**6-Amino-2,3-diphenyl-8-ethoxypyrido[2,3-*b*]pyrazine (22).**—A solution of **17** (200 mg, 1.01 mmol) in EtOH (10 ml) was stirred with Raney nickel (300 mg, weighed wet with ethanol) in the presence of $H_2$ at atmospheric pressure and room temperature for 1.5 hr. The resulting colorless solution of **21** was carefully filtered under $N_2$ and treated with benzil (247 mg, 1.18 mmol). After standing for 18 hr under $N_2$ this solution deposited pale green crystals which were collected by filtration, washed with EtOH, and dried *in vacuo* over $P_2O_5$ to yield 318 mg (92%), mp 266–268° (Mel-Temp). The analytical sample, mp 268°, was obtained by recrystallization of a portion of the product from EtOH: $\lambda_{max}$ in mμ ($\epsilon \times 10^{-3}$), pH 1—227 (32.1), 265 (sh) (17.6), and 370 (24.7), pH 7—228 (26.3), 266 (sh) (22.9), and 380 (20.6), pH 13—228 (27.7), 266 (23.8), and 380 (20.7); $\bar{\nu}$ in $cm^{-1}$, 3600–2800 (NH, CH), 1630 ($NH_2$), 1604, 1550, and 1533 (ring stretching), 1205 (C–O–C), 740 and 696 (monosubstituted phenyl).

*Anal.* Calcd for $C_{21}H_{18}N_4O$: C, 73.66; H, 5.30; N, 16.36. Found: C, 73.41; H, 5.40; N, 16.15.

**Ethyl 2,3-Diphenyl-8-ethoxypyrido[2,3-*b*]pyrazine-6-carbamate (23).**—Ethyl chloroformate (1 ml) was added dropwise to a stirred solution of **22** (100 mg, 0.292 mmol) in pyridine (2 ml) and dioxane (10 ml). After the exothermic reaction had ceased, the solution was refluxed for 30 min. The cooled reaction mixture was treated dropwise with additional ethyl chloroformate (1 ml), refluxed for 1.5 hr, and evaporated to dryness under reduced pressure. The residue was triturated with $H_2O$ (5 ml), collected by filtration, air dried, and crystallized two times from EtOH–$H_2O$. The crystalline product was collected by filtration and dried at 100° *in vacuo* over $P_2O_5$ for 3 days to yield 63 mg (52%): mp 111–114° (soft at 108°, Mel-Temp); $\lambda_{max}$ in mμ ($\epsilon \times 10^{-3}$), pH 1—241 (34.2), 269 (23.8) and 373 (25.5), pH 7—223 (sh) (24.8), 254 (36.6), and 368 (22.9), pH 13—231 (27.2), 258 (30.0), 275 (sh) (27.8), and 382 (22.5); $\bar{\nu}$ in $cm^{-1}$, 3450 and 3120 (NH), 3055, 2975, and 2930 (CH), 1739 (C=O), 1604 (sh), 1596, 1539, and 1508 (ring stretching), 1195 (C–O–C), 740 and 693 (monosubstituted phenyl).

*Anal.* Calcd for $C_{24}H_{22}N_4O_3$: C, 69.55; H, 5.35; N, 13.52. Found: C, 69.46; H, 5.55; N, 13.67.

**Ethyl 2,3-Diphenyl-5-ethoxypyrido[3,4-*b*]pyrazine-7-carbamate (24).**—A sealed glass tube containing **20** (contaminated with **19**) (300 mg, 0.779 mmol), isoamyl nitrite (183 mg, 1.56 mmol), anhydrous HCl (28.4 mg, 0.779 mmol), and EtOH (20 ml) was refrigerated overnight and heated in a $H_2O$ bath at 100° for 35 min. The solution was cooled to room temperature, filtered, and evaporated to dryness under reduced pressure. The residue was crystallized first from 1:1 EtOH–$H_2O$ (3 ml) and then from propanol (5 ml) to give a yellow crystalline product which was collected by filtration and dried *in vacuo* over $P_2O_5$ to yield 70 mg (22%): mp 205°; $\lambda_{max}$ in mμ ($\epsilon \times 10^{-3}$), pH 1—256 (18.0), 304 (25.2), and 390 (8.0), pH 7—256 (17.8), 304 (21.3), and 391 (10.4), pH 13—256 (18.6), 305 (23.2), and 390 (9.0); $\bar{\nu}$ in $cm^{-1}$, 3440 and 3230 (NH), 3057, 2980, 2930, 2900, and 2860 (CH), 1720 (C=O), 1608, 1570, 1530, and 1490 (ring stretching), 1218 and 1195 (C–O–C), 742 and 692 (monosubstituted phenyl).

