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Synthesis of 2-Acyl-1-benzyl-, 1-phenylethyl- and spirobenzyltetrahydroisoquinolines

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SYNTHESIS OF 2-ACYL-1-BENZYL-, 1-PHENYLETHYL- AND SPIROBENZYLTETRAHYDROISOQUINOLINES

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Abstract: N-Acyl-1-benzyl-, 1-phenylethyl- and 1-spirobenzyltetrahydroisoquinolines are obtained from N-acyl-2-phenylethylamines and arylalkyl aldehydes or cyclic ketones in acidic media.

1-Benzyl-,1- phenylethyl- and spirobenzylisoquinoline skeletons occupy a paramount position in alkaloid chemistry because they act as in vivo precursors to so many of the other naturally occurring isoquinolines as morphines, proaporphines, homoaporphines, protoberberines, pavines, bisbenzylisoquinolines, etc.[1-3]

The last several years we successfully developed the intramolecular α -amidoalkylation of N-acyl-2-phenylethylamines with aromatic aldehydes as a variant of Pictet-Spengler reaction for the synthesis of 1-phenyl-2-acyl-tetrahydroisoquinolines, including some alkaloids.[4]

Now we report our efforts to extend this reaction for synthesis of N-acyl- 1-benzyl-, 1-phenylethyl- and spirobenzyltetrahydroisoquinolines by α -amidoalkylation of N-acyl-2-phenylethylamines **1** with arylalkyl aldehydes and

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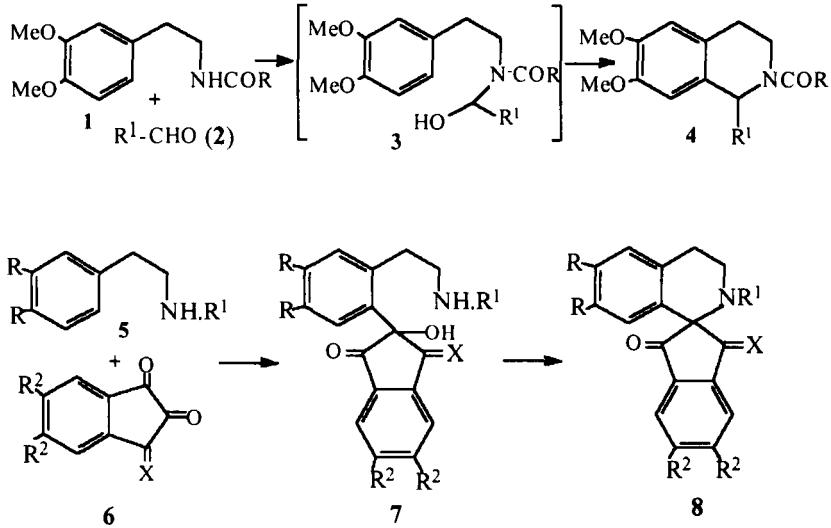
ketones. The cyclization reaction of N-acyl-2-phenylethylamines **1** with phenylacetaldehyde, cinnamaldehyde, hydrocinnamaldehyde **2,** cyclo-hexanone, 1,2-indandione **6**($X=H_2$), and ninhydrin **6** (X=O) was investigated.



The preliminary experiments showed that the intramolecular α -amido-alkylation of N-acyl-2-phenylethylamines **1** with the above aldehydes **2** strongly depended from the acidic media of the reaction. It was found that phenylacetaldehyde reacted only with amide **1** (R=OEt) in H_2SO_4-AcOH (25%) for 72 h at room temperature to afford **4a** in 25% yield. However, its acetal reacted with amides **1a-c** in the presence of catalytic amount of p-toluenesulphonic acid at reflux in dichloroethane for 6 h at 80°C to the corresponding 1-benzyl-2-acyltetrahydroisquinolines in very good yields (**Table 1, 4a-c**). The reaction of hydrocinnamaldehyde and cinnamaldehyde with amide **1** (R=OEt) proceeded smoothly to the corresponding 2-acyl-1-phenylethyl **4d** and 2-acyl-1-styrenetetrahydroisoquinolines **4e,f (Table 1)** only in a solution of dichloromethane and CF_3COOH at room temperature.

