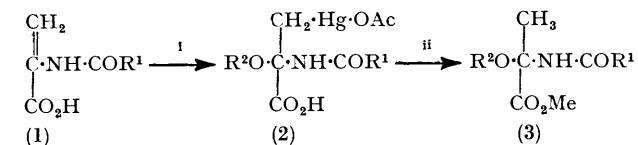


Synthesis of 2-Alkoxy-2-acylaminoacrylic Acids by Alkoxymercuration-Demercuration of 2-Acylaminoacrylic Acids

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Alkoxymercuration of 2-acylaminoacrylic acids (1) with alcohols and mercury(II) acetate, followed by demercuration with sodium borohydride in aqueous sodium hydroxide, leads to 2-alkoxy-2-acylaminoacrylic acids, together with the starting acids. The products have been isolated as the methyl esters. The orientation of the addition to the ethylenic double bond is controlled by mesomeric donation by the nitrogen atom.

2-ALKOXY- AND 2-HYDROXY-2-ACYLAMINOCARBOXYLIC ACIDS or their derivatives occur in nearly all Ergot



R¹ R²
 a; CH₂Ph Me
 b; CH₂OPh Me
 c; Ph Me
 d; C₆H₁₁ Me
 e; CH₂Ph Et

Reagents: i, R²OH, Hg(OAc)₂;
 ii, NaBH₄, 2N-NaOH; H₃O⁺; CH₂N₂

alkaloids. Owing to their poor stability, only few methods of synthesis have been successful; these are

¹ E. S. Chaman and M. M. Shemyakin, *J. Gen. Chem. (U.S.S.R.)*, 1955, **25**, 1309; M. M. Shemyakin, E. S. Chaman, and L. T. Denisova, *Doklady Akad. Nauk S.S.S.R.*, 1956, **106**, 675.

confined to 2-benzamido-¹ and 2-phenylacetamido-² derivatives. In the total synthesis of ergotamines,³ the 2-alkoxy-2-acylamino-function is introduced by an independent method only at the latest stages.

We describe here a new method of synthesis, as shown in the Scheme. As well as known 2-acylamino-derivatives, 2-phenoxyacetamido- and 2-cyclohexanecarboxamido-2-methoxypropionic acids have also been prepared.

The structure of the methyl esters (3) has been deduced on the basis of analytical (Table 2) and spectroscopic (Table 1) data, and established by direct comparison

² G. Lucente, G. M. Lucente, F. Pantanella, and A. Romeo, *Ann. Chim. (Italy)*, 1970, **60**, 259.

³ A. Hofmann, A. J. Frey, and H. Ott, *Experientia*, 1961, **17**, 206; A. Hofmann, H. Ott, R. Griott, P. A. Stadler, and A. J. Frey, *Helv. Chim. Acta*, 1963, **46**, 2306; P. A. Stadler, A. J. Frey, H. Ott, and A. Hofmann, *ibid.*, 1964, **47**, 1911.

with an authentic specimen⁴ in the case of compound (3a). The n.m.r. spectra of all the products (3) show the signal of the C-3 protons as a singlet (3H), indicating that the alkoxy-group has entered at C-2.

Addition Step.—When methanol and mercury(II) acetate were used, each of the acrylic acids (1a—d) gave the intermediate mercurial [probably (2)] as a white precipitate, in almost quantitative yield and in less than 1 h at room temperature. Other alcohols (ethanol, propan-2-ol, and benzyl alcohol) were tested in the alkoxymercuration of (1a). In these cases the disappearance of the acrylic acid was monitored by t.l.c.;

Demercuration Step.—The intermediate mercurials were demercurated with sodium borohydride in aqueous sodium hydroxide. The resulting acids were extracted and methylated with diazomethane to give methyl esters of the starting acylaminoacrylic acid and of the appropriate 2-alkoxy-2-acylaminoacrylic acid (3) as main products. The yields of the two products are apparently very sensitive to structural changes in both the acylamino- and the alkoxy-systems. For example, 2-isopropoxy- and 2-benzyloxy-2-phenylacetamidopropionic acid methyl esters were not isolated at all. The overall yields are reported in Table 2 for the other

TABLE 1
N.m.r. and i.r. data for methyl 2-acylamino-2-alkoxypropionates (3a—e)

	δ (p.p.m.)					$\nu_{\max.}/\text{cm}^{-1}$		
	CMe	OR ²	CO ₂ Me	NH·CO	COR ¹	Amide NH	Ester CO	Amide CO
(3a)	1.68(3H,s)	3.15(3H,s)	3.77(3H,s)	6.53(1H,s)	3.58(2H,s) 7.33(5H,s)	3405, 3380	1750, 1736	1675
(3b)	1.81(3H,s)	3.23(3H,s)	3.83(3H,s)	7.63(1H,s)	4.51(2H,s) 7.20(5H,m)	3405, 3380	1750, 1736	1688
(3c)	1.90(3H,s)	3.30(3H,s)	3.87(3H,s)	7.20(1H,s)	7.55(5H,m)	3400	1740, 1725	1668
(3d)	1.73(3H,s)	3.25(3H,s)	3.48(3H,s)	6.51(1H,s)	1.75(1H,m)	3405	1750, 1733	1680
(3e)	1.75(3H,s)	3.38(2H,q) 1.12(3H,t) J 7 Hz	3.78(3H,s)	6.72(1H,s)	3.60(2H,s) 7.38(5H,s)	3400	1735	1675

