Measurement of Osmotic Pressure——Osmotic pressure was measured at 60° by the use of Knauer Electronic Membrane Osmometer. The sample was dissolved in water, and 0.4, 0.3, 0.2, and 0.1% solution were used.

Measurement of Sedimentation Equilibrium——Sedimentation equilibrium was measured at 23° by the use of Hitachi model UCA-1A ultracentrifuge. The original polysaccharide was dissolved in water at 0.179%. The solutions of the original, 3/4, 1/2, and 1/4 concentrations were centrifuged at 6520 rpm for 20 hr. The deacetylated product was dissolved in water at 0.665%. The solutions of the original, 3/4, 1/2, and 1/4 concentrations were centrifuged at 10490 rpm for 3 hr.

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Preparation of Some Ring-Oxygenated Phenacyl Bromides[1]

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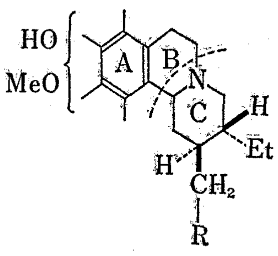
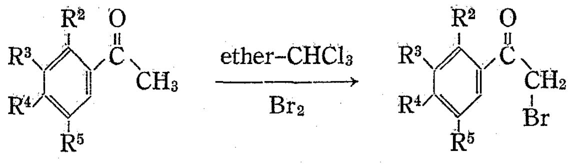
3,4-Dimethoxy, 3-benzyloxy-4-methoxy, 3,4,5-trimethoxy, 2-hydroxy-3,4-dimethoxy, and 2-benzyloxy-3,4-dimethoxy derivatives (**3a**—**e**) of phenacyl bromide have been prepared in 44—84% yields from the corresponding acetophenones by bromination with bromine in a mixture of ether and chloroform.

Keywords——oxygenated phenacyl bromide; oxygenated acetophenone; Friedel-Crafts reaction; bromination; bromine; IR; NMR

The synthetic strategy we have adopted for our syntheses in the Ipecac[3–5] and *Alangium* alkaloids[5–9] (type **1**) and related areas[10] has featured the connection of an adequate phenethyl synthon (fragment A and B in **1**) with a piperidine synthon (*e.g.*, fragment C). This operation has been feasible by the "lactim ether method"[11] in the racemic series[3–5,7,9,10] and by the



1: R=CH$_2$OH or a heterocyclic moiety



2a—**e** **3a**—**e**

a : R^2=H, R^3=R^4=OMe, R^5=H
b : R^2=H, R^3=OCH$_2$Ph, R^4=OMe, R^5=H
c : R^2=H, R^3=R^4=R^5=OMe
d : R^2=OH, R^3=R^4=OMe, R^5=H
e : R^2=OCH$_2$Ph, R^3=R^4=OMe, R^5=H

Chart 1

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[1] Part of this work was reported in a preliminary form.[5]
[2] Location: *13-1 Takara-machi, Kanazawa 920, Japan.*
[3] T. Fujii and S. Yoshifuji, *Tetrahedron Lett.*, **1975**, 731.
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"cincholoipon-incorporating method"[3,6,8] in the chiral series. The appropriate forms of the phenethyl synthon would be ring-oxygenated phenacyl bromides and we had occasion to examine the preparation of some new and some known bromides (type **3**) from the corresponding acetophenone derivatives (type **2**). A detailed account of this investigation forms the subject of the present paper.

Bromination of 3,4-dimethoxyacetophenone (**2a**) with an equimolar amount of bromine in chloroform was reported to give the corresponding phenacyl bromide (**3a**) in 80% yield.[12] When that procedure was followed, we could not reproduce such a high yield of **3a**: the yield did not exceed 45%. However, replacement of the reaction solvent by ether–chloroform (5 : 3, v/v) in that procedure enabled it to increase to 67%. A similar bromination of **2a** but with *ca.* 1.7 equivalent mole of bromine has been found to produce the phenacylidene dibromide derivative in 77% yield.[13] Pictet and Gams prepared the starting acetophenone (**2a**) in an unspecified yield from veratrole by the Friedel–Crafts reaction with acetyl chloride in carbon disulfide.[14] We found that the use of the solvent benzene instead of carbon disulfide in their procedure afforded **2a** in 95% yield, whereas the original procedure, in 62% yield.

