Potential Antimicrobial Furans

William Hoyle,* Gordon P. Roberts,

Pharmaceutical Research Laboratories, Ciba-Geigy (UK) Limited, Manchester M17 1WT, Great Britain

and Otto Meth-Cohn

University of Salford, Salford 5, Great Britain.
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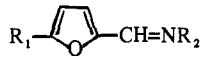
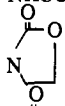
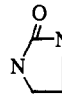
Since the discovery of the antimicrobial properties of nitrofurans,[1] numerous active derivatives have been prepared.[2] Until recently, however, the possibility of using alternative functional groups in place of the nitro group to give new compounds with improved chemotherapeutic indices has not been seriously considered. Lately, this aspect has been investigated and nitrofuran analogs containing trifluoromethyl,[3] substituted phenyl,[4] and alkylsulfonyl[5] groups in place of the nitro group have been reported. We have explored an alternative approach and synthesized furan derivatives having isosteric and isoelectronic functional groups, *viz.*, sulfo, sulfamoyl, carboxyl, methoxycarbonyl, carbamoyl, and cyano groups, in place of the nitro group.

Chemistry. The required azomethines shown in Table I were prepared by condensing appropriately substituted

Table I

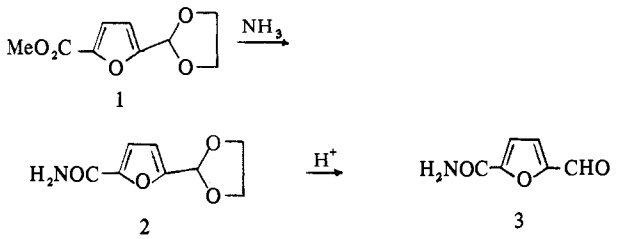


Compd	R_1	R_2	Yield, %	Mp, °C	Purifien solvent	Formula	Analyses
9	NaO_3S	$NHCONH_2$	98[a]	263[b]	H_2O	$C_6H_6N_3NaO_5S$	C, H, N, S
10	NaO_3S		72	226 dec	EtOH–H_2O	$C_6H_7N_2NaO_6S \cdot H_2O$	C, H, N, S
11	NaO_3S		52[a]	>330	EtOH–H_2O	$C_8H_6N_3NaO_6S$	C, H, N, S
12	HO_2C	$NHCONH_2$	93	268 dec	H_2O	$C_7H_7N_3O_4$	C, H, N
13	HO_2C		96	251 dec	H_2O	$C_9H_8N_2O_5$	C, H, N
14	HO_2C		61	307 dec	H_2O	$C_9H_7N_3O_5 \cdot H_2O$	C, H, N
15	MeO_2C	$NHCONH_2$	96[a]	219–220[c]	MeOH	$C_8H_9N_3O_4$	C, H, N
16	MeO_2C		94	212–213	EtOH	$C_{10}H_{10}N_2O_5$	C, H, N
17	MeO_2C		50[a]	249–250	EtOH	$C_{10}H_9N_3O_5$	C, H, N
18	H_2NOC	$NHCONH_2$	84	264 dec	H_2O	$C_7H_8N_4O_3$	C, H, N
19	H_2NOC		90	252 dec	H_2O	$C_9H_9N_4O_4$	C, H, N
20	H_2NOC		71	325 dec	H_2O	$C_9H_8N_4O_4$	C, H, N
21	NC	$NHCONH_2$	73	231 dec	$CH_3OCH_2CH_2OH$	$C_7H_6N_4O_2$	C, H, N
22	NC		71	189–190	$CH_3OCH_2CH_2OH$	$C_9H_7N_3O_3$	C, H, N
23	NC		52	274 dec	$CH_3OCH_3CH_2OH_2$	$C_9H_6N_4O_3$	C, H, N
24	H_2NO_2S	$NHCONH_2$	72	233–234	EtOH–H_2O	$C_6H_8N_4O_4S$	C, H, N
25	H_2NO_2S		78	259 dec	H_2O	$C_8H_9N_3O_5S$	C, H, N
26	H_2NO_2S		53	279 dec	H_2O	$C_8H_8N_4O_5S$	C, H, N

[a] Reaction buffered using NaOAc. [b] Ch. Ivanov and L. Yankov, *God. Khim.-Tekhnol. Inst.*, 7, 231 (1960); *Chem. Abstr.*, **58**, 4495 (1963); no literature melting point. [c] Reference 12, mp 211–212°.

furaldehydes with semicarbazide, 3-amino-2-oxazolidinone,[6] and 1-aminohydantoin.[7] Treatment of the protected aldehyde **1** (Scheme I) with ammonia gave the amide **2** from

Scheme I



which the aldehyde **3** was liberated. Reaction of 5-iodo-2-furaldehyde[8] with $Cu_2(CN)_2$ in DMF gave 5-formyl-2-furonitrile (**4**). Hydrolysis of 2-dichloromethyl-5-furansulfonamide (**5**) gave 5-formyl-2-furansulfonamide (**6**). 5-Formyl-2-furoic acid[9] (**7**) with MeOH-HCl gave the ester **8**.

