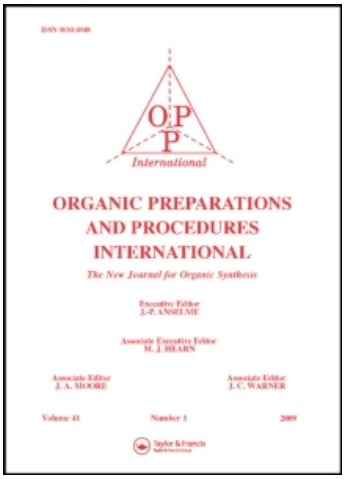

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PREPARATION OF N-BENZOYL-1-(5,6-DIMETHOXYINDANYLMETHYLAMINE) FROM 5,6-DIMETHOXYINDANONE

D. G. Tombari[a]; A. G. Moglioni[a]; F. P. Dominici[a]; G. Y. Moltrasio de Iglesias[a]
[a] Departamento de Química Orgánica, Facultad de Farmacia y Bioquímica, Universidad de Buenos Aires, Buenos Aires, Argentina

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OPPI BRIEFS

PREPARATION OF N-BENZOYL-1-(5,6-DIMETHOXYINDANYLMETHYLAMINE) FROM 5,6-DIMETHOXYINDANONE

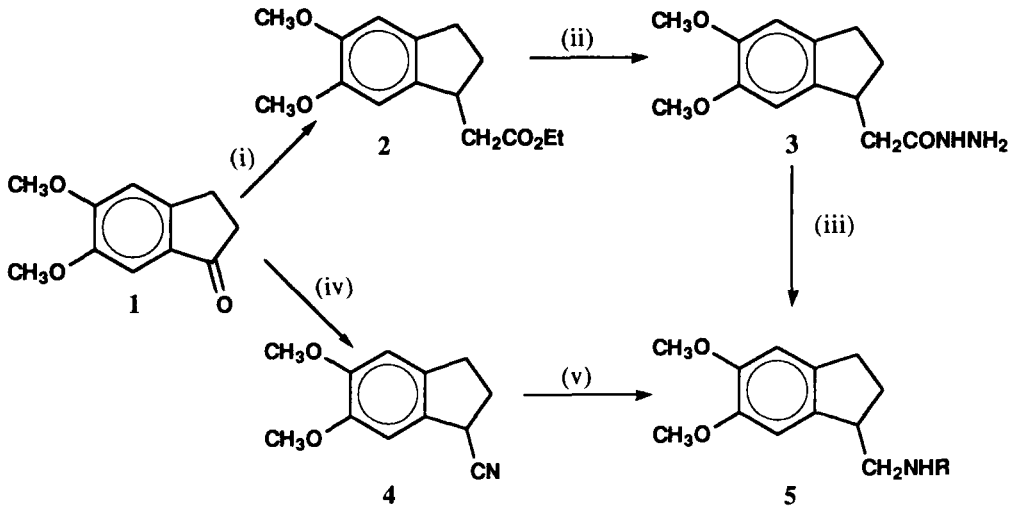
Submitted by (01/14/91)

D. G. Tombari, A. G. Moglioni, F. P. Dominici, and G. Y. Moltrasio de Iglesias*

Departamento de Química Orgánica
Facultad de Farmacia y Bioquímica
Universidad de Buenos Aires, Junín 956
(1113) Buenos Aires, ARGENTINA

As part of our research on the synthesis of naturally occuring indanes, we prepared amide **5b** as one of the key intermediate compounds. The parent system of the title compound was previously prepared by Huisgen *et al.*[1] Ketone **1** was converted to ester **2** by a Reformatsky reaction with ethyl bromoacetate[2] followed by catalytic reduction. Treatment of **2** with hydrazine afforded the acylhydrazine **3** which was converted *via* a Curtius rearrangement,[3] to the amine thence to the desired amide **5b.** However, since the overall yield from **1** proved unsatisfactory (18%), a new synthetic approach was undertaken.

