A Novel Rearrangement Reaction. A Single-step Conversion of Tetrahydro-1-isoquinolinecarboxylic Acids into 1-Isoquinolones [1]

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The preparation of 2-acyl-6,7-dimethoxy-1,2,3,4-tetrahydro-1-isoquinolinecarboxamides is described. The mixed anhydride of 2-acyl-6,7-dimethoxy-1,2,3,4-tetrahydro-1-isoquinolinecarboxylic acid with isobutyl chloroformate was reacted with the corresponding hydrazines at −10, −15°. Besides those compounds, isoquinolones occur through a new side reaction. The structure of those products was established by ^{13}C and ^{1}H nmr and mass spectroscopy. A possible mechanism of the reaction is discussed.

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In this report new 1-substituted 1,2,3,4-tetrahydroisoquinoline derivatives **6** were synthesised in the hope they may be of potential antiparasitic value.

The mixed anhydride method [2-3] used in peptide synthesis appeared suitable for this purpose. The secondary amine of the 1-carboxy-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **1** was protected by an acetyl, propionyl or butyryl group. The mixed anhydride of acid **1** with an alkyl chloroformate, formed in THF solution in the presence of triethylamine, was reacted with the corresponding hydrazine at −10 to −15°.

During the course of exploratory work on this route, we came across a new side reaction [4]. A novel rearrangement reaction led to a facile one-step synthesis of *N*-substituted isoquinolone **2** from the corresponding 1-carboxy-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **1**. Isoquinolone is formed either in the presence or absence of a primary hydrazine or in the presence or absence of an inert atmosphere. Moreover, it seems to form rapidly (Table I, reaction time, ¼ hour). The nature of the chloroformate seems not to influence the reaction. The same products are prepared with benzyl, ethyl or 2,2,2-trichloroethyl chloroformate.

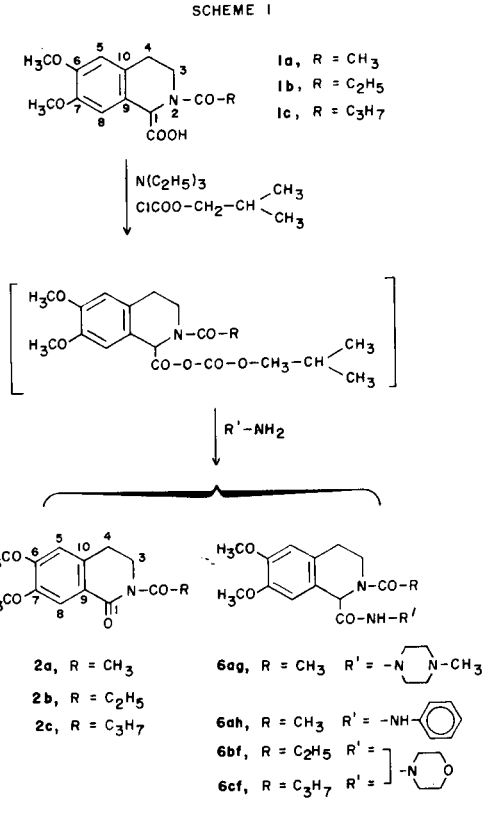
Table I

1a + $N(C_2H_5)_3$ + $ClCOO\text{-}CH_2\text{-}CH(CH_3)_2$

Time	Temperature (°C)	Hydrazine $R'NH_2$	Final Products Hydrazide	Yield of **2**
16	20	+	no	55%
16 [a]	20	+	no	55%
16	−10	+	yes	50%
¼ [b]	−10	0	no	60%
16 [b]	−10	0	no	60%

[a] Addition to −10°, then overnight at room temperature. [b] Under nitrogen.

SCHEME I



A previous synthetic route for the preparation of such isoquinolones **2** has been described but it requires drastic experimental conditions [6]. Our method is a new simple single-step synthetic procedure to isoquinolones.

Thus, it appeared necessary to study the structural question systematically by means of physicochemical methods. The structure of the final isoquinolones **2** were established by ^{1}H and ^{13}C nmr and mass spectroscopy. The ir absorption spectrum exhibits a strong double band at 1700-1650 cm^{-1}, which supports the imide structure [9].

