Synthesis of 3(2*H*)-Furanones by the Iron Carbonyl-promoted Cyclocoupling Reaction of α,α'-Dibromo Ketones and Carboxamides. A Convenient Route to Muscarines[1,2]

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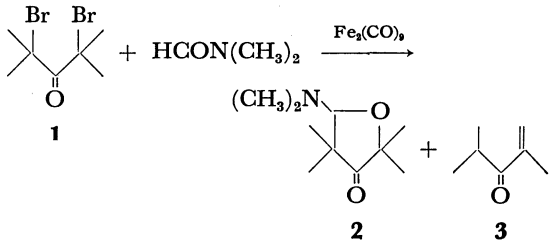
(Received February 21, 1977)

Reaction of α,α'-dibromo ketones and *N,N*-dimethylcarboxamides with the aid of $Fe_2(CO)_9$ affords the corresponding reductive cyclocoupling products, 5-(dimethylamino)tetrahydro-3-furanones. In usual, the adducts derived from di-*s*-alkyl ketone dibromides easily eliminated dimethylamine to afford 3(2*H*)-furanones. *N,N*-Dimethylformamide (DMF), *N,N*-dimethylacetamide, *N,N*-dimethylbenzamide, and *N*-methylpyrrolidone have been used as dibromo ketone receptors. Thus, this general method provides a new, singleflask procedure for the preparation of the oxygen-containing five-membered ketones. The iron carbonyl-promoted 3+2 cyclocoupling reaction is interpreted as proceeding *via* a stepwise cycloaddition of a reactive 2-oxyallyl–Fe(II) intermediate and carboxamide. A facile conversion of such furanones to muscarine alkaloids is described.

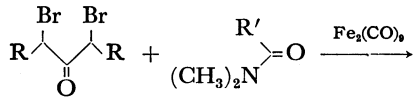
We have developed the iron carbonyl-assisted cyclocoupling reaction between α,α'-dibromo ketones and olefins[3] or dienes,[4] which provides a new tool for making various carbocyclic frameworks. Our recent work has shown that this reaction can be extended to the preparation of a heterocyclic system, 3(2*H*)-furanones, when carboxamides are employed as the unsaturated substrate.[2] The furanones are an important class of compounds in connection with the chemistry of various natural products; particularly, they may be expected to serve as versatile precursors of muscarine alkaloids. These unsaturated five-membered compounds are also followed with great theoretical interest as significant substances for the examination of possible keto-enol tautomerization of heterocycles.[5] Consequently, a variety of preparative methods have been reported.[5] However, most of them can form the derivatives of only certain paticular types and are not generally useful. The approaches that have a general usefulness are, we feel: (1) The preparation of 5-alkyl derivatives by the hydrogenolysis of 3-alkylisoxazoles, followed by acid-catalyzed cyclization;[6] (2) the acid-catalyzed rearrangement of 4-alkylidene-1,3-dioxolanes to alkylated 3(2*H*)-furanones;[7,8] (3) the synthesis of 2-acyl-3-alkyl derivatives by the pyrolytic reaction of dimethylsulfonium acyl-(3-alkylpropionyl)methylide,[9] and (4) the formation of the 2,2-dialkyl compounds *via* the reaction of 2-lithio-2-(2,2-dimethoxyethyl)-1,3-dithiane and ketones, followed by hydrolysis.[10] This paper will describe a general, expeditious route to 2,4-dialkyl-3(2*H*)-furanones *via* the iron carbonyl aided 3+2 cyclocoupling of α,α'-dibromo ketones and carboxamides, and its application to the synthesis of muscarines.

Results and Discussion

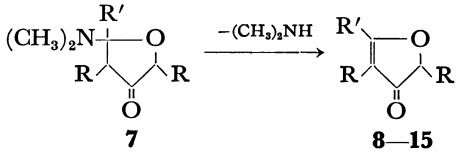
Cyclocoupling Reaction between α,α'-Dibromo Ketones and Carboxamides. A. Reaction with Tertiary Dibromoketones: Reduction of 2,4-dibromo-2,4-dimethyl-3-pentanone (**1**) with $Fe_2(CO)_9$ (1 : 1 mol ratio) was carried out in dry DMF solvent containing disodium dihydrogen ethylenediaminetetraacetate (Na_2H_2edta) under nitrogen atmosphere. The reaction proceeded smoothly at room temperature to give, after usual extractive work-up, the cyclic product **2** and the enone **3** in 3 and 80% yields, respectively. The minor compound **2** gave, in its IR spectrum, the carbonyl absorption at 1756 cm^{-1} characteristic of five-membered ketones, and NMR data identical with those previously reported.[7]



1 **2** **3**



4: R = CH_3
5: R = C_2H_5
6: R = $CH(CH_3)_2$
16: R = $C(CH_3)_3$



7 **8—15**

Scheme 1.

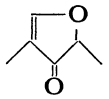
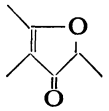
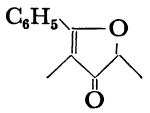
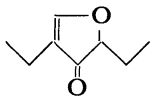
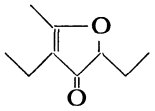
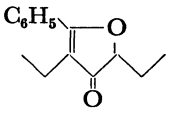
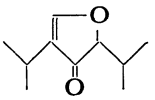
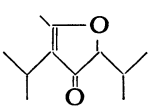
B. Reaction with Secondary Dibromo Ketones: As is outlined in Scheme 1, the reaction of secondary dibromo ketones and *N,N*-dimethylated carboxamides with the aid of $Fe_2(CO)_9$ first led to labile 2,4-dialkyl-5-(dimethylamino)tetrahydro-3-furanones of type **7**, which in turn underwent the facile elimination of dimethylamine to produce 3(2*H*)-furanone derivatives **8**—**15**. The overall transformation can be viewed formally as the construction of a carbon-oxygen bridge between the α and α' positions of the parent dialkyl ketones.

For example, stirring of a mixture of the dibromide **4** and $Fe_2(CO)_9$ (1 : 1.2 mol ratio) in DMF in the presence of Na_2H_2edta at room temperature for 22 h gave, after extractive work-up and distillation, the 3(2*H*)-

furanone **8** in 53% yield. Here, the absence of Na_2H_2-edta in the reaction system resulted in a drastic decrease in yield of this coupling product. Structure determination of **8** was based on the spectral analysis. This product showed strong IR stretching bands at 1704 (C=O) and 1624 cm^{-1} (C=C),[11] and a UV maximum at 270 nm (log ε 3.89) characteristic of 3(2*H*)-furanones.[5-10,12] The NMR spectrum also supported the assigned structure. The presence of an $OCH(CH_3)$-C=O linkage was deduced from a methyl doublet appearing at δ 1.39 with J=7.5 Hz and a one-proton quartet with the same coupling constant at a rather low field, δ 4.31. The vinylic methyl group exhibited a doublet signal at δ 1.67, indicating that the splitting (J=2 Hz) is due to a long-range coupling with the vinylic proton, giving a quartet at δ 7.90.[7] The mass spectrum exhibited a molecular-ion peak confirming the the formula of $C_6H_8O_2$. Notably, this product exists solely in a keto form and did not give a positive $FeCl_3$ test.

