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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

Helmut Dorn, and Rüdiger Ozegowski

Berlin, Zentralinstitut für Organische Chemie

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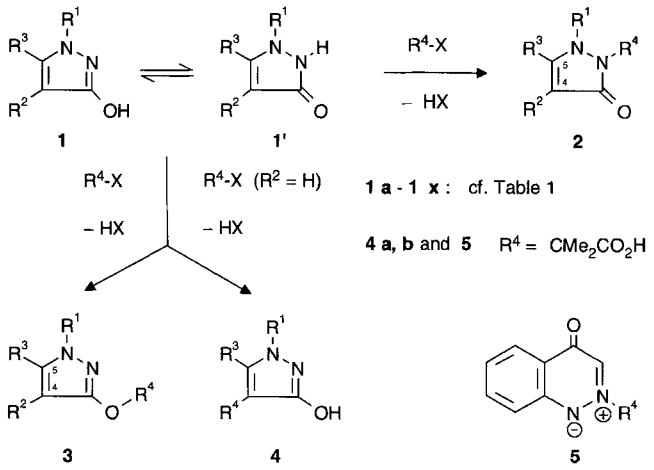
Dedicated to Prof. Dr. Dr. h. c. mult. A. R. Katritzky, FRS, on the Occasion of his 70th Birthday

Abstract. 1-Substituted 3-hydroxy-1*H*-pyrazoles **1** react with chloroform, NaOH, and aceton resp. butan-2-one O-regiospecifically 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 $SOCl_2$ result in 6-chloro- **37** resp. 7-chloro-β-oxa-γ-lactams **38** *via* chlorosulfinylation 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 I_2) 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]. Particulary **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 I_2 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.

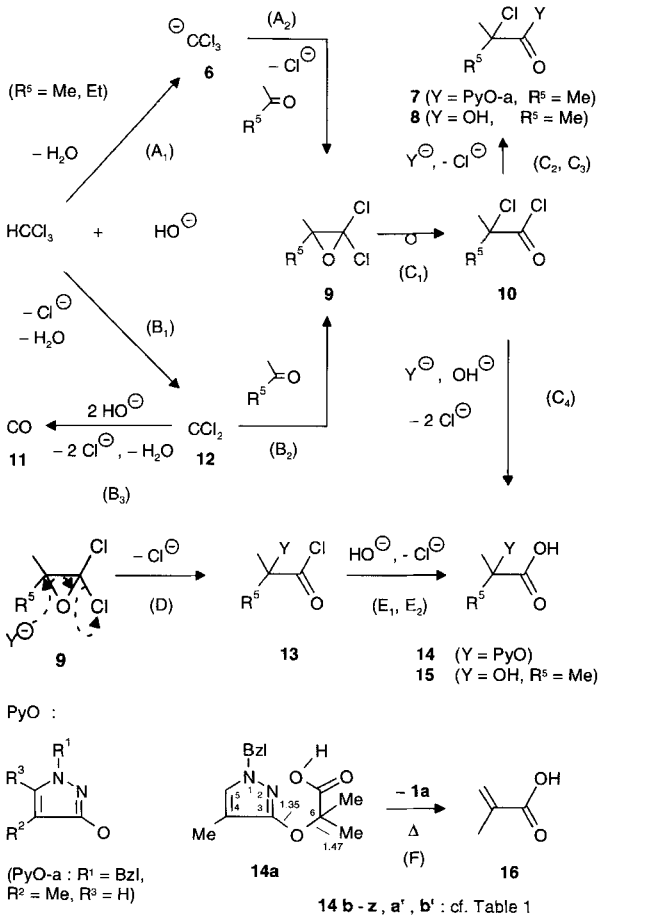
LINK Synthesis with 1-Substituted 3-Hydroxy-1*H*-pyrazoles – 1-Substituted 3-Carboxyisoalkyloxy-1*H*-pyrazoles

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 R^4-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 ^{1}H NMR and IR. If R^2 = R^3 = H, J_{45} = 3.5 Hz (type **2** in $CDCl_3$) resp. 2.4 Hz (type **3** in $CDCl_3$); for **2** the very strong ν (C=O) = 1640–1650 cm^{-1} (in $CHCl_3$) is characteristic. Sodium salts of 1-substituted 3-hydroxy-1*H*-pyrazoles **1** in aceton 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 = *i*Pr 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-1*H*-pyrazoles **1** regiospecifically 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, aceton, 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-1*H*-pyrazol-3-yl)oxy]-propanoic acid (**14a**) from 1-benzyl-3-hydroxy-4-methyl-1*H*-pyrazole (**1a**), chloroform and sodium hydroxide in the molar ratio 1.00 : 2.00 : 8.00 in aceton 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 aceton 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 aceton 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 aceton or **1a**-Na in DMF) did not react, phase transfer reaction gave 4% **14a** (**1a**, benzene, 50% aqueous NaOH, TEBA,

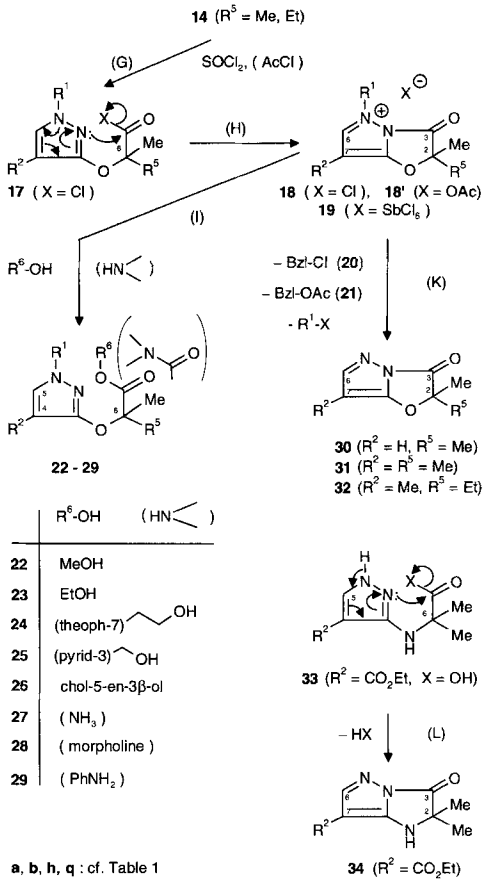
55 °C). All this resembles the behaviour of chlorooxiranes, which much faster than α-chloroaldehydes or -ketones react with nucleophiles [15, 16]. Knowledge about the course of the reaction enabled us further to extend the scope of the LINK synthesis to 3- and 5-amino-pyrazoles, yielding 3- and 5-carboxyisoalkylamino-1*H*-pyrazoles[17].