TABLE I. NMR and IR Spectra of Compounds Related to Phenacyl Bromide

Compd.	Chemical shift (δ) in $CDCl_3$[a]								Carbonyl ν_{CO} (cm^{-1})		
	$COCH_2$	OCH_3	$OC\underline{H}_2Ph$	$OCH_2\underline{Ph}$	OH	$H_{(2)}$	$H_{(5)}$	$H_{(6)}$	Nujol mull	$CHCl_3$[b] 0.2 M	$CHCl_3$[b] 0.004 M
3a	4.39 (s)	3.93 (s) 3.96 (s)	—	—	—	7.52 (d)[c]	6.88 (d)[d]	7.59 (d-d)[e]	1680	1673	1673
3b	4.33 (s)	3.95 (s)	5.16 (s)	7.20—7.55 (m)	—	7.57 (d)[c]	6.89 (d)	7.60 (d-d)	1677	1672	1673
3c	4.40 (s)	3.91 (s)[f] 3.94 (s)[f]	—	—	—	7.22 (s)	—	7.22 (s)	1692	1675	1676
3d	4.40 (s)	3.92 (s) 3.97 (s)	—	—	11.98 (s)	—	6.55 (d)	7.55 (d)	1641[g]	1629[g]	1629[g]
3e	4.44 (s)	3.90 (s) 3.96 (s)	5.22 (s)	7.44 (s)	—	—	6.80 (d)	7.60 (d)	1687	1678	1677
4	4.66 (s)	3.98 (s) 4.02 (s)	—	—	—	—	6.73 (d)[h]	$H_{(4)}$, 7.42 (d)[h]	—[i]	1704	1704

a) Measured at 5—7% (w/v) concentration. The letter in parentheses refers to the multiplicity or shape of the signal with the abbreviations appeared at the head of Experimental section. Unless otherwise stated, d designates doublet with $J=9$ Hz; d-d, doublet-of-doublets with $J=9$ and 2 Hz.
b) Measured in ethanol-free $CHCl_3$ at 0.2 M or 0.004 M concentration.
c) $J=2$ Hz.
d) $J=8$ Hz.
e) $J=8$ and 2 Hz.
f) Part of nine-proton signals.
g) With ν_{OH} 2600—3500 cm^{-1} (b, weak).
h) $J=8.5$ Hz.
i) Three medium bands at 1728, 1716, and 1702 cm^{-1} were observed in the carbonyl region.

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We next applied the above improved bromination procedure to the acetophenones (**2b**—**e**) and the corresponding new (**3b**,**e**)[1] and known phenacyl bromides (**3c**,**d**) were obtained in 44—84% yields. The phenolic acetophenone (**2d**) has been synthesized by the Friedel–Crafts reaction of pyrogallol trimethyl ether with acetyl chloride in carbon disulfide.[15] Repetition of that procedure furnished **2d** but in only 37% yield. When the reaction solvent was modified as described above for the preparation of **2a**, the yield of **2d** was improved to 85%. The synthesis of **2e** from **2d** by benzylation with benzyl bromide and potassium carbonate has been reported by Kapadia *et al.* but without any experimental details.[16] We followed the same route and the results[1] are also described in Experimental section.

Since one of the purposes of our alkaloid syntheses described above has been to establish the exact location of the phenolic hydroxyl and the methoxyl groups in ring A's of alkaloids of type **1**, the structures of starting ring-oxygenated phenacyl bromides should not be open to doubt. Proof of the correctness of structures **3a**—**e** was provided by the way in which they were generated and by their nuclear magnetic resonance (NMR) and infrared (IR) spectra as summarized in Table I. In its solution IR spectrum the phenolic phenacyl bromide (**3d**) displays the C=O stretching vibration in the 1629 cm^{-1} region, whereas the other non-phenolic phenacyl bromides (**3a**—**c**, **3e**), in the range 1672—1678 cm^{-1}. Since **3d** shows no change in its C=O band position even on dilution (0.004 M), the observed lower shift of the C=O frequency by 43—49 cm^{-1} is undoubtedly a reflection of its chelate ring structure (**3d** in Chart 2).[17] The broad, weak OH stretching vibration in the 2600—3500 cm^{-1} region, observed for **3d**, also supports this view.[18] The *o*-hydroxyphenacyl structure of **3d** was further confirmed by its cyclization to the known coumaranone (**4**).[19] The NMR and IR spectra of **4** are also summarized in Table I. As described before, both **3d** and **3e** were derived from the same phenolic ketone (**2d**) in the present syntheses. Thus, this chemical correlation serves as additional evidence for the *o*-benzyloxyphenacyl structure of **3e**.

