TABLE I

α,β-DICYANO-ESTERS AND SUCCINIC ACIDS

Carbonyl compound	Yield, %	Dicyano-ester B. p., °C.	Mm.	Succinic acid	Yield, %	M. p., °C.
Acetone	70	136–141	9	α,α-Dimethylsuccinic acid	76	138–139
Methyl ethyl ketone	49	145–146	10	α-Methyl-α-ethylsuccinic acid[a]	73	101–102
Cyclohexanone	75	177–179	10	1-Carboxycyclohexylacetic acid[b]	75	131–132
Propionaldehyde	53	158–160	12	Ethylsuccinic acid[c]	60	98–100
Isobutyraldehyde	67	151–155	10	Isopropylsuccinic acid[d]	78	115–116
Acetophenone	17	140–145	0.1	α-Phenyl-α-methylsuccinic acid[e]	60	157–158
Benzaldehyde	[f]	145–158	0.1	Phenylsuccinic[f] acid and α-cyanocinnamic acid	12	

[a] Higson and Thorpe[6] report ethyl α,β-dicyano-β-methylvalerate, b. p. 162° (20 mm.), and α-ethyl-α-methylsuccinic acid, m. p. 102–103°. [b] Dickens, Horton and Thorpe, *J. Chem. Soc.*, 125 (1934), report ethyl 1-cyanocyclohexylcyanoacetate, b. p. 210–212° (22 mm.), and (1-carboxycyclohexyl)-acetic acid, m. p. 132°. [c] Ethyl α,β-dicyanovalerate: *Anal.* Calcd. for $C_9H_{12}O_2N_2$: N, 15.56. Found: N, 15.62.[7] [d] Ethyl α,β-dicyano-γ-methylvalerate: *Anal.* Calcd. for $C_{10}H_{14}O_2N_2$: N, 14.43. Found: N, 14.41.[7] Von Braun and Reinhardt, *Ber.*, **62**, 2585 (1929), report isopropylsuccinic acid, m. p. 116°. [e] α-Phenyl-α-methylsuccinic acid: *Anal.* Calcd. for $C_{11}H_{12}O_4$: C, 63.45; H, 5.77; neut. equiv., 104. Found: C, 63.32; H, 5.82[8]; neut. equiv., 107. [f] The mixture of esters was hydrolyzed without separation to give phenylsuccinic acid and α-cyanocinnamic acid, which were separated by means of the solubility of the former in hot water, in 12% over-all yield each.

The product was obtained in a very pure state by evaporation to a volume of about 125 ml., heating to boiling with 1 l. of benzene, and allowing to stand until crystallization was complete (about one day); yield 77 g. (76%), m. p. 138–139° (lit. 139°[5]). The acid can also be recovered from the hydrolysis mixture more simply, but in lower yield (*ca.* 60%), by allowing crystallization to take place instead of distilling the mixture to dryness, and extracting the filtered solids with ether as described.

The hydrolyses of the other dicyano-esters reported in the table were essentially the same, except that 1-carboxycyclohexylacetic acid had to be precipitated from benzene solution by the addition of petroleum ether (60–75°), and α-phenyl-α-methylsuccinic acid was freed from ammonium chloride by crystallization from hot water.

(7) Analysis by Micro-Tech Laboratories, Skokie, Illinois.

Summary

A convenient synthesis for certain succinic acids is described which employs the condensation of aldehydes or ketones with cyanoacetic ester and potassium cyanide.

ANN ARBOR, MICHIGAN RECEIVED MAY 31, 1949

[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

Synthetic Analogs of Oxytocic Drugs. II. β-Hydroxyphenethyl-β-alanine Esters[1]

BY RICHARD BALTZLY AND ARTHUR P. PHILLIPS

Oxytocic activity having been found in a family of phenethyl-β-alanine esters[2] the effect of introducing an hydroxyl group in the side-chain was studied. Data on the compounds prepared for this purpose and on new intermediates are presented in Table I.

Although the available methods of assay render any precise conclusions on the influence of the hydroxyl group questionable, its presence appears advantageous. While compounds IV and V were not clearly more active than the comparable substances without the hydroxyl group, compounds I–III are also of the same order of activity, whereas in the phenethyl series[2] maximum activity was observed only with two alkoxyl substituents on the aromatic ring.