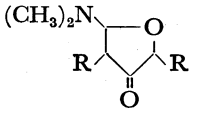
This cyclocoupling reaction is operationally quite simple and has a wide application. In place of DMF, *N*,*N*-dimethylacetamide and *N*,*N*-dimethylbenzamide can be employed as well. Furanones obtained by the cyclocoupling reaction of the secondary dibromides and carboxamides are summarized in Table 1. The product

Table 1. Iron carbonyl-promoted furanone synthesis

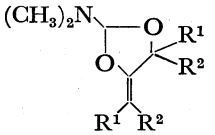
Dibromo ketone	Carboxamide	Furanone product	Yield, %	IR absorptions of neat film, cm^{-1} $\nu_{C=O}$ and $\nu_{C=C}$	UV absorption in C_2H_5OH, nm (log ε)
4	DMF	 **8**	53[b,c]	1695 and 1621 1704 and 1624[d]	270(3.89)
4	$CH_3CON(CH_3)_2$	 **9**	21[c]	1703 and 1636	273(4.06)
4	$C_6H_5CON(CH_3)_2$	 **10**	25[c]	1697 and 1620[d]	225(3.77), 232(3.97) 242(3.79), 306(4.04)
5	DMF	 **11**	78, 64[b]	1700 and 1617	272(3.68)
5	$CH_3CON(CH_3)_2$	 **12**	51[c]	1696 and 1633	272(4.00)
5	$C_6H_5CON(CH_3)_2$	 **13**	42[b,c]	1696 and 1623[d]	237(3.73), 306(3.91)
6	DMF	 **14**	89[e]	1699 and 1618	269(3.89)
6	$CH_3CON(CH_3)_2$	 **15**	87[c,e]	1691 and 1631	273(3.98)

a) Determined by an NMR analysis of the crude reaction mixture. b) Isolated yield. c) Na_2H_2edta (three equiv of the dibromide) was added to the reaction system. d) In CCl_4 solution. e) Result obtained after heating the initial product at 110 °C for 10 min.

yield is usually moderate to high. When the dibromide bears bulky alkyl substituents, the initial adduct **7** can be isolated in a stable form after usual work-up. In such a case, in order to attain complete deamination, brief heating at an elevated temperature is required. Thus, the highly sterically crowded adduct **17** produced from the dibromo ketone **16** and DMF was quite stable and remained unchanged even after heating at 110 °C

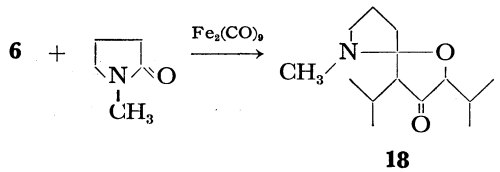


17: R=C(CH$_3$)$_3$
21: R=CH(CH$_3$)$_2$



20: R^1=alkyl; R^2=H
29: R^1=R^2=CH$_3$

for 20 min. Certain lactams can also be used as dibromo ketone receptors. For instance, the reaction of the dibromo ketone **6** and *N*-methylpyrrolidone at room temperature gave rise to the amino furanone **19** in 26% yield. Apparently the formation of **19** resulted from intramolecular deamination of the initial spiro-fused intermediate **18**. Unfortunately, methyl ketone dibromides gave no or little cyclocoupling products. For example, the reaction of α,α′-dibromoacetone and DMF under ordinary reaction conditions failed to afford the coupling product. The use of Fe(CO)$_5$ in place of



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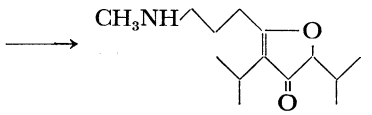

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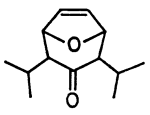
Fe$_2$(CO)$_9$ did not reduce dibromo ketones under comparable thermal conditions; in this case, irradiation by visible light was necessary to achieve the reaction. As has been reported previously,[13] the use of Zn–Cu couple as the reducing agent forms another type of 1:1 coupling product, 1,3-dioxolane **20**, in a fair to good yield; the product can be converted to the furanones by acid treatment.

Reaction Mechanism of the 3+2 Cyclocoupling Reaction. A. The Reactive Species: In the absence of Fe$_2$(CO)$_9$, no reaction took place between dibromo ketones and carboxamides. By contrast, when a reducing agent was added to such a mixture, the cyclocoupling reaction proceeded smoothly. When the reaction of **6** and Fe$_2$(CO)$_9$ was carried out in a 1:1 DMF–furan mixture, both the DMF adduct **21** (65%) and the furan adduct **22**[4a,c] (27%) were produced. These observations strongly indicate that reactive 2-oxyallyl–Fe(II) intermediates of type **23**[14] are generated under the present reaction conditions. The occurrence of such species in DMF has also been suggested by the reductive rearrangement of 2,4-dibromo-6,6-diphenylbicyclo[3.1.0]-hexan-3-one[14] and nucleophilic trapping experiments.[14] This view is also consistent with the formation of the enone **3** as a major product in the reaction of **1**. Thus, carboxamides serve as extremely efficient trapping agents of the oxyallyl intermediate and even compete well with furan. It is also worthwhile to note that the oxyallyl–Fe(II) species **24**, which smoothly undergoes a neopentyl-type rearrangement in benzene,[14] affords the DMF adduct **17** prior to the skeletal change.



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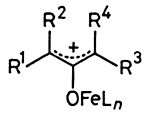
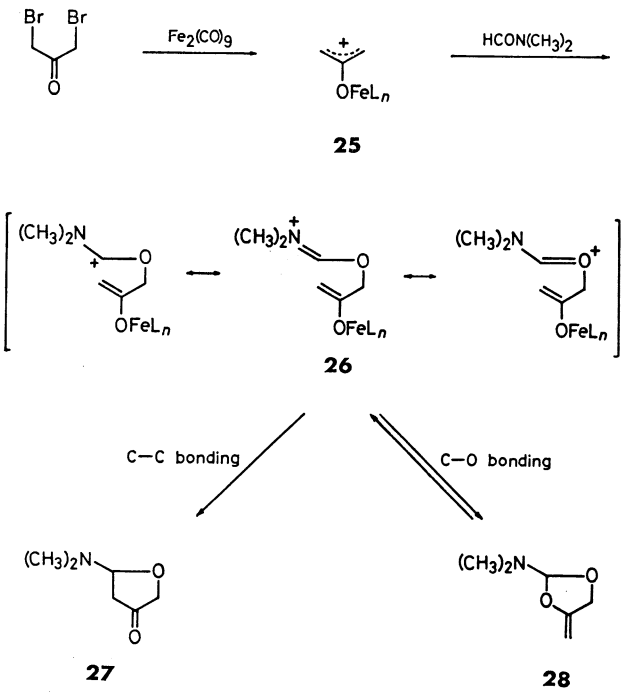


23, R^1—R^4=alkyl or H
24, R^1=R^4=C(CH$_3$)$_3$; R^2=R^3=H
L=CO, Br, solvent, *etc.*

B. Reaction Course of Cycloaddition of the Oxyallyl Species and Carboxamides: The cycloaddition is best accounted for by the path outlined in Scheme 2, where, for the sake of simplicity, the reaction of unsubstituted oxyallyl **25** and DMF is taken up. First, there occurs the electrophilic attack of **25** on the oxygen atom of DMF, producing the highly stable ionic intermediate **26**. Subsequent cyclization through bonding between the cationic and enolate carbons results in the adduct **27**. The zwitterionic intermediate **26** may also undergo the C–O cyclization, thus giving the dioxolane product **28**;[13] the reverse process, if possible, could lead ultimately to the more stable product **27**. Indeed, treatment of **29** with FeBr$_2$ in DMF gave **2** in a moderate (20—30%) yield. However, there has not yet been any direct evidence for the presence of the equilibrium, **26**⇄**28**. When the reaction course was monitored, the dioxolane

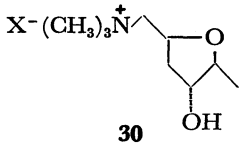


Scheme 2.

product **28** could not be detected at any stage of the reaction.

