

## WYKŁAD 7

### Układy pięcioczłonowe z jednym heteroatomem



**Furan**



**1H-Pirol**



**Tiofen**



**Benzofuran**



**1H-Indol**



**Benzo[b]tiofen**



**Tetrahydrofuran**



**Pirolidyna**



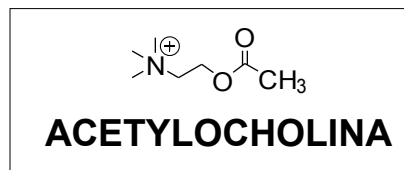
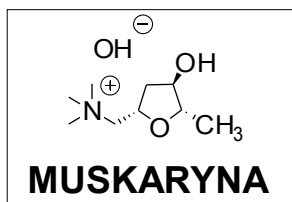
**Tiolan**

# 1. Muskaryna (INN, *muscarine*)

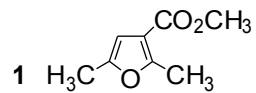
Alkaloid pochodzenia naturalnego obecny w wielu grzybach. Nie ma zastosowania terapeutycznego. Ze względu na silne właściwości trujące i podobieństwo strukturalne, pierwszy systematycznie zbadany analog acetylocholiny.



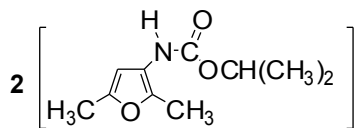
**Amanita muscaria**



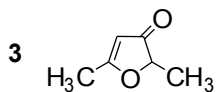
**Acetylocholina** - neurotransmitter odpowiedzialny za funkcjonowanie układu pokarmowego i oddechowego, wzroku, serca oraz gruczołów wydzielania (np.: potowych, ślinowych, łojowych, trawiennych).



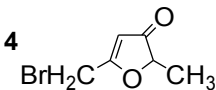
↓ (1)  $\text{NH}_2\text{NH}_2$ ; (2)  $\text{HNO}_2/i\text{-C}_3\text{H}_7\text{OH}$



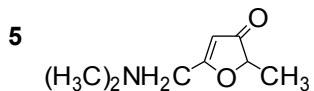
↓  $\text{H}^+$



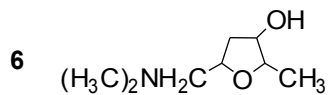
↓ NBS



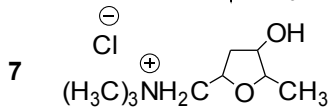
↓  $\text{NH}(\text{CH}_3)_2$



↓ [H]