Table II

Compound	R	R'	Yield %	Mp °C	Formula	Analysis Calcd./Found C	H	N	O
1a	CH_3	—	35	209 Diox	$C_{14}H_{17}NO_5$	60.21	6.13	5.01	28.64
				Lit 210 [5]	M = 279.3	60.34	6.17	4.92	28.39
1b	CH_2CH_3	—	40	150	$C_{15}H_{19}NO_5$	61.43	6.52	4.77	27.28
				H_2O/AA	M = 293.3	61.08	6.51	4.59	27.35
1c	$CH_2CH_2CH_3$	—	50	150	$C_{16}H_{21}NO_5$	62.53	6.88	4.56	26.03
				H_2O/AA	M = 307.3	62.18	6.96	4.60	26.07
2a	CH_3	—	50	132 AA	$C_{13}H_{15}NO_4$	62.63	6.06	5.62	25.67
				Lit 131 [6]	M = 249.3	62.43	6.22	5.47	25.55
2b	CH_2CH_3	—	25	139 AA	$C_{14}H_{17}NO_4$	63.87	6.50	5.32	24.31
					M = 263.3	63.85	6.54	5.29	24.60
2c	$CH_2CH_2CH_3$	—	14	128 AA	$C_{15}H_{19}NO_4$	64.97	6.90	5.05	23.08
					M = 277.3	64.58	6.97	4.94	23.35
6ag	CH_3	*N*-Methyl-piperazino	35	180	$C_{19}H_{28}N_4O_4$	60.63	7.49	14.88	17.00
				Et Ac	M = 376.4	60.49	7.54	14.48	17.28
6ah	CH_3	Anilino	30	215 AA	$C_{20}H_{23}N_3O_4$	65.03	6.27	11.37	17.33
					M = 363.4	65.00	6.29	11.50	17.37
6bf	CH_2CH_3	Morpholino	25	171	$C_{19}H_{27}N_3O_5$	60.47	7.20	11.13	21.20
				AA/Iso Et	M = 377.4	60.54	7.19	11.03	21.19
6cf	$CH_2CH_2CH_3$	Morpholino	40	176	$C_{20}H_{29}N_3O_5$	61.37	7.46	10.73	20.44
				AA/Iso Et	M = 391.4	61.76	7.33	10.56	20.61

AA = Absolute Alcohol. Iso Et = Isopropyl ether. Et Ac = Ethyl Acetate. Diox = Dioxane.

Moreover, the OH stretching vibration of the carboxyl groups has vanished.

Proton nuclear magnetic resonance spectroscopy has enabled us to determine unambiguously the structure of **2**. The results of the nmr studies appear in Table III. In the lower field part of the spectra of compounds **2**, the 1-H deshielded proton has disappeared (δ = 5.78). The ^{13}C nmr signals were assigned by off-resonance decoupling techniques. The carbonyl resonances of imides fall into the range 160 to 180 ppm [7]. The cyclic carbonyl group is expected to be observed at lower field in comparison with the aliphatic signals (Table IV).

Moreover the structural assignment was substantiated by a mass spectroscopic examination. Fragmentation of the molecular ion and rearrangement accounted for the appearance of peaks at m/e 206, m/e 178, 150, 135 (for R = CH_3). The base peak corresponds to the loss of the acyl group. Intermediates occur as previously reported for