Table 1. Compounds **4a-g**, Prepared

Pro-duct	R	R^1	Yield (%)	mp (°C)	^{1}H-NMR ($CDCl_3$ / TMS),J(Hz), δ, ppm	Mol.Formula, MS, m/z (M^+)
4a	OEt	$C_6H_5CH_2$	93	119-120	1.21(t,3H,J=11),2.60(t,2H, J=8),2.90(t,2H,J=8), 3.13(d,2H,J=10), 3.60(s,3H), 3.80(s,3H), 4.20(q,2H,J=8),5.90(m,1H),6.20(s,1H), 6.50(s,1H), 7.50(s,5H)	$C_{21}H_{25}NO_4$ 355(355.5)
4b	Me	$C_6H_5CH_2$	90	115-116	2.10(s,3H),2.70(t,2H,J=6),3.06(t,2H,J=6),3.30 (d,2H,J=8),3.78(s,3H),3.83(s,3H),6.08(s,1H), 6.40(s,1H0,6.58(s,1H),7.15(m,5H)	$C_{20}H_{23}NO_3$ 325(325.4)
4c	C_6H_5	$C_6H_5CH_2$	42	123-124	2.65(m,2H),3.10(m,2H),3.23(d,2H,J=6),3.60(s,3H), 3.70(s,3H),6.12(t,1H,J=8),6.20(s,1H),6.50(s,1H), 6.80(s,5H),7.15(s,5H)	$C_{25}H_{25}NO_3$ 387(387.5)
4d	OEt	$C_6H_5CH_2CH_2$	73	102-103	1.26(t,3H,J=10),2.20(m,2H),2.70(t,2H,J=8),3.25 (t,2H,J=6), 3.80(s,6H),4.24(q,2H,J=10),5.30-5.65 (m,2H),6.20(m,1H),6.52(s,1H),6.65(s,1H),7.20(s,5H)	$C_{22}H_{27}NO_4$ 369 (369.5)
4e	OEt	C_6H_5CH=CH	86	oil	1.30(t,3H,J=12),2.70(t,2H,J=8),3.10(t,2H,J=8),3.45 (d,1H,J=6),3.80(s,3H),3.86(s,3H),4.20 (q,2H,J=8), 4.55(d,1H,J=6),5.70(m,1H),6.35(s,1H),6.60(s,1H), 7.22(s,3H), 7.40(s,2H)	$C_{22}H_{25}NO_4$ 367 (367.4)
4f	H	C_6H_5CH=CH	70	142-143	2.75(t,2H,J=8),3.25(t,2H,J=8),3.60(m,1H),3.80, (s,3H),3.85(s,3H), 4.40(m,1H),6.07(d,1H,J=6), 6.38(s,1H),6.62(s,1H),7.28(s,5H),8.13, 8.30(s,s,1H)	$C_{20}H_{21}NO_3$ 323 (323.4)
4g	OEt	cyclo-C_6H_{11}	84	oil	1.25(t,3H,J=8),1.30-210(m10H),2.70-2.85(m,2H), 3.25-3.50(m,2H),3.80(s,6H),4.15(q,2H,J=8),6.60 (s,1H),6.80(s,1H)	$C_{19}H_{27}NO_4$ 333 (333.4)

In an order to examine farther the reaction of N-acyl-2-phenylethylamines **1** with cyclic ketones as an approach to 2-acylspirobenzyltetrahydroisoquinolines, we carried out first the reaction with cyclohexanone and 5,6-dimethoxy-1,2-indandiones **6** ($X=H_2$). It was found that the reaction N-carboxyethyl 2-(3,4-dimethoxyphenyl) ethylamine (**1a**) with cyclohexanone to spiroisoquinoline **4g** (**Table 1**) was successful only when it was carried out in PPA for 12 h at 60°C. The reaction of **1a** with 5,6-dimethoxy-1,2-indandiones **6** (R^2=OMe, $X=H_2$) proceeded in a mixture of CF_3COOH-AcOH (2:3) at room temperature for 72 h to a product (yield 60%), which was identified as 2-Carboxyethyl-6,7-dimethoxytetrahydroisoquinoline-1-spiro-2'-(5',6'-dimethoxy-1'-indanone) **8** (R^2=OMe, $X=H_2$).

