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Synthetic Inhibitors of Alcohol Dehydrogenase. Pyrazoles Containing an Unsaturated Hydrocarbon Residue in the 4-Position

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A series of pyrazoles containing an unsaturated hydrocarbon residue in the 4-position has been synthesized and tested for ability to inhibit the activity of the enzyme liver alcohol dehydrogenase. These compounds were found to be less active than the corresponding saturated analogues.

Previous work in our laboratories has shown that pyrazoles substituted with an alkyl group in the 4-position are very potent inhibitors of the enzym horse liver alcohol dehydrogenase (LADH) *in vitro*.[1,2] The activity seems to be correlated to the lipophilicity of the substituent as the inhibitory power is increased for each carbon atom that is added to an unbranched chain and decreased by branching or cyclization of the chain. A number of these inhibitors have been tested in rats. It was found that pyrazole derivatives with long alkyl substituents strongly inhibit the ethanol metabolism *in vivo* too. However, the duration turned out to be shorter than that of the lowest homologue in the series, 4-methylpyrazole.[3] This may be due to different rates of metabolism and/or different distribution. These findings induced us to make a number of modifications of the substituent in the 4-position in the hope of finding compounds with longer duration. The present paper describes the synthesis of some pyrazoles containing an unsaturated hydrocarbon residue in the 4-position and results from *in vitro* tests for their ability to inhibit the activity of LADH.

CHEMISTRY

Pyrazoles having a substituent in the 4-position containing a triple bond have been synthesized from copper(I) acetylides and 4-halogenopyrazoles,[4,5] or by dehydrohalogenation of 4-halogenoacylpyrazoles [6] or 2-bromo-3-(4-pyrazolyl)acrylic acid derivatives.[7] However, these methods require forcing reaction conditions and do not offer convenient procedures for the preparation of the desired compounds.

During the last years, coupling of acetylenes and organometallic compounds with aryl or alkenyl halides using transition metal catalysts has received considerable attention.[8-14] It has been reported[9] that coupling of acetylenes with iodoarenes, bromopyridines and bromoalkenes proceeds smoothly at room temperature in diethylamine using cuprous iodide and bis(triphenylphosphine)palladium dichloride as catalysts. We found that this reaction could be used for the synthesis of 4-alkynylpyrazoles in good yields. However, 4-iodopyrazole could not be used as starting material apparently due to the acidity of the NH proton. The introduction of a protecting group was therefore necessary and the 2,4,6-trimethylbenzoyl group was found to be excellent. Unlike the benzoyl and *o*-toluyl groups, which were also tried it is stable during the reaction yet is easily removed. Thus, reaction of 4-iodo-1-(2,4,6-trimethylbenzoyl)pyrazole (*1*) with the appropriate acetylene compound in diethylamine in the presence of catalytic amounts of bis(triphenylphosphine) palladium dichloride and cuprous iodide afforded the pyrazoles *2a* – *2c* (Scheme 1) in excellent yields (83 – 97 %).

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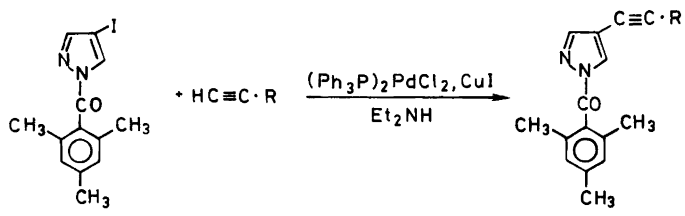

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2a R = CH_2OH

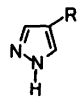
b R = C_4H_9

c R = C_6H_5

Scheme 1.

Compounds *2b* and *2c* were then treated with sodium hydroxide in aqueous methanol under mild conditions giving *5* and *6*.

