[CONTRIBUTION FROM THE COLLEGE OF PHARMACY, UNIVERSITY OF MICHIGAN]

Antispasmodics. XXIV. β-Diethylaminoethyl Esters of Substituted β-Hydroxypropionic Acids

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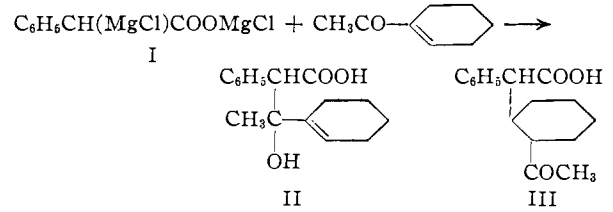
Substituted β-hydroxypropionic acids were prepared by interaction of the chloromagnesium salt of the chloromagnesium derivative of phenylacetic acid, an Ivanov reagent, with a number of carbonyl compounds. The acids were converted into their β-diethylaminoethyl esters. The antispasmodic activity of some of the ester salts has been reported.

Since certain basic esters of β-substituted α-phenyl-β-hydroxypropionic acids have been found to be potent antispasmodics,[3,4] a further study of such esters seemed desirable. All of the acids except II, required for the preparation of the esters described in this paper, were obtained by reaction of the chloromagnesium derivative of chloromagnesium phenyl acetate (I) (an Ivanov reagent) with the following aldehydes and ketones: cyclopentanecarboxaldehyde,[5] 1-cyclopentene-1-carboxaldehyde,[6] cyclohexanecarboxaldehyde,[7] 3-cyclohexene-1-carboxaldehyde,[8] methyl cyclopropyl ketone,[9] methyl cyclohexyl ketone[10] and methyl 1-cyclohexene-1-yl ketone.[11]

α-Phenyl-β-(1-cyclohexenyl)-β-hydroxybutyric acid (II, compound 7, Table I) was synthesized by interaction of I with methyl 1-cyclohexene-1-yl ketone. Proof that the reaction product possessed structure II and not that of the isomeric acid III, which might have been formed by 1,4-addition[12] of the Ivanov reagent, was obtained by catalytic hydrogenation; both the aromatic ring and the olefinic bond were hydrogenated to produce α,β-dicyclohexyl-β-hydroxybutyric acid, a compound which had been obtained previously by another method.[4] The hydrogenation was also carried out stepwise.



Compound II was hydrogenated to α-phenyl-β-cyclohexyl-β-hydroxybutyric acid; when this acid was hydrogenated, α,β-dicyclohexyl-β-hydroxybutyric acid was formed.

α-Phenyl-β-(1-cyclopentenyl)-β-hydroxypropionic acid (compound 2, Table I) was obtained by the interaction of I with 1-cyclopentene-1-carboxaldehyde. Upon hydrogenation of this product, an acid was isolated which was identical with that formed by interaction of I with cyclopentanecarboxaldehyde.

α-(1-Cyclohexenyl)-α-(1-hydroxycyclohexyl)-acetic acid (compound 8, Table I) was obtained by interaction of the Ivanov reagent prepared from 1-cyclohexenylacetic acid and cyclohexanone. Hydrogenation of the acid converted it into α-cyclohexyl-α-(1-hydroxycyclohexyl)-acetic acid.[4]

The acids prepared by reaction of I with aldehydes, and also acid 8, were converted into β-diethylaminoethyl esters by the use of the Horenstein–Pählicke procedure[13] (Table II). Unsuccessful attempts were made to convert acids 5, 6 and 7 (Table I) into basic esters by this method. In these instances, β-diethylaminoethyl diphenyl acetate hydrochloride was obtained as a reaction product due to the decomposition of either the original acid or the basic ester during the esterification process.

