Journal of Chemical and Engineering Data, Vol. 24, No. 4, 1979 **379**

Some Amides, Anilides, and Bis(hydrazides) of Expected Biological Activity

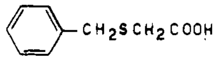
Abou-Elfotooh G. Hammam

National Research Centre, Dokki, Giza, Arab Republic of Egypt

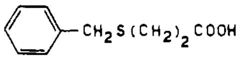
The amides, anilides, toluidides, and bis(hydrazides) of (benzylthio)acetic acid, 3-(benzylthio)propanoic acid, 4-(phenylthio)butanoic acid, 4-(*p*-tolylthio)butanoic acid, 4-(phenylsulfonyl)butanoic acid, 4-(*p*-tolylsulfonyl)butanoic acid, 4-(*o*-chlorophenoxy)butanoic acid, and 4-(*p*-bromophenoxy)butanoic acid were prepared by the reaction of the corresponding acid chlorides with amines, anilines, and hydrazine hydrate, respectively.

It was reported that amides, anilides, toluidides, and bis(hydrazides) possess biological activity (*2*, *4*, *6*). This induced the author to prepare some new amides, anilides, toluidides, and bis(hydrazides) in the hope that they may be absorbed more efficiently when administered orally.

In this work (benzylthio)acetic acid (I) (*3*), 3-(benzylthio)propanoic acid (II) (*1*), 4-(phenylthio)butanoic acid (IIIa), 4-(*p*-tolylthio)butanoic acid (IIIb) (*5*), 4-(phenylsulfonyl)butanoic acid (IVa), 4-(*p*-tolylsulfonyl)butanoic acid (IVb), 4-(*o*-chlorophenoxy)butanoic acid (Va), and 4-(*p*-bromophenoxy)butanoic acid (Vb) were prepared and transformed to the acid chlorides.



I



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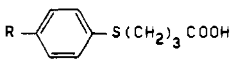

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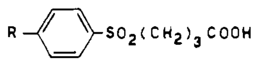

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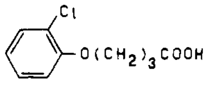
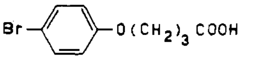


V a



V b

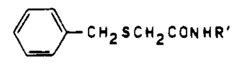
The acid chlorides reacted with the amines to give the amides. The amides VIa, VIIIa,g, and Xa also were prepared directly from the acids by fusion with urea at 180 °C. The IR spectra of the amides where R_1 = H show absorption around 1660 cm^{-1} (CONH) and 3220 and 3450 cm^{-1} (NH), the other amides where R_1 = $(CH_2)_2CH_3$ or $CH_2CH(CH_3)_2$ show absorption around 1650 cm^{-1} (CONH) and 3320 cm^{-1} (NH).

The anilides were prepared from the acid chlorides and aniline and its derivatives. The anilides (VI, VII) show absorption at ca. 1675 cm^{-1} (CONH) and 3340 cm^{-1} (NH) and VIII shows absorption at ca. 1660 cm^{-1} (CONH) and 3310 cm^{-1} (NH), IX at ca. 1670 cm^{-1} (CONH) and 3340 cm^{-1} (NH), and X at ca. 1670 cm^{-1} (CONH) and 3320–3350 cm^{-1} (NH).

Hydrazine hydrate reacted with the acid chlorides to give the bis(hydrazides) (VIe, VIId, VIIIf,l, IXh,p, and Xf,j). Compounds VI and VII show absorption at ca. 1640 cm^{-1} (CONH) and 3280 cm^{-1} (NH) and VIII shows absorption at ca. 1660 cm^{-1} (CONH) and 3290 cm^{-1} (NH), IX at ca. 1640 cm^{-1} (CONH) and 3300 cm^{-1} (NH), and X at ca. 1640 cm^{-1} (CONH) and 3250 cm^{-1} (NH).

The amides, anilides, and bis(hydrazides) are being tested for their biological activity and the results of such tests will be reported elsewhere.

Chart I. (Benzylthio)acetic Acid Derivatives (VI)[a]

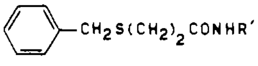


VI

compound	R′	mp, °C	solvent[b]
VIa	H	100	M
b	C_6H_5	70	C
c	$C_6H_4CH_3$-*o*	77	C
d	$C_6H_4CH_3$-*p*	73	C
e	$NHCOCH_2SCH_2C_6H_5$	145	M

[a] Elemental analyses in agreement with theoretical values were obtained. [b] Solvent key: E = ethanol, C = cyclohexane, D = dioxane, L = petroleum ether (40–60 °C), L′ = petroleum ether (60–80 °C), L″ = petroleum ether (80–110 °C), M = methanol, W = water.

