3-Substituted Flavones. 1. Reduction of and Conjugate Addition to (*E*)-2-Methoxy-3-(carbethoxymethylene)flavones

Manning A. Smith,* Leonard E. Klebanoff, Christopher T. Morrow, and Bonnie B. Sandel

Department of Chemistry, Bucknell University, Lewisburg, Pennsylvania 17837

Received August 20, 1981

The methyl 3-hemiketal of 2-methoxy-3,4-flavandiones **3** react readily with the ylide ethyl (triphenylphosphoranylidene)acetate **12** to form (*E*)-2-methoxy-3-(carbethoxymethylene)flavanones **4**. Compounds **4** are readily reduced by zinc and acetic acid to form the 3-(carbethoxymethyl)flavones **5**. Conjugate addition of bromide and cyanide to the enone system converts **4** to the substituted (carbethoxymethyl)flavones **9**. When X in **9** is cyanide, the side chain is readily methylated to **11** and decarboxylated to **10**.

Flavonoids are generally synthesized by constructing the heterocyclic ring from acyclic components[1] carrying the aryl components. Reseasrch from these laboratories have yielded a procedure of some generality for the synthesis of 3-substituted flavonoids where the substituent is a functionalized carbon atom.[2] In this paper, the first of a series, the C-3 substituent is CHXCOOEt where X is hydrogen, halogen, or cyano. The flavonoid precursors are the readily prepared 3-hydroxyflavones (flavonols) **1** (Chart I).

Earlier we reported the oxidation of flavonols **1** to 2-methoxy-3,4-flavandiones **2** by periodic acid in methanol.[3] The isolated products, the hemiketals **3**, react in a straightforward Wittig reaction with the stabilized phosphorane ethyl (triphenylphosphoranylidene)acetate **12** in refluxing ethanol to yield (*E*)-3-(carbethoxymethylene)-2-methoxyflavanones **4**. Of the two carbonyls in **2**, the one at C-3 should be the more reactive, flanked as it is by two rather positive carbons. An infrared study of the hemiketal **3**[3] as well as a spiro 3-epoxide[4] established that **3** was the more reactive carbonyl since the bathochromic effects of a 7-methoxyl affected the aromatic ketone carbonyl frequency. This technique did not prove useful in the case of **4** (see Experimental Section), possibly because the effects of alkene and ester groups swamped out any perturbations arising from a C-7 substituent. However, the chemistry of the Wittig products fully supports the structures **4**. As α,β-unsaturated ketones, **4a–e** are readily reduced with zinc and acetic acid[5a] to the 3-(carbethoxymethyl)flavones **5**. Presumably the intermediate enolates **8** (X = H) eject methoxide to form compounds **5**.

The stereochemistry assigned to the Wittig products **4** is supported by precedent and spectral data. Wittig reactions with stabilized phosphoranes generally produce the more stable alkene.[5b,6] The steric crowding about C-2 should make **4** more stable than its diastereomer. This *E* stereochemistry is confirmed through both ^{1}H and ^{13}C NMR spectra. The olefinic protons of **4**'s produce ^{1}H NMR signals near δ 5.7, a result consistent with those reported in Keane's work[7] on diastereomeric pairs of several 3-benzylideneflavanones **6**.

The $^3J_{CH}$ coupling constant between the C-4 carbonyl and the olefinic proton of **4** confirms the assigned configuration. Kingsbury[8] has shown that the $^3J_{CH}$ coupling constants for diastereomeric enones are 8–9 Hz for the cis isomer and 6.5 Hz for the trans. In the case of **4**, we found a value of 9.7 Hz, indicating that the flavanone carbonyl carbon and the exocyclic alkene proton of **4** were trans to each other.

The Wittig products **4**, like Keane's[7] benzylideneflavanones **6**, are enones locked in a s-cis position. The ketone carbonyl frequencies of **4** are about 10 cm^{-1} higher than those of Keane's, probably an effect of the carbethoxy moiety in **4**. The ester carbonyl frequency of **4** is also higher than that expected for acrylates.[9]

The ^{1}H NMR spectra of the Wittig products **4** are consistent with the formulation given. We have already discussed the stereochemical implications of the chemical shift for the olefinic proton. The three-proton singlet at δ 3.1 is due to the 2-methoxy substituent as reported earlier.[4] The low-resolution mass spectrum of **4a** showed a weak molecular ion and a base peak corresponding to the loss of a carbethoxy group (see Experimental Section).

