α,β-Unsaturated Lactones. I. Condensation of 5-Bromo-2(5*H*)-furanones with Adenine and Uracil Derivatives[1]

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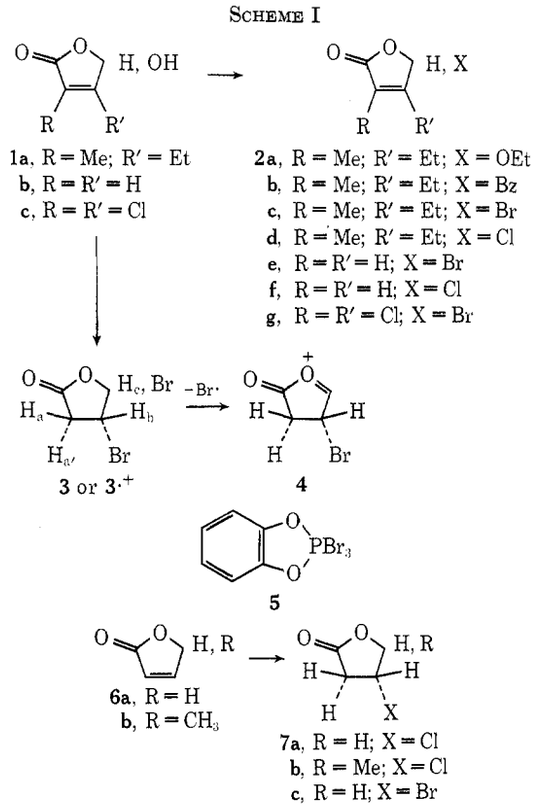
The syntheses of some 5-(pyrimidin-1-yl)- and 5-(purin-9-yl)-2(5*H*)-furanone derivatives, which are nonsugar nucleoside analogs of potential biological interest, are described. 5-Bromo-3-methyl-4-ethyl-2(5*H*)-furanone (**2c**) and its 3,4-unsubstituted and -dichloro analogs **2e** and **2g** were synthesized from the corresponding 5-hydroxy-2(5*H*)-furanone derivatives. Using the Hilbert–Johnson procedure, reaction of 2,4-dimethoxypyrimidine with **2c** and **2e** gave 4-methoxypyrimidinyl intermediates which were hydrolyzed to 5-(uracil-1-yl)-4-ethyl-3-methyl-2(5*H*)-furanone (**9a**) and the unsubstituted analog **9b** in good yields. In the dichlorofuranone series, the pyrimidinyl intermediate **8c**, but not the uracilyl analog **9c**, was prepared. Alkylation of adenine with 5-bromofuranone **2c** in DMF containing K_2CO_3 gave 5-(6-amino-9*H*-purin-9-yl)-4-ethyl-3-methyl-2(5*H*)-furanone (**11**) in 22% yield, together with an isomeric product (yield 6%). The proposed structure for the isomer was a tricyclic adenine derivative (**12a**), which contains a diazepine ring. It could be prepared in higher yield by changing the reaction solvent to pyridine. Isomer **12a** was chlorinated with $SOCl_2$ to the 7-chlorodiazepino analog **12b**, which was converted into 7-methoxy and -ethoxy analogs **12c** and **12d**. Uv, ir, mass spectra, pmr, and L1210 screening data are reported and discussed.

In the past decade, it has been demonstrated that certain five- and six-membered α,β-unsaturated lactone derivatives possess, in addition to other pharmacological properties,[4] tumor-inhibitory activity.[5-8] This laboratory was interested in the synthesis and antitumor properties of nonsugar nucleoside analogs where an α,β-unsaturated γ-lactone was substituted for the sugar moiety of nucleosides. The present paper describes the preparation of 5-(uracil-1-yl)-2(5*H*)-furanone (**9b**)[9] and its 4-ethyl-3-methyl analog **9a**, and 5-(6-amino-9*H*-purin-9-yl)-4-ethyl-3-methyl-2(5*H*)-furanone (**11**) and its nonlactonic isomer **12a** (see Schemes II and III). The mycotoxin 5-acetamido-2(5*H*)-furanone[10] is a recently synthesized simple analog of the pyrimidinyl furanone **9b**.

The first part of this study involved the preparation of known and unknown 5-bromofuranones as the desired alkylating agents for the purines and pyrimidines. Three types of furanone moieties were investigated, *i.e.*, where the carbon–carbon double bond was unsubstituted or substituted with alkyl or chloro groups (Scheme I). The obvious precursors of the 5-bromofuranones were the 5-hydroxyfuranones. It should be noted that these derivatives can exist in two open tautomeric forms, *i.e.*, *cis*- and *trans*-β-formylacrylic acid. The lactol tautomer, however, has been established as the predominant form under a variety of conditions.[11-13] As would be expected in reactions involving the hydroxy hemiacetal group, hydroxyfuranones and monosaccharides react similarly. This is exemplified by reactions of the known 4-ethyl-3-methyl-5-hydroxy-2(5*H*)-furanone (**1a**), which was obtained in good yield by the method of Schreiber and Wermuth.[12] Under sugar acetalization conditions,

SCHEME I



(1) (a) Presented in part to the Division of Organic Chemistry at the 160th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1970. (b) Preliminary publication: *Tetrahedron Lett.*, 667 (1970). (c) Taken in part from the Ph.D. Thesis of I. L. D., University of Connecticut, 1971. (d) This investigation was supported in part by funds from the University of Connecticut Research Foundation and The National Cancer Institute, National Institutes of Health, U. S. Public Health Service (Grant No. CA 10316).

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(4) Leading references to the extensive literature on the biological activity of unsaturated lactones are given in the following: (a) L. J. Haynes, *Quart. Rev., Chem. Soc.*, **2**, 46 (1948); (b) N. Hellstrom, *Acta Agr. Scand.*, **8**, 285 (1958); (c) K. H. Chemnitus, *Arzneim.-Forsch.*, **11**, 277 (1961); (d) F. Dickens and H. E. H. Jones, *Brit. J. Cancer*, **15**, 85 (1961); (e) *ibid.*, **19**, 392 (1965).

(5) F. Dickens and H. E. H. Jones, *Brit. J. Cancer*, **17**, 100 (1963).

(6) (a) S. M. Kupchan, R. J. Hemingway, and J. C. Hemingway, *J. Org. Chem.*, **34**, 3894 (1969); (b) S. M. Kupchan, M. A. Eakin, and A. M. Thomas, *J. Med. Chem.*, **14**, 1147 (1971), and references cited therein.

(7) M. Semonsky, W. Rockova, V. Zikan, B. Kakac, and V. Jelinek, *Collect. Czech. Chem. Commun.*, **28**, 377 (1963).

(8) V. Zikan, M. Semonsky, and V. Jelinek, *Collect. Czech. Chem. Commun.*, **34**, 2157 (1969).

(9) An alternate name for compound **9b**, which is preferred by Chemical Abstracts Service, is 1-(2,5-dihydro-5-oxo-2-furyl)uracil. This nomenclature would also be applicable to analogs **9a**, **8a**, **8b**, and **8c**.

(10) S. G. Yates in "Microbial Toxins," S. Kadis, A. Ciegler, and S. J. Ajli, Ed., Academic Press, New York, N. Y., 1971, pp 191–206, and references cited therein.

(11) D. T. Mowry, *J. Amer. Chem. Soc.*, **72**, 2535 (1950).

(12) J. Schreiber and C. G. Wermuth, *Bull. Soc. Chim. Fr.*, **8**, 2242 (1965).

(13) S. H. Schroeter, R. Appel, R. Brammer, and G. O. Schenck, *Justus Liebigs Ann. Chem.*, **697**, 42 (1966).

1a gave solely the 5-ethoxyfuranone **2a**.[12] We found that reaction of **1a** with benzoyl chloride in pyridine gave the 5 benzoate **2b**. On treatment of **1a** with HBr in glacial acetic acid, a theoretical yield of the 5-bromofuranone **2c** was obtained. The chloro analog **2d** was prepared by the action of titanium tetrachloride on **1a**.

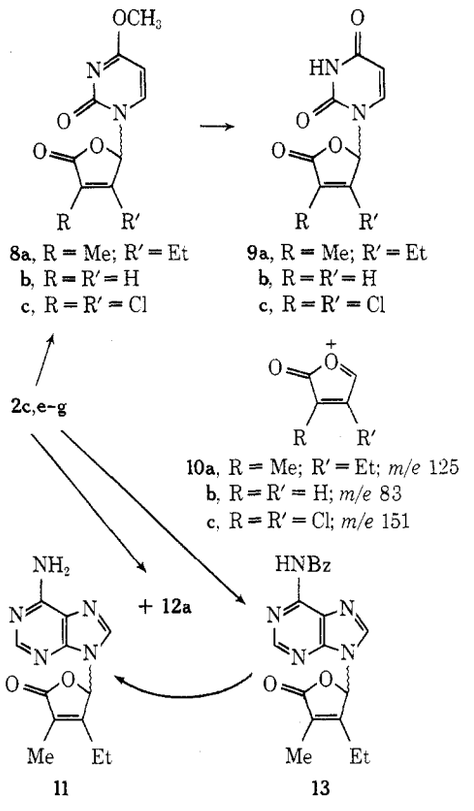
5-Hydroxy-2(5*H*)-furanone[14] has been synthesized in two steps from furfural:[15,16] dye-sensitized photooxygenation of a furfural–ethanol mixture to 5-ethoxy-2(5*H*)-furanone followed by acid hydrolysis of the 5-ethoxy analog to **1b**. In our study, using a modified procedure, photolysis of furfural was rapid in the presence of excess oxygen, and 5-hydroxyfuranone **1b** (not the ethoxy analog) was obtained in one step (yield 43%). Reaction of **1b** with HBr in acetic acid failed to give 5-bromo-2(5*H*)-furanone (**2e**), which had previously been prepared by Elming and Clauson-Kaas[17] using another method. Upon work-up of the reaction, a colorless, HBr-evolving liquid was obtained. The ir, pmr, and mass spectral data suggested that the liquid consisted mostly of *cis*- and *trans*-3,4-dibromobutanolide (**3**, Scheme I). No attempt was made to isolate the isomers **3**. The ir spectrum of the mixture **3** showed lactonic carbonyl absorption at 1825 cm^{-1}. In recent studies on the reaction of hydrogen halides with α,β-unsaturated lactones, Ducher and Michet[18] found that preferential reaction occurred with the conjugated system. Buten-2-olide (**6a**) and β-angelica lactone (**6b**) reacted with HCl to give the β-chlorolactones **7a**[18a] and **7b** (cis and trans isomers),[18b] respectively. Reaction of **6a** with HBr gave the β-bromolactone **7c**.[18a] The pmr data of **7c** reported in deuterated acetone had two multiplet centers due to the methylene protons (δ 3.10) and H_β (δ 4.78). These values compared closely to the corresponding values for protons a, a′ (δ 3.13), and b (δ 4.85) of diastereoisomers **3**. The mass spectral data of **3** showed no peak at *m/e* 242 for the molecular ion $3\cdot^+$. However, major even-electron ion peaks were detected, among them the peak at *m/e* 163 due to the [M − Br] ion **4**.

