ing was continued for a total of 240 min before the final NMR analyses were done.

Pyrolysis of 3-Oxatricyclo[3.2.0.0^{2,4}]hept-6-ene (1a). Sealed tubes[13] of **1a** in tetrachloroethene were inserted in the condensing vapors of toluene (109.5 °C) and *p*-dioxane (97.8 °C) and the reaction progress monitored by NMR spectroscopy.

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

Registry No.—**1a**, 16622-65-4.

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2-Acyloxymethylbenzoic Acids. Novel Amine Protective Functions Providing Amides with the Lability of Esters

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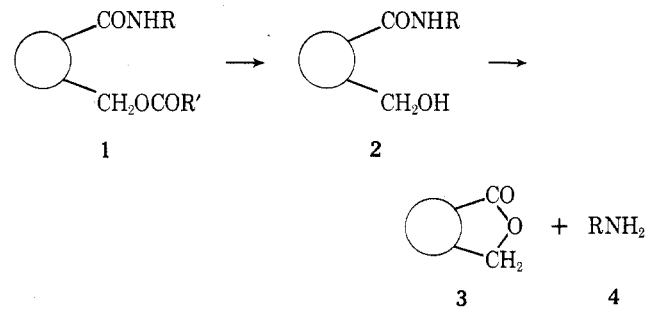
To confer more desirable pharmacokinetic properties on certain antitumor agents a novel drug latentiation scheme was earlier proposed.[2] To release agent from the latentiated derivatives a trigger mechanism utilizing a hydroxy acid component was suggested; elimination of the hydroxy acid unit as the corresponding lactone would release the core antitumor agent. In the example provided (Scheme I) the carbonyl group of the hydroxy acid component is linked to drug –NH– in an amide bond. Such hydroxy amides (**2**) are relatively unstable, the products of intramolecular hydroxyl group attack on amide carbonyl being the lactone **3** and amine **4**. Masking of hydroxyl function in **2** by acylation provides stable derivatives **1** which can be readily manipulated and purified. It was envisaged that in vivo serum esterase action on such acyl derivatives (**1**), by providing the unstable hydroxylic compound **2**, could trigger the release of the core species **4**.

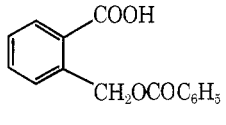
Scheme I



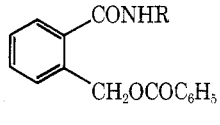
1 2 3 4

Similarly in vitro, any chemical treatment resulting in ester cleavage or exchange in the acyloxy amides (**1**) could result in liberation of the amine component **4**. Such amides might then also be useful for the protection of amino groups during synthesis with the ultimate ease of demasking approaching the ease of cleavage of an ester.

For the preparation of acyloxy amides of type **1** the most readily available precursors are the lactones but no directly useful example of a reaction for conveniently modifying a lactone could be found. Possibly the simplest method of obtaining useful intermediates from lactone precursors, Schotten–Baumann acylation of alkaline hydrolysates of a lactone, appears not to have been successfully applied. Employing phthalide as a model compound it was found that addition of benzoyl chloride to alkaline solutions of this lactone provided 2-benzoyloxymethylbenzoic acid (**5**) in 62% yield. Attempted acid chloride preparation from this acid with thionyl chloride alone returned phthalide and benzoyl chloride. However, by inclusion of 1 mol of pyridine in such reactions crystalline 2-benzoyloxymethylbenzoyl chloride could be isolated in 89% yield. From this acid chloride amide derivatives and the 4-nitrophenyl ester could be readily prepared. The latter 4-nitrophenyl ester also resulted from the action of tri(4-nitrophenyl) phosphite on the acid **5** in pyridine solution. The 4-nitrophenyl ester with suitable amines also furnished amide derivatives and phosphorazo[3,4] coupling of amines and **5** provided a further route to the amides.



5



6a, R = CH_2CONH_2
b, R = 4-$CH_3C_6H_4$

An aliphatic (**6a**) and an aromatic amide (**6b**) of 2-benzoyloxymethylbenzoic acid were prepared and subjected to usually employed reagents and conditions for protective group removal in peptide synthesis;[5] details are tabulated in Table I. The first reagent listed (NaOMe–MeOH) is not normally applied in peptide chemistry but is commonly employed to catalyze ester exchange. It can be noted that those reagents which are normally considered to promote ester hydrolysis or exchange are those which produced amide cleavage in **6a** and **6b** (Table I).

