Analogues of Biologically Active Compounds, IV[1]:

Synthesis of Some 8-Arylazoguanines

Analoga biologisch aktiver Verbindungen, 4. Mitt.: Synthese einiger 8-Arylazoguanine

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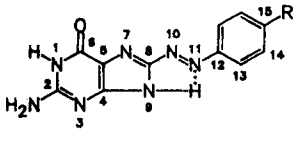
As in previous papers[1-3] devoted to the preparation of some derivatives of 1,2,4-benzotriazine structurally related to folic acid, here we report the synthesis of several analogues of pteroic or folic acid respectively, derived from guanine.

8- Arylazoguanines **1a-1d** have been prepared in satisfactory yield by diazotization of aniline, 4-aminobenzoic acid, *N*-(4-aminobenzoyl)-L-glutamic acid, and sulphanilamide followed by coupling of the formed diazonium salts with guanine. Moreover, using ^{15}N-aniline (96% enrichment) the azocompound **1a** containing ^{15}N in position 11 was prepared.

The ability of guanine for coupling with diazonium salts was described by *Burian*[4] who speculated that coupling proceeded at position 7. This erroneous opinion was corrected by *Fischer*[5] and *Hung* and *Stock*[6]. The coupling of diazonium salts with guanine takes place only in strong alkaline medium where the NH group in position 1 is deprotonated, and the reactivity of the formed mesomeric anion is focused at C-8.

Besides the 8-arylazo-9*H*-purine structure **1** the structure of the 8-arylhydrazono-8*H*- tautomeric form **2** may be considered. We carried out a study of the tautomerism in compound **1a** by IR, ^{13}C-, and ^{15}N-NMR spectroscopy with the



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1	R
a	-H
b	-COOH
c	-CO-NH-CH(-CH_2-CH_2-COOH)-COOH
d	-SO_2NH_2

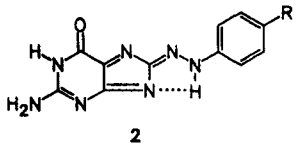

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Table 1: Effect of ^{14}N-^{15}N substitution on IR-absorption band maxima and ^{13}C- and ^{15}N-NMR chemical shifts of compound **1a**

IR ^{14}N / ^{15}N cm^{-1} (KBr)	1643/1641, 1489/1487, 1481/1477, 1413/1404, 1395/1393, 1195/1189, 909/899, 569/566
^{13}C-NMR / ppm (DMSO)	122.10 (C-13), 129.30 (C-14), 131.29 (C-15), 152.93 (C-12), 156.76, 154.74, 152.90, 152.15, 149.00
^{15}N-NMR / ppm	120.3 (N-11)[a] $^1J_{N_{11}C_{12}}$ = 3.8 Hz

[a] in the presence of $Cr(acac)_3$

derivative containing ^{15}N in position 11. This ^{14}N-^{15}N substitution resulted in the shift of the maximum of some absorption bands in the IR-spektrum (table 1) and thus assignment of the following bands was possible: bands over 3000 cm^{-1} are due to stretching vibration of N-H bonds, bands at 1709 and 1693 cm^{-1} are due to stretching vibration of the free and hydrogen bound C=O bonds, bands at 1662, 1643, 1598, and 1587 cm^{-1} are due to stretching vibration of C=N and C=C bonds and in-plane deformational vibration of the NH_2 group. Stretching vibration of the C-N bond between C-12 and C-13 exhibits intense band at 1413 cm^{-1}, while deformation vibration between atoms 8, 10, 11, and 12 results in the absorption bands at 909 and 569 cm^{-1}. Any of the absorption bands in the region over 3000 cm^{-1} does not exhibit a shift due to ^{14}N-^{15}N substitution so that an existence of the tautomeric form **2a** in the solid state may be excluded[7]. Existence of **2a** was also not proved in the NMR spectra (DMSO-d_6). ^{13}C- and ^{15}N-NMR chemical shifts are given in table 1. ^{15}N chemical shift was referred to external neat nitromethane (25% ^{15}N; δ=0.0 ppm). A positive value denotes downfield shift. ^{15}N chemical shift in ^{15}N labelled compound **1a** (96% ^{15}N) was measured after addition of $Cr(acac)_3$ as an relaxation reagent and proton-noise decoupling was used. The measurement of other nitrogen chemical shifts was impossible even using INEPT technique because of extremely low solubility of the compound. There were nine signals in the ^{13}C-NMR spectrum of **1a**. Only CH signals and C-12 were assigned (table 1), five signals in the region 156.76-149.00 ppm (quaternary carbons) are given in table 1 without an assignment. Spin-spin coupling between

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Table 2: Data of compounds **1a - 1d**

Compd.	Yield %	Mol. formula	Mol. mass	Analysis Calcd. Found C	H	N (%)
1a	95	$C_{11}H_{11}N_7O_2$	273.3	48.4	4.06	35.9
				48.2	3.96	36.0
1b	82	$C_{12}H_{13}N_7O_5$	335.3	43.0	3.69	27.6
				43.1	3.55	27.9
1c	62[a]	$C_{17}H_{18}N_8O_7$[b]	446.4	45.7	4.06	25.1
				45.9	3.97	24.9
1d	68	$C_{11}H_{12}N_8O_4S$	352.3	37.5	3.43	31.8
				37.8	3.15	32.1

[a] As dihydrate. [b] Monohydrate obtained after recrystallization from aqueous ethanol.

$^{15}N_{11}$ and $^{13}C_{12}$ made possible to assign the signal at δ = 152.93 ppm to C-12, the coupling constant $^1J_{N\text{-}11\ C\text{-}12}$ being 3.8 Hz. The assignment of tautomer **1a** is fully convincing because practically the same value of δ (^{15}N) was obtained as in trans-azobenzene[8]. ^{15}N chemical shifts of NH groups in compounds existing completely in hydrazone forms resonate at negative chemical shifts (about -200 ppm)[9]. These results correspond to the conclusions[6] based on ^1H-NMR spectroscopy.

Experimental Part

Melting points: *Boetius* block, uncorrected. - IR-spectra: IR-75 spectrometer (VEB Carl Zeiss Jena), KBr. - NMR spectra: Bruker AM 400 in DMSO-d_6 at 25°C.

2-Amino-8-arylazo-1,6-dihydro-9H-purin-6-ones **1a-1d**

The solution or suspension of 2 mmol of the corresponding aromatic amine in a mixture 2.0 ml 37% HCl and 7-15 ml water was cooled to 0°C and diazotized with the solution of 138 mg (2.00 mmol) $NaNO_2$ in 4 ml icecold water. The mixture was stirred for 20 min at 0°C and it was added within 5 min portionswise under stirring and cooling to solution of 500 mg (2.24 mmol) guanine dihydrate hydrochloride in 100 ml 1.5% aqueous NaOH at 0°C. The reaction mixture was stirred for 20-40 min at 0°C and then acidified with acetic acid. The formed red precipitate was collected after 2 h, washed with water and dried on air at room temp. Azocompouns **1a** and **1d** were obtained as monohydrates, azocompounds **1b** and **1c** as dihydrates. **1a-1d** were purified best by reprecipitation from the dilute solutions in $NaHCO_3$ (**1b** and **1c**), Na_2CO_3 (**1d**) and NaOH (**1a**) by acetic acid. **1c** can be purified also by recrystallization from aqueous ethanol. Compounds **1a-1d** do not melt up to 350°C. For the respective data see table 2.

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