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% solutions 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 0.065%. The solutions of the original, 3/4, 1/2, and 1/4 concentrations were centrifuged at 10490 rpm for 3 hr.

Preparation of Some Ring-Oxygenated Phenacyl Bromides

Tozo Fuji, Shigeyuki Yoshifuji, and Masashi Ohba

Faculty of Pharmaceutical Sciences, Kanazawa University

(Received April 10, 1978)

3,4-Dimethoxy, 3-benz oxy-4-methoxy, 3,4,5-trimethoxy, 2-hydroxy-3,4-dimethoxy, and 2-benzoyl-3,4-dimethoxy derivatives (3a—e) of phenacyl bromide have been prepared in 44—94% 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 alkaloids and Alangium alkaloids (type I) and related areas 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” in the racemic series and by the

![Diagram](image)

1: R=CH₂OH or a heterocyclic moiety

2a—e

- a: R²=H, R⁴=R⁶=OMe, R³=H
- b: R²=H, R⁴=OCH₃Ph, R⁶=OMe, R³=H
- c: R²=H, R⁴=R⁶=OMe
- d: R²=OH, R⁴=R⁶=OMe, R³=H
- e: R²=OCH₃Ph, R⁴=R⁶=OMe, R³=H

Chart 1

1) Part of this work was reported in a preliminary form.
2) Location: 12-1 Takara-machi, Kanazawa 920, Japan.
4) S. Yoshifuji and T. Fuji, Abstracts of Papers, 40th Meeting of Hokuriku Branch, Pharmaceutical Society of Japan, Kanazawa, June 21, 1975, p. 3.
"cincholone- incorporating method" in the chiral series. The appropriate forms of the phenethyl synthons would be ring-oxygenated phenacyl bromides and we had occasion to examine the preparation of some new and 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. 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. 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. 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>
<thead>
<tr>
<th>Compd</th>
<th>Chemical shift (δ) in CDCl₃</th>
<th>Carbonyl νₑ₀ (cm⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>COCH₃</td>
<td>OCH₃</td>
</tr>
<tr>
<td>3a</td>
<td>4.39</td>
<td>3.93</td>
</tr>
<tr>
<td></td>
<td>(s)</td>
<td>(s)</td>
</tr>
<tr>
<td>3b</td>
<td>4.33</td>
<td>3.95</td>
</tr>
<tr>
<td></td>
<td>(s)</td>
<td>(s)</td>
</tr>
<tr>
<td>3c</td>
<td>4.40</td>
<td>3.91</td>
</tr>
<tr>
<td></td>
<td>(s)</td>
<td>(s)</td>
</tr>
<tr>
<td>3d</td>
<td>4.40</td>
<td>3.92</td>
</tr>
<tr>
<td></td>
<td>(s)</td>
<td>(s)</td>
</tr>
<tr>
<td></td>
<td>3.97</td>
<td>(s)</td>
</tr>
<tr>
<td>3e</td>
<td>4.44</td>
<td>3.90</td>
</tr>
<tr>
<td></td>
<td>(s)</td>
<td>(s)</td>
</tr>
<tr>
<td></td>
<td>3.96</td>
<td>(s)</td>
</tr>
<tr>
<td>4</td>
<td>4.66</td>
<td>3.98</td>
</tr>
<tr>
<td></td>
<td>(s)</td>
<td>(s)</td>
</tr>
<tr>
<td></td>
<td>4.02</td>
<td>(s)</td>
</tr>
</tbody>
</table>

---

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

---

*a*) Measured at 5—7% (v/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=8 Hz; d-d, doublet-of-doublets with J=8 and 2 Hz.

*b*) Measured in ethanol-free CHCl₃ 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 νₑ₀ 3000—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.

---


We next applied the above improved bromination procedure to the acetophenones (2b–e) and the corresponding new (3b,e)\(^{11}\) 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.\(^{12}\) 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.\(^ {13}\) 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 \(\text{m}\)), the observed lower shift of the C=O frequency by 48–49 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 \(\alpha\)-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 \(\alpha\)-benzyloxyphenacyl structure of 3e.

**Experimental**

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

\(\text{1-[(3,4-Dimethoxyphenyl)ethane] (2a)}\) — 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 crushed 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 \(\text{H}_2\text{O} (50 \text{ ml})\), 10\% aq. NaOH (2×50 ml), and \(\text{H}_2\text{O} (2×50 \text{ ml})\), dried over anhyd. Na\(_2\)SO\(_4\), and evaporated \(\text{in vacuo}\). The residual oil was purified by vacuum distillation to give 2a (102.6 g, 95\%) as a colorless oil, bp 125\° (2.5 \text{mmHg}) [lit.\(^ {14}\) bp 206\° (16 \text{mmHg})], which solidified (mp 49—51\°) on standing: Recrystallization from EtOH yielded colorless prisms, mp 50—51\° (lit.\(^ {14}\) mp 49—50\°); IR \(\nu_{\text{max}}\) 1687 cm\(^{-1}\) (CO); NMR (CDCl\(_3\)) \(\delta\) 2.57 (3H, s, COCH\(_3\)), 3.85 (6H, s, two MeO's), 6.86 (1H, d, \(J=8 \text{ Hz}\), H\(_{17}\)), 7.50 (1H, d, \(J=2 \text{ Hz}\), H\(_{21}\)), 7.57 (1H, d-d, \(J=8\) and 2 Hz, H\(_{18}\)). This sample was identical [by mixed melting-point test,

---

18) cf. ref. 17a, p. 30 and ref. 17b, pp. 103—106.
thin-layer chromatography (TLC), and IR spectrum] with an authentic sample prepared according to the procedure of Picot and Gams.19)

