with a solution of 5 g. of sodium carbonate in 50 ml. of water. After several minutes a solid gelatinous precipitate formed which was recovered by filtration and dried. The weight of the precipitate was 5.5 g. and an additional 1.4 g. was obtained on cooling the water solution in ice (84%). A sample of this substance was recrystallized from water–alcohol to give a white crystalline solid m.p. 68–69°.

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LAFAYETTE, IND.

[CONTRIBUTION FROM THE CHEMICAL RESEARCH DIVISION OF SCHERING CORPORATION]

Amides of Ethylenediamines. II. Substituted Cinnamides as Local Anesthetic Agents[1]

BY FRANK J. VILLANI, JOSEPH LANG AND DOMENICK PAPA

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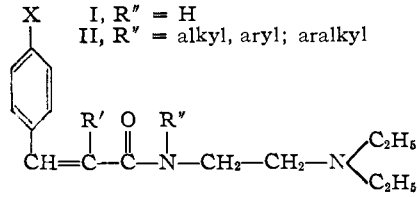
Several cinnamamides of substituted ethylenediamines were prepared and evaluated for their local anesthetic action. N'-Benzyl-N'-cinnamoyl-N,N-diethylethylenediamine was the most active compound in this series.

The local anesthetic activity of dialkylaminoalkyl cinnamamides of formula I has been reported some time ago in the patent literature.[2] As part of a program on the synthesis of amides of substituted ethylenediamines,[3] it was of interest to prepare and evaluate pharmacologically a series of cinnamamides, wherein the amide nitrogen is further substituted by alkyl, aryl, or aralkyl groups, as shown in formula II. This paper describes the synthesis and local anesthetic activity of a number of these compounds, as well as cinnamamides having substituents in the *para* position of the phenyl ring. Included in this study are compounds with substituents, such as methyl and phenyl, on the alpha carbon of the cinnamic acid.



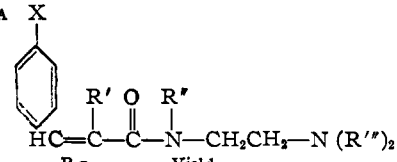
The compounds were prepared by the reaction of the cinnamoyl chloride and the appropriately substituted ethylenediamine in benzene with pyridine as the acid acceptor. N'-*p*-Aminocinnamoyl-N'-benzyl-N,N-diethylethylenediamine was prepared from the corresponding *p*-nitro derivative by reduction with ammoniacal ferrous sulfate.

To ascertain whether or not unsaturation in these compounds was essential for local anesthetic activity, one hydrocinnamoyl amide was synthesized for comparative purposes. A furan substituted compound also was prepared in order to determine structure–activity relationships.

The amides listed in Table I were obtained as light yellow, high boiling, viscous oils, readily soluble in dilute hydrochloric acid.

TABLE I

COMPOUNDS OF THE FORMULA



No.	X	R′	R″	R″	B.p. °C.	Mm.	Yield, %	n_D	t	Formula	Nitrogen, % Calcd.	Found
1	H	H	H	C_2H_5	184–187	1	70	1.5665	21	$C_{15}H_{22}ON_2$	11.38	11.59
2	H	H	*n*-C_3H_7	C_2H_5	191–196	3	58	1.5463	27	$C_{18}N_{28}ON_2$	9.72	9.42
3	H	H	C_6H_5	C_2H_5	200–207	1	70	1.5868	27	$C_{21}H_{26}ON_2$	8.69	8.60
4	H	H	$C_6H_5CH_2$	CH_3	220–225	0.5	73	1.595		$C_{20}H_{24}ON_2$	9.08	9.11
5	H	H	$C_6H_5CH_2$	C_2H_5	225–232	0.5	62	1.583		$C_{22}H_{28}ON_2$	8.32	8.51
6	Cl	H	$C_6H_5CH_2$	C_2H_5	236–241	1	64	1.5891	28	$C_{22}H_{27}ON_2Cl$	7.56	7.68
7	NO_2	H	$C_6H_5CH_2$	C_2H_5	*a*		*b*			$C_{22}H_{27}O_3N_3$	11.62	11.99
8	NH_2	H	$C_6H_5CH_2$	C_2H_5	*c*		*b*	1.5863	26	$C_{22}H_{29}ON_3$	11.96	11.68
9	$(CH_3)_2CH$–	H	$C_6H_5CH_2$	C_2H_5	228–231	1	55	1.5717	23	$C_{25}H_{34}ON_2$	7.61	7.94
10	H	CH_3	$C_6H_5CH_2$	C_2H_5	198–201	0.5	67	1.5625	24	$C_{23}H_{30}ON_2$	7.99	8.49
11	H	C_6H_5	$C_6H_5CH_2$	C_2H_5	247–252	1	63	1.5917	29	$C_{28}H_{32}ON_2$	6.79	7.07
12	Cl	C_6H_5	$C_6H_5CH_2$	C_2H_5	258–261	1	39	1.5993	23	$C_{28}H_{31}ON_2Cl$	6.28	6.74
13	H	H	*p*-OCH_2–$C_6H_4CH_2$	CH_3	265–270	1	34	1.5928	27	$C_{21}H_{26}O_2N_2$	8.28	8.32

