herabgesetzt, z.B. auf 1 h, so erhielten wir nach Durchführung der Reduktion ein Gemisch von IV und VII, das sich überraschend glatt durch Kristallisation aus Aceton auftrennen liess. Die Löslichkeitsunterschiede (IV ist schwerer löslich als VII) sind so ausgeprägt, dass auf diese Weise eine präparative Trennung der 5α- und 5β-Isomeren des Androstan-17β-ol-3-ons möglich ist.

Im weiteren Verlauf der Synthese wurde dann VII mit *p*-Toluolsulfonsäure in Aceton zum 5β-Androstan-17β-ol-3-on verseift, das Rohprodukt chromatographisch gereinigt und nach üblicher Methode acetyliert. Wir erhielten in 51%iger Ausbeute (bezogen auf VII) 5β-Androstan-17β-ol-3-on-17-acetat (VIII); Fp.: 146–147,5°C ([10,11] 143–144°C); $[\alpha]_D$: + 21° ([10] + 27,1°); das IR-Spektrum stimmte mit dem einer authentischen Probe überein, ν_{max}: 1720, 1740 cm^{-1} (CS_2)[12].

Summary. 5α- and 5β-androstane-17β-ol-3-one-17-acetate have been prepared from 5β-androstane-6α,17β-diol-3-one-17-acetate by a synthesis involving directed HUANG-MINLON-reduction.

Separation of 5α-androstane-17β-ol-3-one from its 5β-isomer could readily be achieved by crystallisation of their 3-ethylenketals from acetone.

S. SCHWARZ, W. POHNERT,
A. STACHOWIAK und D. ONKEN

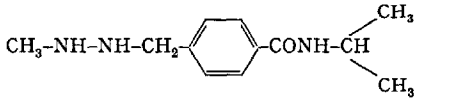
Wissenschaftliche Laboratorien des VEB Jenapharm, Jena (Deutschland), 12. Oktober 1962.

[10] A. BUTENANDT, K. TSCHERNING und G. DANNENBERG, Hoppe-Seylers Z. *248*, 205 (1937).
[11] A. ERCOLI, Ber. dtsch. chem. Ges. *71*, 650 (1938).
[12] Wir danken Frl. G. KRETZSCHMANN für ihre experimentelle Mitarbeit und Herrn Dr. K. HELLER (Wissenschaftliche Laboratorien des VEB Jenapharm) für Aufnahme und Interpretation der IR-Spektren.

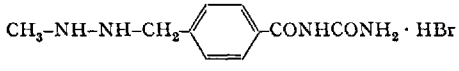
Methylhydrazine Derivatives, a New Class of Cytotoxic Agents

When testing a series of hydrazines for another purpose 1-methyl-2-benzyl-hydrazine[1] was found to have a pronounced tumour inhibitory effect[2]. The systematic variation of its structure showed that efficacious compounds were of general formula *R*–NH–NH–CH_3, *R* representing a wide variety of organic radicals, particularly substituted benzyl groups.

Screening of several hundred compounds revealed some forty to be efficient tumour inhibitors among which 1-methyl-2-*p*-(isopropylcarbamoyl)benzyl-hydrazine hydrochloride I[3] and 1-methyl-2-*p*-allophanoylbenzyl-hydrazine hydrobromide II[4] were chosen for extended biological and clinical trials.



I



II

Known synthetic procedures lead to the above mentioned compounds. Methylhydrazine reacts with benzyl chloroformate to give 1-methyl-1,2-bis(benzyloxycarbonyl)-hydrazine, a crystalline substance. This product is transformed to the sodium salt with sodium hydride in dimethylformamide. Alkylation of this salt with methyl *p*-(bromomethyl)benzoate leads to 1-methyl-2-*p*-(methoxycarbonyl)benzyl-1,2-bis(benzyloxycarbonyl)-hydrazine which after hydrolysis of the methyl ester group yields the crystalline 1-methyl-2-*p*-carboxybenzyl-1,2-bis(benzyloxycarbonyl)-hydrazine. The preparation of the acid chloride by means of thionyl chloride and reaction of the latter with isopropylamine or with urea leads to the bis-(benzyloxycarbonyl) derivatives of I and II. Removal of the protecting groups by treatment with hydrogen bromide in acetic acid or by hydrogenolysis and transformation to the desired salts are the final stages of the synthesis.

Whereas crystalline salts of these hydrazines are quite stable compounds, their solutions, especially in water, tend to be oxidized. The primary oxidation products, the corresponding azo derivatives, isomerize rapidly, at least in the case of the benzyl compounds, to the hydrazones which are biologically inactive. Some of the azo compounds and also higher oxidation products such as azoxy derivatives show antitumour activity *in vivo* but are less stable and less well characterized than the parent hydrazines.

The oxidation of the above mentioned hydrazines, whereby hydrogen peroxide is produced from molecular oxygen may be an essential step in the tumour inhibiting mechanism[5].

Extensive biochemical and physicochemical investigations in addition to clinical trials are under way to learn more about this new lead in cancer chemotherapy.

Zusammenfassung. Ausgehend von der Beobachtung, dass 1-Methyl-2-benzyl-hydrazin tumorhemmend wirkt, wurden durch systematische Variationen die für diese Wirkung essentiellen Strukturmerkmale festgelegt. Aus einer grösseren Anzahl von Verbindungen wurden 1-Methyl-2-*p*-(isopropylcarbamoyl)benzyl-hydrazin-hydrochlorid und 1-Methyl-2-*p*-allophanoylbenzyl-hydrazin-hydrobromid für ausgedehnte experimentelle und klinische Versuche ausgewählt.

P. ZELLER, H. GUTMANN, B. HEGEDÜS,
A. KAISER, A. LANGEMANN, and M. MÜLLER

Chemische Forschungsabteilung, F. Hoffmann-La Roche & Co. AG., Basel (Switzerland), December 14, 1962.

[1] J. THIELE, Liebigs Ann. Chem. *376*, 239 (1910).
[2] W. BOLLAG and E. GRUNBERG, Exper. *19*, 130 (1963).
[3] I = Ro 4-6467/1.
[4] II = Ro 4-6824.
[5] K. BERNEIS et al., Exper. *19*, 132 (1963).