The reaction of 2-phenylethylamines with ninhydrin for synthesis of spirobenzylisoquinoline alkaloids is well known.[5] The reaction of ninhydrin with N-alkylacteamides was also reported.[6] We investigated the reaction of N-acyl-2-phenylethylamines **5** with ninhydrin (**6**, R^2=H, X=O) expecting one α -amidoalkylation to the corresponding 2-acylspirobenzyltetrahydroisoquinolines **8.** It was found that the reaction of N-acyl-2-phenylethylamines **5** without electron donating groups in the aromatic ring as with N-benzenesulphonyl-2-phenylethylamine in PPA for 24 h at room temperature led to **8d (Table 2).** However, the reaction of **5a-e** with electron donating groups in the aromatic ring with ninhydrin at the same reaction conditions unexpectedly led to N-acyl-[4,5-dimethoxy-2-(2`-hydroxy-indane-1,3-dione) phenyl]ethylamine **(Table 2, 7a-e).** Compounds **7** cyclized farther to **8** in PPA for 9 days at room temperature depending on the nature of N-acyl group. Products **8** can be obtained directly from **5** and ninhydrin in PPA for 10 days at room temperature (**Procedure A**,**Table 2, 8a-c**).

Recently[7] we isolated and characterized acetoxy esters of carbinolamides **3** as intermediates of an intramolecular α -amidoalkylation reaction of

Table 2. Compounds **7a-f** (R^2=H) and **8a-d** Prepared (R^2=H)

Pro-- duct	R	R^1	Yield (%)	mp (°C)	^{1}H-NMR ($CDCl_3$/TMS) J(Hz)	Mol.Formula MS, m/z(M^+)
7a	MeO	SO_2Me	85	179-181	2.50(t,2H,J=6),2.80(s,3H),3.00(t,2H,J=8),3.70(s,3H), 3.80(s,3H),4.50 (s,1H),5.00 (d,1H,J=6), 6..80,6.85(s,s,1H),7.25(s,1H),8.10(s,4H)	$C_{20}H_{21}NO_7S$ 419 (419.4)
7b	MeO	$SO_2C_6H_5$	86	163-165	3.30(s,4H),3.65(s,3H),3.75(s,3H),4.25-4.80(m,2H), 6.40(s,1H),6.55(s,1H), 7.25-7.80(m,5H),7.85-8.25(m,4H)	$C_{25}H_{23}NO_7S$ 481 (481,5)
7c	MeO	COOEt	71	135-136	1.25(t,3H,J=8),3.40(t,2H,J=8),3.60(s,3H),3.80(s,3H),3.85(t,2H,J=8),4.15 (q,2H,J=12),4.75(s,1H),5.15(s,1H),6.60(s,1H),6.80(s,1H),7.90-8.30(m,4H)	$C_{22}H_{23}NO_7$ 413 (413.4)
7d	MeO	$COCH_2Cl$	66	148-149	2.55,2.65(t,t,2H,J=6),3.15,3.20(t,t,J=6),3.65(s,3H),3.80(s,3H),3.95 (s,2H),4.25-4.80(m,2H),6.80(s,1H),6.90(s,1H),7.90-825(m,4H)	$C_{21}H_{20}ClNO_6$ 418 (417.5)
7e	MeO	COMe	54	205-207	1.80(s,3H),2.50-2.75(m,2H),3.15-3.40(m,2H),3.75(s,3H), 4.25-4.60(m,2H),6.80,6.95(s,s,1H),7.25(s,1H),7.85-8.25(m,4H)	$C_{21}H_{21}NO_6$ 3.83 (383.4)
8a	MeO	SO_2Me	86	201-204	3.15(s,3H),3.20(t,2H,J=8),3.80(s,6H),3.90(t,2H,J=8), 6.00(s,1H), 6.75(s,1H),7.80-8.25(m,4H)	$C_{20}H_{19}NO_6S$ 401 (401.4)
8b	MeO	$SO_2C_6H_5$	87	223-224	2.95(t,2H,J=8),3.40(s,3H),3.70(s,3H),3.75(t,2H,J=10), 6.00(s,1H), 6.65(s,1H),7.50-8.25(m,9H)	$C_{25}H_{21}NO_6S$ 463 (463.5)
8c	MeO	COOEt	71	oil	1.25(t,3H,J=8),3.40(t,2H,J=8),3.55(s,3H),3.75(s,3H), 3.80(t,2H,J=8), 4.10(q,2H,J=11),6.60(s,1H),6.80(s,1H), 7.80-8.25(m,4H)	$C_{22}H_{21}NO_6$ 395 (395.4)
8d	H	$SO_2C_6H_5$	68	202-204	2.90(t,2H,J=6),3.70(t,2H,J=10),6.75-7.25(m,5H),7.35-7.75(m,4H), 7.80-8.25(m,4H)	$C_{23}H_{17}NO_4S$ 395 (395.4)

