

LINK Synthesis with 3-Hydroxy-1*H*-pyrazoles: 3-Carboxyisoalkyloxy-1*H*-pyrazoles – Bicyclic Acylpyrazolium Salts and γ -Lactams – 3-Carboxyisoalkyloxy-4,5-dihydro-1*H*-pyrazol-5-ones

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Dedicated to Prof. Dr. Dr. h. c. mult. A. R. Katritzky, FRS, on the Occasion of his 70th Birthday

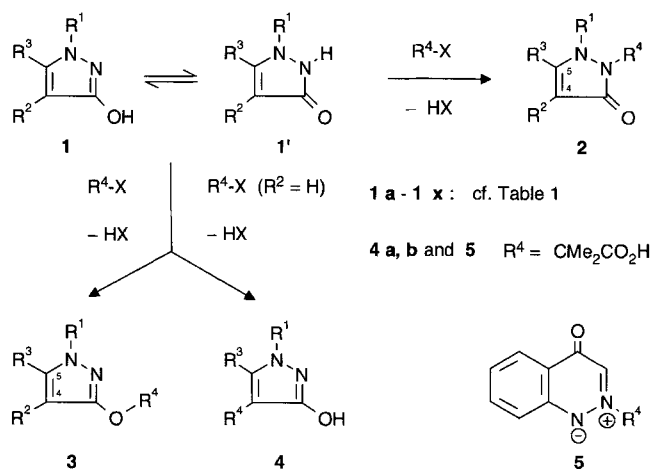
Abstract. 1-Substituted 3-hydroxy-1*H*-pyrazoles **1** react with chloroform, NaOH, and acetone resp. butan-2-one O-regio-specifically to yield 2-methyl-2-[(1*H*-pyrazol-3-yl)oxy]-propanoic resp. -butanoic acids **14** via a dichlorocarbene (**12**) – dichlorooxirane (**9**) pathway. Chlorides **17** of **14** easily cyclize to *N*-acylpyrazolium salts **18/19**, which quantitatively afford esters **22–26** and amides **27–29** of **14**. Enantiomers of the butanoic acid **14h**, obtained via their diastereomeric cholesterol esters, differ in their stimulus to peroxisome proliferation. At 140 °C pyrazolium salts **18** undergo thermolysis to bicyclic β -

oxa- γ -lactams **30–32**. 3-Carboxyisoalkylamino-pyrazoles similarly give 1*H*- β -aza- γ -lactams **34**. Reactions of **14** with surplus SOCl₂ result in 6-chloro-**37** resp. 7-chloro- β -oxa- γ -lactams **38** via chlorosulfonylation and extrusion of SO, and in 4,4-bispyrazolyl-sulfoxide **39**. A mild introduction of additional O-functions into pyrazoles affording 4,5-dihydro-3-hydroxy-5-oxo-1*H*-pyrazoles **52–57** is presented. Biological effects of the new pyrazoles are protection against shock and ADP-induced thromboembolism, reduction of serum lipids and improvement of blood flow.

We designed new antisclerogenic drugs, which were to improve blood flow without blocking the biosynthesis of antiaggregatory prostacyclin (PG I₂) and to lower the serum levels of triglycerides (TGL) and low density lipoprotein cholesterol (LDL-Ch). Now we report on the synthesis and chemistry of 3-carboxyisoalkyloxy-1*H*-pyrazoles, many of which exhibited the desired pharmacological profile [1, 2]. Particular **14a** and **14b** caused decrease of TGL and LDL-Ch in men, in mini-LEWE-pigs and other mammals, prolongation of bleeding time in the same order as ASA without affecting cyclooxygenase, PG I₂ and plasma coagulation, protection against ADP-induced thromboembolism and against traumatic and endotoxin shock after oral (*p.o.*) application with high bioavailability and very low toxicity; *e.g.* mini-LEWE-pigs tolerated 150 mg **14a**/kg/d. *p.o.* for 12 months. **14a** has a lasting sweet taste, stimulating the pigs' appetite. Chiral 1-substituted 3-carboxyisoalkyloxy-1*H*-pyrazoles (**14h**) enantiospecifically induced the proliferation of liver cell peroxisomes [3], in which *e.g.* enzymes for the β -oxidation of saturated fatty acids are located.

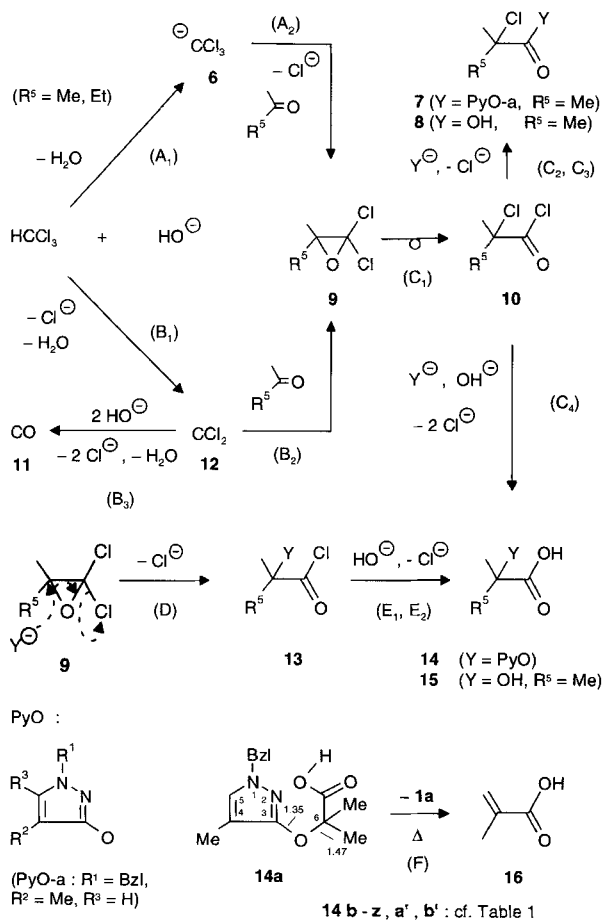
LINK Synthesis with 1-Substituted 3-Hydroxy-1*H*-pyrazoles – 1-Substituted 3-Carboxyisoalkyloxy-1*H*-pyrazoles

As 1-substituted 3-hydroxy-1*H*-pyrazoles, most of which easily are obtainable via DORN rearrangement [4], mainly exist as the OH-tautomers **1**, they are named as such and not as 1,2-dihydro-3*H*-pyrazol-3-ones (**1'**). This does not mean O-regiospecific alkylation in reactions of **1** with R⁴-X (Scheme 1). While alkali salts of **1** by chloroacetonitrile in butan-2-one [5], by methyl dichloroacetate (two O-specific substitutions in *n*-butanol) [6] and by epichlorohydrin in DMF are O-substituted (type **3**), by epichlorohydrin in alcohols O- (**3**) and N-derivatives (**2**) are formed [7]. Structures **2** resp. **3** easily can be assigned by ¹H NMR and IR. If R² = R³ = H, *J*₄₅ = 3.5 Hz (type **2** in CDCl₃) resp. 2.4 Hz (type **3** in CDCl₃); for **2** the very strong ν (C=O) = 1640–1650 cm⁻¹ (in CHCl₃) is characteristic. Sodium salts of 1-substituted 3-hydroxy-1*H*-pyrazoles **1** in acetone or butan-2-one by the short living dichlorooxiranes **9** (Scheme 2) are regiospecifically O-substituted un-



Scheme 1

der the conditions discussed below (type **3**); if R^1 in **1** causes relatively high electron density (e.g. $R^1 = iPr$ or $c-C_6H_{11}$), some additional substitution at C-4 (**4a, b**) was observed. 4-Hydroxy-cinnoline under the same conditions as 3-hydroxy-1H-pyrazoles **1** regioselectively is N-substituted by a dichlorooxirane **9** to give an azomethinimine **5**[8].



Scheme 2

When the demand for herbicides and antihyperlipidemics, e.g. ethyl 2-(4-chloro-phenoxy)-2-methylpropanoate (clofibrate), caused a renaissance of the LINK synthesis [9], i.e. the reaction of phenols, acetone, chloroform and alkali to aryloxyisobutyric acids, little was known about its mechanism. The extension to costly and tautomerizing hydroxy-N-heterocycles required some insight into the course and side reactions (Scheme 2).

Chloroform in the presence of base generates the trichloromethanid anion (**6**) in a fast reaction at 0–5 °C (A_1), while at higher temperatures (54–58 °C) the dichlorocarbene (**12**) pathway (B_1) is favoured. **6** as well as **12** react *via* (A_2) resp. (B_2) with a carbonyl compound to a dichlorooxirane **9**, which intramolecularly can rearrange (0–20 °C; JOCICZ rearrangement [10], cf. [11–13]) to an α -chlorocarboxylic acid chloride **10** (C_1) or can directly be attacked by a nucleophile Y^- (D), cf. [11, 14]. We decided to avoid the rearrangement (C_1), because the exchange of Cl in **10** for Y (C_4) contrary to (D) is a slow reaction (e.g. the half life for $Y^- = MeO^-$ at 40 °C is 7 h. [11]), and successfully employed the dichlorocarbene **12** pathway [Scheme 2; (B_1), (B_2), (D), (E_1)].

Using optimum conditions for the synthesis of 2-methyl-2-[(4-methyl-1-benzyl-1H-pyrazol-3-yl)oxy]-propanoic acid (**14a**) from 1-benzyl-3-hydroxy-4-methyl-1H-pyrazole (**1a**), chloroform and sodium hydroxide in the molar ratio 1.00 : 2.00 : 8.00 in acetone at 49–54 °C, we found 0.77 mol **14a** [*via* (D), (E_1)], 0.15 mol 2-hydroxy-2-methylpropanoic acid [**15**; *via* (D), (E_2)], 0.07 mol methacrylic acid [**16**; *via* (D), (E_2) from **15**], 0.94 mol carbon monoxide [**11**; *via* (B_3)] and traces of 2-chloro-2-methylpropanoic acid [**8**; *via* (C_1), (C_3)], i.e. 96.5% of the chloroform resultants; 0.10 mol of **1a** were regained. By checking the consumption of $CHCl_3$ and evolution of CO it became evident, that the fractional addition of NaOH at 49–54 °C caused a steady supply with dichlorocarbene **12**. Firstly we warned of the danger of toxic CO during technical LINK syntheses. Unavoidable were aldol-condensation products of the ketones, thus from acetone we got per 1.00 mol **1a** 0.06 mol diacetone alcohol and 0.19 mol mesityl oxide. These as well as **8**, **15** and **16** can be separated from **1** and **14** by treatment with water.