In any events, the intermediacy of the resonance-stabilized ionic intermediate **26** appears to be crucial for the cyclization to proceed. Thus, the overall process can be envisaged as a stepwise [$_\pi$2+$_\pi$2] cycloaddition. A related stepwise mechanism has been claimed for the reaction forming certain carbocyclic five-membered skeletons.[3] The dioxolane **28**, even if formed, cannot be derived through a concerted [$_\pi$2+$_\pi$4]-type cycloaddition of an electron-accepting oxyallyl, **23**, and an electron-donating carboxamide, because, in the lowest unoccupied molecular orbital of **23**, the orbital does not develop over the oxygen atom to any great extent.[15]

Application to Muscarine Synthesis. In the natural field, there are many compounds with the furanone or related skeletons. Muscarine (**30**) isolated from fly agaric [*Amantia muscaria* (L. ex Fr.) Quel.] is a representative compound. This alkaloid has long attracted the attention of pharmacologists and chemists because of its marked and peculiar actions on the autonomic nervous system. This product, however, exists in such small amounts in natural plants that a satisfactory supply of the alkaloids is difficult to obtain only by extraction; hence, an efficient method of preparing muscarine



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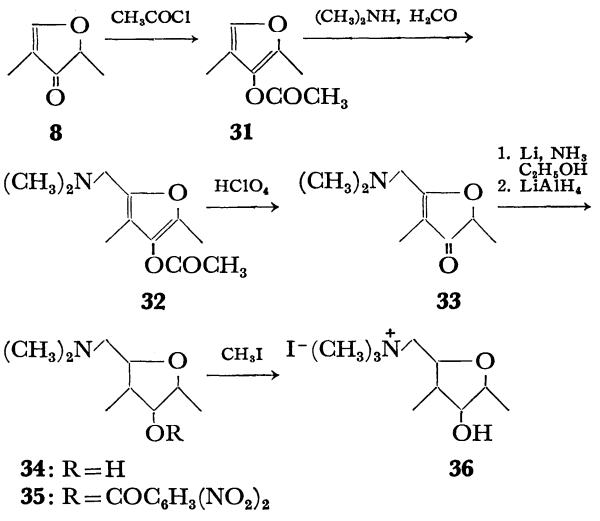
chemically has been sought for a long period. The synthetic methods thus far developed can be broadly divided, in terms of the construction mode of the heterocyclic system, into the following four types:[16] (1) the diazotization of β,γ-dihydroxy α-amino acids such as glucosamine[17] and 2-amino-4,5-dihydroxyhexanoic acid,[18] affording 3-hydroxytetrahydrofuran rings; (2) the condensation of iodopropionic ester and malic ester[19] or, more conveniently, of α-hydroxypropionic ester and maleic or fumaric ester[20] to form 4,5-bis-(ethoxycarbonyl)-2-methyltetrahydro-3-furanone; (3) the condensation of epichlorohydrin and sodioacetoacetic ester, giving α-acetyl-δ-chloro-γ-valerolacetone;[21] and (4) the condensation of glucose or mannose and β-keto carboxylic ester to produce 2-methyl-5-tetrahydroxybutylfuran-2-carboxylic ester.[22] We will describe here a new general entry into muscarine analogs[23] starting from the 2,4-dialkyl-3(2*H*)-furanones obtained by the iron carbonyl-promoted cyclocoupling reaction of dibromo ketones and DMF. The method is based on the introduction of a dimethylaminomethyl group to the C_5 position of the furanones.

The route to 4-methylmuscarine iodide (**36**) is shown in Scheme 3. First, treatment of **8** with acetyl chloride in 1,2-dimethoxyethane afforded the acetoxy furan **31** in 68% yield. The IR absorption at 1760 cm^{-1} was instructive in determining the enol acetate structure. Further, in the NMR spectrum, a sharp three-proton singlet appeared at δ 2.21, confirming the presence of an acetyl group. The furan-ring structure was supported



Scheme 3.

by a finely splitting quartet at δ 6.92. The Mannich aminomethylation of **31** was performed with 40% aq dimethylamine and 37% aq formaldehyde in acetic acid[24] at 70 °C, producing the amino furan **32** in 80% yield. The IR spectrum showed absorptions of the $N(CH_3)_2$ group at 2840, 2795, and 2745 cm^{-1}. In addition, the introduction of the dimethylaminomethyl function to C_5 was confirmed by the NMR characteristics, *viz.*, the appearance of two singlets at δ 2.28 and 3.42 (3: 1 ratio), and the disappearance of a low-field signal due to the vinyl proton. Hydrolysis of **32** by heating with 70% $HClO_4$ gave the furanone **33** in >95% yield. The occurrence of 3(2*H*)-furanone skeleton was confirmed by strong IR bands at 1698 (C=O) and 1623 cm^{-1} (C=C) as well as by a UV maximum at 274 nm (log ε 4.01).[12] In the NMR spectrum, there appeared a coupled three-proton doublet and a one-proton quartet at δ 1.37 and 4.24 (J=7.0 Hz), respectively, indicating the presence of an $OCH(CH_3)C{=}O$ moiety. The Birch reduction of **33** using Li–ethanol, followed by $LiAlH_4$ treatment,[25] formed desired 4-methylnormuscarine (**34**, two stereoisomers) in 61% yield. The presence of the OH function was confirmed by a broad IR absorption at 3400—3200 cm^{-1}, and the NMR spectrum confirmed the existence of two secondary methyls. Finally, treatment of **34** with methyl iodide in benzene produced 4-methylmuscarine iodide (**36**) quantitatively. The quaternization was monitored by appearance of the NMR signal at δ 3.21 due to $\overset{+}{N}(CH_3)_3$.[26] 4-Methylmuscarine iodide (**36**) thus obtained displayed the physiological activities characteristic of muscarine alkaloids; the smooth muscle of the intestinal tract was stimulated, increasing tone and mobility, while atropine inhibited these actions.

Experimental

General. All melting and boiling points are uncorrected. The IR spectra were measured on a JASCO IR-A-I or JASCO DS-402G spectrometer in the noted phase. The UV spectra were taken on a Perkin-Elmer Model 202 or a Hitachi Model 323 spectrometer in ethanol solution. The IR and UV spectral data of 3(2*H*)-furanones **8**—**15** are listed in Table 1.

