The crude ester was washed once with hot water. The dry crude ester, obtained in nearly quantitative yield, was recrystallized to a constant melting point from 95% ethanol (5 ml./g.).

The higher alcohol esters were prepared by refluxing 15.8 g. of 9,10-dihydroxystearic acid, 0.06 mole of the alcohol, 200 ml. of benzene, and 0.316 g. of naphthalene-β-sulfonic acid for eight hours. The water formed during the reaction was removed azeotropically, and the benzene was returned to the reaction mixture. The quantitative amount of water was liberated. The benzene solution was evaporated to dryness, and the crude ester was melted and washed once with hot water. The aqueous layer was discarded, and the dried product, obtained in quantitative yield, was recrystallized to a constant melting point from 95% ethanol (5 ml./g.).

Summary

The 9,10-dihydroxystearic acids, m. p. 95° and 130°, have been esterified with twelve saturated aliphatic primary alcohols. The products are fairly high melting solids with very low vapor pressures. They may be useful as plasticizers or high-melting waxes.

PHILADELPHIA, PA. RECEIVED MARCH 10, 1945

[CONTRIBUTION FROM THE AVERY LABORATORY OF CHEMISTRY OF THE UNIVERSITY OF NEBRASKA]

Cinnamamides. I. α,β-Diamino Derivatives

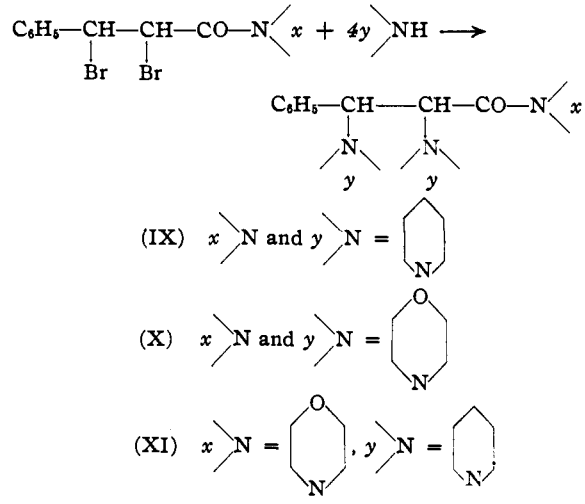
BY NORMAN H. CROMWELL AND JOHN A. CAUGHLAN[1]

Although cinnamamide and various N-substituted derivatives have been known for many years, only a few studies have been made of the chemistry of these α,β-unsaturated carbonyl compounds. It seemed of interest to carry out several experiments to compare the reactivity of such compounds with that of the α,β-unsaturated ketones with which we have been concerned in this Laboratory.[2]

Vorländer[3] showed that N-substituted cinnamamides added sodiomalonate in the normal way and added bromine at the olefinic double bond. Also Kohler[4] found this α,β-unsaturated carbonyl system to be reactive in the usual manner toward the Grignard reagent.

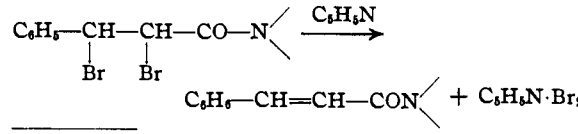
In the present investigation cinnamoyl chloride was treated with various secondary amines to give excellent yields of cinnampiperidide (I), cinnammorpholide (II), cinnamdiethylamide (III) and cinnamtetrahydroisoquinolide (IV). These unsaturated amides were readily converted into their corresponding dibromides (V), (VI), (VII) and (VIII) in carbon tetrachloride solution.

It was of interest to compare the reactivity of these dibromides with secondary amines, with similar studies that have been made with dibromo ketones.[5] The dibromide (V) reacted with piperidine in pyridine solution or without solvent to give the α,β-diamino amide (IX), while (VI) reacted with morpholine to form (X) and with piperidine to give (XI). All three of these products[6] resulted in low yields and it seemed apparent that a large portion of the dibromides had engaged in a parallel reaction.



When the dibromides (VII) and (VIII) were treated in the same way with diethylamine and tetrahydroisoquinoline, respectively, no diamino amides could be isolated. The only products resulting from these latter reactions were the unsaturated amides (III) and (IV), respectively. Moreover, it was found that refluxing the dibromides (V) and (VI) with pyridine alone gave from 25–35% yields of the corresponding unsaturated amides (I) and (II), respectively.