Experimental

Preparation of the Acids (Table I).—To the stirred Grignard reagent, obtained from 10.7 g. of magnesium, 100 cc. of ether, 1 cc. of isopropyl bromide and 50 cc. of isopropyl chloride, there was added 300 cc. of ether and then, dropwise, 27.2 g. (0.20 mole) of phenylacetic acid or 1-cyclohexenylacetic acid[14] dissolved in 100 cc. of benzene. After the addition of 200 cc. of ether, the mixture was refluxed for 18 hours, cooled to room temperature and 0.24 mole of the required carbonyl compound dissolved in 100 cc. of ether, was added. The mixture was refluxed for 4 hours and then poured into an ice-cold mixture of 60 cc. of concentrated hydrochloric acid and 500 cc. of water. The organic layer was separated and extracted with sodium bicarbonate solution. After this solution had been washed with ether, it was cooled with ice and acidified to congo red with hydrochloric acid. The oily precipitate, which solidified when rubbed, was recrystallized from toluene.

In order to obtain compound 5 in crystalline condition, the only precipitate was extracted with benzene and heptane was added to the dried solution until it became slightly cloudy. The benzene was allowed to evaporate until the volume of the solution was about 200 cc. The solid product which separated when the solution was cooled and stirred in an ice-bath was recrystallized from carbon tetrachloride–petroleum ether (60–75°).

In the preparation of acid 8, the reaction mixture was poured into 400 cc. of stirred, ice-cold, 10% ammonium chloride solution. The ether layer was separated, extracted with ammonium chloride solution the combined aqueous

(1) This paper represents part of a dissertation submitted by Harold Zinnes in partial fulfillment of the requirements for the Ph.D. degree in the University of Michigan.

(2) American Foundation for Pharmaceutical Education Fellow.

(3) F. F. Blicke and R. H. Cox, THIS JOURNAL, **77**, 5401 (1955).

(4) F. F. Blicke and R. H. Cox, *ibid.*, **77**, 5403 (1955).

(5) J. English, Jr., J. D. Gregory and J. R. Trowbridge, II, *ibid.*, **73**, 615 (1951).

(6) J. B. Brown, H. B. Henbest and E. R. H. Jones, *J. Chem. Soc.*, 3639 (1950).

(7) C. E. Wood and M. A. Comley, *J. Soc. Chem. Ind.*, **42**, 429T (1923).

(8) Purchased from Distillation Products Industries, Division of Eastman Kodak Company, Rochester, N. Y.

(9) Purchased from Matheson, Coleman and Bell, Norwood, Ohio.

(10) C. D. Nenitzescu and E. Ciorănescu, *Ber.*, **69**, 1820 (1936).

(11) R. E. Christ and R. C. Fuson, THIS JOURNAL, **59**, 893 (1937).

(12) Several instances have been reported in which an Ivanov reagent was allowed to react with an α,β-unsaturated carbonyl compound (D. Ivanov, M. Mikhova and T. Christova, *Bull. soc. chim.*, [4] **51**, 1321 (1932); D. Ivanov, M. Mikhova and I. P. Petrova, *Ann. Univ. Sofia II, Faculté phys.-math., Livre 2*, **31**, 199 (1935); *C. A.*, **31**, 7419 (1937)). Interaction with mesityl oxide yielded a 1,2-addition product while in the case of phorone and dypnone, 1,4-addition products were obtained.

(13) H. Horenstein and H. Pählicke, *Ber.*, **71**, 1644 (1938).

(14) V. H. Harding, W. N. Haworth and W. H. Perkin, Jr., *J. Chem. Soc.*, **93**, 1943 (1908).

TABLE I

SUBSTITUTED β-HYDROXYPROPIONIC ACIDS $RCHCOOH$ (R′R″COH)[a]

Compounds 1, 6 and 7 were recrystallized from toluene; 3, 4 and 5 from carbon tetrachloride; 2 from benzene; 8 from petroleum ether (90–100°).

	R′	R″	M.p., °C.[b]	Yield, %	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Neut. equiv., Calcd.	Neut. equiv., Found
1	H	Cyclopentyl	145–148	75	$C_{14}H_{18}O_3$	71.77	71.70	7.74	7.74	234.3	235.1
2	H	1-Cyclopentenyl	147–149	75	$C_{14}H_{16}O_3$	72.39	72.32	6.94	7.05	232.3	231.7
3	H	Cyclohexyl	131–134	81	$C_{15}H_{20}O_3$	72.55	72.50	8.12	8.32	248.3	249.1
4	H	3-Cyclohexenyl	128–131	61	$C_{15}H_{18}O_3$	73.14	73.11	7.37	7.31	246.3	247.0
5	CH_3	Cyclopropyl	92–94	57	$C_{13}H_{16}O_3$	70.89	70.76	7.32	7.41	220.3	221.4
6	CH_3	Cyclohexyl	165–167	65	$C_{16}H_{22}O_3$	73.25	73.59	8.45	8.47	262.3	264.0
7	CH_3	Cyclohexenyl	142–144	73	$C_{16}H_{20}O_3$	73.82	73.64	7.74	7.82	206.3	261.2
8	Pentamethylene		131–132	37	$C_{14}H_{22}O_3$	70.55	70.57	9.31	9.38	238.3	237.6