4-Ethynylpyrazole (*4*) could not be prepared directly by this method since the use of acetylene would give a disubstituted acetylene.[9] However, Atkinson and co-workers[15] have shown that α,β-acetylenic aldehydes easily undergo deformylation, and the synthesis of *4* was accomplished by coupling *1* with 2-propyn-1-ol and subsequent oxidation of the resulting alcohol *2a* to the aldehyde *3* with active manganese dioxide in benzene at room temperature. Treatment of *3* with sodium hydroxide in aqueous methanol at 50 °C resulted in simultaneous deformylation and removal of the protecting group, thus affording *4*. Hydrogenation of *4* and *5* over a Lindlar catalyst gave the olefins *7* and *8a* (*Z* isomer), respectively. The *E* isomer *8b* was obtained in a rather sluggish reaction by treatment of *5* with lithium aluminium hydride in diglyme[16]



	R		R
4	C≡CH	*11*	$CH(OH)\cdot C_6H_5$
5	$C\equiv C\cdot C_4H_9$	*12*	$CH_2\cdot C_6H_5$
6	$C\equiv C\cdot C_6H_5$	*13*	$CH_2\cdot CH_2\cdot C_6H_5$
7	$CH=CH_2$	*14*	$(CH_2)_3\cdot Br$
8a	$CH=CH\cdot C_4H_9$ *(Z)*	*15*	$(CH_2)_3\cdot C\equiv CH$
8b	$CH=CH\cdot C_4H_9$ *(E)*	*16*	$(CH_2)_3\cdot CH=CH_2$
9a	$CH=CH\cdot C_6H_5$ *(Z)*	*17*	$(CH_2)_4\cdot CO\cdot C_6H_5$
9b	$CH=CH\cdot C_6H_5$ *(E)*	*18*	$(CH_2)_5\cdot C_6H_5$

at 155 °C. The geometrical isomers of 4-(2-phenylethenyl)pyrazole (*9a,b*) were obtained similarly from *6*.

Some compounds with the unsaturated residue separated from the pyrazole ring by one or more methylene groups were also prepared.

4-Benzylpyrazole (*12*) was obtained in the following manner. Reaction of 4-bromo-1-(2-tetrahydropyranyl)pyrazole (*10*) with butyllithium at −78 °C gave a 4-lithiopyrazole intermediate, which on reaction with benzaldehyde and subsequent hydrolysis of the protecting group afforded 4-(α-hydroxybenzyl)pyrazole (*11*). Reduction of *11* with hydrogen over a palladium catalyst gave the desired 4-benzylpyrazole (*12*). 4-(2-Phenylethyl)-pyrazole (*13*) was obtained by catalytic hydrogenation of *6*. 4-(3-Bromopropyl)pyrazole (*14*), obtained from the corresponding alcohol by treatment with thionyl bromide, reacted with sodium acetylide to give 4-(4-pentynyl)pyrazole *15* which was subsequently hydrogenated to the olefine *16*. Treatment of *14* with the sodium salt of ethyl benzoylacetate followed by hydrolysis of the ester and decarboxylation afforded 4-(5-oxo-5-phenylpentyl)pyrazole (*17*), which was submitted to Wolff-Kishner reduction to yield 4-(5-phenylpentyl)pyrazole (*18*).

EXPERIMENTAL

General. Melting points were determined in an electrically heated metal block using open capillary tubes and calibrated Anschütz thermometers. ^1H NMR spectra were recorded in $CDCl_3$ unless otherwise stated with TMS as internal standard, using a Perkin-Elmer R 12 B spectrometer. IR spectra were recorded on a Perkin-Elmer 157 G spectrophotometer, using KBr discs. GLC analyses

were run on a Varian 1700 chromatograph. Columns: 3 m long glass column packed with 3 % XE 60 or 5 % OV 25 on Chromosorb W (80–100 mesh). Individual compounds were isolated on a 250 × 0.9 cm glass column packed with 10 % XE 60 on Chromosorb W (60–80 mesh). For column chromatography silica gel 60, Merck, was used. Microanalyses were carried out at the Microanalytical Laboratory, Royal Agricultural College, Uppsala. All reactions with bis(triphenylphosphine)palladium dichloride were performed under nitrogen.