*Anal.* Calcd for $C_{24}H_{22}N_4O_3$: C, 69.55; H, 5.35; N, 13.52. Found: C, 69.67; H, 5.41; N, 13.25.

**Registry No.**—Pyruvaldehyde, 78-98-8; benzil, 134-81-6; **1** HCl, 16335-89-0; **4**, 16335-90-3; **5**, 16335-91-4; **7**, 16335-92-5; **7** HBr, 16335-93-6; **8**, 16335-94-7; **9**, 16335-95-8; **11**, 16335-96-9; **12**, 16335-97-0; **15**, 16335-98-1; **16**, 16335-99-2; **17**, 16336-00-8; **19**, 16336-01-9; **19** HBr, 16336-02-0; **20**, 16336-03-1; **22**, 16336-04-2; **23**, 16336-05-3; **24**, 16336-06-4.

**Acknowledgments.**—The authors are indebted to Dr. W. J. Barrett and the members of the Analytical and Physical Chemistry Division of Southern Research Institute for the spectral and microanalytical determinations. Some of the analyses reported were performed by the Galbraith Laboratories, Knoxville, Tenn. The authors also wish to thank Dr. N. F. Wood for his work on the preparation of **5**.

# The Quaternization of Isoxazoles with Alcohols and Perchloric Acid

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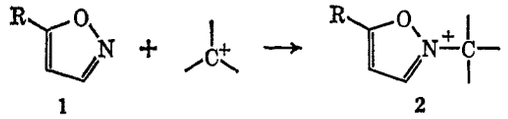
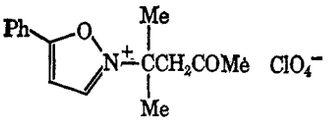
The reaction of isoxazoles and perchloric acid with alcohols which are efficient sources of carbonium ions has general utility as a method for the preparation of isoxazolium salts with branched quaternizing groups. The rate of reaction increases with the relative stability of the intermediate carbonium ion, while the equilibrium becomes less favorable for the formation of 3,5-dimethylisoxazolium cations as the bulk of the N-alkyl substituent is made greater.

In 1963, Eugster, Leichner, and Jenny, postulated[1] that combination of *t*-alkyl carbonium ions and unprotonated, 3-unsubstituted isoxazoles (**1**) gave isoxazolium salts (**2**) as reactive intermediates in sulfuric acid.

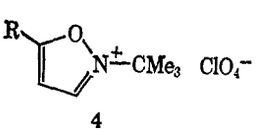


**1** **2**

Subsequently, isolation of the perchlorate **3** from the reaction of 5-phenylisoxazole and mesityl oxide under the same conditions confirmed that this novel isoxazole quaternization had taken place, and it was found that 5-substituted N-*t*-butylisoxazolium salts (**4**) could conveniently be prepared simply by mixing *t*-butyl alcohol and the isoxazole with 70% perchloric acid.[2]



**3**



**4**

A further study of the quaternization method was undertaken, because of the potential importance of the SN1 process as a general synthetic route to isoxazolium salts with branched groups on nitrogen. Such cations cannot be obtained with the normal SN2 alkylating agents,[3] and 3-unsubstituted isoxazolium salts with bulky nitrogen substituents have special significance as reagents for the preparation of stable enol ester acylating agents in peptide synthesis.[4–6] In addition it was

(1) C. H. Eugster, L. Leichner, and E. Jenny, *Helv. Chim. Acta*, **46**, 543 1963).

(2) R. B. Woodward and D. J. Woodman, *J. Org. Chem.*, **31**, 2039 (1966).