For drug latentiation purposes 2-acyloxymethyl functions other than that containing the lipophilic benzoyl residue were desired. Use of acetic anhydride in the initial Schotten–Baumann conditions provided mixtures and TLC of these showed that the desired 2-acetoxymethylbenzoic acid was being produced but the marked lability of this, providing acetic acid and phthalide, prevented com-

Table I[a]

Reagents and conditions	6a	6b
NaOMe–MeOH, 20 °C	Cleaved[b]	Cleaved[b]
1 N HCl–MeOH, 20 °C	Cleaved[c]	Cleaved[d]
80% HOAc, 15 min, 100 °C	Unchanged	Unchanged
CF_3COOH, 1 h, 20 °C	Unchanged	Unchanged
2 N HBr–HOAc, 30 min, 20 °C	Unchanged	Unchanged
1 N NaOH–80% MeOH, 1 h, 20 °C	Cleaved	Cleaved
45 psi H_2–10% Pd/C, 20 °C	Reduced[e]	Reduced[f]

[a] Reactions were monitored by TLC and the nature of the products confirmed by isolation and direct comparison with authentic samples. Unless otherwise noted the products of cleavage were phthalide and glycinamide from **6a** and phthalide and *p*-toluidine from **6b**. [b] Extremely rapid; reaction complete on mixing. [c] Slow reaction, 48 h necessary for complete reaction of ninhydrin reactive product then glycine methyl ester. [d] Slow, 48 h necessary for completion. [e] Product 2-(2-methylbenzamido)acetamide. [f] Product 2-methyl-*N*-(4-methylphenyl)benzamide.

plete purification. In contrast to most other acylating agents tried, acyl cyanides[6,7] were found to selectively acylate hydroxyl functions without affecting carboxylate anions. For example, the potassium salt of 2-hydroxymethylbenzoic acid in DMF solution with benzoyl cyanide provided the potassium salt of 2-benzoyloxymethylbenzoic acid. Final addition of tri(4-nitrophenyl) phosphite to such reaction mixtures provided 2-benzoyloxymethylbenzoic acid 4-nitrophenyl ester directly. By using equivalent conditions isolation of the unstable 2-acetoxymethylbenzoic acid could then be avoided; reaction of potassium 2-hydroxymethylbenzoate and acetyl cyanide in DMF with following addition of tri(4-nitrophenyl) phosphite provided the stable 2-acetoxymethylbenzoic acid 4-nitrophenyl ester.

Experimental Section

Melting points were determined on an Electrothermal melting point apparatus with the makers supplied stem corrected thermometer; melting points are as read. Analyses were performed by Dr. A. D. Campbell, Microchemical Laboratory, University of Otago, Dunedin, New Zealand. Ir spectra (KBr) were recorded on a Beckman 237 Infracord. Uv spectra were recorded on a Shimadzu UV-200.

Chromatography used Merck SiO_2 F_{254} Al TLC sheets.

2-Benzoyloxymethylbenzoic Acid (5). Method A. Phthalide (15 mmol) was dissolved by heating in aqueous NaOH (12.5 ml of 20%) and the solution cooled to 5 °C. Crushed ice (100 g) was added and vigorous sweep stirring instituted. Benzoyl chloride (2.7 ml) was added in one portion and stirring continued until the odor of benzoyl chloride disappeared. Ice-cold HCl (25 ml, 2 N) precipitated crude acid, which, after washing well with hot water (60 °C) and drying, was crystallized from C_6H_6–light petroleum. Further crystallization from *n*-BuOH provided pure material as massive prisms, mp 128–129 °C (2.37 g, 62%), ir 1686, 1715 cm^{-1}.

Method B. Potassium 2-hydroxymethylbenzoate was prepared by solution of phthalide (6 mmol) and KOH (6 mmol) in 85% MeOH–H_2O, boiling for 30 min, then evaporating to dryness and drying at 110 °C in vacuo. The crystalline salt was dissolved by warming in dry DMF (12 ml) and the solution cooled to below 0 °C. Benzoyl cyanide (12 mmol) was then stirred in. After 30 min of stirring at this temperature Et_3N (0.05 ml) was added and stirring continued for 30 min more. Following addition of MeOH (20 mmol) and stirring for 10 min as much solvent as possible was removed in vacuo at steam bath temperature. The residue was dissolved in cold H_2O (15 ml) and neutrals (methyl benzoate and phthalide) removed by Et_2O extraction. After vacuum stripping of Et_2O from the aqueous phase acidification at 0 °C precipitated crude acid. Crystallization as above gave pure acid (87% yield) of the same melting point, mixture melting point, and TLC behavior.

