1,2,4-Triazoles, V[1]:

A Facile Synthesis of 1,5-Diphenyl-3-(substituted oxy)-1*H*-1,2,4-triazoles

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A series of 1,5-diphenyl-3-alkoxy (or acyloxy)-1*H*-1,2,4-triazoles were synthesized and assayed in the rat adjuvant induced arthritis model. Some compounds show significant anti-inflammatory activity.

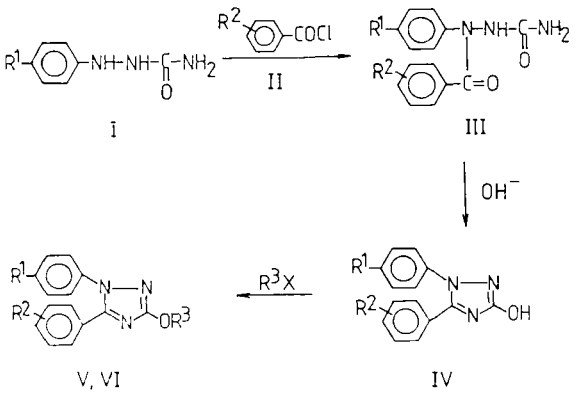
1,2,4-Triazole, 5. Mitt.[1]:
Einfache Synthese von 1,5-Diphenyl-3-(O-substituierten)-1*H*-1,2,4-triazolen

Eine Serie von 1,5-Diphenyl-3-alkoxy (oder acyloxy)-1*H*-1,2,4-triazolen wurde synthetisiert und auf ihre antiphlogistische Aktivität an Ratten im Adjuvans-Arthritis-Test untersucht. Einige dieser Verbindungen zeigen günstige entzündungshemmende Aktivität.

The potent and long-lasting anti-inflammatory activity of some diarylheterocycles[2,3] encouraged us the investigation of modified analogues. In the case of triazoles various 3-substituted derivatives with alkylthio[2], CF_3[4], and NH[5] groups have been synthesized, but only a few of them possess high biological activity. Compounds with RO groups had received little attention. This paper reports the synthesis and anti-inflammatory activity of new 1,5-diphenyl-3-alkoxy (or acyloxy)-1*H*-1,2,4-triazoles.

Using of our experiences with thio ether compounds[2] the intermediate hydroxy compounds **VI** were prepared from 1-phenyl-semicarbazides[6,7] **I** (obtained from phenylhydrazines with KOCN) by acylation with benzoyl chlorides **II** followed by cyclization of **III** under base conditions.

3-Methoxy-derivatives **V** were obtained by alkylation of **VI** with Me_2SO_4, the 3-alkoxy-ones with basic side chains **V** from **IV** with alkylchlorides in dioxane/K_2CO_3. Acylation of **IV** with Ac_2O, benzoyl chloride and sulfonyl chlorides lead to 3-(O-acylated)-derivatives VI (Scheme).



R^1 = Cl, F,
R^2 = 4-Cl, 4-F, 2-SMe
R^3 = Me, basic side chain, Ac, C_6H_5CO, $R'SO_2$

The structures of **1-31** were characterized by satisfactory microanalyses and by IR- and ^{1}H-NMR-spectral data. Chemical data of the compounds are summarized in Tables 2 and 3.

Adjuvant-induced arthritis (Newbould's preventive test[8])

Adult Long Evans male rats weighing 200-250 g were used. Arthritis was induced in rats by injecting heat-killed *Mycobacterium tuberculosis ravenel* (*Freund* adjuvant) in 0.1 ml of liquid paraffin suspension into the left hind paw on day 1. Compounds (dissolved in water containing Tween 80) were administered orally at low doses (6.25 and 12.5 mg/kg for 21 days starting on day 1). Control animals were given vehiculum.

Plethysmographic measurements of the primary lesion (injected paw) and the secondary lesion (non-injected paw) were made by mercury displacement on day 0, 3, 6, 10, 13, 17, 20, and 22 after injection of phlogist compared with controls.

