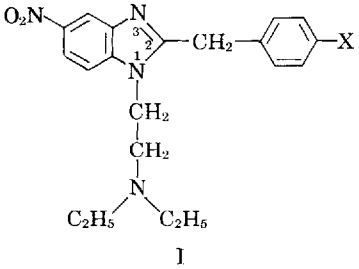
Synthetic Analgesics I

N-(2-Dialkylaminoethyl)-2-phenylacetanilides

By JAMES F. STUBBINS* and TAITO O. SOINE

A series of 24 *N*-(2-dialkylaminoethyl)-2-phenylacetanilides was prepared for testing as potential analgesics. The structure of these compounds can be related to certain nitrobenzimidazole and propionanilide analgesics. The compounds were prepared by treating *N,N*-dialkyl-*N'*-phenyl- or *N,N*-dialkyl-*N'*-(*p*-nitrophenyl)-ethylenediamine hydrochlorides with various phenylacetyl chlorides. The products were obtained as the hydrochloride or perchlorate salts. The previously unknown intermediates—*p*-ethoxyphenylacetyl chloride, *N,N*-dimethyl-*N'*-(*p*-nitrophenyl)-ethylenediamine hydrochloride, and 1-[(*p*-nitroanilino)-ethyl]-piperidine hydrochloride—also are described.

HUNGER *et al.*, in 1957, reported the synthesis of some nitrobenzimidazole derivatives (I) possessing very significant analgesic activity (1). These compounds differ rather radically in structure from other potent analgesics. The degree of activity in this series of compounds is highly dependent upon the *p*-substituent in the benzyl moiety. I*c* and I*d* are 100 and 1000 times as potent as morphine, respectively (2), the latter compound being the most active analgesic known at that time. The unsubstituted (I*a*) or chloro-substituted (I*b*) compounds are only slightly more active than morphine. The nitro group in the 5 position of the benzimidazole ring appears to be an essential feature in this series; if the nitro group is removed or moved to a different position of the ring, activity is markedly reduced or abolished. Another peculiarity of these compounds is that the diethylamino moiety in the basic side chain seems to lead to higher activity than a dimethylamino or heterocyclic amino group.

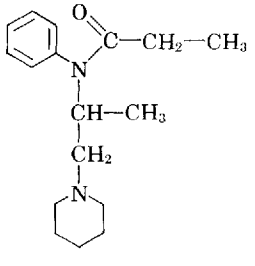


I*a*, X = H
b, X = Cl
c, X = OCH_3
d, X = OC_2H_5

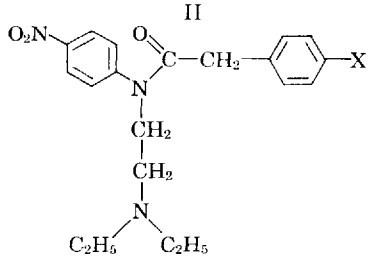
I

Later Wright *et al.* reported that a series of propionanilides showed analgesic properties (3, 4). A typical member of this series is phenampromid (II). These propionanilides resemble the methadone analgesics except that they contain one less phenyl ring and that the usual quaternary carbon atom has been replaced by a tertiary nitrogen atom.

If it is assumed that the carbon-nitrogen double bond of the imidazole ring can simulate a carbonyl group, then the nitrobenzimidazole and propionanilide analgesics may be closely related. Opening of the imidazole ring of I between the benzene ring and the 3 position and replacement of the N^3 nitrogen atom by oxygen leads to compounds of general structure III. This is seen to differ from the propionanilide-type only in the replacement of the propionyl group by the phenylacetyl group and by the added nitro group. Structure III has served as the model for the present series of compounds.