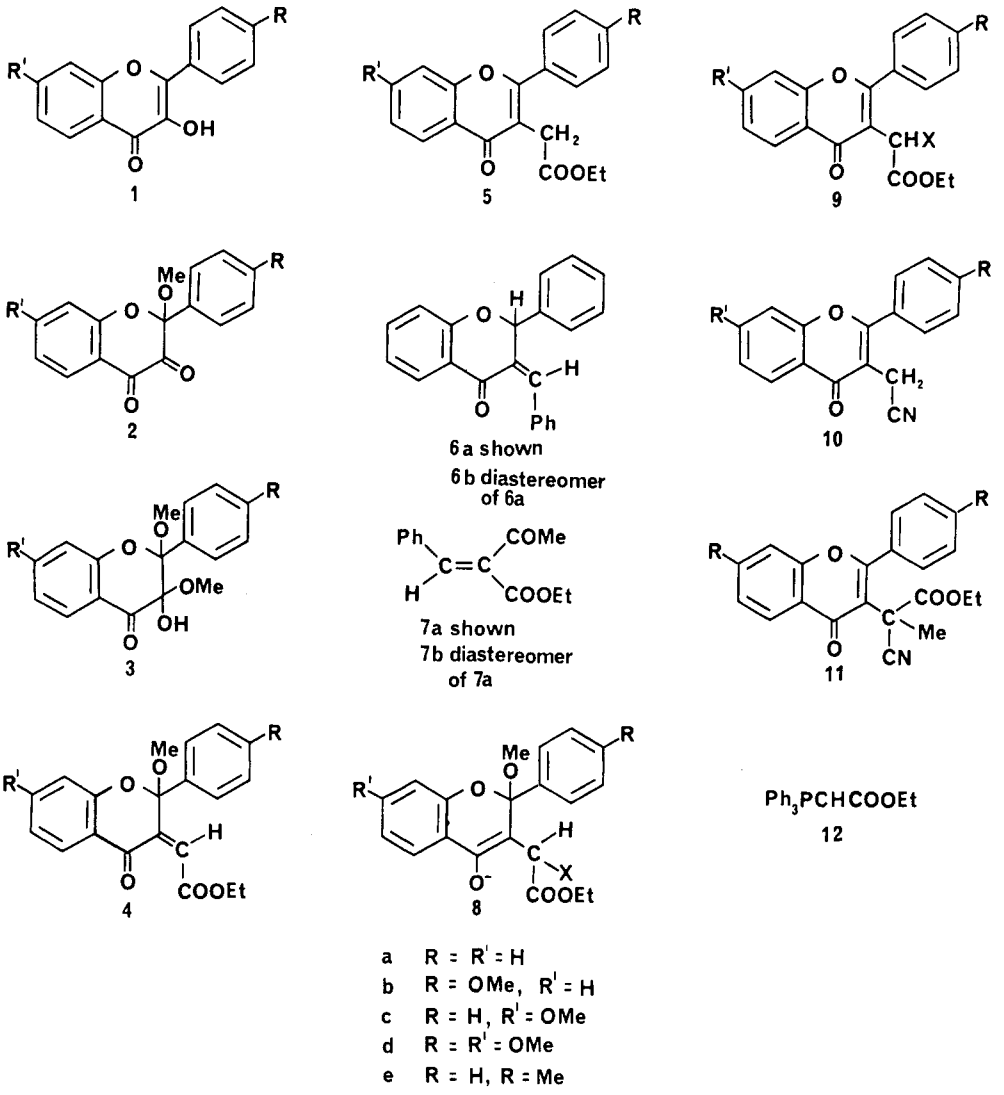
As stated above, the reduction of **4a,b,d,e** with zinc and acetic acid yields 3-(carbethoxymethyl)flavones **5a,b,d,e**. The spectra of these **5**'s clearly establish them as flavones. In contrast to the precursors **4**, the flavones **5a,b,d,e** yield ^{1}H NMR spectra with a single proton expressed as a complex pair of multiplets between 8.1 and 8.3 ppm. This is a characteristic of flavones, the signal arising from the C-5 proton of flavones.[10a] There are no three proton singlets at δ 3.1, indicating that the 2-methoxyl groups of **4** have been lost. The exocyclic methylene protons absorb near δ 3.6 and the expected ethyl multiplets are normal for esters. In the IR spectra, the carbonyl regions have ester and flavone bands (see Experimental Section). The ultraviolet spectra of these flavones reflect their unhydroxylated character.[10b,11a] Band I appears near 300 nm, while band II is at 240–245 nm, values in good agreement with flavone itself (294, 250 nm with a shoulder at 370 nm).[10c]

The mass spectra of flavones have been studied extensively.[11b,12a,b] The molecular ion (M) is often the base peak

(1) Wagner, H.; Farkas, L. In "The Flavonoids"; Harborne, J. B., Mabry, T. J., Mabry, H., Ed; Academic Press: New York, 1975; Part 1, Chapter 4.
(2) For a preliminary report on this work, see Smith, M. A. *Tetrahedron Lett.* **1973**, 3083.
(3) Smith, M. A.; Webb, R. A.; Kline, L. J. *J. Org. Chem.* **1965**, *30*, 995.
(4) Smith, M. A.; Boswell, W. D., Jr.; Henzel, K. G.; Miller, D. G. *J. Org. Chem.* **1972**, *37*, 2774.
(5) House, H. O. "Modern Synthetic Reactions", 2nd ed.; W. A. Benjamin: Menlo Park, CA, 1972; (a) p 173, (b) p 702.
(6) Schlosser, M. *Top. Stereochem.* **1970**, *5*, 5.
(7) Keane, D. D.; Marathe, K. G.; O'Sullivan, W. I.; Philbin, E. M.; Simons, R. M.; Teague, P. C. *J. Org. Chem.* **1970**, *35*, 2286.
(8) Kingsburg, C. A.; Draney, D.; Sopchick, A.; Rissler, W.; Durham, D. *J. Org. Chem.* **1976**, *41*, 3863.
(9) Bellamy, L. J. "The Infrared Spectra of Complex Molecules", 3rd ed.; Wiley: New York, 1975; p 207.
(10) Mabry, T. J.; Markham, K. R.; Thomas, M. B. "The Systematic Identification of Flavonoids"; Springer-Verlag: New York, 1970; (a) p 264, (b) pp 41–5, (c) p 62.
(11) Markham, K. R.; Mabry, T. J. In "The Flavonoids"; Harborne, J. B., Mabry, T. J., Mabry, H., Ed.; Academic Press: New York, 1975; Part 1, (a) pp 46–50, (b) pp 82–90.

0022-3263/82/1947-1702$01.25/0

Chart I



and a variety of fragmentations include a retrograde Diels–Alder reaction and the loss of carbon monoxide. In compounds **5a,b** the molecular ions are prominent as are the M – C_2H_6O and the M – COOEt ions. Strong bands in each spectrum can be ascribed to the B-ring fragment from the RDA cleavage, the molecular ion first having lost the carbethoxy group. Neither spectrum shows any trace of the RDA fragment from ring A.

The esters **5a,b,e** are hydrolyzed to the corresponding acids **5** (Et = H). The spectral properties of these products lend further support to a flavone formulation. The infrared spectra manifest bands for the carbonyls of the acid and flavone functionalities. In the ^1H NMR, the C-5 multiplet occurs between δ 8.0 and 8.5. Unlike the esters **5a,b**, the corresponding carboxylic acids show no molecular ions, the base peak being M – COOH. Also prominent are M – H_2O and M – CO_2 and the RDA fragment from ring B after decarboxylation.

The Wittig products **4** are examples of the β-acrylacrylate family.[13] In those cases where the regioselectivity of conjugate addition has been rigorously established, it is the enone that serves as the Michael acceptor.[14a–c] Hydrogen halides[13a–c] and hydrogen cyanide[13a] have been among the reagents which add to those systems. When these nucleophiles react with our Wittig products **4**, flavones **9** are produced (X = halide or cyanide). Conjugate addition to the Wittig products **4** presumably generates the enolate ions **8**, which then form the flavones **9** by ejecting methoxide.

A refluxing solution of hydrogen bromide in ethanol converts the Wittig products **4a,b,e** into 3-(bromocarbethoxymethyl)flavones **9a,b,e** (X = Br) in fair to good yields. These structural assignments are fully supported by spectral and analytical data. The molecular ions of the mass spectra were weak and no significant peaks containing bromine could be found (see Experimental Section).