[a] In compounds 1–7, R = phenyl; in compound 8, R = 1-cyclohexenyl. [b] The acids 1–7 softened 5–10° below their melting points and melted with decomposition.

TABLE II

SALTS OF β-DIETHYLAMINOETHYL ESTERS OF SUBSTITUTED β-HYDROXYPROPIONIC ACIDS

$RCHCOOCH_2CH_2N(C_2H_5)_2$[a]·HCl or CH_3Br (R′R″COH)

Compounds 5 and 7 were crystallized from isopropyl alcohol–methyl ethyl ketone; 1, 2, 6 and 8 from isopropyl alcohol–ether; 3 from methyl ethyl ketone; 4 from acetone–ether; 9 from isopropyl alcohol; 10 from isopropyl alcohol–isopropyl ether.

	R′	R″	Salt	M.p., °C.	Yield, %	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Halogen Calcd.	Halogen Found	Antispasmodic activity; % of atropine sulfate
1	H	Cyclopentyl	HCl	153–154	61	$C_{20}H_{32}O_3NCl$	64.94	64.96	8.72	9.02	9.58	9.54	31.0
2				126–128		$C_{21}H_{34}O_3NBr$	58.88	58.84	8.00	8.14	18.65	18.76	62.0
3	H	1-Cyclopentenyl	HCl	129–132[b]	56	$C_{20}H_{30}O_3NCl$	65.29	65.10	8.22	8.28	9.64	9.76	
4				134–138[b]		$C_{21}H_{32}O_3NBr$	59.15	59.18	7.57	7.56	18.74	18.77	
5	H	Cyclohexyl	HCl	171–172	58	$C_{21}H_{34}O_3NCl$	65.70	65.58	8.93	8.98	9.23	9.17	10.0
6				160–161		$C_{22}H_{36}O_3NBr$	59.71	59.85	8.20	8.44	18.07	18.14	21.0
7	H	3-Cyclohexenyl	HCl	154–155	53	$C_{21}H_{32}O_3NCl$	66.06	66.27	8.44	8.63	9.23	9.17	11.0
8				157–158		$C_{22}H_{34}O_3NBr$	59.99	60.11	7.57	7.56	18.74	18.77	28.0
9	Pentamethylene		HCl	148–149	63	$C_{20}H_{36}O_3NCl$	64.23	64.25	9.72	9.76	9.48	9.62	
10				185–187[b]		$C_{21}H_{38}O_3NBr$	58.33	58.40	8.85	8.96	18.48	18.34	

[a] In compounds 1–8, R = phenyl; in compounds 9 and 10, R = 1-cyclohexenyl. [b] Melts with decomposition.

solutions were washed with ether and then acidified to congo red with dilute sulfuric acid.

α,β-Dicyclohexyl-β-hydroxybutyric Acid. (A).—A suspension of 3.3 g. of α-phenyl-β-(1-cyclohexenyl)-β-hydroxybutyric acid (acid 7) and 0.2 g. of platinum oxide catalyst in 40 cc. of acetic acid was hydrogenated under an initial pressure of 50 lb. until approximately 4 molecular equivalents of hydrogen had been absorbed. After filtration and removal of the solvent, 50 cc. of petroleum ether (30–40°) was added to the residue and the mixture was placed in a refrigerator. The solid was recrystallized from toluene; m.p. and mixed m.p. 141–143°.[15]

(B).—α-Phenyl-β-cyclohexyl-β-hydroxybutyric acid (described below) was hydrogenated in the manner described above until about 3 molecular equivalents of hydrogen had been absorbed; m.p. and mixed m.p. 141–143°.