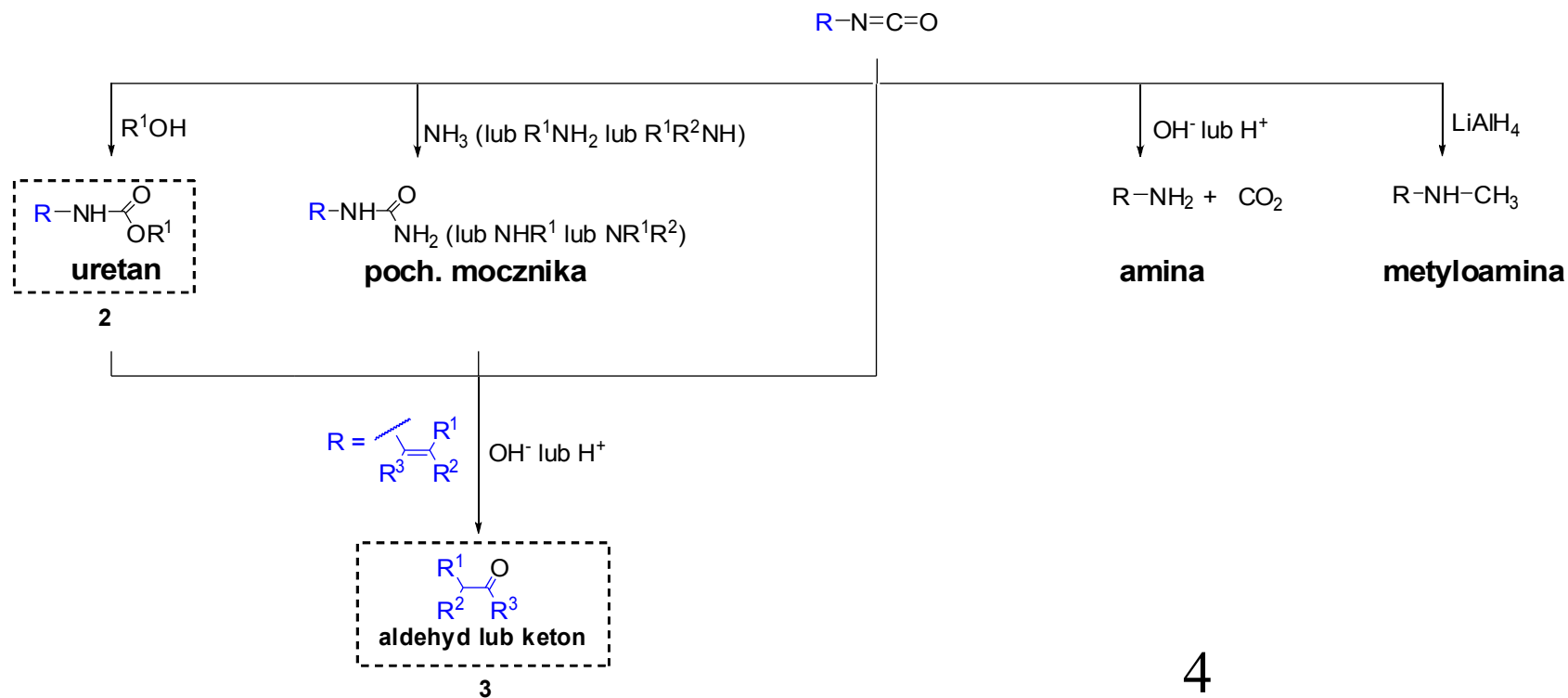
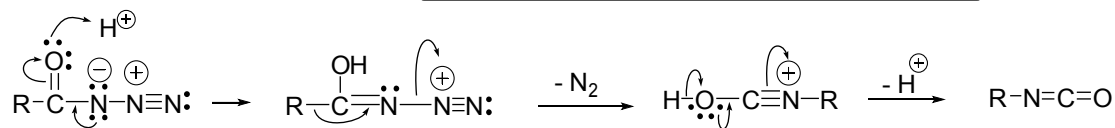
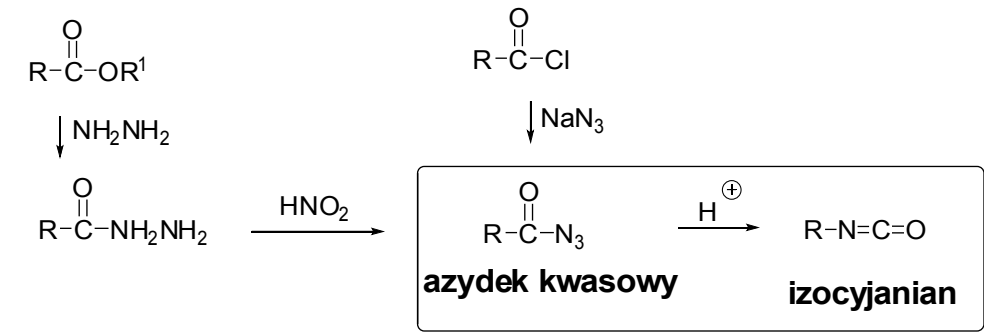
↓  $\text{CH}_3\text{Cl}$



Mieszanina izomerów

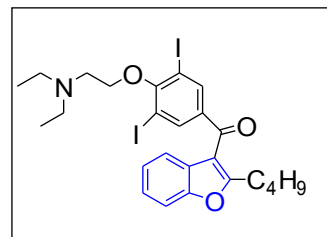
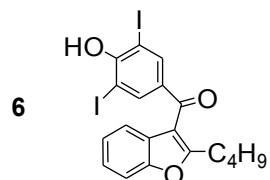
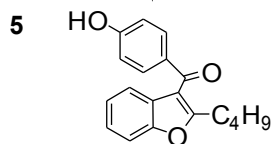
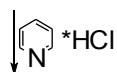
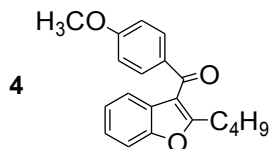
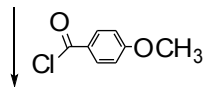
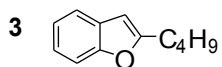
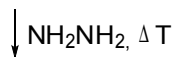
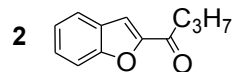
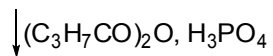
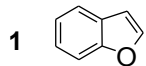
# 1.1. Wyjaśnienie przebiegu wybranych etapów. Reakcja Curtiusa (1890 r)

Org. React. III, 1946, pp. 337.



## 2. Amiodaron (INN, *amiodarone*)

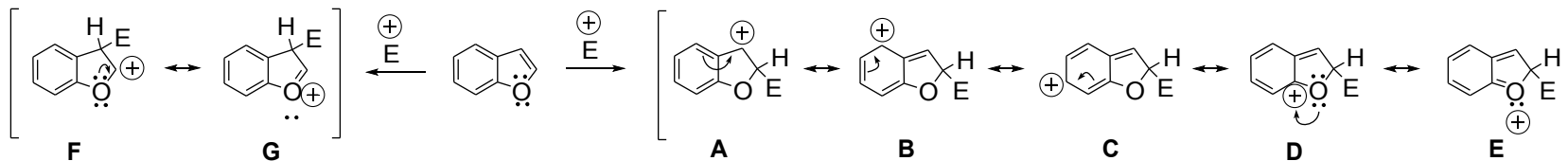
Fr. Patent 1.339.389 (1962).  
US Patent 3.248.401 (1966).



