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Tetrazole Analogues of Ibuprofen and Flurbiprofen

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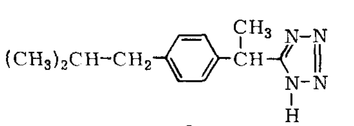
The pharmacological properties of the tetrazole analogues of ibuprofen and flurbiprofen are reported.

Tetrazol-Analoga des Ibuprofens und Flurbiprofens

Tetrazol-Analoga des Ibuprofens und Flurbiprofens und ihre pharmakologischen Eigenschaften werden beschrieben.

Tetrazole derivatives, apart the well known leptazol, have received in the past decade an increasing interest amongst medicinal chemists as may be seen in a recent review that covers this literature until 1980[1]. Since the acid strenght of this heterocycle with free NH is comparable to that of aliphatic carboxylic acid, its bioisosteric replacement in a number of drugs bearing a carboxy group has been successfully experienced[1]. This modification is often attempted in order to eliminate unwanted side effects or to potentiate some components of the pharmacological spectrum of the parent drug.

We refer in this note the potentiation of the analgesic effect induced by the tetrazole analogues of ibuprofen (1) and flurbiprofen (2).



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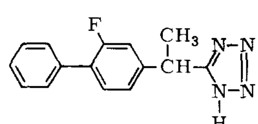

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These compounds were prepared as usual by reacting the corresponding nitrile derivatives with sodium azide[2].

Pharmacology

Methods

1. *Acute toxicity*: Male albino mice, 25–30 g, were given the test compounds suspended in 10 % acacia by mouth. Approximate LD_{50} values were determined by inspection from mortalities occurring within 7 days. Animals always showed acute signs of prostration and sedation and death occurred mainly from perforated gastric ulcers, in agreement with the typical ulcerogenic properties of the non steroidal anti-inflammatory agents.

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2. *Central analgesic activity*: The central analgesic properties were determined by hot-plate technique according to *Eddy* and *Leimbach*[3]. Each mouse was first conditioned to the hot-plate by three exposures. The time (sec) from contact with the plate at 55 ± 0.5° until a hind paw lick or jump occurred, was recorded as the responce latency. The mice with baseline latencies greater than 15 sec or less than 10 sec were omitted from the study. The responses were recorded at 30 min intervals after oral administration of the compounds as suspension in 10 % acacia, with a cut-off time of 45 sec. The degree of analgesia was expressed in terms of average temporal differences (sec) relative to the baseline in groups of ten mice/experiment.

3. *Peripheral analgesic activity*: The acetylcholine-induced writhing in mice was selected because this test does not mainly involve an anti-inflammatory reaction, but it is envisaged as specific to evaluate peripheral analgesic effects. This is especially true if the writhing is estimated for only 4–5 min after the i.p. injection; a so short latency makes it very probable that pain receptors are being stimulated directly, and inflammatory factors are not involved[4]. Nevertheless some autacoids as prostaglandins seem necessary to a full development of writhing, and so it is possible that the above test is useful to evaluate both the analgesic and anti-inflammatory activities. Therefore it was chosen for comparative studies on these phenylpropionic acid derivatives as peripheral analgesic and anti-inflammatory agents.

Ibuprofen, flurbiprofen and their tetrazole derivatives were tested in four graded doses by mouth in groups of five mice/dose. The test was repeated six times, giving a total of 30 mice per dose group. Acetylcholine chloride (0.25 ml of a 200 μg/ml solution) was injected i.p. 60 min after administration of the above compounds. The animals were immediately placed in individual glass containers and observed during the 4 min at which maximal writhing occurred in control animals. The number of writhes/mouse was counted and the dose which reduced the writhing rate by 50 % (ED_{50}) was calculated from the dose response curve.

Results

The degree of activity in the acetylcholine-induced writhing test was always increased substituting tetrazole for carboxyl in the two reference drugs, ibuprofen and flurbiprofen. In table 1, for brevity, the activity of both the parent compounds was made =1 and the degree of increased activity was calculated on molar base.

From the data of the table 1 it appears clearly that the replacement of the carboxyl by tetrazolyl increases in both cases the anti-inflammatory activity of the parent compounds, however this effect is counterbalanced by an increased toxicity.

Table 1: *ED_{50} comparison of ibuprofen* **(1)**, *flurbiprofen* **(2)** *and their tetrazole analogues* **3** *and* **4**

Compound	mmol/kg 10^{-3}	Relative potency	LD_{50} per os mg/kg
1	8	1	800
3	4	2	400
2	1.4	1	750
4	1.1	1.27	350

Finally the analgesic studies by mouse hot plate, which crearly differentiate the centrally acting analgesic from the peripherally acting ones, have indicated that either ibuprofen and flurbiprofen or their tetrazole-derivatives fall into the latter group. Indeed the experiments carried out with the same graded doses orally administred in mice exposed to hot plate have shown no significant lengthenings of mean reaction times.

Therefore the tetrazole-derivatives of ibuprofen and flurbiprofen, in a number of conventional animal tests, appear more powerful than the parent compounds in analgesic activity which is of peripheral rather than central type.

