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Synthesis of Potential Specific Inhibitors of Certain Amino Acid Decarboxylases

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A number of potential specific inhibitors of amino acid decarboxylases were synthesized by subjecting amino acids and their derivatives to Dakin–West reaction conditions. In some cases the Dakin–West conditions were modified. Pyridine and imidazole were found to be suitable as bases in the Dakin–West reaction.

The Dakin–West reaction (*3*) on α-amino acids yields 1-substituted-1-*N*-acetamidopropanones. The acetamidopropanone obtained from histidine as well as the aminopropanone (obtained by the hydrolysis of the acetamidopropanone) have been shown to be specific inhibitors of histidine decarboxylase (*7–9*).

This report is a continuation of our attempts (*6–8*) to synthesize active-site-directed reversible inhibitors of enzymes utilizing amino acids as substrates.

Potential inhibitors of specific amino acid decarboxylases were synthesized by subjecting selected amino acids and their derivatives to Dakin–West reaction conditions. In some cases the Dakin–West reaction was modified to obtain the desired products (Tables I–III) (Figure 1).

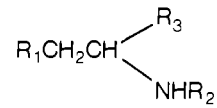
L-Cysteine (I) underwent Dakin–West reaction to give 4-acetylthio-3-acetamido-2-butanone (II) (Table I). Acid hydrolysis of II afforded 4-mercapto-3-amino-2-butanone hydrochloride (III). Treatment of compound II with trifluoroacetic anhydride yielded the oxazole IV (Table II) along with a small amount of the free mercaptooxazole V (4-mercaptomethyl-2,5-dimethyloxazole), identified by its NMR spectrum.

L-Cysteine hydrochloride monohydrate was dehydrated to cysteine hydrochloride (*1*) which in turn was converted quantitatively to *S*-benzhydrylcysteine (*4*) (VI). Compound VI upon treatment with Ac_2O and pyridine gave 4-diphenylmethylthio-3-acetamido-2-butanone (VII). *S*-Triphenylmethylcysteine (VIII) was obtained from L-cysteine hydrochloride (*13*) and converted to 4-triphenyl-methylthio-3-acetamido-2-butanone (IX).

DL-Methionine (X) gave the normal Dakin–West product XI. The acetamido ketone XI was converted to the corresponding oxazole XII.

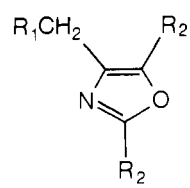
The Dakin–West reaction on L-proline (XIII) or *N*-acetyl-L-proline (obtained in 95% yield from XIII, Ac_2O, and pyridine) or *N*-trifluoroacetyl-L-proline (XIV) was unsuccessful. Compound

Table I

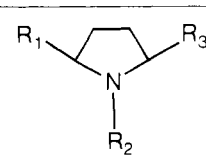


Compound	R_1	R_2	R_3
II	CH_3COS	$COCH_3$	$COCH_3$
III	HS	H·HCl	$COCH_3$
VI	$(C_6H_5)_2CHS$	H	COOH
VII	$(C_6H_5)_2CHS$	$COCH_3$	$COCH_3$
VIII	$(C_6H_5)_3CS$	H	COOH
IX	$(C_6H_5)_3CS$	$COCH_3$	$COCH_3$
XI	CH_3SCH_2	$COCH_3$	$COCH_3$
XIX	CH_3COOCO	$COCH_3$	$COCH_3$
XXIII	C_6H_5	$COCF_3$	COOH
XXIV	$[C_6H_5$	$COCF_3$	$CO]_2O$
XXVI	C_6H_5	$COCF_3$	$COOC_6H_5$
XXVIII	C_6H_5	$COCH_3$	$COCH_3$
XXIX	H	$COCH_3$	$COCH_3$

