RĪGAS TEHNISKĀ UNIVERSITĀTE
RIGA TECHNICAL UNIVERSITY

MATERIĀLZINĀTNES UN LIETIŠĶĀS ĶĪMIJAS FAKULTĀTE
FACULTY OF MATERIAL SCIENCE AND APPLIED CHEMISTRY

Nelli BATENKO

2,5-BISHETEROARILAIZVIETOTU l,4-BENZOHINONU SINTĒZE

SYNTHESIS OF 2,5-BISHETEROARYL SUBSTITUTED 1,4-BENZOQUINONES

Promocijas darba kopsavilkums

Summary of doctoral thesis

ZINĀTNISKIE VADĪTĀJI:
SUPERVISORS:
Dr. habil. chem. profesors Raimonds Valters
Dr. chem. Gatis Karlivāns

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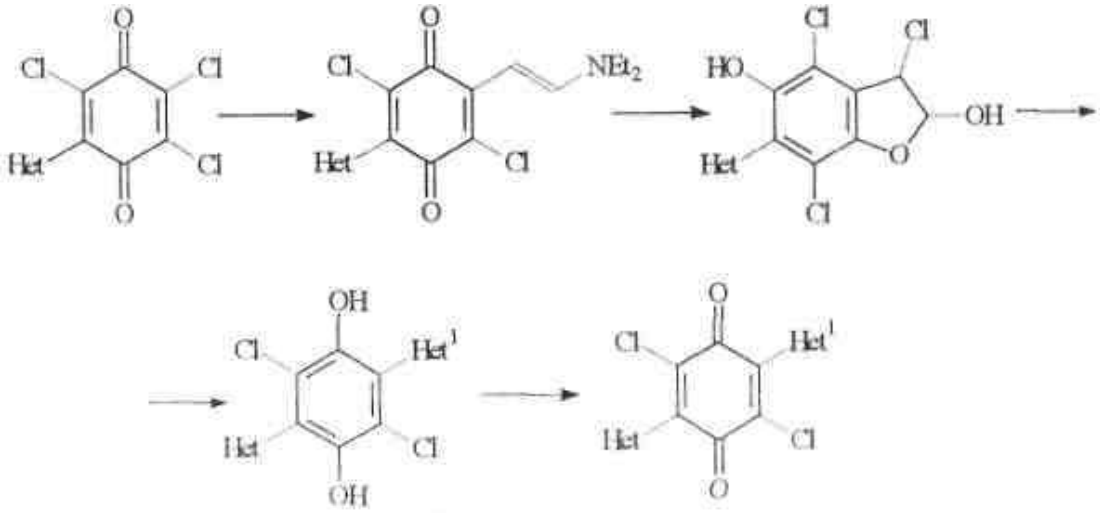
Problēmas būtība un aktualiate

Pēdējos gados strauji audzis publikāciju skaits, kurās aprakstīti pētījumi par hinonu atvasinājumu iegūšanu un īpašībām. Starp hinonu atvasinājumiem ir atrastas vielas ar nozīmīgu bioloģisko (pretvēža, pretsēnīšu, pretparazītu, antidiabētisku un anti - HIV) aktivitāti. Hinonu atvasinājumus izmanto kā elektronakceptoras komponentes dažādu donor-akceptoru kompleksu iegūšanai, arī kā sintonus un reaģentus organiskajā sintēzē. Hinonu īpašības ir tieši saistītas ar aizvietotāja dabu. Heteroarilaizvietotiem hinoniem ir divas dažādas grupas - hinons un heterocikls. Savienojot tos vienā molekulā, iespējams iegūt atvasinājumus ar jaunām īpašībām vai pielietošanas iespējām. Svarīgi atzīmēt, ka ir samērā maz universālu un vispārīgu sintēzes metožu heteroarilgrupu ievadīšanai 1,4-benzohinona un 1,4-naftohinona gredzenā [1],

