New Compounds: Synthesis of Certain *p*-Alkoxyphenylacetamide Derivatives as Potential Analgesic Agents

A. A. ABOU OAUF, M. A. ELDAWY*, and H. H. FARAG

Abstract □ A recent pharmacological screening of certain *p*-alkoxyphenylacetamides revealed their analgesic activity. This communication outlines the synthesis of some related compounds involving certain analgesically active pharmacophores which are thought to increase potency and decrease toxicity.

Keyphrases □ *p*-Alkoxyphenylacetamide derivatives—synthesized as potential analgesic agents □ Analgesic agents, potential—*p*-alkoxyphenylacetamide derivatives synthesized □ IR spectrophotometry—structure, identification

Nguyen *et al.* (1) investigated a series of *p*-alkoxyphenylacetohydroxamic acids. They found that the *p*-butoxyphenylacetohydroxamic acid (I) has anti-inflammatory activity and that its high analgesic potency exceeds that of aspirin, aminopyrine, and phenacetin.

In an extension of their investigation (2), it was found that the replacement of the hydroxamic acid moiety by an amide group abolishes the anti-inflammatory activity and enhances the analgesic potency. Experimental pharmacometrics proved that the *p*-*n*-butoxyphenylacetamide (II) is the derivative of choice.

This report describes the synthesis of certain new compounds designed to have the recently reported phenylacetamide moiety embodied together with other analgesically active pharmacophores in one and the same molecule.

The described compounds were prepared by condensation of the properly substituted acyl chlorides with the appropriate amines (3). The corresponding parent acids were synthesized by application of Willgerodt's reaction (4) on the respective *p*-alkoxyphenylketones. The latter were obtained *via* the Fries rearrangement (5) of the corresponding acyl phenols. The original conditions of the Fries rearrangement were modified to increase the yield of the desired *p*-substituted phenols. The synthesis was carried out as shown in Scheme I.

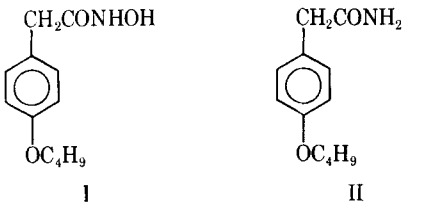
The structures of the prepared compounds (Table I) were assigned on the bases of reaction mechanisms, microanalytical data, and IR spectra (6).

EXPERIMENTAL[1]

4-Hydroxyacetophenones—These compounds were prepared according to the method of organic reactions (7), increasing the amount of nitrobenzene solvent and controlling the temperature throughout the reaction time so that it did not exceed 40°. This method led to a higher percentage of the desired *p*-isomers.

4-Alkoxyacetophenones—These compounds were prepared by Williamson's etherification synthesis (8) of the corresponding phenols with the appropriate alkyl halides.

4-Alkoxyphenylacetic Acids—In a 250-ml. round-bottom flask, 0.013 mole of 4-alkoxyacetophenone was mixed with 0.2 mole of morpholine and 0.19 mole of sulfur. The mixture was refluxed on an oil bath at 130° for 14 hr. and then poured slowly as a thin stream on cold water while being stirred until the yellowish mass, which was initially formed (crude *p*-alkoxyphenylthioacetomorpholide), solidified.



I II

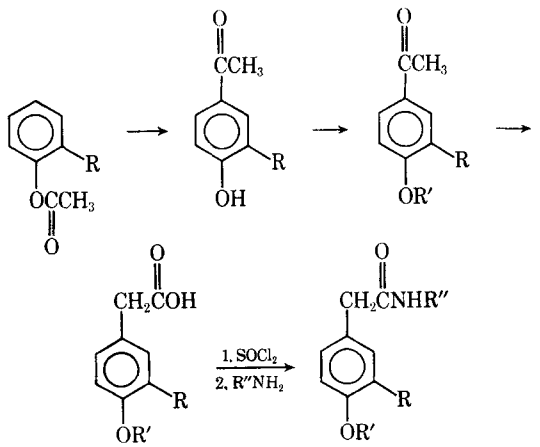
The crude product was isolated and triturated in a mortar with 20 ml. of water, filtered, and then refluxed with 250 ml. of 10% alcoholic sodium hydroxide in a 500-ml. round-bottom flask for 10 hr. Alcohol was then distilled over, and the residue was gradually acidified with dilute hydrochloric acid. The crude *p*-alkoxyphenylacetic acid was extracted with ether and obtained in a crude form after recovery of ether; it was then crystallized from *n*-hexane.

