Alkyl-Oxygen Cleavage of an Ester by Primary and Secondary Amines

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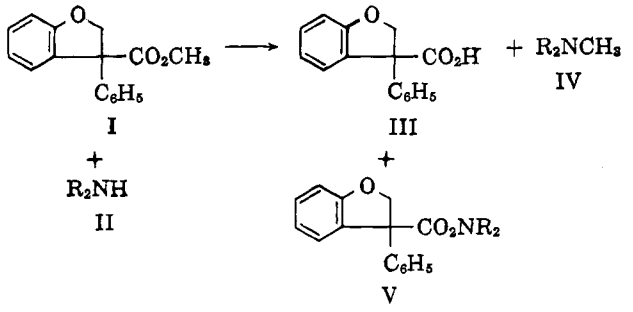
Methyl 2,3-dihydro-3-phenyl-3-benzofurancarboxylate (I) reacts at 80° with secondary amines and with cyclohexylamine solely by alkyl-oxygen cleavage. Products are the acid III and the corresponding methylated amines. With *n*-butylamine, acylation to the amide V (R_2 = HC_4H_9-*n*) occurs only twice as fast as does cleavage to the acid III. *t*-Octylamine is inert under these conditions. Kinetic studies show that nucleophilic reactivity towards displacement of the carboxylate anion from the methyl group in the ester I is in the order pyrrolidine (10) > piperidine (5) > morpholine (1). This is consistent with the order observed by previous workers in a number of halogen displacement reactions. In the temperature range, 70–90°, the Arrhenius activation energy for the methylation of pyrrolidine by the ester I is 8.2 ± 1.0 kcal./mole.

Previous studies of the amine-induced alkyl-oxygen cleavage reactions of esters have been confined to the use of tertiary amines which do not generally react irreversibly with the ester carbonyl group.[1-3] In all cases, quaternary salts were formed either as intermediates or as products.

$$RCO_2R' + (R'')_3N \longrightarrow RCO_2^- \cdot (R'')_3\overset{+}{N}R'$$

Hammett and Pfluger[2] discovered that, at 100° in methanol solution, a number of methyl esters furnished ammonium salts with trimethylamine. They showed, further, that the reaction rate was proportionl to the stability of the carboxylate anion (*i.e.*, the acidity of the conjugate acid) and was unaffected by steric hindrance in the R group of the methyl ester, RCO_2CH_3. Recently, Pierce and Joullié[3] demonstrated that esters of the strong acids, trichloro- and tribromoacetic, will quaternize triethylamine at room temperature. In contrast, trifluoroacetic esters, being less hindered at the carbonyl group, behave as acylating agents towards various nucleophiles.

It is to be expected, therefore, that sufficiently hindered esters also will alkylate primary and secondary amines by alkyl-oxygen cleavage. Such an ester has been encountered in methyl 2,3-dihydro-3-phenyl-3-benzofurancarboxylate (I).[4]



Heating the ester I, for example, in excess dry pyrrolidine at 80° for twenty-four hours gave the corresponding carboxylic acid III in 85% yield together with N-methylpyrrolidine (*i.e.*, IV), readily identifiable even in the presence of excess pyrrolidine, using gas chromatography. To define further its scope, this reaction was conducted under modified conditions and extended to other amines. Results are summarized in Table I.[5]

TABLE I

PREPARATIVE REACTIONS OF AMINES (II) WITH METHYL 2,3-DIHYDRO-3-PHENYL-3-BENZOFURANCARBOXYLATE (I)[a]

	Yield, %		
Amine II	Recovered ester I	Acid III	Amide V
Pyrrolidine[b]	11	85	0
Pyrrolidine	26	68	0
Pyrrolidine[c]	36	65	0
Pyrrolidine[d]	38	60	0
Pyrrolidine[e]	27	64	0
Morpholine[e]	91	10	0
n-Butylamine[b]	56	15	29
Cyclohexylamine[b]	92	7	0
1,1,3,3-Tetramethylbutylamine[b,f]	100	0	0

[a] Except where otherwise noted, all reactions (5 g. of I + 5 ml. of II) were conducted for 24 hr. at 80° in the presence of toluene (5 ml.) and were worked up according to the general procedure detailed in the Experimental section. [b] The toluene was omitted. [c] Reaction was carried out in the presence of 0.38 g. (0.002 mole) of *p*-toluenesulfonic acid monohydrate. [d] Reaction was conducted in the presence of 0.248 g. (0.002 mole) of lithium perchlorate monohydrate. [e] Bicyclohexyl (5 ml.) was used in place of toluene. [f] *t*-Octylamine.