Results

Table 1 contains the biological data of the most active compounds.

Important structure-activity relationships can be summarized as follows.

1. Active compounds contain halogen substituents (as previously found[2,5]) in the para position on the phenyl rings (MeS-ones are inactive).
2. the highest effect resides in the methoxy and other alkoxy compounds having basic side chain
3. the hydroxy, benzoylated and sulfonylated derivatives exhibit no biological activity.

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Conclusion

12 proved to be the most active compound in comparison with naproxen but the representatives of other series[2,5] (SR, SO_2R, NHR) were superior to **12** in detailed studies.

Table 1: Anti-inflammatory activity

Comp.	Inhibition of adjuvant induced arthritis in rats* (preventive adm.) % in 6.25 mg/kg po	Comp.	Inhibition of adjuvant induced arthritis in rats (preventive adm.) % in 6.25 mg/kg po.
7	33	**17**	30+
8	33	**18**	37
12	67	**22**	42
14	31	Naproxen	44
15	49+		

* The % inhibitory effect shows the decrease of the hind-paw volumen after treatment in comparison with the increase of the hind-paw volume of controls

+ In 12.5 mg/kg po.

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Experimental Part

Mp: Boetius apparatus, uncorr. - Analyses: C, H, N, S, and halogen were within ± 0.5 % of the theoretical values. - IR: Bruker IFS 85. - ^{1}H-NMR: Varian XL-100 FT. - TLC: Kieselgel 60 F_{254} (Merck), benzene/methanol 10:1.

General procedure for the preparation of 1,5-diphenyl-3-hydroxy-1,2,4-triazoles **IV (1-6)**

A mixture of 25 mmole of I, 28 mmole of II, and 2.4 ml of pyridine in 63 ml of benzene was heated for 3 h. After cooling the product was filtered off, washed with water and heated in a mixture of 62 ml 10 % KOH (aqueous) and 31 ml of ethanol at 60°C under N_2 for 1 h. The warm solution was acidified to pH 4, and after cooling the product was washed with water and recrystallized from dioxane. Products (R^1; R^2; mp. °C; yield %): **1**: Cl, 4-Cl, 278-280, 95; **2**: F, 4-Cl, 260-263, 87; **3**: Cl, 4-F, 303-305, 70; **4**: F, 4-F, 297-300, 85; **5**: Cl, 2-SMe, 267-270, 93; **6**: F, 2-SMe, 267-270, 86.

Table 2: Chemical data of compounds **V**

Comp. V	R^1	R^2	R^3	Mp (°C)	Yield (%)	Molecular formula	Mol.W.
7	Cl	4-Cl	Me	120-122	67	$C_{15}H_{11}Cl_2N_3O$	320.1
8	F	4-Cl	Me	85-87	30	$C_{15}H_{11}ClFN_3O$	303.7
9	F	4-F	Me	93-95	50	$C_{15}H_{11}F_2N_3O$	287.2
10	Cl	2-SMe	Me	98-100	44	$C_{16}H_{14}ClN_3OS$	331.8
11	F	2-SMe	Me	118-120	41	$C_{16}H_{14}FN_3OS$	315.3
12*	Cl	4-Cl	$-(CH_2)_2NMe_2$	255-257	30	$C_{18}H_{19}Cl_3N_4O$	410.7
13*	F	4-Cl	$-(CH_2)_2NMe_2$	233-236	28	$C_{18}H_{19}Cl_2FN_4O$	397.2
14	Cl	4-Cl	$-(CH_2)_3$-Mf	109-111	70	$C_{21}H_{22}Cl_2N_4O_2$	433.3
15	F	4-Cl	$-CH_2)_3$-Mf	88-89	83	$C_{21}H_{22}ClFN_4O_2$	416.8
16	Cl	4-F	$-(CH_2)_3$-Mf	87-89	70	$C_{21}H_{22}ClFN_4O_2$	416.8
17	F	4-F	$-(CH_2)_3$-Mf	71-74	68	$C_{21}H_{22}F_2N_4O_2$	400.42
18+	Cl	4-Cl	$-(CH_2)_3$-Mp	237-240	41	$C_{22}H_{27}Cl_4N_5O$	519.2
19+	F	4-Cl	$-(CH_2)_3$-Mp	227-230	86	$C_{22}H_{27}Cl_3FN_5O$	502.8
20+	Cl	4-F	$-(CH_2)_3$-Mp	221-224	68	$C_{22}H_{27}Cl_3FN_5O$	502.8