Anal. Calcd for $C_{15}H_{12}O_4$: C, 70.3; H, 4.7. Found: C, 70.5; H, 4.8.

2-Benzoyloxymethylbenzoyl Chloride. To a suspension of the above acid (4.7 mmol) in C_6H_6 (2 ml) was added Py (4.7 mmol) followed by freshly redistilled $SOCl_2$ (5 ml). After 10 min of boiling the solution was concentrated in vacuo and the remaining solid extracted with dry, boiling C_6H_6 (3 × 25 ml). Evaporation provided the acyl chloride as a thick oil which crystallized on trituration with light petroleum. One crystallization from light petroleum provided product as large prisms, mp 47–49 °C (1.2 g, 89%). Further crystallization raised the melting point to 51–52 °C.

Anal. Calcd for $C_{15}H_{11}O_3Cl$: C, 65.6; H, 4.0; Cl, 12.9. Found: C, 66.0; H, 4.0; Cl, 12.9.

2-Benzoyloxymethylbenzoic acid 4-nitrophenyl ester was isolated from H_2O-diluted reaction mixtures by extraction into EtOAc, washing of the organic layer with 10% Na_2CO_3, 2 N HCl, and 20% NaCl, drying (Na_2SO_4), and evaporation. Crystallization was from MeOH monitoring homogeneity by TLC.

Method C. Reaction of 2-benzoyloxymethylbenzoyl chloride (10 mmol) with a solution of 4-nitrophenol (11 mmol) in Py (10 ml) on the steam bath for 30 min provided product in 89% yield.

Method D. A solution of tri(4-nitrophenyl) phosphite was prepared by dropwise addition of PCl_3 (3 mmol) to a well-cooled solution of 4-nitrophenol (10 mmol) in excess Py. Addition of acid **5** (6 mmol) and 30 min of heating on the water bath gave, after workup, a 72% yield of pure ester.

Method E. A DMF solution of the potassium salt of 2-benzoyloxymethylbenzoic acid was prepared exactly as in method B but MeOH was not then added. A solution of tri(4-nitrophenyl) phosphite from 4-nitrophenol (11 mmol) and PCl_3 (3 mmol) in Py was then added and after 30 min of heating on the steam bath as much solvent as possible was removed in vacuo.

Pure product separated from MeOH as colorless, glistening plates, mp 78.5–79 °C.

Anal. Calcd for $C_{21}H_{15}NO_6$: C, 66.7; H, 4.0; N, 3.7. Found: C, 66.9; H, 4.0; N, 3.4.

2-[2-(Benzoyloxymethyl)benzamido]acetamide (6a). 2-Benzoyloxymethylbenzoic acid (2 mmol) and glycinamide hydrochloride (2 mmol) were suspended in Py (25 ml) and the whole stirred while cooling to −5 °C. Et_3N (6.5 mmol) was added and then PCl_3 (1.33 mmol) in dropwise fashion maintaining the temperature below 0 °C. After stirring at 0° for 24 h excess Py was removed in vacuo, H_2O added, and product removed in EtOAc. The extracts were washed with 2 N HCl, 10% $KHCO_3$, and 20% NaCl, dried (Na_2SO_4), and evaporated. Shaking with light petroleum initiated crystallization. Recrystallization was by solution in excess boiling EtOAc, clarification, then distillation of solvent until crystallization commenced. Pure product (78% yield) was obtained as colorless needles, mp 206–207 °C.

Alternatively, the corresponding 4-nitrophenyl ester (3 mmol) and glycinamide hydrochloride (3 mmol) were suspended in DMF (7.5 ml) at room temperature and Et_3N (3 mmol) was added to the stirred suspension. After 48 h at room temperature isolation, as above, provided product (72% yield) having the same melting point, mixture melting point, and TLC behavior.

Anal. Calcd for $C_{17}H_{16}N_2O_4$: C, 65.4; H, 5.2; N, 9.0. Found: C, 65.4; H, 5.0; N, 8.9.

2-(Benzoyloxymethyl)-*N*-(4-methylphenyl)benzamide (6b). Reaction between 2-benzoyloxymethylbenzoyl chloride and *p*-toluidine in Py in the usual fashion provided this product (91% yield). Alternatively, addition of PCl_3 (2 mmol) to a solution of acid (3 mmol) and amine component (3 mmol) in excess Py and isolation, as in other examples, provided an 87% yield of product. Pure product separated from EtOH–H_2O as colorless plates, mp 102–103 °C.

