SOME 1-ALKYL-3-AROYL UREAS

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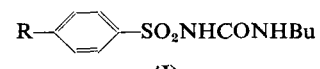
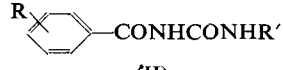
Some 1-alkyl-3-aroylureas and a few related types have been synthesised for examination as anticonvulsants. Maximum activity was found in 3-benzoyl-1-n-butylurea and 1-n-butyl-3-*o*-toluoylurea.

IN 1956 preliminary reports on the promising hypoglycaemic activity of the 3-arylsulphonyl-1-n-butylureas (cf. I) of the "carbutamide" type (I; R = NH_2) led us to synthesise some formally related 3-aroyl-1-n-butylureas (II; R′ = n-Bu) for biological study.



(I)



(II)

Our first two compounds (II; R = H or *p*-NH_2, R′ = n-Bu) were found by Dr. A. David and his colleagues (Department of Pharmacology, Godalming) to be devoid of hypoglycaemic activity. The former compound, however, proved to be an anticonvulsant agent against both leptazol and electroshock-induced convulsions in rats, an observation which led us to a wider study of the group. Acyl-, diacyl- and phenacylureas had previously been synthesised by such workers as Volweiler and Tabern (1936), Blicke and Centolella (1938), Stoughton (1938) and Stoughton, Dickison and Fitzhugh (1939) and Spielman, Geiszler and Close (1948), who had noted their formal similarity to "open-chain" barbiturates and had consequently examined them for sedative, hypnotic and anticonvulsant properties. While our work was in progress Budesinsky, Emr, Muzil, Perina and Zikmund (1959) described the preparation of a few compounds of type (II) for study as hypoglycaemic agents.

The 3-aroyl-1-n-butylureas listed in Table I (see Experimental) were synthesised, except where otherwise indicated, by condensation of n-butylurea with an aroyl chloride on the steam bath, generally in a solvent such as benzene and in the presence of a hydrogen chloride abstractor such as pyridine or phenazone, or by reaction between the aroyl amide and n-butyl isocyanate in the presence of triethylamine. Their biological study revealed peak anticonvulsant activity when R was H or *o*-Me. Attempts to increase potency still further by replacement of the n-butyl group (R′) by alkyl groups containing 3 to 6 carbon atoms or by benzyl or cyclohexyl groups proved wholly unsuccessful.

The 1-butyl-3-*o*- and -*p*-nitrobenzoylureas (above) were reduced to the corresponding amino compounds. 3-*o*-Acetamidobenzoyl-1-n-butylurea (II; R = *o*-NHAc, R′ = n-Bu) was obtained from the amine (III) by reaction with acetic anhydride in benzene at room temperature. Its attempted preparation by heating the amine with glacial acetic acid led