Contrary to azomethinimines **5**, which easily are decarboxylated at 65 °C [8], the 3-carboxyisoalkyloxy-1*H*-pyrazoles **14** (R^5 = 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 = Me), **14b** (R^2 = Cl) and **14e** (R^2 = H); **14c** (R^2 = 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 ^{1}H NMR spectra of **14** (R^2 = R^3 = H) display J_{45} = 2.3–2.4 Hz, typical for type **3** (Scheme 1), and moreover for **14** (R^3 = H) $\Delta^{CDCl_3}_{HMPT(A)}$ = [δ (5-H), $CDCl_3$)] – [δ (5-H), 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-carboxyisoalkyloxy-1*H*-pyrazoles **14** (R^1 = aralkyl, R^5 = 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) [δ (6-H) = 8.25 resp. 8.25 ppm] and at (N–CH_2) [δ = 5.60 resp. 5.70 ppm] compared to the acids **14a** resp. **14h** [δ (5-H) = 6.96 resp. 7.08 ppm; δ ((N–CH_2) = 4.99 resp. 5.10 ppm], and ν(CO) = 1828 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 = 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 = 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 δ (5-H) and δ (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 (E_1) (Scheme 2) in the LINK synthesis of **14**.



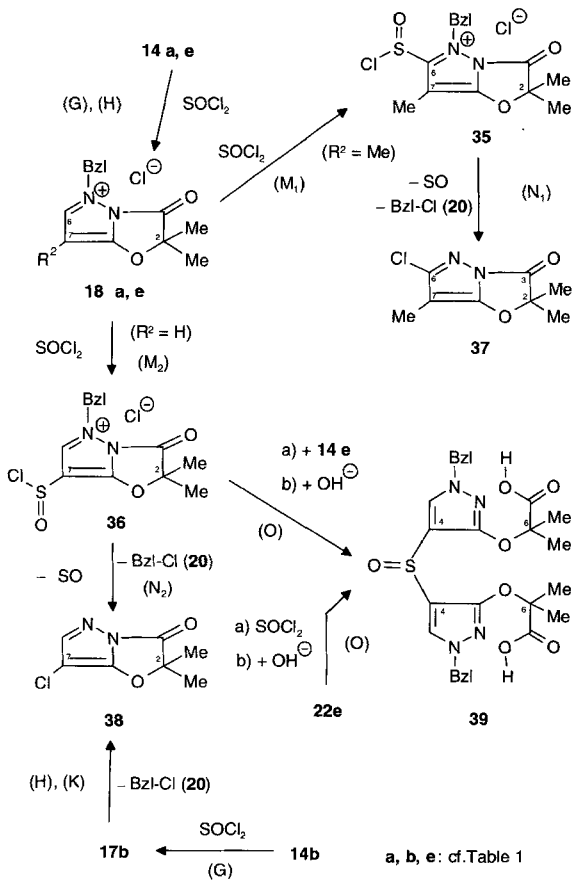
Scheme 3

To learn, if bulky substitution at (C-6) is essential for biological effects of 3-carboxyisoalkyloxy-1*H*-pyrazoles **14**, we needed enantiomers of **14h**. We did not succeed in isolating pure diastereomeric salts of **14h** with untoxic and easily available chiral 1-desoxy-1-methylamino sugar alcohols [21], but separated the two diastereomeric cholesterol esters **26h** (R^2 = Me, R^5 = 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

the enhancement of PSO proliferation enantioselectivity at (C-6) of **14** was demonstrated.

Heating pyrazolium chlorides **18** (R^1 = Bzl; R^2 = H, Me, Cl; R^5 = Me, Et) to 140 °C causes splitting (K) to benzyl chloride (**20**) and bicyclic β-oxa-γ-lactams **30-32, 38** (Schemes 3 and 4) [22]. Thermolysis of pyrazolium salts with evolution of MeCl was used to synthesize 1-benzyl-3-chloro-1*H*-pyrazole (140 °C [18]) and 3-hydroxy-1-methyl-1*H*-pyrazole (200 °C [23]). The γ-lactams **30** [**14e**], **31** [**14a**], **32** [**14h**] and **38** [**14b**] show lower field shifts for δ (6-H) (0.6–0.7 ppm) compared to δ (5-H) of the acids **14** (in [ ]), and ν (CO) about 1780 cm^{-1}. **31** resp. **32** are synthesized with c. 80% yield by thermolysis of the crude pyrazolium chlorides **18a** resp. **18h**. To avoid side reactions, discussed below, **30** (R^2 = H) is prepared by heating the acid **14e** with acetyl chloride, thus intermediately a mixture of pyrazolium chloride **18** and acetate **18'** (Scheme 3) is formed, which at 140 °C liberates benzyl chloride (**20**) and acetate (**21**) (K).

Carboxyisoalkylamino-1*H*-pyrazoles[17], *e.g.* **33**, easily undergo a similar reaction (Scheme 3) to 1*H*-β-aza-γ-lactams, *e.g.* **34** (L). We found that (L) is a general reaction of α-amino-1*H*-*N*-heterocycles, leading to systems with the potential to mimic β-lactams.



Scheme 4

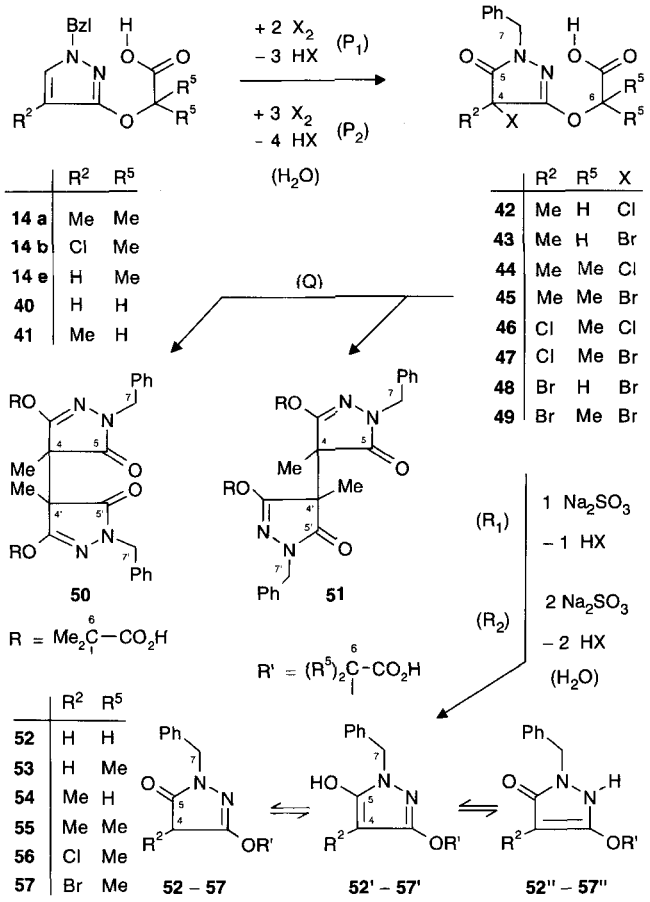
With nucleophiles the β-oxa-γ-lactams give 3(5)-carboxyisoalkyloxy-1*H*-pyrazoles, with amides *via* transamidation amides of 1-acylated 3-carboxyisoalkyloxy-1*H*-pyrazoles [22].