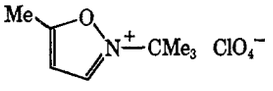
(3) G. F. Duffin, *Advan. Heterocycl. Chem.*, **3**, 2 (1964).

(4) R. B. Woodward, R. A. Olofson, and H. Mayer, *Tetrahedron Suppl.*, **8**, 321 (1966).

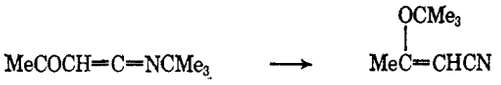
(5) R. B. Woodward, D. J. Woodman, and Y. Kobayashi, *J. Org. Chem.*, **32**, 388 (1967).

(6) R. B. Woodward and D. J. Woodman, *J. Amer. Chem. Soc.*, **90**, 1371 (1968).

of interest to determine if the alkylation technique would be applicable to isoxazoles substituted in the 3 position, because a substantial steric repulsion might be anticipated between the 3-alkyl group and bulky quaternizing substituent in the derived isoxazolium cation. It had earlier been found that the $N^+$–R bond of the relatively unhindered N-*t*-butyl-5-methylisoxazolium perchlorate (**5**) was sufficiently labile that **5** served as a carbonium ion donor in the catalysis of the isomerization of N-*t*-butylacetylketenimine (**6**) to β-*t*-butoxycrotononitrile (**7**).[7] It was considered possible, then, that the unfavorable steric interaction might cause 3-substituted N-*t*-butylisoxazolium salts to be still less stable than **5** and perhaps preclude their formation.



**5**

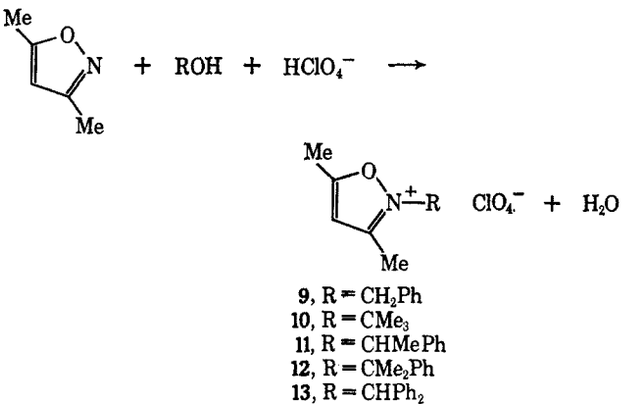


**6** **7**

That *t*-butylation in fact is successful with 3-substituted isoxazoles was established using 3,5-dimethylisoxazole (**8**). Nmr assay of a mixture of equivalents of **8**, *t*-butyl alcohol, and 70% perchloric acid revealed that the alkylation was 20% complete within 0.5 hr, and there was no change in the composition of the mixture after 70% conversion, achieved within 1 week.

Next the effect of alcohol structure on the quaternization of **8** was investigated. In accord with the proposed[1] SN1 mechanism,[8] nmr assay of neat reaction mixtures revealed that alkylation was less rapid with benzyl alcohol (20% reaction within 2 months), and no reaction was observed with isopropyl alcohol. Spectral monitoring of neat mixtures with alcohols which provide carbonium ions of greater stability was complicated by product precipitation, but the problem was overcome when it was found that the reaction proceeded equally well in nitromethane solution. In further spectral tests in nitromethane, as expected, the rates increased through the series *t*-butyl alcohol (7% at 5 min), α-methylbenzyl alcohol (19% at 5 min), and α,α-dimethylbenzyl alcohol and benzhydrol (both near 70% at 5 min). However, the only reaction observed with 1,1-diphenylethanol was elimination to the stable alkene and the spectrum of a solution of **8** and perchloric acid with triphenylmethanol also showed no isoxazolium salt.

