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Strong Analgesics. The Preparation of Some 4-Acyloxy-1-aralkyl-4-phenylpiperidines

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The enhanced analgesic effect of replacing the N-methyl group in meperidine by a cinnamyl group led to the preparation of a number of 4-acyloxy-1-aralkyl-4-phenylpiperidines. These were evaluated by the rat thermal stimulus method for analgesic potency. The cinnamyl group is not generally effective but does have a strong potentiating effect in certain piperidine analgesics.

It was reported[1] recently that replacement of the N-methyl group of meperidine, ethyl 1-methyl-4-phenylpiperidine-4-carboxylate hydrochloride, by the N-cinnamyl group gave a compound having increased analgesic potency. We therefore were interested in determining whether a similar effect could be obtained in other series of analgesics, of which a number have been developed in the past two decades. Most of these analgesic types fall into one of several classes of compounds. Perhaps the most important of these is the 4-phenylpiperidine group of compounds of which meperidine is the chief example. Another important example in the 4-phenylpiperidine group is α-prodine, 1,3-dimethyl-4-phenyl-4-propionoxypiperidine hydrochloride.[2] A second main group is composed of basic diaryl ketones of which methadone, 2-dimethylamino-4,4-diphenyl-5-heptanone hydrochloride,[3] is exemplary. A third class of analgesics is composed of basic dithienylalkenes and is represented by 3-dimethylamino-1,1-di-(2-thienyl)-1-butene hydrochloride.[4] A great many other types of compounds have been reported to have strong analgesic activity, but few of these have received as much attention from chemists and pharmacologists as have the groups indicated above.

Accordingly a cinnamyl analog of an example from each of the classes was prepared: namely, 1-cinnamyl-4-phenyl-4-propionoxypiperidine, 2-(N-cinnamyl-N-methylamino)-4,4-diphenyl-5-heptanone and 3-(N-cinnamyl-N-methylamino)-1,1-di-(2-thienyl)-1-butene.

The pharmacological evaluation of these compounds for analgesic potency was carried out using the Bass–VanderBrook[5] modification of the D'Amour–Smith[6] rat thermal stimulus method. It was found that 3-(N-cinnamyl-N-methylamino)-1,1-di-(2-thienyl)-1-butene had little or no analgesic activity. The cinnamyl analog of methadone was too toxic to be evaluated satisfactorily by this method. However, in the prodine series high activity was observed, and so a number of related compounds in the prodine series were prepared and studied.

The piperidones[7] required as intermediates for the preparation of the 4-acyloxy-1-substituted-4-phenylpiperidines were obtained by condensing the appropriate primary amine with two moles of methyl acrylate, cyclizing the resulting bis-ester, hydrolyzing and decarboxylating. It was found that better over-all yields were obtained if none of the intermediates was purified but was used immediately as is. The piperidones were treated with phenyllithium and the resulting complex was allowed to react directly with the appropriate anhydride to give the desired compound.

The methadone analog was prepared by treating benzylmethylamine with propylene oxide, converting the resultant secondary aminoalcohol to the corresponding chloride and condensing it with diphenylacetonitrile to give 4-(N-benzyl-N-methylamino)-2,2-diphenyl-4 (or 3)-methylbutane nitrile. No attempt was made to ascertain the exact isomer obtained, although by analogy it might be assumed to be the same as is obtained in the regular methadone series. The nitrile was catalytically debenzylated and then N-cinnamylated with cinnamyl bromide. On treatment with ethylmagnesium bromide the desired compound was obtained.

The butene analog was prepared by condensing ethyl crotonate with methylamine. The resultant ethyl 3-methylaminobutyrate was treated with cinnamyl bromide to give ethyl 3-(N-cinnamyl-N-methyl)-aminobutyrate. On reaction with 2-thienyllithium, 3-(N-cinnamyl-N-methyl)-amino-1,1-di-(2-thienyl)-butane-1-ol was formed which on dehydration gave the desired butene.