Dilution with inert solvents (toluene or bicyclohexyl) lowered the yield (from 85% to 68%) as expected, but addition of a strong acid catalyst or an inert salt had little effect on the yield of acid obtained in the standard twenty-four-hour reaction period. The less basic morpholine was decidedly less reactive (10% *vs.* 64%) than pyrrolidine.

Three primary amines also were used. In the absence of an inert solvent, *n*-butylamine was acylated twice as fast as it was methylated (29% yield of amide *vs.* 15% yield of acid); cyclohexylamine, however, was methylated (7% yield of III), but not acylated; *t*-octylamine (1,1,3,3-tetramethylbutylamine) was completely inert. Since all three primary amines are of comparable basicity (pK_a 10.4–10.6), these results suggest that both acylation and methylation in this system are subject to steric hindrance in the amine, but that acylation, just as it is more susceptible to hindrance in the acylating agent, is more sensitive than is methylation to hindrance in the amine reactant.

The kinetics of the reaction of the methyl ester I with three secondary amines, pyrrolidine, piperidine, and morpholine also were studied. This was ac-

(1) (a) R. Willstätter, *Ber.*, **35**, 584 (1902); (b) R. Willstätter and W. Kahn, *ibid.*, **35**, 2757 (1902); (c) E. L. Eliel and R. P. Anderson, *J. Am. Chem. Soc.*, **74**, 547 (1952); (d) M. S. Newman and H. A. Lloyd, *ibid.*, **74**, 2672 (1952).

(2) L. P. Hammett and H. L. Pfluger, *ibid.*, **55**, 4079 (1933).

(3) A. C. Pierce and M. M. Joullié, *J. Org. Chem.*, **27**, 3968 (1962).

(4) H. E. Zaugg, R. W. DeNet, and R. J. Michaels, *ibid.*, **26**, 4821 (1961).

(5) It should be emphasized that the carboxylic acid III is not unusually strong (pK_a 3.1). Hence, unlike the trihalogenated acetic esters studied by Pierce and Joullié,[3] the methyl ester I does not possess an extraordinarily stable leaving group tending to enhance its methylating capability.

complished by gas chromatographic measurement of the rate at which the corresponding N-methylated amine was formed. An inert internal standard (toluene, methylcyclohexane, or bicyclohexyl) was used for reference. Results are summarized in Table II.

TABLE II

RATES OF REACTIONS OF SECONDARY AMINES (II) WITH METHYL 2,3-DIHYDRO-3-PHENYL-3-BENZOFURANCARBOXYLATE (I)

Amine II	[II], *M*	[I], *M*	Temp., °C.	Wt. % of internal standard[a]	$k_2 \times 10^4$ l. mol.$^{-1}$ min.$^{-1}$
Pyrrolidine	4.08	1.32	70	31.5	1.20
Pyrrolidine	4.08	1.32	70	31.5	1.21
Pyrrolidine	3.94	1.31	90	31.9	4.36
Pyrrolidine	3.94	1.31	90	31.9	4.61
Pyrrolidine	4.03	1.32	80	31.9	2.17
Pyrrolidine	4.08	1.32	80	31.5	2.36
Pyrrolidine	4.21	2.04	80	15.3	2.07
Pyrrolidine	4.08	1.32	80	30.6	2.64[b]
Pyrrolidine	4.08	1.32	80	30.9	2.95[c]
Piperidine	3.36	1.30	80	29.0[d]	0.946
Piperidine	3.36	1.30	80	29.0[d]	1.06
Morpholine	3.87	1.32	80	30.6[e]	0.217
Morpholine	3.87	1.32	80	30.6[e]	0.213

[a] Except when otherwise indicated, toluene was the internal standard. [b] *p*-Toluenesulfonic acid monohydrate was present in 0.134 *M* concentration. [c] Lithium perchlorate monohydrate was present in 0.134 *M* concentration. [d] Methylcyclohexane was the internal standard. [e] Bicyclohexyl was the internal standard.

