lized thrice from ether–ethanol, m. p. 93–95.5°; mixed m. p. with authentic (I) 93–93.5°. *Anal.* Calcd. for $C_9H_{19}O_3N$: N, 7.40. Found: N, 7.36.

N-(1,1-Dimethyl-3-hydroxybutyl)-lactamide (I).—The aminolysis reaction was repeated, using 1 mole each of ester and amine; after sixteen days, titration indicated 89% reaction. An aliquot was seeded with (I) and cooled; it became a semi-solid mass. This was filtered, and the solid was crystallized once from ether–ethanol yielding 12% of crude (I) (m. p. 88–90°). The crude (I) was recrystallized several times from ether–ethanol, m. p. 94–95.5°. *Anal.* Calcd. for $C_9H_{19}O_3N$: C, 57.1; H, 10.1; OH, 18.1. Found: C, 56.8; H, 10.0; N, 7.52; OH, 18.5.[7]

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Synthetic Analogs of Oxytocic Drugs. IV. Miscellaneous Substituted-β-alanine Esters

BY ARTHUR P. PHILLIPS

Oxytocic activity having been discovered in a series of phenethyl-β-alanine esters[1] an exploration was made of the effect of modifying various portions of the molecular structure.[2,3] This paper reports the preparation of a variety of β-alanine ester types: (1) bearing purely aliphatic substituents on the nitrogen; (2) N-benzyl or N-phenethyl derivatives having not one but two 2-carbomethoxyethyl groups on the nitrogen; and (3) in which the β-nitrogen is part of a saturated heterocyclic ring.

None of these compounds possessed significant oxytocic activity, but most of them are of extremely low toxicity.

The substances included were all synthesized by reaction of the appropriate amine with methyl acrylate giving excellent yields in most cases. The substituted bis-2-carbomethoxyethylamines were made by heating under reflux a mixture of the particular primary amine and about five moles of methyl acrylate for from ten to twenty hours.

Experimental

Data on the compounds are included in Table I. The method of preparation and isolation are illustrated by a few examples.

6,7-Dimethoxy-N-(2-carbomethoxyethyl)-1,2,3,4-tetrahydroisoquinoline Hydrochloride.—A mixture of 10 g. (0.05 mole) of 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline with 12 cc. (nearly 0.15 mole) of methyl acrylate in 25 cc. of benzene was refluxed for twenty-four hours. Basic material was extracted from benzene with 3 *N* hydrochloric acid. The aqueous acid extracts were basified with potassium carbonate and liberated base was extracted with ether. After drying over anhydrous potassium carbonate addition of a slight excess of methanolic hydrogen chloride to the ethereal solution precipitated the product as the hydrochloride. The yield of white crystals was 8 g. (50%) and after several crystallizations from methanol–ether mixtures these melted at 177–178°.

TABLE I

MISCELLANEOUS SUBSTITUTED-β-ALANINE ESTER SALTS $\begin{matrix}R\\R'\end{matrix}\!\!>\!N\text{—}CH_2CH_2COOCH_3\cdot HCl$

R	R′	Crystn. solvent[a]	Yield, %	M. p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
(1) R and R′ = simple aliphatic groups (or hydrogen)								
CH_3	H[b]	Free base	44	B. p. 71–73, 29 mm.				
n-C_3H_7	*n*-C_3H_7[c]	Ac	67	134–135	51.99	51.87	8.37	8.31
n-C_4H_9	*n*-C_4H_9[c,d]	Ac. E.	50	125–126.5	55.08	55.15	8.92	8.72
n-C_5H_{11}	*n*-C_5H_{11}[c]	M. Ac. E.	80	232–234	57.60	57.55	9.38	9.74
(2) R′ = $CH_2CH_2COOCH_3$								
CH_3[b]		Free base	37	B. p. 133–135, 12 mm.				
$C_6H_5CH_2$		M. Ac. E.	80	85.5–87	57.02	56.78	7.03	7.05
4-$CH_3OC_6H_4CH_2CH_2$		M. Ac. E.	100	118–119	56.71	56.73	7.29	7.62
3,4-$(CH_3O)_2C_6H_3CH_2CH_2$		Ac. E.	90	124–125	55.42	55.66	7.25	7.44
(3) $\begin{matrix}R\\R'\end{matrix}\!\!>\!N$ = a saturated heterocyclic ring								
$C_5H_{10}N$[e,f]		M. E.	90	195–196	52.05	52.57	9.35	9.13
$C_9H_{10}N$[g]		M. E.	100	157–158	61.02	60.85	7.10	6.89
$C_{11}H_{14}NO_2$[h]		M. E.	50	177–178	57.02	57.01	7.02	7.34
$C_{12}H_{16}NO_2$[i]		M. E.	90	192–193	58.23	58.55	7.34	7.33
$C_{11}H_{15}N_2$[j,k]		M. Ac.	95	225–226	53.70	53.84	7.22	7.58