With surplus $SOCl_2$ the 3-carboxyisoalkyloxy-1*H*-pyrazoles **14** undergo side reactions (M_1) resp. (M_2) (Scheme 4) leading *via* (N_1) resp. (N_2) to bicyclic 6- resp. 7-chloro-β-oxa-γ-lactams. Thus **14a** (R^2= Me) *via* the 6-chlorosulfinyl compound **35** and thermolysis gave **37**, and **14e** (R^2 = H) *via* the 7-chlorosulfinyl compound **36** gave the 7-chloro-β-oxa-γ-lactam **38**, which resulted from **14b** *via* cyclisation of the acid chloride **17b** and thermolysis as well [Scheme 4; (G), (H), (K)]. A radical reaction with extrusion of sulfur monoxide similarly converts 10-chlorosulfinylanthrone into 10-chloroanthrone [24]. A further side reaction [Scheme 4; (O)] is the 4-sulfinylation of **14e** (R^2 = H) by the 7-chlorosulfinyl intermediate **36**. Using **14** (R^2 = H), surplus $SOCl_2$ and temperatures below 80 °C, we isolated 14% of **14e** as bis-(pyrazol-4-yl)sulfoxide **39**. Similarly the methyl ester of **14e** (**22e**) after work up with methanolic NaOH gave 32% of the sulfoxide **39**. Arylsulfinyl chlorides react with pyrrole to 3- (mainly) and 2-(arylsulfinyl)pyrroles [25].

Easy New Access to 3-Carboxy(iso)alkyloxy-4,5-dihydro-1*H*-pyrazol-5-ones

While "1-substituted 5-hydroxy-1*H*-pyrazoles", better named 4,5-dihydro-5-oxo-1*H*-pyrazoles, easily undergo reactions like carbonyl compounds (KNOEVENAGEL condensation, α,α-dihalogenation) [26], 1-substituted 3-hydroxy-1*H*-pyrazoles preferably behave like phenols (electrophilic 4-substitution). Surprisingly salts of 1-substituted 3-carboxy(*iso*)alkyloxy-1*H*-pyrazoles **14**, **40** and **41** and bromine (Scheme 5) under very mild conditions (water, 20 °C) afforded 4-mono- (P_1) resp. 4,4-dibromo-5-oxo-acids (P_2) **43**, **45**, **47–49** in high yields [27], formally a 4,5-addition of hydrogen monooxobromate (HOBr), followed by attack of Br^+ at the new secondary alcohol function (5-CHOH). In the 4-bromo-5-oxo-acids X = Br can easily be exchanged for SCN, N_3 or NHOH, giving rise to complexing agents. With sulfite (water, 20 °C) salts of the 4-bromo-5-oxo-acids *via* (R_1) or (R_2) (Scheme 5) gave 4,5-dihydro-5-oxo-acids **52–54**, **56** and **57** in high yields as well; in the 4,4-dibromo-5-oxo-acids **48** and **49** stepwise exchange of Br for H is possible. Thus an easy process for the introduction of a second O-function became available.

The 4-bromo-5-oxo-acid **45**, the 4-position of which is shielded by three methyl groups, with sulfite and other agents useful for (R_1)/(R_2) (dithionite in water, Zn in boiling ethanol) yielded a mixture of the diastereomer-



	R²	R⁵
14 a	Me	Me
14 b	Cl	Me
14 e	H	Me
40	H	H
41	Me	H

	R²	R⁵	X
42	Me	H	Cl
43	Me	H	Br
44	Me	Me	Cl
45	Me	Me	Br
46	Cl	Me	Cl
47	Cl	Me	Br
48	Br	H	Br
49	Br	Me	Br

	R²	R⁵
52	H	H
53	H	Me
54	Me	H
55	Me	Me
56	Cl	Me
57	Br	Me

Scheme 5

ic 4,4'-bis-pyrazolyls **50** (*meso*) and **51** (*rac*) (Q), which were separated. Structures **50** resp. **51** were assigned by ^{1}H 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 ^{1}H NMR and ^{13}C NMR in [D$_6$] 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*)alkyloxy-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-aralkyl-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 4N HCl or phosphoric acid with 2 mol Br_2 per mol **1** and catalytic amounts of KBr, followed by exchange of Br for H according to (R_1) [28]. By passing air through the aqueous solutions of sodium salts of 1-aralkyl-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

^{1}H NMR: Tesla 587.4 (100 MHz) and Bruker MSL 400, int. standard TMS, hexamethyldisiloxane (δ = 0.06 ppm) or $Me_3Si(CH_2)_3SO_3Na$ (δ = –0.02 ppm). – ^{13}C NMR: Varian CFT 20 (20 MHz), int. standard hexamethyldisiloxane (δ = 1.92 ppm in $CDCl_3$, 1.91 in [D$_6$] DMSO, 2.30 in D_2O). – 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%) ($CHCl_3$); 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 aceton silylated with hexamethyldisilazane/Me_3SiCl/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 ν = 2143 cm^{-1} (Infralyt, Junkalor, Dessau) and after total oxidation (two layer catalyst Pt/Al_2O_3, 450 °C; Co_3O_4/pumice, 650 °C) to CO_2 as K_2CO_3 by titration with 0.1N HCl[29].