Some exclusion of the formation of addition products **3** was avoided when catecholphosphorus tribromide (**5**)[19] was used as the brominating agent of **1b**. Reaction of 5-hydroxyfuranone **1b** with **5** in methylene chloride gave a crude product containing the 5-bromofuranone **2e** and the addition products **3**. After purification of the crude product, the desired monobromide was obtained in yields that varied from 10 to 20%.

5-Bromo-3,4-dichloro-2(5*H*)-furanone (**2g**) was prepared in 55% yield by bromination of mucochloric acid (**1c**) using the tribromide **5**. When HBr in glacial acetic acid was used as the brominating agent of **1c**, different results were obtained. In addition to the formation of the major monobromo product, a small amount of displacement of the 3- or 4-chloro atom with bromine occurred, producing either of two proposed structures, 4,5-dibromo-3-chlorofuranone or its 3,5-dibromo isomer. This new dibromofuranone was not detected in the **2g**-containing mixture, but its presence was proved in the 2,4-dimethoxypyrimidine-alkylation product discussed below.

The Hilbert–Johnson procedure[20] for the syntheses of 1-substituted uracils was used to prepare the uracilyl furanones (Scheme II). Reaction of 5-bromofuranone

SCHEME II



2c with 2,4-dimethoxypyrimidine[20a] in methylene chloride for 7 days at room temperature gave the 4-methoxypyrimidine derivative **8a** (yield 75%). On treatment of an aqueous ethanolic solution of **8a** with 1 *N* HCl, 5-(uracil-1-yl)-4-ethyl-3-methyl-2(5*H*)-furanone (**9a**) was obtained in high yield. The unsubstituted 5-bromofuranone **2e** alkylated 2,4-dimethoxypyrimidine more rapidly than the dialkylated analog **2c**. The 4-methoxy derivative **8b** was obtained in 1 day (yield 53%). Derivative **8b** was also prepared from the 5-chlorofuranone **2f** in 29% yield under more strenuous conditions. Acid hydrolysis of the 4-methoxy compound **8b** gave 5-(uracil-1-yl)-2(5*H*)-furanone (**9b**) in 58% yield. Alkylation of dimethoxypyrimidine with 5-bromo-3,4-dichlorofuranone **2c** gave the 4-methoxy compound **8c** in only 23% yield. The yield of **8c** could not be improved. Preparation of the uracil analog **9c** from **8c** was not achieved because of the ease of N–C bond cleavage in these compounds in aqueous acid. Thus, the reaction of **8c** in dilute acid gave a mixture of products containing predominantly uracil and mucochloric acid (**1c**) as detected by tlc, ir, and uv. Cleavage of the N–C bond also oc-

(14) H. Fecht, *Ber. Deut. Chem. Ges.*, **38**, 1272 (1905).

(15) (a) G. O. Schenck, *Justus Liebigs Ann. Chem.*, **584**, 156 (1953); (b) K. Gollnick and G. O. Schenck in "1,4-Cycloaddition Reactions," J. Hammer, Ed., Academic Press, New York, N. Y., 1967, p 255.

(16) M. D. Grove, S. G. Yates, W. N. Tallent, J. J. Ellis, I. A. Wolff, N. R. Kosuri, and R. E. Nichols, *J. Agr. Food Chem.*, **18**, 734 (1970).

(17) N. Elming and N. Clauson-Kaas, *Acta Chem. Scand.*, **6**, 565 (1952).

(18) (a) S. Ducher and A. Michet, *C. R. Acad. Sci., Ser. C*, **264**, 597 (1967); (b) *ibid.*, **267**, 1617 (1969).

(19) (a) H. Gross and U. Karsch, *J. Prakt. Chem.*, **29**, 315 (1965); (b) I. Farkas, M. Menyhart, H. Bognar, and H. Gross, *Chem. Ber.*, **98**, 1419 (1965).

(20) (a) G. E. Hilbert and T. B. Johnson, *J. Amer. Chem. Soc.*, **52**, 2001, 4489 (1930); (b) J. Phiml and H. Prystas, *Advan. Heterocycl. Chem.*, **8**, 115 (1967), a recent review.

TABLE I

PROTON MAGNETIC RESONANCE DATA OF N HETEROCYCLES

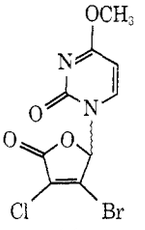
Compd	Solvent	Chemical shift, δ (J, Hz)			
		$C_{5(7)}$ H[a]	$C_{3(9)}$ CH_3(H)	$C_{4(8)}$ C_2H_5(H)	Others
8a	$CDCl_3$	7.36 (b s)	1.97 (s)	2.38 (m),[b] 1.14 (t, 7.5)	7.12, 6.00;[c] 4.20[d]
8b	$CDCl_3$	7.36 (t, 1.8)	6.47 (dd, 5.5, 1.3)	7.56 (dd, 5.5, 1.8)	7.32, 6.00;[c] 4.81[d]
8c	DMSO-d_6	7.41 (s)			8.28, 6.34;[c] 3.99[d]
9a	P-d_5–D_2O	7.36 (b s)	1.97 (s)	2.25 (m),[b] 1.05 (t, 7.5)	7.50, 6.00[c]
9b	DMSO-d_6	7.27 (t, 2.0)	6.77 (dd, 6, 2)	7.94 (dd, 6, 2)	7.55, 5.80[c]
11	TFA	7.36 (b s)	2.13 (s)	2.54 (m),[b] 1.18 (t, 7.5)	8.68, 8.63[e]
12a	TFA	6.54 (b s)	2.13 (s)	2.47, 1.28 (q, t, 9)	9.00, 8.95[e]
12c	$CDCl_3$	6.56 (b s)	1.97 (s)	2.50, 1.30 (q, t, 8)	8.95, 8.53;[e] 11.50;[f] 3.37[d]
13	P-d_5	7.25 (b s)	1.92 (s)	2.28 (m),[b] 0.92 (t, 7.5)	9.03, 8.88;[e] 12.48;[f] 8.33, 7.49[g]

[a] The broad peak width at half-height ranged from 3.5 to 6 Hz. [b] Multiplet spin decoupled: **8a**, $\Delta\gamma_{AB}$ = 21.1 Hz, J_{AB} = 13 Hz; **9a**, $\Delta\gamma_{AB}$ = 20.2 Hz, J_{AB} = 14 Hz; **11**, $\Delta\gamma_{AB}$ = 28.3 Hz, J_{AB} = 15 Hz; **13**, $\Delta\gamma_{AB}$ = 23.1 Hz, J_{AB} = 14 Hz. For compounds **11** and **13**, the values cited in ref 1b have been corrected. [c] Pyrimidine H-6 and H-5. [d] OCH_3. [e] Purine H-8 and H-2. [f] NH proton, disappeared on deuteration. [g] Aryl protons.

curred when the uracil derivative **9b** was boiled in water for 15 hr. Tlc analysis of the reaction mixture revealed two uv-absorbing spots of equal intensity corresponding to uracil and analog **9b**.

The uv spectra of the five pyrimidinylfuranones in stable solutions were similar to those of their respective 1-substituted 4-methoxypyrimidine and -uracil analogs,[21,22] except for small changes due to the chromophoric furanone moiety. The ir data of pyrimidines **8a**, **8b**, **8c**, and **9b** showed characteristic lactonic carbonyl absorption in the range 1762–1777 cm^{-1}.[13,14,23] From the mass spectral data of these derivatives, the furanone moieties were identifiable as abundant peaks due to the appropriate oxonium lactone ion, *i.e.*, **10a**, **10b**, or **10c** (Scheme II). These ions arose from their respective molecular ions *via* an α-cleavage process, which is a common fragmentation route of furanone derivatives reported here and in the literature.[24a] The pmr data (Table I) for derivatives **8a**, **8b**, **8c**, **9a**, and **9b** were consistent with these structures. Interestingly, the methylene protons of the 4-ethyl group in analogs **8a** and **9a** appeared as a multiplet.[25]

As discussed above, reaction of mucochloric acid (**1c**) with HBr in glacial acetic acid gave a mixture containing products 5-bromofuranone **2g** and 3,5- (or 4,5-) dibromo-4- (or 3-) chlorofuranone. The presence of the latter compound in the mixture was implied from physical data on the Hilbert–Johnson product. Reaction of 2,4-dimethoxypyrimidine with the (HBr–acetic acid + **1c**) product gave a mixture of the dichlorofuranone **8c** and a bromo chloro analog with proposed structures **14** or **15**. The mass spectrum of the mixture



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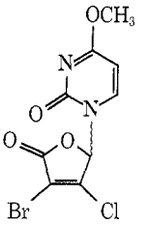

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exhibited a small peak at *m/e* 320 (1.5%) that was attributed to the molecular ion of the product **14** (or **15**). From the elemental analysis the amount of bromo chloro product **14** (or **15**) present in the mixture was calculated to be 12.7%, the remainder being the dichloro product **8c**. From their work on dihalogenofuranones, Wasserman and Precopio[26] have proposed that the reaction of nucleophiles occurs preferentially at the 4 position in all dihalogenofuranones that are exclusively in the cyclic form. By analogy, therefore, the 4-bromofuranone derivative **14** would be favored as a replacement product over the 4-chloro analog **15**.

Alkylations of adenine under basic conditions have been reported to give the 7- or 9-substituted product as the predominating isomer.[27,28] The reaction of adenine with 5-bromofuranone **2c** in DMF containing K_2CO_3 gave 5-(6-amino-9*H*-purin-9-yl)-4-ethyl-3-methyl-2(5*H*)-furanone (**11**, yield 22%, Scheme II). In addition to **11**, an isomeric product **12a** was also isolated in 6% yield. The structure of the furanone compound **11** was confirmed as follows. The ir spectrum showed a sharp band at 1773 cm^{-1} due to the lactonic carbonyl. Compound **11** was established as the 9-purinyl and not the 7, 1, or 3 isomer from the uv data.[29] The pmr data for derivative **11** are listed in Table I and showed signals due to the H_5 proton, the methyl and ethyl groups, and the adenine moiety. The chemical shift difference for the 2 and 8 position purine protons in DMSO-d_6 solution has been used to predict substitution products of the purine ring.[29] In this regard the Δδ of 6 Hz for **11** is consistent with

(21) D. Shugar and J. J. Fox, *Biochim. Biophys. Acta*, **9**, 199 (1951).

(22) J. J. Fox and I. Wempen, *Advan. Carbohyd. Chem.*, **14**, 283 (1959).

(23) J. F. Grove and H. A. Willis, *J. Chem. Soc.*, 877 (1951).

(24) (a) Q. N. Porter and J. Baldos, "Mass Spectrometry of Heterocyclic Compounds," Wiley-Interscience, New York, N. Y., 1971, pp 195–198; (b) pp 484–485; (c) pp 313–315.

