[CONTRIBUTION FROM THE CHEMICAL DIVISION OF SCHERING CORPORATION]

The Analgesic Activity of N,N-Dialkyl Amides[1]

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In the course of screening compounds for pharmacological action, it was observed that α-phenyl-N,N-diethyl cinnamamide potentiated nembutal hypnosis in rats. A similar synergistic effect has been observed previously by Loewe[3] and Seifert[4] who have reported that the combination of phenobarbital with morphine results in an increase in the intensity of the analgesic effect of morphine. More recently, the comparative potentiating effects of acetylsalicylic acid, amidopyrine, demerol and morphine on the hypnotic effect of evipal sodium have been demonstrated.[5] Although potentiation of hypnotic effect has been shown to be non-specific for analgesic drugs, it, nevertheless, appeared of interest to investigate a series of amides, particularly cinnamamides, for non-opiate analgesic activity.

The amides (Table I) synthesized in the course of this investigation are of the general formula I, wherein R is aryl or heterocyclic and the alkyl, halogen, hydroxyl, acetoxy, nitro and acetylamino derivatives, R′ is hydrogen, alkyl, aryl and alicylic and R″ is hydrogen or a lower alkyl group. In addition, a number of other amides, dialkyl amides and heterocyclic nitrogen derivatives of aryl and heterocyclic carboxylic acids have been prepared for pharmacological study.

$$RCH{=}CR'{-}CON(R'')_2 \quad I$$

In general, the amides of formula I have been prepared by the reaction of the appropriate acid chlorides with ammonia, monoalkylamines or the dialkylamines by conventional methods. The ring-substituted cinnamic acids[6] were secured by the Perkin condensation of the appropriately substituted benzaldehydes and potassium acetate or by the Doebner condensation of the benzaldehydes and malonic acid. The α-alkyl,[6] aryl[6] or alicylic[7] cinnamic acids were prepared by known methods.

The preliminary pharmacological assay of the amides did not indicate any analgesic activity comparable to that of either morphine, demerol or other synthetics of the latter type. In view of the uncertainties common to the standard tests for analgesic activity, particularly when applied to compounds of the type of acetyl salicylic acid and phenacetin, a new test for analgesic activity was developed by our Pharmacology Laboratory.[8] This test is based upon the analgesic effect of the test drug, given orally in a starch suspension, against inflamed joint pain artificially produced in animals. For purposes of comparison, the ED/50 for acetylsalicylic acid, phenacetin and amidopyrine was determined and the amides (Table I) compared with these standards. Preliminary toxicity and analgesic assay indicated an order of activity for the unsubstituted N,N-dialkyl cinnamamides comparable to that of the standard drugs. In particular, N,N-diethylcinnamamide and N,N-dibutylcinnamamide showed an analgesic effect approximately three times that of phenacetin and an extremely favorable therapeutic ratio in experimental animals.

The antipyretic action of the amide was determined by the effectiveness of the compounds under test in reducing fever produced in rats. In this study, the compounds were administered orally in starch suspension in water. N,N-Diethylcinnamamide has an antipyretic action twice that of the standard drugs at approximately the same dose level.

In a limited clinical study, N,N-diethylcinnamamide was found to be less effective than acetyl salicylic acid and was not well tolerated. Among the side reactions observed with this drug were gastric irritation, nausea and occasional vomiting.

Experimental

Preparation of Acid Chlorides.—Purified thionyl chloride (125 cc.) was added with efficient cooling to 0.2 mole of the cinnamic acid. After the initial reaction had subsided, the mixture was refluxed on the steam-bath for three hours. The excess thionyl chloride was removed under vacuum and the residue distilled under reduced pressure. All of the cinnamoyl chlorides, with the exception of the *p*-nitro-, the diaryl and aryl-alicyclic compounds, were distilled prior to use.

Preparation of Amides.—A mixture of 0.2 mole of the cinnamoyl chloride, 0.4 mole of the amine and 200 ml. of anhydrous benzene was refluxed on the steam-bath for two hours. The product was poured into ice-water, the organic layer was separated and washed successively with dilute (10%) hydrochloric acid, dilute (10%) sodium bicarbonate and finally with water. After removal of the benzene, the residue was either distilled *in vacuo* and/or recrystallized.

For the preparation of *p*-acetylaminocinnamoyl diethyl amide, the *p*-amino-compound, formed by the reduction of *p*-nitrocinnamoyl diethyl amide with ferrous sulfate and ammonia, was acetylated in the conventional manner using acetyl chloride. Other amides which were prepared and are not included in Table I are as follows:

Diethylamide of α,β-diphenylpropionic acid, yield 68%, b. p. 164–166° (1 mm.). *Anal.* Calcd. for $C_{19}H_{23}ON$: N, 4.98. Found: N, 5.00

(1) Presented in abstract before the Division of Medicinal Chemistry, American Chemical Society Meeting, Atlantic City, 1949.

