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

Synthesis of New 1,5-Diphenyl-3-1*H*-1,2,4-triazoles Substituted with H-, Alkyl, or Carboxyl Groups at C-3

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Amidines obtained from benzamides and DMF- or DMA-dimethylacetal were cyclized with phenylhydrazines to 3*H*- or 3-methyltriazoles. 3-Ethyltriazoles were synthesized from diacylamides. Triazole-3-carboxylic acides were prepared starting from anilines. The compounds were assayed in the rat adjuvant induced arthritis model. Some compounds show significant anti-inflammatory activity.

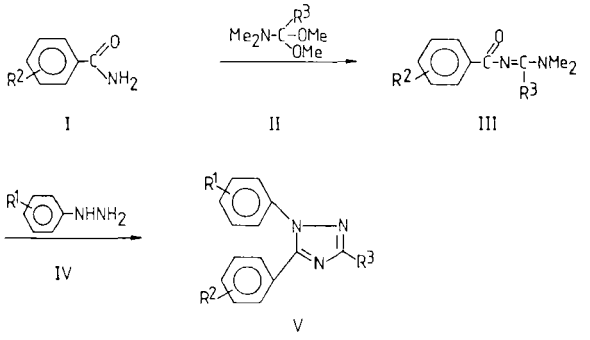
1,2,4-Triazole, 6. Mitt.[1]:
Synthese von 3*H*-(bzw. Alkyl)-1,5-Diphenyl-1,2,4-triazolen und 1,5-Diphenyl-1*H*-1,2,4-triazol-3-carbonsäuren

Die aus Benzamiden mit DMF-dimethylacetal darstellbaren Amidine lassen sich mit Phenylhydrazinen zu 3*H*-oder 3-methyl-triazolen cyclisieren. Die Synthese von 3-Ethyltriazole gelang aus Diacylamiden. Ausgehend von Anilinen wurden Triazol-3-carbonsäuren hergestellt. Einige dieser Verbindungen zeigten günstige antiphlogistische Aktivität im Adjuvans-Arthritis Test.

We reported upon the synthesis of several 1,5-diphenyl-triazoles with alkylthio[2], CF_3[3], amino[4] and alkoxy[1] substituents in position 3, which exhibit significant anti-inflammatory activity. In a continuing search for new and useful anti-inflammatory agents we now report upon the synthesis of 3-*H*-(alkyl, CO_2R)-1*H*-1,2,4-triazoles. This paper also describes some features of the structure-activity relationships observed in this series.

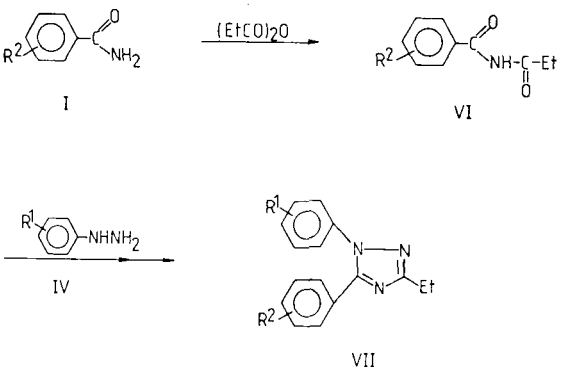
On the basis of experiences of *Yang-i Lin*[5] with condensation of acylamidines with hydrazines in acetic acid we have developed a synthetic route for the preparation of 1,5-diaryl-3-H(methyl)-1*H*-1,2,4-triazoles.

Reaction of benzamides **I** with DMF-or DMA-dimethylacetales **II** in methanol led to the acylamidines **III** which were cyclized with phenylhydrazines **IV** in acetic acid in the presence of 15 % aqueous NaOH to the 3-H(methyl)-triazole derivatives **V** (Scheme 1).



R^1 = Cl, F, CF_3, Me
R^2 = Cl, F, SMe, NO_2
R^3 = H, Me

Treatment of **I** with propionic acid anhydride in benzene containing a small amount of H_2SO_4 afforded diacylamide **VI** which succesfully underwent cyclization with phenylhydrazines **IV** in acetic acid in the presence of NaOAc to the 3-ethyl-triazole derivatives **VII** (Scheme 2).



An useful synthetic route to 3-CO_2R derivatives leads through an amidrazone **X** as versatile intermediate containing a CO_2R. Some representatives of this class were described only by *Bowak* and *Lapwortil*[6] in 1905.