Starting materials. 4-Bromopyrazole,[17] 4-iodopyrazole[17] and 4-(3-hydroxypropyl)pyrazole[18] were prepared according to the literature. 2,4,6-Trimethylbenzoyl chloride was prepared from the commercially available 2,4,6-trimethylbenzoic acid. Bis(triphenylphosphine)palladium dichloride, 2-propyn-1-ol, 1-hexyne and phenylacetylene were commercially available.

4-Iodo-1-(2,4,6-trimethylbenzoyl)pyrazole (1). 2,4,6-Trimethylbenzoyl chloride (18.3 g, 0.1 mol) was added dropwise at room temperature to a solution of 4-iodopyrazole (17.6 g, 0.091 mol) and triethylamine (10.1 g, 0.1 mol) in dry benzene–ether (120 ml, 5:1). The reaction mixture was refluxed for 8 h and filtered. The filtrate was washed with water and after drying ($MgSO_4$) and evaporation of the solvent *in vacuo* the solid residue was recrystallized from hexane affording 21.8 g (71 %) of product, m.p. 84–85 °C. Anal. $C_{13}H_{13}IN_2O$: C, H, N. IR: 1725 cm^{-1}. ^1H NMR: δ 2.14 (6H, s), 2.32 (3H, s), 6.93 (2H, s), 7.71 (1H, s), 8.44 (1H, s).

4-(3-Hydroxy-1-propynyl)-1-(2,4,6-trimethylbenzoyl)pyrazole (2a). To a stirred solution of *1* (10.0 g, 0.029 mol) and 2-propyn-1-ol (1.7 g, 0.03 mol) in diethylamine (100 ml) a catalytic amount of bis(triphenylphosphine)palladium dichloride and cuprous iodide was added. The mixture was stirred at room temperature and the reaction was followed by TLC (silica gel; ether–light petroleum 1:2 until completion (24 h). The solvent was then evaporated *in vacuo* and ether was added to precipitate the salts. After filtration and evaporation, the crude product was purified on a silica gel column (ether–light petroleum) affording 7.7 g (97 %) of a slowly crystallizing product. A small sample was recrystallized from ether–hexane, m.p. 72.5–73.5 °C. Anal. $C_{16}H_{16}N_2O_2$: C, H, N. IR: 2240, 1720 cm^{-1}. ^1H NMR: δ 2.13 (6H, s), 2.32 (3H, s), 6.42 (2H, s), 6.95 (2H, s), 7.77 (1H, s), 8.41 (1H, s).

4-(1-Hexynyl)-1-(2,4,6-trimethylbenzoyl)pyrazole (2b) was prepared from *1* (2.5 g) and 1-hexyne (0.7 g) according to the procedure described above. After purification on a silica gel column (ether–light petroleum) the title compound was obtained as an oil (2.0 g, 90 %). Anal: $C_{19}H_{22}N_2O$: C, H, N. IR (film): 2240, 1720 cm^{-1}. ^1H NMR: δ 0.93 (3H, t), 1.2–1.8 (4H, m), 2.30 (6H, s), 2.31 (3H, s), 2.39 (2H, t), 6.92 (2H, s), 7.71 (1H, s), 8.34 (1H, s).

4-Phenylethynyl-1-(2,4,6-trimethylbenzoyl)pyrazole (2c) was prepared similarly from *1* (2.5 g) and phenylacetylene (0.8 g). After column chromatography (silica gel, ether) and recrystallization (methanol), 1.9 g (83 %) of *2c* was obtained, m.p. 122–123 °C. Anal. $C_{21}H_{18}N_2O$: C, H, N. IR: 1720 cm^{-1}. ^1H NMR: δ 2.16 (6H, s), 2.31 (3H, s), 6.93 (2H, s), 7.20–7.60 (5H, m), 7.82 (1H, s), 8.47 (1H, s).

4-Formylethynyl-1-(2,4,6-trimethylbenzoyl)pyrazole (3). To a solution of *2a* (7.0 g, 0.026 mol) in dry benzene (150 ml) was added active manganese dioxide (34 g, 0.4 mol). The reaction mixture was shaken vigorously for 10 h until the starting material was consumed (TLC). After filtration through celite, the solvent was evaporated *in vacuo* affording 6.0 g (87 %) of a yellow oil, which was used without additional purification in the next step. IR (film): 2740, 2200, 1720, 1660 cm^{-1}. ^1H NMR: δ 2.14 (6H, s), 2.32 (3H, s), 6.94 (2H, s), 7.88 (1H, s), 8.51 (1H, s), 9.39 (1H, s).