(25) The protons of the 4-ethyl group in pyrimidine derivatives **8a** and **9a** as well as in purine analogs **11** and **13** constitute an ABX_3 spin system (Table I). In these compounds the methyl protons (X_3) appeared as a well-resolved triplet, $J_{AX,BX}$ = 7.5 Hz, whereas the methylene protons (AB) showed up as a multiplet having five to six visible lines. Double irradiation of the X resonance position in each compound reduced the multiplet having five to six visible lines. Double irradiation of the X resonance position in each compound reduced the multiplet to an AB quartet from which $\Delta\gamma_{AB}$ and J_{AB} were obtained. The main factors that are considered responsible for the large nonequivalence effect in these compounds are the magnetic anisotropy associated with the N heterocycle and the intrinsic nonequivalence of the C_4 methylene adjacent to the chiral C_5–N bond. Preferred conformer populations due to restricted rotation about the C_4 methylene bond may also contribute. In comparison to the above data, the pmr spectra of 4-ethylfuranones **1a**,[12] **2a**,[12] **2b**, **2c**, and **2d** displayed an A_2 pattern for the methylene protons indicating their apparent equivalence.

(26) H. H. Wasserman and F. M. Precopio, *J. Amer. Chem. Soc.*, **76**, 1242 (1954), and references cited therein.

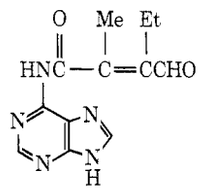
(27) (a) N. J. Leonard and J. A. Deyrup, *J. Amer. Chem. Soc.*, **84**, 2148 (1962); (b) N. J. Leonard and T. Fujii, *ibid.*, **85**, 3719 (1963); (c) M. Rasmussen and N. J. Leonard, *ibid.*, **89**, 5439 (1967).

(28) (a) J. A. Montgomery and H. J. Thomas, *J. Heterocycl. Chem.*, **1**, 115 (1964); (b) *J. Amer. Chem. Soc.*, **87**, 5442 (1965).

(29) (a) L. B. Townsend, R. K. Robins, R. N. Loeppky, and N. J. Leonard, *J. Amer. Chem. Soc.*, **86**, 5420 (1964); (b) K. R. Darnall and L. B. Townsend, *J. Heterocycl. Chem.*, **3**, 371 (1966).

other 9-substituted adenines. The adenyl furanone **11** was also obtained by the mercury salt method, which has been used to synthesize numerous adenine nucleosides. Condensation of 6-benzamidochloromercuripurine with the 5-bromofuranone **2c** (in refluxing toluene) gave 5-(6-benzamido-9*H*-purin-9-yl)-4-ethyl-3-methyl-2(5*H*)-furanone (**13**, yield 20%, Scheme II). Debenzoylation of **13** with picric acid in methanol gave the picrate of **11**, which was converted into the free base.

The Tricyclic Purine Side Product 12a.—As mentioned above, the reaction of adenine and the bromofuranone **2c** in basic DMF yielded furanone **11** and a small quantity of an isomer. Fortunately, it was found that the isomer could be prepared in higher yield (20–40%) from adenine and **2c** merely by changing the solvent to pyridine and omitting the K_2CO_3. This study was carried out in order to further explore the chemical reactivities of the bromofuranone with adenine. The 1-, 3- or 7-adenyl furanone isomers of **11** were excluded as structures of isomer **12a** by the following data: (1) the absence of the lactonic carbonyl band in the ir; (2) the absence of the lactonic oxonium ion **10a** in the mass spectrum; (3) the presence in the uv spectrum of a maximum at 290 nm in neutral, acid, and basic solutions; and (4) a pK_a[1] of 1.98. Furthermore, isomer **12a** was not an open derivative, such as the amido or aldimine isomers **16** and **17**, because an



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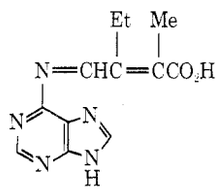

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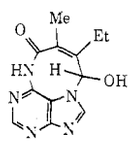
aldehydo or carboxyl group was not detected by either chemical tests[30] or ir and pmr data.

In a preliminary experiment isomer **12a** was found to hydrolyze readily in boiling 1 *N* sodium hydroxide to adenine and unknown product(s). However, certain data given below established the isomer as a tricyclic purine with 8-ethyl-7-hydroxy-9-methyl-3*H*-[1,3]diazepino[2,1-*i*]purin-10(7*H*)-one (**12a**, Scheme III) as the favored structure.[31]

Owing to the low solubility of **12a**, the only suitable solvent for the pmr was TFA. Except for the imino and exchangeable hydroxy protons, all protons of the diazepino structure **12a** were accounted for, *i.e.*, purine protons, 9-methyl, 8-ethyl, and aminal-like proton H_7 (Table I). The chemical shift values of these protons were similar to those for the purine, methyl, ethyl, and H_5 protons of **11**. In the ir, the carbonyl of the cyclic

(30) *E.g.*, compound **12a** was insoluble in sodium bicarbonate, did not form phenylhydrazones, and was not reduced with sodium borohydride.

(31) The chemical and physical data do not unequivocally support the 1 to N[6] structure **12a** for the isomer. The possibility that the isomer is the diazacino compound I, which contains the hitherto unknown 7 to N[6] cyclic system, could not be ruled out.



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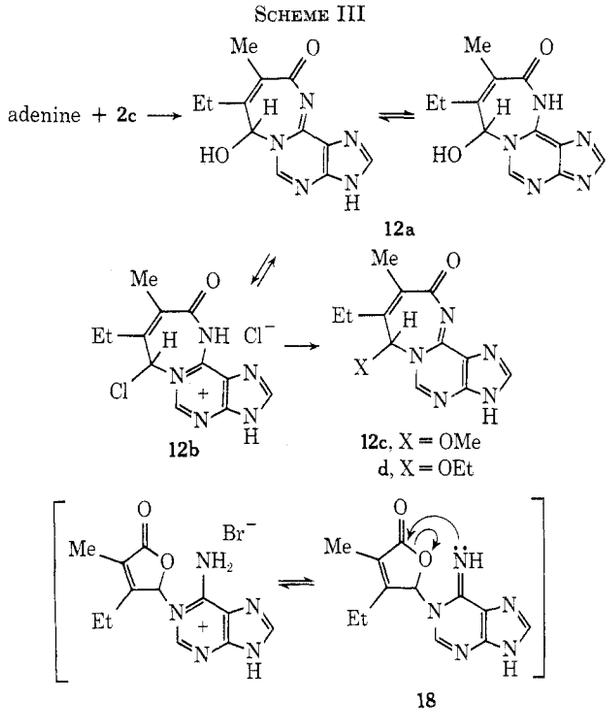
SCHEME III



amide moiety of **12a** absorbed at 1712 cm^{-1}. High-resolution mass spectral data also supported structure **12a**, as discussed below.

Consistent with structure **12a**, the hydroxy group underwent certain replacement reactions (Scheme III). On treating **12a** with thionyl chloride, 7-chloro-8-ethyl-3,7,10-tetrahydro-9-methyl-10-oxo[1,3]diazepino-[2,1-*i*]purin-6-ium chloride (**12b**) was obtained (yield 88%). This derivative was readily hydrolyzed back to compound **12a**. The 7-chloro derivative **12b**, upon treatment with anhydrous base in absolute methanol or ethanol, was converted to the respective 7-alkoxy derivative **12c** or **12d**. In the pmr spectrum of the methoxy analog **12c** ($CDCl_3$), all protons were accounted for (Table I). On the addition of D_2O, the imino proton (δ 11.50) disappeared.

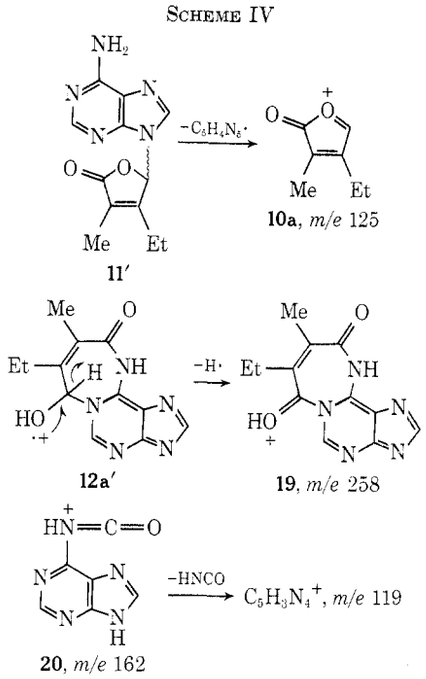
Mechanism of Formation of 12a.—$N^6 \rightarrow 1$ cyclization of N^6-substituted adenines is by far the most numerous type of ring closure involving the adenine moiety.[32] It should be noted that, although a ring closure of N-7 was also possible, only closure involving N-1 has been observed. There is only one example of a cyclization proceeding $1 \rightarrow N^6$. Chheda and Hall[33] found that alkylation of 9-methyladenine with *tert*-butyl bromoacetate gave *tert*-butyl 6-imino-9-methylpurine-1-acetate. On treatment of this 1,9-disubstituted derivative with alkali, instantaneous intramolecular acylation to 3-methyl-3*H*-imidazo[2,1-*i*]purin-8(7*H*)-one occurred. A possible mechanism for the formation of the diazepino derivative **12a** also may involve an intramolecular $1 \rightarrow N^6$ cyclization as shown in Scheme III. Hence, the first step in the formation of **12a** would be the alkylation of the 1 nitrogen of adenine by the bromofuranone **2c**, yielding the intermediate 6-imino purinyl furanone **18**. The carbonyl end of the lactone moiety then aminoacylates *in situ*, giving the cyclic amide product **12a**.

(32) N. J. Leonard and R. A. Swaringen, *J. Org. Chem.*, **34**, 3814 (1969), and references cited therein.

(33) G. B. Chheda and R. H. Hall, *J. Org. Chem.*, **34**, 3492 (1969).

Mass Spectra of Isomers 11 and 12a.—The low-resolution mass spectra of the diazepino derivative **12a** compared to that of its isomer **11** exhibited peaks due to different and common ions. With regard to the high mass common ions, which are listed in Table II, both compounds had peaks at *m/e* 259 (M), 258, 230, 202, 136, 135, 108, and 81. Peaks at *m/e* 136–81 are associated with the mass spectra of adenine and some of its derivatives. The peak at *m/e* 135 is attributable to the molecular ion adenine.[24b,34] The spectra of **11** and **12a** did show notable differences. For example, the spectrum of **11** (but not **12a**) contained a peak at *m/e* 125 due to the oxonium lactone ion **10a**, which resulted from N–C bond cleavage in molecular ion **11′** (Scheme IV). The low-resolution mass spectrum

SCHEME IV



of the diazepino derivative **12a** exhibited many peaks not present in isomer **11**, *e.g.*, at *m/e* 241, 229, 216, 162, and 119. In addition two peaks common to both compounds at *m/e* 258 and 230 had significantly greater abundances in compound **12a**. In isomers **11** and **12a**, the peaks at *m/e* 230 were attributable to [M − C_2H_5] and/or [M − CHO] ions (metastable 204.3). The high-resolution mass spectrum of **12a** was determined in order to find the exact mass of fragment ions (see Experimental Section). Most peaks from **12a** are associated with the fragmentation of the diazepino ring. As in the above low-resolution mass spectrum of **12a**, chief fragmentation ions were at *m/e* 258 [M − 1] and 230 [M − 29]. The [M − 1] ion probably resulted from cleavage of the hydrogen atom α to the 7-hydroxy group of molecular ion **12a′**, giving cation **19** (Scheme IV). Two isobaric species contributed to the ion at *m/e* [M − 29]. This ion was due to both the loss of C_2H_5 (100%) and CHO (20%). The loss of ethyl may have occurred in a single step or in a two-step process [M − H − C_2H_4]. The cation at *m/e* 244 was due to the [M − CH_3] ion. The alcoholic nature of **12a** was established by the odd-electron ion at *m/e* 241 [M − H_2O] and the strong *m/e* 18 peak. The very abundant peaks at *m/e* 162 and 119 supported the cyclic amide structure of **12a**. These peaks are associated with the following pathway.