IR spectral analysis showed a broad peak in the range of 3300–2900 cm.$^{-1}$, which is usually assigned to hydrogen-bonded O—H stretching of —COOH, and an acid —CO— band around 1700 cm.$^{-1}$, and an ether —C—O—C band around 1250 cm.$^{-1}$.

4-Alkoxyphenylacetamide—(*A*) *Acid Chlorides*—In a 250-ml. round-bottom flask, fitted with a reflux condenser and a gas trap, 0.048 mole of 4-alkoxyphenylacetic acid was treated with 0.065 mole of thionyl chloride. Effervescence immediately occurred, and the mixture slowly changed into a greenish liquid. After gases ceased to evolve, the mixture was warmed gently and then heated on a water bath for about 1 hr. or until no more gases evolved. Excess thionyl chloride was removed by distillation under vacuum.

The produced acid chloride was vacuum distilled before being used in condensation with the appropriate amines.

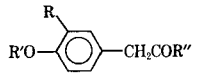
(*B*) *Amides*—In a 100-ml. round-bottom flask, 0.01 mole of the desired amine was dissolved in 10 ml. of ether in which 2.4 g. anhydrous potassium carbonate was suspended. A 0.01-mole solution of *p*-*n*-alkoxyphenylacetyl chloride in ether was added slowly, with constant shaking, to the amine solution. The mixture was then boiled under reflux for 30 min. Ether was distilled, 30 ml. of water was added to the residue, and the mixture was shaken vigorously. The solid was filtered and washed on the filter paper successively with cold dilute sodium hydroxide, water, warm dilute sulfuric acid,

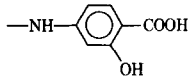
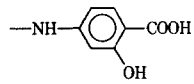


Scheme I

[1] Melting points are uncorrected. Elemental analyses were conducted by Janssen Pharmaceutica, Beerse, Belgium. IR absorption spectra were determined in a Beckman IR spectrophotometer model IR-4 at the Drug Research and Control Center, Cairo, U.A.R.