α-Phenyl-β-cyclohexyl-β-hydroxybutyric Acid.—The procedure A described above was repeated except that 50 cc. of absolute ethanol was used as the solvent and the hydrogenation was stopped after about one molecular equivalent of hydrogen had been absorbed. The product was recrystallized from toluene; m.p. and mixed m.p. with compound 2, Table I, 165–167°.

α-Cyclohexyl-α-(1-hydroxycyclohexyl)-acetic Acid.—This acid was obtained in 84% yield by hydrogenation of acid 8 according to procedure A except that absolute ethanol was used as the solvent; m.p. and mixed m.p., 156–157° after recrystallization from toluene.

α-Cyclohexyl-β-cyclopentyl-β-hydroxypropionic Acid.—When α-phenyl-β-(1-cyclopentenyl)-β-hydroxypropionic acid was hydrogenated in the described manner A the product, which did not decolorize bromine, melted at 124–126° after recrystallization from benzene–petroleum ether (60–75°).

Anal. Calcd. for $C_{14}H_{24}O_3$: C, 69.96; H, 10.07; neut. equiv., 240.3. Found: C, 69.94; H, 9.92; neut. equiv., 239.4.

The same product was obtained when α-phenyl-β-cyclopentyl-β-hydroxypropionic acid was hydrogenated by procedure B; m.p. and mixed m.p. 124–126°.

Basic Ester Hydrochlorides and Methobromides.—To a stirred, refluxing mixture of 0.04 mole of the required acid and 60 cc. of isopropyl alcohol there was added, dropwise, during a period of 1 hour, 0.040 mole of β-diethylaminoethyl chloride dissolved in 5 cc. of benzene. The mixture was refluxed for 8 hours, filtered, 60 cc. of ether was added to the filtrate and the mixture was refrigerated.

In the case of compound 7, Table II, the reaction mixture was refluxed for only 4 hours and the solvents were then removed completely. After the addition of 20 cc. of acetone to the residue and filtration, ether was added until the solution became cloudy.

In the case of acids 1, 2 and 3 (Table I), β-diethylaminoethyl phenyl acetate hydrochloride was obtained instead of the salts of the desired esters. In order to isolate the former salt, the reaction mixture was concentrated to a volume of 25 cc. and then poured slowly into 500 cc. of stirred, ice-cold ether. After several days in a refrigerator, the very hygroscopic precipitate (69–81%) was dissolved in reagent acetone, ether was added until the solution became cloudy and the mixture was then refrigerated; the hygroscopic salt melted at 78–80°.

Anal. Calcd. for $C_{14}H_{22}O_2NCl$: N, 5.15; Cl, 13.05. Found: N, 5.13; Cl, 12.84.

(15) Reference 4, m.p. 141–143°.

The crude methobromides precipitated almost quantitatively when a mixture of an ethereal solution of the ester base and a four molar excess of methyl bromide was allowed to remain at room temperature for 2 days and was then placed in a refrigerator for several days.

ANN ARBOR, MICHIGAN

[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

Stereochemistry of Allylic Rearrangements. VII. The Acid-catalyzed Hydrolysis of *cis* and *trans*-5-Methyl-2-cyclohexenyl *p*-Nitrobenzoate in Aqueous Acetone[1]

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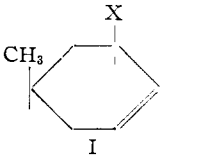
The kinetics of the hydrolysis of *cis*-(Ic) and *trans*-5-methyl-2-cyclohexenyl *p*-nitrobenzoate (IIc) in 80% aqueous acetone at 80 and 100° have been investigated to obtain information concerning the nature of intermediates involved in solvolysis and allylic rearrangements. The hydrolysis involves alkyl-oxygen cleavage and is catalyzed by perchloric acid. In the presence and absence of acid the polarimetric and titrimetric rate constants, k_α and k_t, are reproducible and steady during the reactions. The rate of the acid-catalyzed hydrolysis is proportional to the perchloric acid concentration over the concentration range investigated (to 0.1 *M*). At an acid concentration of 0.05 *M*, where the acid-catalyzed hydrolysis is essentially isolated from the uncatalyzed process, k_α and k_t are indistinguishable (within the combined experimental errors). In the absence of acid, $k_\alpha > k_t$ for both geometric isomers (*i.e.*, internal return is observed). The observation that internal return occurs during the uncatalyzed hydrolysis but not during the acid-catalyzed hydrolysis is consistent with the concept that ion-pair intermediates are involved in internal return. The greater polarimetric than titrimetric rate for the uncatalyzed hydrolysis is due to partial racemization of the reactant by an intramolecular allylic rearrangement—geometric isomerization does not occur—prior to hydrolysis. In this case the hydrolysis evidently involves the reversible formation of an intermediate which can at present best be described as an ion-pair which is irreversibly converted to product. The reversible step (internal return) represents the S_Ni' isomeric allylic rearrangement.