[a] Ac = acetone; E = ether; M = methanol. [b] Known compound; see Morsch, *Monatsh.*, **63**, 220 (1933). [c] Acid oxalate salt since the hydrochloride seemed intractable. [d] The base had b. p. 108° (6 mm.). [e] The base had b. p. 110–111° (21 mm.). [f] $C_5H_{10}N$ = 1-piperidino-. [g] $C_9H_{10}N$ = 1,2,3,4-tetrahydro-2-isoquinolino-. [h] $C_{11}H_{14}NO_2$ = 6,7-dimethoxy-1,2,3,4-tetrahydro-2-isoquinolino-. [i] $C_{12}H_{16}NO_2$ = 6-ethoxy-7-methoxy-1,2,3,4-tetrahydro-2-isoquinolino-. [j] $C_{11}H_{15}N_2$ = N′-benzyl-N-piperazino-. [k] The dihydrochloride.

N,N-Bis-(2-carbomethoxyethyl)-homoveratrylamine Hydrochloride.—A mixture of 36 g. (0.2 mole) of homoveratrylamine and 120 g. (1.3 moles) of methyl acrylate was refluxed for twenty-four hours on a steam-bath. The

(1) Baltzly, Dvorkovitz and Phillips, THIS JOURNAL, **71**, 1162 (1949).
(2) Baltzly and Phillips, *ibid.*, **71**, 3419 (1949).
(3) Baltzly and Phillips, *ibid.*, **71**, 3421 (1949).

reaction mixture was diluted with a large volume of absolute ether and treated with an excess of methanolic hydrogen chloride. Scratching gave a white crystalline product, 70 g. (90%), melting at 120–125°. After several crystallizations from acetone–ether mixtures the pure substance melted at 124–125°. A mixture of this with the pure mono-ester (N-homoveratryl-β-alanine methyl ester)[1] of m. p. 121–122° showed a depression and melted at 105–112°.

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Preparation of Homopiperonylamine by Hydrogenation of 3,4-Methylenedioxybenzyl Cyanide over Raney Cobalt Catalyst

BY WILKINS REEVE AND WILLIAM M. EARECKSON, III

The preparation of homopiperonylamine by the hydrogenation of 3,4-methylenedioxybenzyl cyanide over Raney cobalt catalyst has been studied incidental to the preparation of this compound for some synthetic work. This preparation is of interest both because it appears to be the best method of preparing the frequently used homopiperonylamine and because it provides an excellent illustration of the advantage of Raney cobalt over Raney nickel in the reduction of nitriles to primary amines. Although the use of cobalt catalysts in the reduction of nitriles has been the subject of a number of patents,[1] these catalysts do not seem to have received the recognition they deserve.

The more important methods previously used for the preparation of homopiperonylamine are (a) the hydrogenation of small amounts of 3,4-methylenedioxy-ω-nitrostyrene, dissolved in a large amount of acetic acid and in the presence of an excess of sulfuric acid and 35% of its weight of a palladium catalyst (84–93% yield)[2]; (b) the hydrogenation of 3,4-methylenedioxybenzyl cyanide, 85% yield when carried out in methanol–ammonia over Raney nickel catalyst,[3] 93% yield when carried out in acetic acid over platinum in the presence of sulfuric acid[4]; (c) the electrolytic reduction of 3,4-methylenedioxy-ω-nitrostyrene (67–75% yield)[5]; and (d) the Hofman degradation of β-(3,4-methylenedioxyphenyl)-propionamide (88% yield).[6]

Table I gives the yields we have obtained of homopiperonylamine by the hydrogenation of 3,4-methylenedioxybenzyl cyanide over Raney nickel and Raney cobalt catalysts in anhydrous ethanol–ammonia, anhydrous ethanol and in anhydrous dioxane. It is to be noted that Raney cobalt in dioxane solvent with no ammonia gives as good results as Raney nickel, even when the latter is used with the ethanol–ammonia solvent. 3,4-Methylenedioxy-ω-nitrostyrene was also reduced over Raney cobalt catalyst to the primary amine, but only in 26% yield. Under the same conditions, but with Raney nickel, a 10% yield was obtained.