Pharmacology. The compounds in Table I were tested for antibacterial activity *in vitro* using a standard agar-dilution technique[10] against the following organisms: *Staphylococcus aureus* NCTC 7447; *Escherichia coli* NCTC 86; *Klebsiella pneumoniae* NCTC 7242; and *Salmonella typhi* NCTC 8383. None of the compounds were found to possess significant antibacterial activity. The results confirm the essential role of the nitro group in conferring activity.

Experimental Section

Melting points were determined on a Büchi apparatus and are uncorrected. Elemental analyses for the elements stated in Table I were within ±0.4% of the theoretical values. The structures of the compounds were verified from ir spectra on a Unicam SP 200 spectrophotometer and from nmr spectra on a Varian T-60 spectrophotometer.

Preparation of Azomethines. General Procedure. To an aqueous solution of the *N*-amino compound (or its hydrochloride) was added an equivalent weight of aldehyde dissolved in hot H_2O or hot EtOH. The product was collected by filtration and recrystallized from a suitable solvent (Table I). In some cases buffering to pH 4–5 using NaOAc improved the rate of reaction.

2-(5-Carbamoyl-2-furyl)-1,3-dioxolane (2). A mixture of 1[11] (22 g, 0.11 mol) and concentrated aqueous NH_3 solution was stirred for 20 hr and then evaporated to give **2** as an oil (19.4 g, 96%) which was subsequently hydrolyzed to **3** without purification.

5-Formyl-2-furamide (3). Concentrated HCl (1 ml) was added to a suspension of **2** (19.4 g, 0.105 mol) in H_2O (200 ml). The product was collected (11.1 g, 76%) and recrystallized from H_2O, mp 206–207°. *Anal.* ($C_6H_5NO_3$) C, H, N.

5-Formyl-2-furonitrile (4). A mixture of 5-iodo-2-furaldehyde (44.4 g, 0.2 mol), $Cu_2(CN)_2$ (23 g, 0.12 mol), and DMF (200 ml) was stirred and heated under reflux for 3 hr. After cooling, H_2O (400 ml) was added and the suspension filtered. Extraction of the filtrate with $CHCl_3$ and evaporation gave the product (19.6 g, 81%). Distillation gave pure **4**, bp 108–109° (20 mm), mp 19–20°. *Anal.* ($C_6H_3NO_2$) C, H, N.

5-Formyl-2-furansulfonamide (6). A suspension of **5** (23 g, 0.1 mol) in H_2O (250 ml) was heated at 70° for 15 min. Evaporation of the H_2O gave a gum (17.7 g, 94%) which crystallized on standing. Recrystallization from H_2O gave mp 107–108°. *Anal.* ($C_5H_5NO_4S$) C, H, N.

Methyl 5-Formyl-2-furoate (8). A solution of **7** (2.8 g, 0.02 mol) in MeOH-HCl (25 ml) was allowed to stand overnight. Evaporation of the solvent and recrystallization from cyclohexane gave 2.7 g (87%) of **8**, mp 92–93° (lit.[12] mp 93°). *Anal.* ($C_7H_6O_4$) C, H.

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dl-α-[4-Isobutyl(cyclohexen-1-yl)]alkanoic Acids and Derivatives as Fibrinolytic and Thrombolytic Compounds

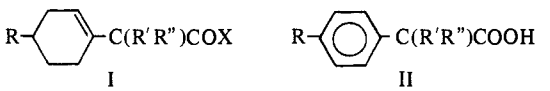
Michel Vincent,* Georges Remond,

Chemical Research Division

Pierre Desnoyers, and Jacqueline Labaume

Vascular Pharmacological Research Division, Science Union et Associes, Groupe de Recherches des Laboratoires Servier, 92-Suresnes, France. *Received July 3, 1972*

In a previous publication[1] we have described the synthesis and antiinflammatory properties of several *dl*-α-[4-cycloalkyl(cyclohexen-1-yl)]alkanoic acids and derivatives (I, R = cycloalkyl). Compound I (R = cyclohexyl; R′ = H; R″ = CH_3; X = OH) was the most active product in the uv erythema test, the carrageenan edema test, and the adjuvant-induced arthritis assay. Thus, partial saturation of the benzene nucleus of the well-known α-(phenyl)alkanoic acids (II, R = cyclohexyl; R′ and/or R″ = H or alkyl)[2] did not suppress antiinflammatory activity.



As compound II (R = isobutyl; R′ = H; R″ = CH_3) also showed high antiinflammatory activity,[3] we have synthesized a series of corresponding *dl*-α-[4-isobutyl(cyclohexen-1-yl)]alkanoic acids and derivatives (I, R = isobutyl).

None of the compounds (I, R = isobutyl) retained any antiinflammatory activity in the rat hind-paw carrageenan edema test[4] at doses as high as 200 mg/kg po. As antiinflammatory activity appears to correlate well with fibrinolytic activity within a group of acidic antiinflammatory drugs,[5] all compounds (I, R = cycloalkyl) previously described and I (R = isobutyl) were screened for fibrinolytic activity. Surprisingly, at 100 mg/kg po all compounds (I, R = cycloalkyl) were devoid of fibrinolytic activity (see Biological Testing, test 2) but several compounds (I, R = iso-