[a] M.p. 72–73°. [b] See Experimental section. [c] 230–239° (3 mm). (dec.).

(1) Presented in abstract before the Division of Medicinal Chemistry of the American Chemical Society, Atlantic City, New Jersey, September, 1952.

(2) W. A. Lott, U. S. Patents 2,103,265 (1937); 2,139,687 (1938); 2,251,287 (1941); 2,251,946 (1941); 2,310,973 (1943).

(3) For paper I in this series, see F. J. Villani, N. Sperber, J. Lang and D. Papa, THIS JOURNAL, 72, 2724 (1950).

Pharmacology.—The local anesthetic action was determined by the infiltration technique in guinea pigs. Five-hundredths of a cubic centimeter of a 1% solution of the hydrochloride of the test substance, buffered to a *p*H of 6–7.4, was injected intradermally and the response to a stimulus was determined at five-minute intervals. Each substance was tested on a minimum of four animals.

N′-Cinnamoyl-N,N-diethylethylenediamine (no. 1) had an average local anesthetic action, as determined by this test, of 25–30 minutes duration. The introduction of a substituent on the amide nitrogen resulted in a marked increase in the duration of local anesthesia. N′-Benzyl-N′-cinnamoyl-N,N-diethylethylenediamine (no. 5) was the most active compound in this series, with an activity lasting 240–300 minutes. Compounds with substituents in the aromatic ring (no. 6, 7, 8, 9) or on the alpha carbon atom of the cinnamic acid (no. 10, 11, 12) decreased the local anesthetic activity to approximately $^1/_2$ to $^2/_3$ that of the parent compound, no. 5. A similar effect was noticed in the replacement of the N,N-diethyl group by the N,N-dimethyl group (no. 4, 13). The N′-hydrocinnamoyl-N′-benzyl-N,N-diethylethylenediamine and N-β-(α-furyl)-acryloyl - N - benzoyl - N′,N′ - diethylethylenediamine had activities lasting 135–180 minutes and 118–126 minutes, respectively, as compared with 240–300 minutes for No. 5.

Experimental

The N′-phenyl and N′-benzyl substituted N,N-disubstituted ethylenediamines were obtained by the methods previously described.[3] N′-(*n*-Propyl)-N,N-diethylethylenediamine was prepared by the method of Kermack.[4] The substituted cinnamic acids were obtained by known procedures.[5]

N′-(*p*-Chlorocinnamoyl)-N′-benzyl-N,N-diethylethylenediamine.—Fifty milliliters of purified thionyl chloride was added slowly with occasional shaking to 9.1 g. (0.05 mole) of *p*-chlorocinnamic acid, and the mixture was then refluxed for two hours on the steam-bath. The excess thionyl chloride was distilled off under vacuum, 50 ml. of anhydrous benzene was added, and the benzene was removed under vacuum. To the residue, a solution of 4 g. of dry pyridine in 50 ml. of anhydrous benzene was added, the mixture was cooled to 10–15° and a solution of N′-benzyl-N,N-diethylethylenediamine in 50 ml. of anhydrous benzene was added dropwise with occasional shaking. The resulting mixture was heated under reflux for six hours and kept overnight at room temperature. The dark red mixture was poured into ice-water, made alkaline with dilute sodium hydroxide and extracted with ether. The ether extract was extracted with 10% hydrochloric acid, and the acid phase was then made alkaline with dilute sodium hydroxide. The red oil which precipitated was taken up in ether and the solution was dried over anhydrous sodium sulfate and distilled.