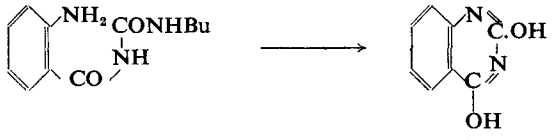
TABLE I

UREAS

R.CO.NH.CO.NH.R′

R	R′	Method	Yield per cent	m.p. °C	Formula	Found				Required			
						C	H	Cl	N	C	H	Cl	N
$(C_6H_5)_3CH$-	n-C_4H_9-	b	73	61–62	$C_{11}H_{22}N_2O_2$	61·3	10·4	—	13·2	61·6	10·4	—	13·1
Cl_3C-	n-C_4H_9-	b	30	66–68	$C_7H_{13}Cl_3N_2O_2$	32·2	4·4	41·6	11·0	32·1	4·2	40·7	10·7
Furyl	n-C_4H_9-	b	80	102–104	$C_{10}H_{14}N_2O_3$	57·0	6·7	—	13·1	57·2	6·7	—	13·3
C_6H_5-	i-C_3H_7-	c	71	116–117	$C_{11}H_{14}N_2O_2$	64·3	7·1	—	13·9	64·1	6·8	—	13·6
	n-C_4H_9-	c, e	67, 37	91–92	$C_{13}H_{16}N_2O_2$	65·7	7·4	—	13·2	65·4	7·3	—	12·7
	n-C_5H_{11}-	d	78	76–78	$C_{13}H_{18}N_2O_2$	67·2	7·8	—	12·0	66·6	7·7	—	12·0
	i-C_5H_{11}-	d	75	109–110	$C_{13}H_{18}N_2O_2$	67·1	7·6	—	12·1	66·6	7·7	—	12·0
	n-C_6H_{13}-	d	70	87–88	$C_{14}H_{20}N_2O_2$	67·7	8·1	—	11·2	67·7	8·1	—	11·3
	cyclohexyl	d	72	162–163	$C_{14}H_{18}N_2O_2$	68·4	7·6	—	11·1	68·3	7·4	—	11·4
	$C_6H_5.CH_2$-	d	76	168–169	$C_{15}H_{14}N_2O_2$	71·3	5·7	—	10·8	70·8	5·6	—	11·0
o-$CH_3.C_6H_4$-	n-C_3H_7-	d	55	114–116	$C_{12}H_{16}N_2O_2$	—	—	—	12·5	65·4	7·3	—	12·7
	i-C_3H_7-	c	56	139–140	$C_{12}H_{16}N_2O_2$	65·8	7·3	—	12·5	65·4	7·3	—	12·7
	n-C_4H_9-	c	55	90–91	$C_{13}H_{18}N_2O_2$	66·5	7·9	—	11·8	66·6	7·7	—	12·0
	i-C_4H_9-	d	72	114–115	$C_{13}H_{18}N_2O_2$	66·8	7·8	—	12·0	66·6	7·7	—	12·0
	s-C_4H_9-	d	60	93–95	$C_{13}H_{18}N_2O_2$	66·4	7·6	—	11·8	66·6	7·7	—	12·0
	t-C_4H_9-	d	60	144–145	$C_{13}H_{18}N_2O_2$	67·1	7·9	—	11·8	66·6	7·7	—	12·0
	i-C_5H_{11}-	d	80	109–111	$C_{14}H_{20}N_2O_2$	—	—	—	11·5	67·7	8·1	—	11·3
m-$CH_3.C_6H_4$- ..	n-C_4H_9-	d	63	64–66	$C_{13}H_{18}N_2O_2$	—	—	—	11·9	66·6	7·7	—	12·0
p-$CH_3.C_6H_4$-	n-C_4H_9-	d	80	133–134	$C_{13}H_{18}N_2O_2$	66·5	8·1	—	11·7	66·6	7·7	—	12·0
p-$CH_3O.C_6H_4$- ..	n-C_4H_9-	d	63	118–119	$C_{13}H_{18}N_2O_3$	62·4	7·3	—	11·3	62·4	7·2	—	11·2
o-$Cl.C_6H_4$-	n-C_4H_9-	d	50	115–116	$C_{12}H_{15}ClN_2O_2$	57·0	6·0	14·0	11·1	56·6	5·9	13·9	11·0
p-$Cl.C_6H_4$-	n-C_4H_9-	b	52	139	$C_{12}H_{15}ClN_2O_2$	56·7	6·2	14·0	11·0	56·6	5·9	13·9	11·0
o-$NO_2.C_6H_4$-	n-C_4H_9-	a	40	137–139	$C_{12}H_{15}N_3O_4$	54·5	5·9	—	15·9	54·3	5·7	—	15·8
p-$NO_2.C_6H_4$-	n-C_4H_9-	a, e	60, 38	150–152	$C_{12}H_{15}N_3O_4$	54·4	5·6	—	15·6	54·3	5·7	—	15·8
o-$NH_2.C_6H_4$-	n-C_4H_9-	—	—	134–136	$C_{12}H_{17}N_3O_2$	61·6	7·4	—	18·1	61·3	7·3	—	17·9
o-$CH_3.CO.NH.C_6H_4$- ..	n-C_4H_9-	—	—	131–132	$C_{14}H_{19}N_3O_3$	61·0	6·8	—	15·3	60·6	6·9	—	15·2
p-$NH_2.C_6H_4$-	n-C_4H_9-	—	—	167–168	$C_{12}H_{17}N_3O_2$	61·4	7·1	—	17·9	61·2	7·3	—	17·9
$C_6H_5.O.CH_2$-	i-C_3H_7-	c	80	104–105	$C_{12}H_{16}N_2O_3$	60·9	6·6	—	12·0	61·0	6·7	—	11·9
$C_6H_5.O.CH_2$-	n-C_4H_9-	c	80	108–109	$C_{13}H_{18}N_2O_3$	62·6	7·6	—	10·8	62·4	7·3	—	11·2
$C_6H_4.C(C_2H_5)_2$- ..	n-C_4H_9-	e	30	112–113	$C_{17}H_{26}N_2O_2$	70·0	9·0	—	9·6	70·3	8·8	—	9·7
$C_6H_5.CH:CH$- ..	n-C_4H_9-	b	62	131–132	$C_{14}H_{18}N_2O_2$	68·7	7·1	—	11·2	68·3	7·4	—	11·4