Diazotation of anilines **VIII** followed by reaction with ethyl acetoacetate in aqeuous ethanol containing NaOAc afforded **IX**. Treatment of **IX** with Br_2 and at last with NH_4OH lead to the key intermediate **X** which was cyclized with substituted benzoyl chlorides **XI** in dioxane solution containing pyridine to the ester **XII**.

Hydrolysis of esters **XII** in aqueous ethanolic KOH yielded in the 3-CO_2H derivatives **XIII** which contain 0.5 mole of crystall water (over 105°C **XIII** decomposes).

The structures of **1-25** were characterized by satisfactory microanalyses and by IR-, ^{1}H-NMR- and mass spectral data. Chemical data are summarized in Tables 2 and 3.

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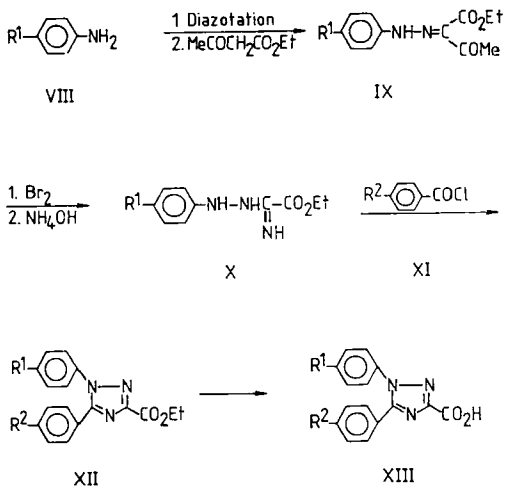

Pharmacological Test

Adjuvant-induced arthritis (*Newbould's* preventive test[7])

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 mol 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 measurement 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. All active compounds contain a halogeno substituent (as already found[2]) in the para position on the phenyl rings (MeS-ones are less active).
2. The highest activity resides in the 3-methyl-, ethyl- and carboxylic acid derivatives.
3. The 3-esters exhibit no anti-inflammatory activity.

Conclusion

16, 23 and **25** proved to be the most active compounds superior to naproxen. It is thought to develop one of the compounds for detailed studies.

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Experimental Part

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

Table 1: Anti-inflammatory activity

Comp.	Inhibition of adjuvant induced arthritis in rats* (preventive adm.) % in 12.5 mg/kg po	Comp.	Inhibition of adjuvant induced arthritis in rats* (preventive adm.) % in 12.5 mg/kg po
10	42	**22**	20
11	26	**23**	65
13	12	**25**	76
16	67	Naproxen	34
17	19		

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

General procedure for the preparation of **V (1-15)**

A mixture of 10 mmole of **III**[5,10-12] (obtained from substituted benzamide **I** and **II**[8,9]), 11 mmole of substituted phenylhydrazine **IV**, 15 ml of acetic acid and 5 ml of 10 % aqueous NaOH was heated for 2.5 h. After cooling crystalls were filtered and recrystallized from ethanol-petroleum-ether.

General procedure for the preparation of **VII (16,17)**

Step A: A solution of 25 mmole of **I**, 5 ml (40 mmole) of propionic acid anhydride, and 0.5 ml of conc. H_2SO_4 in 40 ml of benzene was refluxed for 10 h, then treated with active carbon and evaporated. The residue was stirred with water and afforded **VI** (recrystallization from ethanol); products (R^2, mp, %); **VIa**: 4-Cl, 163-165°, 48 **VIb**: 2-SMe, 122-123°, 53.

Step B: A solution of 15 mmole substituted phenylhydrazine **IV**, 15 mmole of **VI** and 20 mmole of NaOAc in 20 ml of acetic acid was refluxed for 8 h. After evaporation the residue was dissolved in CH_2Cl_2, washed with water, dried and evaporated yielding **16,17** (recrystallized from benzene-petroleumether).

General procedure for the preparation of **XII (18-21)**

Step A: To a stirred solution of 26 ml of ethyl acetoacetate, 100 ml of ethanol, 45 g of NaOAc and 100 ml of water 0.2 mole of the pertinent aqueous diazonium solution was dropped at 0°C, then 100 ml of ethanol and 50 ml of water were added. After 30 min the mixture was filtered, washed with water and the solids were recrystallized from ethanol affording **IX**; products (R^1, mp, %): Cl, 81-82°, 93; F, 88-90°, 94.