To check pathway (C_4) (Scheme 2) we treated **1a**-Na in acetone at 53 °C with α -chloroisobutyryl chloride (**10**, $R^5 = Me$) and found 78% of the O-acylation product of **1** [**7**; *via* (C_2)]. Methyl α -bromoisobutyrate under CLAISEN conditions (**1a** and K_2CO_3 in acetone or **1a**-Na in DMF) did not react, phase transfer reaction gave 4% **14a** (**1a**, benzene, 50% aqueous NaOH, TEBA,

55 °C). All this resembles the behaviour of chlorooxiranes, which much faster than α -chloroaldehydes or ketones react with nucleophiles [15, 16]. Knowledge about the course of the reaction enabled us further to extend the scope of the LINK synthesis to 3- and 5-amino-pyrazoles, yielding 3- and 5-carboxyisoalkylamino-1*H*-pyrazoles [17].

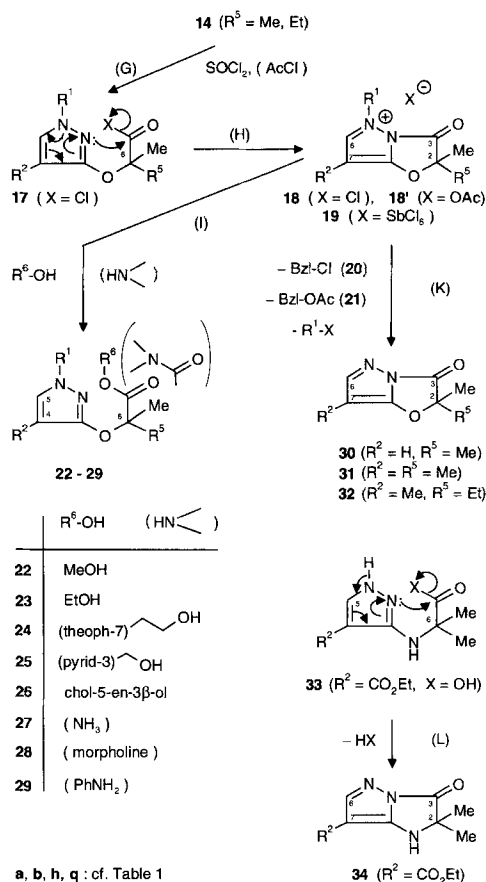
Contrary to azomethinimines **5**, which easily are decarboxylated at 65 °C [8], the 3-carboxyisoalkoxy-1*H*-pyrazoles **14** ($R^5 = \text{Me}$) thermally are split into 3-hydroxy-1*H*-pyrazoles **1** and methacrylic acid **16** at 0–15 °C about their *m.p.*'s, caused by the unusual (C-6)-O bond length (1.47 Å in **14a**). We studied the quantitative thermolysis (F) of **14a** ($R^2 = \text{Me}$), **14b** ($R^2 = \text{Cl}$) and **14e** ($R^2 = \text{H}$); **14c** ($R^2 = \text{Br}$) violently decomposed. Energy-rich radiation also causes reaction (F). Salts of **5** (**5-Na**, *m.p.* 180–182 °C) and **14** (**14a-Na**, *m.p.* 197–198 °C) are stable.

The ^1H NMR spectra of **14** ($R^2 = R^3 = \text{H}$) display $J_{45} = 2.3\text{--}2.4$ Hz, typical for type **3** (Scheme 1), and moreover for **14** ($R^3 = \text{H}$) $\Delta_{\text{HMPT(A)}}^{\text{CDCl}_3} = [\delta(5\text{-H}), \text{CDCl}_3] - [\delta(5\text{-H}), \text{HMPT(A)}]$ in a range characteristic of 1,3-disubstituted pyrazoles (Table 2) [18].

Bicyclic *N*-Acyl-Pyrazolium Salts–Diastereomeric Esters–Amides–Thermolysis to Bicyclic β -Oxa- γ -Lactams

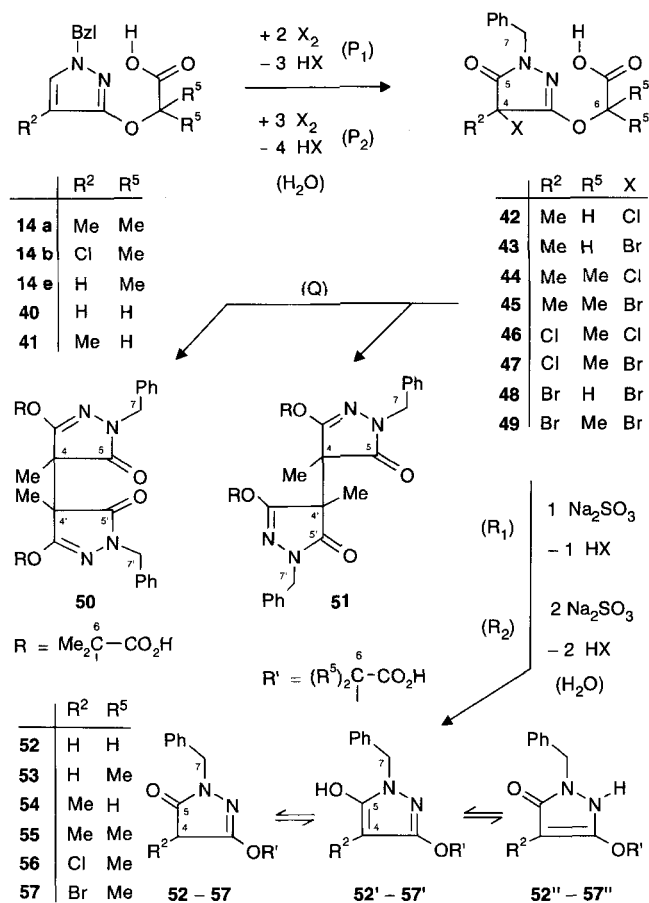
With equimolar amounts of acid chlorides, which replace OH for Cl under formation of volatile products, *i.e.* with thionyl chloride (SOCl_2) or dichloromethyl methyl ether (CHCl_2OMe), the 3-carboxyisoalkoxy-1*H*-pyrazoles **14** ($R^1 = \text{aralkyl}$, $R^5 = \text{Me}$ or Et) readily yield a new type of bicyclic acylpyrazolium salts **18** (Scheme 3). With SOCl_2 in dry dichloromethane reaction (H) proceeds quantitatively at 20–50 °C. The solutions of **18** or the crude pyrazolium chlorides **18** even with bulky alcohols or with amines react (Scheme 3) to esters or amides of **14** in nearly 100% yield (I) [19]. For the stable acylpyrazolium salts **19a** resp. **19h**, obtained by addition of antimon pentachloride to the solution of **18a** resp. **18h**, considerable deshielding at (C-6) [$\delta(6\text{-H}) = 8.25$ resp. 8.25 ppm] and at (N-CH₂) [$\delta = 5.60$ resp. 5.70 ppm] compared to the acids **14a** resp. **14h** [$\delta(5\text{-H}) = 6.96$ resp. 7.08 ppm; $\delta(\text{N-CH}_2) = 4.99$ resp. 5.10 ppm], and $\nu(\text{CO}) = 1828\text{ cm}^{-1}$ is characteristic. Anhydro-1-hydroxy-3-oxopyrazolo[1,2-*a*]pyrazolium hydroxides, the only known systems somewhat similar to **18/19**, display low field NMR signals adjacent to N⁺ [20]. The easy intramolecular pyrazolium salt formation is a new example of the gem-dialkyl effect. Conformations of acid chlorides **17** ($R^5 = \text{Me}$, Et) with minimum steric hindrance are disposed for nucleophilic attack of the sp^2 pyrazole-(N-2) on -C(=O)Cl, assisted

by the sp^3 pyrazole-(N-1) (Scheme 3). This assistance is weakened by an e -acceptor R^1 and/or R^2 , thus **17b** ($R^2 = \text{Cl}$) can be isolated *via* (G). On further heating **17b** slowly undergoes reactions (H) and (K) (Scheme 4). The acid chloride **17b** doesn't show lower field shift for $\delta(5\text{-H})$ and $\delta(\text{N-CH}_2)$, compared to the acid **14b**. With **17** and **18** new bulky acyls were introduced to yield semisynthetic penicillins. One cannot exclude pyrazolium salts **18** as intermediates during step (E₁) (Scheme 2) in the LINK synthesis of **14**.



Scheme 3

To learn, if bulky substitution at (C-6) is essential for biological effects of 3-carboxyisoalkoxy-1*H*-pyrazoles **14**, we needed enantiomers of **14h**. We did not succeed in isolating pure diastereomeric salts of **14h** with un toxic and easily available chiral 1-deoxy-1-methylamino sugar alcohols [21], but separated the two diastereomeric cholesterol esters **26h** ($R^2 = \text{Me}$, $R^5 = \text{Et}$) of **14h** and saponified **26h** [dia I] to (+)-**14h** (93.3% (+)-enantiomer) and **26h** [dia II] to (-)-**14h** (99.1% (-)-enantiomer). For 14 d. six mice each were given water [100] resp. 0.5 mmol/kg/d. **14a** [255], *rac*-**14h** [274], (-)-**14h** [314] and (+)-**14h** [143] as sodium salts in water, and liver cell peroxisomes (PSO) counted under an electron microscope (in [] normalized number of PSO/unit area [3]). Amendments are desirable, but for



Scheme 5

ic 4,4'-bis-pyrazolyls **50** (*meso*) and **51** (*rac*) (Q), which were separated. Structures **50** resp. **51** were assigned by ¹H NMR using the characteristic OMe-signals of their dimethyl esters, from which only that of dimethyl-**51** was split after addition of a chiral shift reagent. We achieved the 4,5-dihydro-5-oxo-acid **55** from the 4-bromo-5-oxo-acid **45** with ascorbic acid.

From the three possible tautomers of 1-benzyl-[(4,5-dihydro-5-oxo-1*H*-pyrazol-3-yl)oxy]-carboxylic acids by ¹H NMR and ¹³C NMR in [D₆] DMSO, which favours the (5-OH)-type **52'**–**57'**, only two were monitored, i.e. **52** (37%), **53** (60%), **54** (29%), **55** (38%), **56** (9%) and **57** (28%) resp. **52'** (63%) – **57'** (72%) (Table 4).

4-Mono- (**42**, **44**) resp. 4,4-dichloro-5-oxo-acids (**46**) are available by addition of hydrogen peroxide to 1-substituted 3-carboxy(*iso*)alkoxy-1*H*-pyrazoles (**41**, **14a**, **14b**) in hydrochloric acid. We extended the scope of the new process for the introduction of a second pyrazole O-function to 1-alkyl-3-hydroxy-1*H*-pyrazoles **1**. While it failed in aqueous solutions of sodium salts of **1**, it worked well at 15–20 °C in 4*N* HCl or phosphoric acid with 2 mol Br₂ per mol **1** and catalytic amounts of KBr, followed by exchange of Br for H according to

(R₁) [28]. By passing air through the aqueous solutions of sodium salts of 1-alkyl-4,5-dihydro-3-hydroxy-5-oxo-1*H*-pyrazoles (**52**–**57**, R' = H) at 20–30 °C a third O-function (4-OH) easily is introduced [28].