The conjugate addition of cyanide ions is carried out in the refluxing ethanol. After acidification with acid, the products **9** (X = CN) are collected. The reactions with alkenes **4a,b,e** yield reasonably pure **9**'s in fair to moderate yield. However, with **4c** and **4d**, the yields are capricious and the crude products very low melting. Repeated crystallizations yield analytically satisfactory samples but the method is clearly an unsatisfactory one when methoxyl

(12) (a) Porter, Q. N.; Baldas, J. "Mass Spectrometry of Heterocyclic Compounds"; Wiley-Interscience: New York, 1971; pp 171–174. (b) Drewes, S. E. "Progress in Mass Spectrometry"; Budzikiewicz, H., Ed.; Verlag Chemie: Weinheim/Bergstr., Germany, 1974; Vol. 2, pp 41–47.

(13) (a) Bougault, J. *Ann. Chim. Phys.* **1908**, *15*, 491. (b) Lutz, R. E.; Scott, G. W. *J. Org. Chem.* **1948**, *13*, 284. (c) Oddy, H. J. *J. Am. Chem. Soc.* **1923**, *45*, 2156.

(14) (a) Frazer, M. M.; Raphael, R. A. *J. Chem. Soc.* **1950**, 2245. (b) Cromwell, N. H.; Creger, P. L.; Cook, K. E. *J. Am. Chem. Soc.* **1956**, *78*, 4412. (c) Meyer, W. L.; Vaughan, W. R. *J. Org. Chem.* **1957**, *22*, 1560.

groups are at position 7.[15] This effect may be due to the reduction in the positive character of the C-4 carbonyl by the methoxy substituent.

The spectra of the products isolated in all five cases support the formulations **9a–e** (X = CN). The infrared spectra have nitrile, ester, and flavone bands. The other spectral data are consistent with a flavone formulation (see Experimental Section).

Further evidence for the side-chain structure was provided by the facile C-methylation of **9b,d** (X = CN) at the α-cyanoacetate position, using potassium carbonate and methyl iodide in acetone. The methine proton at δ 4.8 in the ^{1}H NMR spectra of **9b,d** (X = CN) is missing in **11b,d** and in its place is a three-proton singlet at δ 1.75. All other spectral data are in accord with the assigned structure (see Experimental Section).

The cyanated products **9a–e** (X = CN) are isolated after acidifying the red reaction mixture of **4**, potassium cyanide, and ethanol. In the case of **9b** and **9d** the reaction mixture was evaporated without acidification, red solids being isolated. Their UV spectra show strong flavone maxima near 295 and 245 nm, which shows that they are the enolates of **9** (X = CN) rather than the postulated intermediates **8** (X = CH). This conclusion receives further support from the IR spectra (mulls) of **9b,c** (X = CN). The prominent ester carbonyl of **9** (X = CN) at 1745 cm^{-1} is no longer present in these enolates. The nitrile bands suffers a small change from 2260 cm^{-1} in **9b,c** (X = CN). Both of these effects can be attributed to the delocalization of the anionic charge of the enolate through the ester and nitrile functionalities. With iodomethane in refluxing acetone, these red solids yielded the *C*-methyl compounds **11b** and **11d**. Spectra and elemental analyses support these formulations (see Experimental Section).

It would be expected that the cyanoacetic esters **9** would readily hydrolyze and decarboxylate to yield 3-(cyanomethyl)flavones **10**. In the case of **4b** and **4d**, our cyanation procedures yield small amounts of **10b** and **10d**. The structures assigned to these decarboxylated products are fully supported by elementary analyses and spectra analyses (see Experimental Section). In the case of **10b**, the mass spectrum shows a strong molecular ion, the M − 1 ion being the base peak. The only other prominent fragment is M − 28 (30%) presumably the familiar decarbonylation fragment of flavones.[11b,12]

Experimental Section

The solution infrared spectra were recorded on a Perkin-Elmer 337 grating spectrophotometer and the Nujol mulls on a P-E 137 instrument. All spectra were calibrated to the 1601-cm^{-1} band of polystyrene. Mass spectra were provided through the courtesy of Dr. Charles C. Sweeley and his associates at Michigan State University. Proton NMR spectra were determined on a Varian A-60A spectrometer. Carbon-13 NMR spectra and analyses were provided by Dr. Alan Douglas through the courtesy of Merck Sharp and Dohme Laboratories. Ultraviolet spectra were recorded on a Beckman DB spectrophotometer. The Schwarzkopf Microanalytical Laboratory carried out the elemental analyses. Melting points were determined on a Mel-Temp apparatus and are uncorrected.

The flavonols **1** used were prepared by a one-pot modification of the standard Algar Flynn Oyamada peroxide oxidation sequence from hydroxyacetophenones and aryl aldehydes without isolation of the intermediate chalcones.[16]

(*E*)-3-(Carbethoxymethylene)-2-methoxyflavanone (4a). A solution of 10 g (33 mmol) of **3a**[3] and 12 g (34.5 mmol) of the ylide **12** in 65 mL of EtOH was refluxed for 2 h. When the solution cooled, large slightly yellow crystals separated: 8.2 g (73%) of **4a**, mp 109–111 °C; the analytical sample (EtOH) melted at 111–112 °C; **4a** IR (CCl_4) 1732 cm^{-1} (ester CO), 1685 (ketone CO); ^{1}H NMR ($CDCl_3$) δ 1.25 (t, 3, OCH_2CH_3), 3.15 (s, 3, OCH_3), 4.25 (q, 2, OCH_2CH_3), 5.65 (s, 1, vinyl H), 6.9–8.1 (m, 9, ArH); mass spectrum, *m/z* (relative intensity) 338 (0.3), 265 (100), 145 (17). Anal. Calcd for $C_{20}H_{18}O_5$: C, 71.00; H, 5.36; OCH_3, 18.34; mol wt 338. Found: C, 71.03; H, 5.45; OCH_3, 18.39; mol wt (MS) 338.