$$M\cdot^{+} \xrightarrow[x \text{ steps}]{-C_6H_8O} C_6H_4N_5O^{+},\ m/e\ 162 \xrightarrow[m^*]{-HNCO} C_5H_3N_4^{+},\ m/e\ 119$$

A metastable peak at *m/e* 87.4 (low-resolution mass spectrum) confirmed the fragmentation *m/e* 162 → 119. Structure **20** is proposed for the cation at *m/e* 162. The loss of HNCO from other ionic fragments may be involved in the formation of ions at *m/e* 215 and 199. Other cyclic amides commonly lose HNCO, *e.g.*, 2-pyrrolidone.[24c]

Screening Data.—It was hoped that the furanone derivatives would initiate a new series of compounds with antitumor activity. Preliminary L1210 screening data on a few of these derivatives, including the diazepino compound **12a**, have been obtained. Six mice, infected with L1210 lymphoid leukemia, were treated with a single dose of the drug.[35] The uracilyl, diazepino, and adenyl derivatives **8a**, **12a**, and **11** exhibited a weak positive effect on the mean survival time of mice at the 400-mg dose having *T/C* values of 102, 103, and 113%, respectively. The uracilyl analog **9b**, which bore the most chemically reactive furanone moiety, was toxic at the 100-mg dose to five out of six mice, but had a weak positive effect on the surviving mouse (*T/C* 116%). We are currently synthesizing and testing other furanone derivatives to determine if activity can be enhanced.

Experimental Section

General.—Melting points were determined on a Thomas-Hoover apparatus in capillaries and are corrected. Infrared (ir) spectra were obtained using a Beckman Microspec or a Perkin-Elmer Model 21 (P-E) spectrophotometer. Ultraviolet (uv) spectra were determined on a Cary 15 spectrophotometer. The apparent pK_a[1] of 1.98 for compound **12a** was determined spectrophotometrically using buffers and techniques previously employed.[21,22] Elemental analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich. Proton magnetic resonance (pmr) spectra were determined using a Varian A-60 spectrometer. Spin–spin decoupling studies were carried out using a Jeol JNMC-60HL spectrometer.[36] Chemical shifts (δ) are given in parts per million downfield from internal TMS. The low-resolution mass spectra were obtained with an AEI MS-12 spectrometer using solid probe introduction. High-resolution mass spectra were obtained with a CEC 21-110B double-focusing mass spectrometer,[37a] except in the case of compounds **12c** and **12d**, which were measured on an AEI MS902 spectrometer.[37b] They were all determined at 70 eV. Thin layer chromatography (tlc) was carried out on Eastman silica gel plates (6060) using the following solvent systems: (1) cyclohexane–ethyl acetate (8:2); (2) acetone; (3) ethyl acetate; (4) benzene; (5) acetone–chloroform–water (5:1:1). The products were visualized by uv absorption and/or iodine vapor. Column chromatography was carried out using J. T. Baker silica gel

(34) S. Hanessian, D. C. DeJongh, and J. A. McCloskey, *Biochim. Biophys. Acta*, **117**, 480 (1966).

(35) Assays were performed under the auspices of the Drug Development Branch, National Cancer Institute, National Institutes of Health, using procedures described in *Cancer Chemother. Rep.*, **25**, 1 (1962).

(36) These studies were carried out through the courtesy of Jeol Inc., Cranwood, N. J.

(37) The high-resolution mass spectra were obtained by support of the Division of Research Resources, National Institutes of Health, U. S. Public Health Service; (a) A. D. Little, Cambridge, Mass.; (b) Battelle Columbus Laboratories, Columbus, Ohio.

(3405). Paper electrophoretic data was obtained using a Kenco Model 50 apparatus with an organic pH 3.3 buffer (K-100). The furfural photochemical oxidation was carried out using a 650-W lamp (Sylvania Sungun, DWY), which was contained in an Hanovia quartz immersion well in a 1-l. reaction vessel bearing a circular filter disk (Ace Company) through which O_2 was passed.

Furfural was distilled at 20–25 mm immediately before use in the photolysis. DMF was dried over P_2O_5, distilled at 15 mm, and stored over molecular sieve. Pyridine was dried over BaO and then distilled. Thionyl chloride was distilled according to the procedure of Rigby.[38] Using the method of Schreiber and Wermuth,[12] 4-ethyl-3-methyl-5-hydroxy-2(5*H*)-furanone (**1a**, mp 50°) was prepared in comparable yield and gave identical pmr and ir data with those reported. 5-Hydroxy-2(5*H*)-furanone (**1b**, 20 mmol) was allowed to react with $SOCl_2$ (56 mmol) to give 5-chlorofuranone **2f** in 30% yield (lit.[18] 45%): pmr (CCl_4) δ 6.73 (t, 1, $J_{3,5} = J_{4,5} = 1.3$ Hz, C_5 H), 7.70 (dd, 1, $J_{3,4} = 5.5$, $J_{4,5} = 1.5$ Hz, C_4 H), 6.37 (dd, 1, $J_{3,4} = 5.5$, $J_{4,5} = 1.3$ Hz, C_3 H). Pyrocatecholphosphorus tribromide (**5**, 100 g),[19] because of its reactivity, was dissolved in methylene chloride and divided into 25-g batches. The solvent was removed and the solid tribromide was kept in the freezer until use.

5-Ethoxy-4-ethyl-3-methyl-2(5*H*)-furanone (2a).—Schreiber and Wermuth[12] prepared this compound by another method. Furanone **1a** (0.5 g) was dissolved in absolute ethanol (30 ml) containing HCl gas. The reaction mixture was boiled for 0.5 hr and then cooled. The ethanol was evaporated and the residue was azeotroped with benzene to remove the HCl. The liquid weighed 0.55 g and contained only product **2a**. The pmr data (CCl_4) were identical with those reported. Using tlc solvent 1, **2a** had R_f 0.42 (**1a**, R_f 0.15); ir (CCl_4) 1754 (s), 1672 cm^{-1} (w) (lit.[12] ir 1785, 1700 cm^{-1}).

5-Benzoyl-4-ethyl-3-methyl-2(5*H*)-furanone (2b).—Furanone **1a** (2 g, 14.1 mmol) was dissolved in dry pyridine (50 ml) and the solution was cooled to 0°. Benzoyl chloride (1.9 ml, 14.8 mmol) was added. Pyridine hydrochloride precipitated. The reaction was allowed to stand overnight at room temperature and then ethanol (2 ml) was added. The pyridine was evaporated, leaving a syrup. Residual pyridine was removed from the syrup by evaporation with 50% ethanol. The residue was dissolved in methylene chloride and dried ($MgSO_4$). The solvent was evaporated and the residue was crystallized from an ether–petroleum ether (bp 30–60°) mixture. White crystals were obtained: 2.6 g (75%); mp 69–71°; mass spectrum *m/e* (rel intensity) 234 (14). Using tlc solvent 1, **2b** had R_f 0.57 (**1a**, R_f 0.2); ir (CCl_4) 1785 (s, lactone C=O), 1710 (benzoyl C=O), 1695 cm^{-1} (w, C=C); pmr (CCl_4) δ 6.92 (b s, 1, C_5 H), 1.87 (s, 3, C_3 CH_3), 2.45 (q, 2, $-CH_2-$), 1.17 (t, 3, J = 7.5 Hz, CH_3), 7.95 and 7.43 (m, 5, aryl H).

Anal. Calcd for $C_{14}H_{14}O_3$: C, 68.28; H, 5.72. Found: C, 68.23; H, 5.63.

5-Bromo-4-ethyl-3-methyl-2(5*H*)-furanone (2c).—Glacial acetic acid (15 ml) containing HBr gas (40% by weight) was added to a small flask containing **1a** (1 g, 7.04 mmol). The flask was sealed for 5 days at room temperature. The solvent was rotary evaporated at 40° and the residue was azeotroped five times with toluene in order to remove residual HBr. The final product contained only **2c** by tlc (solvent 1, R_f 0.7): pmr (CCl_4) δ 6.79 (b s, 1, C_5 H), 1.90 (s, 3, C_3 CH_3), 2.57 (q, 2, $-CH_2-$), 1.20 (t, 3, J = 7.5 Hz, CH_3).

5-Chloro-4-ethyl-3-methyl-2(5*H*)-furanone (2d).—Furanone **1a** (0.14 g, 0.96 mmol) was dissolved in distilled ethylene dichloride, and a solution of titanium tetrachloride (0.99 mmol) in ethylene dichloride (3 ml) was added. The reaction mixture was refluxed for 5 hr, during which time a white solid precipitated. Methylene chloride and water were added, dissolving the solid. The organic layer was washed with water and dried (Na_2SO_4). The solvent was evaporated, giving a liquid product (yield 84%), which was chromatographically pure by tlc (solvent 1, R_f 0.7): ir (CCl_4, P-E) 1792 (s, C=O), 1686 cm^{-1} (w, C=C); pmr (CCl_4) δ 6.48 (b s, 1, C_5 H), 1.87 (s, 3, C_3 $-CH_3$), 2.57 (q, 2, $-CH_2-$), 1.21 (t, 3, J = 7.5 Hz, CH_3).

5-Hydroxy-2(5*H*)-furanone (1b).—This procedure is a modification of the photooxygenation of furfural as described by Schenck[13,15] and Grove[16] and coworkers. Our procedure gave a different major product, the 5-hydroxy analog **1b** rather than 5-ethoxy-2(5*H*)-furanone.[39]

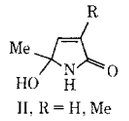
A solution of freshly distilled furfural (90.5 g) in absolute ethanol (850 ml) containing rose bengal (1.3 g)[40] was photolyzed in the presence of a vigorous stream of oxygen. An external ice bath was used to keep the temperature of the reaction between 25 and 32°. The reaction was monitored by removing aliquots and determining the loss of uv absorption at 276 nm. After about 6 hr, a 97% decrease in absorption was observed. The solvent was evaporated and an acidic red syrup was obtained. On the addition of carbon tetrachloride (150 ml), an orange-colored crystalline product (50 g) precipitated and was filtered.[41] Product **1b** was purified on a silica gel column (150 g) using methylene chloride as eluent. The eluate, upon evaporation, gave an almost colorless syrup, which crystallized on addition of chloroform. After recrystallization from chloroform, the yield of **1b** was 43%: mp 56–58° (lit.[18] mp 58–59°); ir (CCl_4) shoulder 1786, 1757 cm^{-1} (s) (lit.[13] ir 1795, 1761 cm^{-1}); mass spectrum *m/e* (rel intensity) 101 (12), 100 (12), 85 (10), 72 (14), 55 (55), 29 (23), 27 (39), 18 (11). The pmr data of **1b** ($CDCl_3$) agreed with those reported by Catala and Defaye.[42]