2-Methyl-2-[[4-methyl-1-(phenylmethyl)-1H-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 aceton, 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 aceton (free of $CHCl_3$ 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 $NaHCO_3$ (168.0 g, 2.00 mol), which must be free of Na_2CO_3,

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	*m.p.* (°C)	emp. formula (mol. mass)	calcd./found C	H	N/+Cl/Br
14b	Bzl	Cl	H	Me	126 – 127	$C_{14}H_{15}ClN_2O_3$	57.05	5.13	+12.03
					[a]	(294.7)	56.92	5.03	+11.95
14c	Bzl	Br	H	Me	132	$C_{14}H_{15}BrN_2O_3$	49.57	4.46	+23.56
					[b]	(339.2)	49.85	4.51	+23.69
14d	Bzl	NO_2	H	Me	126 – 127	$C_{14}H_{15}N_3O_5$	55.08	4.95	13.76
					[a]	(305.3)	55.20	4.90	13.59
14e	Bzl	H	H	Me	129 – 130	$C_{14}H_{16}N_2O_3$	64.60	6.20	10.76
					[c]	(260.3)	64.33	6.26	10.89
14f	Bzl	H	H	Et	111 – 112	$C_{15}H_{18}N_2O_3$	65.67	6.61	10.21
					[d]	(274.3)	65.49	6.57	10.17
14g	Bzl	H	Me	Me	139 – 140	$C_{15}H_{18}N_2O_3$	65.67	6.61	10.23
					[a]	(274.3)	65.72	6.71	10.41
rac-**14h**	Bzl	Me	H	Et	86 – 87	$C_{16}H_{20}N_2O_3$	66.65	6.99	9.71
					[d]	(288.4)	66.30	6.92	9.68
14i	Bzl	Me	Me	Me	107 – 108	$C_{16}H_{20}N_2O_3$	66.65	6.99	9.71
					[c]	(288.4)	66.52	7.06	9.74
14k	Bzl	Me	Me	Et	99 – 99.5	$C_{17}H_{22}N_2O_3$	67.50	7.33	9.27
					[d]	(302.4)	67.43	7.36	9.22
14l	Bzl	Cl	Me	Me	126 – 127	$C_{15}H_{17}ClN_2O_3$	58.35	5.55	9.07
					[e]	(308.8)	57.98	5.49	9.08
14m	4-*i*Pr-Bzl	H	H	Me	87 – 88	$C_{17}H_{22}N_2O_3$	67.50	7.33	9.27
					[f]	(302.4)	67.55	7.33	9.24
14n	4-*i*Pr-Bzl	Cl	H	Me	102 – 103	$C_{17}H_{21}ClN_2O_3$	60.62	6.28	+10.52
					[e]	(336.8)	60.53	6.23	+10.62
14o	4-*i*Pr-Bzl	Br	H	Me	97 – 98	$C_{17}H_{21}BrN_2O_3$	53.55	5.55	+20.96
					[a]	(381.3)	53.68	5.50	+21.12
14p	4-Cl-Bzl	H	H	Me	147 – 148	$C_{14}H_{15}ClN_2O_3$	57.05	5.13	9.51
					[c]	(294.7)	57.19	5.10	9.47
14q	4-Cl-Bzl	Me	H	Me	113 – 114	$C_{15}H_{17}ClN_2O_3$	58.35	5.55	+11.48
					[e]	(308.8)	58.20	5.57	+11.65
14r	4-Cl-Bzl	Cl	H	Me	139	$C_{14}H_{14}Cl_2N_2O_3$	51.08	4.29	+21.54
					[b]	(329.2)	51.01	4.32	+21.71
14s	4-MeO-Bzl	H	H	Me	131	$C_{15}H_{18}N_2O_4$	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	$C_{16}H_{19}ClN_2O_4$	56.73	5.65	8.27
					[g]	(338,8)	56.79	5.73	8.18
14u	Bzl	H	Ph	Me	148 – 149	$C_{20}H_{20}N_2O_3$	71.41	5.99	8.33
					[c]	(336.4)	71.38	5.97	8.31
14v	Bzl	Cl	Ph	Me	174 – 175	$C_{20}H_{19}ClN_2O_3$	64.78	5.16	+9.56
					[a]	(370.8)	65.12	5.21	+9.66
14w	(Fur-2-yl)-methyl	H	H	Me	99	$C_{12}H_{14}N_2O_4$	57.59	5.64	11.19
					[a]	(250.3)	57.56	5.70	11.08
14x	Ph	H	H	Me	105 – 106	$C_{13}H_{14}N_2O_3$	63.40	5.73	11.37
					[c]	(246. 3)	62.96	5.79	11.18
14y	Ph	Cl	H	Me	155 – 156	$C_{13}H_{13}ClN_2O_3$	55.62	4.67	+12.63
					[a]	(280.7)	56.04	4.71	+12.75
14z	Ph	Br	H	Me	166 – 167	$C_{13}H_{13}BrN_2O_3$	48.02	4.03	+24.58
					[a]	(325.2)	48.37	4.00	+24.28
14a'	*i*Pr	H	H	Me	66 – 67	$C_{10}H_{16}N_2O_3$	56.59	7.60	13.20
					[e]	(212.3)	56.86	7.55	13.14
14b'	Cyclohex	H	H	Me	79 – 80	$C_{13}H_{20}N_2O_3$	61.88	7.99	11.10
					[e]	(252.3)	62.19	8.05	11.02
4a	*i*Pr	[h]	H	Me	191 – 192	$C_{10}H_{16}N_2O_3$	56.59	7.60	13.20
					[i]	(212.3)	56.84	7.73	13.12
4b	Cyclohex	[h]	H	Me	180 – 181	$C_{13}H_{20}N_2O_3$	61.88	7.99	11.10
					[g]	(252.3)	61.71	8.03	11.04

Crystallized from toluene [a], xylene [b], aqu. EtOH [c], CCl_4 [d], cyclohexane [e], *n*-hexane [f], EtOH [g], PrOH [i], [h] $R^4 = CMe_2CO_2H$; 5 – 6% separated by fractional crystallization, less soluble in cyclohexane than **14a'**, **14b'**.

in 2.0 l water. When the evolution of CO_2 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 CCl_4 (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 ($CHCl_3$ and KBr): ν/cm^{-1} = 1725 (C=O: CO_2), no absorption in the range of 1650. – ^{13}C NMR ($CDCl_3$): δ/ppm = 6.8 (4-Me), 25.0 (Me_2), 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 (CO_2H). – MS: *m/z* = 274 [M$^+$], 188 [**1a**$^+$], 91 [$PhCH_2^+$]. – pKa in MeOH/H_2O (9:1 [v/v]) = 4.3.

