of water was added, and the evaporation was repeated, affording a clear yellow syrup. This was dissolved in 5 ml of water and centrifuged, and the clear supernatant liquid was treated with 348 mg (5.8 mmol) of glacial acetic acid and cooled to 5°. After 2 hr, the white crystals were collected, washed with water, and dried. Concentration of the mother liquor afforded a second crop which was combined with the first crop, affording 162 mg (92% yield) of white needles, mp 263–265°. Recrystallization from methanol–water produced the analytical specimen as white needles, mp 270–271° (gas evolution).

Anal. Calcd for $C_9H_{11}N_3O_3$: C, 51.67; H, 5.27; N, 20.09. Found: C, 51.5; H, 5.3; N, 20.1.

3,4,5,8,9,10-Hexahydro-2-amino-9-carbomethoxyquinazolin-4-one (5). A.—To a solution of 524 mg (1.98 mmol) of adduct **3**, mp 197–200°, in 30 ml of methanol was added 0.5 ml (6 mmol) of concentrated hydrochloric acid. The solution was refluxed for 11 hr, after which the solvent was evaporated at reduced pressure. The resulting cloudy syrup was taken up in 10 ml of water, filtered, and concentrated to 5 ml. Addition of 0.5 ml of concentrated ammonium hydroxide caused crystalline amino ester **5** to separate after a few minutes. There was isolated 345 mg (mp 245–255°) after combination of several crops. Two recrystallizations from water afforded the analytical specimen as white needles, mp 259–260° dec. The mass spectrum included, in addition to an intense parent ion peak at *m/e* 223, the following intense peaks: *m/e* 192 (M − 31, loss of OCH_3), 191 (M − 32, loss of $HOCH_3$), 169 (M − 54, loss of butadiene), and 164 (M − 59, loss of O_2CCH_3).

Anal. Calcd for $C_{10}H_{13}N_3O_3$: C, 53.81; H, 5.83. Found: C, 53.5; H, 5.84.

B.—To 5 ml of methanol saturated with hydrogen chloride was added 100 mg (0.480 mmol) of amino acid **4**, mp 269–272°, and the resulting mixture was refluxed for 6 hr. Evaporation of the solvent at reduced pressure afforded a foam which was dissolved in 2 ml of water, filtered, and concentrated to 1 ml. Addition of three drops of concentrated ammonium hydroxide caused the amino ester to crystallize upon cooling. There was isolated 100 mg (84%) of amino ester **5**, mp 240–255°. Recrystallization from water afforded a sample, mp 258–260°, admixture of which with authentic **5** showed no melting point depression.

A 42-mg sample of **5**, mp 254–255°, was heated at 100° in 0.2 ml of acetic anhydride until solution was effected. Excess solvent was then removed under vacuum and the crystalline residue was triturated with ether. Removal of the solvent afforded 44 mg (88%) of adduct **3**, mp 198–199°, admixture of which with authentic **3** showed no melting point depression.

3,4,5,8,9,10-Hexahydro-2-acetamido-9-carboxyquinazolin-4-one (6).—A mixture of 500 mg (2.39 mmol) of amino acid **4**, mp 267–270°, and 3 ml of acetic anhydride was heated with stirring under nitrogen until solution was effected (30 min). Removal of the solvent under reduced pressure produced a foam which was dissolved in 3 ml of chloroform and vigorously stirred for 6 hr in the presence of 3 ml of water. The resulting solid was isolated by centrifugation, washed with carbon tetrachloride, and dried, affording 482 mg (90%) of the title compound as a white powder, mp 159–163° dec. Two recrystallizations from ethyl acetate afforded the analytical specimen as a white microcrystalline powder, mp 171–173° (solvate containing 0.5 mol of acetic acid per mol of **6**). The mass spectrum included, in addition to an intense parent ion peak at *m/e* 251, the following prominent peaks: *m/e* 207 (M − 44, loss of HO_2C), 197 (M − 54, loss of butadiene), and 60 (acetic acid).

Anal. Calcd for $C_{11}H_{13}N_3O_4 \cdot {}^1/_2CH_3CO_2H$: C, 51.24; H, 5.38. Found: C, 51.2; H, 5.20.