A. 5-Bromo-2(5*H*)-furanone (2e) *via* Pyrocatecholphosphorus Tribromide (5).—The furanone **1b** (3 g, 30 mmol), dissolved in methylene chloride (20 ml), was placed in a three-necked flask fitted with a condenser and $CaCl_2$ tube. Powdered molecular sieve (3A, 15 g) was added. The suspension was stirred and **5** (12.1 g, 31 mmol) in methylene chloride (20 ml) was added dropwise. The reaction mixture was refluxed for 1.8 hr. (HBr was evolved vigorously near the end of the reaction.) Upon filtration of the reaction mixture, a bright orange filtrate was obtained, which was rapidly washed with 400-ml aliquots of cold, saturated $NaHCO_3$ solution two times and then with water. The organic layer was dried ($MgSO_4$) and evaporated, giving a pale yellow syrup (4.3 g), which was distilled bulb to bulb using a Kugelrohr distilling apparatus and gave a colorless liquid (1.0 g), bp 96–102° (12 mm) [lit.[17] bp 69–70° (0.1 mm)]. The distillate showed two spots at R_f 0.6 and 0.75 (tlc solvent 4) corresponding to product **2e** (92%) and addition products **3** (8%). (The relative per cents of products were determined from pmr integration data.) The yield of **2e** in the mixture was 18%. (The crude product darkens rapidly if not kept under refrigeration.) A pure sample of **2e** was obtained using a silica gel column with cyclohexane–benzene (1:1) as eluent. The ir spectrum of **2e** (CCl_4) exhibited a strong band at 1805 cm^{-1} (C=O, lactone); pmr (CCl_4) δ 7.08 (t, 1, $J_{3,5} = J_{4,5} = 1.3$ Hz, C_5 H), 7.80 (dd, 1, $J_{3,4} = 5.5$, $J_{4,5} = 1.3$ Hz, C_4 H), 6.35 (dd, 1, $J_{3,4} = 5.5$, $J_{3,5} = 1.3$ Hz, C_3 H).

B. Identification of 3,4-Dibromobutanolides 3.—In other preparations of **2e**, the per cent of 1,4-addition products **3** was higher, varying from 10 to 50%, than in the above distillate. Products **3** were isolated as follows. A silica gel column (20 g) was prepared with benzene. A 50% mixture of **2e** and **3** (2.8 g) was dissolved in benzene and applied to the column. Benzene was used as the eluent and 5-ml fractions, which were monitored by tlc, were taken. Fractions 4 and 5 contained mostly compounds **3**. These fractions were combined and gave, after evaporation, a liquid product (1.4 g), ir (CCl_4) 1825 cm^{-1} (s). From pmr integration, the liquid contained 88% of **3** and 12% of **2e**.

(38) W. Rigby, *Chem. Ind. (London)*, **18**, 1508 (1969).

(39) Why the 5-hydroxyfuranone **1b** is the predominant product in our reaction is not clear. However, the presence of **1b** in the photolysis reaction is not wholly unexpected. Recently it has been found that in the photooxygenolysis of 2-methylpyrrole, where intermediates analogous to those in the furan series[13,15] have been proposed, the predominant products are the 5-hydroxylactams II: D. A. Lightner and L. K. Low, *J. Heterocycl. Chem.*, **9**, 167 (1972).



II, R = H, Me

(40) Eosin could be substituted for rose bengal, although the photooxygenation took longer (20 hr, 85% reaction).

(41) The carbon tetrachloride was evaporated from the filtrate and a residue was obtained, which upon distillation gave 1.0 g of 5-ethoxy-2(5*H*)-furanone, bp 95–97° (12–14 mm) [lit.[13] bp 95° (12 mm)]. The pmr data for this derivative were identical with those kindly supplied by Dr. Michael D. Grove, U. S. Department of Agriculture, Agriculture Research Service, Peoria, Ill.

(42) F. Catala and M. J. Defaye, *C. R. Acad. Sci., Ser. C*, 4094 (1964).

The pmr spectrum (CCl_4) exhibited multiplet patterns in three regions (disregarding signals due to **2e**): 391–397 (four peaks), 278–300 (eight peaks), and 180–207 Hz (eight peaks). The relative intensity of absorption in the three regions was 1:1:1.7. Other products in the mixture besides **2e** and **3** have not been ruled out. Fractions 6–8 contained mostly **2e** (purity 97%). On evaporation 1.0 g of liquid product was obtained.

3,4-Dibromobutanolides 3 *via* **HBr–Acetic Acid.**—To furanone **1b** (3 g) was added ethylene dichloride (60 ml) and glacial acetic acid containing HBr gas (40%, 16 ml). The flask was sealed and pressure was applied to the glass stopper to prevent escape of HBr. The reaction mixture was allowed to stand at room temperature for 6 hr. Carbon tetrachloride (150 ml) was added and a yellow oil separated. The layers were washed with cold water and saturated $NaHCO_3$ and again with water. After the organic layer was dried and the solvent was evaporated, a colorless residue (3.4 g) was obtained. Distillation of the residue gave dibromobutanolides **3** [0.88 g, bp 69–76° (0.7 mm)], ir (CCl_4) 1825 cm^{-1} (C=O). The presence of small amounts of other products in this sample was not ruled out. The sample exhibited a single spot (R_f 0.73) in tlc solvent 4. The pmr spectrum (CCl_4) showed multiplets in three regions: 394–400 (five peaks), 287–297 (four peaks), and 186–200 Hz (six peaks); the relative intensity of absorption in the three regions was 1:1:2. In the mass spectrum no parent peak (*m/e* 242) was observed for **3**. Major even-electron ion peaks were present at *m/e* (rel intensity) 163 (100, M − Br), 135 (23), 119 (38), 107 (38). According to the intensity of the P + 2 peaks, each of the ions contained one bromine atom. Butanolides **3** gave off HBr and darkened at room temperature and were more stable under refrigeration.

Method A. 5-Bromo-3,4-dichloro-2(5*H*)-furanone (2g).—A mixture of mucochloric acid (**1c**, 11.9 mmol), powdered molecular sieve (5 g), and methylene chloride (10 ml) was treated with tribromide **5** (14 mmol) in 20 ml of methylene chloride. The mixture was kept at room temperature for 3 hr and worked up as in the preparation of **2e**. The residual liquid (1.8 g) was distilled [111–116° (12 mm)], giving the bromofuranone **2g** in 55% yield, ir (CCl_4) 1815 cm^{-1}, pmr (CCl_4) δ 6.92 (s, C_5 H).

Method B. 2g *via* **HBr–Acetic Acid.**—The acid **1c** (2.97 mmol) was placed in a small flask and about 1 ml of HBr–acetic acid (40%) was added. The flask was sealed. After 3 days at room temperature, carbon tetrachloride (40 ml) was added to the bright yellow reaction mixture. The organic layer was washed with cold $NaHCO_3$ solution and water and dried ($MgSO_4$). Upon evaporation, a residue (0.39 g) was obtained, which was distilled [60–66° (0.7 mm)] to give 0.29 g of product, ir (CCl_4) 1815 cm^{-1} (s). In a latter reaction (see Preparation B for **8c**), this product was shown to contain a dibromofuranone along with the major component **2g**.

5-(1,2-Dihydro-2-oxo-4-methoxypyrimidin-1-yl)-4-ethyl-3-methyl-2(5*H*)-furanone (8a).[9]—To furanone **2c** (7.04 mmol) and methylene chloride (10 ml) in a small flask equipped with a $CaCl_2$ tube, 2,4-dimethoxypyrimidine (7.2 mmol) was added. The reaction mixture was stirred for 7 days. Tlc analysis indicated that all starting materials had been consumed. The solvent was removed and the white residue was rubbed with petroleum ether and filtered. The product **8a** (1.6 g) was recrystallized from ethyl acetate and gave colorless needles: mp 188–195° (yield 75%); ir (KBr, P-E) broad 3472 (m), 2941 (m), 1777 (s), broad 1675 (s), 1643 cm^{-1} (s); uv max (50% EtOH) 275 nm (ε 6100), min 246 (3000); pmr, see Table I; high-resolution mass spectrum *m/e* 250.09460 (calcd 250.09535), selected peaks and assignments *m/e* 235.07143 (M − CH_3), 221.09182 (M − CHO), 125.03459 (M − $C_7H_9O_2$), and 125.05865 (M − $C_5H_5O_2N_2$). Using tlc solvent 3, compound **8a** had R_f 0.79 (2,4-dimethoxypyrimidine, R_f 0.88).

Anal. Calcd for $C_{12}H_{14}N_2O_4$: C, 57.59; H, 5.63; N, 11.20. Found: C, 57.76; H, 5.65; N, 10.96.

5-(Uracil-1-yl)-4-ethyl-3-methyl-2(5*H*)-furanone (9a).[9]—Compound **8a** (1.8 g, 7.2 mmol) was dissolved in warm 50% ethanol (50 ml). The solution was cooled and 5.5 ml of 1 *N* HCl was added. Precipitation of product occurred immediately. The reaction was refrigerated overnight. Upon filtration 1.0 g of **9a**, mp 162–166°, was obtained. The mother liquor gave additional product, bringing the total yield to 91%. Recrystallization of **9a** from water gave mp 165–168°; ir (KBr, P-E) broad 3380 (m), 3045 (m), 1768 (s), broad 1687 (s), broad 1632 cm^{-1} (s); uv max (pH 3–7) 255 nm (ε 9800), min 229 (7600); mass spectrum *m/e* (rel intensity) 236 (16), 207 (3), 125 (100), 41 (55); pmr, see Table I. Using tlc solvent 3, **9a** had R_f 0.73 (**8a**, R_f 0.81).

Anal. Calcd for $C_{11}H_{12}N_2O_4$: C, 55.93; H, 5.12; N, 11.85. Found: C, 55.79; H, 5.00; N, 11.79.

Method A. 5-(1,2-Dihydro-2-oxo-4-methoxypyrimidin-1-yl)-2-(5*H*)-furanone (8b).[9]—Furanone **2e** (0.9 g, 5.5 mmol) in dry methylene chloride (8 ml) was allowed to react with 2,4-dimethoxypyrimidine (0.8 g, 5.7 mmol) using the method described for analog **8a**. The reaction was completed in 1 day. Washing the solidified reaction mixture with petroleum ether and ethyl acetate gave the product (0.85 g, mp 161–165°). Recrystallization from ethyl acetate gave colorless platelets: mp 168–173° (yield 53%); ir (KBr, P-E) broad 3490 (m), broad 3062 (m), shoulder 1787, broad 1657 (s), broad 1622 cm^{-1} (s); uv max (50% EtOH) 274 nm (ε 5600), min 241 (1800); mass spectrum *m/e* (rel intensity) 208 (33), 179 (24), 127 (100), 83 (54), 70 (14), 27 (16); pmr, see Table I. Using tlc solvent 3, compound **8b** had R_f 0.52.

Method B.—Reaction of 5-chlorofuranone **2f**[18] (0.3 g, 2.6 mmol) with 2,4-dimethoxypyrimidine (0.4 g) at 50–60° under house vacuum for 6 days gave a black residue. The product was purified on a small silica gel column using methylene chloride as eluent, and 15-ml fractions were taken. Tubes 20–30, containing **9b**, were combined and the solvent was evaporated. The white crystals of **9b** were recrystallized from ethyl acetate (yield 29%, mp 165–170°). Uv, ir, pmr, and tlc data were identical with those given under method A.