Darba mērķis

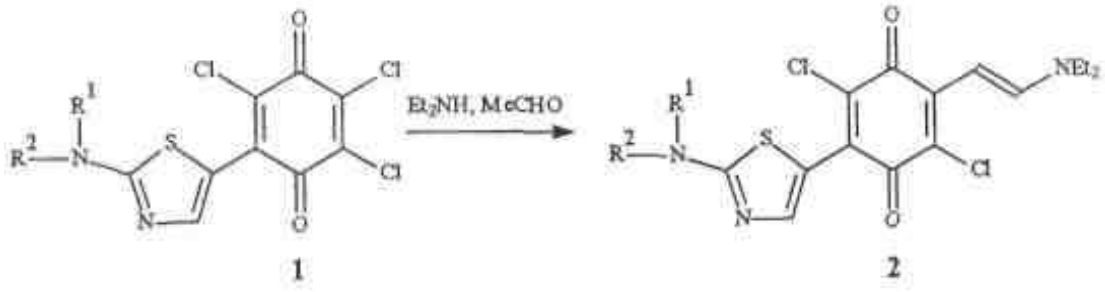
Promocijas darba uzdevums bija izstrādāt bisheteroarilaizvietotu 1,4-benzohinonu (ar vienādiem vai dažādiem heteroarilaizvietotājiem) sintēzes vispārīgu metodi uz monoheteroarilaizvietotu 1,4-benzohinonu bāzes, izmantojot tās iestrādes, kas monoheteroarilaizvietotu 1,4-benzohinonu sintēzes jomā jau veiktas RTU Materiālzinātnes un lietišķās ķīmijas fakultātē (R. Valters, G. Karlivāns, M. Utināns, J. Gulbis). Darba mērķis bija izpētīt iespējas ievadīt 2-heteroaril-3,5,6-trihlor-l,4-benzohinonu molekulā otru heteroarilgrupu, izmantojot to pašu sintēzes stratēģiju:



Savā darbā pētījām iespēju iegul universālus sintonus - 6-(2-*N*,*N*-dialkilaminotiazol-5-il)-2,5-dihidroksi-3,4,7-trihlor-2,3-dihidrobenzo[*b*]furānus. Šie savienojumi, reaģējot ar sēru saturošiem bifunkcionāliem reaģentiem, var veidot 2,5-bisheteroarilaizvietotus 1,4-benzohinonus. Darbā arī pētītas 2,5-bis(2-piperidinotiazol-5-il)-3,6-dihlor-l,4-benzohinona reakcijas ar nukleofiliem reaģentiem.

1. 6-(2-*N*,*N*-Dialkilaminotiazol-5-ļl)-2,5-dihidroksi-3,4,7-trihlor-2,3-dihidrobenzo[*b*]furāni [2]

Šim nolūkam vispirms pētījām visvieglāk iegūstamo *2-(2-N,N*-dialkilaminotiazol-5-il)-3,5,6-trihlor-l,4-benzohinonu **(1a-e)** reakcijas ar dietilamīnu un acetaldehīdu. Reakcijā no dietilamīna un acetaldehīda veidojas enamīns, kurš aizvieto hlora atomu pozīcijā 5. Ieguvām 2-(2-*N*,*N*-dialldlaminotiazol-5-il)-5-(2-*N*,*N*-dietilaminoetenil)-3,6-dihlor-l,4-benzohinonus **(2a - e)**.