Lek stosowany w arytmii serca.

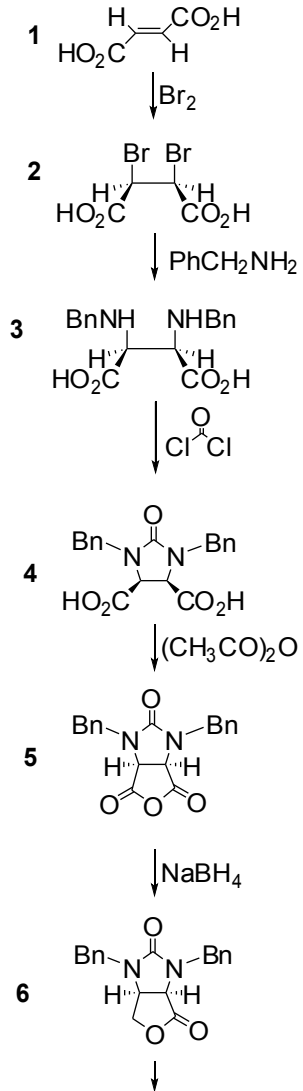
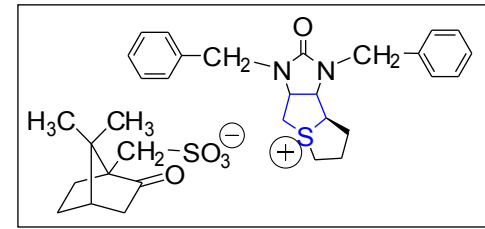
## 2.1. Wyjaśnienie przebiegu wybranych etapów.

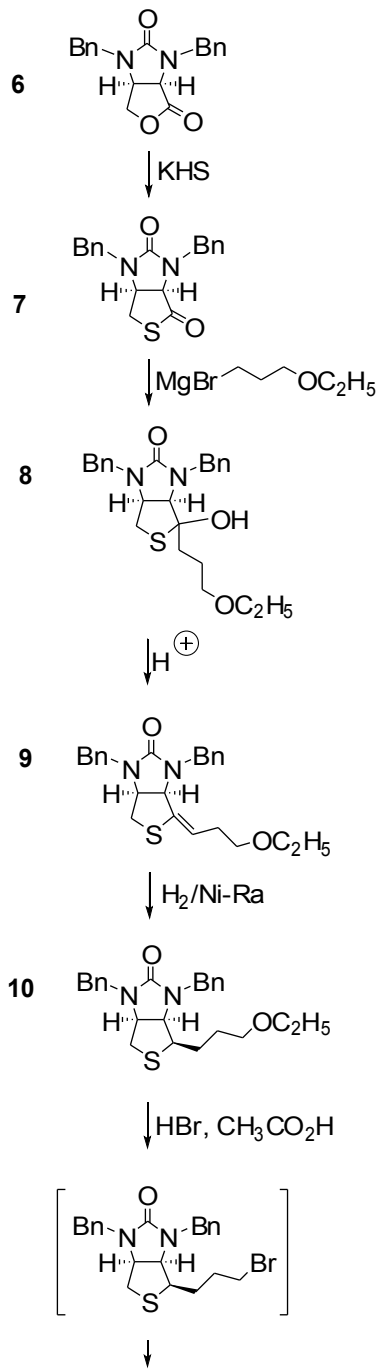
### Regioselektywność aromatycznej substytucji elektrofilowej benzofuranu



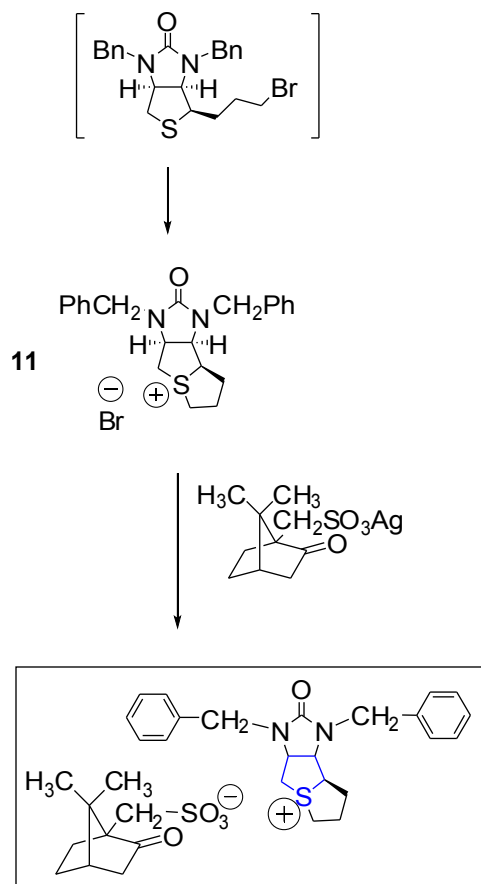
### 3. Trimetafan (INN, *trimethaphan*)

Lek stosowany do kontroli ciśnienia krwi w czasie operacji chirurgicznych, do szybkiej interwencji podczas ostrych skoków ciśnienia krwi oraz w wypadkach gdy inne leki nie mogą być użyte.