1,2,3,4,5,8,9,10-Octahydro-9-carbomethoxyquinazolin-2,4-dione (8).—To 1.00 g (5.72 mmol) of methyl orotate (**7**),[7] mp 240–241°, in a 40-ml glass liner was added 30 ml of dry tetrahydrofuran, 10 mg of hydroquinone, and 10 ml of 1,3-butadiene. Care was taken to exclude water. The glass liner was then placed in a 127-ml stainless steel pressure reactor and heated at 165 ± 2° for 48 hr, after which time the resulting slightly yellow solution was evaporated to dryness and then treated with three 25-ml portions of boiling hexane, which removed butadiene-derived hydrocarbons. The resulting white gummy solid was boiled with 75 ml of chloroform for 30 min and filtered, affording 52 mg (5%) of starting methyl orotate, mp 235–238°. Concentration of the filtrate followed by cooling afforded 1.19 g of a white solid, two recrystallizations of which from ethyl acetate produced 1.02 g (78%) of adduct **8**: mp 201–203°; λ_{max}^{KBr} 2.9–3.6 (s), 5.7–6.2 (s), 6.64 (w), 6.98 (s), 7.65 (m), 8.37 (m), and 9.36 μ (m). The nmr spectrum ($CDCl_3$) displayed a complex multiplet (5 H) at δ 2.3–2.8 (allylic and methine protons), a singlet (3 H) at 3.70 (methyl ester protons), and a multiplet (2 H) at 5.6 (vinyl protons). The mass spectrum included, in addition to a prominent parent ion peak at *m/e* 224, prominent peaks at *m/e* 170 (M − 54, loss of butadiene) and 165 (M − 59, loss of O_2CCH_3).

Anal. Calcd for $C_{10}H_{12}N_2O_4$: C, 53.47; H, 5.36. Found: C, 53.3; H, 5.33.

Under the above reaction conditions, acetyluracil (**9**) afforded uracil in near-quantitative yield.

(7) J. J. Fox, N. Yung, and I. Wempen, *Biochim. Biophys. Acta*, **28**, 295 (1957).

Registry No.—**2**, 21615-58-7; **3**, 21615-59-8; **4**, 21615-60-1; **5**, 21615-61-2; **6**, 21615-62-3; **8**, 21615-63-4; 2-amino-6-carbomethoxy-4(3H)-pyrimidone, 21615-64-5.

Acknowledgment.—The authors wish to extend their thanks to the National Science Foundation (GP 10736) and the National Institutes of Health (5-ROI-NB-07586-01) for support of this research. F. P. Mason thanks the National Science Foundation for an institutional training fellowship.

Alkylation by Alcohols in the Presence of Dicyclohexylcarbodiimide.[1] Alkylation of Thymine, Uracil, Thymidine, and Uridine by Alcohols

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Received November 15, 1968

In a previous publication[2] from this laboratory it was shown that methanol could be used to methylate thymidine. This reaction occurred in the presence of N,N′-dicyclohexylcarbodiimide (DCC); it resulted in the synthesis of 3-methylthymidine (2′-deoxy-3,5-dimethyluridine). We now wish to present evidence that alkylation of the N-3 position of thymidine and uridine, or of the N-1 and N-3 positions of thymine and uracil by a variety of alcohols in the presence of DCC can be considered to be a general reaction.

The synthesis of alkyl aryl ethers from alcohols and phenols in the presence of DCC was shown to occur by Vowinkel in 1962.[3] In 1965 Bach studied this reaction with the use of ^{18}O ethanol and was able to show that none of the ^{18}O was found associated with the alkyl aryl ether but rather that all the ^{18}O was found associated with the DCU formed as a by-product of the reaction.[4] Consequently, Bach suggested that the original attack on DCC is by the ethanol. The resultant

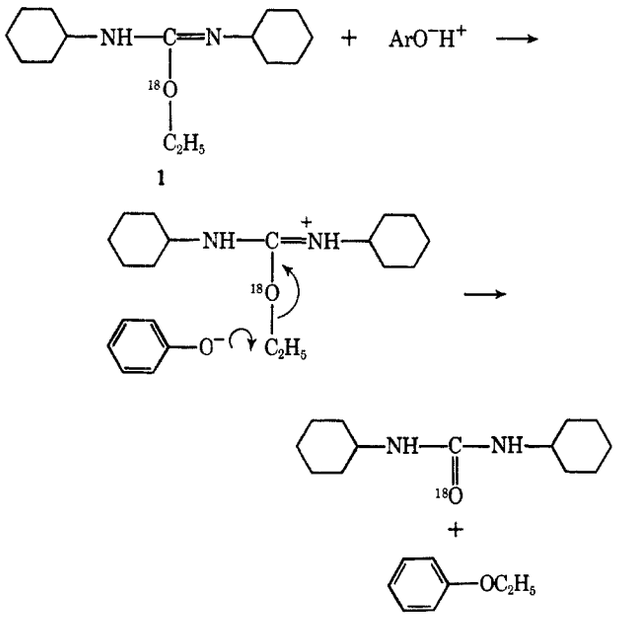
(1) This research was in part supported by U. S. Public Health Service Training Grant No. 5-T4 CA 5012 to R.T.M., Research Career Award U. S. Public Health Service 5 K06-GM-3070 to E. S. C., and by U. S. Public Health Service Grant PHS CA-4823.