Experimental

¹H NMR: Tesla 587.4 (100 MHz) and Bruker MSL 400, int. standard TMS, hexamethyldisiloxane ($\delta = 0.06$ ppm) or Me₃Si(CH₂)₃SO₃Na ($\delta = -0.02$ ppm). – ¹³C NMR: Varian CFT 20 (20 MHz), int. standard hexamethyldisiloxane ($\delta = 1.92$ ppm in CDCl₃, 1.91 in [D₆] DMSO, 2.30 in D₂O). – IR: Specord 75-IR (Carl Zeiss; Jena). – EA: Carlo Erba 1106 (C, H, N). – Melting points: Boëtius micro *m.p.* apparatus. → MS (70 eV, 140 °C): Hewlett Packard 5985. – Optical rotation: Polamat A (Carl Zeiss Jena). – GC (FID, 195 °C): Varian 2400, capillary column, 37 m, 1.5 ml argon per min, isothermal, 50 °C, Carbowax 20M (treated with water vapor, 0.3%) (CHCl₃); Varian 1868, steel column, 1.5 m, 2 mm, 30 ml nitrogen per min, isothermal; 130 °C, 15% FFAP on Chromosorb W.AW 60/80 mesh (a: **16**, 4-hydroxy-4-methyl-2-pentanone and 4-methyl-3-penten-2-one); 72 °C, 10% SE-30 on Chromosorb W.AW DMCS 80/100 mesh (b: **8** and **15**, in acetone silylated with hexamethyldisilazane/Me₃SiCl/pyridine 6:2:1[v/v/v]); evaluation with calibrating plots, using *n*-hexadecane (a) resp. *n*-decane (b) as int. standard. – CO-analysis: by recording the IR intensity at $\nu = 2143$ cm⁻¹ (Infralyt, Junkalor, Dessau) and after total oxidation (two layer catalyst Pt/Al₂O₃, 450 °C; Co₃O₄/pumice, 650 °C) to CO₂ as K₂CO₃ by titration with 0.1*N* HCl[29].

2-Methyl-2-[[4-methyl-1-(phenylmethyl)-1*H*-pyrazol-3-yl]oxy]-propanoic acid (**14a**)

In a 6-l sulfonation flask, equipped with a stirrer (10 blades, teflon-coated stainless steel), intensive reflux condenser and thermometer, one neck intermediately fitted with a solid addition funnel, 3.00 l acetone, chloroform (477.6 g, 4.00 mol) and 3-hydroxy-4-methyl-1-(phenylmethyl)-1*H*-pyrazole (**1a**; 376.4 g, 2.00 mol) were heated (bath 65 °C) with stirring to 45 °C, while part of **1a** remains suspended. After removal of the bath and addition (30 sec.) of NaOH (100 g, 2.50 mol; Add. 1) with vigorous stirring, the exothermic reaction starts, further **1a** is dissolved, part of **1a**-Na and NaCl is deposited and within 20 min. of stirring the internal temp. rises up to 56–58 °C. Stirring is continued for further 20 min., whereby the internal temp. decreases to 49–52 °C. Now the bath (35 °C) is replaced and at intervals of 15 min. further NaOH (24 portions each of 22.5 g, altogether 13.5 mol; Add. 2–25) is added, whereby an internal temp. of 49–54 °C and a bath temp. of 35–45 °C is maintained by occasional cooling. The reflux condenser is then replaced by a distillation head, the bath temp. gradually increased to 70–75 °C and 2.00 l acetone (free of CHCl₃ according to GC) distilled off, while stirring is continued as long as possible. The residue is dissolved in 2.4 l water and with stirring and cooling 37% hydrochloric acid is added up to pH 3. The crude mixture of **14a** and unreacted **1a** occasionally is precipitated as a grease, the crystallization of which is accelerated by separation from the mother liquor (ML-1) and stirring with added water of 25 °C to dissolve the by-

products. The crystalline mixture is filtered by suction and washed with 12 portions of water (26 °C, 300 ml each; ML-

2), then gradually added at internal 30 °C to the stirred solution of NaHCO₃ (168.0 g, 2.00 mol), which must be free of Na₂CO₃,

Tab. 1 Analytical data of (N-1)-substituted 2-methyl-2-[(1*H*-pyrazol-3-yl)oxy]-propanoic and -butanoic acids (**14a–z**, **a'**, **b'**) and 2-methyl-2-(3-hydroxy-1*H*-pyrazol-4-yl)-propanoic acids (**4a**, **4b**)

| | R ¹ | R ² | R ³ | R ⁵ | <i>m.p.</i> (°C) | emp. formula (mol. mass) | calcd./found | | |
|-------------------------|--------------------|-----------------|----------------|----------------|------------------|---|--------------|------|----------|
| | | | | | | | C | H | N/+Cl/Br |
| 14b | Bzl | Cl | H | Me | 126 – 127 | C ₁₄ H ₁₅ ClN ₂ O ₃ | 57.05 | 5.13 | +12.03 |
| | | | | | ^{a)} | (294.7) | 56.92 | 5.03 | +11.95 |
| 14c | Bzl | Br | H | Me | 132 | C ₁₄ H ₁₅ BrN ₂ O ₃ | 49.57 | 4.46 | +23.56 |
| | | | | | ^{b)} | (339.2) | 49.85 | 4.51 | +23.69 |
| 14d | Bzl | NO ₂ | H | Me | 126 – 127 | C ₁₄ H ₁₅ N ₃ O ₅ | 55.08 | 4.95 | 13.76 |
| | | | | | ^{a)} | (305.3) | 55.20 | 4.90 | 13.59 |
| 14e | Bzl | H | H | Me | 129 – 130 | C ₁₄ H ₁₆ N ₂ O ₃ | 64.60 | 6.20 | 10.76 |
| | | | | | ^{c)} | (260.3) | 64.33 | 6.26 | 10.89 |
| 14f | Bzl | H | H | Et | 111 – 112 | C ₁₅ H ₁₈ N ₂ O ₃ | 65.67 | 6.61 | 10.21 |
| | | | | | ^{d)} | (274.3) | 65.49 | 6.57 | 10.17 |
| 14g | Bzl | H | Me | Me | 139 – 140 | C ₁₅ H ₁₈ N ₂ O ₃ | 65.67 | 6.61 | 10.23 |
| | | | | | ^{a)} | (274.3) | 65.72 | 6.71 | 10.41 |
| <i>rac</i> - 14h | Bzl | Me | H | Et | 86 – 87 | C ₁₆ H ₂₀ N ₂ O ₃ | 66.65 | 6.99 | 9.71 |
| | | | | | ^{d)} | (288.4) | 66.30 | 6.92 | 9.68 |
| 14i | Bzl | Me | Me | Me | 107 – 108 | C ₁₆ H ₂₀ N ₂ O ₃ | 66.65 | 6.99 | 9.71 |
| | | | | | ^{c)} | (288.4) | 66.52 | 7.06 | 9.74 |
| 14k | Bzl | Me | Me | Et | 99 – 99.5 | C ₁₇ H ₂₂ N ₂ O ₃ | 67.50 | 7.33 | 9.27 |
| | | | | | ^{d)} | (302.4) | 67.43 | 7.36 | 9.22 |
| 14l | Bzl | Cl | Me | Me | 126 – 127 | C ₁₅ H ₁₇ ClN ₂ O ₃ | 58.35 | 5.55 | 9.07 |
| | | | | | ^{c)} | (308.8) | 57.98 | 5.49 | 9.08 |
| 14m | 4- <i>i</i> Pr-Bzl | H | H | Me | 87 – 88 | C ₁₇ H ₂₂ N ₂ O ₃ | 67.50 | 7.33 | 9.27 |
| | | | | | ^{f)} | (302.4) | 67.55 | 7.33 | 9.24 |
| 14n | 4- <i>i</i> Pr-Bzl | Cl | H | Me | 102 – 103 | C ₁₇ H ₂₁ ClN ₂ O ₃ | 60.62 | 6.28 | +10.52 |
| | | | | | ^{e)} | (336.8) | 60.53 | 6.23 | +10.62 |
| 14o | 4- <i>i</i> Pr-Bzl | Br | H | Me | 97 – 98 | C ₁₇ H ₂₁ BrN ₂ O ₃ | 53.55 | 5.55 | +20.96 |
| | | | | | ^{a)} | (381.3) | 53.68 | 5.50 | +21.12 |
| 14p | 4-Cl-Bzl | H | H | Me | 147 – 148 | C ₁₄ H ₁₅ ClN ₂ O ₃ | 57.05 | 5.13 | 9.51 |
| | | | | | ^{c)} | (294.7) | 57.19 | 5.10 | 9.47 |
| 14q | 4-Cl-Bzl | Me | H | Me | 113 – 114 | C ₁₅ H ₁₇ ClN ₂ O ₃ | 58.35 | 5.55 | +11.48 |
| | | | | | ^{c)} | (308.8) | 58.20 | 5.57 | +11.65 |
| 14r | 4-Cl-Bzl | Cl | H | Me | 139 | C ₁₄ H ₁₄ Cl ₂ N ₂ O ₃ | 51.08 | 4.29 | +21.54 |
| | | | | | ^{b)} | (329.2) | 51.01 | 4.32 | +21.71 |
| 14s | 4-MeO-Bzl | H | H | Me | 131 | C ₁₅ H ₁₈ N ₂ O ₄ | 62.27 | 5.92 | 9.65 |
| | | | | | ^{g)} | (290.3) | 61.99 | 5.96 | 9.57 |
| 14t | 3-Cl,4-MeO-Bzl | Me | H | Me | 123 – 124 | C ₁₆ H ₁₉ ClN ₂ O ₄ | 56.73 | 5.65 | 8.27 |
| | | | | | ^{g)} | (338.8) | 56.79 | 5.73 | 8.18 |
| 14u | Bzl | H | Ph | Me | 148 – 149 | C ₂₀ H ₂₀ N ₂ O ₃ | 71.41 | 5.99 | 8.33 |
| | | | | | ^{c)} | (336.4) | 71.38 | 5.97 | 8.31 |
| 14v | Bzl | Cl | Ph | Me | 174 – 175 | C ₂₀ H ₁₉ ClN ₂ O ₃ | 64.78 | 5.16 | +9.56 |
| | | | | | ^{a)} | (370.8) | 65.12 | 5.21 | +9.66 |
| 14w | (Fur-2-yl)-methyl | H | H | Me | 99 | C ₁₂ H ₁₄ N ₂ O ₄ | 57.59 | 5.64 | 11.19 |
| | | | | | ^{a)} | (250.3) | 57.56 | 5.70 | 11.08 |
| 14x | Ph | H | H | Me | 105 – 106 | C ₁₃ H ₁₄ N ₂ O ₃ | 63.40 | 5.73 | 11.37 |
| | | | | | ^{c)} | (246.3) | 62.96 | 5.79 | 11.18 |
| 14y | Ph | Cl | H | Me | 155 – 156 | C ₁₃ H ₁₃ ClN ₂ O ₃ | 55.62 | 4.67 | +12.63 |
| | | | | | ^{a)} | (280.7) | 56.04 | 4.71 | +12.75 |
| 14z | Ph | Br | H | Me | 166 – 167 | C ₁₃ H ₁₃ BrN ₂ O ₃ | 48.02 | 4.03 | +24.58 |
| | | | | | ^{a)} | (325.2) | 48.37 | 4.00 | +24.28 |
| 14a' | <i>i</i> Pr | H | H | Me | 66 – 67 | C ₁₀ H ₁₆ N ₂ O ₃ | 56.59 | 7.60 | 13.20 |
| | | | | | ^{e)} | (212.3) | 56.86 | 7.55 | 13.14 |
| 14b' | Cyclohex | H | H | Me | 79 – 80 | C ₁₃ H ₂₀ N ₂ O ₃ | 61.88 | 7.99 | 11.10 |
| | | | | | ^{e)} | (252.3) | 62.19 | 8.05 | 11.02 |
| 4a | <i>i</i> Pr | ^{b)} | H | Me | 191 – 192 | C ₁₀ H ₁₆ N ₂ O ₃ | 56.59 | 7.60 | 13.20 |
| | | | | | ⁱ⁾ | (212.3) | 56.84 | 7.73 | 13.12 |
| 4b | Cyclohex | ^{h)} | H | Me | 180 – 181 | C ₁₃ H ₂₀ N ₂ O ₃ | 61.88 | 7.99 | 11.10 |
| | | | | | ^{g)} | (252.3) | 61.71 | 8.03 | 11.04 |