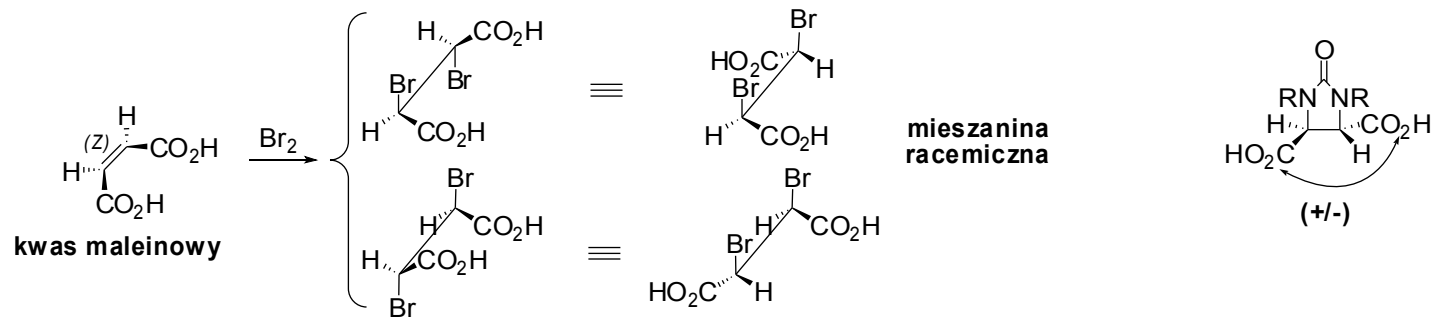
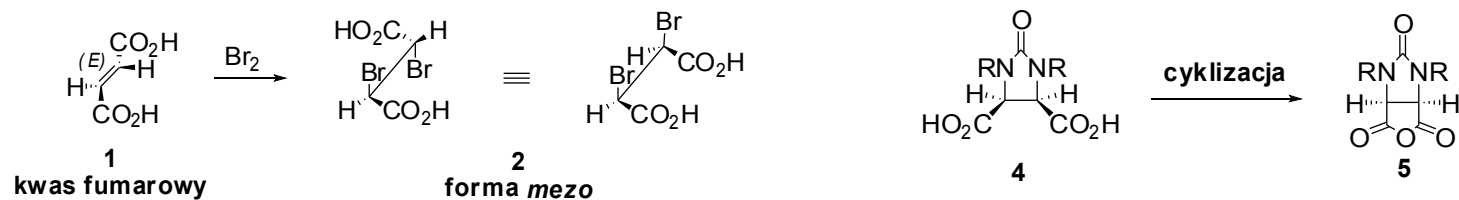




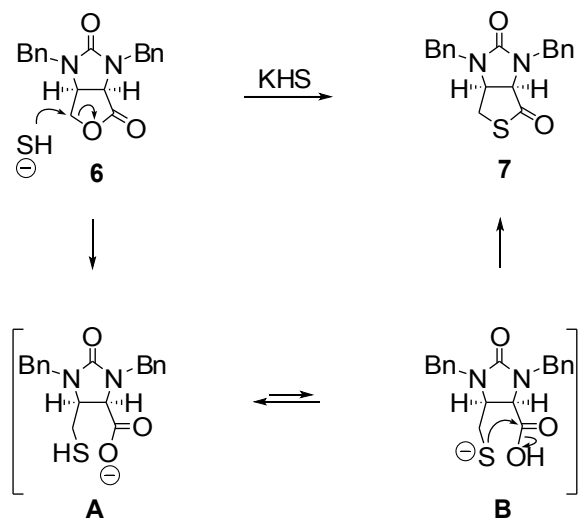
US Patent 2.489.238 (1949); US Patent 2.519.720 (1950); US Patent 3.740.416 (1973); *Agr. Biol. Chem.* 1976, 40, 1658; *J. Am. Chem. Soc.* 1978, 100, 1558.