II



III

The structure of III was varied at X to provide compounds for comparison with the active benzimidazoles; thus, X may be a hydrogen, chloro, methoxy, or ethoxy group. In addition, compounds were prepared lacking the nitro group

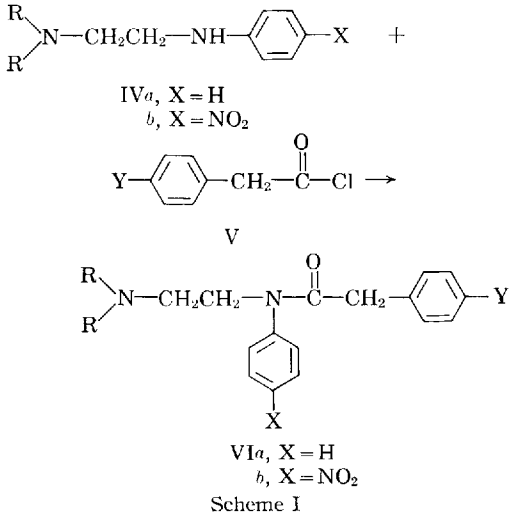
Received September 14, 1965, from the Department of Pharmaceutical Chemistry, College of Pharmacy, University of Minnesota, Minneapolis.
Accepted for publication June 28, 1966.
Presented to the Scientific Section, A.PH.A., Detroit meeting, March 1965.
This investigation was supported in part by a research fellowship (1961–1962) from Rowell Laboratories, Baudette, Minn.
* Present address: School of Pharmacy, Medical College of Virginia, Richmond.

and having dimethylamino or piperidino groups in place of the diethylamino group of the model. It was felt that the special requirements for the nitro and diethylamino groups in the benzimidazole analgesics might be peculiar to that ring system and might be unnecessary in non-benzimidazole analogs.

Thus, all combinations of the variations mentioned yield a set of 24 compounds of general structure (VI). It was hoped that the synthesis and testing of these compounds would establish more structure–activity relationship in this area and that, perhaps, a bridge linking the benzimidazole analgesics to others could be found.

DISCUSSION

In the first attempts to prepare the phenylacetanilides, *N,N*-diethyl-*N'*-phenylethylenediamine (IV*a*, R = C_2H_5) and *N,N*-diethyl-*N'*-(*p*-nitrophenyl)-ethylenediamine (IV*b*, R = C_2H_5) were treated with phenylacetyl chloride in benzene. In both cases large amounts of tar were obtained, and most of the diamine could be recovered. No amide was detected in repeated trials. (Scheme I.)



Scheme I

When phenylacetic anhydride was employed in place of the acid chloride, the desired amides (VI*a* and *b*, R = C_2H_5; Y = H) were obtained in low yield. The products were isolated as the free bases. VI*b* (R = C_2H_5, Y = H) was converted to the hydrochloride salt. All attempts to obtain a salt of VI*a* (R = C_2H_5, Y = H) with various organic and inorganic acids failed to yield a solid until a crystalline perchlorate was prepared according to the method of Caudle *et al.* (5).

The substituted phenylacetic anhydrides required proved to be difficult to obtain in a pure state. Therefore, attempts were made to prepare the amide directly from the acid by use of the "mixed anhydride" methods. Both the sulfonic acid (6) and carbonic acid (7) anhydride methods failed to yield amide. Numerous attempts employing dicyclohexylcarbodiimide (8) as a condensing agent also failed.

When the diamines were treated with the acid chlorides (V), dehydrohalogenation might have occurred in preference to amide formation. To avoid this difficulty, the hydrochloride salt of the diamines (IV) was used in place of the free base. When the various substituted ethylenediamine hydrochlorides were treated with phenylacetyl or *p*-substituted phenylacetyl chlorides in benzene, the phenylacetanilides were obtained as the hydrochloride salts. If the hydrochloride salt would not crystallize, the free base was isolated and converted to the perchlorate salt. All 24 of the desired compounds were obtained by this procedure (Table I). The crude products usually were badly contaminated with the starting material, and purification frequently was difficult. In a few cases the product was soluble in the hot benzene and slowly separated upon cooling, resulting in a much cleaner product.