As expected, all reactions obeyed the second-order rate law. In line with the preparative experiments (Table I), the rate of methylation of pyrrolidine was relatively insensitive to the addition of strong acid or inert salt. The rate measurements at three temperatures (70°, 80°, and 90°) furnished an Arrhenius activation energy for the pyrrolidine methylation of 8.2 ± 1.0 kcal./mole.

At 80° the relative rates of methylation of pyrrolidine, piperidine, and morpholine were in the ratio, 10:5:1, respectively. Since piperidine is as basic as pyrrolidine (pK_a 11.2), its slightly lower reactivity may be a reflection of a steric effect. The much lower reactivity of morpholine, however, clearly stems largely from its lower basicity (pK_a 8.3).

This nucleophilic order is generally consistent with that observed by previous workers. Thus, Williams[6] found that pyrrolidine reacts with chloroform faster than does piperidine. Chapman, Parker, and Soanes[7] reported that piperidine displaces the halogen atom of *o*- and *p*-nitrohalobenzenes five to ten times faster than does morpholine; and Hall[8] observed that pyrrolidine and piperidine effect the rapid amidation of ethyl chloroformate about a hundred times faster than morpholine does. The only exception appears to be in the work of Földeak and Matkovics[9] who reported the nucleophilic order, piperidine > pyrrolidine > morpholine, in displacement reactions of ethyl α-haloacetates.

(6) H. Williams, *J. Pharm. Pharmacol.*, **11**, 400 (1959).

(7) N. B. Chapman, R. E. Parker, and P. W. Soanes, *J. Chem. Soc.*, 2109 (1954).

(8) H. K. Hall, Jr., *J. Am. Chem. Soc.*, **79**, 5439 (1957).

(9) S. Földeak and B. Matkovics, *Acta Univ. Szeged. Acta Phys. Chem.*, **5**, 43 (1959); *Chem. Abstr.*, **54**, 15389 (1960).

Experimental

Materials.—Methyl 2,3-dihydro-3-phenyl-3-benzofurancarboxylate,[4] m.p. 48–49°, was purified by distillation and recrystallization from pentane. Amines were dried over potassium hydroxide and distilled from fresh potassium hydroxide (several times if necessary) and their purities were assayed gas chromatographically with results as follows: pyrrolidine, 98.3%; piperidine 98.6%; morpholine, >99.9%; *n*-butylamine, >99.9%; cyclohexylamine, >99%; and *t*-octylamine, 97.7%. The internal standards similarly assayed as follows: toluene, 99.8%; methylcyclohexane, 99.5%; and bicyclohexyl, 99.2%. Detectable quantities of water were not present in the reagents used.

Gas Chromatography.—All gas chromatographic analyses were conducted with a Burrell Chromatog Model K-2, fitted with 0.25-in. outside diameter copper columns in hairpin form. A 2-m. column containing 20% Carbowax 20,000 on alkaline Chromosorb W (80–100 mesh) was employed with specially designed injector heated to 200° with an immersion type heater. The carrier gas was helium at an exit flow rate of 80 ml./min. Detector temperature was 200° and the sample size was 2 λ.

For the reactions with pyrrolidine and piperidine, column temperatures in the range 105–115° were used; toluene served as an internal standard for the former and methylcyclohexane for the latter. In the morpholine reactions, the column temperature was 175° and bicyclohexyl was the internal standard.

Peak areas were measured by means of a Disc integrator. Relative response factors were determined by the method of Rosie and Grob[10] but using the Disc integrator.

Rate Measurements.—To a weighed quantity of methyl 2,3-dihydro-3-phenyl-3-benzofurancarboxylate (I)[4] in a 2-ml. glass serum vial was added a measured volume (pipet or syringe) of the liquid internal standard. The vial was then sealed with a rubber serum stopper using an appropriate aluminum sealing ring and crimping tool. After this vessel had been immersed in the thermostat long enough for temperature equilibration to occur, a measured volume of the secondary amine was introduced by means of a syringe, and the reaction vial was replaced in the thermostat. This was taken as zero time. At appropriate intervals, samples of the reaction mixture were withdrawn by syringe and injected directly into the gas chromatograph. The quantity of N-methylated amine IV was determined by comparing its peak area with that of the internal standard, both areas being corrected by relative response factors predetermined using synthetic mixtures of known concentrations.