### 3.1. Wyjaśnienie przebiegu wybranych etapów

#### 3.1.A. Dobór wyjściowego substratu: dlaczego kwas fumarowy a nie maleinowy?

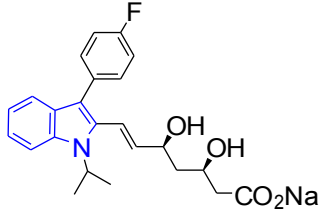


### 3.1.B. Przekształcenie laktonu (6) w tiolakton (7)

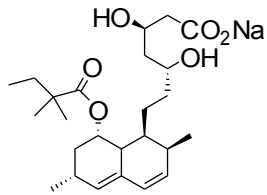


## 4. Fluwastatyna (INN, *fluvastatin*)

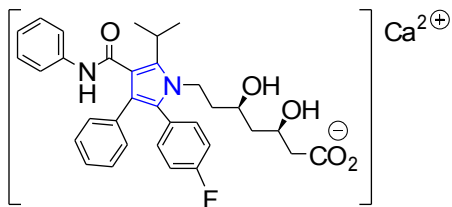
Leki stosowane w hipercholesterolemii.



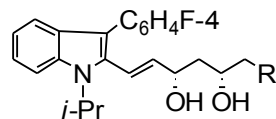
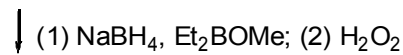
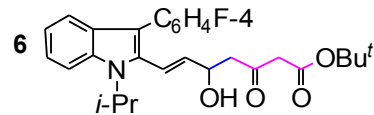
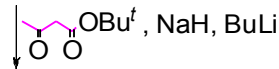
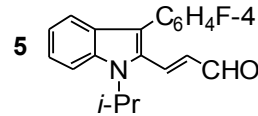
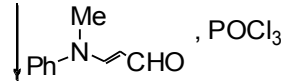
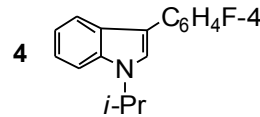
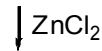
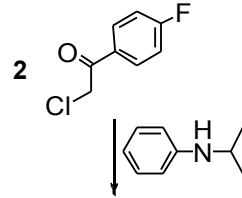
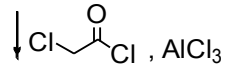
**Fluwastatyna**  
(INN, *fluvastatin*)



**Symwastatyna**  
(INN, *symvastatin*)



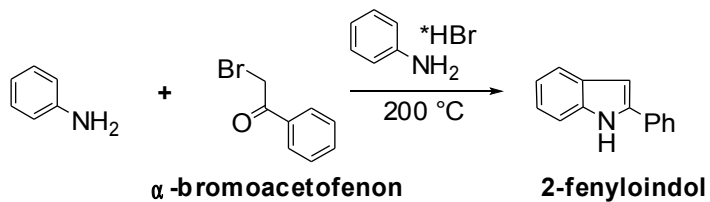
**Atorwastatyna**  
(INN, *atorvastatin*)



7, R = CO<sub>2</sub>Bu<sup>t</sup>  
FLUWASTATYNA, R = CO<sub>2</sub>Na

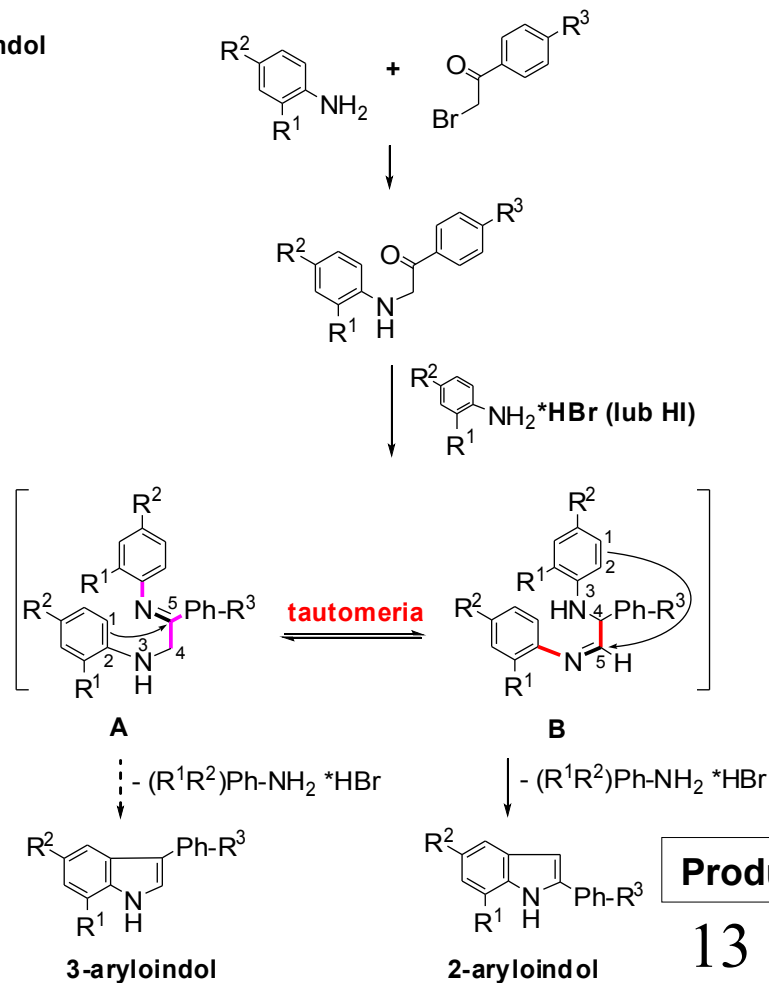
## 4.1. Wyjaśnienie przebiegu wybranych etapów