Table II



Compound	R_1	R_2
IV	CH_3COS	CH_3
V	HS	CH_3
XXII	CH_3SCH_2	CH_3
XX	CH_3COOCO	CH_3
XXI	HOOC	CH_3
XXV	C_6H_5	CF_3



Compound	R_1	R_2	R_3
XIV	H	$COCF_3$	COOH
XV	[H	$COCF_3$	$CO]_2O$
XVII	=O	$COCH_3$	$COCH_3$

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Table III

Starting compound	Product	Yield, %	Mp (solvent)[a] or bp (°C) (at mm pressure)	IR (cm^{-1})[b]	Analyzed for[c]	Reaction conditions[d] temp (°C)/h	Purification[e] method
I	II	73	81–82 (benzene)	1725, 1698, 1658	$C_8H_{13}NO_3S$	A, 1. 65–70/14 2. 25/12	P-1
II	III	13	132–133.5 (*i*-PrOH)	1725, 2500	$C_4H_{10}NOSCl$	B, 97–98/2	Q
II	IV	70	79/0.35 mm	1690	$C_8H_{11}NO_2S$	C, 1. 25/0.3 2. 60/0.15	P-2
VI	VII	38	94–95 ($CHCl_3$–Et_2O)		$C_{17}H_{21}NO_2S$	A, 1. 65/5 2. 25/12	P-1
VIII	IX	12	116–119 ($CHCl_3$–Et_2O)		$C_{25}H_{25}NO_2S$	A 25/14	P-1
X	XI	80	138/0.25 mm	1715, 1650	$C_{18}H_{25}NO_2S$	A 60–65/5	P-2
XI	XII	42	68/0.5 mm	1585	$C_8H_{13}NO_2S$	C 1. 25/0.3 2. 60/0.15	P-2
XIII	XIV	57	108.5–110.5 ($CHCl_3$–Et_2O–pet ether 5:2:1)	1705, 1735	$C_7H_8NO_3F_3$	C 25/4	Q
XVI	XVII	30	66–67 (Et_2O–$CHCl_3$) lit. (*5*) 68–69	1750, 1700		A 1. 45–50/5 2. 65/28	P-1
XVIII	XIX	15	169–171 ($CHCl_3$)	1725, 1620	$C_9H_{13}NO_5$		
	XXI	<5	90–92 ($CHCl_3$:Et_2O 4:1)	1810, 1760	$C_9H_{13}NO_5$	A 69/12	P-3
	XX	<5	140–150 ($CHCl_3$)		$C_9H_{11}NO_4$		
XXII	XXIII	28	119–122 (Et_2O–pet ether) lit. (*13*) mp 120–121				
	XXIV	37	148–149.5	1820, 1750	$C_{22}H_{18}N_2O_5F_6$	C 25/18	R
XXII	XXVI	72	138–140/0.08 mm	1750, 1700	$C_{17}H_{14}NO_3F_3$	A 1. 125–130/0.5 2. 120–125/6	S
XXII	XXVIII	*f*	97–98 ($CHCl_3$–Et_2O) lit. (*2*) 98–99			A 95–100/6	P-1
XXVII	XXIX	*g*	83–85/0.2–0.3 mm lit. (*12*) 103/2 mm			A 95–100/6	P-2