The NMR spectra were recorded on a JEOL C-60H instrument in CCl_4 solution unless otherwise stated; the chemical shifts are given in ppm downfield from internal tetramethylsilane. 1,1,2,2-Tetrachloroethane or tetralin was used as the standard for the quantitative analysis. The mass spectra (MS) were obtained on a Hitachi RMU-6C mass spectrometer, operating with an ionization energy of 70 eV. The exact MS were performed at the Faculty of Agriculture, Nagoya University, and at the Hitachi Naka Works. Elemental analyses were carried out at the Analytical Centers of Kyoto University and Meijo University. All $Fe_2(CO)_9$-assisted cyclocoupling reactions were performed under nitrogen atmosphere. Drying of organic extracts was done over anhyd Na_2SO_4. For concentration of organic solvents, a vacuum (60—90 Torr) rotary evaporator was used. Products on TLC plates were detected by irradiation of UV-light (254 nm), by a spray of $Ce(SO_4)_2$ in 65% H_2SO_4 or molybdophosphoric acid in 10% ethanol, followed by heating, or by exposure to I_2 vapor.

Chromatography. GLPC analysis and separation were performed on a Yanagimoto Model G-8, Yanagimoto Model GCG-3D, or Varian 1700 instrument. Columns used were: A, 3 mm×2 m 5% poly(ethylene glycol succinate) on Chromosorb W AW; B, 3 mm×2 m 5% poly(ethylene glycol) on Celite 545; C, 4 mm×4 m 10% LAC on Chromosorb W AW; D, 3 mm×2 m 5% Silicone OV-1 on Chromosorb W AW; E, 4 mm×2 m 12% diisodecyl phthalate on Neopak 1A; F, 3 mm×2 m 5% Apiezon grease L on Diasolid M; G, 5 mm×2 m 33% Apiezon grease L on Neopak 1A. Analytical and preparative TLC were done on E. Merck alumina GF_{254} plates. For column chromatography, Woelm basic alumina (Activity I) was employed.

Solvents and Materials. α,α′-Dibromo ketones **1**, **4**—**6**, and **16** were prepared by the procedures in the literature.[27,28] Oily dibromides were purified by passing them through a short alumina column immediately before use. Photolytic preparation of $Fe_2(CO)_9$ from $Fe(CO)_5$ was carried out according to the method of King.[29] The carbonyl complex was used after drying over KOH in a vacuum desiccator. 2-Dimethylamino-4-isopropylidene-5,5-dimethyl-1,3-dioxolane (**29**) solution in DMF (*ca.* 0.3 M) was obtained by the procedure of Hoffmann.[13] Dry DMF was produced by refluxing over CaH_2 at 60 °C under reduced pressure (20 mm) for 4 h, followed by distillation *in vacuo*; it was stored over molecular sieves 3A under nitrogen. Other carboxamides were used after a simple distillation of the commercially supplied ones. Benzene, tetrahydrofuran (THF), and 1,2-dimethoxyethane (DME) were distilled from $LiAlH_4$. Furan was distilled from CaH_2. Disodium dihydrogen ethylenediaminetetraacetate (Na_2H_2edta) dihydrate was dehydrated by heating it at 120 °C (0.01 mm) for 12 h.

Reaction of 2,4-Dibromo-2,4-dimethyl-3-pentanone (1) with $Fe_2(CO)_9$ in DMF. A mixture of the dibromo ketone **1** (833 mg, 3.06 mmol), $Fe_2(CO)_9$ (1.31 g, 3.60 mmol), and octane (32.5 mg, 0.29 mmol, an internal standard for GLPC analysis) in DMF (10.5 ml) was stirred at room temperature for 18 h. GLPC analysis of the reaction aliquots taken up at appropriate intervals showed the formation of three products. These products were identified, by comparison with authentic samples, as 5-(dimethylamino)tetrahydro-2,2,4,4-tetramethyl-3-furanone (**2**) [retention time (t_r) 9.8 min, column F, 130 °C, 3% yield], 2,4-dimethyl-1-penten-3-one (**3**) (t_r 7.8 min, column E, 90 °C, 80% yield), and 2,4-dimethyl-3-pentanone (t_r 6.5 min, column E, 90 °C, 9% yield). An analytical sample of **2** was obtained by GLPC separation (column G, 123 °C). Its spectral (IR, NMR, and mass) data were identical with the reported ones[9] (Found: C, 65.00; H, 10.47%).

2,4-Dimethyl-3(2H)-furanone (8). A mixture of 2,4-dibromo-3-pentanone (**4**) (8.70 g, 35.6 mmol), $Fe_2(CO)_9$ (15.6 g, 42.8 mmol), and Na_2H_2edta (18.0 g, 53.3 mmol) in DMF (80 ml) was stirred at room temperature for 12 h. After addition of benzene (80 ml), the reaction mixture was left at room temperature for 10 h and then poured into water (400 ml). The aq mixture was extracted with 1:1 ether-petroleum ether (160 ml×5). The combined organic extracts were washed with water (120 ml×3) and dried. The solvent was removed to give a dark brown oil (4.06 g). Upon addition of petroleum ether (80 ml), dark brown precipitates appeared immediately, which were then removed by filtration. Concentration of the filtrate gave a yellow oil (2.46 g), which was distilled at room temperature—70 °C (0.2 Torr) to afford the furanone **8** (2.11 g, 53% yield) as a colorless oil. NMR δ 1.39 (d, 3, J=7.5 Hz, CHC$\underline{H}_3$), 1.67 (d, 3, J=2 Hz, =CC$\underline{H}_3$), 4.31 (q, 1, J=7.5 Hz, C$\underline{H}$CH$_3$), and 7.90 (q, 1, J=2 Hz, =CH); MS *m/e* 112 (M^+). Found: *m/e* 112.0519. Calcd for $C_6H_8O_2$: M, 112.0523.

2,4,5-Trimethyl-3(2H)-furanone (9). A mixture of the dibromide **4** (488 mg, 2.00 mmol), $Fe_2(CO)_9$ (876 mg, 2.40 mmol), and Na_2H_2edta (2.03 g, 6.00 mmol) in *N,N*-dimethylacetamide (7.0 ml) was magnetically stirred at room temperature for 19 h. The reaction mixture was quenched by addition of saturated KNO_3 solution (20 ml) and extracted with ethyl acetate (5 ml×6). The combined organic extracts were washed with water (5 ml×3), dried, and concentrated, thus giving a red oil (168 mg). The NMR analysis showed that the furanone **9** was produced in 21% yield. An analytical sample (R_f 0.70) was obtained by TLC separation (CH_2Cl_2), followed by distillation. NMR δ 1.35 (d, 3, J=7.5 Hz, CHC$\underline{H}_3$), 1.62 (s, 3, =CC$\underline{H}_3$), 2.15 (s, 3, =CC$\underline{H}_3$), and 4.25 (q, 1, J=7.5 Hz, C$\underline{H}$CH$_3$); MS *m/e* 126 (M^+). Found: *m/e* 126.0690. Calcd for $C_7H_{10}O_2$: M, 126.0680.