(2) R. T. Markiw and E. S. Canellakis, *Tetrahhdron Lett.*, 657 (1968).

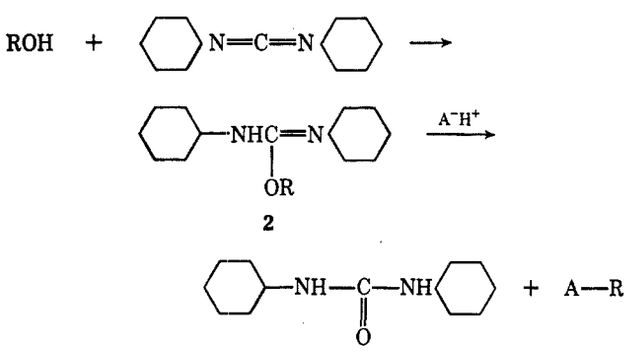
(3) E. Vowinkel, *Chem. Ber.*, **95**, 2997 (1962).

(4) F. L. Bach, *J. Org. Chem.*, **30**, 1300 (1965).

ethanol–DCC adduct **1** is then subjected to an SN2 attack by a phenoxide ion resulting in the formation of the alkyl aryl ether.



The formal similarity of this reaction to the alkylation of thymine, uracil, thymidine, or uridine by an alcohol permits us to give a general formulation to this type of reaction. A^- would represent the anionic form of



phenol, thymine, thymidine, uracil, etc. Such a general consideration of this reaction permits us to regard the alcohol–DCC adduct **2** as an active alkylating intermediate which in the presence of the appropriate acceptor anion results in the synthesis of an alkylated product.

Reagents used for the N alkylation of pyrimidines have included diazomethane,[5] methyl iodide in alcoholic potash,[6] and dimethyl or diethyl sulfate in alkali;[7-9] however, the problem of mixed O and N alkylation has limited the usefulness of this synthetic approach. Alternate synthetic procedures have involved the alkylation of related thio ethers[6,10-15] or through unambiguous primary synthesis.[15,16]

In the present study a uniform procedure has been used for the alkylation of uracil, uridine, thymine and thymidine by various alcohols. As stated previously,[2] the methylation of thymidine in the presence of DCC and methanol proceeds optimally at 80° With the higher alcohols used in the present investigation, it has been found necessary to raise the temperaure and to increase the reaction time. The yields of alkylated pyrimidines tend to decrease as the molecular weight of the alcohols increases.

In all cases the products have been N-alkylpyrimidine nucleosides; this is based on the analytical data and on the results of acid hydrolysis which yield N-alkylpyrimidines. No free pyrimidines have been obtained after acid hydrolysis which would have been the case if O substitution had occurred. Pilot studies carried out in an attempt to alkylate uridine in the presence of *n*-amyl, isoamyl, and tertiary amyl alcohol indicated higher yields with the primary alcohol than the secondary alcohol while no 3-(*t*-amyl)uridine could be identified.

Experimental Section

In general it has been found that at least a 3:1 ratio of DCC to pyrimidine is required; the yield can be increased with more DCC although not in proportion to the amount of DCC added. Complete alkylation has not been achieved even with a 6:1 ratio of DCC to pyrimidine and a reaction time of 100 hr.

Various attempts were made to investigate the fate of 50% of the thymidine which cannot be accounted for. To this end the residue from the reaction mixture obtained after the methylation of thymidine was hydrolyzed in glacial acetic acid–hydrochloric acid (2:1), for 1 hr, at 100°.[17] Using a variety of extraction procedures no appreciable uv absorbing material could be extracted, showing that degradation of thymidine occurred concurrently with its alkylation. Since the yield of 3-alkylthymidine is not affected by greatly increased reaction times, it would appear that once formed it is not degraded to an appreciable extent. This would be in keeping with Janion and Shugar's observation that 3-methylthymidine is stable under alkaline conditions.[18]