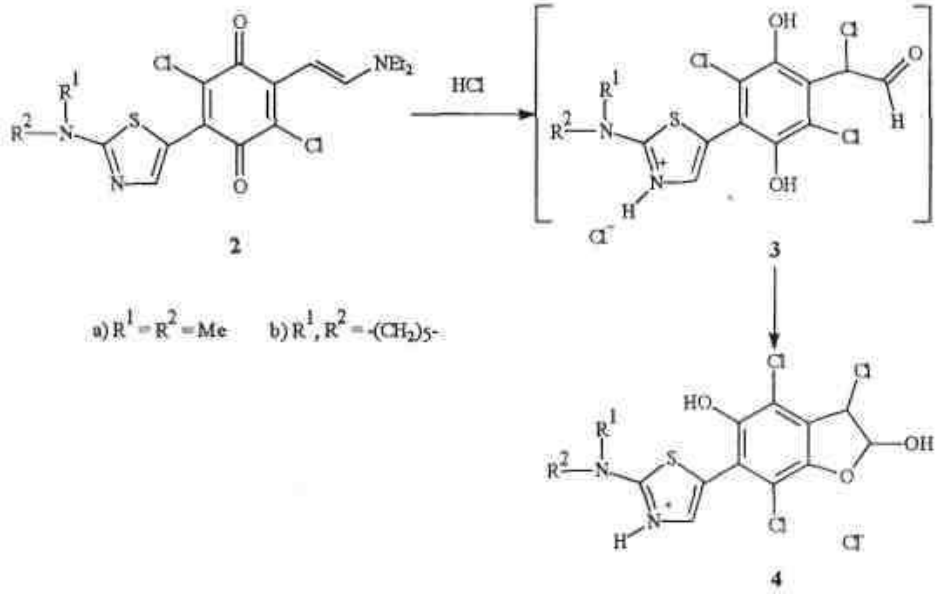
1 2

a) $R^{1=}R^2$ =Me; b) R^1,R^2=-(CH_2)4-; c)R^1,R^2=-$(CH_2)_5$-; d)R^1,R^2 = -$CH_2)_6$-; e)R^1,R^2 = -$(CH_z)_2O(CM_2)$2-

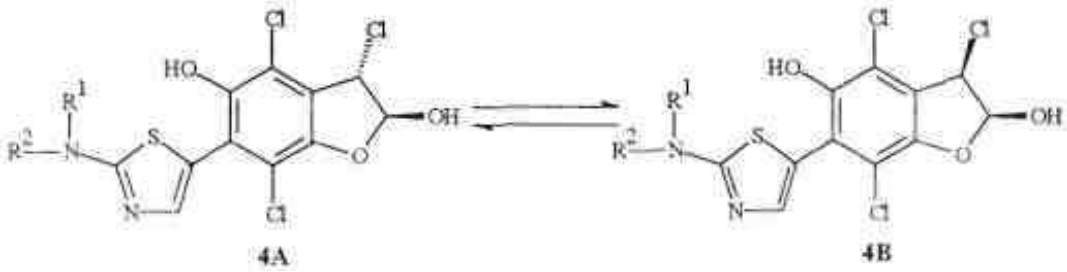
Benzohinoni **2a-e** ir dziļi krāsotas kristāliskas vielas (> 250 °C ar sadalīšanos). To 'H-KMR spektros etenilgrupas signālus novērojām kā divus dupletus pie 8,36-8,44 un 5,56-5,64 m.d. Spinu mijiedarbības konstante (^3J =13-14 Hz) apstiprina etenilgrupas *E*-konfigurāciju. Elektronu spektros novēro absorbcijas joslas pie 350 un 557 - 566 nm. Alkil- un cikloalkilaminoaizvietotiem tiazolilhinoniem reakcijas iznākums ir 90 - 95% (izņēmums morfolinoatvasinājums 2e - 45 %). Neaizvietotas aminogrupas gadījumā savienojumu 2 (R^1 = R^2 = H) neizdevās izolēt.

Otra heterocikla konstruēšanai, lai iegūtu attiecīgos 2,5-bisheteroaril-3,6-dihlor-1,4-benzohinonus, nepieciešams pārvērst savienojumus **2a-e** par 6-(2-N,N-

dialkilaminotiazol-5-il)-2,5-dihidroksi-3,4,7-trihlor-2,3-dihidrobenzo[*b*]furāniem(**4a,b)**. Benzofurānus **4a,b** ieguvām kā hidrogēnhlondus, realizējot enamīnu hidrolīzes reakciju acetonitrilā ar trīskāršu HC1 pārākumu. Var uzskatīt, ka enamīna hidrolīzes procesā vispirms veidojas a-hloracetaldehīds 3, kurš tālāk tautomerizējas par cikliskas struktūras savienojumu 4.