Crystallized from toluene ^{a)}, xylene ^{b)}, aqu. EtOH ^{c)}, CCl₄ ^{d)}, cyclohexane ^{e)}, *n*-hexane ^{f)}, EtOH ^{g)}, PrOH ⁱ⁾, ^{h)} R⁴ = CMe₂CO₂H; 5 – 6% separated by fractional crystallization, less soluble in cyclohexane than **14a'**, **14b'**.

in 2.0 l water. When the evolution of CO₂ is finished, undissolved **1a** is filtered by suction, washed twice with 100 ml of water (to filtrate), treated with methanol (50 ml; 40 °C), cooled and filtered; white **1a** (37.4 g, 0.20 mol; *m.p.* 162–163 °C) is recovered. To the cooled filtrate 37% hydrochloric acid gradually is added with stirring up to pH 4, **14a** filtered by suction (ML-3), washed with 10 portions of water (25 °C, 200 ml each; to ML-3), dissolved in ethanol (1.0 l; 70 °C) and water (600 ml; 25 °C) added with stirring. On cooling **14a** crystallizes, 423.5 g (1.54 mol, 77.2%); white leaflets, *m.p.* 114–115 °C. **14a** must be dried at 25 °C below its *m.p.* and protected against UV. To get colourless solutions, **14a** can be slurried in CCl₄ (400 ml, 60 °C), cooled to 10 °C and filtered, *m.p.* 114–115 °C. – UV (MeOH): λ_{max}/nm (lg ε) = 207 (9.95), 235 (7.66). – IR (CHCl₃ and KBr): ν/cm⁻¹ = 1725 (C=O: CO₂), no absorption in the range of 1650. – ¹³C NMR (CDCl₃): δ/ppm = 6.8 (4-Me), 25.0 (Me₂), 55.6 (N–C), 81.4 (C-6), 104.6 (C-4), 127.6 and 128.7 (Ph: C-2, C-6 and C-3, C-5), 127.9 (Ph: C-4), 129.5 (C-5), 136.6 (Ph: C-1), 158.2 (C-3), 176.7 (CO₂H). – MS: *m/z* = 274 [M⁺], 188 [1a⁺], 91 [PhCH₂⁺]. – pK_a in MeOH/H₂O (9:1 [v/v]) = 4.3.

C₁₅H₁₈N₂O₃ calcd.: C 65.67 H 6.61 N 10.21
(274.3) found: C 65.55 H 6.57 N 10.27.

Analogously the 2-methyl-2-[(pyrazol-3-yl)oxy]-propanoic acids **14e, g, i, m, p, q, s, t, u, w, x, a', b'** and with butan-2-one the -butanoic acids **14f, h, k**. (Table 1) were prepared, yields 68–76%.

In three identical runs we perforated aliquots (250 ml) of the combined ML-1 and ML-2 with 250 ml of ether for 3 d. each. After removal of ether, in the residue 2-chloro-2-methylpropanoic acid (**8**, 2.00 mmol), 2-hydroxy-2-methylpropanoic

acid (**15**, 299 mmol), methacrylic acid (**16**, 129 mmol), 4-hydroxy-4-methyl-2-pentanone (123 mmol) and 4-methyl-3-penten-2-one (380 mmol) were estimated by GC, whereby **15** + **16** (428 mmol) was nearly constant (± 0.8%). We also perforated aliquots of ML-3 and found **15** (2.80 mmol), **16** (10.1 mmol) and 4-hydroxy-4-methyl-2-pentanone (4.50 mmol); mmoles given in brackets refer to the average contents of the whole ML-1 and ML-2 resp. ML-3. – In two similar runs with 0.50 mol **1a**, 1.00 mol CHCl₃ and 4.00 moles NaOH the apparatus was supplemented by a gas-inlet tube and a gas outlet on top of the intensive condenser, connected with three cooling traps, followed by a U-tube with molecular sieve 3 Å, an Infralyt with recorder, a reactor with the oxidation catalysts, a second Infralyt for monitoring total oxidation of CO to CO₂ and three gas wash bottles with 2.35N KOH. When the fast addition of NaOH (Add. 1) was finished, the inlet of air, cleared of H₂O and CO₂ by passing through KOH, was started and after 12–15 min. CO was monitored. Whenever further NaOH was added (Add. 2 – 25), within 20 sec. a fast increasing amount of CO was observed, which strongly decreased after 15 min. After Add. 24 the last CHCl₃ in the reaction mixture was detectable by GC, after Add. 25 no further CO was traced. We found an average of 0.47 mol CO (**11**).

*2-Chloro-2-methyl-[4-methyl-1-(phenylmethyl)-1*H*-pyrazol-3-yl]-propanoate (7)*

1a-Na (4.20 g, 20.0 mmol), 2-chloro-2-methylpropanoic acid chloride (**10**, R⁵ = Me; 2.82 g, 20.0 mmol) and 30 ml acetone were stirred at 53 °C for 5 h. After removal of acetone the residue was treated with 50 ml 0.1N NaOH, the filtered product washed twice with water and crystallized from aqueous ethanol, **7** (4.57 g, 78%), *m.p.* 93.5–94 °C. – ¹H NMR

Tab. 2 ¹H NMR of (N-1)-substituted 2-methyl-2-[(1*H*-pyrazol-3-yl)oxy]-propanoic and butanoic acids **14** in CDCl₃ [in HMPT(A)]

| | δ(6-C=Me ₂) δ(6-C-Me) | δ(N-CH ₂) δ(N-CH) | δ(R ²) | δ(R ³) | Δ _{HMPT(A)} ^{CDCl₃} J ₄₅ (Hz) |
|-------------------------|--------------------------------------|----------------------------------|------------------------|------------------------|--|
| 14a | 1.61 (s, 6H) [1.58] | 4.99 [5.11] | 1.89 (d, 3H) [1.86] | 6.96 (q, 1H) [7.44] | -0.48 |
| 14b | 1.66 (s, 6H) [1.61] | 4.99 [5.18] | – | 7.16 (s, 1H) [8.00] | -0.84 |
| 14c | 1.69 (s, 6H) [1.61] | 5.00 [5.22] | – | 7.14 (s, 1H) [8.10] | -0.96 |
| 14d | 1.75 (s, 6H) | 4.95 | – | 7.79 (s, 1H) | |
| 14e | 1.59 (s, 6H) [1.54] | 5.06 [5.20] | 5.74 (d, 1H) [5.55] | 7.14 (d, 1H) [7.73] | -0.59 2.4 [2.2] |
| 14f | 1.58 ^{a)} [1.49] | 5.10 [5.20] | 5.76 (d, 1H) [5.60] | 7.17 (d, 1H) [7.71] | -0.54 2.4 [2.3] |
| 14g | 1.60 (s, 6H) | 5.04 | 5.55 | 2.14 | |
| <i>rac</i> - 14h | 1.52 ^{b)} [1.57] | 5.10 [5.18] | 1.92 (d, 3H) [1.87] | 7.08 (q, 1H) [7.40] | -0.32 |
| 14i | 1.56 (s, 6H) | 5.04 | 1.82 | 2.04 | |
| 14k | 1.50 ^{c)} | 5.16 | 1.87 | 2.10 | |
| 14l | 1.66 (s, 6H) | 4.96 | – | 2.07 | |
| 14u | 1.64 (s, 6 H) [1.56] | 5.04 [5.16] | 5.79 (s, 1H) [5.73] | 7.14 – 7.40 (m) | |
| 14a' | 1.63 (s, 6H) [1.52] | 4.30 ^{d)} [4.33] | 5.70 (d, 1H) [5.46] | 7.23 (d, 1H) [7.60] | -0.37 2.3 [2.2] |
| 14b' | 1.62 (s, 6H) [1.53] | | 5.70 (d, 1H) [5.48] | 7.23 (d, 1H) [7.58] | -0.35 2.3 [2.2] |

ABM₃: δ/ppm [(C-6)–CH₂Me] = 0.98 [0.91] ^{a)}, 0.98 [0.92] ^{b)}, 0.99 ^{c)}; δ/ppm (N–C=Me₂) = 1.37, 1.47 [1.31, 1.41] ^{d)}

(CDCl₃): δ /ppm = 1.87 (d, 3H, 4-Me), 1.90 (s, 6H, CMe₂), 5.13 (br. s, 2H, N-CH₂), 7.07 (q, 1H, 5-H), no OH. The aqueous filtrates were acidified and the deposited mixture of **1a** (0.38 g, 2.0 mmol) and **14a** (0.09 g, 1.5 %) separated with aqueous NaHCO₃.

C₁₅H₁₇ClN₂O₂ calcd.: C 61.53 H 5.85 Cl 12.11 N 9.57
(292.8) found: C 61.39 H 5.81 Cl 12.04 N 9.52.

