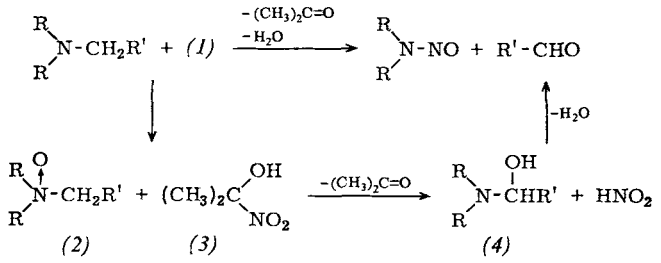
A New Degradation of Amines

By *Burchard Franck, Jens Conrad,* and *Peter Misbach*[*]

We have found a simple procedure for converting tertiary into secondary amines that consists of a combination of degradations by peroxide[1,2] and by nitrous acid[1,3] and gives good yields under very mild conditions.

$$(CH_3)_2CH\text{-}NO_2 + O_2 \xrightarrow{CuCl} (CH_3)_2C(OOH)(NO_2)$$

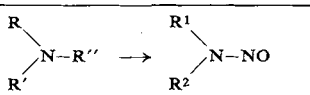
(1)



(2) *(3)* *(4)*

2-Nitroprop-2-yl hydroperoxide *(1)*, which is formed as intermediate during autoxidation of 2-nitropropane[4] and can be considered as an adduct of the hypothetical "peroxynitrous acid" to acetone, reacts with tertiary aliphatic amines with removal of one alkyl group as aldehyde or ketone and formation of a nitrosamine. To carry out the reaction it is only necessary to shake the tertiary amine in pyridine with 2-nitropropane and CuCl under oxygen. The nitrosamine formed can be easily separated and reduced to secondary amine. The tertiary amine remains unchanged in the absence of 2-nitropropane. Investigations of the reaction mechanism show that *(1)* oxidizes the amine to the amine oxide *(2)*, being converted itself into 2-nitro-2-propanol *(3)* which decomposes to acetone and HNO_2. The HNO_2 traps the secondary amine formed from the amine oxide *(2)* after rearrangement to the carbinol-amine *(4)* as nitrosamine.

The relative rates of removal of alkyl groups are k_{CH_3}: $k_{C_2H_5}$: $k_{n\text{-}C_3H_7}$: $k_{i\text{-}C_3H_7}$: $k_{tert\text{-}C_4H_9}$ = 100:62:57:(6—25):0, and correspond approximately to the relative numbers of protons in α-positions. It is remarkable that



R	R′	R″	R¹	R²	Yield (%)
C_2H_5	C_2H_5	C_2H_5	C_2H_5	C_2H_5	50
CH_3	CH_3	C_3H_7	CH_3	C_3H_7	59
			CH_3	CH_3	17
CH_3	$i\text{-}C_3H_7$	$i\text{-}C_3H_7$	CH_3	$i\text{-}C_3H_7$	7
			$i\text{-}C_3H_7$	$i\text{-}C_3H_7$	60
C_2H_5	$i\text{-}C_3H_7$	$i\text{-}C_3H_7$	C_2H_5	$i\text{-}C_3H_7$	21
			$i\text{-}C_3H_7$	$i\text{-}C_3H_7$	65
CH_3	CH_3	$t\text{-}C_4H_9$	CH_3	$t\text{-}C_4H_9$	60
C_2H_5	$i\text{-}C_3H_7$	$t\text{-}C_4H_9$	C_2H_5	$t\text{-}C_4H_9$	15
			$i\text{-}C_3H_7$	$t\text{-}C_4H_9$	59
CH_3	$-(CH_2)_5-$		$-(CH_2)_5-$		58

strongly hindered amines such as ethyldiisopropylamine (the Hünig base) and even *tert*-butylethylisopropylamine[5] which resist degradation by cyanogen bromide are dealkylated in particularly good yield. Amines whose nitrogen forms part of a five-membered ring are not degraded, and ring nitrosation is the predominant reaction of aromatic amines.