4-Ethynylpyrazole (4). To a solution of *3* (6.0 g, 0.023 mol) in methanol (120 ml), 5 M NaOH (40 ml) was added at 50 °C. The solution was stirred at 50 °C for 0.5 h and was then concentrated during 0.5 h to *ca.* 50 ml under reduced pressure. Water (40 ml) was added and the solution was extracted with ether in a Soxhlet apparatus. The ethereal solution was dried ($MgSO_4$) and evaporated *in vacuo*. The residue was purified on a silica gel column using ether–hexane as eluent, affording 1.4 g (70 %) of *4*, m.p. 101–103 °C (solidified oil). Anal. $C_5H_4N_2$: C, H, N. IR: 3280, 2110 cm^{-1}. ^1H NMR: δ 3.03 (1H, s), 7.80 (2H, s). *Hydrochloride:* m.p. 118–119 °C (dec.) from ethanol–ether). Anal. $C_5H_4N_2 \cdot HCl$: C, H, N.

4-(1-Hexynyl)pyrazole (5) was prepared from *2b* (2.0 g) using the procedure described for *4*. Purification on a silica gel column (ether–light petroleum) afforded 0.89 g (89 %) of the title compound, m.p. 37–38 °C (solidified oil). Anal. $C_9H_{12}N_2$: C, H, N. IR: 2220 cm^{-1}. ^1H NMR: δ 0.93 (3H, t), 1.1–1.8 (4H, m), 2.38 (2H, t), 7.67 (2H, s). *Hydrochloride:* m.p. 93.5–94.5 °C (dec.) (from ethanol–ether). Anal. $C_9H_{12}N_2 \cdot HCl$: C, H, N.

4-Phenylethynylpyrazole (6) was prepared similarly by hydrolysis of *2c* (1.8 g) during 1 h. Extraction with ether, drying ($MgSO_4$) and evaporation of the solvent *in vacuo* afforded a crystalline residue which was recrystallized from ether–hexane to give 0.85 g (88 %) of the title compound, m.p. 134–134.5 °C. Anal. $C_{11}H_8N_2$: C, H, N. IR: 2220 cm^{-1}. ^1H NMR: δ 7.2–7.7 (5H, m), 7.80 (2H, s). *Hydrochloride:* m.p. 125.5–126.5 °C (dec.) (from ethanol–ether). Anal. $C_{11}H_8N_2 \cdot HCl$: C, H, N.

4-Ethenylpyrazole (7). A solution of *4* (1.0 g,

0.011 mol) in ethanol (25 ml) was hydrogenated at room temperature over a Lindlar catalyst at atmospheric pressure until the starting material had been consumed (48 h), the reaction being followed by GLC. After filtration through celite and evaporation of the solvent, the residue was recrystallized (light petroleum) affording 0.4 g (40 %) of *7*, m.p. 88–89 °C. Anal. $C_5H_6N_2$: C, H, N. ^{1}H NMR: δ 5.0–5.7 (2H, m), 6.4–6.9 (1H, m) 7.71 (2H, s). *Hydrochloride:* m.p. 124–126 °C (dec.) (from ethanol–ether). Anal. $C_5H_6N_2 \cdot HCl$: C, H, N.

*(Z)-4-(1-Hexenyl)pyrazole (*8a*).* A solution of *5* (0.8 g) in ethanol (25 ml) was hydrogenated similarly over a Lindlar catalyst for 24 h. After filtration through celite and evaporation of the solvent *in vacuo*, the product was isolated by preparative GLC affording 0.23 g (29 %) of *8a*, m.p. 39.5–40.5 °C (solidified oil). ^{1}H NMR: δ 0.91 (3H, t), 1.1–1.7 (4H, m), 2.0–2.6 (2H, m), 5.25–6.15 (2H, m), 7.59 (2H, s). *Hydrochloride:* m.p. 111.5–112.5 °C (dec.) (from ethanol–ether). Anal. $C_9H_{14}N_2 \cdot HCl$: C, H, N.