to the formation of 2,4-dihydroxyquinazoline (IV) by elimination of butylamine:



(III) (IV)

The last product (IV) has been described by Diels and Wagner (1912) who obtained it by a similar reaction involving the treatment of *o*-aminobenzoylurea with mineral acid.

Replacement of the aroyl group of (II) by diethylacetyl, trichloroacetyl, furoyl, phenoxyacetyl, diethylphenylacetyl, and cinnamoyl groups yielded compounds with virtually no anticonvulsant activity. The formally related 1-n-butyl-3-(1-hydroxy-2,2,2,trichloroethyl)urea (V) was obtained by condensing chloral hydrate with n-butylurea. Reaction between n-butyl isocyanate and benzhydrazide yielded 1-benzoyl-4-n-butylsemicarbazide (VI).

$CCl_3.CHOH.NH.CO.NHBu$ (V)

$Ph.CO.NH.NH.CO.NHBu$ (VI)

Experimental

The compounds listed in Table I were prepared by reaction of the acid chloride with the substituted urea or by reaction of the acid amide with the appropriate alkyl isocyanate. These methods are illustrated below with specific examples [(a) to (e)].

(a) 1-*n-Butyl*-3-p-*nitrobenzoylurea.* A mixture of n-butylurea (1·3 g.) and *p*-nitrobenzoyl chloride (1·86 g.) was heated on the steam bath for 2 hr. The residual solid was crystallised from ethanol to yield the *product* (1·6 g.) as cream-coloured needles, m.p. 150–152°.

(b) 1-*n-Butyl*-3-*furoylurea.* A solution of n-butylurea (11·6 g.) in dry benzene (100 ml.) was treated with furoyl chloride, pyridine (0·2 ml.) was added as catalyst and the mixture heated under reflux for 3 hr. The benzene was boiled off and the residual gum stirred with water. The resultant solid (16·8 g.) had m.p. 102–104° after crystallisation from ethanol.

(c) 1-*n-Butyl*-3-*phenoxyacetylurea.* A mixture of n-butylurea (11·6 g.), and phenoxyacetyl chloride (17 g.), in benzene (50 ml.), was treated with pyridine (7·9 g.) and the mixture heated under reflux for 2 hr. Benzene and pyridine were distilled off at reduced pressure, the solid residue was stirred with water and just acidified with hydrochloric acid. The *product* (20 g., m.p. 108–109°) crystallised from ethanol in prismatic needles.

(d) 1-*n-Butyl*-3-p-*toluoylurea.* A mixture of n-butylurea (19·5 g.), *p*-toluoyl chloride (25·8 g.) and phenazone (37·6 g.) in benzene (100 ml.) was heated under reflux for 4 hr. The solvent was boiled off and the residual solid stirred with water, collected and washed with water. The *product* (31·3 g.), had m.p. 133–134° after crystallisation from methanol.