TABLE 2
Methyl 2-alkoxy-2-acylaminoacrylates from 2-acylaminoacrylic acids

	M.p. (°C)	Solvent †	Formula	Analysis (%) ‡			Yield (%) *
				C	H	N	
(3a)	103—105	EtOAc-PE	C ₁₃ H ₁₇ NO ₄	62.05	6.8	5.55	82
				62.15	6.8	5.55	
(3b)	76—77	Pr ^t ₂ O	C ₁₃ H ₁₇ NO ₅	58.4	6.4	5.2	29
				58.4	6.4	5.25	
(3c)	128—130	Pr ^t ₂ O	C ₁₂ H ₁₅ NO ₄	60.65	6.4	5.95	20
				60.75	6.35	5.9	
(3d)	81—83	Et ₂ O-PE	C ₁₂ H ₂₁ NO ₄	59.3	8.7	5.85	12
				59.25	8.7	5.75	
(3e)	108—110	Et ₂ O-PE	C ₁₄ H ₁₉ NO ₄	63.45	7.2	5.35	16
				63.4	7.2	5.3	

* Of purified isolated product. † PE = light petroleum. ‡ Upper figures, found; lower figures, calc.

the intermediate mercurials were not precipitated and were recovered by evaporation of the solutions.

The orientation of the addition to the double bond is expected to be affected by both the acylamino- and the carboxy-function. The carboxy-group should decrease the reactivity of the double bond towards the electrophilic attack⁵ of the mercury(II) ion, and promote the addition of the nucleophile to C-3 (as in solvomercuration of $\alpha\beta$ -unsaturated carbonyl compounds⁶). On the other hand, conjugative displacement of the unshared electrons of the nitrogen atom should enhance the reactivity of the double bond and promote the addition of the nucleophile to C-2 (as in solvomercuration of enamines⁷ and *N*-vinylphthalimide⁸). Although it carries an acyl group, in our case the nitrogen atom appears to control the orientation as well as the kinetics when in competition with the carboxy-group.

Demercuration with hydrogen sulphide in alcoholic pyridine⁹ resulted in lower yields of 2-alkoxy-2-acylamino-derivatives. The present method would be more attractive for preparative purposes if a more efficient demercuration procedure could be devised.

EXPERIMENTAL

M.p.s were measured with a Büchi oil-bath apparatus; u.v. spectra were recorded for solutions in 95% ethanol on a Cary 14 instrument, i.r. spectra for solutions in chloroform on a Perkin-Elmer 521 spectrophotometer, and n.m.r. spectra for solutions in deuteriochloroform with tetramethylsilane as an internal standard, on a Varian A60D spectrometer.

2-Cyclohexanecarboxamidoacrylic Acid (1d).—Pyruvic acid (13.6 g) and cyclohexanecarboxamide (13.6 g) in benzene (300 ml) were refluxed for 4 h in a Dean-Stark apparatus

⁴ G. Lucente, F. Pantanella, and A. Romeo, *J. Chem. Soc. (C)*, 1967, 1264.

⁵ R. D. Bach and H. F. Henneiche, *J. Amer. Chem. Soc.*, 1970, **92**, 5589.

⁶ A. J. Bloodworth and R. J. Bunce, *Chem. Comm.*, 1970, 753.

⁷ R. D. Bach and D. K. Mitra, *Chem. Comm.*, 1971, 1433.

⁸ K. Kato, *Nippon Kagaku Zasshi*, 1960, **81**, 829.

⁹ G. Wright, *J. Amer. Chem. Soc.*, 1935, **57**, 1933.

and the mixture was then allowed to cool. The solid was extracted with diethyl ether (100 ml); the solution was filtered and evaporated. The residue crystallized from ethyl acetate to give 2-cyclohexanecarboxamidoacrylic acid (1.8 g), m.p. 176—178° (Found: C, 60.9; H, 7.65; N, 7.1. $C_{10}H_{15}NO_3$ requires C, 60.9; H, 7.65; N, 7.1%), λ_{max} 242 nm (ϵ 6500), ν_{max} 3400, 2920, 1705, 1650, and 1630 cm^{-1} .

The acylaminoacrylic acids (1a and b)¹⁰ and (1c)¹¹ were prepared as described in the literature.

Alkoxymercuration-Demercuration. General Procedure.—A solution of mercury(II) acetate (440 mg, 0.002 mol) in methanol (12 ml) was added to a solution of 2-phenylacetamidoacrylic acid (410 mg, 0.002 mol) in methanol (12 ml) and the mixture was stirred for 40 min at 25°. The resulting white solid was filtered off, washed with methanol, and dissolved in 2N-sodium hydroxide (15 ml). The solu-

tion was stirred for 2 h while sodium borohydride (85 mg) was added, saturated with sodium chloride after removal of metallic mercury, ice-cooled, acidified with 2N-hydrochloric acid (Congo Red), and immediately extracted with ethyl acetate. The organic layer was washed with brine, dried (Na_2SO_4), and concentrated at reduced pressure; the residue was treated with ethereal diazomethane. Evaporation of the solvent and crystallization gave methyl 2-methoxy-2-phenylacetamidopropionate (430 mg).

When larger amounts of the starting acrylic methyl ester were present, crystallization was induced by washing and trituration with light petroleum (b.p. 30—60°).

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¹⁰ T. Wieland, G. Ohnacker, and W. Ziegler, *Chem. Ber.*, 1957, **90**, 194.

¹¹ E. Duranti, *Studi Urbinati*, 1968, **41c**, 329.