Isodextropimaric Acid.—The previously described chromium trioxide oxidation procedure was used without modification to oxidize 1.40 g. of the isodextropimarinal-containing carbonyls isolated above. The resulting acids were isolated by basic extraction from ether solution as before. Evaporation of the ether solution yielded 0.65 g. of unoxidized carbonyl compounds which gave a positive test with 2,4-dinitrophenylhydrazine and a negative Tollens test. A very small quantity of white crystals which precipitated from the dilute alkaline solution was presumed to be sodium dextropimarate and discarded. Acidification of the alkaline solution with 2 *M* acetic acid followed by heptane extraction, removal of excess acetic acid by several water washings, and treatment of the heptane solution with 2-amino-2-methyl-1-propanol yielded 0.20 g. of the amine salt, $[\alpha]^{24}D$ −11.2°. Successive recrystallizations of the salt from acetone solution served to increase the negative rotation to −14.4°. The amine salt showed very low absorption in the ultraviolet, indicative of only minor amounts of contaminants: general absorption 235–275 mμ, λ_{max} 248–256 mμ (α 2.0). Conversion of the salt to the cyclohexylamine salt followed by recrystallization from acetone showed similar results. However, the cyclohexylamine salt of isodextropimaric acid was found to be concentrated in the mother liquors. Treatment of the cyclohexylamine salt, $[\alpha]^{26}D$ ±0°, with acetic acid yielded isodextropimaric acid, m.p. 161–163.5°.

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[CONTRIBUTION FROM THE ORGANIC CHEMISTRY LABORATORIES OF THE UNIVERSITY OF FLORIDA]

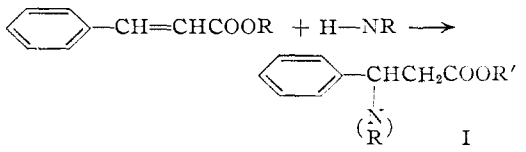
The Addition of Saturated Heterocyclic Amines to Cinnamate Esters

BY C. B. POLLARD AND G. C. MATTSON

RECEIVED SEPTEMBER 8, 1955

A series of esters of β-(N-heterocyclic)-β-phenylpropionic acid was prepared for pharmacological testing. The addition of saturated heterocyclic amines to cinnamate esters has been shown to be a practical method of synthesizing these compounds.

The object of this research was to prepare β-(N-heterocyclic)-β-phenylpropionic esters (I) for pharmacological testing in the hope of obtaining a clinically useful analgesic. It was decided to attempt the formation of these compounds by the addition of saturated heterocyclic secondary amines to cinnamate esters.



The addition of amines to acrylate esters constitutes a useful method of synthesizing N-substituted β-aminopropionate esters.[1-4] However, there are few literature reports of the reaction of amines with the less reactive, substituted acrylate esters such as the cinnamate esters. In addition to the reaction of the amine with the olefinic bond, it is also possible for aminolysis of the ester group to occur. This competing reaction is known to occur and under certain conditions the amide is the only product isolated. The products of the reactions of ammonia, methylamine and diethylamine with ethyl cinnamate have been studied by Morsch.[5] The reactions of ammonia and methylamine with ethyl cinnamate gave low yields of the β-amino esters, whereas the only product isolated from the reaction of diethylamine with ethyl cinnamate was the amide, N,N-diethylcinnamide.

The reaction of saturated heterocyclic amines with cinnamate esters was effected by refluxing equimolar quantities of the reactants with or without a solvent. A marked increase in yield of β-(N-heterocyclic)-β-phenylpropionate ester was obtained either by employing tetramethylammonium hydroxide as a catalyst or by using an excess of the secondary amine. All of the products were isolated as the hydrochloride salts, by the same general procedure. The yields reported refer to purified products and are based upon the molar quantity of cinnamate ester used.

The corresponding amide may be formed by changing the conditions of the reaction and the method of isolation.

Experimental

Preparation of Intermediates.—The piperidine, pyrrolidine and morpholine were commercial grade materials and were redistilled before use. 4-Methylpiperidine was prepared by the hydrogenation of γ-picoline under 4000 pounds pressure at 200°, using a Raney nickel catalyst, according to the method used by Adams and Leonard.[4]

The cinnamate esters, other than the ethyl ester which was commercially available, were prepared by the reaction of cinnamyl chloride with the corresponding alcohol in the presence of pyridine. Cinnamyl chloride was formed by refluxing a benzene solution of cinnamic acid and thionyl chloride for 8 hr. The solvent was then removed on the steam-bath under water-pump vacuum. The cinnamyl chloride so obtained was used without further purification.