In the evaluation of the analgesic potency of the compounds reported here, it was found that the 4-propionoxy compounds were more potent than the corresponding 4-acetoxy compounds. This is in agreement with the results reported[2] on the corresponding derivatives of prodine. All of the compounds except the N-benzyl derivatives were considerably more potent than morphine.

Experimental[8]

The preparation of 1-cinnamyl-4-phenyl-4-propionoxypiperidine is typical of all of the preparations of this type considered in this paper.

Dimethyl β,β'-(Cinnamylimino)-dipropionate.—Cinnamylamine (175 g., 1.3 moles) was dissolved in 250 ml. of methanol and 350 ml. of methyl acrylate added with stirring during a 15-minute period, allowing the heat of reaction to cause reflux. After the reaction mixture was refluxed for a total of 8 hours, the methanol and excess methyl acrylate

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(1) B. Elpern, L. Gardner and L. Grumbach, THIS JOURNAL, **79**, 1951 (1957).

(2) A. Ziering and J. Lee, *J. Org. Chem.*, **12**, 894 (1947).

(3) Report No. 981, Office of the Publication Board, Washington, D. C.

(4) D. W. Adamson and A. F. Green, *Nature*, **165**, 122 (1950).

(5) W. B. Bass and M. J. VanderBrook, *J. Am. Pharm. Assoc., Sci. Ed.*, **41**, 569 (1952).

(6) F. E. D'Amour and D. L. Smith, *J. Pharmacol. Exptl. Therap.*, **72**, 74 (1941).

(7) The preparation of the piperidones follows the general method of McElvain: S. M. McElvain and K. Rorig, THIS JOURNAL, **70**, 1820, 1826 (1948); S. M. McElvain, *i id.*, **46**, 1721 (1924); **48**, 2179 (1926).

(8) Melting points corrected.

TABLE I

N-SUBSTITUTED PIPERIDONES RN(CH$_2$—CH$_2$)$_2$C=O

R	Empirical formula	B.p. °C.	Mm.	Yield, %	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
$C_6H_5CH_2$–[b]	$C_{12}H_{15}NO$	114–117	0.3	59	...	...	..	..	..	..
$C_6H_5(CH_2)_2$–	$C_{13}H_{17}NO$	117–118	.1	70	78.56	78.66	8.35	8.05	6.11	6.08
$C_6H_5(CH_2)_3$–	$C_{14}H_{19}NO$	114–115	.2	43	77.38	77.11	8.81	8.84	7.36[a]	7.10[a]
$C_6H_5(CH_2)_4$–	$C_{15}H_{21}NO$	135–136	.3	46	77.88	77.83	9.15	9.02	6.92[a]	6.75[a]
C_6H_5CH=$CHCH_2$–	$C_{14}H_{17}NO$	138–140	.3	70	78.10	78.35	7.96	8.46	6.51	6.43
$C_6H_5O(CH_2)_3$–	$C_{14}H_{19}NO_2$	136–139	.2	75	72.07	72.24	8.21	8.01	6.00	5.90

[a] Analysis for oxygen. [b] G. Stork and S. M. McElvain, THIS JOURNAL, **68**, 1053 (1946).

TABLE II

4-ACYLOXY-1-ARALKYL-4-PHENYLPIPERIDINES R—N(CH$_2$—CH$_2$)$_2$C(C$_6$H$_5$)(OR′)