5-(Uracil-1-yl)-2(5*H*)-furanone (9b).[9]—Compound **8b** (0.28 g, 1.4 mmol) in 50% methanol was stirred with 1 *N* HCl (1.4 ml) for 1 day at room temperature. Colorless prisms of **8b** (yield 58%) precipitated and their purity was determined using tlc solvent 3, R_f 0.38 (analog **8b**, R_f 0.47). Product **9b** was recrystallized from water: mp 242–246°; ir (KBr, P-E) broad 3490 (w), 3044 (w), 1803 (s), 1774 (m), broad 1702 (s), 1626 cm^{-1} (m); uv max (pH 3–7) 255 nm (ε 9800), min 229 (3800); at pH 13 compound was unstable, max 240–280 (6200); mass spectrum *m/e* (rel intensity) 194 (15), 165 (10), 83 (100), 27 (19); pmr, see Table I.

Anal. Calcd for $C_8H_6N_2O_4$: C, 49.49; H, 3.12; N, 14.43. Found: C, 49.23; H, 3.06; N, 14.20.

In order to test the stability of the N–C bond, compound **9b** (8 mg) was boiled in water (5 ml) for 15 hr. Using tlc solvents 2 and 3, the reaction revealed two spots of equal intensity corresponding to uracil and starting material **9b**.

Preparation A. 5-(1,2-Dihydro-2-oxo-4-methoxypyrimidin-1-yl-3,4-dichloro-2(5*H*)-furanone (8c).[9]—Furanone **2f** (0.92 g, 3.3 mmol) in dry methylene chloride (5 ml) was stirred with 2,4-dimethoxypyrimidine (0.63 g, 4.5 mmol) for 10 days at room temperature, using the method described for compound **8a**. The reaction slowly turned amber-colored and a small amount of solid precipitated. The solvent was evaporated and the dark brown residue was rubbed with ethyl acetate. Filtration gave product **8c** as an off-white, crystalline solid, mp 210–214° dec (yield 23%). Recrystallization of the compound from 95% ethanol gave 123 mg of colorless crystals: mp 219–228° dec; ir (KBr) broad 3550 (m), 3010 (m), 1805 (s), 1686 (s), 1639 cm^{-1} (s); uv max (50% EtOH) 268 nm (ε 6300), 231 (12,900); at pH 0 cleavage of N–C bond occurred, max 231 nm (ε 12,900); high-resolution mass spectrum *m/e* 275.97070 (calcd 275.97046, 65%), selected peaks and assignments, *m/e* 246.96256 (M − CHO), 240.99541 (M − Cl), 213.00287 (M − COCl, 100%), 150.93488 (M − $C_5H_5N_2O_2$), and 125.03491 (M − $C_4HO_2Cl_2$); tlc, solvent 3, **8c** had R_f 0.82 (2,4-dimethoxypyrimidine, R_f 0.89).

Anal. Calcd for $C_9H_6N_2O_4Cl_2$: N, 10.11; Cl, 25.55. Found: N, 10.05; Cl, 25.66.

Preparation B. Detection of Bromochlorofuranone Analogs 14 (or 15).—Furanone **2f** (1.25 mmol), prepared by method B, was stirred with 2,4-dimethoxypyrimidine (1.26 mmol) in methylene chloride (3 ml) as described in preparation A. The reaction gave an off-white solid (0.1 g), which was recrystallized from 95% ethanol. The ir, tlc, and uv data were identical with those reported for compound **8c**. However, the elemental analysis showed the presence of bromine.

Anal. Calcd for sample containing $C_9H_6Cl_2N_2O_4$ (87.3%) + $C_9H_6BrClN_2O_4$ (12.7%): C, 38.61; H, 2.15; N, 9.94; Br, 3.16. Found: C, 38.08; H, 2.35; N, 9.81; Br, 3.16.

The mass spectral data supported the $C_9H_6N_2O_4BrCl$ structure **14** (or **15**). The contaminant **14** (or **15**) gave a weak peak at *m/e* 320 (1.5%) [M]. A weak peak at *m/e* 195 (8%) was observed and was attributed to the bromochloro analog of ion **10c** (*m/e* 151). The existence of these bromochloro ions was supported by the relative intensities of the halogen isotope peaks. The

major peaks in the spectrum were due to the dichloro derivative **8c**: mass spectrum *m/e* (rel intensity) 276 (92), 241 (91), 213 (97), 151 (100).

Acid Hydrolysis of 8c.—The procedure used for **9b** was followed. Compound **8c** (50 mg) was stirred with 1 *N* HCl (0.2 ml) in 50% methanol (25 ml) for 24 hr. Spectral patterns indicated that N–C bond cleavage had occurred: uv (water) max 252–255 nm, shoulder 235 nm, min 224 nm; uv (acid) max 235 nm, shoulder 255 nm, min 220 nm. The reaction mixture was treated with ion exchange resin (acetate form), which removed most of the mucochloric acid (**1c**). Using the tlc solvent 5, the resin-treated solution showed three uv-absorbing spots at R_f 0.55 (uracil, R_f 0.55), 0.87 (**8c**, R_f 0.89), and 0.67 (**1c**, R_f 0.65). The uracil spot was very intense and the other spots were faint. Upon concentration of the solution to 1 ml, uracil (5 mg) precipitated, mp 330° dec. The melting point, uv, and ir data were identical with those of authentic uracil.

Method A. 5-(6-Amino-9*H*-purin-9-yl)-4-ethyl-3-methyl-2(5*H*)-furanone (11) and Isomer 12a.—To a flask containing dry adenine (4.1 g, 30.4 mmol), anhydrous K_2CO_3 (4.2 g, 30.1 mmol), dry DMF (190 ml), and a magnetic stirring bar was added furanone **2c** (28.3 mmol) in DMF (10 ml). The reaction mixture, which was protected from moisture by a $CaCl_2$ tube, immediately developed a yellow color. After stirring at room temperature for 3 days, the reaction mixture was filtered. The white solid obtained contained adenine[43] and salts. The yellow filtrate was evaporated and a light orange residue (11.9 g) was obtained. The residue was treated with hot acetone (200 ml) and filtered. The acetone insolubles (2.4 g), a cream-colored solid, contained adenine[43] and salts. Upon evaporation of the filtrate, an orange residue was obtained. This residue was extracted with methylene chloride (35 ml) and filtered. (The methylene chloride filtrate A was saved for later isolation of isomer **12a**.) The methylene chloride insolubles, an off-white solid (2.7 g), contained product **11** contaminated with small amounts of adenine and isomer **12a**, which were removed as follows.

The 2.7-g mixture was dissolved in warm acetone (400 ml) and passed through a 100-g silica gel column. The uv-absorbing fractions were collected and the solvent was evaporated. A white, crystalline solid (2.3 g, mp 210–220° dec) was obtained. By uv spectrometry, the solid was composed of a mixture of **11** (92%) and **12a** (8%). The solid was dissolved in hot methanol (300 ml) and treated with a methanolic solution of picric acid (2.1 g). The picrate of **11** precipitated and was collected, 3.7 g, mp 252–258° dec.

Anal. Calcd for $C_{18}H_{16}N_8O_9$: N, 22.73. Found: N, 22.94.

The methanolic filtrate B was saved for the isolation of **12a**. The picrate of **11** was dissolved in aqueous acetone (50%) and the solution was passed through an ion exchange column (acetate form). Evaporation of the uv-absorbing eluate gave a white solid, which was recrystallized from 95% ethanol. Colorless crystals of **11** precipitated (yield 22% based on adenine): mp 187–190°; ir (KBr, P-E) 3289 (m), 3115 (m), 2907 (w), 1773 (s), 1661 (s), 1600 cm^{-1} (s); uv max (pH 7.5) 258 nm (ϵ 14,600), pH 0 max 257 (14,800); at pH 14 compound decomposed, max 262 (22,000); pmr, see Table I; mass spectrum, see Table II.

TABLE II

COMPARISON OF LOW-RESOLUTION MASS SPECTRAL DATA FOR ISOMERS 11 AND 12a

Common peaks[a]	Unique peaks, **11**	Unique peaks, **12a**
259 (36/47), 258 (2/30)	125 (32)	244 (10)
230 (9/36), 202 (11/16)	124 (33)	242 (6)
136 (40/11), 135 (21/11)		241 (3)
108 (18/6), 97 (11/6)		216 (13)
81 (23/8), 53 (21/19)		229 (100)
41 (100/62), 39 (20/22)		162 (63)
28 (26/37), 18 (8/90)		119 (11)

[a] *m/e* (rel intensity **11**/**12a**).

Anal. Calcd for $C_{12}H_{13}N_5O_2$: C, 55.59; H, 5.05; N, 27.01. Found: C, 55.42; H, 5.36; N, 26.87.

Derivative **11** was subjected to rapid paper electrophoresis (200 V, 41 mA) using an organic pH 3.3 buffer. After 2 hr, the spot of **11** was visualized under uv light and had a cathodic migration of +13 mm (adenine, +46 mm). The isolation of isomer **12a** from the above filtrates A and B is discussed below.

Most of the solvent, but not all, was evaporated from the picrate filtrate B. Aqueous acetone (40 ml) was added to the residue. The resulting solution was passed through an ion-exchange column (acetate form). The uv-absorbing fractions were evaporated. The white residue was suspended in ethanol (10 ml) and filtered. White crystals of the diazepino derivative **12a** (0.14 g, 2%) were obtained. The compound was recrystallized from 85% ethanol (yield 0.104 g): mp 236–241° eff; ir (KBr, P-E) 3280 (m), 3004 (m), 2833 (w), 1712 (s), 1682 cm^{-1} (s); high-resolution mass spectrum *m/e* 259.1060 (calcd 259.1042, 70%); selected peaks (assignments, rel intensity) were *m/e* 258.0985 (M − H, 80%), 244.0828 (M − CH_3, 40%), 241.0960 (M − H_2O, 40%), 230.1032 (M − CHO, 20%), 230.0673 (M − C_2H_5, 100%), 216.0890 (M − C_2H_3O, 40%), 215.0924 (M − CH_2NO, 20%), 162.0410 (M − C_6H_9O, 70%) 135.0541 (M − $C_7H_6O_2$, 50%), 119.0360 (M − $C_7H_{10}NO_2$, 60%); uv max (pH 0) 292 nm (ϵ 21,200), 209 (23,700), min 252 (5700); pH 3–7 max 290 (16,800), 207 (23,400); at pH 13 the compound decomposes slowly, max 295 (10,900); after 24 hr, max 271 (14,300); pmr data, see Table I; low-resolution mass spectral data, see Table II. Using tlc solvent 2, derivative **12a** had an R_f of 0.57 (isomer **11**, R_f 0.78).

Anal. Calcd for $C_{12}H_{13}N_5O_2$: C, 55.59; H, 5.05; N, 27.01. Found: C, 55.52; H, 5.14; N, 27.06.

