4H, q), 7·6 (4H, m), 5·82 (1H, m), 3·8 (3H, s), 1·54 (3H, s), and 1·45 (3H, s); *m/e* 294 (M^+), 279, 254, 236, 221, 152, and 119
(4) [b]	78—80	85	$C_{21}H_{23}N_3O_2$	72·05 (72·2)	6·55 (6·65)	11·95 (12·05)	$\nu_{max.}$ (Nujol) 1608 cm^{-1}; δ (CCl_4) 7·70 (4H, m), 4·75 (2H, t), 3·81 (3H, s), 2·93 (4H, m), and 1·76 (4H, m)
(5)	Oily liquid	10	$C_{15}H_{19}N_3O$				$\nu_{max.}$ (neat) 2975, 1620, 1580, 1500, 1160, 1100, 765, 740, and 685 cm^{-1}; δ ($CDCl_3$) 7·5 (4H, m), 4·75 (2H, t), 3·0 (2H, t), 2·7 (7H, m), and 1·8 (4H, m)
(9)	76—78	80	$C_{33}H_{52}O$	85·0 (85·3)	10·9 (11·3)		$\nu_{max.}$ (neat) 1595, 1580, 1490, 1380, 1240, 1160, 995, and 740 cm^{-1}; δ ($CDCl_3$) 7·0 (5H, m), 4·5 (1H, m), and 1·0 (46H, m)
(10)	109—110	65	$C_{33}H_{51}BrO$	72·75 (72·9)	9·1 (9·45)		$\nu_{max.}$ (neat) 2950, 1480, 1245, 1160, 995, and 820 cm^{-1}; δ ($CDCl_3$) 7·1 (4H, q), 4·5 (1H, m), and 1·0 (46H, m)
(11) [c]	147—149	65	$C_{33}H_{50}O$				
(12)	162—164	60	$C_{33}H_{49}BrO$				$\nu_{max.}$ (neat) 2925, 1585, 1480, 1235, 1065, 1032, 965, and 818 cm^{-1}; δ ($CDCl_3$) 7·15 (4H, q), 5·8 (1H, m), 3·92 (1H, m), and 1·2 (43H, m); *m/e* 542/540 (M^+)
(13)	213—214	50	$C_{58}H_{96}N_2O_2$	81·75 (81·7)	11·25 (10·9)	3·3 (3·3)	$\nu_{max.}$ (Nujol) 1598, 1580, 1245, and 990 cm^{-1}; δ ($CDCl_3$) 7·0 (2H, m), 4·5 (2H, m), and 1·1 (92H, m)
(16)	218—220	43	$C_{30}H_{40}O_7$	70·75 (70·3)	7·85 (7·7)		$\nu_{max.}$ (neat) 2990, 2925, 1730, 1605, 1495, 1380, 915, 890, 860, and 670 cm^{-1}; δ ($CDCl_3$) 6·85 (3H, m), 5·5 (1H, d), 4·35 (4H, m), 4·1 (2H, s), 2·8 (3H, m), 1·8 (12H, m), 1·5 (3H, s), 1·45 (3H, s), 1·33 (6H, s), and 0·9 (3H, s)

[a] The figures in parentheses refer to required values. [b] Ref. 4. [c] Ref. 5.

temperature under anhydrous conditions. The reaction time depended upon the reagents and varied from 24 h to 4 days. The solution was concentrated under reduced pressure and then diluted with a small quantity of ether. Any precipitated solid was rejected. The filtrate after concentration was chromatographed over neutral alumina (Brockmann Grade 1) using 10% benzene–hexane as eluant. The products in the first few fractions were invariably oily liquids. Some of them solidified and were crystallized from appropriate solvents.

The analytical and spectral data on the new compounds synthesized by this method are given in the Table.

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