General Alkylation Procedure.—The pyrimidine (thymine or uracil) or its nucleoside (thymidine or uridine) was suspended in a solution of DCC in the alcohol to be used for alkylation. The tube (10 ml) was sealed and kept in an oven at the desired temperature for a given period of time. The reaction mixture was then left at room temperature for several hours and the supernatant fluid was separated from the precipitated DCU. The latter was washed with several 3-ml portions of petroleum ether followed by several 3-ml portions of water. The original supernatant as well as the petroleum ether and water washing were combined and shaken. The resulting aqueous layer was repeatedly extracted with three 5-ml portions of petroleum ether while the combined petroleum ether extracts were repeatedly extracted with water (five 5-ml portions). Any basic substances present in the aqueous fractions were removed by percolating the aqueous layer and the water extracts of the petroleum ether through a 3 cm × 0.78 cm² Dowex-50-H^+ column. The eluates of this column were then percolated through a 3 cm × 0.78 cm² Dowex-1-Acetate or Dowex-1-Formate column to remove complex decomposition products and coloration. These columns were subsequently washed with water until no appreciable uv absorbing material remained. The final eluates were concentrated to a gum which was streaked on Whatman 3 MM paper and developed in one of the following three solvent systems: solvent system A (isopropyl alcohol–concentrated ammonium hydroxide–water 7:1:2), solvent system B (isopropyl alcohol–water 7:3), solvent system C (*n*-butyl alcohol–water 86:14). The bands containing the desired product were eluted off the

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(6) T. B. Johnson and S. H. Clapp, *J. Biol. Chem.*, **5**, 49 (1908).
(7) (a) D. Davidson and O. Baudisch, *J. Amer. Chem. Soc.*, **48**, 2379 (1926); (b) J. P. Scannell, A. M. Crestfield, and F. W. Allen, *Biochim. Biophys. Acta*, **32**, 406 (1959).
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(12) S. Senda, M. Honda, K. Maeno, and H. Fujimura, *ibid.* **6**, 490 (1958).
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(14) H. L. Wheeler and T. B. Johnson, *ibid.*, **42**, 30 (1909).
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(16) C. W. Whitenhead, *J. Amer. Chem. Soc.*, **74**, 4267 (1952).
(17) M. Hoffer, *Chem. Ber.*, **93**, 2777 (1960).
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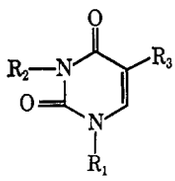
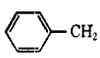
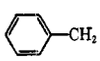
TABLE I[a]



No.	R_1	R_2	R_3	Time, hr	Temp, °C	% yield	Mp, °C	Recrystn solvent	R_f (solvent)
I	2'-dR	C_2H_5	CH_3	40	130	38	Gum		0.84 (A)
II	H	C_2H_5	CH_3			90	202.5	Water	0.84 (A)
III[b]	2-dR		CH_3	40	130	32	167–168	Water	0.84, 0.70 (A, B)
IV[b]	H		CH_3			85	207	Water	0.84 (A)
V	2'-dR	$CH_3(CH_2)_2CH_2$	CH_3	40	130	31	Gum		0.84 (A)
VI	H	$CH_3(CH_2)_2CH_2$	CH_3			75	73	Ether–petroleum ether	0.84 (A)
VII	2'-dR	$CH_3(CH_2)_6CH_2$	CH_3	66	140	2.2	Gum		0.70 (A)
VIII	CH_3	CH_3	CH_3	30	100	71.5	155	Ethanol	0.86 (A)
IX	C_2H_5	C_2H_5	CH_3	47	130	83	56–57	Water	0.86 (A)
X	C_2H_5	H	CH_3			10	223	Water	0.77 (A)
XI	Rb	CH_3	H	20	90	18	115–116	Methanol–ethyl acetate, petroleum ether	0.68 (A)
XII[c]	H	CH_3	H			75[d]	184[d]	Ethanol	
XIII	Rb	$CH_3(CH_2)_2CH_2$	H	40	130	17	Gum		0.42, 0.76 (A, B)
XIV[c]	H	$CH_3(CH_2)_2CH_2$	H			73[e]	152–153[e]	Ethyl acetate	0.75, 0.83, 0.72 (A, B, C)
XV	Rb		H	40	130	7	174–175	Ethyl acetate, ether–petroleum ether	