Introduction

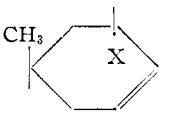
In the work described in previous papers in this series it was found that internal return[3] is involved in the solvolysis of the isomeric 5-methyl-2-cyclohexenyl acid phthalates (Ia and IIa) in aqueous acetone[4] and chlorides (Ib and IIb) in ethanol and acetic acid.[5] In each case the method[3] of comparing polarimetric (k_α) and titrimetric (k_t) first-order rate constants was used to measure internal return and it was found that this phenomenon does not result in the interconversion of the *cis* (I) and *trans* (II) isomers. Similar results were obtained in a study of the isomeric allylic rearrangement of the acid phthalates (Ia and IIa) in acetonitrile.[6] In this case it was observed that with both isomers, racemization is more rapid than geometric isomerization. As pointed out in previous papers in this series all of these observations appear to be consistent with the idea[3] that a common intermediate, presumably an ion-pair,[3,7] is involved in solvolysis and internal return (which in an allylic system corresponds to the S_Ni'[8] isomeric allylic rearrangement).[4]

This present work was undertaken to obtain information concerning the intramolecular (S_Ni') rearrangement of allylic esters and the nature of the presumably common intermediate involved in this process and solvolysis. In this connection we investigated the uncatalyzed and acid-catalyzed hydrolysis of *cis*- (Ic) and *trans*-5-methyl-2-cyclohexenyl *p*-nitrobenzoate (IIc) in aqueous acetone. In the uncatalyzed hydrolysis, alkyl-oxygen cleavage results in the formation of ions, and ion-pair intermediates are possible. In the acid-catalyzed hydrolysis, where the conjugate acid of the ester undergoes alkyl-oxygen cleavage, ion-pair intermediates are not possible. According to the ion-pair interpretation,[3] internal return is possible in the uncatalyzed hydrolysis but not in the acid-catalyzed hydrolysis. We have indeed observed that internal return is observed in the uncatalyzed hydrolysis, *i.e.*, $k_\alpha > k_t$, but not in the acid-catalyzed hydrolysis.



I

a, X = $O_2CC_6H_4CO_2H$
b, X = Cl
c, X = $O_2CC_6H_4NO_2$



II

a, X = $O_2CC_6H_4CO_2H$
b, X = Cl
c, X = $O_2CC_6H_4NO_2$

Results

The hydrolyses of 0.05 *M* Ic and IIc in 80% acetone[9] at 80 and 100° are first order and are catalyzed by perchloric acid. The polarimetric (k_α) and titrimetric (k_t) first-order rate constants (pseudo first order for the acid-catalyzed reactions) were determined in the absence of perchloric acid and at an acid concentration of 0.05 *M*. The results of the kinetic experiments are presented in Table I.

The titrimetric first-order rate constants (k_t) were determined by periodically titrating the *p*-nitrobenzoic acid produced. The constants were steady over the ranges that the reactions were followed (to 80% completion in some cases) for both the acid-catalyzed and uncatalyzed reactions.

(1) This work was supported by the Office of Ordnance Research.

(2) National Science Foundation Fellow, 1954–1955.

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(6) H. L. Goering, J. P. Blanchard and E. F. Silversmith, *ibid.*, **76**, 5409 (1954).

(7) D. J. Cram, *ibid.*, **74**, 2129 (1952).

(8) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p. 596.

(9) The 80% acetone was prepared by mixing 4 volumes of purified acetone with one volume of water at 25°.