4-Chlorination, 4-bromination and 4-nitration of **14** (R² = H)

To 25 mmol **14e** in 75 ml dichloromethane, cooled to -3 °C, SO₂Cl₂ (3.38 g, 25 mmol), [Br₂ (4.00 g, 25 mmol)] in 25 ml CH₂Cl₂ is added with stirring and cooling at 0-3 °C in 30 min. Within 45 min. the temp. is increased to 20 °C, the solution twice extracted with water and the organic layer dried (Na₂SO₄). After removal of CH₂Cl₂ the residue **14b**, **1**, **n**, **r**, **v**, **y** [**14c**, **o**, **z**,] is crystallized (Table 1), yields 90-92%. - To **14e** (25 mmol) and NaNO₂ (0.02 g) in 70 ml CHCl₃ 68% nitric acid (10 ml) is added with vigorous stirring (10 min., 15 °C). After further stirring (60 min., 20 °C) ice-water is added, the organic phase separated, twice extracted with water, dried (Na₂SO₄), CHCl₃ removed, the residue treated with aqueous NaHCO₃ (30 °C), filtered and the filtrate acidified to pH 4. The deposited **14d** (82%) is dried at 70 °C and recrystallized from toluene.

Thermolysis of **14a**, **14b** and **14c**

In a dry semimicro still **14a** (2.06 g, 7.50 mmol) gradually was heated (silicone oil bath, preheated to 105 °C) under reduced pressure, the receiver cooled with liquid nitrogen, up to a bath temperature of 150 °C (35 °C above *m.p.* of **14**) within 5 h. Methacrylic acid (**16**, *b.p.* 64 °C/12 Torr) in the receiver was identified by ¹H NMR (NMR Spectra Catalog, vol. 1 and 2, Varian, no. 62). The solution of the residue in CHCl₃ was filtered and extracted with 0.5N NaOH, the aqueous phase acidified to pH 4 and the deposited **1a** (1.20 g, 85.1%; *m.p.* 163-164 °C and ¹H NMR identical with **1a** [30]) and **14a** (0.26 g, 12.6%; *m.p.* 114-115 °C), separated with aqueous NaHCO₃ (30 °C) and purified as described above. **1a** (R_f 0.74) and **14a** (R_f 0.60) can be distinguished by TLC [Kieselgel G, Merck; PrOH/EtOAc/25% aqu. NH₃ (5:3:2); 2.50 g tartaric acid, 2.09 g FeCl₃ and 0.50 g I₂ in 12.5 ml acetone]. - Analogously **14b** gave 83.8% 1-benzyl-4-chloro-3-hydroxy-1H-pyrazole (**1b**), *m.p.* 176 °C (EtOH). - ¹H NMR (CDCl₃): δ /ppm = 5.05 (N-CH₂), 7.13 (s, 1H, 5-H) [6] and **14e** 80.2% 1-benzyl-3-hydroxy-1H-pyrazole (**1e**), *m.p.* 158 °C. - ¹H NMR (CDCl₃): δ /ppm = 5.57 (d, 1H, 4-H), 7.07 (d, 1H, J₄₅ = 2.4 Hz, 5-H) [30].

2-(1,2,3,6-Tetrahydro-1,3-dimethyl-2,6-dioxo-7H-purin-7-yl)ethyl 2-methyl-2-[[4-methyl-1-(phenylmethyl)-1H-pyrazol-3-yl]oxy]-propanoate (**24a**) and -butanoate (**24h**)

With exclusion of water to the stirred and cooled solution of **14a** (54.86 g, 200 mmol) resp. **14h** (57.68 g, 200 mmol) in 400 ml dry dichloromethane SOCl₂ (24.40 g, 205 mmol) in 80 ml dry dichloromethane was added within 1 h. at 12-15 °C, then within 3 h gradually heated to 45-50 °C and stirring continued for 3 h at 45-50 °C. The resulting colourless solution (S-A₁) directly was used for the reactions with alcohols

R⁶-OH, otherwise the solvent, surplus SOCl₂ and HCl were removed, at last under reduced pressure and exclusion of moisture, while the bath temp. did not exceed 60 °C. The white residue (A₂; crude **18a** resp. **18h**) or its solution in dry dichloromethane (S-A₂) was used for further syntheses; S-A₁ and S-A₂ can be stored for some days at room temp. To S-A₁ at 30 °C 7-(2-hydroxyethyl)theophylline (44.64 g, 200 mmol) was added and the stirred mixture heated to reflux. After 15 min. a clear solution resulted, from which after 75 min. **24a**·HCl resp. **24h**·HCl began to precipitate, while stirring and refluxing were continued for 10 h.. The stirred mixture was cooled to 15 °C, 205 ml 1N NaOH added, the organic phase separated, washed with water (4 × 100 ml) and dried (Na₂SO₄). After removal of CH₂Cl₂ white crystalline **24a** (97.7%) resp. **24h** (95.8%) was left.

Analogously the 2-methyl-2-[[4-methyl-1-(4-chlorophenyl)-1H-pyrazol-3-yl]oxy]-propanoate **24q** was prepared from **14q**, yield 96.4%.

(Pyrid-3-yl)methyl 2-methyl-2-[[4-methyl-1-(phenylmethyl)-1H-pyrazol-3-yl]oxy]-propanoate (**25a**)

14a (200 mmol) and (pyrid-3-yl)methanol (21.82 g, 200 mmol) analogously gave **25a** (93.7%) as a colourless oil, from which in EtOH or EtOAc directly or after CC (Al₂O₃ neutral, activity A I, Greiz-Dörlau; Et₂O) crystalline salts were formed with the equimolar amounts of acids.

Cholest-5-en-3-ol(3 β) 2-methyl-2-[[4-methyl-1-(phenylmethyl)-1H-pyrazol-3-yl]oxy]-propanoate (**26a**) and -butanoate (**26h**)

To the stirred S-A₂ [from 100 mmol **14a** resp. **14h**; CH₂Cl₂ (240 ml)] further 100 ml dry CH₂Cl₂ and cholest-5-en-3 β -ol (38.66 g, 100 mmol) were added, refluxed for 15 h., the solvent removed and the residue, (**26a**) resp. mixture of diastereomers **26h** [dia I] and **26h** [dia II] (cf. Table 3) (92.2%), crystallized from acetone or purified by CC (Al₂O₃ neutral, activity A I, Greiz-Dörlau; benzene).

Methyl (**22a**) and ethyl 2-methyl-2-[[4-methyl-1-(phenylmethyl)-1H-pyrazol-3-yl]oxy]-propanoate (**23a**)

18a (A₂, 200 mmol) was stirred and heated with anhydrous methanol resp. ethanol (100 ml) for 45 min., the alcohol removed, at last under reduced pressure. **22a** (95%) remains as white crystals, **23a** as colourless oil.

2-Methyl-2-[[4-methyl-1-(phenylmethyl)-1H-pyrazol-3-yl]oxy]-propanamide (**27a**)

To **18a** (A₂, 200mmol) 100 ml 25% aqueous NH₃ gradually were added with stirring. After 4 h the precipitated **27a** (90.2%) was filtered and washed with ice-water or extracted with CH₂Cl₂ or Et₂O.

4-(2-Methyl-2-[[4-methyl-1-(phenylmethyl)-1H-pyrazol-3-yl]oxy]-1-oxopropyl)-morpholine (**28a**)

To **18a** (A₂, from 10.0 mmol **14a**) in 10 ml dry CH₂Cl₂ morpholine (1.74 g, 20.0 mmol) in dry CH₂Cl₂ was added with stirring at 10-12 °C within 30 min. After further 5 h stirring at 25 °C and removal of CH₂Cl₂ the crystalline residue was

Tab. 3 Analytical data of chloride (**17b**), esters (**22a**, **23a**, **24a**, **h**, **g**, **25a**, **26a**, **26h** [dia I], **26h** [dia II]) and amides (**27a**, **28a**, **h**, **g**, **29a**) of 1-substituted 2-methyl-2-[(1*H*-pyrazol-3-yl)oxy]propanoic and -butanoic acids, of bicyclic acylpyrazolium salts (**19a**, **h**), bicyclic γ -lactams (**30**, **31**, **32**, **34**, **37**, **38**) and bis-(1*H*-pyrazol-4-yl)sulfoxide (**39**). – ¹H NMR: δ /ppm in CDCl₃