General procedure:

A solution of a tertiary amine (0.1 mole) in pyridine (100 ml) and CuCl (5 g, 0.05 mole) are placed in a double-walled flask that can be heated by connecting it with a thermostat and the mixture is saturated with O_2. The 2-nitropropane (30 ml, *ca.* 0.3 mole) is added and the mixture is shaken under O_2 at 50 °C. After 2—3 h (O_2 uptake 0.1—0.15 mole) the contents of the flask are poured on a mixture of ice (1 kg) and concentrated HCl (180 ml) and extracted with $CHCl_3$. The extract is dried over Na_2SO_4 and the residue obtained on evaporation is distilled from a bulb-tube and separated by layer chromatography on silica gel G. The quantitative composition of the nitrosamine mixture was determined by gas chromatography.

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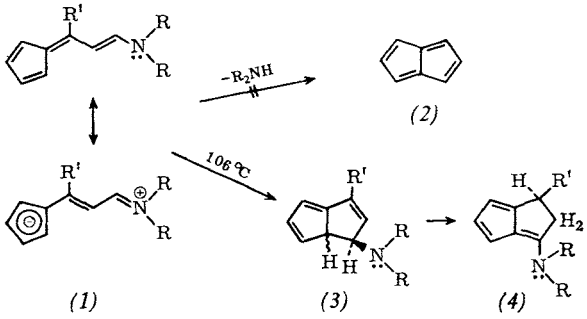
A Simple Synthesis of 1,2-Dihydropentalene and its Substitution Products

By *Reinhard Kaiser* and *Klaus Hafner*[*]

Whereas thermolysis of 6-(4-amino-1,3-butadienyl)fulvenes yields azulenes[11], it is not unexpected that the corresponding reaction of 6-(2-aminovinyl)fulvenes *(1)* does not lead to the desired but presumably highly thermolabile pentalene *(2)*[2]. Surprisingly, however, fulvenes of type *(1)* undergo ready cyclization to give 1,2-dihydropentalenes, of which only a few, multiply substituted representatives have hitherto been known[3].

During attempts to prepare stabilized pentalenes[4,5] from substituted 6-vinylfulvenes[4] we found that *N,N*-dialkyl derivatives of *(1)* are converted into 3-dialkylamino-1,2-dihydropentalenes *(4)* in boiling piperidine [*(4a)*, pale

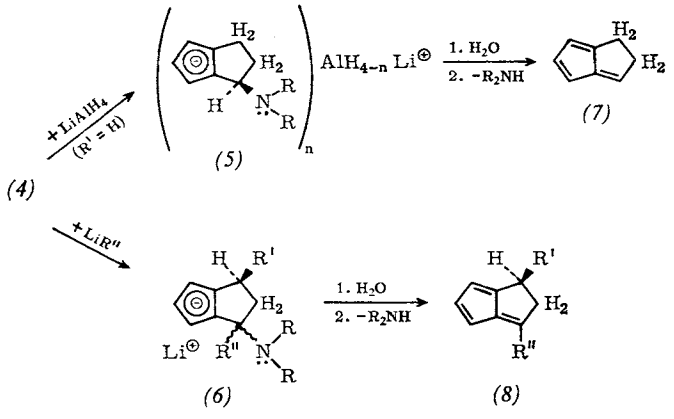


(1) *(3)* *(4)*

	2 R	R′	M.p. (°C)	Yield (%)
(4a)	$2\ CH_3$	H	121—122	71
(4b)	$-(CH_2)_5-$	H	99—100	75
(4c)	$-(CH_2)_2-O-(CH_2)_2-$	CH_3	102—103	62
(4d)	$-(CH_2)_5-$	CH_3	83—84	70

yellow needles, λ_{max} = 314 nm (log ε = 4.43) in *n*-hexane; NMR spectrum (in $CDCl_3$): multiplets centered at τ = 3.09 (H-5), 3.79 (H-4), 4.09 (H-6), broad singlet at τ = 6.75 ($N(CH_3)_2$), multiplet centered at τ = 6.97 (H_2-1, H_2-2)]. Intramolecular Michael addition is followed by base-catalyzed isomerization of the intermediate *(3)* to the thermodynamically more stable 6-aminofulvene derivatives (1,2-dihydropentalenes) *(4)*.