Anal. Calcd for $C_{22}H_{19}NO_3$: C, 76.6; H, 5.6; N, 4.1 Found: C, 76.6; H, 5.7; N, 4.3.

2-Acetoxymethylbenzoic Acid 4-Nitrophenyl Ester. Acetyl cyanide was prepared from acetyl bromide and cuprous cyanide[8] and had bp 93–93.5 °C (760 mm) [lit.[8] 93 °C (760 mm)]. A solution of potassium 2-hydroxymethylbenzoate (12 mmol) in dry DMF (30 ml) was stirred at 0 °C and acetyl cyanide (24 mmol) added. After 30 min of stirring Et_3N (0.02 ml) was added and stirring continued for another 1 h when a solution of 4-nitrophenol (18 mmol) and PCl_3 (6 mmol) in Py (15 ml) was added. The mixture was heated at 100 °C for 30 min and then solvents removed in vacuo. Product was removed in EtOAc in the usual way after addition of water. The gummy residue obtained on removal of EtAc crystallized on rubbing with light petroleum. Two crystallizations from EtOH provided TLC-homogenous material as colorless plates of mp 112–113 °C (52% yield).

Anal. Calcd for $C_{16}H_{13}NO_6$: C, 60.9; H, 4.2; N, 4.5. Found: C, 61.1; H, 4.3; N, 4.8.

2-(2-Methylbenzamido)acetamide. Hydrogenation (45 psi H_2)

in EtOH solution of **6a** at 20 °C over 10% Pd/C catalyst provided a product crystallizing from absolute EtOH as colorless needles, mp 206–207 °C.

Anal. Calcd for $C_{10}H_{12}N_2O_2$: C, 62.5; H, 6.3; N, 14.6. Found: C, 62.8; H, 6.4; N, 14.8.

Phosphorazo coupling[6,7] of 2-methylbenzoic acid and glycinamide, as in earlier examples, provided a product which was identical by melting point, mixture melting point, and TLC criteria with that obtained from the hydrogenation.

In similar fashion hydrogenation of **6b** provided 2-methyl-*N*-(4-methylphenyl)benzamide, mp 143.5–144 °C, identical in melting point, mixture melting point, and TLC behavior with a synthesized sample.

Registry No.—**5**, 58249-83-5; **6a**, 58249-84-6; **6b**, 58249-85-7; phthalide, 87-41-2; benzoyl chloride, 98-88-4; potassium 2-hydroxymethylbenzoate, 58249-86-8; benzoyl cyanide, 613-90-1; 2-benzoyloxymethylbenzoyl chloride, 58249-87-9; 2-benzoyloxymethylbenzoic acid 4-nitrophenyl ester, 58249-88-0; 4-nitrophenol, 100-02-7; tri(4-nitrophenyl) phosphite, 23485-35-0; glycinamide, 598-41-4; *p*-toluidine, 106-49-0; acetyl cyanide, 631-57-2; 2-(2-methylbenzamide)acetamide, 6754-94-5; 2-methyl-*N*-(4-methylphenyl)-benzamide, 58249-89-1.

References and Notes

(1) This work was supported by the Auckland Division of the New Zealand Cancer Society Inc., and in part by the Medical Research Council of New Zealand.
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Synthesis of 2-Benzyl-4-phenyl-2,4-dihydropyrrolo[3,4-*b*]indole

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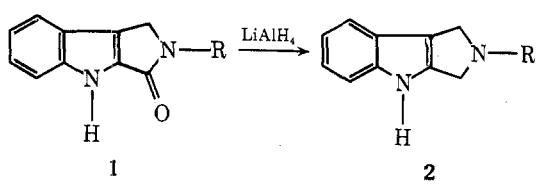
The preparation of a limited number of 1,2,3,4-tetrahydropyrrolo[3,4-*b*]indoles has been reported in the literature, but no compounds of the corresponding 2,4-dihydropyrrolo[3,4-*b*]indole series have been described. We report here the preparation of the first example of this series via lithium aluminum hydride reduction of the corresponding 2-benzyl-1,4-dihydropyrrolo[3,4-*b*]indol-3(2*H*)-one.