| | <i>m.p./b.p.</i> (°C/ Torr) | emp. formula (mol. mass) | calcd./found | | | 4/7-H 5/6-H | 4/7-Me (N-CH ₂) | 2/6=Me ₂ 2/6-Me |
|------------|--------------------------------|---|----------------|--------------|------------------|-----------------------------|--------------------------------|-------------------------------|
| | | | C | H | N/+Cl | | | |
| 17b | 141–145 /0.3 | C ₁₄ H ₁₄ Cl ₂ N ₂ O ₂ (313.2) | 53.69 53.65 | 4.51 4.46 | +44.17 +44.03 | – 7.14 (s) | – (4.98) | 1.72 (s) – |
| 22a | 50–51 a) | C ₁₆ H ₂₀ N ₂ O ₃ (288.3) | 66.65 66.35 | 6.99 7.04 | 9.71 9.78 | – 6.90 (q) | 1.89 (d) (4.98) | 1.63 (s) b) |
| 23a | 143–145 /0.5 | C ₁₇ H ₂₂ N ₂ O ₃ (302.4) | 67.52 68.03 | 7.33 7.29 | 9.26 9.18 | – 6.91 (q) | 1.89 (d) (4.98) | 1.62 (s) c) |
| 24a | 114–115 d) | C ₂₄ H ₂₈ N ₆ O ₅ (480.5) | 59.99 59.73 | 5.87 5.91 | 17.49 17.35 | – 7.01 (q) | 1.91 (d) (4.95) | 1.47 (s) – |
| 24h | 84–85 d) | C ₂₅ H ₃₀ N ₆ O ₅ (494.5) | 60.72 60.67 | 6.11 6.07 | 17.00 16.88 | – 7.01 (q) | 1.92 (d) (4.94) | e) 1.53 (s) |
| 24q | 91–92 d) | C ₂₄ H ₂₇ ClN ₆ O ₅ (515.0) | 55.97 55.63 | 5.28 5.32 | +6.89 +6.95 | – 7.00 (q) | 1.90 (d) (4.89) | 1.56 (s) – |
| 25a | 126–127 f) g) | C ₂₁ H ₂₅ N ₃ O ₇ S (463.5) | 54.41 54.14 | 5.44 5.49 | 9.07 8.99 | – 6.93 (q) | 1.89 (d) (5.00) | 1.59 (s) – |
| 26a | 106–108 h) | C ₄₂ H ₆₂ N ₂ O ₃ (642.9) | 78.46 78.19 | 9.72 9.67 | 4.36 4.30 | – 6.90 (q) | 1.89 (d) (4.98) | 1.61 (s) – |
| 26h | 80–90 i) | C ₄₃ H ₆₄ N ₂ O ₃ (657.0) | 78.60 78.25 | 9.82 9.74 | 4.26 4.21 | – 6.89 (q) | 1.89 (d) (4.97) | – 1.52 (s) |
| 27a | 75–76 k) | C ₁₅ H ₁₉ N ₃ O ₂ (273.3) | 65.92 66.17 | 7.01 6.96 | 15.38 15.32 | – 6.98 (q) | 1.89 (d) (5.06) | 1.56 (s) – |
| 28a | 86–87 k) | C ₁₉ H ₂₅ N ₃ O ₃ (343.4) | 66.45 66.12 | 7.34 7.32 | 12.24 12.09 | – 6.97 (q) | 1.86 (d) (5.01) | 1.65 – |
| 28h | 59–61 k) | C ₂₀ H ₂₇ N ₃ O ₃ (357.4) | 67.21 67.12 | 7.61 7.63 | 11.76 11.67 | – 6.96 (q) | 1.86 (d) (4.99) | l) 1.59 (s) |
| 28q | 93–94 k) | C ₁₉ H ₂₄ ClN ₃ O ₃ (377.9) | 60.38 60.39 | 6.40 6.38 | +9.38 +9.45 | – ^{m)} 7.45 (q) | 1.83 (d) (5.05) | 1.54 (s) – |
| 29a | 95–96 k) | C ₂₁ H ₂₃ N ₃ O ₂ (349.4) | 72.18 72.10 | 6.64 6.61 | 12.03 11.96 | – 7.04 (q) | 1.94 (d) (5.06) | 1.63 (s) – |
| 19a | 186–188 n) | C ₁₅ H ₁₇ Cl ₆ N ₂ O ₂ Sb (591.8) | 30.44 30.47 | 2.90 2.87 | +35.95 +36.00 | – ^{o)} 8.25 (q) | 2.01 (d) (5.60) | 1.79 (s) – ^{p)} |
| 19h | 125–126 n) | C ₁₆ H ₁₉ Cl ₆ N ₂ O ₂ Sb (605.8) | 31.72 31.74 | 3.16 3.18 | +35.12 +35.17 | – 8.25 (q) | 2.14 (d) (5.70) | q) 1.87 |
| 30 | 60–61 a) | C ₇ H ₈ N ₂ O ₂ (152.2) | 55.24 55.36 | 5.30 5.29 | 18.41 18.31 | 5.47 (d) 7.84 (d) | – ^{r)} – | 1.70 – |
| 31 | 71–72 a) | C ₈ H ₁₀ N ₂ O ₂ (166.2) | 57.82 58.02 | 6.07 6.04 | 16.86 16.93 | – ^{s)} 7.68 (q) | 1.92 (d) – | 1.68 (s) – ^{y)} |
| 32 | 92–94 /0.3 ^{u)} | C ₉ H ₁₂ N ₂ O ₂ (180.2) | 59.98 59.92 | 6.72 6.78 | 15.55 15.44 | – 7.65 (q) | 1.93 (d) – | v) 1.63 (s) |
| 34 | 218–219 d) | C ₁₀ H ₁₃ N ₃ O ₃ (223.2) | 53.81 53.88 | 5.87 5.86 | 18.82 18.85 | – ^{w)} 8.02 (s) | – – | 1.63 (s) – |
| 37 | 100–102 a) | C ₈ H ₉ ClN ₂ O ₂ (200.6) | 47.90 48.14 | 4.52 4.48 | 13.96 14.02 | – ^{x)} – | 1.92 (s) – | 1.68 (s) – |
| 38 | 97–99 a) | C ₇ H ₇ ClN ₂ O ₂ (186.6) | 45.05 45.26 | 3.78 3.74 | +19.00 +18.85 | – 7.71 (s) | – – | 1.72 (s) – ^{y)} |
| 39 | 178–79 d) | C ₂₈ H ₃₀ N ₄ O ₇ S (566.6) | 59.35 59.72 | 5.34 5.37 | 9.89 9.89 | – ^{z)} 7.67 (s) | – (5.06) | 1.43 (s) – |

Crystallized from *n*-hexane ^{a)}, EtOH ^{d)}, BuOH ^{g)}, acetone ^{h)}, cyclohexane ^{k)}, dioxane ⁿ⁾. – ^{b)} δ /ppm = 3.58 (s, OMe). – ^{c)} δ /ppm = 1.06 (t, OCH₂Me), 4.01 (q, OCH₂). – ^{f)} **25a**-sulfate; **25a**-oxalate *m.p.* 92 – 93 °C (EtOH). – ⁱ⁾ *m.p.* EA and ¹H NMR refer to the mixture of the diastereomers **26h** [dia I, less soluble in acetone and butan-2-one, *m.p.* 105 – 108 °C, [α]_D²⁰ = – 11.5° (c = 0.02, CH₂Cl₂)] and **26h** [dia II, *m.p.* 99 – 103 °C, [α]_D²⁰ = – 30.8° (c = 0.1, CH₂Cl₂)]. – ^{l)} δ /ppm = 0.96 (t, 6-CH₂Me), 2.07 (q, 6-CH₂). – ^{m)} In [D₆] DMSO. – ^{o)} In CD₃CN. – ^{p)} ν (CO) = 1828 cm^{–1} (KBr). – ^{q)} δ /ppm = 0.97 (t, 2-CH₂Me), 2.16 (q, 2-CH₂). – ^{r)} J_{67} = 1.8 Hz. – ^{s)} ¹H NMR in HMPT(A): δ /ppm = 1.68 (s, 2=Me₂), 1.90 (d, 7-Me), 7.99 (q, 6-H); ¹³C NMR in CDCl₃: δ /ppm = 5.9 (7-Me), 23.9 (2=Me₂), 91.6 (C-2), 94.0 (C-7), 155.6 (C-6), 159.3 (C-7a), 167.7 (C-3). – ^{t)} ν (CO) = 1772 (*n*-hexane); *m/z*: 166 [M⁺], 138 [M⁺ – CO], 69 [CH₂C(Me)=C=O⁺]. – ^{u)} n ²⁰_D = 1.499. – ^{v)} δ /ppm = 0.93 (t, 2-CH₂Me), 2.01 (q, 2-CH₂). – ^{w)} ¹H NMR in [D₆] DMSO (in CDCl₃): δ /ppm = 1.27 (1.37) (t, 3H, OCH₂Me), 1.45 (1.63) (s, 6H, 2=Me₂), 4.19 (4.30) (q, 2H, OCH₂), 8.97 (5.89) (br.s, 1H, NH), 8.00 (8.02) (s, 1H, 6-H); cf. ¹H NMR of **33** in [D₆] DMSO: δ /ppm = 1.26 (t, 3H, OCH₂Me), 1.55 (s, 6H, 6=Me₂), 4.20 (q, 2H, OCH₂), 7.92 (s, 1H, 5-H); *m/z*: 223 [M⁺], 195 [M⁺ – CO], 149 [M⁺ – CO – EtOH], 108 [M⁺ – CO – EtOH – MeC=CH₂⁺]; ν (CO) = 1757 (3-CO), 1697 (CO₂Et) (KBr). – ^{x)} ¹³C NMR in CDCl₃: δ /ppm = 5.8 (7-Me), 23.8 (2=Me₂), 91.3 (C-2), 92.6 (C-7), 156.0 (C-7a), 158.4 (C-6), 166.4 (C-3); ν (CO) = 1780 (KBr); *m/z*: 200 [M⁺], 69 [CH₂C(Me)=C=O⁺]. – ^{y)} ν (CO) = 1788 (KBr); *m/z*: 186 [M⁺], 158 [M⁺ – CO], 69 [CH₂C(Me)=C=O⁺]. – ^{z)} In [D₆] DMSO; ν (CO) = 1700 (KBr); S: calcd., 5.65, found, 5.72; *m/z*: 550 [M⁺ – O], 464 [M⁺ – O – **16**], 378 [M⁺ – O – **16** – **16**].

treated with ice-water, **28a** (91.3%) filtered and washed with ice-water.

Analogously **14h** gave the 2-methyl-1-oxobutyl-morpholine **28h** and **14q** the 2-methyl-1-oxopropyl-morpholine **28q**.

2-Methyl-2-[[4-methyl-1-(phenylmethyl)-1H-pyrazol-3-yl]oxy]-N-phenyl-propanamide (29a)

18a (A₂, from 10.0 mmol **14a**) in 10 ml dry CH₂Cl₂ and aniline (1.86 g, 20.0 mmol) in 10 ml CH₂Cl₂, reacted as above, yielded **29a** (88.7%).

2,2,7-Trimethyl- (19a) and 2,7-dimethyl-2-ethyl-pyrazolo[5,1-b]oxazol-3(2H)-one hexachloroantimonate (19h)

To **18a** resp. **18h** (A₂ from 20.0 mmol **14a** resp. **14h**), dissolved in 20 ml dry CH₂Cl₂, the solution of SbCl₅ (6.28 g, 21.0 mmol) in 20 ml dry CCl₄ was added at 20 °C. After 1 h. the crystalline **19a** (79.8%) resp. **19h** (86.5%) was filtered and washed with cold CCl₄. **19a** and **19h** are not as sensitive to moisture as **18a** and **18h**; boiling of **19a** with methanol yielded **22a**.

2,2,7-Trimethyl- (31) and 2,7-dimethyl-2-ethyl-pyrazolo[5,1-b]oxazol-3(2H)-one (32)

14a (54.86 g, 200 mmol), resp. **14h** (57.68 g, 200 mmol), 300 ml dry CH₂Cl₂ and SOCl₂ (25.00 g, 210 mmol) gradually were heated with exclusion of water, refluxed for 5 h., then solvent

and surplus SOCl₂ distilled off, at last under reduced pressure, and the bath temp. gradually increased to 140 °C, while benzyl chloride [**20**, 20.68 g, 81.7%; *b.p.* 78–80 °C/20 Torr, GC (capillary; Chromosorb AW-DMCS, 4% Silicone Fluid DC 550) identical with auth. **20**] was distilled through a short column. After further reduction of pressure (bath 140 °C) **31** (26.69 g, 80.3%), *b.p.* 79 °C/0.5 Torr, resp. **32** (28.36 g, 78.7%), *b.p.* 92–94 °C/0.3 Torr, was fractionated.