### 4.1.A. Bischlera-Möhlau synteza indolu (wariant „klasyczny”)

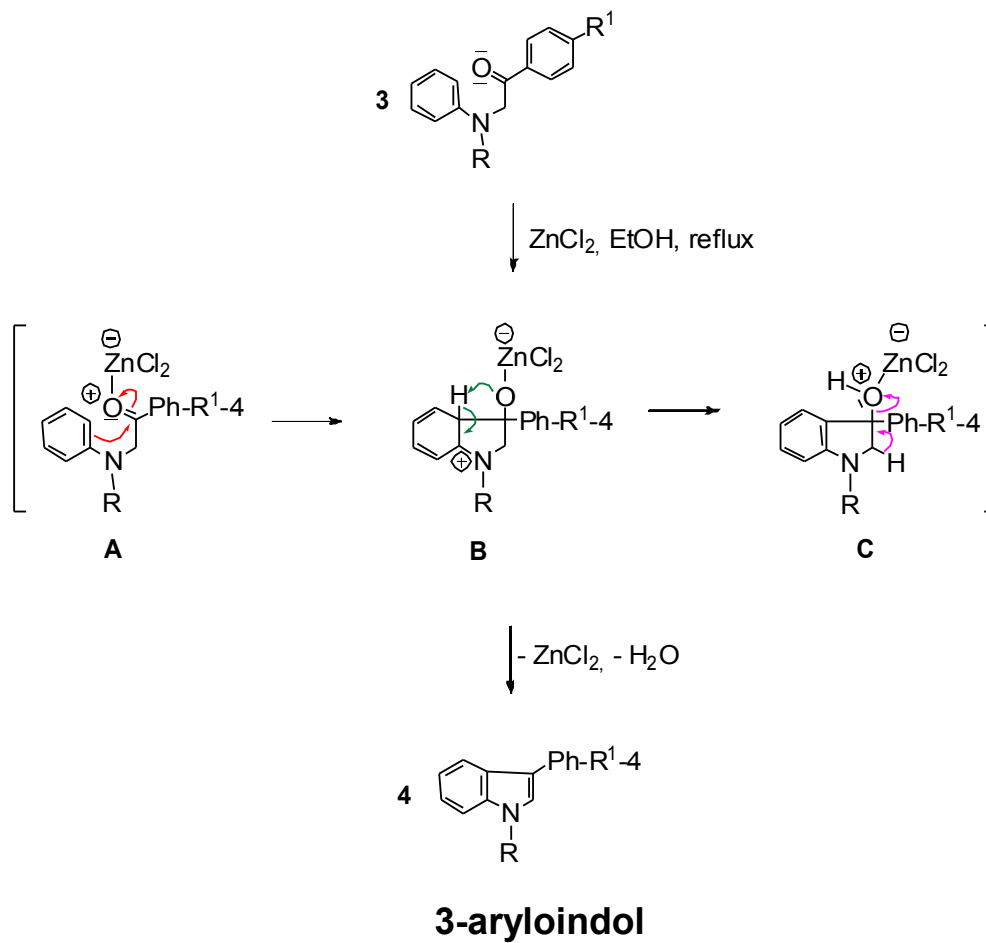


*Ber.* 1881, 14, 171; *Ber.* 1882, 15, 2480;  
*Ber.* 1892, 25, 2860; *Ber.* 1892, 26, 1336.

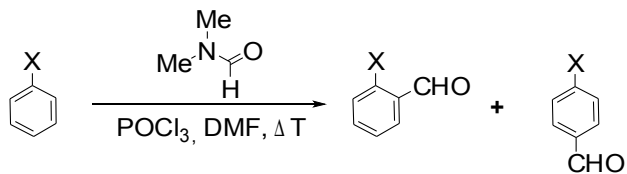
Postulowany mechanizm:



Wariant zmodyfikowany – reakcja z dodatkiem  $\text{ZnCl}_2$  (5-10 ekw.); w większości przypadków powstają pochodne 3-aryloindolu.