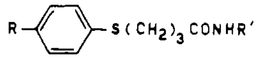
Chart II. 3-(Benzylthio)propanoic Acid Derivatives (VII)



VII

compound	R′	mp, °C	solvent
VIIa	C_6H_5	85	C
b	$C_6H_4CH_3$-*o*	93	C
c	$C_6H_4CH_3$-*p*	90	C
d	$NHCO(CH_2)_2SCH_2C_6H_5$	128	M

Chart III. 4-(Phenylthio)butanoic Acid and 4-(*p*-Tolylthio)butanoic Acid Derivatives



VIII

compound	R	R′	mp, °C	solvent
VIIIa	H	H	96	E
b	H	$(CH_2)_2CH_3$	78	M
c	H	C_6H_5	90	C
d	H	$C_6H_4CH_3$-*o*	86	C
e	H	$C_6H_4CH_3$-*p*	110	C
f	H	$NHCO(CH_2)_3SC_6H_5$	146	E
g	CH_3	H	96	E
h	CH_3	$(CH_2)_2CH_3$	70	M
i	CH_3	C_6H_5	93	C
j	CH_3	$C_6H_4CH_3$-*o*	100	C
k	CH_3	$C_6H_4CH_3$-*p*	125	C
l	CH_3	$NHCO(CH_2)_3SC_6H_5CH_3$-*p*	170	E

Experimental Section

***(Benzylthio)acetic Acid* (*I*).** To 100 g of *S*-benzylisothiuronium chloride was added 80 g of sodium hydroxide in 200 mL of water and the mixture was heated on the water bath for 15 min and cooled. Then 50 g of chloroacetic acid in 60 mL of ethanol was slowly added with shaking during 30 min. The mixture was refluxed for 2 h, cooled, and acidified with hydrochloric acid. The whole mixture was cooled in ice with stirring and the solid product so obtained was filtered off, washed with

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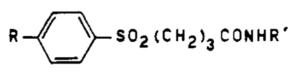
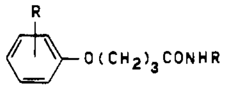
Chart IV. 4-(Phenylsulfonyl)butanoic Acid and 4-(*p*-Tolylsulfonyl)butanoic Acid Derivatives



IX

compound	R	R′	mp, °C	solvent
IXa	H	H	100	E
b	H	$(CH_2)_2CH_3$	82	E
c	H	$CH_2CH(CH_3)_2$	95	E
d	H	C_6H_5	150	E
e	H	$C_6H_4NO_2$-*p*	164	M
f	H	$C_6H_4CH_3$-*o*	155	M
g	H	$C_6H_4CH_3$-*p*	160	M
h	H	$NHCO(CH_2)_3SO_2C_6H_5$	150	E
i	CH_3	H	140	M
j	CH_3	$(CH_2)_2CH_3$	95	E
k	CH_3	$CH_2CH(CH_3)_2$	105	E
l	CH_3	C_6H_5	178	E
m	CH_3	$C_6H_4NO_2$-*p*	180	E
n	CH_3	$C_6H_4CH_3$-*o*	155	M
o	CH_3	$C_6H_4CH_3$-*p*	160	M
p	CH_3	$NHCO(CH_2)_3SO_2C_6H_4CH_3$-*p*	197	E

Chart V. 4-(*o*-Chlorophenoxy)butanoic Acid and 4-(*p*-Bromophenoxy)butanoic Acid Derivatives



X

compound	R	R′	mp, °C	solvent
Xa	*o*-chloro	H	110	W
b	*o*-chloro	$(CH_2)_2CH_3$	68	L
c	*o*-chloro	C_6H_5	91	L″
d	*o*-chloro	$C_6H_4CH_3$-*o*	117	C
e	*o*-chloro	$C_6H_4CH_3$-*p*	95	L′
f	*o*-chloro	$NHCO(CH_2)_3OC_6H_4Cl$-*o*	185	E
g	*p*-bromo	$(CH_2)_2CH_3$	90	D
h	*p*-bromo	C_6H_5	130	C
i	*p*-bromo	$C_6H_4CH_3$-*o*	127	C
j	*p*-bromo	$NHCO(CH_2)_3OC_6H_4Br$-*p*	215	L′

water, and crystallized from cyclohexane: mp 62 °C; yield 80% (lit. (*3*) gives mp 62–63 °C).