2,4-Dimethyl-5-phenyl-3(2H)-furanone (10). To a suspension of $Fe_2(CO)_9$ (876 mg, 2.40 mmol) and Na_2H_2edta (2.03 g, 6.00 mmol) in benzene (5.0 ml) were added *N,N*-dimethylbenzamide (7.0 ml) and then the dibromo ketone **4** (488 mg, 2.00 mmol). The resulting mixture was stirred at room temperature for 19 h. The mixture was added to saturated KNO_3 solution (10 ml), and the aq mixture was extracted with 1:2 benzene–hexane (6 ml×6). The organic layers were collected, washed with water (6 ml×6), and dried. Evaporation of the solvent afforded a pale yellow oil, NMR analysis of which indicated the formation of the furanone **10** in 25% yield. TLC (1:10 ether–hexane, R_f 0.70), followed by short-path distillation, formed an analytical specimen of **10**. NMR δ 1.48 (d, 3, J=7.5 Hz, CHC$\underline{H}_3$), 1.95 (s, 3, =CC$\underline{H}_3$), 4.46 (q, 1, J=7.5 Hz, C$\underline{H}$CH$_3$), and 7.45 (m, 3) and 7.74 (m, 2) (C_6H_5); MS *m/e* 188 (M^+). Found: *m/e* 188.0854. Calcd for $C_{12}H_{12}O_2$: M, 188.0836.

2,4-Diethyl-3(2H)-furanone (11). A mixture of 3,5-dibromo-4-heptanone (**5**) (462 mg, 1.70 mmol) and $Fe_2(CO)_9$ (876 mg, 2.40 mmol) in DMF (7.0 ml) was stirred at room temperature for 12 h. The reaction mixture was treated with saturated aq Na_2H_2edta solution (40 ml) and extracted with 1:1 ethyl acetate–hexane (8 ml×5). The collected organic extracts were washed with water (8 ml×3) and dried. The solvent was removed under reduced pressure at room temperature to afford a residual oil (273 mg). Its NMR spectrum indicated that the furanone **11** was produced in 92% yield. This oil was dissolved in ethyl acetate (5 ml) and passed through a short column packed with alumina using ethyl acetate as eluent. Concentration of the filtrate gave the

furanone **11** (152 mg, 64% yield) as a pale yellow oil. An analytical sample was obtained by preparative GLPC (column A, 120 °C). NMR δ 0.97 (t, 3, J=7.0 Hz, CH_3), 1.08 (t, 3, J=7.0 Hz, CH_3), 1.5—2.4 (m, 4, 2 CH_2), 4.21 (dd, 1, J=4.5 and 7.0 Hz, OCHCO), and 7.90 (br s, 1, =CH); MS *m/e* 140 (M^+). Found: C, 68.38; H, 8.87%. Calcd for $C_8H_{12}O_2$: C, 68.54; H, 8.63%.

2,4-Diethyl-5-methyl-3(2H)-furanone (12). To a mixture of $Fe_2(CO)_9$ (876 mg, 2.40 mmol) and Na_2H_2edta (2.03 g, 6.00 mmol) was added *N,N*-dimethylacetamide (7.0 ml), followed by the dibromo ketone **5** (462 mg, 1.70 mmol). The resulting mixture was stirred at room temperature. After 19 h, saturated KNO_3 solution (20 ml) was added to the reaction mixture, and the aq layer was extracted with ethyl acetate (6 ml×5). The combined organic extracts were washed with water (40 ml×3) and dried. On removal of the solvent there was obtained a pale yellow oil. Addition of benzene (2 ml) yielded insoluble brown solides. The precipitates were removed by filtration through a short column of alumina and evaporation of the solvent afforded a colorless oil (130 mg). Yield of the furanone **12**, as estimated by NMR analysis, was 51%. Preparative TLC (1: 1 benzene–hexane) gave **12** as an oil. An analytical sample was obtained by preparative GLPC (column A, 120 °C). NMR δ 0.96 (t, 3, J=7.0 Hz, $CH_2C\underline{H}_3$), 1.01 (t, 3, J=7.5 Hz, $CH_2C\underline{H}_3$), 2.15 (s, 3, $=CCH_3$), 1.4—2.4 (m, 4, 2 CH_2), and 4.12 (dd, 1, J= 6.0 and 7.0 Hz, OCH); MS *m/e* 154 (M^+). Found: C, 70.32; H, 9.57%. Calcd for $C_9H_{14}O_2$: C, 70.01; H, 9.15%.

2,4-Diethyl-5-phenyl-3(2H)-furanone (13). To a mixture of $Fe_2(CO)_9$ (876 mg, 2.40 mmol) and Na_2H_2edta (2.03 g, 6.00 mmol) in benzene (5.0 ml) was added *N,N*-dimethylbenzamide (7.0 ml) and the dibromide **5** (462 mg, 1.70 mmol). The resulting mixture was kept, with stirring at room temperature for 14 h and then quenched with saturated KNO_3 solution. The aq layer was extracted with ethyl acetate (6 ml×5), and the combined organic extracts were washed with water (6 ml ×2) and dried. Removal of the solvent gave a feebly yellow oil (6.0 g), which without solvent, was heated at 110 °C for 15 min under nitrogen. After dilution with 1: 2 benzene–hexane (10 ml), the product was washed with water (4 ml×4) and dried. The organic solvent was evaporated to afford a pale yellow oil (873 mg). Purification by preparative TLC (benzene) yielded the furanone **13** (R_f 0.38, 175 mg, 42% yield) as a colorless oil. NMR δ 1.00 (t, 3, J=7.0 Hz, CH_3), 1.13 (t, 3, J=7.0 Hz, CH_3), 1.6—2.2 (m, 2, $CHC\underline{H}_2$), 2.41 (q, 2, J=7.0 Hz, $=CCH_2$), 4.32 (dd, 1, J=5.0 and 6.5 Hz, OCH), and 7.40 (m, 3) and 7.72 (m, 2) (C_6H_5); MS *m/e* 216 (M^+). Found: *m/e* 216.1119. Calcd for $C_{14}H_{16}O_2$: M, 216.1149.

2,4-Diisopropyl-3(2H)-furanone (14). A mixture of 3,5-dibromo-2,6-dimethyl-4-heptanone (**6**) (300 mg, 1.00 mmol) and $Fe_2(CO)_9$ (437 mg, 1.20 mmol) in DMF (3.5 ml) was stirred at room temperature for 12 h. The reaction mixture was poured into saturated aq $NaHCO_3/KNO_3$ solution (10 ml) and extracted with ethyl acetate (4 ml×5). The collected organic extracts were washed with water (4 ml×3) and dried sufficiently. The solvent was removed under reduced pressure to give a crude yellow oil (192 mg) containing mainly 5-(dimethylamino)-2,4-diisopropyltetrahydro-3-furanone (**21**). IR (neat film) 1753 cm^{-1} (C=O); NMR δ 0.8—1.3 (m, 12, 2 $CH(C\underline{H}_3)_2$), 1.8—2.4 (m, 3, 2 $C\underline{H}(CH_3)_2$ and $CHC\underline{H}CO$), 2.47 (s, 6, $N(CH_3)_2$), 3.40 (d, 1, J=4.5 Hz, OCHCO), and 4.57 (d, 1, J=9.0 Hz, OCHN); MS *m/e* 213 (M^+). The neat oil was heated at 140 °C for 15 min under nitrogen, followed by distillation *in vacuo* (60 °C, 1 Torr), to afford the furanone **14** (149 mg, 89% yield). NMR δ 0.83 (d, 3, J= 7.0 Hz, $CHCH(C\underline{H}_3)_2$), 1.12 (d, 3, J=6.5 Hz, $CHCH(C\underline{H}_3)_2$), 1.15 (d, 6, J=7.0 Hz, $=CCH(C\underline{H}_3)_2$), 2.0—2.8 (m, 2, 2 $C\underline{H}(CH_3)_2$), 4.10 (d, 1, J=3.8 Hz, OCHCO), and 7.89 (br s, 1, =CH); MS *m/e* 168 (M^+). Its structure was further confirmed by converting it through hydrogenation, into 2,4-diisopropyltetrahydro-3-furanone. A suspension of 10% Pd–C (500 mg) in ethanol (4 ml) was stirred at room temperature for 24 h under 1-atm hydrogen. To this was added a solution of **14** (1.00 g, 5.95 mmol) in ethanol (4 ml), and the resulting mixture was stirred at room temperature for 24 h under an atmospheric pressure of hydrogen. The mixture was passed through a Celite 545 column, and the filtrate was concentrated, giving the tetrahydro-3-furanone (*ca.* 1 g) as a single isomer (stereochemistry unconfirmed). An analytical sample of the product was collected by GLPC separation (column B, 100 °C). IR (neat film) 1750 cm^{-1} (C=O); NMR δ 0.8—1.1 (m, 12, 4 CH_3), 1.5—2.4 (m, 3, 2 $C\underline{H}(CH_3)_2$ and $C\underline{H}CH_3$), 3.40 (d, 1, J=5.5 Hz, OCH), and 3.9—4.2 (m, 2, OCH_2); MS *m/e* 170 (M^+). Found: C, 70.30; H, 10.75%. Calcd for $C_{10}H_{18}O_2$: C, 70.54; H, 10.66%.