Step B: To a stirred solution of 10 mmole of **IX**, 10 ml of acetic acid and 1.2 g of NaOAc 10 mmole of Br_2 were dropped. After 10 min the solution was poured into 150 ml of water and extracted with CH_2Cl_2. After drying and evaporation the residue was dissolved in 20 ml of acetone, then to this solution 4 ml of 25 % aqueous NH_4OH in 15 ml of acetone were dropped under stirring. After 30 min the solvent was evaporated, the residue was dissolved in 30 ml of 10 % aqueous HCl and extracted with benzene. The aqueous phase was alkalized to pH 8 yielding **X** after filtration and recrystallization from ethanol; products (R^1, mp, %): Cl, 155-157°, 78; F, 126-128°, 77.

Step C: A mixture of 10 mmole of **X**, 11 mmole of pyridine, and 11 mmole of subst. benzoylchloride **XI** in 50 ml of dioxane was refluxed for 3 h. After evaporation the residue was dissolved in CH_2Cl_2 and washed with 4 % HCl, water, 10 % K_2CO_3 solution, and then water. The CH_2Cl_2 solution was dried, evaporated and the residue was crystallized from ethanol to give **XII**.

Table 2: Chemical data of compounds **1-17** (V, VII)

Comp. V, VII	R^1	R^2	R^3	Mp (°C)	Yield (%)	Molecular formula	(Mol.W.)
1	4-Cl	4-Cl	H	135-137	95	$C_{14}H_9Cl_2N_3$	290.1
2	4-F	4-Cl	H	74-76	96	$C_{14}H_9ClFN_3$	273.6
3	4-Cl	4-F	H	93-94	79	$C_{14}H_9ClFN_3$	273.6
4	4-F	4-F	H	117-119	63	$C_{14}H_9F_2N_3$	257.2
5	3-CF_3	4-Cl	H	66-68	66	$C_{15}H_9ClF_3N_3$	323.6
6	4-Cl	2-SMe	H	86-88	57	$C_{15}H_{12}ClN_3S$	301.8
7	4-Me	4-Cl	H	107-109	63	$C_{15}H_{12}ClN_3$	269.7
8	4-F	2-SMe	H	97-98	77	$C_{15}H_{12}FN_3S$	285.3
9	4-Me	2-SMe	H	107-109	55	$C_{16}H_{15}N_3S$	281.4
10	4-Cl	4-Cl	Me	112-114	70	$C_{15}H_{11}Cl_2N_3$	304.2
11	4-F	4-Cl	Me	71-72	73	$C_{15}H_{11}ClFN_3$	287.7
12	4-F	2-SMe	Me	100-102	75	$C_{16}H_{14}FN_3S$	299.4
13	4-Cl	2-SMe	Me	92-94	67	$C_{16}H_{14}ClN_3S$	315.8
14	4-Cl	4-NO_2	Me	156-158	62	$C_{15}H_{11}ClN_4O_2$	314.7
15	4-Me	4-Cl	Me	121-122	68	$C_{16}H_{14}ClN_3$	283.7
16	4-Cl	4-Cl	Et	94-95	40	$C_{16}H_{13}Cl_2N_3$	318.2
17	4-F	2-SMe	Et	62-64	30	$C_{17}H_{16}FN_3S$	313.3

Table 3: Chemical data of compounds **18-25** (XII, XIII)

Comp. XII, XIII	R^1	R^2	R*	Mp (°C)	Yield (%)	Molecular formula	(Mol.W.)
18	Cl	Cl	Et	72-74	58	$C_{17}H_{13}Cl_2N_3O_2$	362.2
19	F	Cl	Et	104-106	56	$C_{17}H_{13}ClFN_3O_2$	345.7
20	Cl	F	Et	114-115	35	$C_{17}H_{13}ClFN_3O_2$	345.7
21	F	F	Et	127-129	36	$C_{17}H_{13}F_2N_3O_2$	329.3
22	Cl	Cl	H	192-196	93	$C_{15}H_9Cl_2N_3O_2$	334.2
23	F	Cl	H	183-186	80	$C_{15}H_9ClFN_3O_2$	317.7
24	Cl	F	H	166-169	88	$C_{15}H_9ClFN_3O_2$	317.7
25	F	F	H	163-166	90	$C_{15}H_9F_2N_3O_2$	301.2

* substituent in the 3 position is CO_2R

General procedure for the preparation of **XIII** **(22-25)**

A solution of 10 mmole **XII** and 10 ml of aqueous KOH in 37 ml of ethanol was heated for 30 min. After evaporation the residue was dissolved in water, treated with active carbon and filtered into aqueous 4 % HCl solution. After cooling products were filtered, recrystallized from methanol, and dried in vacuo at 105°C for 3 h to afford **XIII**.

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