The quaternization is sufficiently rapid at room temperature for preparative convenience in the series of alcohols from *t*-butyl alcohol[10] through benzhydrol, either neat or in nitromethane solution. The products **10**–**13** are readily precipitated after 1 or 2 days in 50–90% yield, and other 3-unsubstituted isoxazoles have been found to give comparable results. The new types of isoxazolium perchlorates are nicely crystalline salts and may be stored without protection from light or atmospheric moisture.[11] However, the stability of **12** is marginal, and it decomposes completely within a few days in nonnucleophilic solvents. The product nmr spectrum shows the isoxazole **8** and complex signals presumably owing to the decomposition of α-methylstyrene in the acidic medium.



**9**, R = $CH_2Ph$
**10**, R = $CMe_3$
**11**, R = CHMePh
**12**, R = $CMe_2Ph$
**13**, R = $CHPh_2$

Although the repulsion between the 3-substituted isoxazole ring and N-*t*-butyl substituent is not so serious as had been feared, the importance of steric factors is evident from a comparison of the equilibrium constants $K$ for the formation of the cations (assuming $K$ = [isoxazole $R^+$][$H_2O$]/[isoxazole $H^+$][ROH]). The final compositions from the earlier test quaternization reactions were checked with spectral tests of the hydrolysis of the isoxazolium salts in nitromethane containing water. Immediate partial hydrolysis was observed with both **12** and **13**, with **10** hydrolysis proceeded very slowly for several days, and no change was observed with **11**. Composition data from both approaches to equilibrium indicate that $K$ is of the order of magnitude of 100 for both **13** and **10**. A smaller value of $K$ (30) was estimated[12] for **12**, while in the case of **11** $K$ must be considerably greater than 100. Although the estimates of the equilibrium constants are relatively crude, a qualitative trend in $K$ for the isoxazolium salts (**11** > **13** ~ **10** > **12**) is established which does not correlate with the polar effects of the quaternizing groups.[13] However, these results are in accord with a predominant steric influence on the equilibrium. Increasing the bulk of the N-alkyl substituent by replacing a methyl group with the larger phenyl group[14] makes the equilibrium less favorable for formation of **12** relative to **10** and for **13** relative to **11**. The effect of increasing the bulk still more with 1,1-diphenylethanol cannot be assessed because of the special stability of the derived alkene, but the equilibrium is clearly unfavorable with the trityl group.

(7) R. B. Woodward and D. J. Woodman, *J. Amer. Chem. Soc.*, **88**, 3169 (1966).

(8) Assuming that under the reaction conditions a phenyl group stabilizes a carbonium ion relative to the carbinol to a somewhat greater extent than do two methyl groups.[9]

(9) A. Streitweiser, Jr., "Solvolytic Displacement Reactions," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p 43.

(10) The N-benzyl salt **9** was isolated in 29% yield from the neat test reaction mixture after 10 months.

(11) It should be noted that some isoxazolium perchlorates have been found to be impact sensitive explosives: B. D. Wilson and D. M. Burness, *J. Org. Chem.*, **31**, 1565 (1966). None of the salts prepared to date have detonated when small samples were subjected to mechanical shock.

(12) The extent of irreversible decomposition with this system at the time of the initial spectral assay, as judged by the rate of change in subsequent spectra, is not great enough to produce a major error in the estimate of $K$.

(13) The $\sigma^*$ values[14] for R of B–$R^+$ are in the order **10** (−0.300) > **12** (estd 0.0) > **11** (0.105) > **13** (0.405).

(14) R. W. Taft, Jr., "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, Chapter 13.

## Experimental Section[15]

**Spectral Tests.**—Assay of the composition of test reaction mixtures was based on the integration of the methyl signals of the isoxazolium salts *vs.* those of the isoxazole at 10–20 cps higher field. Wherever possible integration data for other strong signals was checked against these results. Tests of the preparation of the isoxazolium salts in nitromethane (spectral quality) were conducted with approximately 0.5 *M* concentrations of each reactant, as were hydrolysis tests. With **10**, **11**, and **12** the hydrolysis results were also checked with 0.25 *M* solutions of the isoxazolium salt in nitromethane about 1.1 *M* in water.