Cinnamyl chloride (0.2 mole) was added portionwise, with ice-bath cooling, to a solution of the alcohol (0.2 mole) and pyridine (0.2 mole) in 100 ml. of benzene. The reaction mixture was allowed to stand for 24 hr. It was then extracted with three 50-ml. portions of distilled water. The organic layer was separated and dried over anhydrous cal-

TABLE I

CINNAMATE ESTERS

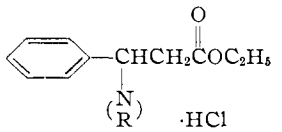
Cinnamate	Boiling range °C.	Mm.	Yield, %	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
Methyl[b]	36[a]		75.0				
n-Propyl[b]	92–94	0.50	79.0				
n-Butyl[c]	98–100	.50	73.0				
1-Methylpropyl	87–89	.35	79.0	76.43	76.54	7.88	7.73
2-Methylpropyl[d]	90–92	.25	86.0				
n-Amyl	104–106	.50	74.0	77.03	77.40	8.30	8.02
1-Methylbutyl	102–104	.50	85.0	77.03	76.72	8.30	7.92
n-Hexyl	114–115	.45	64.0	77.55	77.68	8.68	8.57

[a] Melting point. [b] F. Weger, *Ann.*, **212**, 126 (1883). [c] D. Vorlander and R. Walter, *Z. physik. Chem.*, **118**, 13, 17 (1925). [d] J. J. Sudborough and K. J. Thompson, *J. Chem. Soc.*, **83**, 676 (1903).

(1) A. P. Phillips, THIS JOURNAL, **72**, 3298 (1950).
(2) D. W. Adamson, *J. Chem. Soc.*, Suppl. No. 1, S-144 (1949).
(3) C. A. Weisel, R. B. Taylor, H. S. Mosher and F. C. Whitmore, THIS JOURNAL, **67**, 1071 (1945).
(4) R. Adams and N. J. Leonard, *ibid.*, **66**, 257 (1944).
(5) K. Morsch, *Monatsh.*, **61**, 299 (1932).

TABLE II

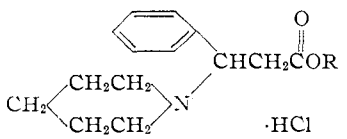
ETHYL β-(N-HETEROCYCLIC)-β-PHENYLPROPIONATE HYDROCHLORIDES



Heterocyclic group	Molecular formula	Yield, %	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
1-Pyrrolidyl	$C_{15}H_{22}NO_2Cl$	18	63.62	63.28	7.82	7.76
1-Piperidyl	$C_{16}H_{24}NO_2Cl$	20	64.52	64.36	8.12	8.22
4-Morpholinyl	$C_{15}H_{22}NO_3Cl$	20	60.09	60.43	7.40	7.49
1-(4-Me)-piperidyl	$C_{17}H_{26}NO_2Cl$	17	65.47	65.42	8.42	8.40

TABLE III

ALKYL β-(1-PIPERIDYL)-β-PHENYLPROPIONATE HYDROCHLORIDES



Alkyl group	Molecular formula	Yield, %	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
Methyl	$C_{15}H_{22}NO_2Cl$	19	63.47	63.34	7.82	7.95
Ethyl	$C_{16}H_{24}NO_2Cl$	20	64.52	64.36	8.12	8.22
n-Propyl	$C_{17}H_{26}NO_2Cl$	22	65.47	65.83	8.42	8.55
n-Butyl	$C_{18}H_{28}NO_2Cl$	16	66.33	66.10	8.67	8.68
n-Amyl	$C_{19}H_{30}NO_2Cl$	12	67.13	67.24	8.91	8.76
n-Hexyl	$C_{20}H_{32}NO_2Cl$	8	67.86	67.76	9.13	9.22
2-Methylpropyl	$C_{18}H_{28}NO_2Cl$	7	66.33	66.16	8.67	8.55
1-Methylpropyl	$C_{18}H_{28}NO_2Cl$	6	66.33	66.48	8.67	8.57
1-Methylbutyl	$C_{19}H_{30}NO_2Cl$	4	67.13	67.10	8.91	8.87

cium sulfate. The solvent was removed by distillation on the steam-bath under water-pump vacuum. The residue was then vacuum distilled. The yields and boiling ranges of these esters are listed in Table I.

Reaction of Saturated Heterocyclic Amines with Cinnamate Esters.—Since the procedure used in preparing the β-(N-heterocyclic)-β-phenylpropionate esters was basically the same in all cases, detailed directions are given for only one representative compound. The physical properties of these compounds are listed in Tables II and III.