*(E)-4-(1-Hexenyl)pyrazole (*8b*).* A solution of *5* (1.5 g) in diglyme (30 ml) was treated with lithium aluminium hydride (0.77 g) at 155 °C for 6 h. After hydrolysis with water and filtration, ether was added. The ethereal solution was washed with water and dried ($MgSO_4$). After evaporation of the solvent, the residue was purified by preparative GLC affording 0.33 g (22 %) of *8b*, m.p. 85.5–86.5 °C. ^{1}H NMR: δ 0.92 (3H, t), 1.1–1.6 (4H, m), 1.9–2.4 (2H, m) 5.6–6.45 (2H, m), 7.53 (2H, s). *Hydrochloride:* m.p. 137–138 °C (dec.) (from ethanol–ether). Anal. $C_9H_{14}N_2 \cdot HCl$: C, H, N.

*(Z)-4-(2-Phenylethenyl)pyrazole (*9a*).* A solution of *6* (1.0 g, 5.9 mmol) in ethanol (30 ml) was hydrogenated over a Lindlar catalyst as described above for compound *7*. Purification on a silica gel column with ether as eluent afforded 0.75 g (75 %) of the title compound, m.p. 51–52.5 °C (solidified oil). ^{1}H NMR: δ 6.38 (2H, s), 7.1–7.5 (7H, m). *Hydrochloride:* m.p. 131–132 °C (from ethanol–ether). Anal. $C_{11}H_{10}N_2 \cdot HCl$: C, H, N.

*(E)-4-(2-Phenylethenyl)pyrazole (*9b*).* A solution of *6* (1.0 g, 5.9 mmol) in diglyme (40 ml) was treated with $LiAlH_4$ (0.5 g) at 120 °C for 5 h as described for *8b*. Yield 0.5 g (50 %), m.p. 216–217 °C (from acetone). Anal. $C_{11}H_{10}N_2$: C, H, N. ^{1}H NMR ($CDCl_3$, CD_3COCD_3): δ 6.88 (1H, d, J=17 Hz), 7.04 (1H, d, J=17 Hz), 7.2–7.5 (5H, m), 7.75 (2H, s). *Hydrochloride:* m.p. 185.5–187 °C (dec.) (from ethanol–ether). Anal. $C_{11}H_{10}N_2 \cdot HCl$: C, H. N.

*4-Bromo-1-(2-tetrahydropyranyl)pyrazole (*10*).* A mixture of 4-bromopyrazole (2.0 g, 13.6 mmol) and catalytic amounts of *p*-toluenesulfonic acid in dihydropyran (15 ml) was refluxed for 7 h. Ether (100 ml) was added and the mixture was washed with saturated Na_2CO_3 solution and water. After drying (Na_2CO_3) and evaporation of the solvent *in vacuo*, the residue was purified by column chromatography [silica gel, ether–light petroleum (1:2)] affording 2.15 g (69 %) of the title compound as a liquid. ^{1}H NMR: δ 1.2–2.3 (6H, m), 3.35–4.2 (2H, m), 5.31 (1H, t), 7.47 (1H, s), 7.62 (1H, s). The compound was used in the next step without being analyzed.

*4-(α-Hydroxybenzyl)pyrazole (*11*).* To a solution of *10* (2.0 g, 8.7 mmol) in dry THF (30 ml) was added dropwise a solution of butyllithium in hexane (7.4 ml, 1.28 *M*) at −78 °C. After 10 min at this temperature benzaldehyde (1.1 g, 10.4 mmol) in THF (5 ml) was added dropwise. After 2 h at −78 °C the reaction mixture was stirred at room temperature overnight. The reaction mixture was treated with saturated NH_4Cl solution and ether (100 ml) was added. The organic phase was washed with water, dried (Na_2CO_3) and evaporated *in vacuo*. The residue was hydrolyzed at room temperature in a mixture (200 ml) of 1 *M* HCl and ethanol (1:1) overnight. The mixture was evaporated to a volume of about 50 ml and extracted with ether, made alkaline with saturated Na_2CO_3 and extracted with $CHCl_3$. After drying ($MgSO_4$) and evaporation *in vacuo* the residue was recrystallized from acetone–hexane affording 0.4 g (26 %) of the title compound, m.p. 92–94 °C. Anal. $C_{10}H_{10}N_2O$: C, H, N. ^{1}H NMR: δ 5.58 (1H, s), 6.9–7.4 (7H, m).