Direct conversion of ketones to nitriles without the simultaneous formation of a hydroxyl group has been amply studied by van Leusen *et al.*[4] This method was used to obtain 5,7-dimethoxyindan-1-carbonitrile in 84% yield, from the corresponding indanone and (*p*-tolylsulfonyl)methylisocyanide (TosMIC) in the presence of potassium *t*-butoxide in DME.[5] When



a) R = H b) R = PhCO

(i) $BrCH_2CO_2Et$, Zn; H_2 Pd/C ii) N_2H_4 iii) $NaNO_2$, AcOH; HCl iv) TosMIC, *t*-BuOK v) $LiAlH_4$

ketone **1** was treated in similar conditions, TosMIC dimerization products were obtained, together with a very low yield of the desired nitrile **4.**

In order to improve the yield in this reaction, several attempts were carried out by varying the solvent and the proportion of potassium *t*-butoxide in order to determine the conditions for obtaining an acceptable amount of nitrile **4.** Thus, 5,6-dimethoxyindan-l-carbonitrile **4** was prepared in 63% yield from **1** in THF. Subsequent reduction with lithium aluminium hydride in ether provided a high yield of **5a**, which was then benzoylated to produce the desired amide **5b.**

EXPERIMENTAL SECTION

Infrared spectra were, performed on a Jasco spectrometer neat or as Nujol mulls. The ^{1}H NMR spectra were obtained on a BRUKER WO SYFT or VARIN FT 80A Spectrometer in deuteriochloroform, chemical shifts, are reported in part per millons downfield from internal tetramethylsilane. The mass spectra were obtained on a VARIAN mat Model CH7A Spectrometer and elemental microanalysis were performed in our laboratories with a Coleman Analyzer. Melting points (uncorrectted, were determined on a Thomas Hoover apparatus.

Ethyl 5,6-Dinethoxyindan-l-acetate (2).- A solution of 5,6-dimethoxyindan-1-one (1.92 g, 10 mmol) and ethyl bromoacetate (1.67 g, 10 mmol) in dry benzene (10 mL) was added over a period of 15 min. to activated zinc wire (0.65 g, 10 mmol) covered with dry benzene (10 mL). The mixture was heated under reflux with stirring for 3-4 hrs until all of the zinc was consumed. The cooled solution was poured into sulfuric acid (10%, 20 mL), and the benzene layer was washed with water and saturated brine, dried (Na_2SO_4) and evaporated in vacuum. The residual oil was extracted with boiling hexane, and the hexane solution was concentrated to give crystals which were recrystallized from hexane (5 mL) to yield 230 mg (80%) of ethyl 5,6-dimethoxyindanyliden-1-acetate, mp. 104-105°, lit.[2] 105-106°. This compound (230 mg) was hydrogenated in ethanol (50 mL) at 50 psi (1 psi: 6.9 kPa), over Pd/C (5%, 30 mg) for 5 hrs at room temperature to give 200 mg (86%) of ethyl 5,6-dimethoxyindan-1-acetate as white crystals, mp. 30-32° (ethanol).

^{1}H NMR: δ 1.30 (t, 3H), 1.55-2.00 (m, 1H), 2.25-2.75 (m, 4H), 2.87 (br t, 2H), 3.85 (s, 6H), 4.20 (c, 2H), 6.75 (br s, 2H).

Anal. Calcd for $C_{15}H_{20}O_4$: C, 69.24; H, 6.84. Found: C, 69.22; H, 6.85

5,6-Dimethoxyindan-1-acethydrazide (3).- A solution of ethyl 5,6-dimethoxyindan-1-acetate (590 mg, 2.23 mol) and hydrazine (0.32 mL, 98%) in absolute ethanol (0.59 mL) was boiled under reflux for 5 hrs. After cooling, 390 mg (70%) of 5,6-dimethoxyindan-1-acethydrazide was obtained as a white solid. Recrystallization from ethanol afforded pure **3**, as a white crystalline solid, mp. 131-132°.