The preferred method of synthesis was by the addition of the appropriate phenylalkanolamine to methyl acrylate

$$RCHOHCH_2NHMe + CH_2{=}CHCOOMe \longrightarrow RCHOHCH_2N(Me)CH_2CH_2COOMe$$

Under the conditions described in the experimental section this reaction appears to be quantitative. Compound I was prepared from *d,l*-ephedrine and ethyl-β-bromopropionate. Compound V was obtained from IV by ester exchange.[2]

The secondary amines required from compounds II–IV are known.[3,4] The intermediate for compound VI, N-methyl-β-hydroxy-β-(3,4-dimethoxyphenyl)-ethylamine (XI)[5] is less easily prepared than might be supposed. When the corresponding benzylmethylaminoketone hydrochloride (VIII) was hydrogenated with Adams catalyst in the expectation of obtaining XI, cleavage of the dimethoxyphenacyl group appeared to compete with debenzylation. A considerable quantity of neutral material less volatile than toluene was present in the reaction mixture and XI was iso-

(1) The work here reported is part of a joint program carried out in collaboration with a pharmacological group in these laboratories.

(2) Baltzly, Dvorkovitz and Phillips, THIS JOURNAL, **71**, 1162 (1949).

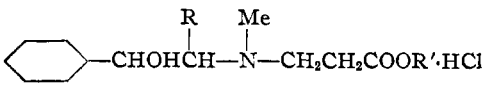
(3) Baltzly and Buck, *ibid.*, **62**, 164 (1940).

(4) Ardis, Baltzly and Schoen, *ibid.*, **68**, 591 (1946).

(5) Mannich, *Arch.*, **248**, 127 (1910), prepared the base but could not obtain crystalline salts.

TABLE I

HYDROCHLORIDES OF N-METHYL-N-(β-HYDROXY-β-PHENYLETHYL)-β-ALANINE ESTERS



Compound	Ring substituents	R	R′	M. p., °C.[a]	Empirical formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
I	None	Me	Et	129–130	$C_{15}H_{24}ClNO_3$	59.69	59.97	8.02	7.82
II	2-OH-5-Me	Me	Me	188.5–189	$C_{15}H_{24}ClNO_4$	56.67	56.93	7.61	7.88
III	2-OMe-5-Me	Me	Me	179–180	$C_{16}H_{26}ClNO_4$	57.88	57.71	7.90	8.29
IV	2,5-$(OMe)_2$	H	Me	156–156.5[b]	$C_{15}H_{24}ClNO_5$	53.95	54.20	7.25	7.66
V	2,5-$(OMe)_2$	H	Et	125–126	$C_{16}H_{26}ClNO_5$	55.22	55.43	7.54	7.27
VI	3,4-$(OMe)_2$	H	Me	127–128 (dec.[c])	$C_{17}H_{25}NO_9$[d]	52.69	52.66	6.51	6.66
				Intermediates					
VII	2,5-$(MeO)_2C_6H_3CHOHCH_2NMeBz\cdot HCl$[e]			165.5–167	$C_{18}H_{20}ClNO_3$	63.96	63.93	7.16	7.61
VIII	3,4-$(MeO)_2C_6H_3COCH_2NMeBz\cdot HCl$			186.5–187.5 (dec.)	$C_{18}H_{22}ClNO_3$	64.38	64.63	6.61	6.95
IX	3,4-$(MeO)_2C_6H_3COCH(CH_3)NMeBz\cdot HCl$			183–184	$C_{19}H_{24}ClNO_3$	65.20	65.48	6.92	7.40
X	3,4-$(MeO)_2C_6H_3CHOHCH_2NMeBz\cdot HCl$			196–198	$C_{18}H_{20}ClNO_3$	63.96	64.14	7.16	7.56
XI	3,4-$(MeO)_2C_6H_3CHOHCH_2NHMe\cdot HCl$			217.5–220[b] (dec.)	$C_{11}H_{18}ClNO_3$	53.31	53.18	7.33	7.39

[a] Melting points below 200° are corrected. [b] Needles. [c] Flattish prisms. [d] Acid oxalate. [e] Bz = Benzyl.

lated with difficulty and in poor yield. A preferable course was to reduce the tertiary amino ketone base with aluminum isopropoxide and debenzylate the resultant tertiary amino alcohol

$$RCOCH_2NMeBz \xrightarrow{Al(i\text{-}PrO)_3} RCHOHCH_2\cdot NMeBz \xrightarrow[H_2]{Pd\text{-}C} RCHOH{-}CH_2NHMe$$

This sequence was also employed in preparing larger quantities of IV and proceeded smoothly and without complications.