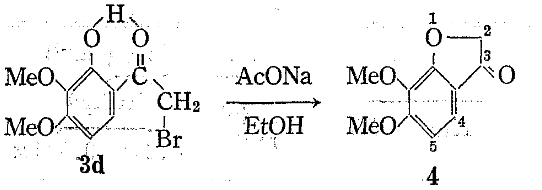

Chart 2

Experimental

All melting points are corrected; boiling points, uncorrected. See ref. 11*b* for details of instrumentation and measurement. The following abbreviations are used: b=broad, d=doublet, d-d=doublet-of-doublets, m=multiplet, s=singlet.

1-(3,4-Dimethoxyphenyl)ethanone (2a)——To an ice-cooled, stirred mixture of finely ground anhyd. $AlCl_3$(96.6 g, 0.72 mol) and a solution of veratrole (82.8 g, 0.6 mol) in dry benzene (400 ml) was added dropwise acetyl chloride (55.0 g, 0.7 mol) over a period of 30 min. After having been stirred at room temp. for 2 hr, the mixture was poured on crashed ice (300 g). The aqueous layer was separated from the benzene layer and extracted with benzene (2×80 ml). The benzene solutions were combined, washed successively with H_2O (50 ml), 10% aq. NaOH (2×50 ml), and H_2O (2×50 ml), dried over anhyd. Na_2SO_4, and evaporated *in vacuo*. The residual oil was purified by vacuum distillation to give **2a** (102.6 g, 95%) as a colorless oil, bp 125° (2.5 mmHg) [lit.[14] bp 206° (16 mmHg)], which solidified (mp 49—51°) on standing. Recrystallization from EtOH yielded colorless prisms, mp 50—51° (lit.[14] mp 49—50°); IR ν_{max}^{Nujol} 1667 cm^{-1} (CO); NMR ($CDCl_3$) δ: 2.57 (3H, s, $COCH_3$), 3.95 (6H, s, two MeO's), 6.86 (1H, d, J=8 Hz, $H_{(5)}$), 7.50 (1H, d, J=2 Hz, $H_{(2)}$), 7.57 (1H, d-d, J=8 and 2 Hz, $H_{(6)}$). This sample was identical [by mixed melting-point test,

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[15] W. H. Perkin, Jr. and C. Weizmann, *J. Chem. Soc.*, **89**, 1649 (1906).

[16] G. J. Kapadia, G. S. Rao, M. B. E. Fayez, B. K. Chowdhury, and M. L. Sethi, *Chem. Ind.* (London), **1970**, 1593.

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[18] *cf.* ref. 17*a*, p. 30 and ref. 17*b*, pp. 103—106.

[19] R. W. Jemison, *Aust. J. Chem.*, **21**, 217 (1968).

thin-layer chromatography (TLC), and IR spectrum] with an authentic sample prepared according to the procedure of Pictet and Gams.[14]

1-(2-Hydroxy-3,4-dimethoxyphenyl)ethanone (2d)——Acetyl chloride (66.7 g, 0.85 mol) was added dropwise, over a period of 45 min, to an ice-cooled, stirred mixture of anhyd. $AlCl_3$ powder (120 g, 0.9 mol), pyrogallol trimethyl ether[20] (126.2 g, 0.75 mol), and dry benzene (600 ml). The mixture was further stirred at room temp. for 1 hr and then at 45—50° for 2.5 hr. The reddish purple gel that resulted was poured into ice water (3 kg). The aqueous mixture was well stirred and extracted with ether (2×1 l). The ether extracts were then extracted with 4% aq. NaOH (2×400 ml, 2×200 ml). The aqueous extracts were combined, acidified (pH 1) with conc. aq. HCl, and extracted with benzene (1×500 ml, 2×300 ml). The combined benzene extracts were washed with H_2O (1×300 ml, 2×100 ml), dried over anhyd. Na_2SO_4, and evaporated *in vacuo*, leaving a slightly brownish solid (125 g, 85%), mp 72—74°, shown to be homogeneous by a single spot on a TLC plate. Recrystallization from MeOH (120 ml) gave **2d** (114 g, 77%) as colorless pillars, mp 78—79° (lit.[15] mp 77°); IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 2400—3400 (b, weak, OH), 1637 (CO); $\nu_{\max}^{\text{CHCl}_3}$ (0.2 M) cm^{-1}: 2500—3200 (b, weak, OH), 1634 (CO), essentially unchanged on dilution to 0.005 M or to 0.0025 M concentration; NMR ($CDCl_3$) δ: 2.56 (3H, s, $COCH_3$), 3.88 and 3.93 (3H each, s, two MeO's), 6.48 (1H, d, $J=9$ Hz, $H_{(5)}$), 7.48 (1H, d, $J=9$ Hz, $H_{(6)}$), 12.54 (1H, s, OH). This specimen was identical (by mixed melting-point test, TLC, and IR spectrum) with the one prepared in 37% yield by the reported procedure.[15]