TABLE I

HYDROGENATION OF 3,4-METHYLENEDIOXYBENZYL CYANIDE OVER RANEY NICKEL AND RANEY COBALT CATALYSTS

Catalyst	Solvent and conditions[a]	Yield of homopiperonylamine, %
Raney nickel	Dioxane	50[b]
Raney nickel	Ethanol–ammonia	82
Raney cobalt	Dioxane	79–87
Raney cobalt	Ethanol–ammonia	88
Raney cobalt	Anhyd. ethanol	65–69

[a] Forty-two grams of nitrile was used in the case of Raney nickel with the dioxane solvent. All other hydrogenations were carried out with 70 g. of compound dissolved in 90 ml. of solvent over 5% catalyst at 125 to 150° at a starting hydrogen pressure of 200 atmospheres at room temperature. The hydrogenations proceeded rapidly; the time necessary at the reaction temperature approximating fifteen minutes. The procedure of Icke and Redemann given in "Organic Syntheses," **23**, 72 (note 5) (1943), for the use of methanol–ammonia was followed, except anhydrous ethanol was saturated with ammonia. [b] 25% Secondary amine was also obtained.

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Experimental

All melting points are corrected.

The dioxane was purified by refluxing over sodium.

Preparation of Catalysts.—Raney nickel was prepared by the W-7 procedure of Adkins.[7] Raney cobalt was prepared by crushing and grinding the 40% cobalt–60% aluminum alloy until all passed a 100-mesh sieve, and then following the W-7 procedure. Both alloys were purchased from the Gilman Paint and Varnish Company, Chattanooga, Tennessee.

3,4-Methylenedioxybenzyl Cyanide.—This was prepared by a modification of the procedures of Bills and Noller,[3] and Kobayashi.[8] 3,4-Methylenedioxybenzyl chloride was prepared from piperonyl alcohol (1.0 mole), concentrated hydrochloric acid (250 ml.) and calcium chloride (sufficient to saturate the aqueous layer). The aqueous layer was extracted twice with 100 ml. portions of benzene, and the benzene solution of the chloride treated directly with 3.5 moles of sodium cyanide and 0.025 mole of mercuric cyanide dissolved in 250 ml. of water. After

(1) Schmidt, German Patent 648,297 (July 27, 1937), *C. A.*, **31**, 7067 (1937), U. S. Patent 2,160,578 (May 30, 1939), *C. A.*, **33**, 7315 (1939); and U. S. Patent 2,165,515 (July 11, 1939); *C. A.*, **33**, 8211 (1939); British Patent 536,940 (June 3, 1941), *C. A.*, **36**, 1331 (1942); Signaigo, U. S. Patent 2,166,183 (July 18, 1939), *C. A.*, **33**, 8211 (1939), Canadian Patent 408,981 (Dec. 1, 1942), *C. A.*, **37**, 1447 (1943; Howk, U. S. Patents 2,166,150, 2,166,151, and 2,166,152 (July 18, 1939), *C. A.*, **33**, 8211 (1939), Canadian Patent 408,983 (Dec. 1, 1942), *C. A.*, **37**, 1449 (1943); Gresham, U. S. Patent 2,429,876 (Oct. 28, 1947), *C. A.*, **42**, 1316 (1948).

(2) Kinder, Brandt and Gehlhaar, *Ann.*, **511**, 211 (1934); Schales, *Ber.*, **68**, 1581 (1935).

(3) Bills and Noller, THIS JOURNAL, **70**, 957 (1948).

(4) Hahn and Schales, *Ber.*, **67B**, 1486 (1934).

(5) Slotta and Haberland, *Angew. Chem.*, **46**, 766 (1933); Tanaka and Midzuno, *J. Pharm. Soc. Japan*, **49**, 255 (1929), *C. A.*, **23**, 3214 (1929).

(6) Faltis, Wagner and Adler, *Ber.*, **77B**, 691 (1944).

(7) Adkins and Billica, THIS JOURNAL, **70**, 698 (1948).

(8) Kobayashi, *Sci. Papers Inst. Phys. Chem. Research (Tokio)*, **6**, 164 (1927).