Table I—*p*-Alkoxyphenylacetamide Derivatives



No.	R	R′	R″	Anal., % Calcd.	Anal., % Found	Yield, %	M.p.[a]
1	H	C_4H_9	—NHC_6H_5	C, 76.32 H, 7.42 N, 4.9	C, 76.40 H, 7.61 N, 5.1	53.0	106–108°
2	H	C_4H_9	*p*-$NHC_6H_4CH_3$	C, 76.76 H, 7.74 N, 4.7	C, 76.75 H, 7.66 N, 4.8	55.2	130–131°
3	H	C_4H_9	*o*-$NHC_6H_4CH_3$	C, 76.76 H, 7.74 N, 4.7	C, 76.82 H, 7.85 N, 4.66	55.0	104–106°
4	H	C_4H_9	*p*-$NHC_6H_4OC_2H_5$	C, 73.39 H, 7.64 N, 4.28	C, 73.45 H, 7.57 N, 4.54	62.5	139–140°
5	H	C_4H_9	*p*-$NHC_6H_4COOC_2H_5$	C, 70.98 H, 7.04 N, 3.94	C, 70.49 H, 6.81 N, 3.97	57.0	132–133°
6	H	C_4H_9		C, 69.31 H, 8.30 N, 5.05	C, 69.53 H, 8.25 N, 5.10	50.0	67–68°
7	H	C_4H_9	—NH—$NHCONH_2$	C, 58.86 H, 7.17 N, 15.80	C, 58.83 H, 7.12 N, 15.58	40.0	178–180°
8	H	C_4H_9	*p*-NHC_6H_4COOH	C, 69.72 H, 6.42 N, 4.25	C, 70.01 H, 6.49 N, 4.45	58.0	264–266°
9	H	C_4H_9		C, 66.46 H, 6.12 N, 4.08	C, 66.22 H, 6.09 N, 3.86	15.5	228–230°
10	H	C_5H_{11}	*p*-NHC_6H_5	C, 76.76 H, 7.74 N, 4.71	C, 76.76 H, 7.70 N, 4.66	54	100–101°
11	H	C_5H_{11}	*p*-NHC_6H_4COOEt	C, 71.54 H, 7.31 N, 3.79	C, 71.60 H, 7.31 N, 3.68	42.0	129–130°
12	H	C_5H_{11}	*p*-$NHC_6H_4CH_3$	C, 77.17 H, 8.03 N, 4.50	C, 77.10 H, 8.08 N, 4.53	45.0	98–99°
13	H	C_5H_{11}	*p*-$NHC_6H_4CH_2COOH$	C, 70.98 H, 7.04 N, 3.90	C, 70.72 H, 7.01 N, 4.00	43.0	179–181°
14	H	C_5H_{11}	*p*-NHC_6H_4COOH	C, 70.38 H, 6.74 N, 4.10	C, 70.21 H, 16.73 N, 4.20	58.0	260–262°
15	H	C_5H_{11}		C, 67.22 H, 6.44 N, 3.92	C, 67.33 H, 7.47 N, 3.70	11.0	227–228°
16	CH_3	C_4H_9	—NH_2	C, 70.58 H, 8.59 N, 6.33	C, 70.16 H, 8.47 N, 6.66	46.0	131–132°
17	CH_3	C_4H_9	*p*-NHC_6H_4COOEt	C, 71.54 H, 7.31 N, 3.80	C, 71.19 H, 7.19 N, 4.00	37.9	135–136°

[a] All melting points are uncorrected.

and water again. The solid was then dried, dissolved in 95% alcohol, decolorized with charcoal, and finally filtered. The alcoholic solution was then concentrated and left to cool. The pure amide separated.

IR spectra showed amide frequency in the range of 3500–3200 cm.$^{-1}$, which was assigned to symmetric and asymmetric N—H stretching of the amide NH_2 group, a —C—O—C— band at 1300–1200 cm.$^{-1}$, and an amide —CO— band at 1675–1575 cm.$^{-1}$.

REFERENCES

(1) M. M. Nguyen, P. Buu-Hoi, G. Lambelin, C. Lepoivre, C. Gillet, M. Cautier, and J. Thiriaux, *Compt. Rend.*, **261**, 2295(1965).

(2) *Ibid.*, **261**, 2907(1965).

(3) A. I. Vogel, "Practical Organic Chemistry," 3rd ed., Wiley, New York, N. Y., 1966, p. 367.

(4) C. Willgerodt, *Chem. Ber.*, **20**, 2467(1887).

(5) R. Adams, "Organic Reactions," vol. I, Wiley, New York, N. Y., 1963, p. 342.

(6) N. B. Colthup, L. M. Daly, and S. E. Wiberley, "Introduction to Infrared and Raman Spectroscopy," Academic, New York, N. Y., 1964.

7) R. Adams, "Organic Reactions," vol. I, Wiley, New York, N. Y., 1963, p. 354.

(8) *Ibid.*, p. 671.

ACKNOWLEDGMENTS AND ADDRESSES

Received August 18, 1969, from the *Department of Pharmaceutical Chemistry, University of Assiut, Assiut, U.A.R.*

Accepted for publication July 28, 1970.

Abstracted from a dissertation submitted by H. H. Farag to the Graduate School, University of Assiut, Assiut, U.A.R., in partial fulfillment of Master of Pharmacy degree requirements.

* To whom all correspondence should be addressed.