R	R′	Empirical formula	M.p., °C. (cor.)	Yield, %	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Chlorine, % Calcd.	Chlorine, % Found	Activity[c]	Toxicity[d]
$C_6H_5CH_2$–	CH_3CO–	$C_{20}H_{23}NO_2$·HCl	207.6–208.2	41	69.46	69.21	6.70	6.60	10.25	10.22	1.1	2.8
$C_6H_5(CH_2)_2$–	CH_3CO–	$C_{21}H_{25}NO_2$·HCl	213.4–214.4	64	70.08	70.17	7.28	7.07	9.85	9.75	27	3.1
$C_6H_5(CH_2)_3$–	CH_3CO–	$C_{22}H_{27}NO_2$·HCl	182.6–185.8	63	70.68	70.40	7.55	7.79	9.48	9.32	142	6.6
$C_6H_5(CH_2)_4$–	CH_3CO–	$C_{23}H_{29}NO_2$·HCl	199.0–200.0	56.4	71.21	71.12	7.80	7.67	9.14	8.83	39	5.5
C_6H_5CH=$CHCH_2$–	CH_3CO–	$C_{22}H_{25}NO_2$·HCl	202–203	22.5	71.05	71.06	7.05	7.24	9.53	9.43	189	10.3
$C_6H_5O(CH_2)_3$–	CH_3CO–	$C_{22}H_{27}NO_3$·HCl	196.4–197.4	16.5	67.77	67.86	7.24	7.22	9.09	8.87	118	6.3
$C_6H_5CH_2$[b]	CH_3CH_2CO–	$C_{21}H_{25}NO_2$·HCl	189–189.8	63	70.08	70.25	7.28	7.47	9.85	9.81	1.4	..
$C_6H_5(CH_2)_2$–	CH_3CH_2CO–	$C_{22}H_{27}NO_2$·NH_2SO_3H	160.8–164	66.5	60.81	60.65	6.96	7.36	6.50[a]	6.34[a]	69	6.2
$C_6H_5(CH_2)_3$–	CH_3CH_2CO–	$C_{23}H_{29}NO_2$·HCl	176.2–177.8	60.5	71.21	71.27	7.80	8.01	9.14	9.06	637	9.7
$C_6H_5(CH_2)_4$–	CH_3CH_2CO–	$C_{24}H_{31}NO_2$·HCl	173.0–175.8	51.5	71.70	71.87	8.03	8.04	8.82	8.64	108	2.8
C_6H_5CH=$CHCH_2$–	CH_3CH_2CO–	$C_{23}H_{27}NO_2$·HCl	182.6–184	50	71.58	71.79	7.31	7.56	9.19	8.97	785	7.6
Morphine											7.9	

[a] Analysis for nitrogen. [b] Ziering, *et al.*, *J. Org. Chem.*, **12**, 894 (1947). [c] Activity (±10%) relative to meperidine = 1 on a molar basis; by injection of rats subcutaneously. [d] Toxicity relative to meperidine = 1.0 on a milligram basis; by injection of rats intravenously.

were removed under vacuum; finally an oil-pump was used to remove the last traces of low boiling material. There was obtained 394 g. (98% of theory) of the bis-ester which was used without purification in the next step.

1-Cinnamyl-4-piperidone.—Sodium hydride (24 g., 1 mole) was suspended in 850 ml. of dry benzene, warmed to 70° and 134 g. (0.45 m.) of the bis-ester carefully added during a 0.75-hour period. (Care must be taken during the beginning of this addition since the reaction is sometimes slow in starting and considerable foaming may take place.) After allowing to reflux for an additional 90 minutes, the reaction mixture was cooled in an ice-bath, and then 300 ml. of water added carefully and then 150 ml. of concentrated hydrochloric acid. After transferring to a separatory funnel, the lower oil layer was drawn off along the intermediate acidic layer. The benzene layer was further washed with 100 ml. of water containing 50 ml. of concentrated hydrochloric acid. The combined acid layers and oil were refluxed for five hours, cooled in an ice-bath and made alkaline with 35% sodium hydroxide solution. The resulting oil was removed by three benzene extractions, the combined extracts washed with water and the solvent removed under vacuum. The residual oil was distilled to give 66 g. (70% of theory) of 1-cinnamyl-4-piperidone boiling at 138–140° (0.3 mm.).