The second-order rate constant (k_2) was derived from the equation

$$k_2 = \frac{2.303}{t([\mathrm{II}] - [\mathrm{I}])} \log \frac{[\mathrm{I}]([\mathrm{II}] - [\mathrm{IV}])}{[\mathrm{II}]([\mathrm{I}] - [\mathrm{IV}])}$$

where [I] and [II] represent initial molar concentrations of reactants and [IV] the molar concentration of methylated amine IV at time *t* (in minutes). These concentrations were calculated from the measured density (at the reaction temperature) of a mixture of the same composition as that used in a given kinetic experiment. (For example, 0.500 g. of the methyl ester I, 0.500 ml. of toluene, and 0.500 ml. of pyrrolidine gave a mixture of density 0.9127 g./ml. at 80.0°.) Molar concentrations [IV] of N-methylated amines were calculated from the weight percentages derived from the chromatograms assuming that the density at time *t* was the same as at zero time. This is, admittedly, an erroneous assumption, but one leading to negligible error compared to that (*ca.* ±15%) ascribable to experimental sources. In all cases, plots of log ([II] − [IV])/([I] − [IV]) against *t*, gave straight lines. Multiplying the slopes of these lines by 2.303/([II] − [I]) gave the rate constants (k_2) directly. The faster reactions with pyrrolidine were generally carried to 50–60% of completion but the slower ones (morpholine and piperidine) were stopped after only 15 to 30% of the reaction had occurred. Results are summarized in Table II.

Preparative Reactions.—The following procedure describing the reaction of methyl 2,3-dihydro-3-phenyl-3-benzofurancarboxylate (I) with pyrrolidine is illustrative of all of the reactions which are summarized in Table I. A mixture of 5 g. (0.0197 mole) of I, 5 ml. (0.0609 mole) of pyrrolidine, and 5 ml. of toluene was heated in a closed system at 80.0° for 24 hr. The toluene and excess pyrrolidine were removed by distillation

(10) D. M. Rosie and R. L. Grob, *Anal. Chem.*, **29**, 1263 (1957).

under reduced pressure (temp., <80°) and the residue was partitioned between chloroform and water. The chloroform layer was extracted with 100 ml. of 10% sodium hydroxide solution and the aqueous extract was acidified with concentrated hydrochloric acid. The precipitated acid was taken up in chloroform, separated, and concentrated to dryness. The residual solid weighed 3.08 g. (67.5% yield), and its infrared spectrum was qualitatively identical to that of 2,3-dihydro-3-phenyl-3-benzofurancarboxylic acid (III).[4] The neutral chloroform extract was concentrated to dryness. The yellow oil that remained (1.28 g., 25.7% yield) solidified slowly and proved, by its infrared spectrum, to be unchanged ester I. No infrared absorption due to an amide carbonyl group (*i.e.*, V) was detectable in the neutral fraction.

Reaction with *n*-Butylamine.—A mixture of 5 g. of the methyl ester I and 5 ml. of *n*-butylamine (no toluene) was heated at 80° for 24 hr. and worked up by the foregoing procedure. From the acidic fraction there was obtained 0.71 g. (15%) of the carboxylic acid III. The semisolid neutral fraction (4.52 g.) was triturated with pentane and filtered. The solid material, m.p. 105–107°, proved by comparison with an authentic sample (mixture melting point and infrared spectrum), to be N-(*n*-butyl)-2,3-dihydro-3-phenyl-3-benzofurancarboxamide (V, R_2 = HC_4H_8-*n*).[11] It weighed 1.70 g., representing a 29% yield. The pentane filtrate was concentrated to dryness and the residual oil (2.80 g., 56%) soon solidified, m.p. 46–47°. It was recovered ester I.

Acknowledgment.—The authors are indebted to Mr. William Washburn for the infrared spectra and to Mr. Victor Papendick for the pK_a determination.

(11) H. E. Zaugg, R. W. DeNet and R. J. Michaels, *J. Org. Chem.*, **28**, 1795 (1963).

Studies on the Alkaloids of *Securinega virosa* Pax. et Hoffm. II.[1] The Absolute Configuration of C-6 in Virosecurinine and the Stereochemical Interrelationship of Virosecurinine, Securinine, and Allosecurinine[2]

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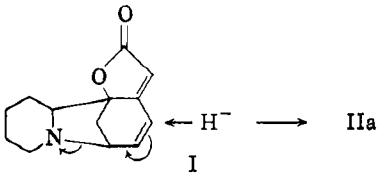
Degradation of virosecurinine (I) has led to the isolation of L-(−)-pipecolic acid and hence to the establishment of the absolute configuration of C-6 in its molecule. The steric relationship of virosecurinine and its related alkaloids, securinine and allosecurinine, has been established.