IR (neat) : 3344, 2944, 1625, 1500, 1460 cm^{-1}.

^{1}H NMR: δ 1.65-2.00 (m, 1H), 2.20-2.65 (m, 3H), 2.70-3.00 (m, 4H), 3.60 (m, 1H), 3.90 (s, 6H), 6.70 (s, 1H), 6.75 (s, 1H), 6.80-6.85 (br s, 1H).

Anal. Calcd for $C_{13}H_{18}O_3N_2$: C, 62.45; H, 7.26; N, 11.16. Found: C, 62.48; H, 7.24; N, 11.18

5,6-Dimethoxyindan-l-carbonitrile (4).- A solution of potassium *t*-butoxide (5.70 g) and *t*-butanol

(1 mL) in dry THF (28 mL) was added dropwise during 10 min. to a stirred solution of 5,6-dimethoxyindan-1-one (1.33 g, 6.93 mmol) and (*p*-tolylsulfonyl)methylisocyanide (1.80 g) in dry THF (25 mL) at -5°. After stirringfor 1.5 hrs at 0° and 72 hrs at room temperature, the mixture was poured into ice-water and HCl (1%) was added in small portions with vigorous stirring until the pH was about 6. Then it was extracted with petroleum ether (60-80°) (3 x 25mL), the organic layer was separated, washed with water and dried (Na_2SO_4). The solvent was evaporated in vacuum to give 880 mg (63%) of a yellow oil that crystallized upon standing at 0° for several hours. This compound was recrystallized from petroleum ether (60-80°), as a yellow crystalline solid, mp. 100-101°.

IR (neat): 2250 cm^{-1} strong; ^1H NMR: δ 2.35-2.75 (m, 2H), 2.85-3.10 (m, 2H), 3.80 (s, 3H), 3.90 (s, 3H), 4.10 (m, 1H), 6.75 (s, 1H), 6.90 (s, 1H).

E.M.: (m/e): 204 (M^+ +1, 13.8) ; 203 (M^+, 100.0) ; 188 (25.0).

Anal. Calcd for $C_{12}H_{13}O_2N$: C, 71.00; H, 6.46; N, 6.90. Found: C, 71.09; H, 6.45; N, 6.89

5,6-Dimethoxyindan-1-methylamine (5a)[3].- To a solution of 5,6-dimethoxyindan-1-acethydrazide (2.30 g, 9.2 mmol), glacial acetic acid (10 mL) at -5° was slowly added a solution of sodium nitrite (1 g, 14.5 mmol) in water (2.5 mL). After 30 min. of stirring at 0-5°, benzene (60 mL) was added and the mixture was carefully poured into a cold solution of sodium carbonate (1.5 N, 320 mL) and the organic layer was separated. The remaining aqueous solution was then extracted twice with benzene (2 x 60 mL). The combined organic layers were washed with water, dried (Na_2SO_4 and $CaCl_2$) and concentrated to a volume of 25 mL. The residue was heated under reflux 1 hr, then HCl (15 mL) was added and the reflux was continued for 2 hrs. After cooling, NaOH (20%) was added until pH 12 and the reaction mixture was extracted with ether, the organic layer was washed with brine (10 mL), and evaporated to yield 1.18 g (62%) of dark oil. An analytical sample was obtained by purification on thin layer chromatography as a colorless oil (silica gel GF_{254}).

^1H NMR: δ 2.20 (br s, 2H, exchange by D_2O), 1.70-2.45 (m, 2H), 2.80-3.20 (m, 4H), 3.60-4.10 (m, 1H), 3.80 (s, 6H), 6.75 (s, 2H).