The structural assignment of the products is supported by the microanalyses and the infrared spectra. All the compounds have a prominent band near 6.0 μ typical of tertiary amides (9). Since this work was started, compound *11* (as the free base) was reported in an Austrian patent (10). It was one of a series of compounds described for use as "narcotic and analgesic drugs," but no pharmacological results were given.

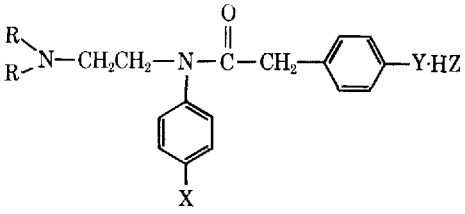
The acid chlorides required were prepared by the method of Elderfield and Meyer (11). *p*-Ethoxyphenylacetyl chloride was the only one not previously known. The intermediate *N,N*-dialkyl-*N'*-phenylethylenediamines were synthesized by condensing dialkylaminoethyl chlorides with aniline according to the method of Stahmann and Cope (12). All the hydrochloride salts have been reported previously (4). However, this method is unsatisfactory for the *N,N*-dialkyl-*N'*-(*p*-nitrophenyl)-ethylenediamines. These were prepared by arylation of *N,N*-dialkylethylenediamines with *p*-nitrochlorobenzene by modification of the method of Mann *et al.* (13). Pyridine was used as solvent and proton acceptor. *N,N*-Diethyl-*N'*-(*p*-nitrophenyl)-ethylenediamine hydrochloride previously has been reported (12).

PHARMACOLOGICAL RESULTS[1]

All of the products were screened initially for possible analgesic activity by the phenyl-*p*-quinone writhing test (14). The compounds were given orally at a dose of 100 mg./Kg. to mice. Compounds *2*, *3*, *5*, *7*, *11*, *14*, *20*, *21*, and *24* (Table I) reduced writhing by at least 50%. These nine compounds were then tested in rats by the D'Amour–Smith procedure (15). At an interperitoneal dose of 25 mg./Kg., only compound *2* increased response time by at least 50%. This is not the compound expected to have the most activity based on comparison with the benzimidazole or propionanilide analgesics. The general lack of activity in the phenylacetanilides is disappointing in view of their close relationship to compounds of significant activity. This would seem to indicate that the benzimidazole ring is an essential feature of that class of analgesics, and that

[1] The authors are indebted to the Pharmacology Department, Lederle Laboratories, Pearl River, N. Y., for the pharmacological results.