The methylene chloride filtrate A contained derivative **12a** as detected by uv spectrometry: uv (50% ethanol) max 287 nm, min 245 nm. Absorption was also observed at 315–320 nm, suggesting the presence of unknown product(s). Filtrate A was evaporated and an orange glass (2.8 g) was obtained. The glass was dissolved in acetone and the solution was applied to a 100-g silica gel column in an attempt to separate the mixture. Acetone was used as the eluent, and 15-ml fractions were taken. As analyzed by tlc (solvent 2), fractions 13–17 contained two unknown uv-absorbing components at R_f 0.93 (X) and 0.89 (Y). Fraction **18** contained four components, R_f 0.93 (X), 0.89 (Y), 0.77 (**11**), and 0.65 (Z). Fractions 21–27, which contained mostly **12a** (R_f 0.55) with small quantities of compounds **11** and Z, were combined and concentrated to dryness. The white residue was crystallized from acetone and gave 132 mg of compound **12a**. As analyzed by tlc, fractions 27–40 contained only **12a**. These fractions were combined and gave 180 mg of **12a**. The total isolable yield of **12a** was 6%.[44] No attempt was made to determine the structures of unknowns X, Y, Z.

Method B. Adenyl Compound 11 from 6-Benzamido Analog 13.—The benzamidopurine analog **13** (0.026 g) was dissolved in ethanol (8 ml) and the solution was refluxed with picric acid (0.050 g) for 2 hr. The picrate of **11** precipitated and was filtered. Yellow crystals (0.029 g, yield 80%) were obtained, mp 250–257° dec. The picrate was converted to the free base (mp 187–189°) in high yield by the resin treatment described in method A. The ir, uv, and tlc properties of the product were identical with those of **11**.

Hydrolysis of 11 in Alkali.—The adenyl analog **11** (84 mg) was dissolved in warm 1 *N* sodium hydroxide. The solution was subjected immediately to rapid paper electrophoresis (200 V, 16 mA, 1.25 hr, pH 3.3). After the paper was dried, a single spot was observed under uv light (cathodic migration +47 mm) which corresponded to adenine (+48 mm). A reference sample of analog **11** had a migration of +15 mm. After 0.5 hr the pale yellow reaction mixture[45a] was neutralized with formic acid to pH 7.6. The solution was concentrated to about 3 ml, whereupon 29 mg (66%) of adenine precipitated. (Uv, ir, and melting point data of the sample were identical with those of authentic adenine.) The filtrate from adenine had ultraviolet patterns in water and alkali showing that mostly furanone **1a** was present together with a small amount of adenine: uv (water) max 260 nm (OD 0.80); uv max (OH^-) 260 nm (OD 1.46).[45b]

(43) By uv spectrometry, the total amount of adenine recovered was 1.4 g (35%).

(44) In another preparation it was found from the uv extinction that filtrate A contained only a small amount of uv-absorbing material, about 13% of **12a**. Most of the material in filtrate A was either non-uv-absorbing or absorbed below 260 nm, explaining the low yield of **12a** obtained on chromatography of the 2.8 g.

(45) (a) On increasing the reaction time, the solution turned progressively darker yellow. Samples of furanone **1a** behaved similarly in alkaline solutions. (b) Ultraviolet absorptions of compound **1a** in water, max 218 nm (ϵ 9670); in 1 *N* NaOH, max 256 nm (ϵ 9730), min 224 nm (ϵ 4000).

8-Ethyl-7-hydroxy-9-methyl-3*H*-[1,3]diazepino[2,1-*i*]purin-10-(7*H*)-one (12a).—To a flask containing adenine (0.49 g, 3.6 mmol) and pyridine (10 ml) was added furanone **2c** (7.04 mmol) in pyridine (1 ml). The reaction mixture turned dark amber in color on heating. After 6 hr of refluxing, the reaction was cooled and quenched with ethanol (1 ml). The pyridine was evaporated, giving a dark amber residue, which was first azeotroped with 50% ethanol to get rid of the residual pyridine, and finally with absolute ethanol to remove the water. The residue was rubbed with chloroform. The procedure gave a pale yellow solid, 0.47 g (50%), mp 230–240°. The crude product was recrystallized from 95% ethanol. Colorless crystals (0.3 g) were obtained, mp 237–243° eff. The compound gave ir, uv, pmr, and tlc data identical with those of compound **12a** isolated in method A.

The mother liquor from the 0.47-g product was spotted in tlc, solvent 2. Five spots were observed at R_f 0.9, 0.77, 0.58, 0.42 and 0.14; the last was the most intense. The compounds with R_f 0.77, 0.58, and 0.14 were probably compounds **11**, **12a**, and adenine, respectively. No attempt was made to determine the structures of the two unknowns.

Hydrolysis of 12a in Alkali.[46]—Derivative **12a** (92 mg) was refluxed in 1 *N* sodium hydroxide (6 ml) for 3 hr. During this time, an intense orange color developed. The uv data in water exhibited max 266 nm (ε 11,500), min 231 (5060), shoulder 275. A broad maximum was also observed at 320 nm that had 23% of the absorption of the 266-nm max. The reaction mixture was cooled and subjected to paper electrophoresis (200 V, 18 mA, 0.75 hr, pH 3.3). After the paper was dried, two spots with cathodic migration were observed under uv light. A uv-absorbing spot corresponded to adenine (+22 mm). The other, a fluorescent pink spot (+5 mm), was due to unknown product(s). (In visible light a brown or pink spot was observed at +5 mm. A reference sample of analog **12a** was visualized as a uv spot at the origin.) The pH of the reaction mixture was adjusted to 7.6 with formic acid. An ethanolic solution of picric acid was added. Needles of adenine picrate precipitated (46 mg, 35%, mp 285° dec). The picrate was dissolved in 50% ethanol and treated with ion exchange resin (acetate form). The solution was evaporated to 3 ml, whereupon crystalline adenine (10 mg) precipitated. The mother liquor from adenine picrate was freed of picric acid with acetate resin. The uv spectrum of this solution in water exhibited max 255 nm (OD 0.35), broad shoulder 310–330 (OD 0.10). Attempts made to isolate other products of the reaction failed.

7-Chloro-8-ethyl-3,7,10,11-tetrahydro-9-methyl-10-oxo[1,3]diazepino[2,1-*i*]purin-6-ium Chloride (12b).—The diazepino derivative **12a** (91 mg) was added to a flask containing thionyl chloride (2 ml) and fitted with a $CaCl_2$ tube. Solution occurred. The reaction was allowed to stand at room temperature overnight. Colorless, iridescent crystals precipitated, which were filtered and washed with ether. The yield of **12b** was 88%: mp 204–210°, red, partial melting, 265° char; mass spectrum *m/e* (rel intensity) 277 (M − HCl, 100), 242 (100), 239 (51), 214 (100), 119 (25), 38 (100); ir (KBr) 1739 (s), 1603 (s), broad 1468 cm^{-1} (s). The uv spectrum of the compound was very similar to that of precursor **12a** in acid, base, and water. Treatment of the salt **12b** with water immediately converted it back to precursor **12a**.

Anal. Calcd for $C_{12}H_{12}ClN_5O \cdot HCl$: N, 22.29; Cl, 22.57. Found: N, 22.20; Cl, 21.29.

Method A. 8-Ethyl-7-methoxy-9-methyl-3*H*-[1,3]diazepino-[2,1-*i*]purin-10(7*H*)-one (12c).—To a solution of the salt **12b** (160 mg, 0.51 mmol) in absolute methanol was added 2 equiv of sodium methoxide. (The total volume of the reaction was about 5 ml.) After the reaction mixture was refluxed for 1 hr, the solvent was removed and a white solid was obtained, which was extracted into chloroform. The organic layer was washed with water, dried (Na_2SO_4), and evaporated, giving a white solid, which was crystallized from methanol–ether (1:1). The yield of **12c** was 63%: mp 127–146°; ir (KBr) broad 3333 (s), broad 3125 (s), broad 2959 (s), 1724 (s), 1600 (s), 1553 (s), 1458 cm^{-1} (s); high-resolution mass spectrum *m/e* 273.1240 (calcd 273.1226, 13%), 274.1304 (calcd 274.1226, M + H, 100%); uv max (50% EtOH) 289 nm (ε 13,800), 207 (21,600), min 258 (5100); pmr, see Table I.

Anal. Calcd for $C_{13}H_{15}N_5O_2$: C, 57.13; H, 5.53; N, 25.64. Found: C, 57.18; H, 5.47; N, 25.55.

Method B.—The salt **12b** (175 mg, 0.56 mmol) was refluxed in methanol (5 ml) containing triethylamine (2 equiv) for 2 hr. The solvent was removed and a white solid was obtained. Trituration of the solid with ethyl acetate gave a theoretical yield of crystalline triethylamine hydrochloride. The ethyl acetate was evaporated and product **12c** was crystallized as in the above preparation. The yield of **12c** was 28%, mp 129–146°.

7-Ethoxy-8-ethyl-9-methyl-3*H*-[1,3]diazepino[2,1-*i*]purin-10-(7*H*)-one (12d).—The procedure used in method A for the 7-methoxy analog **12c** was followed. An ethanolic solution of the salt **12b** (60 mg, 0.23 mmol) was treated with sodium methoxide (2 equiv). The yield of **12d** was 43%: mp 145–150°; high-resolution mass spectrum *m/e* 287.1382 (calcd 287.1382, 2%), 288.1474 (calcd 288.1460, M + H, 100%); ir (KBr) broad 3195 (s), 2985 (s), 1733 (s), 1597 (s), 1555 (s), 1456 cm^{-1} (s). Using tlc solvent 2, the 7-methoxy (**12c**), -ethoxy (**12d**), and -hydroxy (**12a**) derivatives had R_f 0.7, 0.72, and 0.59, respectively.

5-(6-Benzamido-9*H*-purin-9-yl)-4-ethyl-3-methyl-2(5*H*)-furanone (13).—6-Benzamidochloromercuripurine[47] (2.5 g, 5.26 mmol), dried Celite (1 g Manville filtering aid), and dry toluene (210 ml) were added to a three-necked flask equipped with a stirrer, condenser, $CaCl_2$ tube, and take-off head. The suspension was refluxed and 100 ml of toluene was removed. The suspension was cooled to 60° and the furanone **2c** (5.98 mmol) in 10 ml of dry toluene was added. The yellow-colored reaction mixture was refluxed for 3.5 hr, then cooled and filtered. A pale yellow solid was obtained. Evaporation of the filtrate gave a yellow, sticky solid. All the solids from the reaction were combined and extracted with warm chloroform (125 ml). Filtration gave a white, Celite-containing solid (1.68 g), which was discarded. The filtrate was washed with 30-ml portions of a 30% KI solution eight times and then with water twice. The solution was dried ($MgSO_4$) and evaporated, giving a yellow glass. The glass was rubbed with ether and a powdery yellow solid M (1.3 g) was obtained, mp 50–100° eff, uv max (50% ethanol) 280 nm (ε 13,700), shoulder 320 (2850). In solid M three compounds were detected by tlc solvent 2. These were the product **13** (R_f 0.54), the unknown R (R_f 0.8) and 6-benzamidopurine (R_f 0.32). The most intense spot was due to the product **13**. Solid M was purified by using a 60-g silica gel column with benzene–ethyl acetate (85:15) as eluent. Fractions (10 ml) were taken and monitored in tlc solvent 2. In combined fractions 19–39, two compounds, **13** (R_f 0.59) and R (R_f 0.8), were detected. Fractions 40–63 contained only **13** (R_f 0.59). Removal of the solvent from fractions 40–63 gave a colorless syrup. The syrup was dissolved in benzene (15 ml) and cyclohexane was added until turbidity. Colorless, hairlike crystals of **13** precipitated. The crystals were filtered and washed with ether, 129 mg, mp 110°. Fractions 19–39 were evaporated and the residue, crystallized in the above manner, gave **13** (109 mg), mp 105° eff. The total yield of chromatographically pure compound **13** was 16%. The compound was recrystallized from benzene–cyclohexane for analysis. It was found that benzene–cyclohexane solvent was difficult to remove from **13**. The sample was dried at 80° (1 mm): mp 100–130°, 139° eff; ir (KBr, P-E) 3175 (w), 3058, 2900, 1770 (s), 1695, 1613, 1582 cm^{-1}; mass spectrum *m/e* (rel intensity) 363 (10), 334 (33), 240 (5), 125 (24), 105 (100), 77 (100), 40 (50), 29 (12); uv max (50% EtOH) 280 nm (ε 23,000), max (pH 1) 290 (26,300).