**N-Benzyl-3,5-dimethylisoxazolium Perchlorate (9).**—After 10 months the benzyl alcohol spectral test reaction mixture (45% complete by nmr assay) gave 29% of **9** as a gummy solid on dilution with acetone and ether. The pure salt, mp 120–122°, was obtained after several precipitations. The nmr spectrum consisted of signals at $\tau$ 7.43 (s, 3.1), 7.30 (s, 3.0), 4.28 (s, 1.9), 3.15 (s, 1.0), and 2.61 (s, 5.0). The ultraviolet spectrum showed absorption at $\lambda_{max}^{H_2O}$ 232 m$\mu$ ($\epsilon$ 9200) and showed no significant change after 3 days.

*Anal.* Calcd for $C_{12}H_{14}ClNO_5$: C, 50.09; H, 4.91; Cl, 12.31; N, 4.87; O, 27.81. Found: C, 50.23; H, 4.98; Cl, 12.34; N, 5.02; O, 27.74.

**N-*t*-Butyl-3,5-dimethylisoxazolium Perchlorate (10).**—The standard procedure for the preparation of the isoxazolium salts is to add the alcohol (10% excess) and then 70% perchloric acid (10% excess) to the isoxazole slowly with stirring at 0°. On a 50-mmol scale, *t*-butyl alcohol gave 60% of **10** after 2 days upon dilution with acetone followed by a large volume of ether. One precipitation from acetone with ether provided 57% of the pure compound, mp 118–120° dec. The nmr spectrum consisted of signals at $\tau$ 8.17 (s, 9.2), 7.38 (broad, 2.9), 7.22 (s, 2.9), and 3.26 (broad, 1.0). The ultraviolet spectrum had an absorption at $\lambda_{max}^{H_2O}$ 231 m$\mu$ ($\epsilon$ 9100) and showed no change within 1 hr.

*Anal.* Calcd for $C_9H_{16}ClNO_5$: C, 42.61; H, 6.36; Cl, 13.98; N, 5.52; O, 31.54. Found: C, 42.55; H, 6.28; Cl, 13.88; N, 5.50; O, 31.44.

**N-α-Methylbenzyl-3,5-dimethylisoxazolium Perchlorate (11).**—The standard procedure with α-methylbenzyl alcohol resulted in a cloudy mixture which partially solidified when stirred overnight. Dilution with acetone and ether the following day gave an 86% yield of **11**. One precipitation provided 82% of the pure compound, mp 83.5–84.5°. The nmr spectrum consists of signals at $\tau$ 7.95 (d, $J$ = 7 Hz, 3.1), 7.36 (s, 5.9); 3.90 (m, $J$ = 7 Hz, 0.9), 3.18 (s, 0.9), and 2.68 (s, 5.1).

*Anal.* Calcd for $C_{13}H_{16}ClNO_5$: C, 51.75; H, 5.35; Cl, 11.75; N, 4.64; O, 26.51. Found: C, 51.76; H, 5.27; Cl, 11.61; N, 4.66; O, 26.72.

**N-α,α-Dimethylbenzyl-3,5-dimethylisoxazolium Perchlorate (12).**—With α,α-dimethylbenzyl alcohol the standard procedure gave a cloudy mixture which solidified when stirred. After 2 days addition of 1:1 acetone–nitromethane rapidly followed by ether gave 54% of **12**. One precipitation provided 49% of the pure compound, mp 82–83°. The major nmr signals attributable to **12** in a freshly prepared solution were $\tau$ 7.93 (s, 3), 7.85 (s, 6), 7.25 (s, 3), 3.16 (s, 1), and 2.56 (s, 5). The abnormally high-field ($\tau$ 7.93) methyl singlet is assigned to the 3 substituent, shielded by the benzene ring of the quaternizing group.

*Anal.* Calcd for $C_{14}H_{18}ClNO_5$: C, 53.25; H, 5.75; Cl, 11.23; N, 4.44; O, 25.34. Found: C, 53.45; H, 5.73; Cl, 11.10; N, 4.53; O, 25.54.

**N-Benzhydryl-3,5-dimethylisoxazolium Perchlorate (13).**—The standard procedure with enough nitromethane to bring the benzhydrol into solution gave a mixture which partially solidified on standing overnight, and dilution with nitromethane and ether gave 70% of **13**. Precipitation gave 63% of the pure compound, mp 160° dec.