(*E*)-3-(Carbethoxymethylene)-2,4′-dimethoxyflavanone (4b). The same procedure as for **4a** (2 g of **3b**,[3] 2.2 g of **12**, 25 mL of EtOH, reflux 1 h) afforded 1.6 g (72%) of **4b**, mp 151–152 °C, when the solution cooled to room temperature. The analytical sample (EtOH) melted at 154.5–155.0 °C. **4b**: IR (CCl_4) 1725 cm^{-1} (ester CO), 1680 (ketone CO); ^{1}H NMR ($CDCl_3$) δ 1.16 (t, 3, OCH_2CH_3), 3.13 (s, 3, 2-OCH_3), 3.86 (s, 3, ArOCH_3), 4.25 (q, 2, OCH_2CH_3), 5.70 (s, 1, vinyl H), 6.8–8.2 (m, 8, ArH); mass spectrum, *m/z* (relative intensity) 368 (0.2), 295 (100), 175 (20). Anal. Calcd for $C_{21}H_{20}O_6$: C, 68.47;, H, 5.47; OCH_3, 25.27; mol wt 368. Found: C, 68.35; H, 5.34; OCH_3, 25.43; mol wt (MS) 368.

(*E*)-3-(Carbethoxymethylene)-2,7-dimethoxyflavanone (4c). The same procedure as for **4a** (4.63 g (14 mmol) of **3c**, 6.5 g (19 mmol) of **12**, 30 mL of EtOH, reflux 1 h) afforded 4.5 g (87%) of **4c**, mp 94–100 °C. The analytical sample (EtOH) melted at 110–112 °C. **4c**: IR (CCl_4) 1730 cm^{-1} (ester CO), 1680 (ketone CO); ^{1}H NMR ($CDCl_3$) δ 1.26 (t, 3, OCH_2CH_3), 3.14 (s, 3, 2-OCH_3), 3.81 (s, 3, ArOCH_3), 4.19 (q, 2, OCH_2CH_3), 5.59 (s, 1, vinyl H), 6.4–8.0 (m, 8, ArH). Anal. Calcd for $C_{21}H_{20}O_6$: C, 68.47; H, 5.47. Found: C, 68.58; H, 5.67.

(*E*)-3-(Carbethoxymethylene)-2,4′,7-trimethoxyflavanone (4d). Use of the same procedure for **4a** (2.00 g of **3d**, 3.7 g of **12**, 40 mL of EtOH, reflux 2.5 h) afforded 2.02 g (90%) of crude **4d**, mp 115–118 °C. Recrystallization from aqueous EtOH yielded the analytical sample, mp 126–128 °C. **4d**: IR (CCl_4) 1740 cm^{-1} (ester CO), 1680 (ketone CO); ^{1}H NMR ($CDCl_3$) δ 1.26 (t, 3, OCH_2CH_3), 3.13 (s, 3, 2-OCH_3), 3.81 (s, 3, ArOCH_3), 4.20 (q, 2, OCH_2CH_3), 5.63 (s, 1, vinyl H), 6.4–7.9 (m, 7, ArH). Anal. Calcd for $C_{22}H_{22}O_7$: C, 66.32; H, 5.57. Found: C, 65.98; H, 5.57.

(*E*)-3-(Carbethoxymethylene)-2-methoxy-4′-methylflavanone (4e). The same procedure as for **4a** (6 g of **3e**,[4] 11.17 g of **12**, 120 mL of EtOH, reflux 2 h) afforded 4.21 g of **4e** (mp 139–142 °C), with an additional 0.88 g forming after concentration of the filtrate; total yield, 76%. The analytical sample melted at 146–147 °C. **4e**: IR (CCl_4) 1725 cm^{-1} (ester CO), 1680 (ketone CO); ^{1}H NMR ($CDCl_3$) δ 1.23 (t, 3, OCH_2CH_3), 2.40 (s, 3, $ArCH_3$), 3.14 (s, 3, 2-OCH_3), 4.25 (q, 2, OCH_2CH_3), 5.70 (s, 1, vinyl H), 7.0–8.1 (m, 8, ArH); mass spectrum *m/z* (relative intensity) 352 (0.2), 279 (100), 159 (17). Anal. Calcd for $C_{21}H_{20}O_5$: C, 71.58; H, 5.72; mol wt 352. Found: C, 71.64; H, 5.85; mol wt (MS) 352.

3-(Carbethoxymethyl)flavone (5a). The zinc dust (1.6 g, 24 mmol) was washed successively with 3% HCl (2×), H_2O (4×), 2% $CuSO_4$ (2×), H_2O (4×), and EtOH. This was heated with 1.00 g (3.24 mmol) of **4a** and 25 mL of AcOH on a steam bath for 3 h with stirring and filtered, and the zinc was washed with AcOH. The combined AcOH solutions were evaporated with a rotary evaporator. The residue was dissolved in Et_2O, this solution was washed with 5% $NaHCO_3$ (2×), and the ether was dried with saturated brine and $CaSO_4$. Evaporation of the Et_2O left a white powder of flavone **5a**, 0.689 g (76%). Recrystallization of **5a** from CCl_4/hexane afforded the analytical sample, mp 102–102.5 °C. **5a**: IR (mull) 1730 cm^{-1} (ester CO), 1625 (flavone CO); ^{1}H NMR ($CDCl_3$) δ 1.26 (t, 3, OCH_2CH_3), 3.56 (s, 2, CH_2COOEt), 4.16 (q, 2, OCh_2CH_3), 7.2–8.3 (m, 9, ArH); UV max (95% EtOH) 300 nm (log ε 4.00), 280 (4.05), 242 (4.25); mass spectrum, *m/z* (relative intensity) 308 (25), 263 (40), 262 (100), 235 (90), 115 (80). Anal. Calcd for $C_{19}H_{16}O_4$: C, 74.01; H, 5.23; mol wt 308. Found: C, 74.06; H, 5.20; mol wt (MS) 308.

3-(Carbethoxymethyl)-4′-methoxyflavone (5b). The same procedure as for **5a** (1.5 g of Zn, 1.0 g of **4b**, 25 mL of AcOH, 1.5 h) afforded 0.7 g (76%) of a white powder. The analytical sample

(15) Attempts using the Lapworth procedure and Nagata's method were not successful (Nagata, W.; Yoshioka, M. *Org. React.* **1977**, *25*, 1). However, recent work with phase transfer has shown promise, pure **9c** being obtained in 45% yield: Smith, M. A.; Morgan, D., unpublished results.