[a] Abbrevations: 2'-dR, 2'-deoxyribose; Rb, ribose. A, B, and C refer to chromatographic solvents used (see Experimental Section). [b] The benzyl derivatives are strongly retained by resins particularly by Dowex-1. The yields can be increased if the excess benzyl alcohol is extracted with petroleum ether and the use of resins avoided. [c] Prepared by hydrolysis of XI and XIII, respectively, for 1 hr in 70% perchloric acid 100°. [d] lit.[19] 184.0–184.5°; see ref 19 and A. Benitez, L. O. Ross, L. Goodman, and B. R. Baker, *J. Amer. Chem. Soc.*, **82**, 4585 (1960). [e] lit.[20] 152.3°.

paper with water; the water eluates were concentrated. When necessary these were percolated through Dowex-1-Acetate and Dowex-50-H^+ resins. The products were isolated either as chromatographically pure gums or where possible, they were crystallized. A summary of the pertinent data is presented in the accompanying table. This general procedure was used to synthesize the following compounds: 3-ethylthymidine (I), 3-benzylthymidine (III), 3-(*n*-butyl)thymidine (V), 3-(*n*-octyl)-thymidine (VII) (5.3 mg was obtained; structure was assumed from uv spectrum), 1,3-dimethylthymine[5,6,15] (VIII), 1,3-diethylthymine[9] (IX), 1-ethylthymine[19] (X) (as a by-product of synthesis of IX), 3-methyluridine[20,21] (XI), 3-(*n*-butyl)-uridine (XIII), 3-benzyluridine (XV).

Anal. Calcd for $C_{12}H_{18}N_2O_5$ (I): C, 53.32; H, 6.71. Found: C, 53.46; H, 6.92.

Anal. Calcd for $C_{17}H_{20}N_2O_5$ (III): C, 61.44; H, 6.07; N, 8.43. Found: C, 60.86; H, 6.06; N, 7.45.

Anal. Calcd for $C_{14}H_{22}N_2O_5$ (V): C, 56.36; H, 7.43; N, 9.39. Found: C, 53.89; H, 7.84; N, 9.22. Recalcd for $C_{14}H_{22}N_2O_5 \cdot H_2O$: C, 53.15; H, 7.65; N, 8.86. On this basis it is assumed that the derivative contains one water of crystallization.

Anal. Calcd for $C_{13}H_{20}N_2O_6$ (XIII): C, 51.99; H, 6.71; N, 9.33. Found: C, 53.93; H, 7.25; N, 9.38.

Anal. Calcd for $C_{16}H_{18}N_2O_6$ (XV): C, 57.48; H, 5.43; N, 8.38. Found: C, 57.34; H, 5.56; N, 8.10.

The following substituted pyrimidines were prepared from the parent pyrimidine nucleosides by hydrolysis in glacial acetic acid–concentrated hydrochloric acid (2:1, v/v) for 1 hr in a boiling-water bath: 3-ethylthymine (II) from I, 3-benzylthymine[22] (IV) from III, 3-(*n*-butyl)thymine (VI) from V.

Anal. Calcd for $C_7H_{10}N_2O_2R$ (II): C, 54.53; H, 6.54; N, 18.17. Found: C, 54.40; H, 6.64; N, 18.48.

Anal. Calcd for $C_9H_{14}N_2O_2$ (VI): C, 59.32; H, 7.74; N, 15.37. Found: C, 59.09; H, 7.71; N, 15.58.

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(22) T. B. Johnson and J. H. Derby, *Am. Chem. J.*, **40**, 456 (1908).

Registry No.—I, 21473-40-5; II, 21473-20-1; III, 21473-21-2; IV, 21473-22-3; V, 21473-41-6; VI, 5564-91-0; VII, 21473-42-7; VIII, 4401-71-2; IX, 21472-93-5; X, 21472-94-6; XI, 2140-69-4; XIII, 21473-43-8; XV, 14985-34-3; dicyclohexylcarbodimide, 53-87-50; thymine, 65-71-4; uracil, 66-22-8; thymidine, 50-88-4; uridine, 58-96-8.

Hydrodimerization of Acrylic Acid by Sodium Amalgam

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Received April 4, 1969

Electrolytic hydrodimerization of unsaturated acids was reported by Wilson and Wilson.[1] They have shown that sorbic and cinnamic acids can undergo a hydrogenative dimerization to produce a mixture of isomeric saturated dicarboxylic acids.[1] Being conjugated acids, the reduction potentials of these compounds are much lower than that of a proton. In acrylic acid (AA), however, the double bond is not so easily reduced, and one would expect hydrogen evolution or reduction to propionic acid. This is indeed the case when electrolysis of acrylic acid is carried out in aqueous solution or in an ether solvent.

(1) C. I. Wilson and K. B. Wilson, *Trans. Electrochem. Soc.*, **80**, 139 (1941); **84**, 153 (1943).