(e) 3-*Benzoyl*-1-*n-butylurea.* A mixture of n-butyl isocyanate (12·9 g.), benzamide (12·1 g.) and triethylamine (2·5 ml.), was heated on the steam bath for 10 hr. The semi-solid residue was stirred with water and acidified with hydrochloric acid. The resultant solid was collected, washed with water and crystallised from ethanol to yield the *product* (8·1 g.), m.p. 91–92°.

3-o-*Aminobenzoyl*-1-*n-butylurea.* To a suspension of 1-n-butyl-3-*o*-nitrobenzoylurea (28 g.) in 50 per cent ethanol (200 ml.) was added ferrous sulphate (4 g.) and iron powder (50 g.) and the mixture was heated with stirring under reflux for 6 hr. It was filtered hot and the residue extracted with two 100 ml. portions of boiling ethanol. The combined filtrate and washings were boiled with charcoal and filtered. Concentration of the filtrate yielded the *product* (19·6 g.), m.p. 134–136° after crystallisation from aqueous methanol.

A solution of the foregoing amine (1·2 g.) in acetic acid (10 ml.) was heated under reflux for 1 hr., when excess of acid was removed at reduced pressure. The residual solid (0·6 g.) after boiling with ethanol had m.p. 356–358°. Found: C, 59·6; H, 3·7. Calc. for 2,4-dihydroxyquinazoline, $C_8H_6N_2O_2$: C, 59·3; H, 3·7 per cent.

A stirred solution of the *amine* (2 g.) in benzene (20 ml.) was treated with acetic anhydride (2 ml.), added dropwise. After 30 min. the mixture was diluted with light petroleum (b.p. 60–80°) to precipitate 3-o-*acetamidobenzoyl*-1-*n-butylurea* (1·1 g.), m.p. 131–132° after crystallisation from ethyl acetate-light petroleum (b.p. 60–80°).

1-*n-Butyl*-3-(1-*hydroxy*-2,2,2, *trichloroethyl*)*urea.* A mixture of chloral hydrate (16·6 g.) and n-butyl-urea (11·6 g.) was heated on the steam bath for 5 min. The *product* had m.p. 136–138° after crystallisation from ethyl acetate-light petroleum (b.p. 60–80°). Found: C, 32·0; H, 4·6; N, 10·6; Cl, 40·1. $C_7H_{13}Cl_3N_2O_2$ requires C, 31·9; H, 4·9; N, 10·6; Cl, 40·4 per cent.

1-*Benzoyl*-4-*n-butylsemicarbazide.* A suspension of benzhydrazide (13·6 g.) in toluene (50 ml.) was treated with n-butyl isocyanate (9·9 g.) and the mixture heated under reflux for 2 hr. The solids (20 g.) were collected and had m.p. 163–165° after crystallisation from methanol-ethyl acetate. Found: C, 61·3; H, 7·7; N, 17·8. $C_{12}H_{17}N_3O_2$ requires C, 61·2; H, 7·3; N, 17·9 per cent.

References

Blicke, F. F. and Centolella, A. P. (1938). *J. Amer. chem. Soc.*, **60**, 2923–2924.
Budesinsky, Z., Emr, A., Musil, V., Perina, Z. and Zikmund, E. (1959). *Farmacie* (Czechoslovakia), VIII–3, 129.
Diels, O. and Wagner, A. (1912). *Ber.*, **45**, 874–883.
Spielman, M. A., Geiszler, A. O. and Close, W. J. (1948). *J. Amer. chem. Soc.*, **70**, 4189–4191.
Stoughton, R. W. (1938). *J. org. chem.*, **2**, 514–521.
Stoughton, R. W., Dickison, H. L. and Fitzhugh, O. G. (1939). *J. Amer. chem. Soc.*, **61**, 408–410.
Volweiler, E. H. and Tabern, D. L. (1936). *Ibid.*, **58**, 1352–1354.