Anal. Calcd for $C_{12}H_{17}O_2N$: C, 69.62; H, 8.28; N, 6.76. Found: C, 69.60; H, 8.30; N, 6.77

N-Benzoyl-5,6-dimethoxyindan-1-methylenamine (5b).- A solution of nitrile **4** (170 mg, 0.84 mmol) in dry ether (5 mL) was added to a stirred suspension of $LiAlH_4$ (32 mg) in dry ether (5 mL).[6] After stirring for 1 hr at room temperature, water was added dropwise and then a solution of sodium tartrate (20%, 8 mL). The ethereal phase was separated, the aqueous layer was extracted with ether (2 x 10 mL) and the combined ethereal extracts were washed once with water and dried (Na_2SO_4). The solvent was evaporated to leave 120 mg (70%) of practically pure amine **5a.** The spectroscopic data of the compound obtained were identical to the compound obtained by the Curtius degradation. Compound **5a** was converted without purification to the N-benzoyl derivative **5b** in 60% yield by treatment with benzoyl chloride and sodium hydroxide (10%) as a colorless crystalline solid, mp. 113-115° (1:2 ethanol-water).

^1H NMR: δ 1.80-2.50 (m, 2H); 2.70-3.05 (m, 3H); 3.40-3.75 (m, 2H), 3.80 (s, 3H); 3.90 (s, 3H), 6.20 (br s, 1H); 6.80 (s, 2H), 7.30-7.55 (m, 3H), 7.60-7.80 (dd, 2H).

E.M. (m/e): 311 (M^+, 6.0); 190 (100.0); 177 (19.8); 122 (23.2).

Anal. Calcd for $C_{19}H_{21}O_3N$: C, 73.37; H, 6.81; N, 4.50. Found: C, 73.38; H, 6.80; N, 4.48

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REFERENCES

1. G. Seidl, R. Huisgen, and J. H. M. Hill, *Tetrahedron*, **20**, 633, (1964).

2. K. Brewster, R. A. Chittenden, R. M. Pinder and M. Skeeis, *J. Chem. Soc., Perkin I*, 941 (1972).

3. *Org. React., Coll. Vol. III*, John Wiley & Sons, Inc., London, 383 (**1954**).

4. O. H. Oldenzeil, D. van Leusen and A. M. van Leusen, *J. Org. Chem.*, **42**, 3114 (1977).

5. L. Crombie, M. J. Powel and P. Tuchinda, *Tetrahedron Lett.*, **21**, 3603 (1980).

6. R. F. Nystron and W. G. Brown, *J. Am. Chem. Soc.*, **70**, 3738, (1948).

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STEREOSELECTIVE REDUCTION OF PIVALOYLOXYMETHYL (2S,5R,6S)-6-ACETYL-3,3-DIMETHYL-7-OXO-4-THIA-1-AZABICYCLO[3.2.0]HEPTANE-2-CARBOXYLATE WITH SODIUM BOROHYDRIDE

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Daniele Donati*, Carla Marchioro, Bruno Tamburini and Antonella Ursini

Glaxo Research Laboratories, Via A. Fleming 2, 37100 Verona, ITALY

Since the discovery of thienamycin in 1976, several classes of active β-lactam antibiotics enhanced the importance of the hydroxyalkyl side chain[1] at the C-3 position of the β-lactam ring. In particular, the insertion of the α-oriented (1R)-hydroxyethyl chain at the C-6 has been found to be essential, both for antibacterial activity and resistance toward β-lactamases of the penem and carbapenem classes.[2] During our search for new β-lactam antibiotics, we identified pivaloyloxymethyl (S)-6-[(R)-1-hydroxyethyl]penicillanate as a key intermediate and set up a convenient method to prepare it on a laboratory scale. The introduction of the (1R)-hydroxyethyl chain on β-lactams has been widely described;[3] however, the direct introduction of the (1R)-hydroxyethyl chain at position 6 of the penicillanates has been described only in a few cases[3a,c,e,h] and in particular, it has been described only once for the pivaloyloxymethyl ester.[3h] Karaday *et al.*[3a] obtained excellent