Like 6-dimethylaminofulvene[6], the bicyclic fulvenes *(4)* also add lithium tetrahydridoaluminate and alkyl- or aryllithiums in ether at 20 °C to give the organometallic compounds *(5)* and *(6)* respectively. On hydrolysis at 0 °C followed by amine elimination at 25 °C, compound *(5)* affords 1,2-dihydropentalene *(7)* [yellow, air-sensitive and thermolabile oil, b.p. 15 °C/10^{-2} torr; λ_{max} = 378 (2.68), 272 (3.70), 263 (4.04), 258 (4.08), 255 (4.09), 250 (4.04) nm (log ε) in *n*-hexane; NMR spectrum (in CCl_4): multiplets centered at τ = 3.29 (H-3, H-5), 3.96 (H-4), 4.18 (H-6), 6.93 (H_2-2), 7.39 (H_2-1)] and *(6)* gives the corresponding 1,2-dihydropentalene *(8)*.



	R'	R''	M.p. (°C)	B.p. (°C/torr)	Yield (%)
(8a)	H	CH_3	—	30—33/10^{-2}	84
(8b)	H	C_6H_5	61—62	—	82
(8c)	CH_3	CH_3	—	45—47/10^{-2}	81
(8d)	CH_3	C_6H_5	36—37	—	81

The composition and structure of the isolated compounds *(4)*, *(7)*, and *(8)* were confirmed by elemental analysis and by UV, NMR, and mass spectrometry. Experiments on the conversion of *(3)*, *(7)*, and *(8)* into the corresponding pentalenes are in progress.

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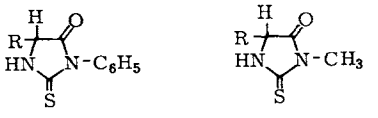
Gas Chromatographic Identification of the Thiohydantoins of Degradation Products of Peptides and Proteins[**]

By *Harald Tschesche*, *Rainer Obermeier*, and *Sigrid Kupfer*[*]

Although the Edman degradation has been developed for the stepwise sequential determination of peptides and proteins and has been extensively schematized and even automated[1], a simple method (cf.[2]) for the identification of the cleaved amino acids — mainly in the form of phenylthiohydantoins *(1)* — has not yet been reported. The compounds *(1)* are not well suited for identification by gas chromatography[3] because of their decomposability and low volatility, which can only be overcome in part by silylation[4].



(1) *(2)*

We have found, however, that the methylthiohydantoins *(2)* are suitable for gas chromatographic identification. With the exception of arginine and histidine all the naturally occurring amino acids, including Phe, Asn, Gln, Tyr, and Trp, can be chromatographed in the form of their methylthiohydantoins; Asp, Glu, and His can be chromatographed after methylation or silylation; and the separation and identification of leucine and isoleucine do not present any difficulties. The dehydrated derivatives of Ser and Thr were prepared and identified (see Table). Preliminary experiments indicate the possibility of coupling with automatic sequenators[6].

Mass spectra were used for the characterization of methylthiohydantoins *(2)* (see Table).

Table. Detection of naturally occurring amino acids in the form of their methylthiohydantoins *(2)*. Varian gas chromatograph 1520 with linear temperature programming of 4 °C/min, starting temperature 130 °C, 2 m column 1/4'', 5% OV-1 on Chromosorb W-AW-DMCS, 50 ml He/min.

Amino acid	Effusion temp. (°C)	Rel. retention time (min)	*m/e* [5]
Ala	152	6.3	144
Gly	157	7.6	130
Ser [a]	157	7.65	142
Val	164	10.0	172
Thr [a]	178	12.7	156
Ile	190	15.4	186
Leu	190	16.0	186
Pro	206	19.6	170
Met	208	19.9	204
Phe	208	20.1	220
Asn	231	24.5	187
Gln	241	26.8	201
Tyr	252	28.5	236
Trp	277	34.8	259

[a] Dehydrated compound.

Experimental

The peptide (1—5 μmole), dissolved in pyridine (0.5 ml, spectral grade) or pyridine/water (1:1), was coupled with methyl isothiocyanate (10 mg) under nitrogen at 0 or 40 °C for 60—90 min in a microflask in a rotary evaporator; solvent and unreacted reagent were removed under vacuum. After repeated extraction with toluene the residue was rubbed with ethyl acetate for separation of the dimethylthiourea and the carbamoyl peptide was centrifuged off. This procedure was repeated once. Trifluoroacetic acid or heptafluorobutyric acid were used for the cleavage and cyclization (50 °C, 45 min). Although the methylthiohydan-