1-(2-Benzyloxy-3,4-dimethoxyphenyl)ethanone (2e)——A mixture of the foregoing phenol (**2d**) (36.1 g, 184 mmol), anhyd. K_2CO_3 (30.5 g, 221 mmol), benzyl bromide (37.8 g, 221 mmol), and acetone (180 ml) was heated at reflux with stirring for 12 hr. The reaction mixture was concentrated *in vacuo* and H_2O (120 ml) was added to the residue. The resulting suspension was extracted with benzene (1×300 ml, 2×100 ml), and the benzene extracts were washed successively with 5% aq. NaOH (1×100 ml, 1×50 ml) and H_2O (3×80 ml), dried over anhyd. Na_2SO_4, and evaporated *in vacuo* to leave a yellowish oil (51.6 g). The oil was dissolved in hot hexane (600 ml) and the solution was allowed to stand at room temp. The crystals that deposited were collected by filtration and dried to afford **2e** (47.5 g, 90%), mp 50—51°. Recrystallization of this sample from hexane yielded an analytical sample as colorless needles, mp 51—52°; IR $\nu_{\max}^{\text{Nujol}}$ 1665 cm^{-1} (CO); $\nu_{\max}^{\text{CHCl}_3}$ (0.2 M) 1667 cm^{-1} (CO); NMR ($CDCl_3$) δ: 2.53 (3H, s, $COCH_3$), 3.91 and 3.96 (3H each, s, two MeO's), 5.17 (2H, s, $O\underline{CH_2}C_6H_5$), 6.77 (1H, d, $J=9$ Hz, $H_{(5)}$), 7.32—7.59 (5H, m, C_6H_5), 7.55 (1H, d, $J=9$ Hz, $H_{(6)}$). *Anal.* Calcd. for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34. Found: C, 71.36; H, 6.26.

2-Bromo-1-(3,4-dimethoxyphenyl)ethanone (3a)——To an ice-cooled, stirred solution of **2a** (18.0 g, 0.1 mol) in a mixture of ether (500 ml) and $CHCl_3$ (200 ml) was added dropwise a solution of Br_2 (16.0 g, 0.1 mol) in $CHCl_3$ (100 ml) over a period of 1.5 hr. After having been stirred at room temp. for 1 hr, the reaction mixture was washed successively with cold H_2O (100 ml), a minimum amount of ice-cold 5% aq. NaOH, and cold H_2O, dried over anhyd. Na_2SO_4, and evaporated *in vacuo* to leave a pinky cake. Recrystallization of the cake from AcOEt–hexane (3:5, v/v) (80 ml) produced **3a** (17.5 g, 67%) as almost colorless scales, mp 80—81° (lit.[12] mp 80—81°); IR and NMR (see Table I). This sample was identical (by mixed melting-point test, TLC, and IR spectrum) with the one prepared according to the reported procedure.[12]

2-Bromo-1-(3-benzyloxy-4-methoxyphenyl)ethanone (3b)——A solution of Br_2 (11.2 g, 70.1 mmol) in $CHCl_3$ (40 ml) was added dropwise, over a period of 2 hr, to an ice-cooled, stirred solution of **2b**[21] (18.0 g, 70.2 mmol) in a mixture of ether (240 ml) and $CHCl_3$ (120 ml). After the reaction mixture had been stirred at room temp. for additional 2 hr, ether (150 ml) was added. The colorless precipitate that resulted was collected by filtration, washed with ether (50 ml), and dried to give **3b** (12.1 g), mp 105—106.5°. The filtrate and ethereal washings were combined, washed successively with H_2O, ice-cold 5% aq. NaOH, and H_2O, dried over anhyd. Na_2SO_4, and evaporated *in vacuo*. The resulting pale orange solid was recrystallized from benzene–hexane (1:1, v/v) to afford a second crop (7.72 g), mp 104—106°. Total yield, 19.8 g (84%). For analysis the crude sample was further recrystallized as described above, producing colorless needles, mp 106—107.5°; IR and NMR (Table I). *Anal.* Calcd. for $C_{16}H_{15}BrO_3$: C, 57.33; H, 4.51. Found: C, 57.35; H, 4.39.