The formation of the α,β-dibromo amides is reversible, and in the presence of a strong halogen acceptor such as pyridine[7] the equilibrium is forced toward the α,β-unsaturated amide. In this respect the dibromo amides differ from the dibromo ketones. It is this reaction



(1) A Parke, Davis and Company research fellow, 1943–1944.

(2) See (a) THIS JOURNAL, **67**, 124 (1945); (b) **66**, 872 (1944); and preceding papers.

(3) Vorländer, *Ann.*, **320**, 66 (1902).

(4) Kohler and Heritage, *Am. Chem. J.*, **33**, 31 (1905).

(5) See Cromwell, Harris and Cram, THIS JOURNAL, **66**, 134 (1944), and preceding papers.

(6) These α,β-diamino amides are of a new type and thus are being "screen tested" for pharmacological activity by the Parke, Davis and Company, Detroit, Michigan.

(7) It has long been known that amines form some sort of addition compounds with halogens under anhydrous conditions; see Hantzsch and Graf, *Ber.*, **38**, 2157 (1905).

TABLE I

PHYSICAL AND ANALYTICAL DATA

Amides	No.	M. p., °C.	Yield, %	Formula	Percentage composition Calcd. C	Calcd. H	Found C	Found H
Cinnamamides								
Piperidide[a]	(I)	122	93					
Morpholide	(II)	94	99	$C_{13}H_{15}NO_2$	71.87	6.96	71.76	7.01
Diethylamide[b]	(III)	72	99					
Tetrahydroisoquinolide	(IV)	101	68	$C_{18}H_{17}NO$	82.10	6.51	82.02	6.65
α,β-Dibromo-β-phenylpropionamides								
Piperidide[c]	(V)	181	84					
Morpholide	(VI)	188	80	$C_{13}H_{15}NO_2Br_2$	41.40	4.01	41.34	3.94
Diethylamide[d]	(VII)	129	84					
Tetrahydroisoquinolide	(VIII)	111–122	77	$C_{18}H_{17}NOBr_2$	51.09	4.05	51.12	4.33
α,β-Dipiperidino-β-phenyl-propionpiperidide	(IX)	189	24	$C_{24}H_{37}N_3O$	75.15	9.72	75.54	10.00
α,β-Dimorpholino-β-phenyl-propionmorpholide	(X)	224	20	$C_{21}H_{31}N_3O_4$	64.76	8.02	64.93	8.24
α,β-Dipiperidino-β-phenyl-propionmorpholide	(XI)	198	14	$C_{23}H_{35}N_3O_2$	71.65	9.15	71.92	9.22

[a] D. Vorländer and P. Hermann, *Ann.*, **320**, 92 (1902). [b] M. p. 66° as prepared by Vorländer. [c] M. p. 189° according to Vorländer. [d] M. p. 127° according to Vorländer.

that seems to account for the low yields experienced in our preparations of the α,β-diamino amides (IX), (X) and (XI).

The reactivity of these dibromides was studied with several other basic media. In none of our experiments was it possible to split out hydrogen bromide to give the expected α-bromocinnamamides, $C_6H_5—CH=\underset{\displaystyle Br}{\underset{|}{C}}—CO—N\!\!\diagup\!\!\diagdown$, which have been prepared by other methods.[8]

It was not possible to add piperidine to the α,β-unsaturated amide (I) to form the β-amino amide, $C_6H_5—\underset{\displaystyle N\!\!\diagup\!\!\diagdown}{\underset{|}{CH}}—CH_2—CON\!\!\diagup\!\!\diagdown$. This conjugated system does not appear to be as reactive toward bases as is that present in α,β-unsaturated ketones.[2b] The chemistry of these compounds is being extended by further studies in this Laboratory.

Experimental

Cinnamamides.—Cinnamoyl chloride (one molar equiv.) was dissolved in benzene and two molar equiv. of the corresponding amine dissolved in benzene was added slowly. After standing at room temperature for twelve hours, the precipitated amine hydrochloride was filtered off. The filtrate was washed with salt water and the benzene layer dried over anhydrous calcium sulfate. Evaporation of the benzene and addition of petroleum ether (b. p. 50–60°) gave white crystalline products. These products were quite pure and further recrystallization from dilute alcohol solutions did not change the melting points.