This lability of a phenacyl group toward hydrogenolysis was unexpected to us at the time. Subsequently one of us (A.P.P.) observed a hydrogenolytic cleavage of a phenacylpyridinium salt and these facts taken together with the unusual speed of dehalogenation of phenacyl chloride[6] suggest that dephenacylation may resemble debenzylation generally. Some phenomena reported from Adkins' laboratory[7] may also be related. Further investigation is planned.

Experimental[8]

β-(2,5-Dimethoxyphenyl)-β-hydroxyethylbenzylmethylamine Hydrochloride (VII).—Thirty-two gram of α-benzylmethylamino-2,5-dimethoxyacetophenone hydrochloride was dissolved in water, and alkali was added to liberate the base. The ethereal solution of the base was dried over potassium carbonate and evaporated. The base so obtained was refluxed in isopropyl alcohol containing 22 g. of aluminum isopropoxide for five hours, the acetone formed being fractionated off. The reduction mixture was cooled and made strongly alkaline with sodium hydroxide solution and extracted five times with ether. The combined ethereal extracts were dried over potassium carbonate and added to an excess of ethanolic hydrogen chloride solution. An oil separated that crystallized on scratching. The crystalline product weighed 28 g. (a 90% yield) and melted at 166–167°. Recrystallization did not raise the melting point. The starting amino ketone hydrochloride melts at 167.5°[3] but a mixture melted at 148–154°.

β-Hydroxy-β-(2,5-dimethoxyphenyl)-ethylmethylamine Hydrochloride.—Seventy millimoles (23.6 g.) of the tertiary aminoalcohol was dissolved in methanol and hydrogenated with palladized charcoal. The catalyst was filtered off, the methanol and toluene evaporated *in vacuo* and the residue was crystallized from an ethanol–ethyl acetate–ether mixture. The product weighed 17 g. (calcd. 17.3 g.) and melted at 151.5°.[3]

N-Methyl-N-(β-hydroxy-β-2,5-dimethoxyphenyl)-ethyl-β-alanine Methyl Ester Hydrochloride.—The base was liberated from the previous preparation, taken into benzene, dried over potassium carbonate and added to 45 g. of methyl acrylate (Eastman Practical Grade). The reaction mixture was allowed to stand at room temperature three days and warmed to about 50° for three hours. On cooling, the solution was poured into about 200 cc. of acetone to which 10 g. of 39% (wt./wt.) methanolic hydrogen chloride had been added. The solution was diluted with ether to the point of turbidity and seeded. The crystalline product weighed 21 g. and melted at 154.5–155°. After one recrystallization from methanol–acetone–ether mixture the m. p. was 156–156.5°, yield 20.5 g. The over-all yield in the last two operations was 90%.

The tertiary aminoketones VIII and IX were prepared by the reaction of 2 mols. of benzylmethylamine with one mol. of bromoacetoveratrone and α-brompropioveratrone, respectively. Compound IX was not employed in further syntheses.

All the compounds reported in Table I have the type of solubilities usual with amine hydrochlorides. The intermediates VII–XI were crystallized from ethanol–ether mixtures, sometimes with addition of ethyl acetate. The β-alanine esters, I–VI, were crystallized by solution in the esterifying alcohol and addition of acetone (or ethyl acetate with I and V) and ether to the point of turbidity.

Acknowledgment.—The authors wish to express their gratitude to Messrs. Walter S. Ide and Samuel Blackman for the microanalyses.

Summary

The preparation of some N-β-hydroxyphenethyl-N-methyl-β-alanine esters with oxytocic action is described.

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(6) Baltzly and Phillips, THIS JOURNAL **68**, 261 (1946).

(7) Sprague and Adkins, *ibid.*, **56**, 2669 (1934); Kuick and Adkins, *ibid.*, **57**, 143 (1935).

(8) The reactions of the secondary aralkanolamines with methyl acrylate were all run in the same manner. One sequence of procedures is described.