$C_{15}H_{18}N_2O_3$	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 $CHCl_3$ 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 3Å, an Infralyt with recorder, a reactor with the oxidation catalysts, a second Infralyt for monitoring total oxidation of CO to CO_2 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 H_2O and CO_2 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 $CHCl_3$ 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)-1H-pyrazol-3-yl]-propanoate (**7**)

1a-Na (4.20 g, 20.0 mmol), 2-chloro-2-methylpropanoic acid chloride (**10**, R^5 = Me; 2.82 g, 20.0 mmol) and 30 ml aceton were stirred at 53 °C for 5 h. After removal of aceton 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. – ^{1}H NMR

Tab. 2 ^{1}H NMR of (N-1)-substituted 2-methyl-2-[(1*H*-pyrazol-3-yl)oxy]-propanoic and butanoic acids **14** in $CDCl_3$ [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)	$\Delta^{CDCl_3}_{HMPT(A)}$ J_{45} (Hz)
14a	1.61 (s, 6H)	4.99	1.89 (d, 3H)	6.96 (q, 1H)	−0.48
	[1.58]	[5.11]	[1.86]	[7.44]	
14b	1.66 (s, 6H)	4.99	–	7.16 (s, 1H)	−0.84
	[1.61]	[5.18]		[8.00]	
14c	1.69 (s, 6H)	5.00	–	7.14 (s, 1H)	−0.96
	[1.61]	[5.22]		[8.10]	
14d	1.75 (s, 6H)	4.95	–	7.79 (s, 1H)	
14e	1.59 (s, 6H)	5.06	5.74 (d, 1H)	7.14 (d, 1H)	−0.59
	[1.54]	[5.20]	[5.55]	[7.73]	2.4 [2.2]
14f	1.58 [a]	5.10	5.76 (d, 1H)	7.17 (d, 1H)	−0.54
	[1.49]	[5.20]	[5.60]	[7.71]	2.4 [2.3]
14g	1.60 (s, 6H)	5,04	5.55	2.14	
rac-	1.52 [b]	5.10	1.92 (d, 3H)	7.08 (q, 1H)	−0.32
14h	[1.57]	[5.18]	[1.87]	[7.40]	
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)	5.04	5.79 (s, 1H)	7.14 – 7.40 (m)	
	[1.56]	[5.16]	[5.73]		
14a'	1.63 (s, 6H)	4.30 [d]	5.70 (d, 1H)	7.23 (d, 1H)	−0.37
	[1.52]	[4.33]	[5.46]	[7.60]	2.3 [2.2]
14b'	1.62 (s, 6H)		5.70 (d, 1H)	7.23 (d, 1H)	−0.35
	[1.53]		[5.48]	[7.58]	2.3 [2.2]

ABM_3: δ/ppm [(C-6)–CH_2Me] = 0.98 [0.91] [a]), 0.98 [0.92] [b]), 0.99 [c]); δ/ppm (N–C=Me_2) = 1.37, 1.47 [1.31, 1.41] [d])

($CDCl_3$): δ/ppm = 1.87 (d, 3H, 4-Me), 1.90 (s, 6H, CMe_2), 5.13 (br. s, 2H, N–CH_2), 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 $NaHCO_3$.

$C_{15}H_{17}ClN_2O_2$ 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 (R^2 = H)

To 25 mmol **14e** in 75 ml dichloromethane, cooled to –3 °C, SO_2Cl_2 (3.38 g, 25 mmol), [Br_2 (4.00 g, 25 mmol)] in 25 ml CH_2Cl_2 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 (Na_2SO_4). After removal of CH_2Cl_2 the residue **14b, l, n, r, v, y** [**14c, o, z,**] is crystallized (Table 1), yields 90–92%. – To **14e** (25 mmol) and $NaNO_2$ (0.02 g) in 70 ml $CHCl_3$ 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 (Na_2SO_4), $CHCl_3$ removed, the residue treated with aqueous $NaHCO_3$ (30°C), filtered and the filtrate acidified to pH 4. The deposited **14d** (82%) is dried at 70 °C and recystallized from toluene.

Thermolysis of 14a, 14b and 14e

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 ^{1}H NMR (NMR Spectra Catalog, vol. 1 and 2, Varian, no. 62). The solution of the residue in $CHCl_3$ 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 ^{1}H NMR identical with **1a** [30]) and **14a** (0.26 g, 12.6%; *m.p.* 114–115 °C), separated with aqueous $NaHCO_3$ (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. NH_3 (5:3:2); 2.50 g tartaric acid, 2.09 g $FeCl_3$ and 0.50 g I_2 in 12.5 ml aceton]. – Analogously **14b** gave 83.8% 1-benzyl-4-chloro-3-hydroxy-1*H*-pyrazole (**1b**), *m.p.* 176 °C (EtOH). – ^{1}H NMR ($CDCl_3$): δ/ppm = 5.05 (N–CH_2), 7.13 (s, 1H, 5-H) [6] and **14e** 80.2% 1-benzyl-3-hydroxy-1*H*-pyrazole (**1e**), *m.p.* 158 °C. – ^{1}H NMR ($CDCl_3$): δ/ppm= 5.57 (d, 1H, 4-H), 7.07 (d, 1H, J_{45} = 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 $SOCl_2$ (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-A_1) directly was used for the reactions with alcohols R^6-OH, otherwise the solvent, surplus $SOCl_2$ 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 (A_2; crude **18a** resp. **18h**) or its solution in dry dichloromethane (S-A_2) was used for further syntheses; S-A_1 and S-A_2 can be stored for some days at room temp. To S-A_1 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 (Na_2SO_4). After removal of CH_2Cl_2 white crystalline **24a** (97.7%) resp. **24h** (95.8%) was left.

Analogously the 2-methyl-2-[[4-methyl-1-(4-chlorophenyl)-1*H*-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 (Al_2O_3 neutral, activity A I, Greiz-Dölau; Et_2O) crystalline salts were formed with the equimolar amounts of acids.

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

To the stirred S-A_2 [from 100 mmol **14a** resp. **14h**; CH_2Cl_2 (240 ml)] further 100 ml dry CH_2Cl_2 and cholest-5-en-3β-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 aceton or purified by CC (Al_2O_3 neutral, activity A I, Greiz-Dölau; benzene).

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

18a (A_2, 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** (A_2, 200mmol) 100 ml 25% aqueous NH_3 gradually were added with stirring. After 4 h the precipitated **27a** (90.2%) was filtered and washed with ice-water or extracted with CH_2Cl_2 or Et_2O.