2,2,-Dimethyl- pyrazolo[5,1-b]oxazol-3(2H)-one (30)

Under exclusion of water **14e** (26.03 g, 100 mmol) and 30 ml acetyl chloride were refluxed for 16 h., then surplus acetyl chloride distilled off and the bath temp. gradually enhanced to 140 °C, while under reduced pressure through a short column benzyl chloride (**20**) and benzyl acetate [**21**, *b.p.* 98–100 °C/15 Torr. – ¹H NMR identical with **21** (NMR Spectra Catalog, vol. 1 and 2, Varian, no. 530)] were removed. After further reduction of pressure (bath 140 °C) **30** (8.33 g, 54.7%), *b.p.* 81–83 °C/0.5 Torr, was fractionated.

2-Methyl-2-[[4-chloro-1-(phenylmethyl)-1H-pyrazol-3-yl]oxy]-propanoic acid chloride (17b) and 7-chloro- 2,2-dimethyl-pyrazolo[5,1-b]oxazol-3(2H)-one (38)

14b (29.47 g, 100 mmol), 100 ml dry CH₂Cl₂ and SOCl₂ (8.96 ml, 125 mmol) gradually were heated under exclusion of moisture, refluxed for 6 h., solvent and surplus SOCl₂ removed

Tab. 4 Analytical data of [[4-bromo(chloro)- (**42**, **43**), [[4,4-dibromo-4,5-dihydro-5-oxo-1-(phenylmethyl)-1H-pyrazol-3-yl]oxy]-acetic acids (**48**), the corresponding 2-methyl-propanoic acids (**44–47**, **49**), of [[4,5-dihydro-5-oxo-1-(phenylmethyl)-1H-pyrazol-3-yl]oxy]-acetic acids (**52**, **54**), and the corresponding 2-methyl-propanoic acids (**53**, **55–57**).

| | <i>m.p.</i> (°C) | emp.formula (mol. mass) | calcd./found | | N +Cl/Br | δ ¹ H (ppm) | |
|-----------|--------------------|---|----------------|--------------|------------------|--|---|
| | | | C | H | | 7=H ₂ | 6=Me ₂ [H ₂] 4-H |
| 42 | 135–136 a) | C ₁₃ H ₁₃ ClN ₂ O ₄ (296.7) | 52.62 52.88 | 4.42 4.45 | +11.95 +11.97 | | |
| 43 | 133–134 b) | C ₁₃ H ₁₃ BrN ₂ O ₄ (341.2) ^l c) | 45.76 46.15 | 3.84 3.88 | +23.42 +23.19 | 4.80 (q) ^d) ^e) | [4.76 (q)] |
| 44 | 125–126 a) | C ₁₅ H ₁₇ ClN ₂ O ₄ (324.8) | 55.46 55.47 | 5.28 5.33 | +10.92 +10.82 | 4.69 (q) ^d) | 1.73 (d) |
| 45 | 138–139 b) | C ₁₅ H ₁₇ BrN ₂ O ₄ (369.2) ^f) | 48.79 48.70 | 4.64 4.59 | +21.64 +21.55 | 4.69 (q) ^d) ^g) | 1.68 (d) |
| 46 | 95–96 b) | C ₁₄ H ₁₄ Cl ₂ N ₂ O ₄ (345.2) | 48.71 49.14 | 4.09 4.14 | 8.12 8.14 | 4.63 (s) ^d) | 1.69 (s) |
| 47 | 114–115 b) | C ₁₄ H ₁₄ BrClN ₂ O ₄ (389.6) ^h) | 43.16 42.84 | 3.62 3.58 | 7.19 7.26 | 4.68 (q) ^d) | 1.72 (d) |
| 48 | 148–149 b) dec. | C ₁₂ H ₁₀ Br ₂ N ₂ O ₄ (406.0) ⁱ) | 35.50 35.72 | 2.48 2.51 | +39.37 +39.28 | 4.83 (s) ^d) | [4.77 (s)] |
| 49 | 131–132 b) | C ₁₄ H ₁₄ Br ₂ N ₂ O ₄ (434.1) ^k) | 38.73 39.11 | 3.25 3.22 | +36.82 +36.99 | 4.67 (s) ^d) | 1.70 (s) |
| 52 | 146–147 a) | C ₁₂ H ₁₂ N ₂ O ₄ (248.2) | 58.06 57.88 | 4.87 4.91 | 11.29 11.33 | 4.68/ 4.90 ^l) ^m) | 3.65 /4.54 ⁿ) |
| 53 | 107 o) | C ₁₄ H ₁₆ N ₂ O ₄ (276.3) | 60.85 60.75 | 5.84 5.81 | 10.14 10.07 | 4.65/ 4.87 ^l) ^p) | 3.57 / 4.83 ^q) |
| 54 | 133–134 b) | C ₁₃ H ₁₄ N ₂ O ₄ (262.3) | 59.52 59.42 | 5.38 5.40 | 10.68 10.59 | 4.69 / 4.92 ^l) ^r) | 3.62 (q) ^s) |
| 55 | 125–126 b) | C ₁₅ H ₁₈ N ₂ O ₄ (290.3) | 62.06 61.98 | 6.25 6.29 | 9.65 9.65 | 4.64 / 4.86 ^l) | 3.50 (q) ^t) |
| 56 | 164–165 u) | C ₁₄ H ₁₅ ClN ₂ O ₄ (310.7) | 54.12 53.95 | 4.86 4.83 | +11.41 +11.48 | 4.64 / 4.93 ^l) | 5.68 |
| 57 | 157–158 v) | C ₁₄ H ₁₅ BrN ₂ O ₄ (355.2) ^w) | 47.34 47.08 | 4.26 4.21 | +22.50 +22.28 | 4.69 / 4.95 ^l) | 5.71 |

Table 4 (continued)

| $\delta^{13}\text{C}$ (ppm) | C-3 | C-4 | C-5 | C-6 (6-Me) | C-7 (6-Me) |
|--------------------------------|-------------|-----------|-------------|-------------|------------------|
| 42 ^d | 162.3 | 57.0 | 169.0 | 63.8 (–) | 48.2 (–) |
| 43 ^d | 162.9 | 45.4 | 169.5 | 63.9 (–) | 48.2 (–) |
| 44 ^d | 160.7 | 57.7 | 168.7 | 81.7 (23.8) | 48.2 (25.5) |
| 45 ^d | 161.1 | 46.5 | 169.1 | 81.6 (23.0) | 48.1 (25.6) |
| 47 ^d | 156.6 | 54.3 | 164.0 | 82.4 (23.9) | 48.6 (24.3) |
| 48 ^d | 158.8 | 36.9 | 164.8 | 64.1 (–) | 48.7 (–) |
| 49 ^d | 157.1 | 38.9 | 164.6 | 82.3 (24.1) | 48.6 |
| 52 ^x | 161.2/159.4 | 35.4/72.2 | 168.5/152.8 | 63.8 | 46.6/48.6 |
| | 164.2 | 71.6 | 163.7 | 68.9 | 48.8 |
| 53 ^x | 159.4/157.5 | 36.0/74.5 | 168.4/152.2 | 80.5/78.4 | 46.6/48.6 |
| | 163.6 | 34.8 | 161.1 | 83.4 | 48.7 |
| 54 ^x | 164.6/157.9 | 39.4/80.1 | 168.5/149.8 | 63.6/63.4 | 46.6/48.8 |
| | 162.3 | 80.0 | 161.3 | 68.0 | 48.9 |
| 55 ^x | 162.9/156.5 | 40.5/82.5 | 171.6/149.5 | 80.6/78.5 | 46.7/48.9 |
| 56 ^x | 157.9/153.1 | 47.2/76.9 | 166.5/147.8 | 79.8 | 47.9/49.6 |
| | | 77.4 | 159.4 | 84.0 | 49.8 |

Crystallized from MeNO₂^a), toluene^b), benzene^c), *i*PrOH^d), aqu. EtOH^e). – ^f ν (5-CO/CO₂H) = 1750/1700 (KBr). – ^g δ_{s} of the AB systems. – ^h ν (5-CO/CO₂H) = 1735/1698 (KBr). – ⁱ $\delta_{\text{A}} = 4.65$, $\delta_{\text{B}} = 4.73$, $J_{\text{AB}} = 16$ Hz. – ^j ν (5-CO/CO₂H) = 1740/1705 (KBr). – ^k ν (5-CO/CO₂H) = 1760/1710 (KBr). – ^l ν (5-CO/CO₂H) = 1753/1698 (KBr). – ^m δ (7=H₂) = 4.93 (anion of **52'** in D₂O + NaOD). – ⁿ δ (6=H₂) = 4.65 ([D₆] DMSO), 4.40 (D₂O + NaOD). – ^o δ (7=H₂) = 4.94 (anion of **53'** in D₂O + NaOD). – ^p δ (6=Me₂) = 1.49 (**53'**)/1.56 (**53**) ([D₆] DMSO), 1.50 (D₂O + NaOD). – ^q δ (7=H₂) = 4.97 (anion of **54'** in D₂O + NaOD). – ^r δ (4-Me) = **1.24**, **1.33** (**54**) and **1.76** (**54'**). – ^s δ (4-Me) = **1.16**, **1.26** (**55**) and **1.69** (**55'**). – ^t MS of **53**, **55**–**57** show [M⁺] and [M⁺ – 86 (**16**)], i.e. splitting like **14**. – ^x In [D₆] DMSO (representative of mixtures of tautomers **52/52'** etc.) see above, in D₂O + NaOD (representative of anions of **52'** etc.) see below. – Bold shifts were used for estimation of tautomer ratios.

and the residue fractionated through a short column under reduced pressure, while the bath temp. gradually was increased to 140–155 °C. After **20**, **38** (5.75 g, 30.8%), *b.p.* 110 °C/0.3 Torr, and **17b** (18.83 g, 60.1%), *b.p.* 141–145 °C/0.3 Torr, distilled off. If the acid chloride **17b** slowly was redistilled, further **20** and further **38** (8.6%) were formed.

14e (26.03 g, 100 mmol) and SOCl₂ (28.7 ml, 400 mmol) gradually were heated under exclusion of water, refluxed for 15 h., surplus SOCl₂ was removed and the residue fractionated through a short column under reduced pressure, while the bath temp. was increased up to 145 °C; **38** (5.84 g, 31.3%), *b.p.* 110 °C/0.3 Torr, was isolated.

6-Chloro-2,2,7-trimethyl-pyrazolo[5,1-*b*]oxazol-3(2*H*)-one (**37**)

As described above **14a** (27.43 g, 100 mmol) was treated with SOCl₂ (28.7 ml, 400 mmol). After benzyl chloride (**20**) and **31**, **37** (9.19 g, 45.8%), *b.p.* 91 °C/0.5 Torr, distilled.