TABLE 1.—*N*-(2-DIALKYLAMINOETHYL)-2-PHENYLACETANILIDES



Compd.	R_2N	X	Y	Z	M.p., °C.	Solvent[a]	Anal. C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
1	Dimethylamino	H	H	Cl	211–213	H–B	67.80	67.76	7.27	7.30	8.78	8.69
2	Dimethylamino	H	Cl	Cl	118–183	H–B	61.10	61.14	6.28	6.31	7.93	8.05
3	Dimethylamino	H	OCH_3	Cl	159–161	D	65.40	65.73	7.22	7.02	8.03	8.18
4	Dimethylamino	H	OC_2H_5	Cl	162–163.5	D	66.19	66.01	7.50	7.10	7.72	7.63
5	Dimethylamino	NO_2	H	Cl	185–187	E	59.41	59.36	6.10	6.24	11.55	11.20
6	Dimethylamino	NO_2	Cl	Cl	159–161	D	54.28	54.10	5.32	5.57	10.55	10.68
7	Dimethylamino	NO_2	OCH_3	Cl	203–205	B	57.93	58.24	6.14	6.27	10.67	10.47
8	Dimethylamino	NO_2	OC_2H_5	Cl	163–164	I–B	58.89	58.80	6.43	6.51	10.30	10.28
9	Diethylamino	H	H	ClO_4	106–107	B	58.46	58.44	6.62	6.66	6.82	6.76
10	Diethylamino	H	Cl	ClO_4	106–108	B	53.94	53.93	5.89	5.87	6.29	6.38
11	Diethylamino	H	OCH_3	ClO_4	119–120	B	57.20	56.90	6.63	6.53	6.35	6.38
12	Diethylamino	H	OC_2H_5	ClO_4	80–82	B/F	58.08	57.90	6.87	6.72	6.16	6.11
13	Diethylamino	NO_2	H	Cl	195–196.5	G–B	61.29	61.12	6.69	6.75	10.72	10.40
14	Diethylamino	NO_2	Cl	Cl	179.5–181	D–I	56.34	56.54	5.91	6.05	9.86	10.01
15	Diethylamino	NO_2	OCH_3	Cl	99–101	C/K	59.78	60.04	6.69	6.47	9.96	9.34
16	Diethylamino	NO_2	OC_2H_5	Cl	129–130.5	J/I	60.61	60.34	6.94	7.09	9.64	9.36
17	Piperidino	H	H	Cl	216–218	D–A	70.27	70.21	7.58	7.54	7.81	7.70
18	Piperidino	H	Cl	Cl	149–150.5	D–H	64.12	64.01	6.66	6.77	7.12	7.33
19	Piperidino	H	OCH_3	Cl	137–139	D–H	67.93	68.02	7.52	7.78	7.20	7.50
20	Piperidino	H	OC_2H_5	ClO_4	105–105.7	B/F	59.15	59.38	6.69	6.66	6.00	5.82
21	Piperidino	NO_2	H	Cl	195–197	G–H	62.44	62.76	6.49	6.50	10.41	10.39
22	Piperidino	NO_2	Cl	Cl	194–196	I/G	57.33	57.02	5.75	5.83	9.59	9.59
23	Piperidino	NO_2	OCH_3	Cl	132–134	H/P	60.89	60.58	6.50	6.32	9.69	9.74
24	Piperidino	NO_2	OC_2H_5	Cl	98–100	H	61.66	61.61	6.75	6.99	9.38	9.52

[a] Solvent: A, methanol; B, ethanol; C, acetone; D, methyl ethyl ketone; E, methyl isobutyl ketone; F, diethyl ether; G, tetrahydrofuran; H, ethyl acetate; I, chloroform; J, benzene; K, hexane. A–B, product dissolved in boiling mixture of solvents A and B. A/B, product dissolved in boiling solvent A and reprecipitated by addition of solvent B.

the activity of that group of compounds is unrelated to other morphine-like analgesics. However, the recent suggestion by Portoghese (16) that analgesics may bind to one site in more than one way must be considered. Thus, the benzimidazole and propionanilide analgesics may bind to the same site by different modes. Then a hybrid structure such as the phenylacetanilide may not be well suited for binding by either mode or may bind by still a third mode which does not lead to the analgesic response.

EXPERIMENTAL

All melting points were obtained on a Thomas-Hoover capillary melting point apparatus and are corrected. All analyses were performed by the University of Minnesota Microanalytical Laboratory or the Scandinavian Microanalytical Laboratory, Herler, Denmark.

p - Ethoxyphenylacetyl Chloride.—*p* - Ethoxyphenylacetic acid (50.0 Gm., 0.280 mole) was dissolved in 100 Gm. (0.840 mole) of thionyl chloride. The solution was stirred at room temperature for 1 hr., then heated on a steam bath for 4 hr. After cooling, the reaction mixture was allowed to stand for 16 hr. more at room temperature. The excess thionyl chloride was removed on a rotary evaporator. The residue was then distilled. The yield was 49.8 Gm. of material boiling at 93–97°/0.7 mm.