In part I[1] of this series, it was shown that virosecurinine, an alkaloid of Formosan *Securinega virosa* Pax. et Hoffm. (fam. *Euphorbiaceae*), has structure I (without stereochemical implications) and that it is antipodal with securinine isolated from *S. suffruticosa* by Russian chemists[3] and also by two groups of Japanese workers.[4,5] The present paper describes the establishment of the absolute configuration of C-6 in virosecurinine and also the stereochemical interrelationship of virosecurinine and its related alkaloids.

Virosecurinine, $C_{13}H_{15}NO_2$ (I), when treated with amalgamated aluminum in ether–methanol (4:1), yielded a liquid unsaturated amino lactone, $C_{13}H_{17}NO_2$ (IIa), analyzed as its crystalline picrate. That the allylic C–N bond was reductively cleaved with the formation of a NH group and that the original α,β-unsaturated γ-lactone system was still intact were indicated by its infrared absorption spectrum ($\lambda_{max}^{CHCl_3}$ 2.85, 3.02, and 5.69 μ). The ultraviolet absorption spectrum (λ_{max}^{EtOH} 210.5 mμ) suggested that this compound has no ethylenic double bond[1] extending the conjugation of its α,β-unsaturated γ-lactone system. Acetylation of IIa with acetic anhydride in pyridine provided the acetate, $C_{15}H_{19}NO_3$ (IIb). The presence of its readily reducible ethylenic double bond was demonstrated by the catalytic hydrogenation of IIb with palladized charcoal in alcohol which resulted in the rapid uptake of one molar equivalent of hydrogen and the formation of III which previously had been obtained by a different route.[1] Reduction of I with amalgamated aluminum apparently proceeded by the attack of the hydride ion on the γ-carbon atom which would involve allylic rearrangement by the SN2′ mechanism leading to the formation of IIa, as indicated.



Support for the assignment of the location of this nonconjugated double bond came in the measurement of the nuclear magnetic resonance spectrum[6] of IIb.

Reduction of IIa with lithium aluminum hydride led to a crystalline unsaturated amino diol, $C_{13}H_{21}NO_2$ (IVa), further characterized as the picrate. Benzoylation of IVa with benzoyl chloride and pyridine gave the benzoate (IVb). On oxidation of IVb with potassium permanganate in aqueous acetone in the presence of magnesium sulfate, there was obtained N-benzoyl-L-

(1) T. Nakano, T. H. Yang, and S. Terao, *Chem. Ind.*, 1651 (1962); *Tetrahedron*, **19**, 609 (1963).

(2) For a preliminary communication of this work, see T. Nakano, T. H. Yang, and S. Terao, *Tetrahedron Letters*, 665 (1963).

(3) V. I. Murav'eva and A. I. Ban'kovskii, *Doklady Akad. Nauk, SSSR*, **110**, 998 (1959).

(4) S. Saito, K. Kodera, N. Sugimoto, Z. Horii, and Y. Tamura, *Chem. Ind.*, 1652 (1962).

(5) I. Satoda, M. Murayama, J. Tsuji, and E. Yoshii, *Tetrahedron Letters*, 1199 (1962).

(6) The spectra were measured with a Varian A-60 spectrometer in deuteriochloroform with tetramethylsilane as an internal standard. Chemical shifts in p.p.m. relative to tetramethylsilane equals zero. The three protons, Ha, and Hb and Hc, appeared at 5.88 p.p.m. and at 5.6–5.7 p.p.m., respectively. There was also an additional low-field proton at 5.1 p.p.m. which also was observed in the n.m.r. spectrum of III. This signal can be assigned to a proton in ring A (most likely to Hq). While this is unusually low field for this proton, it seems the proper assignment on the basis of its being coupled to the high-field protons in the rest of the ring, as confirmed by decoupling. Furthermore, the two proton signal at 3.7 p.p.m. has been identified as the other two protons on the carbon next to the amide by the same method. The signal at 3.2 p.p.m. which was not present in III is quite suggestive of protons which are doubly allylic, and this can be taken as evidence in support of structure IIb. These protons were found to be coupled to the olefinic protons Ha and Hb and/or Hc by decoupling.

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