(16) Smith, M. A.; Neumann, R. M.; Webb, R. A. *J. Heterocycl. Chem.* **1968**, *5*, 425.

melted at 124–125 °C (EtOH). **5b**: IR (CCl_4) 1730 cm^{-1} (ester CO), 1635 (flavone CO); ^1H NMR ($CDCl_3$) δ 1.26 (t, 3, OCH_2CH_3), 3.57 (s, 2, CH_2COOEt), 3.86 (s, 3, $ArOCH_3$), 4.19 (q, 2, OCH_2CH_3), 6.9–8.3 (m, 8, ArH); UV max (95% EtOH) 308 nm (log ϵ 4.34), 245 (sh, 4.12), 227 (4.35); mass spectrum, m/z (relative intensity) 338 (30), 293 (35), 292 (100), 265 (60), 145 (30). Anal. Calcd for $C_{20}H_{18}O_5$: C, 71.00; H, 5.36; mol wt 338. Found: C, 70.50; H, 5.40; mol wt (MS) 338.

3-Carbethoxy-4′,7-dimethoxyflavone (5d). The same procedure as for **5a** (2 g of Zn, 0.539 g of **4d**, 35 mL of AcOH, 1.5 h) afforded 0.409 g (82%) of **5d**, mp 109–111 °C. The analytical sample (aqueous EtOH) melted at 111–113 °C. **5d**: IR (CCl_4) 1730 cm^{-1} (ester CO), 1630 (flavone CO); ^1H NMR ($CDCl_3$) δ 1.25 (t, 3, OCH_2CH_3), 3.53 (s, 2, CH_2COOEt), 3.85 (s, 6, OCH_3), 4.17 (q, 2, OCH_2CH_3), 6.8–8.2 (m, 7, ArH). Anal. Calcd for $C_{21}H_{20}O_6$: C, 68.47; H, 5.47. Found: C, 68.18; H, 5.72.

3-(Carbethoxymethyl)-4′-methylflavone (5e). The same procedure as for **5a** (3.2 g of Zn, 2.03 g of **4e**, 75 mL of AcOH, 2 h) afforded 1.8 g (97%) of solid **5e**, mp 98–100 °C. The analytical sample (aqueous EtOH) melted at 110–111 °C. **5e**: IR (CCl_4) 1730 cm^{-1} (ester CO), 1635 (ketone CO); ^1H NMR ($CDCl_3$) δ 1.27 (t, 3, OCH_2CH_3), 2.40 (s, 3, $ArCH_3$), 3.57 (s, 2, CH_2COOEt), 4.18 (q, 2, OCH_2CH_3), 7–8.4 (m, 8, ArH); UV max (95% EtOH) 287 nm (log ϵ 4.15), 246 (4.30), 220 (4.36). Anal. Calcd for $C_{20}H_{18}O_4$: C, 74.52; H, 5.63. Found: C, 74.75; H, 5.83.

3-(Carboxymethyl)flavone (5a, Et = H). A suspension of 2 g of ester **5a** was held at 50 °C for 2 h in a mixture of 2 g of KOH, 20 mL of H_2O, and 10 mL of EtOH. At the end of the heating, the mixture was clear and acidification with HCl yielded 1.5 g (82%) of acid **5a** (Et = H), mp 165–170 °C. The analytical sample melted at 183–184 °C. **5a**: IR (mull) 1709 cm^{-1} (acid CO), 1640 (flavone CO); ^1H NMR ($CDCl_3$) δ 3.60 (s, 2, CH_2CO), 7.8–8.4 (m, 9, ArH), 10.48 (s, 1, COOH); UV max (95% EtOH) 303 nm (log ϵ 4.12), 281 (4.15), 242 (4.38); mass spectrum, m/z (relative intensity) 262 (40), 236 (55), 235 (100), 205 (20), 115 (40). Anal. Calcd for $C_{17}H_{12}O_4$: C, 72.85; H, 4.32. Found: C, 73.14; H, 4.44.

3-(Carboxymethyl)-4′-methoxyflavone (5b, Et = H). The same procedure as for ester **5a** (2.0 g of **5b**, 10 mL of EtOH, 20 mL of H_2O, 5 g of KOH) afforded 1.2 g (65%) of the acid **5b** (Et = H), mp 175–156 °C. The analytical sample (EtOH, then $CHCl_3$) melted at 176–179 °C. **5b**: IR (mull) 1709 cm^{-1} (acid CO), 1626 (flavone CO); ^1H NMR ($CDCl_3$) δ 3.61 (s, 2, CH_2CO), 3.88 (s, 3, OCH_3), 6.9–8.3 (m, 8, ArH), 12.5 (br s, 1, COOH); mass spectrum, m/z (relative intensity) 292 (25), 266 (40), 265 (100). Anal. Calcd for $C_{18}H_{14}O_5$: C, 69.67; H, 4.54. Found: C, 69.56; H, 4.47.

3-(Carboxymethyl)-4′-methylflavone (5e) (Et = H). The same procedure as for ester **5a** (2.0 g of **5e**, 10 mL of EtOH, 20 mL of H_2O, 2 g of KOH) afforded 1.1 g (61%) of **5e** (Et = H), mp 210–212 °C. The analytical sample melted at 213–215 °C (EtOH). **5e**: IR (mull) 1705 cm^{-1} (acid CO), 1630 (flavone CO); ^1H NMR ($CDCl_3$) δ 2.46 (s, 3, $ArCH_3$), 3.65 (s, 2, CH_2CO), 7.1–8.4 (m, 8, ArH); UV max (95% EtOH) 285 nm (log ϵ 4.17), 244 (4.24). Anal. Calcd for $C_{18}H_{14}O_4$: C, 73.46; H, 4.79. Found: C, 73.75; H, 4.98.

3-(Bromocarbethoxymethyl)flavone (9a, X = Br). A solution of 1.5 g of HBr in 30 mL of EtOH was refluxed for 1 h with 500 mg (1.48 mmol) of **4a**. Neutralization (2 g of $NaHCO_3$, 25 mL of H_2O) and evaporation yielded 500 mg (87%) of **9a**, mp 122–126 °C, light tan solid. The analytical sample melted at 131–132 °C (C_6H_6/hexane). **9a**: IR (mull) 1730 cm^{-1} (ester CO), 1655 (flavone CO); ^1H NMR ($CDCl_3$) δ 1.23 (t, 3, OCH_2CH_3), 4.22 (q, 2, OCH_2CH_3), 5.52 (s, 1, methine H), 7.2–8.5 (m, 9, ArH); UV max (95% EtOH) 247 nm (log ϵ 4.32), 285 (4.00), 305 (4.00); mass spectrum, m/z (relative intensity) 386, 388 (1), 307 (35), 279 (10), 262 (35), 233 (100). Anal. Calcd for $C_{19}H_{15}BrO_4$: C, 58.93; H, 3.90; Br, 20.63; mol wt 387. Found: C, 58.85; H, 3.86; Br, 20.74; mol wt (MS) 386, 388.