*Anal.* Calcd for $C_{18}H_{18}ClNO_5$: C, 59.42; H, 4.99; Cl, 9.75; N, 3.85; O, 21.99. Found: C, 59.17; H, 5.22; Cl, 9.76; N, 3.93; O, 21.72.

**Registry No.**—**9**, 16404-24-3; **10**, 16315-65-4; **11**, 16315-66-5; **12**, 16315-67-6; **13**, 16315-68-7.

**Acknowledgment.**—Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society for support of this research.

(15) Melting points were taken on a Mel-Temp capillary apparatus and are uncorrected. The nmr spectra (Varian A-60 spectrometer) of **9–12** were recorded in deuteriochloroform solution; chemical shifts are reported in $\tau$ values relative to tetramethylsilane as an internal standard ($\tau$ 10.00 ppm). Analyses were performed by Alfred Bernhardt, Mikroanalytisches Laboratorium im Max-Planck Institut, Mülheim (Ruhr), West Germany.

# Synthesis of Certain Naturally Occurring 2-Pyrones *via* 3,5-Diketo Acids[1]

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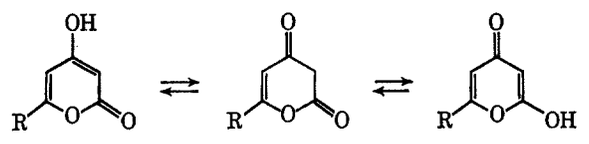
*Received August 23, 1967*

Two naturally occurring 4-methoxy-2-pyrones, 4-methoxyparacotoin and yangonin, were prepared by a three-step procedure involving carboxylation of disodio β-diketones, cyclization of the resulting diketo acids to 4-hydroxy-2-pyrones through the use of acetic anhydride, and O-methylation of the 4-hydroxy-2-pyrones at the 4 position. A partial synthesis of the hydroxypyrone, hispidin, was achieved. The synthesis of anibine was unsuccessful.

A number of 4-hydroxy-2-pyrones[2] and their methyl ethers have been isolated from natural sources.[3] Early interest in these compounds arose from their medicinal properties. In 1953, Birch and Donovan suggested that the 4-hydroxy-2-pyrones are biosynthesized by condensation of two acetate units with appropriate carboxylic acids to give diketo acids which subsequently lactonize.[4] Current interest has stemmed from the




(1) This work was supported by the National Institutes of Health, U. S. Public Health Service (Research Grant GM-12848).

(2) 4-Hydroxy-2-pyrones are in equilibrium with the tautomeric 2-hydroxy-4-pyrones and dihydropyran-2,4-diones. Spectroscopic evidence indicates that the 4-hydroxy-2-pyrone tautomer usually predominates; see F. M. Dean, "Naturally Occurring Oxygen Ring Compounds," Butterworth and Co. Ltd., London, 1963, Chapter 4.

(3) For leading references, see (a) W. B. Mors, O. R. Gottlieb, and C. Djerassi, *J. Amer. Chem. Soc.*, **79**, 4507 (1957); (b) O. R. Gottlieb and W. B. Mors, *J. Org. Chem.*, **24**, 17 (1959); (c) R. L. Edwards, D. G. Lewis, and D. V. Wilson, *J. Chem. Soc.*, 4995 (1961); (d) A. Penttila and J. Sundman, *Acta Chem. Scand.*, **15**, 839 (1961); (e) P. E. Brenneisen, T. E. Acker, and S. W. Tanenbaum, *J. Amer. Chem. Soc.*, **86**, 1264 (1964); (f) A. K. Ganguly, T. R. Govindachari, and P. A. Mohamed, *Tetrahedron*, **21**, 93 (1965); (g) T. M. Harris, C. M. Harris, and R. J. Light, *Biochim. Biophys. Acta*, **121**, 420 (1966); (h) R. Bentley and P. M. Zwitkowits, *J. Amer. Chem. Soc.*, **89**, 676 (1967).

(4) A. J. Birch and F. W. Donovan, *Aust. J. Chem.*, **6**, 360 (1953).