α,β-Dibromo-β-phenylpropionamides.—The unsaturated amides were dissolved in carbon tetrachloride. These solutions were treated with one molar equivalent of bromine in carbon tetrachloride, as rapidly as the bromine color was discharged. Dibromides (V) and (VI) precipitated as white solids and were recrystallized from ethyl alcohol. It was necessary to partially evaporate the carbon tetrachloride and add petroleum ether to precipitate (VII). (VIII) came down as an oil but crystallized readily from 95% ethyl alcohol, although the melting point range remained wide.

α,β-Diamino-β-phenylpropionamides.—Although various solvents and conditions were tried, the following directions gave the best yields.

(1) The dibromides (V) and (VI) (0.027 mole) were mixed with 30 ml. of pyridine and the corresponding secondary amines (0.107 mole) added. On refluxing these mixtures for thirty minutes all of the dibromide dissolved and the solutions turned dark red. The cooled solutions were filtered to remove the precipitated hydrobromides and the pyridine evaporated under vacuum from the filtrate. The residues were extracted with hot benzene and these solutions washed with dilute salt water and dried over anhydrous calcium sulfate. Evaporation of the benzene and addition of petroleum ether caused the diamino amides to crystallize out. These products were recrystallized from alcohol and water solutions.

(2) The dibromides (V) and (VI) were refluxed for either ten minutes or five hours with four molar equivalents of the corresponding secondary amines. To the cooled, dark mixtures was added 100 ml. of water and the crude semi-solid products filtered off. The crude products were purified by dissolving in 95% alcohol and treating with decolorizing charcoal. White crystalline products (IX), (X) and (XI) in 10–12% yields were obtained in this way.

When method (1) was applied in an attempt to prepare α,β-bis-(diethylamino)-β-phenylpropiondiethylamide, the only product that could be isolated was a 40% yield of cinnamdiethylamide, m. p. 71–72°. Also when the dibromide (VIII) was treated with tetrahydroisoquinoline by method (1) only the unsaturated amide (IV), m. p. 100–101° resulted in low yields.

Reaction of Dibromides with Pyridine.—Ten grams of the dibromides (V) and (VI) was refluxed for two hours, each with 50 ml. of dry pyridine. The dark red solutions were evaporated under vacuum, and the black residues extracted with about 100 ml. of hot benzene. The benzene solutions were washed several times with water, once with 0.1 *N* hydrochloric acid, again with water and dried with anhydrous calcium sulfate. The benzene was mostly evaporated and petroleum ether (b. p. 60–70°) added to give almost colorless products. From the dibromide (V) was obtained 2.0 g. of product, m. p. 121–122°; mixed

(8) Anschütz, *Ber.*, **20**, 1387 (1887); Stoermer and Heyman, *ibid.*, **46**, 1259 (1913); Baucke, *Rec. trav. chim.*, **15**, 130 (1896); Sudborough and James, *J. Chem. Soc.*, **89**, 114 (1906); Ruhemann, *ibid.*, **61**, 279 (1892).

with (I) m. p. 121–122°. From the dibromide (VI), 1.6 g. of a product, m. p. 92–94°, resulted; mixed with (II) m. p. 92–94°.

Dibromides and Various Basic Media.—(1) The dibromide (V) was refluxed with stirring, with potassium acetate in absolute alcohol or in 95% alcohol for nine hours. When the reaction mixtures were cooled at least 90% of the starting material (V) was recovered.

(2) When (V) was refluxed in an absolute alcohol solution of potassium hydroxide for fifteen hours, again much of the starting material was recovered.

(3) Ten grams of (V) was refluxed with 9.1 g. of piperidine in 200 ml. of methyl alcohol for five hours. The solution turned red and all of the dibromide dissolved. On cooling the solution, 0.5 g. of (V) precipitated. The methyl alcohol was evaporated and the residue washed with water and recrystallized several times from alcohol and water to give 4.0 g. of (I), m. p. 120–122°; mixed with (I) m. p. 121–122°.

Amines and Cinnamamides.—A solution of 4 g. of (I) and 1.7 g. of piperidine in 6 ml. of 95% alcohol was refluxed for fifteen minutes and allowed to stand at room temperature for twelve hours. From the cooled solution was obtained 3.8 g. of (I). In another experiment one pellet of potassium hydroxide was added to the reaction mixture but again all of the unchanged starting material was recovered.

Similar results were obtained with morpholine and (II).

Summary

1. Methods for preparing cinnamamides and their dibromides have been described.

2. The reactivity of these dibromides with secondary amines has been studied and several examples of a new type of basic amide have been obtained for pharmacological studies.

3. The conjugated unsaturated system present in cinnamamides has been found to differ in reactivity from that present in α,β-unsaturated ketones.