3-(Bromocarbethoxymethyl)-4′-methoxyflavone (9b, X = Br). The same procedure as for **9a** (0.50 g of **4b**, 1.5 g of HBr, 30 mL of EtOH, reflux 1 h) afforded, upon evaportion and cooling, 0.28 g (49%) of **9b**, mp 131–133 °C. The analytical sample (EtOH) melted at 139 °C. **9b**: IR (mull) 1760 cm^{-1} (ester CO), 1625 (flavone CO); ^1H NMR ($CDCl_3$) δ 122 (t, 3, OCH_2CH_3), 3.88 (s, 3, OCH_3), 4.21 (q, 2, OCH_2CH_3), 5.58 (s, 1, methine H), 7–8.4 (m, 8, ArH); UV max (95% EtOH) 308 nm (log ϵ 4.24), 247 (sh, 4.13), 228 (4.31); mass spectrum, m/z (relative intensity) 416, 418 (1), 353 (25), 337 (50), 309 (20), 292 (30), 263 (100). Anal. Calcd for $C_{20}H_{17}BrO_5$: C, 57.57; H, 4.11; Br, 19.15; mol wt 417. Found: C, 57.45; H, 4.09; Br, 18.85; mol wt (MS) 416, 418.

3-(Bromocarbethoxymethyl)-4′-methylflavone (9e, X = Br). The same procedure as for **9a** (0.5 g of **4e**, 1.5 g of HBr, 25 mL of EtOH, reflux 0.5 h) yielded 0.480 g (84%) of a brown powder, **9e**, mp 142–144 °C upon evaporation of the ethanol. The analytical sample (EtOH) melted at 148–149 °C. **9e**: IR (mull) 1750 cm^{-1} (ester CO), 1640 (flavone CO); ^1H NMR ($CDCl_3$) δ 1.21 (t, 3, OC_2CH_3), 2.43 (s, 3, $ArCH_3$), 4.18 (q, 2, OCH_2CH_3), 5.55 (s, 1, methine H), 7.2–8.4 (m, 8, ArH); UV max (95% EtOH) 294 nm (log ϵ 4.12), 250 (4.26). Anal. Calcd for $C_{20}H_{17}BrO_4$: C, 59.87; H, 4.27; Br, 19.91. Found: C, 60.07;, H, 4.42; Br, 19.79.

3-(Carbethoxycyanomethyl)flavone (9a, X = CN). A solution of 1 g (2.9 mmol) of **4a**, 0.22 g (3.4 mmol) of KCN, 9 mL of EtOH, and 3 mL of H_2O was refluxed for 3 h. The resulting red solution was cooled at 15 °C and acidified, producing 0.83 g of **9a** (84%), mp 142–144 °C. The analytical sample (EtOH) melted at 149–152 °C. **9a**: IR ($CHCl_3$) 2245 cm^{-1} (CN), 1745 (ester CO), 1640 (flavone CO); ^1H NMR ($CDCl_3$) δ 1.30 (t, 3, OCH_2CH_3), 4.25 (q, 2, OCH_2CH_3), 4.80 (s, 1, methine H), 7.3–8.4 (m, 9, ArH); UV max (CH_3CN) 295 nm (log ϵ 4.00), 277 (4.05), 243 (4.33); mass spectrum, m/z (relative intensity) 363 (50), 318 (35), 317 (100), 290 (70), 263 (70). Anal. Calcd for $C_{20}H_{15}NO_4$: C, 72.06; H, 4.54; N, 4.20. Found: C, 72.35; H, 4.69; N, 4.21.

3-(Carbethoxycyanomethyl)-4′-methoxyflavone (9b, X = CN). The same procedure as for **9a** (1 g (2.8 mmol) of **4b**, 0.18 g (2.8 mmol) of KCN, 9 mL of EtOH, 3 mL of H_2O, reflux 1.5 h) afforded a small amount (0.07 g, 9%) of the cyanoflavone **10b**, which was collected. The filtrate was processed as above to yield 0.79 g (80%) of **9b**, mp 150–152 °C. The analytical sample melted at 156–158 °C (EtOH). **9b**: IR ($CHCl_3$) 2250 cm^{-1} (CN), 1750 (ester), 1640 (flavone CO); ^1H NMR ($CDCl_3$) δ 1.32 (t, 3, OCH_2CH_3), 3.91 (s, 3, $ArOCH_3$), 4.32 (q, 2, OCH_2CH_3), 4.88 (s, 1, methine H), 7.0–8.4 (m, 8, ArH); UV max (CH_3CN) 299 nm (log ϵ 4.11), 243 (3.95), 225 (4.20). Anal. Calcd for $C_{21}H_{17}NO_5$: C, 69.41; H, 4.71; N, 3.85. Found: C, 69.26; H, 4.72; N, 3.61.

3-(Carbethoxycyanomethyl)-7-methoxyflavone (9c, X = CN).[15] The same procedure as for **9a** (0.62 g (1.7 mmol) of **4c**, 0.23 g (3.5 mmol) of KCN, 20 mL of EtOH, 0.5 mL of H_2O, reflux 3 h) afforded 0.56 g of very crude **9c** (mp 70–85 °C). Recrystallization from EtOH eventually produced an analytical sample, mp 145.5–147.0 °C. **9c**: IR ($CHCl_3$) 2260 cm^{-1} (CN), 1750 (ester CO), 1635 (flavone CO); ^1H NMR ($CDCl_3$) δ 1.29 (t, 3, OCH_2CH_3), 3.82 (s, 3, $ArOCH_3$), 4.21 (q, 2, OCH_2CH_3), 4.71 (s, 1, methine H), 6.8–8.2 (m, 8, ArH); UV max (CH_3CN), 291 nm (log ϵ 3.93), 240 (4.20), 225 (4.11). Anal. Calcd for $C_{21}H_{17}NO_5$: C, 69.41; H, 4.72; N, 3.85. Found: C, 69.41; H, 4.79; N, 3.83.