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

To **18a** (A_2, from 10.0 mmol **14a**) in 10 ml dry CH_2Cl_2 morpholine (1.74 g, 20.0 mmol) in dry CH_2Cl_2 was added with stirring at 10–12 °C within 30 min. After further 5 h stirring at 25 °C and removal of CH_2Cl_2 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**). – ^{1}H NMR: δ/ppm in $CDCl_3$

	m.p./b.p. (°C/ Torr)	emp. formula (mol. mass)	calcd./found C	H	N/$^+$Cl	4/7-H 5/6-H	4/7-Me (N–CH_2)	2/6=Me_2 2/6-Me
17b	141–145	$C_{14}H_{14}Cl_2N_2O_2$	53.69	4.51	+44.17	–	–	1.72 (s)
	/0.3	(313.2)	53.65	4.46	+44.03	7.14 (s)	(4.98)	–
22a	50–51	$C_{16}H_{20}N_2O_3$	66.65	6.99	9.71	–	1.89 (d)	1.63 (s)
	[a]	(288.3)	66.35	7.04	9.78	6.90 (q)	(4.98)	[b]
23a	143–145	$C_{17}H_{22}N_2O_3$	67.52	7.33	9.26	–	1.89 (d)	1.62 (s)
	/0.5	(302.4)	68.03	7.29	9.18	6.91 (q)	(4.98)	[c]
24a	114–115	$C_{24}H_{28}N_6O_5$	59.99	5.87	17.49	–	1.91 (d)	1.47 (s)
	[d]	(480.5)	59.73	5.91	17.35	7.01 (q)	(4.95)	–
24h	84–85	$C_{25}H_{30}N_6O_5$	60.72	6.11	17.00	–	1.92 (d)	[e]
	[d]	(494.5)	60.67	6.07	16.88	7.01 (q)	(4.94)	1.53 (s)
24q	91–92	$C_{24}H_{27}ClN_6O_5$	55.97	5.28	+6.89	–	1.90 (d)	1.56 (s)
	[d]	(515.0)	55.63	5.32	+6.95	7.00 (q)	(4.89)	–
25a	126–127	$C_{21}H_{25}N_3O_7S$	54.41	5.44	9.07	–	1.89 (d)	1.59 (s)
[f]	[g]	(463.5)	54.14	5.49	8.99	6.93 (q)	(5.00)	–
26a	106–108	$C_{42}H_{62}N_2O_3$	78.46	9.72	4.36	–	1.89 (d)	1.61 (s)
	[h]	(642.9)	78.19	9.67	4.30	6.90 (q)	(4.98)	–
26h	80–90	$C_{43}H_{64}N_2O_3$	78.60	9.82	4.26	–	1.89 (d)	–
	[i]	(657.0)	78.25	9.74	4.21	6.89 (q)	(4.97)	1.52 (s)
27a	75–76	$C_{15}H_{19}N_3O_2$	65.92	7.01	15.38	–	1.89 (d)	1.56 (s)
	[k]	(273.3)	66.17	6.96	15.32	6.98 (q)	(5.06)	–
28a	86–87	$C_{19}H_{25}N_3O_3$	66.45	7.34	12.24	–	1.86 (d)	1.65
	[k]	(343.4)	66.12	7.32	12.09	6.97 (q)	(5.01)	–
28h	59–61	$C_{20}H_{27}N_3O_3$	67.21	7.61	11.76	–	1.86 (d)	[l]
	[k]	(357.4)	67.12	7.63	11.67	6.96 (q)	(4.99)	1.59 (s)
28q	93–94	$C_{19}H_{24}ClN_3O_3$	60.38	6.40	+9.38	– [m]	1.83 (d)	1.54 (s)
	[k]	(377.9)	60.39	6.38	+9.45	7.45 (q)	(5.05)	–
29a	95–96	$C_{21}H_{23}N_3O_2$	72.18	6.64	12.03	–	1.94 (d)	1.63 (s)
	[k]	(349.4)	72.10	6.61	11.96	7.04 (q)	(5.06)	–
19a	186–188	$C_{15}H_{17}Cl_6N_2O_2Sb$	30.44	2.90	+35.95	– [o]	2.01 (d)	1.79 (s)
	[n]	(591.8)	30.47	2.87	+36.00	8.25 (q)	(5.60)	– [p]
19h	125–126	$C_{16}H_{19}Cl_6N_2O_2Sb$	31.72	3.16	+35.12	–	2.14 (d)	[q]
	[n]	(605.8)	31.74	3.18	+35.17	8.25 (q)	(5.70)	1.87
30	60–61	$C_7H_8N_2O_2$	55.24	5.30	18.41	5.47 (d)	– [r]	1.70
	[a]	(152.2)	55.36	5.29	18.31	7.84 (d)	–	–
31	71–72	$C_8H_{10}N_2O_2$	57.82	6.07	16.86	– [s]	1.92 (d)	1.68 (s)
	[a]	(166.2)	58,02	6.04	16.93	7.68 (q)	–	– [t]
32	92–94	$C_9H_{12}N_2O_2$	59.98	6.72	15.55	–	1.93 (d)	[v]
	/0.3 [u]	(180.2)	59.92	6.78	15.44	7.65 (q)	–	1.63 (s)
34	218–219	$C_{10}H_{13}N_3O_3$	53.81	5.87	18.82	– [w]	–	1.63 (s)
	[d]	(223.2)	53.88	5.86	18.85	8.02 (s)	–	–
37	100–102	$C_8H_9ClN_2O_2$	47.90	4.52	13.96	– [x]	1.92 (s)	1.68 (s)
	[a]	(200.6)	48.14	4.48	14.02	–	–	–
38	97–99	$C_7H_7ClN_2O_2$	45.05	3.78	+19.00	–	–	1.72 (s)
	[a]	(186.6)	45.26	3.74	+18.85	7.71 (s)	–	– [y]
39	178–79	$C_{28}H_{30}N_4O_7S$	59.35	5.34	9.89	– [z]	–	1.43 (s)
	[d]	(566.6)	59.72	5.37	9.89	7.67 (s)	(5.06)	–