SCHEME II

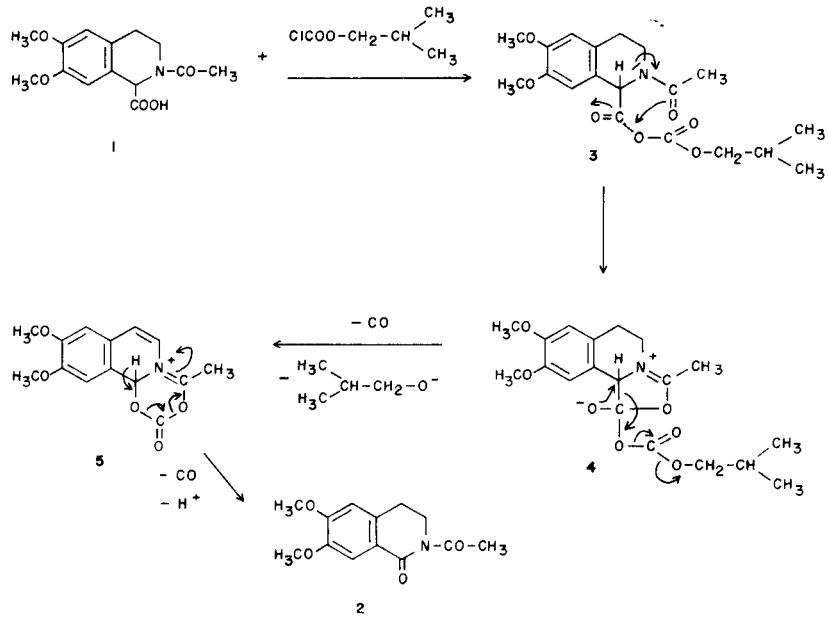


Table III

^{1}H NMR Spectral Data of the Acids **1** and Imides **2** Derivatives

Compound	CH_3O	(CH) 1	(CH_2) 3	(CH_2) 4	H 5	H 8	COOH	Others
1a	4.00 (s, 6H)	5.78 (s, 1H)	2.88 (t, 2H) J_{3-4} = 6	3.70 (t, 2H) J_{4-3} = 6	6.63 (s, 1H)	7.00 (s, 1H)	8.45 (s, 1H)	R′ = CH_3 (2.21, s, 3H)
1b	3.90 (s, 6H)	5.75 (s, 1H)	2.85 (m, 2H)	3.80 (m, 2H)	6.65 (s, 1H)	7.05 (s, 1H)	8.45 (s, 1H)	R′ = CH_2CH_3 (1.25, t, 3H, J = 8) (2.45, q, 2H, J = 8)
1c	3.90 (s, 6H)	5.75 (s, 1H)	2.85 (m, 2H)	3.75 (m, 2H)	6.60 (s, 1H)	7.00 (s, 1H)	9.20 (s, 1H)	R′ = $CH_2CH_2CH_3$ (0.95, t, 3H, J = 8) (1.60, m, 2H, J = 8) (2.45, t, 2H, J = 8)
2a	4.00 (s, 6H)	—	2.97 (t, 2H) J_{3-4} = 6	4.16 (t, 2H) J_{4-3} = 6	6.80 (s, 1H)	7.75 (s, 1H)	—	R′ = CH_3 (2.67, s, 3H)
2b	4.00 (d, s, 6H)	—	3.10 (t, 2H) J_{3-4} = 6	4.10 (t, 2H) J_{4-3} = 6	6.70 (s, 1H)	7.60 (s, 1H)	—	R′ = CH_2CH_3 (1.25, t, 3H, J = 8) (3.00, q, 2H, J = 8)
2c	3.95 (d, s, 6H)	—	3.00 (t, 2H) J_{3-4} = 6	4.10 (t, 2H) J_{4-3} = 6	6.70 (s, 1H)	7.60 (s, 1H)	—	R′ = $CH_2CH_2CH_3$ (1.00, t, 3H, J = 8) (1.75, m, 2H, J = 8) (2.95, t, 2H, J = 8)

The ^{1}H nmr spectra were recorded for solutions in deuteriochloroform with TMS as internal standard.

Table IV

^{13}C NMR Spectral Data of the Imide Derivatives **2**

Compound	CH_3O	NCO-R′	(CO) 1	(CH_2) 3 and 4 isoq	(CH) 5 and 8 aromatic	(C) 6,7,9,10 aromatic	Others
2a	56.15	165.57	173.69	42.04 27.99	111.23 109.35	153.63 148.54 134.85 121.40	R′ = CH_3 (27.50)
2b	56.16	165.51	177.74	42.22 28.05	111.29 109.29	153.51 148.54 134.73 121.59	R′ = CH_2CH_3 (32.84 – 9.45)
2c	56.10	165.45	176.71	42.16 28.00	111.17 109.29	153.45 148.48 134.73 121.46	R′ = $CH_2CH_2CH_3$ (41.26 – 18.66 – 13.87)

The ^{13}C nmr spectra were recorded for solutions in deuteriochloroform with TMS as internal standard.

similar systems [8].