1-Cinnamyl-4-phenyl-4-propionoxypiperidinium Sulfamate.—Lithium metal (5.55 g., 0.8 g. atom) was cut into short pieces and suspended in 700 ml. of dry ether. Dry bromobenzene (42.5 ml., 0.405 mole) was added slowly during 30 minutes allowing the heat of reaction to cause reflux. After refluxing an additional hour, the reaction mixture was cooled and a solution of 78 g. (0.363 m.) of 1-cinnamyl-4-piperidone in 100 ml. of dry benzene added during 30 minutes, then an additional 600 ml. of dry benzene. The reaction mixture now was refluxed for one hour, cooled in an ice-bath and 130 ml. (1.06 moles) of propionic anhydride added during 15 minutes. The contents of the flask was then heated to reflux temperature, the heat was removed and stirring continued for an additional 30 minutes. The reaction mixture was cooled in an ice-bath, 250 ml. of water was added carefully under a nitrogen atmosphere, and then sufficient 35% sodium hydroxide to render the aqueous layer strongly alkaline. The aqueous layer was separated, extracted with benzene and the combined organic layers were washed three times with water. The solvent was removed under vacuum yielding a semi-solid residue. The solid was removed by filtration and the filtrate concentrated to a clear amber oil weighing 113 g. The oil was dissolved in 250 ml. of isopropyl alcohol and acidified with concentrated hydrochloric acid. The solvent was removed under vacuum, the residue taken up in 150 ml. of ethyl acetate and placed in an ice-bath. The resultant crude hydrochloride weighing 24 g. was suspended in water, covered with benzene and made alkaline with 35% sodium hydroxide. The aqueous layer was separated, extracted once with benzene and the combined benzene layers were washed with water; 21 g. of the free base remained after the solvent was removed under vacuum. This base was taken up in 100 ml. of isopropyl alcohol and 5.78 g. of sulfamic acid in 25 ml. of water added. The resulting solution was concentrated to dryness under vacuum, the residue dissolved in 75 ml. of hot ethanol and then cooled in an ice-bath. There was obtained 25 g. (15.5%) of 1-cinnamyl-4-phenyl-4-propionoxypiperidinium sulfamate.

1-(N-Benzyl-N-methylamino)-2-propanol.—Benzylmethylamine (242.4 g., 2 moles) and propylene oxide (232 g., 2 m.) were combined and placed in an autoclave. After heating for 5 hours at 100° and 100 pounds pressure, the mixture was concentrated to a dark oil and distilled *in vacuo*. There was obtained 334.4 g. (93.4% of theory) of the desired tertiary amine boiling at 152–158° (28 mm.), $n^{25}D$ 1.5070.

Anal. Calcd. for $C_{11}H_{17}NO$: N, 7.81. Found: N, 7.82.

1-(N-Benzyl-N-methylamino)-2-chloropropane Hydrochloride.—1-(N-Benzyl-N-methylamino)-2-propanol (334 g., 1.86 moles) was dissolved in chloroform (800 ml.) and saturated with dry hydrogen chloride. Thionyl chloride (310 g., 2.6 moles) was added at such a rate that refluxing was maintained spontaneously. After the addition was completed, refluxing was continued for an additional hour. The reaction mixture was concentrated to dryness *in vacuo* and the residue was taken up in hot absolute ethanol (700 ml.). On pouring into ether (4 l.) there was obtained a

product, which after drying weighed 404 g. (92.6% of theory) and melted at 158–161°.

Anal. Calcd. for $C_{11}H_{17}Cl_2N$: Cl, 30.28. Found: Cl, 30.15.