(2) American Cyanamid Co., Calco Chemical Division, Bound Brook, New Jersey.

(3) Loewe, *Deutsche Med. Wochnschr.*, **38**, 947 (1912).

(4) Seifert, "Die Nebenwirkungen der modern Azrneimittel," Wurzburg, 1915.

(5) Barlow, Climenko and Homburger, *Proc. Soc. Exp. Biol. and Med.*, **49**, 11 (1942).

(6) "Organic Reactions, The Perkin Reaction," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942.

(7) Schwenk and Papa, THIS JOURNAL, **67**, 1432 (1945).

(8) A preliminary report on this test has been given by LaBelle and Tislow at the November, 1949, meeting of the Society of Pharmacology and Experimental Therapeutics at Indianapolis, Indiana.

TABLE I

AMIDES OF FORMULA R—CH=CR'—CONR''R'''

R	R'	R''	R'''	Yield, %[a]	B. p., °C.	Mm.	M. p., °C.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
CH_3	H	C_2H_5	C_2H_5	86	105–106	16		$C_8H_{15}ON$	68.09	68.23	10.71	10.41		
C_6H_5	H	H	C_2H_5	86			96–96.5[b]							
C_6H_5	H	CH_3	CH_3	88			101–102[f]							
C_6H_5	H	C_2H_5	CH_3	64	160–161	2		$C_{12}H_{15}ON$					7.40	7.47
C_6H_5	H	CH_3	C_3H_7	71	160–162	4		$C_{13}H_{17}ON$					6.89	6.57
C_6H_5	H	C_2H_5	C_2H_5	94			69–70[g]							
C_6H_5	H	C_2H_5	n-C_4H_9	72	170–172	3		$C_{15}H_{21}ON$	77.49	76.92	9.12	9.02		
C_6H_5	H	i-C_3H_7	i-C_3H_7	92	152–154	1		$C_{15}H_{21}ON$					6.05	5.85
C_6H_5	H	C_3H_7	C_3H_7	86	165–167	1.5	53–54[d]	$C_{15}H_{21}ON$					6.05	6.10
C_6H_5	H	n-C_4H_9	n-C_4H_9	76	191–193	4		$C_{17}H_{25}ON$					5.42	5.66
C_6H_5	H	n-C_5H_{11}	n-C_5H_{11}	79	205–207	4								
4-$CH_3C_6H_4$	H	C_2H_5	C_2H_5	84	152–154	2		$C_{14}H_{19}ON$	77.38	77.47	8.81	8.88		
i-$C_3H_7C_6H_4$	H	C_2H_5	C_2H_5	82	178–180	1		$C_{16}H_{23}ON$					5.97	6.08
4-BrC_6H_4	H	C_2H_5	C_2H_5	62			71–72[c]	$C_{13}H_{16}ONBr$					4.94	4.96
3-$NO_2C_6H_4$	H	C_2H_5	C_2H_5	80			85–86[c]	$C_{13}H_{16}O_3N_2$	62.91	63.17	6.52	6.67		
4-$CH_3OC_6H_4$	H	C_2H_5	C_2H_5	75	184–186	1		$C_{14}H_{19}O_2N$	72.07	71.96	8.28	8.26		
2-OHC_6H_4	H	C_2H_5	C_2H_5	68			169–170[e]	$C_{13}H_{17}O_2N$	71.24	71.13	7.82	8.19	6.39	6.50
3-OHC_6H_4	H	C_2H_5	C_2H_5	70			120–121[e]	$C_{13}H_{17}O_2N$	71.24	71.54	7.82	7.70		
3-$CH_3COOC_6H_4$	H	C_2H_5	C_2H_5	60	198–200	3	64–64.5	$C_{15}H_{19}O_3N$	69.11	69.18	7.34	7.43		
4-$CH_3CONHC_6H_4$	H	C_2H_5	C_2H_5	51			157–158[c]	$C_{15}H_{20}N_2O_2$	69.23	69.32	7.69	7.96		
3,4-$OCH_2OC_6H_3$	H	C_2H_5	C_2H_5	48			70–71[c]	$C_{14}H_{17}O_3N$					5.66	5.90
C_6H_5	CH_3	C_2H_5	C_2H_5	74	135–136	1		$C_{14}H_{19}ON$					6.45	6.22
C_6H_5	C_2H_5	C_2H_5	C_2H_5	64	134–135	1		$C_{15}H_{21}ON$					6.05	6.06
C_6H_5	n-C_4H_9	C_2H_5	C_2H_5	78	151–153	0.5		$C_{17}H_{25}ON$					5.45	5.19
α-$C_{10}H_7$	H	C_2H_5	C_2H_5	55			95–96[e]	$C_{17}H_{19}ON$					5.53	5.81
C_6H_5	C_6H_5	H	H	82			130–131[h]							
C_6H_5	C_6H_5	C_2H_5	C_2H_5	73			92–93[c]	$C_{19}H_{21}ON$					5.01	4.99
C_6H_9	C_6H_5	H	H	80			135–136[c]	$C_{15}H_{17}ON$					6.16	6.09
C_6H_9	C_6H_5	C_2H_5	C_2H_5	65	175–177	1		$C_{19}H_{25}ON$					4.94	4.82
C_5H_4N	C_6H_5	C_2H_5	C_2H_5	66			80–81[c]	$C_{18}H_{20}ON_2$					9.99	9.66
C_4H_3O	H	C_2H_5	C_2H_5	62	152–154	5		$C_{11}H_{15}O_2N$					7.25	7.26