N,N - Dimethyl - N' - (p - nitrophenyl) - ethylenediamine Hydrochloride.—To 94.6 Gm. (0.600 mole) of *p*-nitrochlorobenzene suspended in 150 ml. of pyridine was added 52.9 Gm. (0.600 mole) of *N,N*-dimethylethylenediamine. The mixture was stirred and heated under reflux for 24 hr. All of the solid dissolved. The solution was cooled, and most of the pyridine was removed by means of a rotary evaporator. The reddish-brown oil that remained had a bright blue fluorescence. Benzene (200 ml.) was added. The mixture was filtered, and the cake was rinsed with benzene. To the filtrate was added benzene saturated with anhydrous hydrogen chloride in small portions with vigorous stirring. The solid was removed by filtration. The filtrate was again treated with hydrogen chloride in benzene to obtain a further small amount of solid. This solid was filtered off, and the filter cakes were combined and air dried. The yield of crude material was 53.9 Gm.

The product was purified by dissolving it in boiling absolute ethanol, filtering, adding ethyl acetate until precipitation began, and then cooling. Repetition of this process finally yielded bright golden flakes free of any brown coloration. After drying overnight at 110°, the product weighed 32.5 Gm. It melted at 180.5–182.5°.

Anal.—Calcd. for $C_{10}H_{16}ClN_3O_2$: C, 48.88; H, 6.56; N, 17.11. Found: C, 48.77; H, 6.67; N, 17.07.

1 - [2 - (p - Nitroanilino) - ethyl] - piperidine Hydrochloride.—1-(2-Aminoethyl)-piperidine (19.2 Gm., 0.150 mole) and *p*-chloronitrobenzene (23.6 Gm., 0.150 mole) were dissolved in 50 ml. of pyridine. The solution was stirred and heated under reflux for 36 hr. The solution was cooled, and most of the pyridine was removed *in vacuo*. The dark oily residue was dissolved in 100 ml. of benzene. Benzene, saturated with hydrogen chloride, was added in small portions with vigorous stirring until

precipitation was complete. The slurry was filtered, and the filter cake was washed with cold benzene. The crude product weighed 23.6 Gm.

The product was recrystallized once from an ethanol–ethyl acetate mixture, then twice from tetrahydrofuran. The pure material consisted of shiny, golden flakes melting at 207–209°. The yield was 12.8 Gm.

Anal.—Calcd. for $C_{13}H_{20}ClN_3O_2$: C, 54.63; H, 7.05; N, 14.71. Found: C, 54.93; H, 7.23; N, 14.41.

N - (2 - Dialkylaminoethyl) - 2 - phenylacetanilides.—From 0.020–0.030 mole of substituted ethylenediamine hydrochloride was suspended in 100–150 ml. of benzene. The appropriate acid chloride was added in 10–25% molar excess. The suspension was stirred and heated under reflux 24–72 hr. The mixture was cooled and filtered. The crude product was recrystallized from the appropriate solvent (Table I).

In a few instances the product was soluble in the benzene even after cooling. In these cases, an equal volume of petroleum ether was added to force the salt out of solution.

If the crude hydrochloride salt was liquid and could not be induced to crystallize, it was dissolved in dilute hydrochloric acid and neutralized with 10% sodium hydroxide solution. The free base was extracted into ether. The ethereal solution was dried, and the ether was removed *in vacuo*. The residual base was converted to the perchlorate salt by the method of Caudle *et al.* (5).