4-(o-Chlorophenoxy)butanoic Acid and 4-(p-Bromophenoxy)butanoic Acid (Va,b). 4-(*o*-Chlorophenoxy)butanoic and 4-(*p*-bromophenoxy)butanoic acids were prepared by the method described by Traynelis and Love (*5*). *o*-Chlorophenol (65 g, 0.5 mol) or 90 g of *p*-bromophenol was added gradually to a solution of 12.5 g (0.5 g-atom) of sodium in 250 mL of absolute ethanol during 30 min. To this solution was added 45 g (0.5 mol) of γ-butyrolactone in one portion and the whole mixture was refluxed for 4 h. The ethyl alcohol was distilled under vacuum at 120 °C. The white mass left behind was dissolved in boiling water and filtered. The filtrate was acidified with dilute hydrochloric acid and the precipitate formed was collected, dried, and crystallized from cyclohexane: 4-(*o*-chlorophenoxy)butanoic acid, mp 85 °C, yield 90% $C_{10}H_{11}ClO_3$ (214.7); 4-(*p*-bromophenoxy)butanoic acid, mp 135 °C, yield 85% $C_{10}H_{11}BrO_3$ (259.12). Satisfactory elemental analyses were found.

4-(Phenylsulfonyl)butanoic Acid (IVa). A total of 25 g of 4-(phenylthio)butanoic acid (IIIa) was dissolved in 100 mL of acetic acid and treated during 1 h with ca. 24 mL of hydrogen peroxide (37%), in four portions with shaking during addition. The reaction was left overnight and then poured into ice water and extracted twice with methylene chloride. The methylene chloride extract was evaporated and the residue was crystallized from water: yield 98%, mp 95 °C, $C_{10}H_{12}O_4S$ (228.3).

4-(p-Tolylsulfonyl)butanoic Acid (IVb). 4-(*p*-Tolylthio)butanoic acid was oxidized as above to give IVb: mp 110 °C, yield 98% $C_{11}H_{14}O_4S$ (242.3). Satisfactory elemental analysis were found.

General Procedure. (A) The Amides. A mixture of 2 g of the acids I, II, III, IV, or V, 5 mL of thionyl chloride, and 20 mL of dry benzene was refluxed for 2 h. The excess of thionyl chloride and benzene was distilled off and the remaining oil was dissolved in dry benzene, cooled in ice and quickly treated with 2 g of the amine and left overnight. The reaction mixture was filtered and the precipitate was washed with ether. The filtrate and washings were extracted with dilute hydrochloric acid and then with sodium carbonate solution. The ethereal solution was dried and evaporated. The residue was triturated with light petroleum (40–60 °C) and collected, yield over 80%.

(B) The Amides (Where R′ = H). (1) The acid chloride was prepared as in (A) and then added gradually to 20 mL of ammonia solution cooled in ice. The solid obtained was filtered off, washed with sodium carbonate solution, and crystallized from the proper solvent, yield 80%.

(2) A mixture of 2 g of the acid and 2 g of urea was heated in a metal bath, at 130 °C (bath temperature) the mixture melted and at 180 °C ammonia evolved. Heating was continued at 180 °C for 30 min, till no more ammonia evolved. The product was collected, washed with water and then with sodium carbonate solution, and crystallized from the proper solvent, yield 65%. Note: The amides IXa,i were prepared by procedure B-1 only.

The Anilides and Toluidides. The acid chlorides were prepared as in the general procedure and then treated with aniline or *o*- or *p*-toluidine and then the mixture was heated on the water bath for 15 min, left overnight, and worked up as before, yield 90%.

Oxidation of (Phenylthio)butananilide (VIIIc) to the (Phenylsulfonyl)butananilide (IXd) and the Bis(hydrazide) VIIIf to the Bis(hydrazide) IXh. A total of 0.5 g of compound VIIIc or VIIIf was dissolved in 10 mL of hot acetic acid, cooled, and treated with 6 mL of hydrogen peroxide (37%) and then left overnight. The reaction mixture was poured into ice water. The precipitate formed was collected and crystallized from ethanol. No depression in melting point took place when mixed with IXd or IXh, prepared from the corresponding acid.

Literature Cited

(1) Cagniant, P., Cagniant, D., *Bull. Soc. Chim. Fr.*, 1998 (1959).
(2) Gimmil, M. W., Guenther, A., Morgan, J. F., *J. Am. Chem. Soc.*, **68**, 539 (1946).
(3) Kiang, A. K., Mann, F. G., *J. Chem. Soc.*, 1909 (1951).
(4) Protiva, M., Seidlova, V., Svatek, E., Hradil, F., *Collect. Czech. Chem. Commun.*, **37**, 868 (1971).
(5) Traynelis, V. J., Love, R. F., *J. Org. Chem.*, **26**, 2728 (1961).
(6) Zayed, S. M. A. D., Mostafa, I. Y., Farghaly, M., *Arch. Pharm. Ber. Dtsch. Pharm.*, **300**, 526 (1967).

Received for review October 6, 1978. Accepted March 5, 1979.