*4-Benzylpyrazole (*12*).* A solution of *11* (0.35 g, 2 mmol) in HOAc (25 ml) was hydrogenated in the presence of a small amount of 10 % Pd/C in a Parr low pressure hydrogenation apparatus. The catalyst was filtered off, the solvent evaporated *in vacuo* and the residue purified on preparative TLC (silica gel, ether) affording 0.05 g of an oil, which was converted to its *oxalate*, m.p. 150–151 °C (dec.) (from ethanol–ether). Anal. $C_{10}H_{10}N_2 \cdot (CO_2H)_2$: C, H, N. ^{1}H NMR (base): δ 3.76 (2H, s), 7.1–7.5 (7H, m).

*4-(2-Phenylethyl)pyrazole (*13*).* A solution of *6* (0.5 g, 3 mmol) in ethanol (20 ml) was hydrogenated at room temperature over a palladium catalyst (5 % on Al_2O_3) at atmospheric pressure for 3 h, when the calculated amount of hydrogen had been consumed. Filtration and evaporation of the solvent left a solid residue (0.5 g, 100 %). A small amount was recrystallized from hexane, m.p. 94–95 °C. Anal. $C_{11}H_{12}N_2$: C, H, N. ^{1}H NMR: δ 2.82 (4H, s), 7.20 (5H, s), 7.31 (2H, s). *Oxalate:* m.p. 157–158 °C (from ethanol–hexane). Anal. $C_{11}H_{12}N_2 \cdot (CO_2H)_2$: C, H, N.

*4-(3-Bromopropyl)pyrazole (*14*).* To a stirred suspension of 4-(3-hydroxypropyl)pyrazole (5.0 g, 0.04 mol) in dry benzene (25 ml) was added a solution of thionyl bromide (8.2 g, 0.04 mol) in dry benzene benzene (25 ml). The mixture was refluxed for 1 h and cooled. After addition of ether, the product

was filtered off and recrystallized from chloroform–ether to give the *hydrobromide* of the title compound (9.3 g, 87 %), m.p. 147–148 °C. Anal. $C_6H_9BrN_2 \cdot HBr$: C, H, N. The free base had m.p. 58–59 °C. ^1H NMR: δ 2.10 (2H, m), 2.70 (2H, t), 3.41 (2H, t), 7.48 (2H, s).

4-(4-Pentynyl)pyrazole (15). To a solution of sodium acetylide, prepared from sodium (1.2 g, 0.052 mol) in liquid ammonia (100 ml) and acetylene, a solution of *14* (4.0 g, 0.021 mol) in ether (25 ml) was added dropwise at −45 °C. The reaction mixture was stirred at this temperature for 3.5 h when the ammonia was allowed to evaporate. Ice-water was added and the mixture was extracted with ether (3 × 60 ml). The ethereal solution was washed with NH_4Cl solution and dried ($MgSO_4$). Evaporation of the ether *in vacuo* and distillation afforded *15* (0.9 g, 32 %), b.p. 114–115 °C/1 mmHg, m.p. 39–40 °C (solidified oil). The yield was improved considerably (75 %) if the product was purified by column chromatography (silica gel, ether) instead of distillation. Anal. $C_8H_{10}N_2$: C, H, N. IR: 3290, 2120 cm^{-1}. ^1H NMR: δ 1.6–2.5 (5H, m), 2.66 (2H, t), 7.47 (2H, s). *Semioxalate:* m.p. 152–153 °C. Anal. $C_8H_{10}N_2 \cdot 0.5\,(CO_2H)_2$: C, H, N.