REFERENCES

(1) Hunger, A., Keberle, J., Rossi, A., and Hoffman, K., *Experientia*, **13**, 400(1957).
(2) Gross, F., and Turrian, H., *ibid.*, **13**, 401(1957).
(3) Wright, W. B., Jr., Brabander, H. J., and Hardy, R. A., Jr., *J. Am. Chem. Soc.*, **81**, 1518(1959).
(4) Wright, W. B., Jr., Brabander, H. J., and Hardy, R. A., Jr., *J. Org. Chem.*, **26**, 476(1961).
(5) Caudle, R. D., Robson, B. J., and Moshier, R. W., *J. Am. Chem. Soc.*, **71**, 2928(1949).
(6) Brewster, J. H., and Ciotti, C. J., Jr., *ibid.*, **77**, 6214(1955).
(7) Boissonnas, R. A., *Helv. Chim. Acta*, **34**, 874(1951).
(8) Sheehan, J. C., and Hess, G. P., *J. Am. Chem. Soc.*, **77**, 1067(1955).
(9) Bellamy, L. J., "The Infrared Spectra of Complex Molecules," 2nd ed., John Wiley & Sons, Inc., New York, N. Y., 1958, p. 209.
(10) Austrian pat. 221,508 (1962); through *Chem. Abstr.*, **57**, 11115(1962).
(11) Elderfield, R. C., and Meyer, V. B., *J. Am. Chem. Soc.*, **76**, 1883(1954).
(12) Stahmann, M. A., and Cope, A. C., *ibid.*, **68**, 2494(1946).
(13) Mann, F. G., Naylor, F. T., and Porter, J. W. G., *J. Chem. Soc.*, **1947**, 914.
(14) Siegmund, E., Cadmus, R., and Lu, G., *Proc. Soc. Exptl. Biol. Med.*, **95**, 729(1957).
(15) D'Amour, F. E., and Smith, D. L., *J. Pharmacol. Exptl. Therap.*, **72**, 74(1941).
(16) Portoghese, P. S., *J. Pharm. Sci.*, **54**, 1077(1965).

Synthesis of 4-Substituted-7-methylpyrrolo[2,3-*d*]pyrimidines

By RICHARD H. HAMMER

The reactions of 4-chloro-7-methyl-7H-pyrrolo[2,3-*d*]pyrimidine (IV) with ethanolic ammonia, thiourea, and aqueous sodium sulfhydrate solution to give the 4-amino (V) and 4-thione (VI) analogs are described. Ultraviolet data and pKa values for IV, V, and VI are reported.

TUBERCIDIN (I*a*), a naturally occurring nucleoside in streptomyces species (1, 2), has been assigned the structure 4-amino-7-β-D-ribofuranosyl-7H-pyrrolo[2,3-*d*]pyrimidine (7-deazaadenosine) (3–5). It is an inhibitor of several tumor systems, not cross-resistant to 6-mercaptopurine-resistant line tumor systems (6), and incorporated into both DNA and RNA of mouse fibroblasts and several viruses (7, 8). During structural elucidation studies of tubercidin (I*a*), hydrolysis of I*a* to the aglycone (I*b*) and D-ribose was accomplished by refluxing I*a* in 1–3 *N* HCl for 5 hr. (4). From these data the base ribose bond of I*a* appears to be more resistant to acid hydrolysis than a purine base-ribose bond. Subsequently, resistance of I*a* to enzymatic cleavage by *E. coli* nucleoside phosphorylase was demonstrated while 6-mercaptopurine riboside was observed to be rapidly cleaved (9). Significance of the stability of the pyrrolo[2,3-*d*]pyrimidine base-ribose bond in relation to drug distribution and cancer chemotherapy remains to be explained.

Recent studies by Montgomery and Hewson (10, 11) on the cell culture cytotoxicity of 6-mercaptopurine and 6-mercaptopurine-deaza analogs suggests that deaza structures such as 6-mercapto-7-deazapurine (11–13) are not metabolized by the cells to the ribotide form and consequently are 300–500 times less active than 6-mercaptopurine which is readily converted to the ribotide. This raises the question as to whether antitumor activity for pyrrolo[2,3-*d*]-pyrimidine structures may be dependent on a substituent such as a sugar group, cycloalkyl or alkyl group on the 7-nitrogen (corresponding to the 9-position of purine). This is evident by the fact that tubercidin (I*a*) with a β-D-

Received April 25, 1966, from the Department of Pharmaceutical Chemistry, College of Pharmacy, University of Florida, Gainesville.
Accepted for publication July 18, 1966.
Presented to the Medicinal Chemistry Section, A.PH.A. Academy of Pharmaceutical Sciences, Dallas meeting, April 1966.
This investigation was supported from an American Cancer Society Institutional Grant to the University of Florida.
The author thanks D. Shah for his technical assistance.