3-(Carbethoxycyanomethyl)-4′,7-dimethoxyflavone (9d, X = CN). As was the case with **9c**, the procedure was not satisfactory[15] although an analytical sample (absolute EtOH) was obtained, mp 128–131 °C. See below for **10d**, a byproduct. **9d**: IR ($CHCl_3$) 2255 cm^{-1} (CN), 1750 (ester CO), 1635 (flavone CO); ^1H NMR ($CDCl_3$) δ 1.33 (t, 3, OCH_2CH_3), 3.92 (s, 6, $ArOCH_3$), 4.33 (q, 2, OCH_2CH_3), 4.86 (s, 1, methine H), 6.9–8.4 (m, 7, ArH); UV max (CH_3CN) 299 nm (log ϵ 4.38), 249 (4.26), 227 (4.34). Anal. Calcd for $C_{22}H_{19}NO_6$: C, 67.17; H, 4.87; N, 3.56. Found: C, 67.26; H, 4.90; N, 3.45.

3-(Carbethoxycyanomethyl)-4′-methylflavone (9e, X = CN). The same procedure as for **9a** (0.41 g (1.2 mmol) of **4e**, 0.08 g (1.2 mmol) of KCN, 4 mL of EtOH, 1.5 mL of H_2O reflux 1.5 h) afforded **9e**, 0.23 g (55%), mp 121–127 °C. The analytical sample (EtOH) melted at 127–128 °C. **9e**: IR ($CHCl_3$) 2270 cm^{-1} (CN), 1745 (ester CO), 1660 (flavone CO); ^1H NMR ($CDCl_3$) δ 1.32 (t, 3, OCH_2CH_3), 2.47 (s, 3, $ArCH_3$), 4.32 (q, 2, OCH_2CH_3), 4.84 (s, 1, methine H), 7.2–8.4 (m, 8, ArH); UV max (CH_3CN) 290 nm (log ϵ 3.98), 283 (4.00), 245 (4.12). Anal. Calcd for $C_{21}H_{17}NO_4$: C, 72.61; H, 4.93; N, 4.03. Found: C, 72.47; H, 4.88; N, 4.03.

3-(Cyanomethyl)-4′-methoxyflavone (10b). This was isolated as a byproduct, mp 191–197 °C (9%), in the preparation of **9b** (X = CN) (see above). The analytical sample (absolute EtOH) melted at 195–198 °C. **10b**: IR ($CHCl_3$) 2260 cm^{-1} (CN), 1640 (flavone CO); ^1H NMR ($CDCl_3$) δ 3.65 (s, 2, methylene H), 3.92 (s, 3, $ArOCH_3$), 7.0–8.5 (m, 8, ArH); UV max (CH_3CN) 296 nm (log ϵ 4.21), 240 (4.03). Anal. Calcd for $C_{18}H_{13}NO_3$: C, 74.22; H, 4.50; N, 4.81. Found: C, 73.91, 74.44; H, 4.89, 4.76; N, 4.74, 4.99.

3-(Cyanomethyl)-4′,7-dimethoxyflavone (10d). This was isolated as a byproduct (17%) in the above preparation of **9d** (X = CN). Also see the enolate preparation below. The analytical sample melted at 202–204 °C. **10d**: IR ($CHCl_3$) 2250 cm^{-1} (CN), 1625 cm^{-1} (flavone CO); ^1H NMR ($CDCl_3$) δ 3.62 (s, 2, methylene H), 3.93 (s, 6, $ArOCH_3$), 6.9–8.4 (m, 7, ArH); UV max (CH_3CN) 209 nm (log ε 4.25), 244 (4.13), 225 (4.23). Anal. Calcd for $C_{19}H_{15}NO_4$: C, 71.02; H, 4.70; N, 4.36. Found: C, 71.25; H, 5.15; N, 4.34.

Enolate of 9b (X = CN). A solution of 1.5 g (4.1 mmol) of **4b**, 0.27 g (4.1 m mol) of KCN, 15 mL of EtOH, and 5 mL of H_2O was refluxed for 1.5 h. The red solution was cooled, and 0.10 g (8%) of the decarboxylated byproduct **10b** separated. After the removal of **10b**, the filtrate was evaporated, yielding the enolate **9b** as a red powdery residue. This enolate was supended in ether and collected by filtration, 1.48 g (90%), mp 165–167 °C. An analytical sample was not obtained. **9b**: IR (mull) 2164 cm^{-1} (CN), 1620; UV max (CH_3CN) 295 nm (log ε 4.25), 241 (4.26), 220 (4.69).

Enolate of 9d. The same procedure as for the enolate of **9b** (0.62 g (1.5 mmol) of **4d**, 0.12 g (1.9 mmol) of KCN, 25 mL of EtOH, 25 mL of H_2O, reflux 1.5 h) yielded 0.08 g (17%) of the decarboxylated byproduct **10d** (see above) and 0.53 g (80%) of the enolate, mp 167–174 °C. An analytical sample was not obtained. **9d**: IR (mull) 2160 cm^{-1} (CN), 1610–1630 (2 bands); UV max (CH_3CN) 297 nm (log ε 4.29), 246 (4.20), 226 (4.28).

3-(1-Carbethoxy-1-cyanoethyl)-4′-methoxyflavone (11b). The (carbethoxycyanomethyl)flavone **9b** (X = CN) was methylated (1 g (2.7 mmol) of **9b**) in refluxing acetone (5 mL, 8 h) with 0.48 g (3.4 mmol) of iodomethane in the presence of 0.35 g (4.2 mmol) of sodium bicarbonate. After the inorganics were filtered, the solvent was removed and the residue taken up in Et_2O. After filtration followed by evaporation, the Et_2O solution left a gum. Upon trituration with a little ether, the gum changed to a yellow solid, 0.85 g (82%) of crude **11b**, mp 120–135 °C. A single recrystallization (EtOH) raised the melting point to 138–142 °C. The analytical sample melted at 143–145 °C. **11b**: IR ($CHCl_3$) 2225 cm^{-1} (CN), 1745 (ester CO), 1640 (flavone CO); ^1H NMR ($CDCl_3$) δ 1.24 (t, 3, OCH_2CH_3), 1.77 (s, 3, CCH_3), 3.90 (s, 3, $ArOCH_3$), 4.26 (q, 2, OCH_2CH_3), 6.9–8.4 (m, 8, ArH); UV max (CH_3CN) 295 nm (log ε 4.14), 240 (4.19). Anal. Calcd for $C_{22}H_{19}NO_5$: C, 70.02; H, 5.07; N, 3.71. Found: C, 70.17; H, 5.23; N, 3.63. This substance was also prepared by refluxing 1.0 g (2.5 mmol) of the enolate of **9b** and 0.53 g (3.7 mmol) of MeI for 9 h in dry acetone. The resulting solution was worked up as above, affording 0.72 g (76%), of **11b**, mp 133–137 °C.