Anal. Calcd for $C_{19}H_{17}N_5O_3$: C, 62.80; H, 4.71; N, 19.27. Found: C, 63.03; H, 4.87; N, 18.80. The low nitrogen and high carbon suggested the presence of a small amount of cyclohexane. The pmr spectrum (Table I) confirmed the presence of cyclohexane.

In connection with the unknown compound R also formed in this reaction, fractions 16–18 from the silica gel column were evaporated and gave a colorless syrup (25 mg). Using tlc solvent 2, this sample gave one spot at R_f 0.8. Attempts to crystallize the compound failed. The uv spectrum of R (95% ethanol) exhibited a maximum at 303 nm and a minimum at 266 nm. These data suggest that the compound is a purine derivative.

Acknowledgment.—The authors are indebted to Dr. Robert B. Fairweather for his help in mass spectra interpretation.

(46) It was hoped that this experiment would give unequivocal proof of structure **12a** *via* isolation of diazepino ring cleavage purine product(s). However, adenine was the only product isolable. The experiment does not exclude the possibility that these products may be obtainable under less stringent hydrolysis conditions.

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Registry No.—1a, 3816-83-9; 1b, 14032-66-7; 1c, 766-40-5; 2b, 41473-30-7; 2c, 26212-26-0; 2d, 41473-32-9; 2e, 40125-53-9; 2f, 14032-71-4; 2g, 41473-35-2; 3, 41473-36-3; 5, 3712-44-5; 8a, 41473-38-5; 8b, 41611-40-9; 8c, 41473-39-6; 9a, 41473-40-9; 9b, 41473-41-0; 11, 26212-27-1; 11 picrate, 41473-42-1; 12a, 41473-43-2; 12a isomer, 41473-44-3; 12b, 41473-45-4; 12c, 41611-41-0; 12d, 41473-46-5; 13, 26212-28-2; 2,4-dimethoxypyrimidine, 3551-55-1.

Reductive Alkylation of Monoaromatic Ketones

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Metal–ammonia reduction of acetophenone in the presence of *tert*-butyl alcohol is shown to proceed in three ways: dimerization to give *dl*-2,3-diphenylbutane-2,3-diol (**3**), nuclear reduction to form 1-(cyclohexa-2,5-dienylidene)ethanolate (enolate) (**4**), and carbonyl carbon reduction to yield 1-phenethyl alcohol. Subsequent *in situ* methylation of **4** generates 1-acetyl-1-methylcyclohexa-2,5-diene (**1**) and/or 1-(cyclohexa-2,5-dienylidene)-ethyl methyl ether (**5**), a hypothetical intermediate; the latter is supposed to isomerize to 1-phenethyl methyl ether. The product composition depends strongly upon the dissolving metal and methylating conditions used, and is controlled by proper selection of them; thus, reduction in ammonia–THF at −78° with potassium in either order of addition gives potassium enoate **4c** and subsequent methylation with methyl iodide in THF of lithium enolate **4b**, prepared by treatment of **4c** with lithium bromide, affords a regioselective preparative method of compound **1** in yields of >80%. Applicability of the method is established in reductive methylation of *o*-methoxyacetophenone (**6a**), *m*-methoxyacetophenone (**6b**), *p*-methylacetophenone (**6d**), and 1-tetralone. Similarly, 1-acetyl-1-ethylcyclohexa-2,5-diene (**10a**), 1-acetyl-1-allylcyclohexa-2,5-diene (**10b**), ethyl 1-acetylcyclohexa-2,5-dienylacetate (**10c**), and 1-acetylcyclohexa-2,5-dienylacetonitrile (**10e**) were prepared by using ethyl iodide, allyl bromide, ethyl bromoacetate, and chloroacetonitrile as the alkylating agent, respectively. HMO calculation suggests that the difference in the regioselectivity of the reduction according to the kind of counterion can be correlated with changes in electron density of the acetophenone dianion **12** on association with the counterion.

A solution of an alkali metal in ammonia combined with a proton source has long been known to provide an efficient reducing system[1] for aromatic rings. Partial nuclear reduction of benzoic acids by this method to give 1,4-dihydro derivatives as the primary products has been well established.[2,3] It has since been found[3,4] that the reduction can proceed without addition of a proton source, the intermediate enolates being subsequently alkylated *in situ* to afford 1-alkyl-1,4-dihydrobenzoic acids.

Metal–ammonia reduction of aromatic ketones takes a different course:[1] the site of reduction is always localized at the carbonyl carbon. Reduction of acetophenone in liquid ammonia with an excess of potassium and *tert*-butyl alcohol gives ethylbenzene,[5,6] while benzophenone is reduced with sodium in ammonia followed by quenching with water to give diphenylmethanol.[7,8] Conversion of benzophenone, 1-tetralones, and 1-indanones into aromatic hydrocarbons by an excess of lithium[3] in liquid ammonia and ammonium chloride quench has been recently reported.[9] Electrophilic reaction on the benzophenone dianion, produced with an equivalent amount of metal in liquid ammonia, resulting in formation of diphenylmethane derivatives has been investigated in detail.[10]

The apparent difficulty of nuclear reduction of aromatic ketones compared with the smooth nuclear reduction in the benzoic acid series attracted our attention and prompted us to investigate the problem.

We now report our findings that under selected conditions metal–ammonia reduction of acetophenone proceeds by the hitherto unknown nuclear reduction[11–13] and that after cation exchange of the counterion the resulting enolate is selectively methylated *in situ*

(1) For general discussions, see (a) A. J. Birch, *Quart. Rev., Chem. Soc.*, **4**, 69 (1950); (b) A. J. Birch and H. Smith, *ibid.*, **12**, 17 (1958); (c) G. W. Watt, *Chem. Rev.*, **46**, 317 (1950); (d) C. Djerassi, Ed., "Steroid Reactions," Holden-Day, San Francisco, Calif., 1963; (e) H. Smith, "Organic Reactions in Liquid Ammonia, Vol. 1, Part 2, Chemistry in Nonaqueous Ionizing Solvents," Wiley, New York, N. Y., 1963; (f) R. L. Augustine, "Reduction: Techniques and Applications in Organic Synthesis," Marcel Dekker, New York, N. Y., 1968; (g) H. O. House, "Modern Synthetic Reactions," 2nd ed, W. A. Benjamin, Menlo Park, Calif., 1972; (h) R. G. Harvey, *Synthesis*, 161 (1970); (i) E. M. Kaiser, *ibid.*, 392 (1972).

(2) (a) A. J. Birch, *J. Chem. Soc.*, 1551 (1950); (b) A. J. Birch, P. Hextall, and S. Sternhell, *Aust. J. Chem.*, **7**, 256 (1954); (c) H. Plieniger and G. Ege, *Angew. Chem.*, **70**, 505 (1958); (d) M. E. Kuehne and B. F. Lambert, *J. Amer. Chem. Soc.*, **81**, 4278 (1959); (e) A. P. Krapcho and A. A. Bothner-By, *ibid.*, **81**, 3658 (1959); (f) O. L. Chapman and P. Fitton, *ibid.*, **83**, 1005 (1961); **85**, 41 (1963); (g) F. Camps, J. Coll, and J. Pascual, *J. Org. Chem.*, **32**, 2563 (1967); (h) M. E. C. Biffin, A. G. Moritz, and D. B. Paul, *Aust. J. Chem.*, **25**, 1329 (1972).

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(4) For similar reductive methylation of biphenyl and polynuclear aromatic compounds, see D. F. Lindow, C. N. Cortez, and R. G. Harvey, *J. Amer. Chem. Soc.*, **94**, 5406 (1972), and the papers in this series.

(5) A. R. Pinder and H. Smith, *J. Chem. Soc.*, 113 (1954).

(6) Metal was added to the ketone solution.

(7) (a) H. Schlubach, *Chem. Ber.*, **48**, 12 (1915); (b) See also W. E. Bachmann, *J. Amer. Chem. Soc.*, **55**, 1179 (1933).

(8) Ketone was added to the solution of metal in ammonia.

(9) (a) S. S. Hall, S. D. Lipsky, F. J. McEnroe, and A. P. Bartels, *J. Org. Chem.*, **36**, 2588 (1971). The accelerating effect of a catalytic amount of cobalt or aluminum was observed. (b) S. S. Hall, S. D. Lipsky, and G. H. Small, *Tetrahedron Lett.*, 1853 (1971).

(10) (a) P. J. Hamrick, Jr., and C. R. Hauser, *J. Amer. Chem. Soc.*, **81**, 493 (1959); (b) S. Selman and J. F. Eastham, *J. Org. Chem.*, **30**, 3804 (1965); (c) E. L. Anderson and J. E. Casey, Jr., *ibid.*, **30**, 3955 (1965); (d) W. S. Murphy and D. J. Buckley, *Tetrahedron Lett.*, 2975 (1969).

(11) Pinder and Smith[5] have already attempted to prepare 1-acetylcyclohexa-2,5-diene by potassium–*tert*-butyl alcohol–ammonia reduction of the potassium enolate of acetophenone, an equivalent to benzoate, but they recovered acetophenone.

(12) For the lithium–methylamine reduction of acetophenone yielding 1-(cyclohexen-1-yl)ethanol, see (a) R. A. Benkeser, C. Arnold, Jr., R. F. Lambert, and O. H. Thomas, *J. Amer. Chem. Soc.*, **77**, 6042 (1955); (b) R. A. Benkeser, R. K. Agnihotri, M. L. Burrous, E. M. Kaiser, J. M. Mallan, and P. W. Ryan, *J. Org. Chem.*, **29**, 1313 (1964).

(13) Reduction of pivalophenone by magnesium–trimethylsilyl chloride to 1-(*p*-trimethylsilylphenyl)-2,2-dimethylpropane trimethylsilyl ether *via* initial nuclear reduction and subsequent aromatization has been reported. See (a) R. Calas, C. Biran, J. Dunogues, and N. Duffaut, *C. R. Acad. Sci., Ser. C*, **269**, 412 (1969); (b) R. Calas, J. Dunogues, J.-P. Pillot, C. Biran, and N. Duffaut, *J. Organometal. Chem.*, **25**, 43 (1970); (c) J.-P. Pillot, J. Dunogues, R. Calas, and N. Duffaut, *Bull. Soc. Chim. Fr.*, 3490 (1972).