N′-Hydrocinnamoyl-N′-benzyl-N,N-diethylethylenediamine: b.p. 210–213° (2 mm.), $n^{24}D$ 1.5518, yield 58%.

Anal. Calcd. for $C_{22}H_{30}ON_2$: N, 8.28. Found: N, 8.42.

N-β-(α-Furyl)-acryloyl-N′-benzyl-N′,N′-diethylethylenediamine: b.p. 205–208° (1 mm.), $n^{24}D$ 1.5798, yield 64%.

Anal. Calcd. for $C_{20}H_{26}O_2N_2$: N, 8.58. Found: N, 8.54.

N′-(*p*-Aminocinnamoyl)-N-benzyl-N,N-diethylethylenediamine.—Thirty-eight and six-tenths grams (0.2 mole) of *p*-nitrocinnamic acid was converted into the acid chloride by the method described in the preceding paragraph. The acid chloride was treated with a solution of 16 g. of dry pyridine, 39.2 g. (0.2 mole) N′-benzyl-N,N-diethylethylenediamine and 250 ml. of dry benzene and processed as described above. On neutralization of the hydrochloric acid extracts the product precipitated as a brownish-black crystalline mass (72 g.), which was difficult to purify. A small sample was recrystallized for analysis from a large volume of dilute ethanol.

A solution of 306 g. of ferrous sulfate heptahydrate in 1.5 liters of water and 200 ml. of ammonium hydroxide was heated to 85–90°, while a solution of 70 g. (0.18 mole) of the crude nitro compound in 750 ml. of ethanol was added slowly with constant stirring. The mixture was kept alkaline by the occasional addition of ammonium hydroxide, and maintained at 85–90° for one hour. After filtering, the alcohol was removed by distillation under vacuum and the residue was thoroughly extracted with ethyl acetate. After drying, the solvent was removed and the residue was distilled. The distillation was accompanied by excessive charring and decomposition.

BLOOMFIELD, NEW JERSEY

(4) W. O. Kermack and T. W. Wight, *J. Chem. Soc.*, 1421 (1935).

(5) See Adams, "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942, pp. 210–265.

[CONTRIBUTION FROM THE CHEMISTRY DIVISION, U. S. NAVAL ORDNANCE TEST STATION]

Thermal Isomerization of Substituted 5-Aminotetrazoles[1]

BY RONALD A. HENRY, WILLIAM G. FINNEGAN AND EUGENE LIEBER

RECEIVED MAY 29, 1953

The isomerization of 1-substituted 5-aminotetrazole to 5-substituted aminotetrazoles, or *vice versa*, at 180 to 200° in homogeneous systems has been investigated and found to reach an equilibrium. The position of equilibrium is shifted toward the 5-substituted aminotetrazole as the electronegativity of the substituent is increased. An approximately linear relationship exists between the position of equilibrium and the pK_a of the 5-substituted aminotetrazole. In addition there is an excellent correlation between the logarithms of the equilibrium constants and Hammett's σ-values for groups. A mechanism of the isomerization, which involves the distribution of charge on a substituted guanyl azide intermediate, is proposed.

In a previous investigation[2] the isomerization of 5-alkylamino-, 1-aryl-5-amino- and 1-aryl-5-alkylaminotetrazoles at 180–200° to 1-alkyl-5-amino-, 5-arylamino- and 1-alkyl-5-arylaminotetrazoles, respectively, was described. Some evidence was reported which indicated that the isomerizations involved an equilibrium, although essentially quantitative conversions were frequently obtained. Since the isomerized product melted higher than the isomerization temperature in many cases, the equilibrium would be continuously displaced toward the isomerized product by solidification of the melt. A more careful study of the isomerization of monosubstituted 5-aminotetrazoles in homogeneous systems (undisturbed melt or solution in ethylene glycol) definitely confirms this idea of an equilib-

(1) Presented at the 123rd Meeting of the American Chemical Society, March 15–19, 1953.

(2) W. G. Finnegan, R. A. Henry and E. Lieber, *J. Org. Chem.*, **18**, 779 (1953).