[a] The yields reported are based on single experimental runs and do not represent the maximum obtainable. [b] Previously reported melting point 92–93°, Hermann and Vorlander, *Chem. Zentr.*, **70**, I, 730 (1899). [c] Recrystallization solvent, benzene–petroleum ether. [d] Recrystallization solvent, petroleum ether. [e] Recrystallization solvent, aqueous ethanol. [f] Previously reported melting points 96° (ref. b) and 103°, Staudinger and Kon, *Ann.*, **384**, 119 (1911). [g] Previously reported melting point 66° (ref. b). [h] Previously reported melting point 127°, Stoermer, *Ann.*, **409**, 37 (1915).

Diethylamide of undecylenic acid, yield 78%, b. p. 150–153° (1 mm.), $n^{26}D$ 1.4599. *Anal.* Calcd. for $C_{15}H_{29}ON$: N, 5.94. Found: N, 6.04.

N-Cinnamoylmorpholine, yield 54%, m. p. 93–94° after recrystallization from ligroin (b. p. 60–75°). *Anal.* Calcd. for $C_{13}H_{15}O_2N$: N, 6.46. Found: N, 6.64.

N,N'-Dicinnamoylpiperazine, yield 78%, m. p. 270–271° after recrystallization from chloroform–ether. *Anal.* Calcd. for $C_{22}H_{22}O_2N_2$: N, 8.11. Found: N, 7.98.

Diethylamide of *p,p'*-diphenyldiacetic acid, yield 76%, m. p. 115–115.5° after recrystallization from aqueous acetone. *Anal.* Calcd. for $C_{24}H_{32}O_2N_2$: C, 75.76; H, 8.47. Found: C, 75.50; H, 8.51.

Diethylamide of 1,4-phenylenediacetic acid, yield 65%, m. p. 84–85° after recrystallization from benzene–petroleum ether. *Anal.* Calcd. for $C_{18}H_{28}O_2N_2$: C, 71.02; H, 9.27. Found: C, 71.03; H, 9.57.

Diethylamide of diphenylacetic acid, yield 55%, m. p. 70–71° after recrystallization from benzene–petroleum ether. *Anal.* Calcd. for $C_{18}H_{21}ON$: C, 80.86; H, 7.91. Found: C, 80.78; H, 7.96.

2,2-Dibutylhexyl amide of α-phenylcinnamic acid was obtained by refluxing for fifteen hours a mixture of 12.5 g. of α-phenylcinnamoyl chloride, 10 g. of 2,2-dibutylhexyl amine,[9] 30 cc. of pyridine and 50 cc. of benzene. The crude amide was isolated and recrystallized from petroleum ether, m. p. 75–76°. *Anal.* Calcd. for $C_{29}H_{41}ON$: C, 83.00; H, 9.85. Found: C, 83.34; H, 10.05.

Diethylamide of styrylacrylic acid, yield 58%, m. p. 75–76° after recrystallization from dilute ethanol. *Anal.* Calcd. for $C_{15}H_{19}ON$: C, 78.71; H, 8.35. Found: C, 78.80; H, 8.21.

Diethylamide of coumarilic acid; yield 64%, b. p. 157–159° (4 mm.). *Anal.* Calcd. for $C_{13}H_{15}O_2N$: N, 6.45. Found: N, 6.06.

Diethylamide of 3-phenylcoumarilic acid was obtained from 3-phenylcoumariloyl chloride[10] and diethylamine; yield 77%, m. p. 84–85°. *Anal.* Calcd. for $C_{19}H_{19}O_2N$: N, 4.78. Found: N, 4.71.

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Summary

A series of substituted N,N-dialkyl cinnamamides have been prepared and tested for analgesic activity.

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(9) Allardt and Junkmann, U. S. Patent 2,361,524, October 31, 1944.

(10) Fuson, Kaiser and Speck, *J. Org. Chem.*, **6**, 850 (1941).