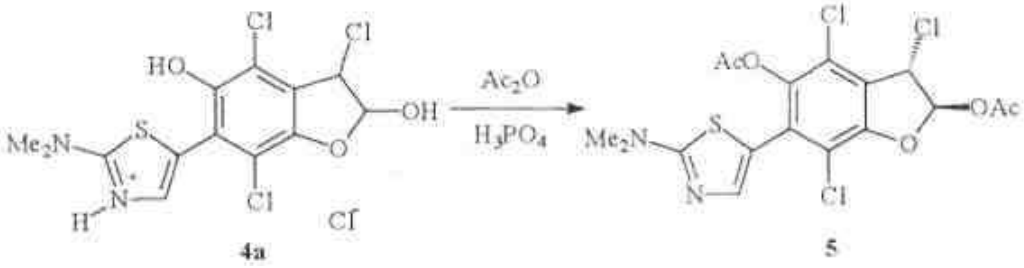


Benzofurānu 4a ^{1}H-KMR spektrā novēro divus mazāk intensīvus dupletus pie 6,11 ($C_{(2)}$-H) un 5,67 ($C_{(3)}$-H) m.d. ar spinu mijiedarbības konstanti ^{3}J = 4,89 Hz, kas atbilst cis-stereoizomēram, un divus intensīvākus dupletus pie 6,02 ($C_{(2)}$-H) un 5,40 ($C_{(3)}$-H) m.d. ar spinu mijiedarbības konstanti ^{3}J = 0,49 Hz, kas atbilst *trans*-stereoizomēram. Līdzīga aina ir benzofurāna **4b** ^{1}H-KMR spektrā. Pēc signālu attiecības aprēķinātā *cis/trans*-stereoizomēru 4B/4A attiecība DMSO-D6 šķīdumā ir 16: 84 **(4a)** un 36 : 64 **(4b)**. Tātad šķīdumā eksistē līdzsvars starp abiem stereoizomēriem, kas ir nobīdīts *trans*-stereoizomēra virzienā.



Uzskatām, ka to savstarpējās pārvērtības notiek pār vaļējo aldehīda tautomēro formu 3, kuru gan ar ' H-KMR metodi šķīdumā neizdodas detektēt.

Karsējot benzofurānu 4a acetanhidrīdā katalītiska ortofoforskābes daudzuma klātbūtnē notiek hidroksilgrupu acetilēšanās un veidojas 2,5-diacetoksi-6-(2-A',A'-dimetilamīnotiazol-5-il)-3,4,7-trihlor-2,3-dihidrobenzo[*b*]furāns (5).



4a 5

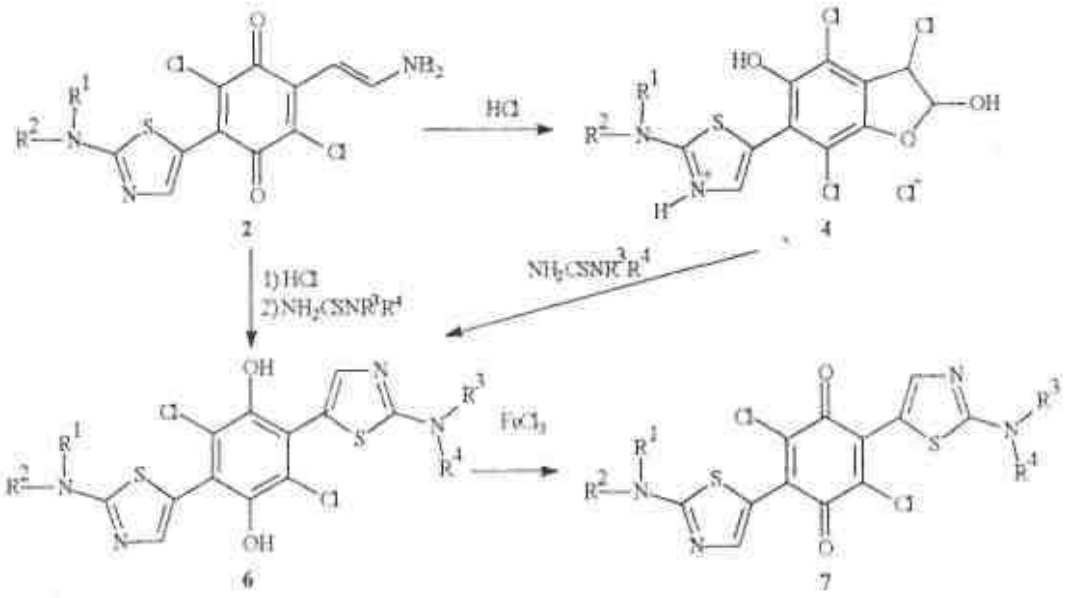
Tā ^{1}H-KMR spektrā novēro $C_{(2)}$-H un $C_{(3)}$-H protonu signālus kā singletus (^3J < 0,5 Hz) attiecīgi pie 6,85 un 5,87 m.d. Tas, ka spinu mijiedarbības konstante ir mazāka par 0,5 Hz apstiprina diacetāta 5 2,3-aizvietotāju *trans*-konfigurāciju. Varam uzskatīt, ka *trans*-stereoizomēra veidošanās ir telpiski izdevīgāka.