Ethyl β-(1-Piperidyl)-β-phenylpropionate.—Ethyl cinnamate (17.6 g., 0.1 mole) and piperidine (8.5 g., 0.1 mole) were dissolved in 30 ml. of heptane and the solution refluxed for 8 hr. After the solution had cooled to room temperature, it was washed with three 30-ml. portions of distilled water. The organic layer was then extracted with two 30-ml. portions of 3 *N* hydrochloric acid. These acid aqueous extracts were combined and made basic to *p*H 8 by the addition of granular potassium carbonate. The resultant oil was then extracted with two 50-ml. portions of ether. The ethereal extracts were combined and dried over anhydrous calcium sulfate. The dry ether solution was then treated with dry hydrogen chloride until acid to congo red paper. The precipitated white solid was recrystallized three times from 2-propanol; yield 6.0 g., 20.1%.

It was found that the yield of product was increased to 45% of the theoretical when the reaction was run in toluene solution in the presence of 1 ml. of a 10% aqueous solution of tetramethylammonium hydroxide solution. By employing a two-mole excess of piperidine, the yield was increased to 75% of the theoretical.

N-Cinnamylpiperidine.—A mixture of ethyl cinnamate (52.8 g., 0.3 mole) and piperidine (25.5 g., 0.3 mole) was refluxed for 70 hr. The unchanged reactants and ethanol were removed by distillation at 0.5 mm. When the temperature reached 80°, the distillation was discontinued. After cooling to room temperature, the material in the pot solidified. This solid material, N-cinnamylpiperidine, was recrystallized twice from absolute ethanol and washed with petroleum ether, yield 46.5 g., 71%.

Anal. Calcd. for $C_{14}H_{17}NO$: C, 78.14; H, 7.97. Found: C, 78.23; H, 8.03.

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[CONTRIBUTION FROM THE DANIEL SIEFF RESEARCH INSTITUTE, WEIZMANN INSTITUTE OF SCIENCE]

Reduction and Benzylation by Means of Benzyl Alcohol. III. Experiments in the Pyridine Series[1]

BY MOSHE AVRAMOFF AND YAÏR SPRINZAK

RECEIVED JANUARY 14, 1956

The behavior of pyridine, its benzologs and their derivatives toward benzyl-alcoholic potassium hydroxide has been studied. Methyl groups in the pyridine ring are readily benzylated. On prolonged heating, dibenzylated products are obtained. It is shown that the reaction involves condensation with benzaldehyde and reduction of the resulting styryl derivative. Two instances of benzylation of a "non-active" side-chain have been encountered. Quinoline is transformed into 1,2,3,4-tetrahydroquinoline, 3-benzylquinoline and 3-benzyl-1,2,3,4-tetrahydroquinoline, which can be obtained in good yield. The formation of these products is explained in terms of partial reduction of the pyridine ring, followed by two concurrent reactions: (1) reduction to 1,2,3,4-tetrahydroquinoline and (2) condensation of dihydroquinoline with benzaldehyde to form 3-benzal-3,4-dihydroquinoline, which isomerizes to 3-benzylquinoline. The latter is then reduced to 3-benzyl-1,2,3,4-tetrahydroquinoline. 3-Methyl- and 3-phenyl-quinoline are also reduced under the same conditions. Carbostyryl yields 3-benzylcarbostyryl. Isoquinoline is benzylated to 4-benzylisoquinoline. No reduction products have been observed in the pyridine and isoquinoline series.

In previous parts[2] of this series we have discussed the carbon-benzylation of fluorene and its derivatives and the nitrogen-benzylation of primary aromatic amines by means of benzyl-alcoholic potassium hydroxide. It was shown that in both cases the reaction involved the formation of intermediate benzylidene derivatives, readily reducible by the reagent. It was further pointed out that this easy reduction was due to the polar character of the newly formed double bond.

In the present work the behavior of nitrogen-containing aromatic heterocyclic compounds toward the reagent has been studied. It was expected that the polarity induced by the presence of the tertiary nitrogen atom would give rise to: (a) reduction of the heterocyclic ring and (b) benzylation of "active" side-chains by a process in-

(1) Presented in part at the XIVth International Congress of Pure and Applied Chemistry, Zurich, July, 1955. Taken in part from the Ph.D. Thesis submitted to the Hebrew University of Jerusalem by Moshe Avramoff.

(2) Y. Sprinzak, (a) THIS JOURNAL, **78**, 466 (1956); (b) *ibid.* **78**, 3207 (1956); *cf.* British Patent 726,545 (Jan. 1, 1953).