Crystallized from *n*-hexane [a], EtOH [d], BuOH [g], aceton [h], cyclohexane [k], dioxane [n]. – [b] δ/ppm= 3.58 (s, OMe). – [c] δ/ppm = 1.06 (t, OCH_2Me), 4.01 (q, OCH_2) . – [f] **25a**-sulfate; **25a**-oxalate *m.p.* 92 – 93 °C (EtOH). – [i] *m.p.* EA and ^{1}H NMR refer to the mixture of the diastereomers **26h** [dia I, less soluble in aceton and butan-2-one, *m.p.* 105 – 108 °C, $[\alpha]_D^{20}$ = – 11.5° (c = 0.02, CH_2Cl_2)] and **26h** [dia II, *m.p.* 99 – 103 °C, $[\alpha]_D^{20}$ = – 30.8° (c = 0.1, CH_2Cl_2)]. – [l] δ/ppm = 0.96 (t, 6-CH_2Me), 2.07 (q, 6-CH_2). – [m] In [D_6] DMSO. – [o] In CD_3CN. – [p] ν (CO) = 1828 cm^{-1} (KBr). – [q] δ/ppm = 0.97 (t, 2-CH_2Me), 2.16 (q, 2-CH_2). – [r] J_{67} = 1.8 Hz. – [s] ^{1}H NMR in HMPT(A): δ/ppm = 1.68 (s, 2=Me_2), 1.90 (d, 7-Me), 7.99 (q, 6-H); ^{13}C NMR in $CDCl_3$: δ/ppm= 5.9 (7-Me), 23.9 (2=Me_2), 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 [$CH_2C(Me)=C=O^+$]. – [u] n^{20}_D = 1.499. – [v] δ/ppm = 0.93 (t, 2-CH_2Me), 2.01 (q, 2-CH_2). – [w] ^{1}H NMR in [D_6] DMSO (in $CDCl_3$): δ/ppm = 1.27 (1.37) (t, 3H, OCH_2Me), 1.45 (1.63) (s, 6H, 2=Me_2), 4.19 (4.30) (q, 2H, OCH_2), 8.97 (5.89) (br.s, 1H, NH), 8.00 (8.02) (s, 1H, 6-H); cf. ^{1}H NMR of **33** in [D_6] DMSO: δ/ppm = 1.26 (t, 3H, OCH_2Me), 1.55 (s, 6H, 6=Me_2), 4.20 (q, 2H, OCH_2), 7.92 (s, 1H, 5-H); *m/z*: 223 [M^+], 195 [M^+ – CO], 149 [M^+ – CO – EtOH], 108 [M^+ – CO – EtOH – $MeC=CH_2^+$]; ν (CO) = 1757 (3-CO), 1697 (CO_2Et) (KBr). – [x] ^{13}C NMR in $CDCl_3$: δ/ppm = 5.8 (7-Me), 23.8 (2=Me_2), 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 [$CH_2C(Me)=C=O^+$]. – [y] ν(CO) = 1788 (KBr); *m/z*: 186 [M^+], 158 [M^+ – CO], 69 [$CH_2C(Me)=C=O^+$]. – [z] In [D_6] 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 (A_2, from 10.0 mmol **14a**) in 10 ml dry CH_2Cl_2 and aniline (1.86 g, 20.0 mmol) in 10 ml CH_2Cl_2, reacted as above, yielded **29a** (88.7%).

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

To **18a** resp. **18h** (A_2 from 20.0 mmol **14a** resp. **14h**), dissolved in 20 ml dry CH_2Cl_2, the solution of $SbCl_5$ (6.28 g, 21.0 mmol) in 20 ml dry CCl_4 was added at 20 °C. After 1 h. the crystalline **19a** (79.8%) resp. **19h** (86.5%) was filtered and washed with cold CCl_4. **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 CH_2Cl_2 and $SOCl_2$ (25.00 g, 210 mmol) gradually were heated with exclusion of water, refluxed for 5 h., then solvent and surplus $SOCl_2$ 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. – ^{1}H 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 CH_2Cl_2 and $SOCl_2$ (8.96 ml, 125 mmol) gradually were heated under exclusion of moisture, refluxed for 6 h., solvent and surplus $SOCl_2$ removed

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

	m.p. (°C)	emp.formula (mol. mass)	calcd./found C	H	N +Cl/Br	δ ^{1}H (ppm) 7=H_2	6=Me_2 [H_2] 4–H
42	135–136	$C_{13}H_{13}ClN_2O_4$	52.62	4.42	+11.95		
	[a]	(296.7)	52.88	4.45	+11.97		
43	133–134	$C_{13}H_{13}BrN_2O_4$	45.76	3.84	+23.42	4.80 (q)	[4.76 (q)]
	[b]	(341.2) [c]	46.15	3.88	+23.19	[d] [e]	
44	125–126	$C_{15}H_{17}ClN_2O_4$	55.46	5.28	+10.92	4.69 (q)	1.73 (d)
	[a]	(324.8)	55.47	5.33	+10.82	[d]	
45	138–139	$C_{15}H_{17}BrN_2O_4$	48.79	4.64	+21.64	4.69 (q)	1.68 (d)
	[b]	(369.2) [f]	48.70	4.59	+21.55	[d] [g]	
46	95–96	$C_{14}H_{14}Cl_2N_2O_4$	48.71	4.09	8.12	4.63 (s)	1.69 (s)
	[b]	(345.2)	49.14	4.14	8.14	[d]	
47	114–115	$C_{14}H_{14}BrClN_2O_4$	43.16	3.62	7.19	4.68 (q)	1.72 (d)
	[b]	(389.6) [h]	42.84	3.58	7.26	[d]	
48	148–149	$C_{12}H_{10}Br_2N_2O_4$	35.50	2.48	+39.37	4.83 (s)	[4.77 (s)]
	[b] dec.	(406.0) [i]	35.72	2.51	+39.28	[d]	
49	131–132	$C_{14}H_{14}Br_2N_2O_4$	38.73	3.25	+36.82	4.67 (s)	1.70 (s)
	[b]	(434.1) [k]	39.11	3.22	+36.99	[d]	
52	146–147	$C_{12}H_{12}N_2O_4$	58.06	4.87	11.29	4.68/**4.90**	**3.65**/4.54
	[a]	(248.2)	57.88	4.91	11.33	[l] [m]	[n]
53	107	$C_{14}H_{16}N_2O_4$	60.85	5.84	10.14	4.65/**4.87**	**3.57/4.83**
	[o]	(276.3)	60.75	5.81	10.07	[l] [p]	[q]
54	133–134	$C_{13}H_{14}N_2O_4$	59.52	5.38	10.68	**4.69/4.92**	3.62 (q)
	[b]	(262.3)	59.42	5.40	10.59	[l] [r]	[s]
55	125–126	$C_{15}H_{18}N_2O_4$	62.06	6.25	9.65	**4.64/4.86**	3.50 (q)
	[b]	(290.3)	61.98	6.29	9.65	[l]	[t]
56	164–165	$C_{14}H_{15}ClN_2O_4$	54.12	4.86	+11.41	**4.64/4.93**	5.68
	[u]	(310.7)	53.95	4.83	+11.48	[l]	
57	157–158	$C_{14}H_{15}BrN_2O_4$	47.34	4.26	+22.50	**4.69/4.95**	5.71
	[v]	(355.2) [w]	47.08	4.21	+22.28	[l]	

Table 4 (continued)