N-formyl-2-phenylethylamines **1** (R=H) and paraformaldehyde at reflux in AcOH. The results from the reaction of **5** with ninhydrin showed that when one stronger electrophil as trione was used at similar reaction conditions, an electrophilic substitution toward the activated aromatic ring to compounds **7** was preferred. The conversion of **7** to **8** probably depended from NH-acidity of amides **5** since the cyclization of compounds **7d,e** to the corresponding 2-acylspirobenzyltetrahydroisoquinolines was not successful at different reaction conditions.

Products **8a-d** can be obtained also when the reaction of **5** and ninhydrin was carried out in a mixture of H_2SO_4-AcOH (1v:1v) for 2 h at room temperature.(**Procedure B**). The formation of **7** as intermediates of the reaction can be detected by TLC in the reaction mixture.

The corresponding 1-benzyl- and 1-phenylethyl- 2-acyltetrahydroisoquinolines **4** and 2-acylspirobenzyltetraisoquinolines **8** can be reduced to the corresponding alkaloids. 1-Styrene-tetrahydroisoquinolines are also known to be pharmacological active.[8]

EXPERIMENTAL

Synthesis of 1-benzyl-2-acyltetrahydroisoquinolines (Table 1, 4a-c); General Procedure: Solution of N-acyl-2-phenylethylamine (**1a-c,** 3 mmol) and phenylacetaldehyde diethyl acetal (3 mmol) in dichloroethane (10 mL) and catalytic amount of p-toluenesulphonic acid (20 mg) was refluxed for 6 h. The solvent was removed under vacuum and the products purified by filtration through a short column of a neutral Al_2O_3 using ether as eluent.

Synthesis of 1-phenylethyl-2-acyltetrahydroisoquinolines (Table 1, 4d-f); General Procedure: Solution of N-acyl-2-phenylethylamines **1d-f** (3 mmol) and aldehydes **2d-f** (3 mmol) in a mixture of CF_3COOH-dichloroethane (1mL: 10mL) was stirred for 10 h at room temperature. Water (20 mL) was added, then the mixture was basified with ammonia and extracted with

$CHCl_3$ (3x10 mL)..The combined extract was dried (Na_2SO_4) and the solvents removed under vacuum to products that were purified by filtration through a short column of a neutral Al_2O_3 using ether as eluent.

Synthesis of 4g: N-Carboxyethyl 2-(3,4-dimethoxyphenyl)ethylamine (**1,** R=OEt, 2 mmol, 0.510g) and cyclohexanone (10 mmol, 0.98g) was stirred in PPA (5g) for 12 h at 60°C. The mixture was treated with crash ice and extracted with CH_2Cl_2 (3x20 mL). The extracts were dried (Na_2SO_4) and after evaporation of the solvent, the residue was purified on a column with silica gel using p.ether and ether as eluents.