Mf = morpholino; Mp = 1-Me-4-piperazino; * = mono HCl salt; + = di-HCl salt

Table 3: Chemical data of compounds **VI**

Comp. VI	R^1	R^2	R^3	Mp (°C)	Yield (%)	Molecular formula	Mol.W.
21	Cl	4-Cl	MeCO	139-141	82	$C_{16}H_{11}Cl_2N_3O_2$	348.1
22	F	4-Cl	MeCO	84-86	70	$C_{16}H_{11}ClFN_3O_2$	331.7
23	Cl	4-F	MeCO	113-114	80	$C_{16}H_{11}ClFN_3O_2$	331.7
24	F	4-F	MeCO	113-115	66	$C_{16}H_{11}F_2N_3O_2$	315.2
25	Cl	4-Cl	C_6H_5-CO	160-162	89	$C_{21}H_{13}Cl_2N_3O_2$	410.2
26	F	4-Cl	C_6H_5-CO	145-148	73	$C_{21}H_{13}ClFN_3O_2$	393.7
27	Cl	4-F	C_6H_5-CO	124-126	90	$C_{21}H_{13}ClFN_3O_2$	393.7
28	F	4-F	C_6H_5-CO	104-106	81	$C_{21}H_{13}F_2N_3O_2$	377.3
29	Cl	4-Cl	2-MeS-C_5H_4-CO	177-179	67	$C_{22}H_{15}Cl_2N_3O_5S$	456.32
30	Cl	4-Cl	$MeSO_2$	137-139	63	$C_{15}H_{11}Cl_2N_3O_3S$	384.16
31	Cl	4-Cl	3,4-$(MeO)_2$-C_6H_3-SO_2	163-165	69	$C_{22}H_{17}Cl_2N_3O_5S$	506.3

General procedure for the preparation of 1,5-diphenyl-3-alkoxy-1,2,4-triazoles **V (7-11)**

Method for **7-11**: A mixture of 10 mmole of IV, 11 mmole of Me_2SO_4 and 1.6 g K_2CO_3 in 60 ml of acetone was refluxed under stirring for 8 h. After evaporation the residue was poured into water, extracted with CH_2Cl_2, dried over Na_2SO_4 and chromatographed on Kieselgel (benzene/methanol 10:1). After evaporation the first fractions gave V from a mixture of ethanol-petrolether.

Method for **12-20**: A stirred mixture of 10 mmole of IV, 12 mmole of alkylchloride and 4.0 g of K_2CO_3 in 50 ml of dioxane was refluxed for 6-8 h, then poured into water and extracted with CH_2Cl_2, finally dried. **14-17** were isolated as base, **12, 13** as HCl-salts in crystalline form.

General procedure for the preparation of 1,5-diphenyl-5-acyloxy-1,2,4-triazoles **VI**

Method for **21-24**: A solution of 10 mmole of IV in 5 ml of Ac_2O was heated for 30 min, then poured into water giving the products (recryst. from ethanol).

Method for **25-29**: A stirred mixture of 10 mmole of IV, 12 mmole (substituted) benzoyl chloride and 4.0 g of K_2CO_3 in 40 ml od dioxane was heated for 8-10 h. The mixture was poured into water, filtered and recrystallized from MeCN.

Method for **30-31**: A mixture of 2 mmole of IV and 0.2 g KOH in 9 ml of dioxane was heated for 1 h, then 2 mmole of sulfonyl chloride in 3 ml of dioxane were dropped in. Then the mixture was heated for 5 h and finally poured into water yielding **30** (from ethanol) and **31** (from MeCN), respectively.

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