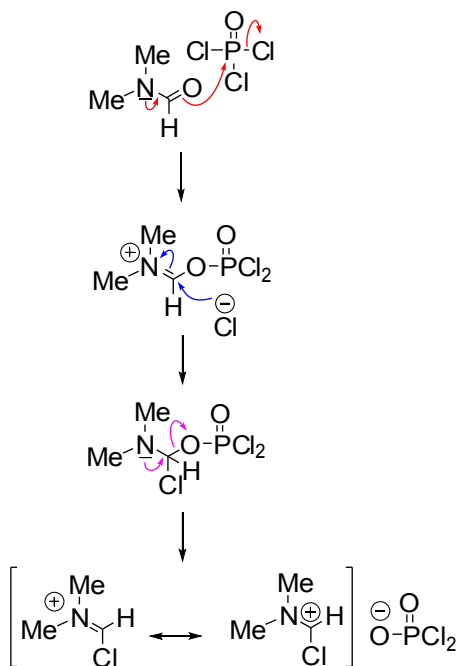


## 4.1.B. Reakcja Vilsmeiera-Haacka



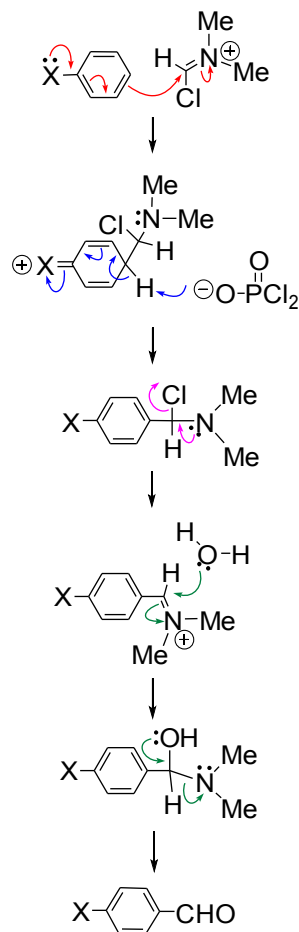
X = gr. elektronodonorowa: OCH<sub>3</sub>, OH, NR<sub>2</sub>  
Reakcja służy także do formylowania związków heterocyklicznych.

### 1. Utworzenie soli chloroiminiowej

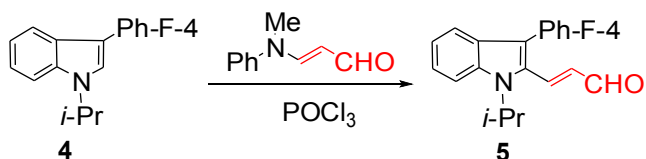


**sól chloroiminiowa  
(reagent Vilsmeiera-Haacka)**

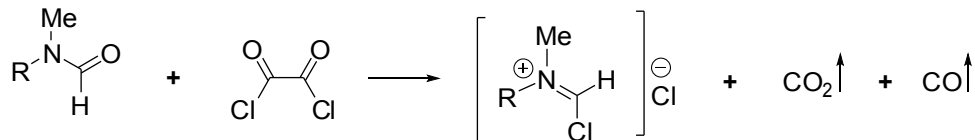
### 2. Alkylowanie pochodnej benzenu



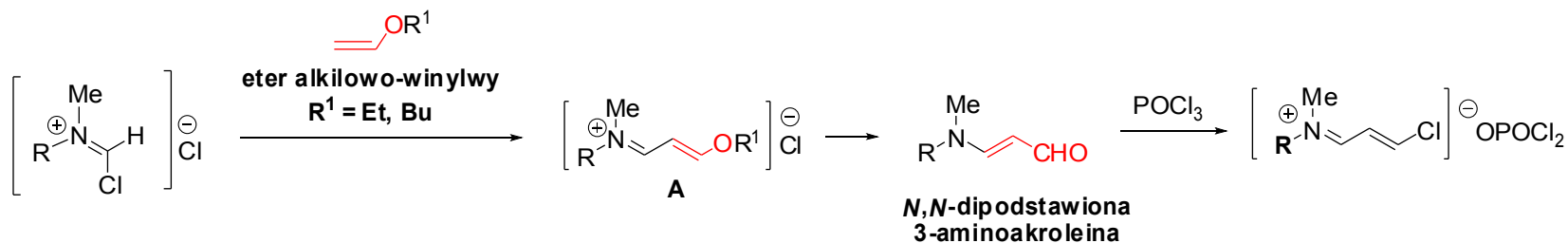
## Modyfikacja reagenta Vilsmeiera-Haacka w celu wprowadzania ugrupowania formylowinylowego



Reakcja ze slajdu 12



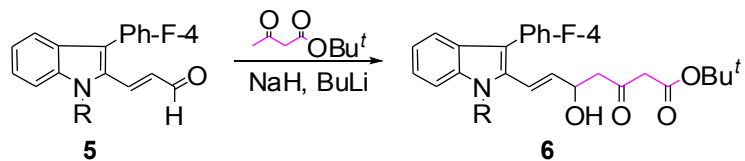
R = Me lub Ph chlorek oksalilu



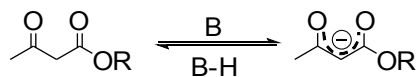
J. Org. Chem. 1992, 57, 3250; Coll. Czech. Commun. 1958, 23, 452.