LINCOLN, NEBRASKA RECEIVED MARCH 5, 1945

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF PARKE, DAVIS AND COMPANY, MONTEFIORE HOSPITAL AND COLUMBIA UNIVERSITY]

Synthetic Anticonvulsants. The Preparation and Properties of Some Benzoxazoles[1]

BY W. G. BYWATER, W. R. COLEMAN, OLIVER KAMM AND H. HOUSTON MERRITT

There is some evidence that in certain series of compounds having hypnotic activity, higher molecular weight members possess anticonvulsant activity without inducing a hypnotic effect, *i. e.*, the change from 5-phenyl-5-ethylhydantoin to dilantin (5,5-diphenylhydantoin) resulted in a greatly increased convulsive threshold and no hypnotic effect. This observation prompted us to investigate the benzoxazoles for three reasons. First, benzoxazolone (2-hydroxybenzoxazole) induces a sleeping state when administered hypodermically to mice but exerted no such action when given orally.[1a] Second, benzoxazolone is relatively non-toxic since it has been isolated as the hydrolytic product of an unknown substance obtained from the urine after feeding formanilide or acetanilide to dogs.[2] Third, 2-ethylbenzoxazole also possesses mild hypnotic activity. We have, therefore, synthesized eight higher homologs of 2-ethylbenzoxazole as well as four aryl substituted derivatives and tested them for anticonvulsant activity.

Two general methods have been applied to the synthesis of 2-alkyl- or 2-arylbenzoxazoles: (I) condensation of an acid, acid chloride, amide, nitrile or ester with *o*-aminophenol by heating the mixture at or near its boiling point for several hours and distilling the product[3]; and (II) reduction of *o*-nitro acyl or aroylphenols, ring closure usually occurring during the reduction.[4] Method (I) has been employed to prepare fourteen benzoxazoles, seven of which have not been previously described. Their physical properties are recorded in Table I.

Experimental

Benzoxazoles, General Method of Preparation.—Molecular equivalents of technical *o*-aminophenol and the appropriate acid, amide or nitrile were heated to boiling for several hours in a Claisen flask. The temperature was slowly increased, as water or ammonia distilled from the flask, until the refluxing temperature remained constant. The black reaction mixture was then distilled at atmospheric pressure. The crude product, if a liquid, was dissolved in petroleum ether and washed with 10% sodium hydroxide solution. This treatment destroyed the characteristic fluorescence noted in many of the crude benzoxazoles. The oil remaining after removal of the petroleum ether was purified by distillation. The liquids were usually straw colored. The solids were pulverized and washed with 10% alkali and water before recrystallizing them from dilute alcohol or acetone. All melting points recorded in Table I are corrected while all boiling points were determined with Anschütz precision thermometers.

Ethyl α-ethyloenanthylate when heated with *o*-aminophenol did not give 1-(α-ethyl-*n*-heptyl)-benzoxazole as expected. It is the only case in which an ester was used.

We have found it convenient to prepare benzoxazolone by fusing urea with technical *o*-aminophenol at 200° (bath temperature) until ammonia is no longer evolved[5] rather than heating N-(*o*-hydroxyphenyl)-urethan.[6] The product is distilled at atmospheric pressure and recrystallized from dilute acetone (1:1 by volume). While the yield is only 35%, the reactants are inexpensive and the process is

(1) Presented in part at the meeting of the Division of Medicinal Chemistry, Detroit, Michigan, September 9–13, 1940.

(1a) Gruhzit, unpublished report.

(2) Jaffe and Hilbert, *Z. physiol. Chem.*, **12**, 229 (1887) [Beilstein, Prager, Jacobson, 4th edition, Springer, Berlin, Vol. 27, 177]; *see also* Kleine, *Z. physiol. Chem.*, **22**, 327 (1897).

(3) (a) Ladenberg, *Ber.*, **9**, 1524 (1876); (b) Skraup, *Ann.*, **419**, 1 (1919); (c) Skraup and Moser, *Ber.*, **55**, 1080 (1922).

(4) Hubner, *Ann.*, **210**, 384 (1882).

(5) Sandmeyer, *Ber.*, **19**, 2656 (1886), prepared benzoxazolone by fusing urea and *o*-aminophenol hydrochloride.

(6) (a) Bender, *Ber.*, **19**, 2269 (1886); (b) see also Desai, *et al.*, *J. Chem. Soc.*, 1187 (1934).