4-(N-Benzyl-N-methylamino)-2,2-diphenyl-4(or 3)-methylbutane Nitrile.—Sodamide (39 g., 1 mole) was suspended in dry benzene (300 ml.). Diphenylacetonitrile (193 g., 1 mole) dissolved in benzene (500 ml.) was added all at once and the resultant blood-red mixture heated at 60–70° for about 2 hours or until the sodamide was consumed. 1-(N-Benzyl-N-methylamino)-2-chloropropane hydrochloride (234 g., 1 mole) was treated to liberate the free base which was taken up in dry benzene (500 ml.). This solution was added to the solution of sodium diphenylacetonitrile at such a rate as to maintain refluxing. When the addition was completed, refluxing was continued for another two hours at which time the mixture was a cloudy light brown. The contents of the flask were cooled to room temperature, water (200 ml.) was carefully added, the organic layer separated, washed with water and concentrated to a red oil *in vacuo*. On distillation there was obtained 311 g. of viscous yellow oil boiling at 160–165° (0.02 mm.). The oil turned to a mush which was taken up in boiling ethanol (500 ml.). On cooling there was obtained 134 g. (37.5% of theory) of a product designated A which melted at 105–106°. The hydrochloride melted at 173–175°.

Anal. Calcd. for $C_{25}H_{26}N_2$: C, 84.70; H, 7.40; N, 7.91. Found: C, 84.67; H, 7.13; N, 7.92.

The filtrates from which A was isolated were concentrated to an oil. The oil was taken up in ether and converted to the hydrochloride. After crystallization from isopropyl alcohol there was obtained 161.5 g. (39% of theory) of a product designated B which melted at 186–190°. This was converted to the hydrobromide and crystallized from ethanol–cyclohexane to give a product melting at 188–190°.

Anal. Calcd. for $C_{25}H_{27}BrN_2$: C, 68.96; H, 6.25; Br, 18.35. Found: C, 68.67; H, 6.60; Br, 18.30.

The isomer designated A was used in the ensuing preparations.

2,2-Diphenyl-4(or 3)-methyl-4-(methylamino)-butane Nitrile.—A mixture of 4-(N-benzyl-N-methylamino)-2,2-diphenyl-4(or 3)-methylbutane nitrile (59 g., 0.17 mole), sodium acetate (1 g.), charcoal (3 g.), palladium chloride (1 g.), acetic acid (50 ml.), water (15 ml.) and sufficient ethanol to make a final volume of 150 ml. was hydrogenated at room temperature and low pressure. The reduction was completed in one hour. The reaction mixture was filtered and the filtrate concentrated *in vacuo*. The resultant oil was made basic with ammonium hydroxide. The mixture was extracted with benzene and the organic extract washed with water, dried and concentrated to a yellow oil which solidified overnight. The solid was distilled, boiling at 130–135° (0.01 mm.), and the distillate crystallized; 41 g. (94%) of the desired debenzylated amine was obtained melting at 103–105°.

Anal. Calcd. for $C_{18}H_{20}N_2$: N, 10.60. Found: N, 10.65.

4-(N-Cinnamyl-N-methylamino)-2,2-diphenyl-4(or 3)-methylbutane Nitrile.—2,2-Diphenyl-4-methylamino-4(or 3)-methylbutanenitrile (40 g., 0.15 mole), cinnamyl bromide (30 g., 0.15 mole), ethanol (200 ml.) and sodium carbonate (40 g.) were refluxed together for 20 hours. The insoluble salts were removed by filtration. The filtrate was concentrated to an amber oil, taken up in benzene (200 ml.) and filtered free of a little more salt. The solvent was removed and an amber oil was obtained which on distillation gave 18 g. (31%) of oil boiling at 170–190° (0.01 mm.).

Anal. Calcd. for $C_{27}H_{28}N_2$: N, 7.36. Found: N, 7.24.

1-(N-Cinnamyl-N-methylamino)-3,3-diphenyl-1(or 2)-methyl-4-hexanone Hydrochloride.—Ethylmagnesium bromide was prepared from ethyl bromide (17.5 g., 0.16 mole), magnesium turnings (3.9 g., 0.16 g. atom) and ether (60 ml.). A solution of 4-(N-cinnamyl-N-methylamino)-4(or 3)-methyl-2,2-diphenylbutanenitrile (15.2 g., 0.04 mole) in toluene (200 ml.) was added to the Grignard reagent and the resultant mixture warmed to drive off the ether. The reaction mixture was heated at 110° for 3 hours to give a bright yellow suspension which was poured carefully, while still hot, into a mixture of concentrated hydrochloric acid (32 ml.) and water (980 ml.). The three-phase mixture was transferred to a separatory funnel and the middle oily layer separated. It was then made alkaline, extracted with benzene, the organic layer washed with water, and the solvent removed *in vacuo* to give an oil; 3 ml. of concentrated hydrochloric acid in absolute ethanol (100 ml.) was added and the solution concentrated to dryness *in vacuo*. Several crystallizations from ethanol gave 1 g. (5% of theory) of the desired product melting at 146–148°.