2,2-Dimethyl-7-ethoxycarbonyl-1*H*-pyrazolo[5,1-*b*]imidazol-3(2*H*)-one (**34**)

To 2-methyl-2-[(4-ethoxycarbonyl-1*H*-pyrazol-3-yl)amino]propanoic acid (**33**; 6.03 g, 25.0 mmol; *m.p.* 169–170 °C [17]) in 30 ml dry CH₂Cl₂ with stirring and cooling (ice-water) SOCl₂ (3.60 ml, 50.0 mmol) in 10 ml CH₂Cl₂ was added. After 6 h. stirring at 50–60 °C (bath) and removal of solvent and SOCl₂ the residue was crystallized from ethanol, to give **34** (4.22 g, 75.6%).

(+)-/(+)-**14h** and (–)-2-Methyl-2-[[4-methyl-1-(phenylmethyl)-1*H*-pyrazol-3-yl]oxy]-butanoic acid ((–)-**14h**)

26h [dia I] (13.14 g, 20.0 mmol), 250 ml methanol, NaOH (0.88 g, 22.0 mmol) and 1.0 ml water were refluxed for 25 h., methanol removed, the residue treated with water (200 ml, 25 °C), cholesterol filtered by suction, the filtrate twice extracted with chloroform, the aqueous phase acidified to pH 4, (+)-**14h** filtered, washed with ice-water, dried at 60 °C and crystallized from cyclohexane, 4.98 g (86.3%), *m.p.* 83–84.5 °C, $[\alpha]_{\text{D}}^{20} = +3.5^{\circ}$ ($c = 0.096$, CH₂Cl₂). According to HPLC on microcrystalline cellulose triacetate (CTA)[31] the product contained 93.3% of the (+)-enantiomer.

Analogously (–)-**14h** (5.09 g, 88.2%) was obtained from **26h** [dia II] (20.0 mmol); *m.p.* 83–84 °C, $[\alpha]_{\text{D}}^{20} = -3.7^{\circ}$ ($c = 0.094$, CH₂Cl₂), 99.1% (–)-enantiomer according to HPLC on CTA. (+)- and (–)-**14h** also can be estimated by ¹H NMR of the methyl esters (with diazomethane in MeOH/Et₂O), using δ /ppm = 3.56, 3H (OMe) in CDCl₃ after addition of Eu(TFC)₃.

Bis-[3-(1-carboxy-1-methyl-ethoxy)-1-(phenylmethyl)-1*H*-pyrazol-4-yl]sulfoxide (**39**)

14e (26.03 g, 100 mmol), 100 ml dry CH₂Cl₂ and SOCl₂ (18.30 ml, 255 mmol) gradually were heated, refluxed for 9 h., solvent and SOCl₂ removed, at last under reduced pressure (bath temp. up to 80 °C), the residue treated with 250 ml 1*N* NaOH of 35 °C, the alkaline solution filtered and acidified to pH 3. The precipitated mixture of **14e**, some **14b** and **39** was dissolved in aqueous NaHCO₃ of 35 °C, filtered, the filtrate acidified to

pH 3, the acids filtered, washed with water and ice-cold EtOH. After fractional crystallization from BuOH **14e** (13.61 g, 52.0%) and **39** (4.07 g, 14.4%) were isolated.

[[4-Bromo-4,5-dihydro-4-methyl- (43) resp. [[4,4-dibromo-4,5-dihydro-5-oxo-1-(phenylmethyl)-1H-pyrazol-3-yl]oxy]-acetic acid (48), 2-methyl-2-[[4-bromo-4,5-dihydro-4-methyl- (45) and 2-methyl-2-[[4-bromo-4-chloro-4,5-dihydro- (47) resp. 2-methyl-2-[[4,4-dibromo-4,5-dihydro-5-oxo-1-(phenylmethyl)-1H-pyrazol-3-yl]oxy]-propanoic acid (49)

To the solution of 100 mmol of the acetic acids **41** resp. **40**, the propanoic acids **14a** and **14b** resp. **14e** in 100 ml 1N NaOH, 200 ml of water and NaHCO₃ (25.2 g, 300 mmol) (P₁) resp. 300 ml of water and NaHCO₃ (33.6 g, 400 mmol) (P₂) were added, then using a pressure equalizing funnel the mixture of Br₂ (32.0 g, 200 mmol) and 35 ml methanol (P₁) resp. Br₂ (48.0 g, 300 mmol) and 55 ml methanol (P₂) was gradually dropped in with stirring at internal 17–22 °C within 3–4 h, stirred for 1 h at room temp., filtered and acidified to pH 3. The deposited yellow 4-bromo-5-oxo- resp. 4,4-dibromo-5-oxo-acids (84–93%) were washed with water and dried at 30 °C below their *m.p.*'s (Table 4). The bromination was carried out as well by passing a stream of air laden with bromine vapor through the aqueous solution.

*[[1-Phenylmethyl)- (40) resp. [[4-methyl-1-(phenylmethyl)-1H-pyrazol-3-yl]oxy]-acetic acid (41) was obtained by stirring and refluxing 1-benzyl-3-hydroxy-1H- (1e) resp. 1-benzyl-3-hydroxy-4-methyl-1H-pyrazole (1a) (100 mmol), ethyl chloroacetate (100 mmol), dry K₂CO₃ (100 mmol) and KI (1.0 mmol) in butan-2-one for 30 h. and alkaline saponification of the ester, *m.p.* 91–92 °C (CCl₄) resp. 99–100 °C (CCl₄).*

[[4-Chloro-4,5-dihydro-4-methyl-5-oxo-1-(phenylmethyl)-1H-pyrazol-3-yl]oxy]-acetic acid (42), 2-methyl-2-[[4-chloro-4,5-dihydro-4-methyl- (44) resp. 2-methyl-2-[[4,4-dichloro-4,5-dihydro-5-oxo-1-(phenylmethyl)-1H-pyrazol-3-yl]oxy]-propanoic acid (46)

To 10.0 mmol **41**, **14a** resp. **14b** and 20 ml aqueous 37% HCl within 15 min. 2.2 ml 30% H₂O₂ were added with stirring and cooling (ice), stirred further 20 min. at 20 °C, 10 g of ice added and the precipitated slightly yellow 4-chloro-5-oxo-acids (70–76%) washed with ice-water.

[[4,5-Dihydro- (52) and [[4,5-dihydro-4-methyl-5-oxo-1-(phenylmethyl)-1H-pyrazol-3-yl]oxy]-acetic acid (54), 2-methyl-2-[[4,5-dihydro- (53), 2-methyl-2-[[4-chloro-4,5-dihydro- (56) and 2-methyl-2-[[4-bromo-4,5-dihydro-5-oxo-1-(phenylmethyl)-1H-pyrazol-3-yl]oxy]-propanoic acid (57)

To the 4-bromo-5-oxo-acid **43**, **47**, **48** or **49** (10.0 mmol) in 10.0 ml 1N NaOH 40 ml water and NaHCO₃ (0.87 g, 10.3 mmol) (R₁) resp. 60 ml water and NaHCO₃ (1.73 g, 20.6 mmol) (R₂) were added and Na₂SO₃ (1.30 g, 10.3 mmol) in 12 ml water (R₁) resp. Na₂SO₃ (2.60 g, 20.6 mmol) in 25 ml water (R₂) dropped in with stirring at 17–22 °C within 1–3 h, stirred for further 90 min., filtered and acidified. The deposited colourless 4,5-dihydro-5-oxo-acids (83–93%) were washed with water and dried at 30 °C below their *m.p.*'s.

2-Methyl-2-[[4,5-dihydro-4-methyl-5-oxo-1-(phenylmethyl)-1H-pyrazol-3-yl]oxy]-propanoic acid (55)

To 12 ml triethylamine, 25 ml methanol and ascorbic acid (2.64 g, 15.0 mmol) **45** (3.69 g, 10.0 mmol) was added with stirring at 20 °C within 20 min., stirred for further 60 min., the colourless solution poured into 100 ml of ice-cold 4N HCl, the precipitated **55** washed with water and triturated with acetonitrile, 2.24 g (77.2%). Heating **55** in acetonitrile with *t*BuOOH gave **50** and **51**.

meso- (50) and rac-4,4'-Bis-[[3-(1-carboxy-1-methyl-ethoxy)-4,5-dihydro-5-oxo-1-(phenylmethyl)-1H-pyrazolyl] (51)

The yellow solution of **45** (11.08 g, 30.0 mmol) and KHCO₃ (6.01 g, 60.0 mmol) in 100 ml water was treated with Na₂SO₃ (3.91 g, 31.0 mmol) as described above for **43**, then the colourless solution acidified and extracted with Et₂O or with CH₂Cl₂. The combined organic phases were dried (Na₂SO₄), solvent removed, the residue triturated with cold Bu₂O or toluene and the crude crystalline mixture crystallized from EtOH. Recrystallization of the less soluble fraction from aqueous EtOH gave **51** (3.76 g, 43.3%), *m.p.* 190–193 °C.

C₃₀H₃₄N₄O₈ calcd.: C 62.27 H 5.92 N 9.68 (578.6) found: C 62.29 H 5.94 N 9.68.

– ¹H NMR (dimethyl ester, from **51** with CH₂N₂; CDCl₃): δ/ppm = 1.46/1.54 (d, 12H, 2×6=Me₂), 1.62 (s, 6H, 2×4-Me), 3.34 (s, 6H, 2×OMe, splitting after addition of Eu(TFC)₃), δ_A = 4.38, δ_B = 4.88, J_{AB} = 15 Hz (4H, 2×7=H₂). – ¹³C NMR ([D₆]DMSO): δ/ppm = 13.6 (4-Me), 22.1/26.2 (6=Me₂), 46.6 (C-7), 48.0 (C-4), 80.7 (C-6), 161.9 (C-3), 170.2 (C-5), 177.6 (CO₂H). Recrystallization of the residue of the ethanolic mother liquor from MeNO₂ gave 1.48 g (17.1%) **50**, *m.p.* 182–185 °C, found C 61.62, H 5.90, N 9.70. – ¹H NMR (dimethyl ester, from **50** with CH₂N₂; CDCl₃): δ/ppm = 1.50/1.53 (d, 12H, 2×6=Me₂), 1.60 (s, 6H, 2×4-Me), 3.29 (s, 6H, 2×OMe, no splitting after addition of Eu(TFC)₃), δ_A = 4.41, δ_B = 4.95, J_{AB} = 15 Hz (4H, 2×7=H₂). – ¹³C NMR ([D₆]DMSO): δ/ppm = 14.5 (4-Me), 22.9/25.8 (6=Me₂), 46.9 (C-7), 48.6 (C-4), 81.1 (C-6), 161.9 (C-3), 170.5 (C-5), 172.6 (CO₂H). By treating the crude mixture of diastereomers with CH₂N₂ and integration of the OMe-signals **50** : **51** = 1:4 was estimated. A mixture of **50** and **51** also resulted from **45** and sodium dithionite (1:1) in water (20 °C) and from **45** with Zn in boiling EtOH.

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