2,4-Diisopropyl-5-methyl-3(2H)-furanone (15). To a mixture of $Fe_2(CO)_9$ (874 mg, 2.40 mmol) and Na_2H_2edta (2.03 g, 6.00 mmol) was added a solution of the dibromo ketone **6** (600 mg, 2.00 mmol) and tetralin (26.4 mg, 0.20 mmol) in *N,N*-dimethylacetamide (7.0 ml). The resulting mixture was stirred at room temperature for 12 h. The reaction mixture was poured into saturated $NaHCO_3/KNO_3$ solution (20 ml) and extracted with ethyl acetate (8 ml×5). The combined organic extracts were washed with water (8 ml ×3) and dried. After evaporation of the solvent, an oil was obtained. The NMR spectrum of this residue showed two doublets at δ 3.95 (J=3.8 Hz) and 3.38 (J=4.5 Hz) due to the C_2 methine proton of **15** and 5-(dimethylamino)-2,4-diisopropyl-5-methyltetrahydro-3-furanone (**7**, R=$CH(CH_3)_2$; R′=CH_3), respectively. The intensity of signals, as compared with that of a singlet due to the aromatic protons of tetralin internal standard, indicated that **15** and the amino tetrahydro-3-furanone were produced in 49 and 39% yields, respectively. When the crude oil was heated at 110 °C for 15 min under nitrogen, **15** was obtained as an oily product (316 mg, 87% yield). Distillation (90 °C, 3 mm), followed by preparative GLPC (column C, 108 °C), afforded an analytical sample. NMR δ 0.79 (d, 3, J=6.5 Hz, $CHCH(C\underline{H}_3)_2$), 1.05 (d, 3, J=6.5 Hz, $CHCH(C\underline{H}_3)_2$), 1.15 (d, 6, J=7.0 Hz, $=CCH(C\underline{H}_3)_2$), 2.15 (s, 3, $=CCH_3$), 2.0—2.8 (m, 2, 2 $C\underline{H}(CH_3)_2$), and 3.95 (d, 1, J=3.8 Hz, OCH); MS *m/e* 182 (M^+). Found: *m/e* 182.1295. Calcd for $C_{11}H_{18}O_2$: M, 182.1305.

2,4-Di-t-butyl-5-(dimethylanmio)tetrahydro-3-furanone (17). To a mixture of 3,5-dibromo-2,2,6,6-tetramethyl-4-heptanone (**16**) (110 mg, 0.34 mmol) and $Fe_2(CO)_9$ (146 mg, 0.40 mmol) was added DMF(1.0 ml). The resulting suspension was stirred at room temperature for 17 h. The reaction mixture was diluted with 1:1 ethyl acetate–hexane (5 ml) and then quenched by saturated aq $NaHCO_3$ solution (5 ml). The organic layer was washed with water and dried. After removal of the solvent, the residue was purified TLC (ethyl acetate) to give **17** (79 mg, 98% yield) as a slightly yellow oil. IR (CCl_4) 1746 cm^{-1} (C=O); NMR δ 0.97 (s, 9, $C(CH_3)_3$), 1.02 (s, 9, $C(CH_3)_3$), 1.93 (d, 1, J=9.0 Hz, $CHC\underline{H}C(CH_3)_3$), 2.48 (s, 6, $N(CH_3)_2$), 3.18 (s, 1, OCHCO), and 4.59 (d, 1, J=9.0 Hz, OCHN); MS *m/e* 241 (M^+). Found: *m/e* 241.2017. Calcd for $C_{14}H_{27}NO_2$: M, 241.2042.

Quaternization of **17** with CH_3I(excess) in benzene at 50 °C for 14 h afforded colorless plates; mp 152—156 °C (from 1: 1 acetone–hexane).

2,4-Diisopropyl-5-(3-methylaminopropyl)-3(2H)-furanone (19). Dry *N*-methylpyrrolidone (25 ml) and the dibromide **6** (0.90 g, 3.00 mmol) were added sequentially to $Fe_2(CO)_9$ (1.30 g, 3.60

mmol), and the resulting mixture was stirred at room temperature for 48 h, during which period a characteristic dark red color developed. The reaction mixture was quenched by saturated NaCl solution and extracted with ethyl acetate. The organic layer was washed with brine and dried. Evaporation of the solvent at room temperature *in vacuo* left a deepred oil (644 mg). This residue was distilled under reduced pressure to give a yellow oil; bp 140 °C (0.05 Torr). Purification by TLC (1:1 ether–hexane) afforded the amino furanone **19** (187 mg, 26% yield) as a pale yellow oil. IR (CCl_4) 1690 (C=O) and 1620 cm^{-1} (C=C); UV 274 nm (log ε 4.04); NMR δ 0.83 (d, 3, J= 6.5 Hz, $CHCH(C\underline{H}_3)_2$), 1.09 (d, 3, J=6.5 Hz, $CHCH(C\underline{H}_3)_2$), 1.17 (d, 3, J=7.0 Hz, $=CCH(C\underline{H}_3)_2$), 1.20 (d, 3, J=7.0 Hz, $=CCH(C\underline{H}_3)_2$), 1.4—2.5 (m, 9, 2 $C\underline{H}(CH_3)_2$, 3 CH_2, and NH), 2.39 (s, 3, NCH_3), and 3.97 (d, 1, J=3.5 Hz, OCH); MS *m/e* 239 (M^+). Found: *m/e* 239.1877. Calcd for $C_{14}H_{25}NO_2$: M, 239.1885.

*Reduction of the Dibromo Ketone **6** with $Fe_2(CO)_9$ in a Mixture of Furan and DMF.* A mixture of the dibromide **6** (300 mg, 1.00 mmol) and $Fe_2(CO)_9$ (437 mg, 1.20 mmol) in freshly distilled furan (2.00 ml, 1.87 g, 27.5 mmol) and DMF (2.13 ml, 2.01 g, 27.5 mmol) was stirred at room temperature for 22 h. The reaction mixture was poured into aq $NaHCO_3$ solution and extracted with 1:1 ethyl acetate–hexane (10 ml×4). The organic layer was washed with water (10 ml) and dried. Concentration *in vacuo* gave a yellow oil (213 mg), the NMR spectrum of which indicated the formation of **21** (49% yield) and 2,4-diisopropyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (**22**) (only the *cis* isomer, 20% yield), and the recovery of the starting dibromide **6** (25%). Yields of **21** and **22** based on **6** consumed were 65 and 27%, respectively.