Anal. Calcd. for $C_{29}H_{34}ClNO$: C, 77.73; H, 7.65; Cl, 7.91. Found: C, 77.62; H, 7.60; Cl, 7.84.

Ethyl 3-(N-Cinnamyl-N-methyl)-aminobutyrate.—A mixture of ethyl 3-methylaminobutyrate (65 g., 0.45 mole) and cinnamyl bromide (43 g., 0.22 mole) was heated on a steam-bath for 16 hours. The reaction mixture was cooled, water (100 ml.) was added and the resultant mixture extracted repeatedly with ether. The ethereal extract was concentrated and the residual oil distilled. There was obtained 22.8 g. (42%) of the desired product, b.p. 108–109° (0.05 mm.), $n^{25}D$ 1.5208.

Anal. Calcd. for $C_{16}H_{23}NO_2$: C, 73.55; H, 8.87; N, 5.36. Found: C, 73.47; H, 8.81; N, 5.33.

3-(N-Cinnamyl-N-methyl)-amino-1,1-di-(2-thienyl)-butane-1-ol.—Lithium wire (0.85 g., 0.12 g. atom) was suspended in ether (25 ml.). Bromobenzene (9.4 g., 0.06 mole) in ether (25 ml.) was added slowly and the reaction mixture stirred until the lithium was consumed; about 2 hours was required. Thiophene (5 g., 0.06 mole) in ether (10 ml.) was added all at once and the mixture refluxed for 2 hours. The contents of the flask was cooled to −50° and ethyl 3-(N-cinnamyl-N-methyl)-aminobutyrate (4.9 g., 0.018 mole) in ether (10 ml.) was added dropwise. The temperature was maintained between −35 and −25° during the addition. When the addition was completed the temperature was allowed to rise to room temperature overnight. Ice (100 g.) was added and the mixture made acid with acetic acid. A light tan solid was collected, suspended in chloroform, and made alkaline with ammonium hydroxide. The organic layer was separated, and concentrated *in vacuo* on a steam-bath to give an oil which turned solid on trituration with ether. After several crystallizations from *n*-hexane there was obtained 3.5 g. (48%) of the desired product, melting at 101.2–102.6°.

Anal. Calcd. for $C_{23}H_{25}NOS_2$: C, 68.90; H, 6.56; S, 16.72. Found: C, 68.68; H, 6.74; S, 17.12.

3-(N-Cinnamyl-N-methyl)-amino-1,1-di-(2-thienyl)-1-butene.—3-(N-Cinnamyl-N-methyl)-amino-1,1-di-(2-thienyl)-butane-1-ol (8.5 g., 0.02 m.) was dissolved in chloroform (50 ml.) and hydrogen chloride was introduced for 15 minutes. The mixture then was concentrated to dryness *in vacuo* on a steam-bath. Concentrated ammonium hydroxide was added to the residue and the mixture was extracted with chloroform. When the solvent was removed from the extract a black tar was obtained. On distillation there was obtained 5.7 g. of yellow-green fluorescent oil, b.p. 150° (0.02 mm.), which crystallized after standing several days. Trituration with ether gave a white solid which could be crystallized from cyclohexane. There was obtained 1.3 g. (16%) of product melting at 153–165.5°.

Anal. Calcd. for $C_{23}H_{23}NS_2$: C, 72.30; H, 6.34; S, 17.64. Found: C, 71.87; H, 6.64; S, 17.52.

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