3-(1-Carbethoxy-1-cyanoethyl)-4′,7-dimethoxyflavone (11d). This was prepared from the enolate of **9b** by refluxing the enolate (0.45 g, 1.0 mmol) with 0.22 g (1.5 mmol) of MeI in 5 mL of dry acetone for 8 h. This was then worked up following the procedure for **11b** from **9b** above, yielding 0.16 g (40%) of **11d**, mp 151–156 °C. The analytical sample melted at 154.5–157 °C (EtOH). **11d**: IR ($CHCl_3$) 2230 cm^{-1} (CN), 1745 (ester CO), 1615 (flavone CO); ^1H NMR ($CDCl_3$) δ 1.25 (t, 3, OCH_2CH_3), 1.75 (3, s, CCH_3), 3.89 (s, 6, $ArOCH_3$), 4.24 (q, 2, OCH_2CH_3), 6.8–8.4 (m, 7, ArH); UV max (CH_3CN) 293 nm (log ε 4.16), 245 (4.20), 226 (4.30). Anal. Calcd for $C_{23}H_{21}NO_6$: C, 67.80; H, 5.19; N, 3.44. Found: C, 67.74; H, 5.12; N, 3.47.

Acknowledgment. Partial support from the Camille and Henry Dreyfus Foundation is gratefully acknowledged.

Registry No. 3a, 1603-46-9; **3b**, 1808-05-5; **3c**, 2047-54-3; **3d**, 1808-02-2; **3e**, 80907-12-6; **4a**, 80907-13-7; **4b**, 80907-14-8; **4c**, 80907-15-9; **4d**, 80907-16-0; **4e**, 80907-17-1; **5a**, 50526-01-7; **5a** (Et = H), 80907-18-2; **5b**, 80907-19-3; **5b** (Et = H), 80907-20-6; **5d**, 80907-21-7; **5e**, 80907-22-8; **5e** (Et = H), 80907-23-9; **9a** (X = Br), 80907-24-0; **9a** (X = CN), 80907-25-1; **9b** (X = Br), 80907-26-2; **9b** (X = CN), 80907-27-3; **9b** enolate (X = CN), 80907-28-4; **9c** (X = CN), 80907-29-5; **9d** (X = CN), 80907-30-8; **9d** enolale (X = CN), 80964-96-1; **9e** (X = Br), 80907-31-9; **9e** (X = CN), 80907-32-0; **10b**, 80907-33-1; **10d**, 80907-34-2; **11b**, 80907-35-3; **11d**, 80907-36-4; **12**, 1099-45-2.

Synthesis of 5-Fluorouracil Derivatives Having *N*-Acylazacycloalkanes and Lactams[1]

Takashi Nishitani, Hiroshi Horikawa, Tameo Iwasaki,* Kazuo Matsumoto, Ichizo Inoue, and Muneji Miyoshi

Department of Synthetic Chemistry, Research Laboratory of Applied Biochemistry, Tanabe Seiyaku Co., Ltd., 3-16-89 Kashima, Yodogawa-ku, Osaka 532, Japan

Received October 6, 1981

5-Fluorouracil derivatives have been synthesized, in 41–84% yield, by the Lewis acid catalyzed condensation of 2,4-bis(trimethylsilyl)-5-fluorouracil with *N*-acyl-2-methoxyazacycloalkanes; the latter have been prepared by anodic oxidation of either *N*-acylprolines and *N*-acylpipecolic acids in methanolic sodium methoxide or *N*-acylperhydroazepines and *N*-acylmorpholines in methanolic tetraethylammonium perchlorate. The method has been extended to the synthesis of the 5-fluorouracil derivatives having five-, six-, and seven-membered lactams.

Chemical modifications of 5-fluorouracil (5-FU)[2] have been investigated extensively during the last two decades in search for effective nontoxic antitumor agents.[3] Interest in this area has been further stimulated by the recent finding that the derivatives represented by 1-(tetrahydrofuran-2-yl)-5-fluorouracil,[4] 1-(hexylcarbamoyl)-5-fluorouracil[5] and 5′-deoxy-5-fluorouridine[6] show significant antitumor activities as well as therapeutic advantages over 5-FU. Of prime importance for the design of new 5-FU derivatives would be the choice of the substituents and of the binding sites of 5-FU onto the substituents, both of which sway the pharmacokinetic properties of the 5-FU derivatives. We have recently directed our attention, as one of our research programs,[7] to the 5-FU derivatives

(1) Synthetic Electroorganic Chemistry. 14. A part of this work was presented at 29th Annual Meeting of the Kinki Branch, Pharmaceutical Society of Japan, Kyoto, Japan, Nov 11, 1979.

(2) Heidelberger, C.; Chaudhuri, N. K.; Danneberg, P.; Mooren, D.; Griesbach, L.; Duschinsky, R.; Schnitzer, R. J.; Pleven, E.; Scheiner, J. *Nature (London)* **1957**, *179*, 663.

(3) (a) Cook, A. F.; Holman, M. J. *J. Med. Chem.* **1980**, *23*, 852. (b) Kametani, T.; *et al. Ibid.* **1980**, *23*, 1324 and references cited therein.

(4) Yasumoto, M.; Yamawaki, I.; Marunaka, T.; Hashimoto, S. *J. Med. Chem.* **1978**, *21*, 738.

(5) Ozaki, S.; Ike, Y.; Mizuno, H.; Ishikawa, K.; Mori, H. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 2406.

(6) Cook, A. F.; Holman, M. J.; Kramer, M. J.; Trown, P. W. *J. Med. Chem.* **1979**, *22*, 1330.

(7) For the synthesis of the 5-FU derivatives having oxacycloalkanes, see: Iwasaki, T.; Nishitani, T.; Horikawa, H.; Inoue, I. *Tetrahedron Lett.* **1981**, 1029.

0022-3263/82/1947-1706$01.25/0