[a] Melting points were determined on a Calibrated Thomas Hoover Unimelt and were corrected. [b] IR spectra were recorded on Beckman IR-8 and IR-10 infrared spectrometers; characteristic frequencies are reported. The NMR spectra were also obtained; the data may be requested from the author (Z.H.I). [c] Microanalyses were carried out by Midwest Microlab, Inc., Indianapolis, Ind. Elemental analyses in agreement with theoretical values (±0.4% for C, H, and N) were obtained (and submitted for review) for all new compounds excet for products: III, calcd, C, 30.87; found, 31.40; IX, calcd C: 74.71, N: 3.47; found C: 72.42, N: 5.18; XX, Calcd, C, 54.82; found, 52.21; XXVI, calcd, C, 60.53; found, 59.49. [d] The experimental conditions were: A. The starting material was mixed with Ac_2O and pyridine in a molar ratio of 1:6:5 and stirred using conditon 1 followed by 2 (if any). B. Compound II was stirred with 1 N HCl. C. Trifluoroacetic anhydride was added to the starting material in a molar ratio of 2:1 and the mixture was stirred using condition 1 followed by 2 (if any). D. The amino acid was heated with Ac_2O and appropriate base (see footnotes *f* and *g*) in the molar ratios of 1:6:5. [e] In all cases the solvent and/or excess reagents were removed in vacuo at 35–40 °C. The crude product was purified by the following procedures: P. Column chromatography on silica gel using either $CHCl_3$, with subsequent crystallization (P-1), or $CHCl_3$–Et_2O, 1:1 (v/v) followed by fractional distillation (P-2). For procedure P-3, one aliquot of the crude product was applied to silica gel and eluted initially with $CHCl_3$ (to yield XXI), then with 8% CH_3OH in $CHCl_3$ (v/v) (to give XIX). Another aliquot of the crude material was fractionally distilled (98–100 °C (1 mm)) prior to chromatography on silica gel (Et_2O–$CHCl_3$) and crystallization (to obtain XX). Q. Recrystallization only. R. The product was triturated with Et_2O; the Et_2O-soluble fraction gave XXIII; the insoluble fraction yielded XXIV. S. Fractional distillation only. [f] The yields of product XXVIII using pyridine, lutidine, collidine, 1,4-diazabicyclo[2.2.2]octane, and imidazole as bases were 62, 19, 45, 45, and 65%, respectively. [g] The yields of product XXIX using pyridine, lutidine, collidine, and 1,4-diazabicyclo[2.2.2]octane as bases were 68, 33, 56, and 56%, respectively.

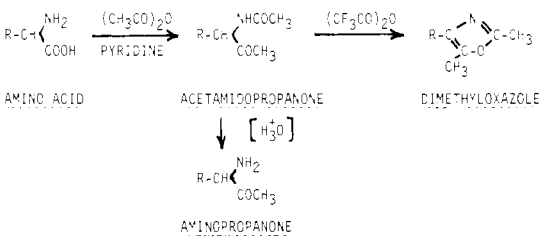

Figure 1. General scheme for the synthesis of potential specific inhibitors of amino acid decarboxylases.

XIV was obtained from XIII and trifluoroacetic anhydride. A minor product of the reaction was identified as *sym*-trifluoroacetylproline anhydride (*10*) (XV).

L-Glutamic acid (XVI), when subjected to Dakin–West reaction conditions, gave 1,2-diacetyl-5-pyrrolidone (XVII) in yields higher than reported previously (*5*).

The Dakin–West reaction on L-aspartic acid (XVIII) gave 3-acetamido-2-ketobutanoic acetic anhydride (XIX), 5-(2,4-dimethyloxazolyl)acetic acetic anhydride (XX), and 2.4-dimethyl-5-carboxymethyloxazole acetate (XXI). Compound XXI is probably formed by initial dehydration of XIX to the oxazole XX followed by hydrolysis.

Treatment of DL-phenylalanine (XXII) with trifluoroacetic anhydride gave several compounds including *N*-trifluoroacetylphenylalanine (*11*) (XXIII), *sym*-*N*-trifluoroacetylphenylalanine anhydride (XXIV), and a small amount of 4-benzyl-2,5-di(trifluoromethyl)oxazole (XXV) (identified by its NMR spectrum). Compound XXIII was also prepared in quantitative yield by heating a mixture of XXII, trifluoroacetic anhydride, and phenyl trifluoroacetate (*11*) (bp 141–143 °C (738 mm), obtained in 80% yield from phenol, trifluoroacetic acid, and P_2O_5). Reaction of XXII with phenyl trifluoroacetate and pyridine gave phenyl 3-phenyl-2-(α,α,α-trifluoroacetamide)propionate (XXVI).