Reaction of 1,3-Dibromo-2-propanone with $Fe_2(CO)_9$ in DMF. 1,3-Dibromo-2-propanone (216 mg, 1.00 mmol) was added to $Fe_2(CO)_9$ (437 mg, 1.20 mmol) in DMF (3.5 ml), and the resulting mixture was stirred at room temperature for 12 h. The complex mixture was obtained after usual work-up, but no coupling product with an appropriate GLPC retention time was detected (column A, 70 °C).

*Reaction of the Dibromide **5** with $Fe(CO)_5$ in* N,N-*Dimethylacetamide. A. Under Thermal Conditions*: To a mixture of $Fe(CO)_5$ (470 mg, 2.40 mmol) and Na_2H_2edta (1.01 g, 3.00 mmol) in *N,N*-dimethylacetamide (3.5 ml) was added the dibromo ketone **5** (230 mg, 0.85 mmol). The mixture was then magnetically stirred at room temperature for 45 h. After quenching by saturated KNO_3 solution (10 ml), the reaction mixture was extracted with ethyl acetate (6 ml×5). The combined organic layers were washed with water (6 ml×2 and 4 ml×5) and dried. Removal of the solvent gave a pale yellow oil (181 mg). The NMR spectrum indicated the recovery of most of the starting dibromide and the absence of any cyclocoupling reaction.

B. Under Photo-irradiation Conditions: A mixture of the dibromide **5** (230 mg, 0.85 mmol), $Fe(CO)_5$ (470 mg, 2.40 mmol), and Na_2H_2edta (1.01 g, 3.00 mmol) in *N,N*-dimethylacetamide (3.5 ml) was stirred at room temperature with irradiation by >350 nm-light with a 200 W high-pressure Hg arc through 5% aq $CuSO_4$ solution. After 24 h the reaction mixture was quenched by the addition of saturated KNO_3 solution (15 ml) and extracted with ethyl acetate (6 ml×5). The collected organic extracts were washed with water (6 ml×4), dried, and concentrated, producing a viscous red oil (125 mg). The residue was dissolved in benzene (2 ml) and passed through a short alumina column. Evaporation of the filtrate gave a pale yellow oil (65 mg). NMR analysis of the oil indicated that the furanone **12** was formed in 41% yield.

*Reaction of the Dibromide **6** and DMF in the Absence of Reducing Agent.* A solution of the dibromide **6** (30.0 mg, 0.10 mmol) and hexadecane (10.0 mg, 0.05 mmol, an internal standard for GLPC analysis) in DMF (0.5 ml) was allowed to stand at room temperature for 12 h. GLPC (column D, 150 °C) of the mixture showed that **6** (t_r 6.8 min) remained unchanged.

*Treatment of 2-(Dimethylamino)-4-isopropylidene-5,5-dimethyl-1,3-dioxolane (**29**) with $FeBr_2$ in DMF.* A solution of $FeBr_2$ in DMF was prepared according to the following known method.[30] Into a solution of $Fe(CO)_5$ (20.0 mg, 0.01 mmol) in DMF (0.5 ml) was added bromine (16.0 mg, 0.01 mmol) with stirring. The color of bromine immedately disappeared, and vigorous gas evolution was observed. To the resulting deep red mixture was added a solution of the dioxolane **29** (26.8 mg, 0.15 mmol) in DMF (0.5 ml), and the mixture was stirred at room temperature for 24 h. The reaction aliquot was passed through a short column packed with alumina–Celite 545 under nitrogen and immediately subjected to NMR analysis, which showed the formation of the amino tetrahydro-3-furanone **2** in 24% yield.

*3-Acetoxy-2,4-dimethylfuran (**31**).* A mixture of the furanone **8** (1.60 g, 14.3 mmol), acetyl chloride (11.3 g, 143 mmol), and DME (20 ml) was heated at 55 °C for 14 h. The reaction mixture was added to ethyl acetate (10 ml), washed with saturated $NaHCO_3$ solution (10 ml×2) and KNO_3 solution (5 ml), and dried. Evaporation of the solvent gave a pale yellow oil (2.0 g), which was distilled with a bulb-to-bulb apparatus (bath temperature 70—110 °C, 20 Torr) to afford the acetate **31** (154 mg, >97% pure, 68% yield). IR (CCl_4) 1760 cm^{-1} (C=O); NMR δ 1.82 (d, 3, J=1.3 Hz, $CH=CCH_3$), 2.12 (s, 3, $C=CCH_3$), 2.21 (s, 3, $COCH_3$), and 6.92 (q, 1, J=1.3 Hz, =CH); MS *m/e* 154 (M^+). The acetate thus obtained was highly volatile and hydrolyzable (especially in the presence of acids); hence, the structure was assigned on the basis only of the spectral characteristics. Its immediate use, without purification, was required for obtaining a high yield in the next step.

*3-Acetoxy-5-(dimethylaminomethyl)-2,4-dimethylfuran (**32**).* To cooled (0—5 °C) acetic acid (0.19 ml) were added 40% aq dimethylamine (0.13 ml; 47.3 mg, 1.05 mmol as dimethylamine), 37% aq formaldehyde (0.08 ml; 32.3 mg, 1.08 mmol as formaldehyde), and the acetate **31** (120 mg, 0.78 mmol). The heterogeneous mixture was allowed to stand at room temperature for 5 min and then heated at 70 °C for 40 min with stirring. The resulting homogeneous solution was diluted with ethyl acetate (5 ml) and washed with saturated $NaHCO_3$/KNO_3 solution (5 ml). After drying, the organic layer was concentrated to leave a pale yellow oil (150 mg) consisting mainly of the amino furan **32**. This product was homogeneous on TLC (ethyl acetate, R_f 0.61), but the NMR analysis showed it to be only 85—90% pure. Yield of the amine was estimated as *ca.* 80%. Bulb-to-bulb distillation of this crude oil (bath temperature 100 °C, 0.2 Torr) gave analytically pure amine (115 mg, 70% yield) as a pale yellow oil. IR (CCl_4) 2840, 2795, and 2745 ($N(CH_3)_2$), and 1760 cm^{-1} (C=O); NMR δ 1.85 (s, 3, $=CCH_3$), 2.15 (s, 3, $=CCH_3$), 2.28 (s, 9, $COCH_3$ and $N(CH_3)_2$), and 3.42 (s, 2, CH_2); MS *m/e* 211 (M^+), 167 ($M^+-N(CH_3)_2$), and 125. Its picrate melted at 170—171 °C. Found: C, 46.23; H, 4.44; N, 12.63%. Calcd for $C_{17}H_{20}N_4O_{10}$: C, 46.36; H, 4.58; N, 12.72%. This amino furan is sensitive to air, turning brown, and so its immediate use is recommended.