Table V

Compound	
2a	249 (M^+, 25), 206 (M-43, 100), 178 (M-71, 44)
2b	263 (M^+, 100), 206 (M-57, 75), 178 (M-85, 53)
2c	277 (M^+, 93), 206 (M-71, 76), 178 (M-99, 48)

It can be concluded that mass spectral data confirm the isoquinolone structure.

Compounds **6** are characterized by their elemental microanalysis. The ir spectra showed the band of the NH group at 3200 cm^{-1}. (The C=O carboxylic acid band at 1700 cm^{-1} has vanished.) The ^{1}H nmr spectrum exhibited, besides the isoquinoline and R′ protons, a singlet at 8 ppm exchangeable with deuterium oxide.

The authors propose here a chemical mechanism which may explain the formation of **2** (Scheme III) in a one-step synthesis. A proximity phenomenon favors the nucleophilic action of the reactive mixed anhydride **3** by an acyl group. The intermediate tricyclic compound **4** rearranges itself with a cycle extension to lead to **5**, combined with a simultaneous elimination of carbon monoxide and isobutylate. The high acidity of the H 1 favors a second decarbonylation leading to **2**.

EXPERIMENTAL

Infrared spectra were recorded with a Beckman-Acculab IV or a Nicolet 7000 spectrometer, using a potassium bromide pellet. The ^1H nmr spectra were recorded with a JEOL C-60 (CW) or with a Bruker WP 80 pulsed Fourier transform spectrometer (80.131 MHz); ^{13}C nmr spectra were obtained with a Bruker WP 80 (20.15 MHz). Tetramethylsilane was used as the internal standard of chemical shifts (δ in ppm) for deuteriochloroform solutions; coupling constants (absolute values) are expressed in Hz. Deuterated solvents provided the internal lock signal. Broad-band decoupled spectra and off-resonance decoupling technique were used to assign chemical shifts. Mass spectra were performed on a Ribermag R-10-10 Combustion analyses were performed by the C.N.R.S. Melting points were measured with a Büchi SMP-20 capillary melting point apparatus and are uncorrected.

General Method.

2-Acyl-6,7-dimethoxy-1,2,3,4-tetrahydro-1-isoquinolinecarboxylic Acid (**1**).

This compound was prepared according to procedure described elsewhere [5]. The yield was calculated from the starting material (ethyl 6,7-dimethoxy-1,2,3,4-tetrahydro-1-isoquinolinecarboxylate).

2-Acyl-6,7-dimethoxy-1,2,3,4-tetrahydro-1-isoquinolone (**2**).

Five mmoles of 2-acyl-6,7-dimethoxy-1,2,3,4-tetrahydro-1-isoquinolinecarboxylic acid in 250 ml of absolute tetrahydrofuran was cooled to -10 to $-15°$, then 0.8 ml of triethylamine and 0.8 ml of isobutyl chloroformate were added simultaneously in 5 minutes under intensive stirring. After a further 15 minutes, 7.5 mmoles of the corresponding hydrazine in tetrahydrofuran solution was added dropwise to the reaction mixture, stirred overnight at -10 to $-15°$. The triethylamine hydrochloride precipitated was filtered and washed with tetrahydrofuran. Then the combined tetrahydrofuran solution was evaporated in vacuum. The residue was hydrolyzed. The precipitate was crystallized in absolute alcohol and furnished the isoquinolone. The aqueous layer was extracted with chloroform. The combined chloroform solution was dried over sodium sulfate, evaporated in vacuum and the residue was recrystallized to furnish **6**.The data of the products obtained are summarized in Table II.

Acknowledgements.

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