A comparative study of the suitability of several bases in the Dakin–West reaction was undertaken (Table III). DL-Phenylalanine (XXII) and DL-alanine (XXVII) were treated with Ac_2O and the base to yield 4-phenyl-3-acetamido-2-butanone (*2*) (XXVIII) and 3-acetamido-2-butanone (*12*) (XXIX), respectively. Pyridine, imidazole, diazabicyclo[2.2.2]octane, and collidine gave 45–68% of the products while lutidine gave lower yields (19–33%).

Experimental Section

The details of the procedures and pertinent properties of the products are summarized in Table III.

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Chemical Shift Nonequivalence of Prochiral Groups in the ^{1}H Nuclear Magnetic Resonance Spectra of Some 3-Alkyl Derivatives of Phthalic Anhydride and Tetrachlorophthalic Anhydride

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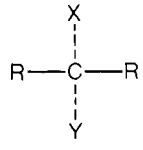
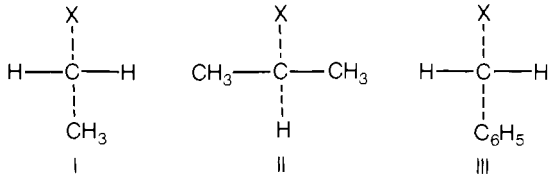
^{1}H NMR spectra of molecules containing prochiral centers such as various 3-alkyl derivatives of phthalic anhydride and tetrachlorophthalic anhydride have been examined and interpreted. This investigation has found the ^{1}H NMR data to be consistent with the concept of prochirality in relation to the chemical shift nonequivalence of geminal groups.

Some reported ^{1}H NMR spectra have been misinterpreted (*16*) because of the unawareness of the effect of the chemical shift nonequivalence of geminal groups and the concept of prochirality. The prochirality concept of Hanson (*15*) and the nomenclature of Mislow and Raban (*19*) are applicable to a prochiral center represented as

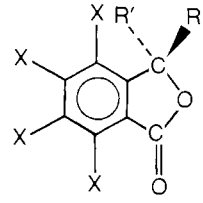


In the ^{1}H NMR spectrum of such a prochiral assembly, the ligands (R) can be equivalent (isochronous) or nonequivalent (anisochronous) in their chemical shift depending on the other substituents, X and Y. This investigation concerns itself primarily with the effect of the ethyl, I, isopropyl, II, and benzyl, III, moieties on the ^{1}H NMR spectra of some 3-alkylphthalides and 3-alkyltetrachlorophthalides.



I II III

There has been considerable interest in various alkylphthalides and their applicability to food flavorings, since some 3-alkylphthalides (**1**, R′, X = H) are known constituents of oil of celery and believed to be responsible for celery flavor (*10, 11*).



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In a prior investigation (*5*), the ^{1}H NMR splitting of some 3,3-dialkylphthalides (**1**, X = H) and 3-alkyltetrachlorophthalides (**1**, R′ = H; X = Cl) have been attributed to molecular asymmetry and the effect of the magnetic anisotropy of the aromatic ring current. Our studies on these and related compounds indicate that the splitting is more accurately attributed to the presence of a prochiral center in the molecule.

Discussion and Results

Chemical shift nonequivalence of chemically equivalent protons has been known for some time (*14*). Usually, phenomena of this type were attributed to different conformer populations which are temperature dependent. Experimentally, systems of this type are detected by running the spectra over a broad temperature range. Several years ago, some phthalic anhydride derivatives were synthesized and their ^{1}H NMR spectra showed several interesting results (*5*). For example, in 3-isopropyltetrachlorophthalide (**1**, R = $(CH_3)_2CH$–; R′ = H; X = Cl), the two geminal methyl groups of the isopropyl moiety were found to be magnetically nonequivalent with a separation of 44 Hz at 60 MHz (0.73 ppm) and were independent of temperature in the range of 25 to 160 °C.

Other compounds such as 3-ethyltetrachlorophthalide (**1**, R = CH_3CH_2–; R′ = H; X = Cl) and 3,3-dibenzylphthalide (**1**, R, R′ = $C_6H_5CH_2$–; X = H) also showed similar spectral features (*5*).