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. AlCl₃ powder (120 g, 0.9 mol), pyrogallol trimethyl ether20) (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 x 1). The ether extracts were then combined with 4% aq. NaOH (2 x 400 ml, 2 x 200 ml). The aqueous extracts were combined, acidified (pH 1) with conc. aq. HCl, and extracted with benzene (1 x 500 ml, 2 x 300 ml). The combined benzene extracts were washed with H₂O (1 x 300 ml, 2 x 100 ml), dried over anhyd. Na₂SO₄, 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 pills, mp 78—79° (lit.15) mp 77°; IR ν_max cm⁻¹: 2400—3400 (b, weak, OH), 1637 (CO); ν_max (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 (CDCl₃): δ: 2.58 (3H, s, COCH₃), 3.88 and 3.93 (3H each, s, two MeO's), 6.48 (1H, d, J = 9 Hz, H₆), 7.18 (1H, d, J = 9 Hz, H₇), 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.19)

1-(2-Benzoxyl-3,4-dimethoxyphenyl)ethanone (2e) — A mixture of the foregoing phenol (2d) (36.1 g, 184 mmol), anhyd. K₂CO₃ (50.5 g, 221 mmol), benzyl bromide (97.8 g, 221 mmol), and acetone (180 ml) was heated at reflux with benzene (2 x 100 ml) and the benzene extracts were washed successively with 5% NaOH (1 x 100 ml, 1 x 50 ml), H₂O, (3 x 80 ml), dried over anhyd. Na₂SO₄, 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 ν_max cm⁻¹ (CO); ν_max (0.2 m) cm⁻¹ (CO): NMR (CDCl₃): δ: 2.53 (3H, s, COCH₃), 3.91 and 3.96 (3H each, s, two MeO's), 5.17 (2H, s, OCH₂C₆H₄), 6.77 (1H, d, J = 9 Hz, H₆), 7.32—7.59 (5H, m, C₆H₅), 7.55 (1H, d, J = 9 Hz, H₇). Anal. Calcd. for C₁₆H₁₄O₂: C, 71.31; H, 6.34. Found: C, 71.36; H, 6.26.

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 CHCl₃ (200 ml) was added dropwise a solution of Br₂ (16.0 g, 0.1 mol) in CHCl₃ (100 ml) over a period of 1 hr. After having been stirred at room temp. for 1 hr, the reaction mixture was washed successively with cold H₂O (100 ml), a minimum amount of ice-cold 5% NaOH, and cold H₂O, dried over anhyd. Na₂SO₄, 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.19 mp 80—81°); IR and NMR (see Table 1). This sample was identical (by mixed melting-point test, TLC, and IR spectrum) with the one prepared according to the reported procedure.19)

Bromo-1-(3-benzoxyl-4-methoxyphenyl)ethanone (3b) — A solution of Br₂ (11.2 g, 70.1 mmol) in CHCl₃ (40 ml) was added dropwise, over a period of 2 hr, to an ice-cooled, stirred solution of 2b20) (18.0 g, 70.2 mmol) in a mixture of ether (240 ml) and CHCl₃ (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 ether washings were combined, washed successively with H₂O, ice-cold 5% NaOH, and H₂O, dried over anhyd. Na₂SO₄, 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 1). Anal. Calcd. for C₁₆H₁₄BrO₂: C, 57.33; H, 4.51. Found: C, 57.35; H, 4.39.

Bromo-1-(3,4,5-trimethoxyphenyl)ethanone (3c) — 3,4,5-Trimethoxyacetophenone22) (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.20 mp 65—67°); IR and NMR (Table 1). Anal. Calcd. for C₁₄H₁₂BrO₂: C, 45.70; H, 4.53. Found: C, 45.66; H, 4.34.

The starting ketone (2c) was prepared according to the procedure22) but with slight modification: the condensation of trimethylglyoxylic chloride with diethyl malonate as required in that procedure was effectuated in boiling ether instead of chlorobenzene at 65°.

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 CHCl₃ (80 ml) was added

20) Z. Horii, Yakugaku Zasshi, 60, 614 (1940).
dropwise a solution of Br₂ (10.4 g, 65 mmol) in CHCl₃ (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 H₂O 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 CHCl₃ (1 × 100 ml, 2 × 60 ml). The CHCl₃ extracts were washed with H₂O, dried over anhyd. Na₂SO₄, 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 C₁₈H₁₇BrO₄: C, 43.66; H, 4.03. Found: C, 44.00; H, 4.03.

2-Bromo-1-(2-benzyl0xy-3,4-dimethoxyphenyl)ethanone (3e)—A solution of the foregoing trioxymethylene ketone (2e) (47.0 g, 164 mmol) in a mixture of ether (1 l) and CHCl₃ (300 ml) was allowed to react with a solution of Br₂ (26.2 g, 164 mmol) in CHCl₃ (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 C₁₈H₁₇BrO₄: C, 55.91; H, 4.60. Found: C, 55.86; H, 4.48.

6,7-Dimethoxy-3(2H)benzofuranone (4)—The following procedure was based on that reported by Jemison.¹⁹ The foregoing phenolic phenacetyl bromide (3d) (900 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 C₁₃H₁₁O₄: C, 61.85; H, 5.19. Found: C, 61.50; H, 4.95.

Acknowledgment Financial support of this work by a Grant-in-Aid for Scientific Research (to Professor Y. Ban) from the Ministry of Education, Science and Culture, Japan, is gratefully acknowledged. We are also grateful to Mr. Y. Ittani and Missey Y. Arano and K. Ohata, Kanazawa University, for elemental analyses and NMR and mass spectral data.