4-(4-Pentenyl)pyrazole (16). A solution of *15* (1.5 g, 0.011 mol) and an equivalent amount of oxalic acid in ethanol (40 ml) was hydrogenated at room temperature over a small amount of Lindlar catalyst at atmospheric pressure until the calculated amount of hydrogen had been consumed and no trace of starting material remained (GLC). The catalyst was filtered off and the solvent evaporated *in vacuo*. The residue was treated with aqueous Na_2CO_3 and extracted with ether. After drying ($MgSO_4$) the ethereal solution was fractionated under reduced pressure affording 1.1 g (73 %) of product, b.p. 90–91 °C/0.3 mmHg. Anal. $C_8H_{12}N_2$: C, H, N. ^1H NMR: δ 1.2–2.3 (4H, m), 2.47 (2H, t), 4.80–5.05 (2H, m), 5.47–6.12 (1H, m), 7.33 (2H, s). *Oxalate:* m.p. 113–114 °C (from ethanol–ether). Anal. $C_8H_{12}N_2 \cdot (CO_2H)_2$: C, H, N.

4-(5-Oxo-5-phenylpentyl)pyrazole (17). To a solution of sodium ethoxide, prepared from sodium (1.2 g, 0.052 mol) and absolute ethanol (60 ml), ethyl benzoylacetate (10.3 g, 0.054 mol) was added and the mixture heated to reflux. A solution of the bromide *14* (6.7 g, 0.035 mol) in absolute ethanol (30 ml) was added dropwise and the reaction mixture was refluxed for 16 h. After filtration, evaporation *in vacuo* and addition of water (20 ml), conc. H_2SO_4 (20 ml) was added dropwise. The mixture was refluxed for 1 h, extracted with ether (4 × 50 ml) and made alkaline with NaOH (50 %). Extraction with ether (6 × 50 ml), drying ($MgSO_4$) and evaporation of the solvent *in vacuo* afforded the title compound, (5.3 g, 65 %), m.p. 83–84 °C (from ethanol–water). IR: 1680 cm^{-1}. ^1H NMR: 1.4–2.1 (4H, m), 2.55 (2H, t), 2.97 (2H, t), 7.25–8.1 (7H, m). *Oxalate:* m.p. 170–171 °C (from ethanol–light petroleum). Anal. $C_{14}H_{16}N_2O \cdot (CO_2H)_2$: C, H, N.

4-(5-Phenylpentyl)pyrazole (18). A solution of the oxo compound *17* (1.5 g), hydrazine hydrate (1 ml, 85 %) and KOH (1.1 g) in diethylene glycol was heated at 140 °C for 1.5 h and then at 200 °C for 1.5 h. After cooling, the reaction mixture was poured into water (50 ml) and extracted with $CHCl_3$. The organic phase was dried ($MgSO_4$), evaporated *in vacuo* and the residue distilled affording *13* (1.0 g, 71 %), b.p. 186 °C/0.6 mmHg. ^1H NMR: δ 1.2–2.0 (6H, m), 2.50 (2H, t), 2.60 (2H, t), 7.23 (5H, s), 7.40 (2H, s). *Oxalate:* m.p. 126–127.5 °C (from ethanol–light petroleum). Anal. $C_{14}H_{18}N_2 \cdot (CO_2H)_2$: C, H, N.

RESULTS AND DISCUSSION

The inhibitory power of the pyrazole derivatives on LADH activity was tested fluorometrically by observing the change of fluorescence of the coenzyme on its reduction with ethanol as substrate, and the inhibition constant, K_I, was determined as previously described.[1,2] The inhibition constants are shown in Table 1 which also includes some corresponding saturated compounds for comparison.