2-Bromo-1-(3,4,5-trimethoxyphenyl)ethanone (3c)——3,4,5-Trimethoxyacetophenone[22] (**2c**) was brominated in a manner similar to that described above for **3a**, and crude product was purified by recrystallization from MeOH to provide **3c** in 50% yield as colorless prisms, mp 69—70° (lit.[23] mp 63—67°); IR and NMR (Table I). *Anal.* Calcd. for $C_{11}H_{13}BrO_4$: C, 45.70; H, 4.53. Found: C, 45.66; H, 4.34.

The starting ketone (**2c**) was prepared according to the reported procedure[22] but with slight modification: the condensation of trimethylgallyl chloride with diethyl malonate as required in that procedure was effected in boiling ether instead of chlorobenzene at 65°.

2-Bromo-1-(2-hydroxy-3,4-dimethoxyphenyl)ethanone (3d)——To an ice-cooled, stirred solution of the above phenolic ketone (**2d**) (12.75 g, 65 mmol) in a mixture of ether (320 ml) and $CHCl_3$ (80 ml) was added

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21) Y. Inubushi, Y. Masaki, S. Matsumoto, and F. Takami, *J. Chem. Soc.* (C), **1969**, 1547.

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23) W. J. Horton and G. Thompson, *J. Am. Chem. Soc.*, **76**, 1909 (1954).

dropwise a solution of Br_2 (10.4 g, 65 mmol) in $CHCl_3$ (65 ml) over a period of 1.5 hr. After having been stirred at room temp. for 30 min, the reaction mixture was washed with H_2O and extracted with cold 4% aq. NaOH (1 × 70 ml, 2 × 30 ml). The alkaline extracts were acidified (pH 1), without delay, with conc. aq. HCl under ice-cooling and extracted with $CHCl_3$ (1 × 100 ml, 2 × 60 ml). The $CHCl_3$ extracts were washed with H_2O, dried over anhyd. Na_2SO_4, and evaporated *in vacuo*. The residual solid (9.20 g) was recrystallized from EtOH to furnish **3d** (7.80 g, 44%) as colorless pillars, mp 143—145°. Repeated recrystallizations gave an analytical sample, mp 144—145° (lit.[19] mp 140—142.5°); IR and NMR (Table I). *Anal.* Calcd. for $C_{10}H_{11}BrO_4$: C, 43.66; H, 4.03. Found: C, 44.00; H, 4.03.

2-Bromo-1-(2-benzyloxy-3,4-dimethoxyphenyl)ethanone (3e)——A solution of the foregoing trioxygenated acetophenone (**2e**) (47.0 g, 164 mmol) in a mixture of ether (1 l) and $CHCl_3$ (200 ml) was allowed to react with a solution of Br_2 (26.2 g, 164 mmol) in $CHCl_3$ (160 ml) as described above for the bromination of **2d** to **3d**. The reaction mixture was then worked up in a manner similar to that described above for the preparation of **3a**. Recrystallization of the resulting crude product (47.6 g) from MeOH (400 ml) yielded **3e** (40.8 g, 68%) as colorless pillars, mp 106—108°; IR and NMR (Table I). *Anal.* Calcd. for $C_{17}H_{17}BrO_4$: C, 55.91; H, 4.69. Found: C, 55.86; H, 4.48.

6,7-Dimethoxy-3(2*H*)benzofuranone (4)——The following procedure was based on that reported by Jemison.[19] The foregoing phenolic phenacyl bromide (**3d**) (990 mg, 3.6 mmol) and anhyd. sodium acetate (1.23 g, 15 mmol) was stirred in boiling EtOH (10 ml) for 2 hr. The EtOH was removed by distillation and the residue was extracted with hot AcOEt (4 × 4 ml). After the AcOEt extracts had been combined and filtered while hot, hexane (16 ml) was added. The yellow scales that resulted were filtered off, washed with two 3-ml portions of AcOEt–hexane (1 : 1, v/v), and dried to give **4** (447 mg, 64%), mp 122—123°. Recrystallization from EtOH produced an analytical sample as colorless scales, mp 123—124° (lit.[19] mp 123.5°); MS *m/e*: 194 (M^+); IR (Table I); NMR (Table I), virtually in agreement with that reported.[19] *Anal.* Calcd. for $C_{10}H_{10}O_4$: C, 61.85; H, 5.19. Found: C, 61.59; H, 4.95.

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