The preparation of 2-substituted 1,2,3,4-tetrahydropyrrolo[3,4-*b*]indoles (**2**) through $LiAlH_4$ reduction of the corresponding pyrrolo[3,4-*b*]indol-3(2*H*)-ones (**1**) at elevated temperatures has been reported by Southwick and Owellen.[1] In conjunction with investigations of the chemistry of 2-substituted pyrrolo[3,4-*b*]indoles bearing a phenyl substituent in the 4 position it was decided to adapt this procedure to our series. Thus, 2-benzyl-4-phenylpyrrolo[3,4-*b*]indol-3(2*H*)-one (**3**), prepared in excellent yield from 1-benzyl-2,3-pyrrolidinedione[2] and diphenylhydrazine, when reduced by the procedure of Southwick and Owellen afforded two major products which were readily separated by silica gel chromatography.



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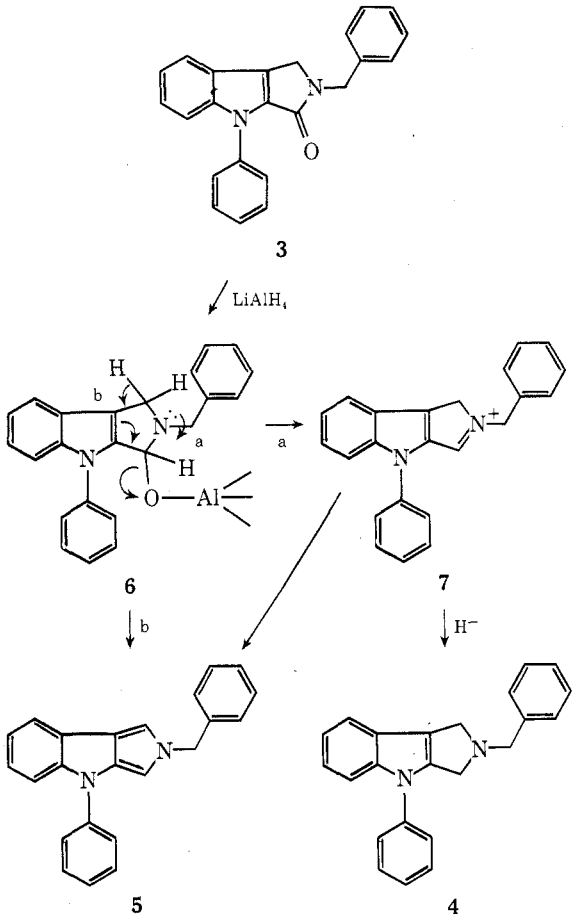

3 6 7 5 4

The more polar of these was identified as the expected 2-benzyl-4-phenyl-1,2,3,4-tetrahydropyrrolo[3,4-*b*]indole (**4**) through spectral and analytical data. Spectral and analytical data obtained on the less polar, relatively stable (>4 weeks at 0 °C) product as the free base or picrate salt confirmed its structure as 2-benzyl-4-phenyl-2,4-dihydropyrrolo[3,4-*b*]indole (**5**). The relatively simple mass spectrum of **5** consisted of the parent ion (*m/e* 322, base peak) and an ion at *m/e* 231 representing loss of the tropylium ion, indicating a highly stable nucleus. In the NMR spectrum of **5**, only the benzyl methylene protons at δ 4.91 lie outside the aromatic region, although both the C(1) and C(3) methine protons can be observed. Proton decoupling experiments demonstrate that these protons are coupled to each other with a coupling constant of 1.8 Hz, consistent with values established for 2,5-proton coupling in pyrrole and its derivatives.

The formation of a dihydropyrrolo[3,4-*b*]indole under these conditions represents a novel and unprecedented action of $LiAlH_4$ which may be rationalized through the following mechanistic considerations. Formation of **7**, the immonium precursor of **4** (path a), by elimination of an oxyaluminum species from the initially formed **6** generates considerable ring strain in the 6-5-5 ring nucleus and is probably not favored energetically. The relative stability of **6** thus allows a second mechanism (path b) to become operative, that is, the abstraction of a relatively acidic (due to polarization of the C(3)–N bond) C(1) proton generating **5** via the 1,4 elimination illustrated. Alternatively, proton abstraction from C(1) in **7** could yield **5**. This pathway is deemed less likely, owing to the known rapid addition of hydride ion to such immonium species.

Further evidence in support of either of these mechanisms was obtained through the reduction of **3** in the presence of the soluble tertiary amine base *N*-ethylpiperidine (bp 130 °C). The yield of **5** under these conditions was increased from 27% to 42% (the yield of **4** remaining the same) reflecting a more