Experimental

α-Methyl-4-(2-methylpropyl)benzeneacetamide **(5)**

37 g (0.165 mole) of α-methyl-4-(2-methylpropyl)benzeneacetyl chloride were added gradually to 150 ml of aqueous NH_3 cooled with an ice bath during the addition. The mixture was stirred at room temp. for 4 h and then filtered: the residue on crystallizing from EtOH afforded 33 g (90 % yield) of a white solid m.p. 114–115°. $C_{13}H_{19}NO$ (205.2). Calcd.: C 76.0 H 9.33 N 6.8; Found: C 76.2 H 9.25 N 6.7.

α-Methyl-3-fluoro-4-phenylbenzeneacetamide **(6)**

With the same procedure starting from 26 g (0.1 mole) of α-methyl-3-fluoro-4-phenylbenzeneacetyl chloride, 22.8 g (95 % yield) of a white solid m.p. 123–125° were obtained (EtOH). $C_{15}H_{14}FNO$ (243.1). Calcd.: 74.0 H 5.80 N 5.8; Found: C 74.0 H 5.70 N 5.7.

α-Methyl-4-(2-methylpropyl)benzeneacetonitrile **(7)**

A mixture of 20 g (0.1 mole) of **5** and 40 g of phosphorus pentoxide was heated with a free flame under reduced pressure (water pump) until no more liquid distils: the nitrile passes over at 150–155°/20 mm. The distillate was dissolved in ether, washed with a little carbonate solution, with water and then dried. After evaporation of the solvent the residue was distilled to afford 12 g (60 % yield) of **7** which passes over at 150–152°/20 mm. $C_{13}H_{17}N$ (187.1). Calcd.: C 83.4 H 9.16 N 7.5; Found: C 83.1 H 9.00 N 7.3.

α-Methyl-3-fluoro-4-phenylbenzeneacetonitrile **(8)**

With the same procedure from 24.3 g (0.1 mole) of **6**, 11.2 g (60 % yield) of product m.p. 73–75° (ligroin) were obtained. $C_{15}H_{12}FN$ (225.1). Calcd.: C 80.0 H 5.37 N 6.2; Found: C 97.8 H 5.22 N 6.1.

α-(1H-tetrazol-5-yl)-4-(2-methylpropyl)ethylbenzene **(3)**

To 200 ml THF precooled in an ice bath were added 12.8 g (0.096 mole) pulverized anhydrous $AlCl_3$, 9 g (0.048 mole) **7** and 12.48 g (0.192 mole) sodium azide in this order and the ice bath was removed. The mixture was then refluxed for 16 h with stirring. 30 ml HCl (15 %) were added to the reaction mixture and the liquid phase was obtained by decantation. After the solvent was evaporated i. vac. and the resulting solid was chromatographed on silica gel. Elution with ethyl acetate/petroleum ether (3/7) gave 4 g of starting nitrile. Continued elution gave 4.2 g (40 % yield) of **3**, m.p. 90–91° (ligroin). $C_{13}H_{18}N_4$ (230.2). Calcd.: C 67.8 H 7.88 N 24.3; Found: C 67.8 H 7.80 N 24.5.

α-(1H-tetrazol-5-yl)-3-fluoro-4-phenylethylbenzene **(4)**

With the same procedure from 4 g (0.0177 mole) of **8**, 2.8 g (60 % yield) of **4**, m.p. 177–179° (benzene), were obtained. $C_{15}H_{13}FN_4$ (268.1). Calcd.: C 67.1 H 4.89 N 20.9; Found: C 67.3 H 4.72 N 20.8.

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Derivatives of 2-Amino-1,2,3,4-Tetrahydronaphthalene, VIII[1)]

Isomerization of *trans*-2-Acetamido-3-hydroxy-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene and Hydrolysis of 5,8-Dimethoxy-2-methyl-3*a*,4,9,9*a*-tetrahydronaphth[2,3-*d*]oxazoline Hydrochloride

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The isomerization of *trans*-2-acetamido-3-hydroxy-5,8-dimethoxytetraline **(1)** under the action of hydrogen chloride was investigated. Hydrolysis of 5,8-dimethoxy-2-methyl-3*a*,4,9,9*a*-tetrahydronaphth[2,3-*d*]oxazoline hydrochloride **(2)** leads to *cis*-2-amino-3-hydroxy-5,8-dimethoxytetraline **(3)**.

Derivate des 2-Amino-1,2,3,4-tetrahydronaphthalins, 8. Mitt.: Isomerisierung von *trans*-2-Acetamido-3-hydroxy-5,8-dimethoxy-tetralin und Hydrolyse von 5,8-Dimethoxy-2-methyl-3*a*,4,9,9*a*-tetrahydronaphth[2,3-*d*]oxazolin-hydrochlorid

Es wurden die Isomerisierung des *trans*-2-Acetamido-3-hydroxy-5,8-dimethoxytetralins **(1)** nach Einwirkung von Chlorwasserstoff, sowie die Hydrolyse des 5,8-Dimethoxy-2-methyl-3*a*,4,9,9*a*-tetrahydronaphth[2,3-*d*]oxazolin-hydrochlorids **(2)**, die zu *cis*-2-Amino-3-hydroxy-5,8-dimethoxytetralin **(3)** als Endprodukt führt, untersucht.

It is well known that isomerisation of N-acyl derivatives of beta-aminocyclanols catalyzed by hydrogen chloride leads to esters of the aminoalcohol (N → O acylmigration) without change in the configuration[2,3)]. Isomerization of the *trans*-isomer with thionyl chloride leads to epimerization

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