*5-(Dimethylaminomethyl)-2,4-dimethyl-3(2H)-furanone (**33**).* A mixture of the amino furan **32** (70 mg, 0.33 mmol), 70% $HClO_4$ (0.5 ml), and DME (1.25 ml) was heated at 50 °C for 30 min. The mixture was then diluted with ethyl acetate (5 ml) and chilled at 0 °C by an ice bath. To the cooled mixture was added saturated $NaHCO_3$ solution until the separated aq layer changed to basic (pH *ca.* 8). The aq layer was extracted with ethyl acetate (5 ml×4). The combined organic extracts were washed with cold saturated KNO_3 solution (5 ml), dried,

and concentrated, affording a colorless oil (66 mg) which contained the amino furanone **33** as a major component [R_f 0.61 (ethyl acetate), >80% pure based on NMR]. Yield of **33** was >95%. IR (CCl_4) 2840, 2795, and 2745 ($N(CH_3)_2$), 1698 (C=O), and 1623 cm^{-1} (C=C); UV 274 nm (log ε 4.01); NMR δ 1.37 (d, 3, J=7.0 Hz, $CHC\underline{H}_3$), 1.66 (s, 3, $=CCH_3$), 2.25 (s, 6, $N(CH_3)_2$), 3.25 (s, 2, CH_2), and 4.24 (q, 1, J=7.0 Hz, OCH); MS *m/e* 169 (M^+). Found: *m/e* 169.1080. Calcd for $C_9H_{15}NO_2$: M, 169.1103.

5-(Dimethylaminomethyl)-3-hydroxy-2,4-dimethyltetrahydrofuran (4-Methylnormuscarine) (34). Into a 30-ml, two-necked flask equipped with a rubber septum and a Dry Ice condenser connected at its top with a bubbler was charged liquid NH_3 (*ca.* 15 ml). To this, ethanol (4.0 ml) and a solution of **33** (66 mg, 0.39 mmol) in DME (1.0 ml) were added through the septum by means of a syringe. After a few minutes, the septum was removed and small-cut Li (540 mg, 90.0 mg-atom) was added quickly. The resulting bronze-colored mixture was magnetically stirred for 1.5 h, quenched by the addition of solid NH_4Cl (2 g) with cooling by a Dry Ice–methanol bath, and warmed up to room temperature. To the voluminous gel was added ice water (20 ml), and the aq mixture was extracted with ethyl acetate (10 ml×4). The combined organic extracts were dried and concentrated to yield an oil (70 mg). The oil was dissolved in benzene, passed through an Na_2SO_4 column, and concentrated, giving a viscous oil. To a solution of the residue in THF (3.0 ml) was added $LiAlH_4$ (100 mg, 2.63 mmol) at −50 °C, after which the mixture was stirred at the same temperature for 1.5 h. The mixture was quenched with ethyl acetate at −78 °C, warmed up, and treated water. The aq layer was extracted with ethyl acetate (20 ml×2 and 10 ml×2), and the organic extracts were collected. Removal of the solvent produced viscous, oily material (60 mg), which was then subjected to preparative TLC (ethyl acetate) to afford the alcohol **34** (R_f 0.3—0.4, 41 mg, 61% yield). IR (CCl_4) 3400—3200 cm^{-1} (OH); NMR δ 1.18 (d, 3, J=7.0 Hz, $CHC\underline{H}_3$), 1.25 (d, 3, J=6.0 Hz, $CHC\underline{H}_3$), 2.45 (s, 6, $N(CH_3)_2$), 1.8—3.0 (complex, 4, $C\underline{H}CH_3$, CH_2, and OH), and 3.3—4.0 (m, 3, 2 OCH and $C\underline{H}OH$); MS *m/e* 173 (M^+) and 155 (M^+-H_2O). The structure of **34** was further confirmed through its quantitative transformation to 5-(dimethylaminomethyl)-3-(3,5-dinitrobenzoyloxy)-2,4-dimethyltetrahydrofuran (**35**).

A solution of **34** (15.0 mg, 0.09 mmol) in 1: 5 DME–benzene (0.8 ml) was mixed with 3,5-dinitrobenzoyl chloride (38 mg, 0.15 mmol) and pyridine (0.03 ml) and then left at room temperature for 20 h. The reaction mixture was diluted with ethyl acetate (4 ml) and washed with water (2 ml×2), saturated $NaHCO_3$ solution (2 ml×2), and KNO_3 solutiom (1 ml). The organic layer was dried and concentrated, affording an oil. TLC separation (1: 5 ether–hexane) of this crude product yielded the 3,5-dinitrobenzoate **35** (R_f 0.4, 31 mg, 97% yield). The NMR spectrum showed two kinds of singlets due to $N(CH_3)_2$ protons at δ 2.25 and 2.49 (*ca.* 9: 1 ratio), suggesting that **35** was a mixture of two difficult-to-separate diastereomers. NMR (major isomer) δ 1.25 (d, 6, J=6.5 Hz, 2 $CHC\underline{H}_3$), 2.0—2.4 (m, 1, $CHC\underline{H}CH_2$), 2.25 (s, 6, $(NCH_3)_2$, 2.4—2.6 (m, 2, CH_2), 3.50 (q-like m, 1, OCH), 3.97 (m, 1, OCH), 5.03 (m, 1, $C\underline{H}OCOC_6H_3(NO_2)_2$), and 8.8—9.0 (m, 3, $C_6H_3(NO_2)_2$). The signals of minor isomer could not be observed for certain. Other spectral data of the diastereomeric mixture were: IR (CCl_4) 1730 cm^{-1} (C=O); MS *m/e* 367 (M^+), 195, and 172 ($M^+-COC_6H_3(NO_2)_2$). Found: *m/e* 367.1392. Calcd for $C_{16}H_{21}N_3O_7$: M, 367.1379.

4-Methylmuscarine Iodide (36). A solution of the alcohol **34** (12 mg, 0.07 mmol) in benzene (0.5 ml) was mixed with methyl iodide (0.01 ml, 22.8 mg, 0.19 mmol) at room temperature. After 1 min, a yellow oil was separated. The heterogeneous mixture was left at room temperature for 5 min and then at 50 °C for 5 min. Most of the organic solvents were evaporated by bubbling in nitrogen gas. The heterogeneous residue, contaminated with a small amount of benzene, was mixed with methanol, and the solvents were removed azeotropically, affording viscous, oily material **36** (20 mg, 100% yield) as a mixture of difficult-to-separate diastereomers. NMR (CD_3OD) [major isomer (*ca.* 90%)] δ 1.07 (d, 3, J= 6.5 Hz, $CHC\underline{H}_3$), 1.11 (d, 3, J=6.5 Hz, $CHC\underline{H}_3$), 1.6—2.4 (m, 1, $C\underline{H}CHCH_2$), 3.21 (s, 9, $\overset{+}{N}(CH_3)_3$), and 3.25—4.25 (m, 5, 2 OCH, $C\underline{H}OH$, and CH_2). The ammonium salt **36** increased the tone and mobility of the smooth muscle of the intestinal tract.

We are grateful to the Ministry of Education, Japanese Government (Grant-in-Aid for Scientific Research, Nos. 743005 and 147022, and Grant-in-Aid for Developmental Scientific Research, No. 984014) for partial financial support. We also wish to thank Mr. Osamu Asano of the Sanwa Kagaku Kenkyusho Co. for testing the physiological effects of 4-methylmuscarine iodide.

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