Table 1 shows that the introduction of a double or a triple bond in the substituent at the 4-position affords compounds which are less active than the corresponding saturated analogues. Compounds *4*, *5* and *7* are considerably less active (17–70 times) than the corresponding saturated derivatives 4-ethyl- and 4-hexylpyrazole, whereas *8a*, *8b*, *15* and *16* are only 4–9 times weaker than the saturated analogues. Apparently, the influence of a multiple bond in the latter compounds is more strongly correlated to the decrease in lipophilicity [20] of the substituents than is the case with compounds *4*, *5* and *7*. We have earlier found a positive correlation between the inhibitory power of 4-substituted alkylpyrazoles and the lipophilicity of the substituent [2] but the present data indicate that also electronic factors have an influence on the inhibitory activity. Some previously published results [1,2] suggest the same trend. Thus, 4-trifluoromethylpyrazole was found to be about 6 times less active than the methyl analogue in spite of its higher lipophilicity, and the difference in inhibitory power between 4-phenyl- and 4-cyclohexylpyrazole is greater than can be expected only from the

Table 1. Inhibitory power of pyrazole derivatives on LADH.

Compound	K_I, μM
4-Ethynylpyrazole (*4*)	0.50
4-(1-Hexynyl)pyrazole (*5*)	0.019
4-Phenylethynylpyrazole (*6*)	0.005
4-Ethenylpyrazole (*7*)	0.12
(*Z*)-4-(1-Hexenyl)pyrazole (*8a*)	0.0045
(*E*)-4-(1-Hexenyl)pyrazole (*8b*)	0.0025
(*Z*)-4-(2-Phenylethenyl)pyrazole (*9a*)	0.03
(*E*)-4-(2-Phenylethenyl)pyrazole (*9b*)	0.0016 [f]
4-Benzylpyrazole (*12*)	0.011
4-(2-Phenylethyl)pyrazole (*13*)	0.0011 [f]
4-(4-Pentynyl)pyrazole (*15*)	0.0073
4-(4-Pentenyl)pyrazole (*16*)	0.0034
4-(5-Phenylpentyl)pyrazole (*18*)	0.0005 [f]
Pyrazole [a]	0.22
4-Methylpyrazole [a]	0.013
4-Ethylpyrazole [a]	0.007
4-Pentylpyrazole [a]	0.0008
4-Hexylpyrazole [b]	0.0005
4-Phenylpyrazole [a]	0.1
4-Cyclohexylpyrazole [b]	0.0078
4-Cyclohexylmethylpyrazole [b]	0.0021
1*H*-Indazole (benzopyrazole) [c]	14
4,5,6,7-Tetrahydro-1*H*-indazole [d]	0.75
1-Methyl-4-propylpyrazole [e]	100

[a] From Ref. 1. [b] From Ref. 2. [c] From Ref. 19. [d] The inhibition constant for this compound was erroneously reported to be 0.075 in Ref. 2. [e] The inhibition constant for this compound was erroneously reported to be 0.10 in Ref. 2. [f] Corrected for the amount of the inhibitor bound by the enzyme.

difference in lipophilicity of the substituents. The high inhibitory activity of 4-phenylethynylpyrazole (*6*) cannot be anticipated when the activities of compound *4* and 4-phenylpyrazole are considered. This is also the case with the *E* isomer of 4-(2-phenylethenyl)pyrazole (*9b*). Evidently, conjugation between the pyrazole and benzene nuclei in compounds *6* and *9b* strongly reinforces the inhibitory activities. In compounds *12* and *13*, where the conjugation is broken, the phenyl group contributes to a lesser extent to the increase in activity when compared to the activities of the parent compounds 4-methyl- and 4-ethylpyrazole.

The pronounced difference in activity between the geometric isomers *9a* and *9b*, the *E (trans)* isomer being about 20 times more potent than the *Z (cis)* isomer, is noteworthy. However, inspection of molecular models shows the likely explanation.

It is reasonable to assume that the two rings are coplanar, and in such a case the 3(5)-position of the pyrazole ring in the *Z* isomer will be effectively blocked by the benzene ring thus making the compound less active, probably owing to steric hindrance. On the other hand, there is little difference in activity between the isomers of 4-(1-hexenyl)-pyrazole (*8a*, *8b*), the *E* isomer being 1.8 times more potent than the *Z* isomer. This may reflect the great conformational flexibility of the 1-hexenyl chain.

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