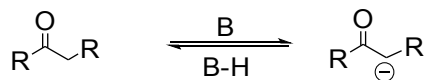
## 4.1.C. Alkilowanie aldehydu (5)



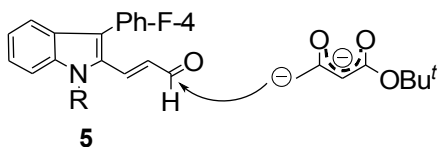
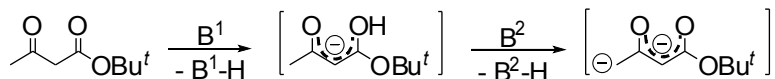
Reakcja ze slajdu 12



$pK_a = 11$

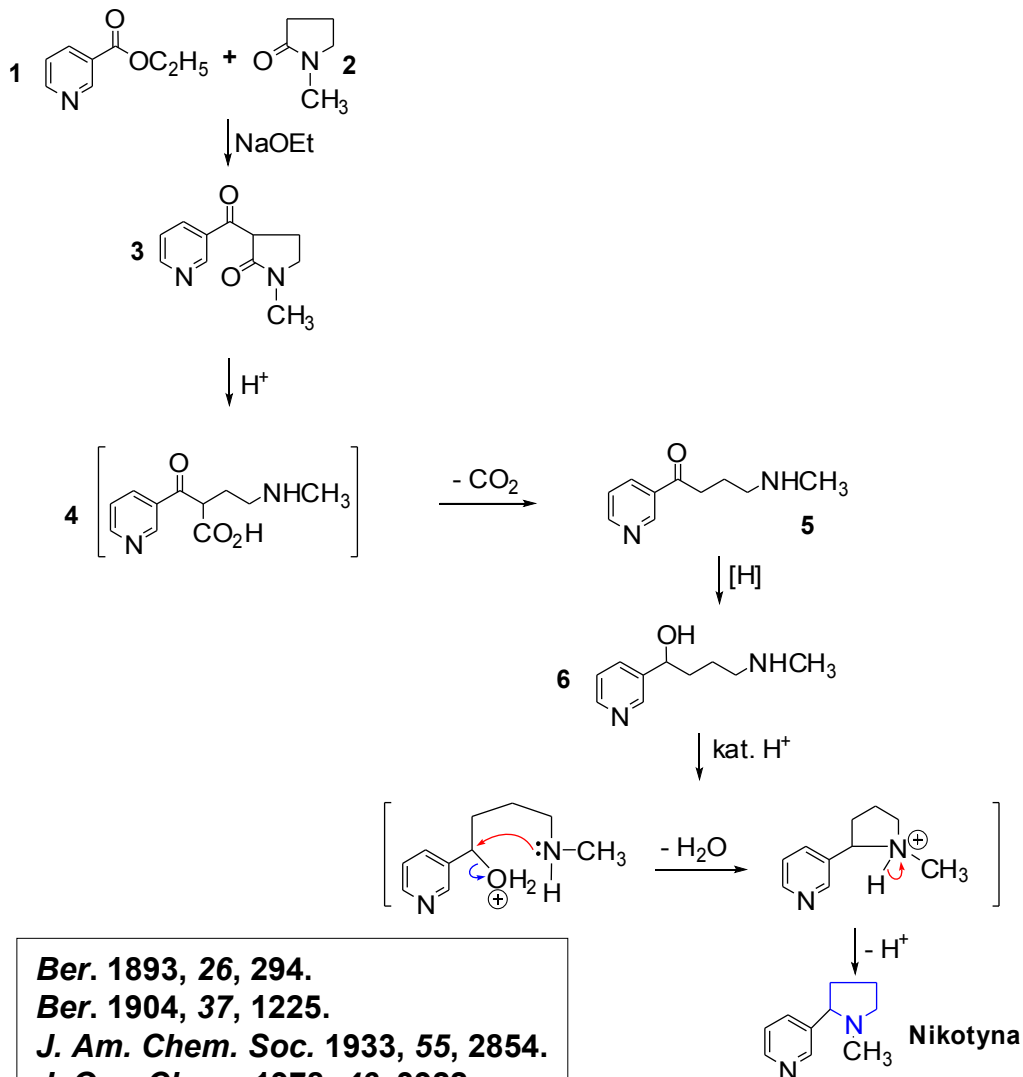


$pK_a = 20-21$



## 5. Nikotyna (INN, *nicotine*)

Stosowana w eksperymentach medycznych ze względu na występowanie w tytoniu, którego palenie jest czynnikiem ryzyka w wielu chorobach, m. in. w chorobie nowotworowej.  
Jedynе zastosowanie terapeutyczne - składnik gumy do żucia w terapii nikotynizmu.



Ber. 1893, 26, 294.

Ber. 1904, 37, 1225.

J. Am. Chem. Soc. 1933, 55, 2854.

J. Org. Chem. 1978, 43, 3922.