2-Carboxyethyl-6,7-dimethoxy-tetrahydroisoquinoline-1-spiro-2'-(5',6'-dimethoxy-1'-indanone) 8 (R^2=OMe, X=H_2): A solution of N-carboxyethyl 2-(3,4-dimethoxyphenyl) ethylamine (**5a** , 0.515g, 2mmol) and 5,6-di-methoxy-1,2-indandione **6** (X=H_2, 0.415g, 3mml) in a mixture of AcOH/ CF_3COOH (6 mL:4 mL) was stirred at room temperature for 72 h. The solution was poured in ice water and extracted with CH_2Cl_2 (3x20 mL). The combined extracts were dried (Na_2SO_4) and after evaporation of the solvent, the product was purified by recrystallization from Et_2O/MeOH (1:1) and obtained as red crystals; yield 0.54g (60%)';mp 172-4°C. IR ($CHCl_3$), ν_{CO} 1714, 1686 cm^{-1}. ^{1}H-NMR ($CDCl_3$/TMS),δ(ppm), J(Hz): 1.25(t,3H,J=6), 2.76(t,2H,J=8), 3.30(t,2H,J=8), 3.48(s,3H.), 3.55 (s,2H), 3..84 (s,3H), 3.92(s,3H),4.00(s,3H), 4.37(q,2H,J=6), 6.21(s,1H), 6.64(s,1H), 6.94(s,1H), 7.27(s,1H); MS, mz(M^+) 441; Calc. for $C_{24}H_{27}NO_7$ 441.4).

Synthesis of N-Acyl-[4,5-dimethoxy-2-(2`-hydroxyindane-1,3-dione) phenyl]ethylamine(Table 2,7a-e): A suspension of N-Acyl-2-phenylethyl-amines **5** (5 mmol) and ninhydrine (5.5 mmol) in PPA (30 g) was stirred for 24 h at room temperature. The mixture was poured on crash ice and the solution was extracted with CH_2Cl_2 (3x30 mL). The combined extracts were dried (Na_2SO_4) and after evaporation of the solvent, the products **7** were purified by recrystallization from Et_2O/MeOH.

Synthesis of 2-acylspirobenzyltetrahydroisoquinolines (Table 2, 8a-e);

Procedure A: A suspension of N-acyl-2-phenylethylamines **5** (5 mmol) and ninhydrine (5.5 mmol) in PPA (30 g) was stirred for 10 days at room temperature. The mixture was worked up as above and the products were purified by recrystallization from Et_2O/MeOH or $CHCl_3$/MeOH.

Procedure B: A solution of N-Acyl-2-phenylethylamines **5** (5 mmol) and ninhydrin(5.5 mmol) in a mixture of H_2SO_4/AcOH (15 mL:15 mL) was stirred at room temperature for 2 h, then poured on crash ice and worked up as above.

REFERENCES

1. Shamma, M. .**The Isoquinoline Alkaloids Chemistry and Pharmacology.,** Acad.Press, New York, NY, **1972**.
2. Kametani,T. in .**The Total Synthesis of Isoquinoline Alkaloids**., vol.**3,** J.ApSimon ed., John Wiley and Sons, Inc., New York, London, **1977**.
3. Kametani,T. and Fukumoto,K. in .**Heterocyclic Compounds.**, vol.**38**, G.Grethe,ed., John Wiley and Sons, Inc., New York, NY, **1981**.
4. Venkov,A. and Lukanov.L. **Synthetic Communications, 1992, 22**, 3235.
5. Joullie,M. and Thompson,T. **Tetrahedron, 1991, 47**, 8791.
6. Crooks,P.A. **Chemistry&Industry 1975**, 176.
7. Venkov,A., Ivanov,I. . **Synthetic Communications, 1993, 23**, 1707.
8. Brossi,A., Besendorf,H., Pellmont,B, Walter,M. and Schnider,O. **Helvetica Chim. Acta, 1960**, 1459.

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