δ ^{13}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 $MeNO_2$ [a], toluene [b], benzene [o], *i*PrOH [u], aqu. EtOH [v]. – [c] ν (5-CO/CO_2H) = 1750/1700 (KBr). – [d] In $CDCl_3$. – [e] δ_s of the AB systems. – [f] ν (5-CO/CO_2H) = 1735/1698 (KBr). – [g] δ_A = 4.65, δ_B = 4.73, J_{AB} = 16 Hz. – [h] ν (5-CO/CO_2H) = 1740/1705 (KBr). – [i] ν (5-CO/CO_2H) = 1760/1710 (KBr). – [k] ν (5-CO/CO_2H) = 1753/1698 (KBr). – [l] In [D_6]DMSO. – [m] δ (7=H_2) = 4.93 (anion of **52'** in D_2O + NaOD). – [n] δ (6=H_2) = 4.65 ([D_6] DMSO), 4.40 (D_2O + NaOD). – [p] δ (7=H_2) = 4.94 (anion of **53'** in D_2O + NaOD). – [q] δ (6=Me_2) = 1.49 (**53'**)/1.56 (**53**) ([D_6] DMSO), 1.50 (D_2O + NaOD). – [r] δ (7=H_2) = 4.97 (anion of **54'** in D_2O + NaOD). – [s] δ (4-Me) = **1,24**, **1.33** (**54**) and **1.76** (**54'**). – [t] δ (4-Me) = **1.16**, **1.26** (**55**) and **1.69** (**55'**). – [w] MS of **53**, **55**–**57** show [M^{+1}] and [M^+ – 86 (**16**)], i.e. splitting like **14**. – [x] In [D_6] DMSO (representative of mixtures of tautomers **52/52'** etc.) see above, in D_2O + 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 $SOCl_2$ (28.7 ml, 400 mmol) gradually were heated under exclusion of water, refluxed for 15 h., surplus $SOCl_2$ 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(2H)-one (**37**)

As described above **14a** (27.43 g, 100 mmol) was treated with. $SOCl_2$ (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-1H-pyrazolo[5,1-b]imidazol-3(2H)-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 CH_2Cl_2 with stirring and cooling (ice-water) $SOCl_2$ (3.60 ml, 50.0 mmol)) in 10 ml CH_2Cl_2 was added. After 6 h. stirring at 50–60 °C (bath) and removal of solvent and $SOCl_2$ the residue was crystallized from ethanol, to give **34** (4.22g, 75.6%).

(+)-((+)-14h) and *(–)-2-Methyl-2-[[4-methyl-1-(phenyl-methyl)-1H-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, $[\alpha]_D^{20}$ = + 3.5° (*c* = 0.096, CH_2Cl_2). 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, $[\alpha]_D^{20}$ = –3.7° (*c* = 0.094, CH_2Cl_2), 99.1% (–)-enantiomer according to HPLC on CTA. (+)- and (–)-**14h** also can be estimated by ^{1}H NMR of the methyl esters (with diazomethane in MeOH/Et_2O), using δ/ppm = 3.56, 3H (OMe) in $CDCl_3$ after addition of Eu(TFC)$_3$.

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

14e (26.03 g, 100 mmol), 100 ml dry CH_2Cl_2 and $SOCl_2$ (18.30 ml, 255 mmol) gradually were heated, refluxed for 9 h., solvent and $SOCl_2$ removed, at last under reduced pressure (bath temp. up to 80 °C), the residue treated with 250 ml 1N 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 $NaHCO_3$ 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 $NaHCO_3$ (25.2 g, 300 mmol) (P_1) resp. 300 ml of water and $NaHCO_3$ (33.6 g, 400 mmol) (P_2) were added, then using a pressure equalizing funnel the mixture of Br_2 (32.0 g, 200 mmol) and 35 ml methanol (P_1) resp. Br_2 (48.0 g, 300 mmol) and 55 ml methanol (P_2) 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)-1*H*-pyrazol-3-yl]oxy]-acetic acid (**41**) was obtained by stirring and refluxing 1-benzyl-3-hydroxy-1*H*- (**1e**) resp. 1-benzyl-3-hydroxy-4-methyl-1*H*-pyrazole (**1a**) (100 mmol), ethyl chloroacetate (100 mmol), dry K_2CO_3 (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 (CCl_4) resp. 99–100 °C (CCl_4).

[[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% H_2O_2 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 $NaHCO_3$ (0.87 g, 10.3 mmol) (R_1) resp. 60 ml water and $NaHCO_3$ (1.73 g, 20.6 mmol) (R_2) were added and Na_2SO_3 (1.30 g, 10.3 mmol) in 12 ml water (R_1) resp. Na_2SO_3 (2.60 g, 20.6 mmol) in 25 ml water (R_2) 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 $KHCO_3$ (6.01 g, 60.0 mmol) in 100 ml water was treated with Na_2SO_3 (3.91 g, 31.0 mmol) as described above for **43**, then the colourless solution acidified and extracted with Et_2O or with CH_2Cl_2. The combined organic phases were dried (Na_2SO_4), solvent removed, the residue triturated with cold Bu_2O 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.

$C_{30}H_{34}N_4O_8$ calcd.: C 62.27 H 5.92 N 9.68
(578.6) found: C 62.29 H 5.94 N 9.68.

– ^{1}H NMR (dimethyl ester, from **51** with CH_2N_2; $CDCl_3$): δ/ppm = 1.46/1.54 (d, 12H, 2×6=Me_2), 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=H_2). – ^{13}C NMR ([D_6]DMSO): δ/ppm = 13.6 (4-Me), 22.1/26.2 (6=Me_2), 46.6 (C-7), 48.0 (C-4), 80.7 (C-6), 161.9 (C-3), 170.2 (C-5), 177.6 (CO_2H). Recrystallization of the residue of the ethanolic mother liquor from $MeNO_2$ gave 1.48 g (17.1%) **50**, *m.p.* 182 – 185 °C, found C 61.62, H 5.90, N 9.70. – ^{1}H NMR (dimethyl ester, from **50** with CH_2N_2; $CDCl_3$): δ/ppm = 1.50/1.53 (d, 12H, 2×6=Me_2), 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=H_2). – ^{13}C NMR ([D_6] DMSO): δ/ppm = 14.5 (4-Me), 22.9/25.8 (6=Me_2), 46.9 (C-7), 48.6 (C-4), 81.1 (C-6), 161.9 (C-3), 170.5 (C-5), 172.6 (CO_2H). By treating the crude mixture of diastereomers with CH_2N_2 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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Address for correspondence:
Prof. Dr. Helmut Dorn
Parchwitzer Str. 100
D-12526 Berlin-Bohnsdorf