2. 2,5-Bis(2-*N*,*N*-dialkilaminotiazo1-5-il)-3,6-dihlor-l,4-benzohinoni [2, 3]

2,5-Bis(2-*N*,*N*-dialkilaminotiazol-5-il)-3,6-dihlor-l,4-benzohinonus (7) ieguvām divējādi: gan tieši iedarbojoties ar tiourīnvielu vai aizvietotām tiourīnvielājn uz 2-(2-*N*,*N*-dialkilaminotiazol-5-il)-5-(2-*N*,*N*-dietilaminoetenil)-3,6-dihlor-l,4-benzohinoniem **(2a - e)** sālskābes klātbūtnē, gan arī 6-(2-*N*,*N*-dialkilamīnotiazol-5-il)-2,5-dihidroksi-3,4,7-trihlor-2,3-dihidrobenzo[b]furānu (**4a,b**) reakcijās ar tiourīnvielām.

Sākumā visus bistiazolilbenzohinonus **7a-f** ieguvām tieši no vinilhinoniem (**2a-e**). Varam uzskatīt, ka pievienojot vinilhinonu **2a-e** šķīdumiem sālskābi, veidojas benzofurāni **4**. Tad šķīdumam pievieno tiourīnvielu (vai aizvietotas tiourīnvielas), notiek hlora atoma nukleofīlā aizvietošanās ar sēra atomu, reciklizācija (furāna cikla atvēršanās un tiazola cikla saslēgšanās) un rodas 2,5-bis(2-*N*,*N*-dialkilaminotiazol-5-il)-3.6-dihlorhidrohinoni (**6**), kurus oksidē, pievienojot $FeCl_3$ ūdens šķīdumu, un iegūst attiecīgos bistiazolilbenzohinonus **7a-f**. Šī metode ir mazāk darbietilpīga, bet ar zemākiem iznākumiem. Iegūtos bistiazolilhidrohinonus **6a-f** neizolējām, bet uzreiz

oksidējām līdz bistiazolilbenzohinoniem **7a-f**. Bistiazolilhidrohinonus 6 grūti izolēt individuālā veidā, jo tie gaisā daļēji oksidējas. Par to liecina C=O grupu absorbcijas joslu parādīšanās pie 1640. 1630 cm^{-1} savienojumu **6a** un **6d** IS spektros un bistiazolilhinoniem raksturīgā absorbcija pie 582 nm savienojuma 6d elektronu spektrā. Ar otru metodi, iedarbojoties ar *N,N*-dimetil- vai *N,N*-pentametilēntiourīnvielu attiecīgi



a) $R^1 = R^2 = R^3 = R^4 = Me$; b) $R^1, R^2 = -(CH)_5-$, $R^3 = R^4 = H$;

c) $R^1, R^2 = -(CH)_5-$, $R^3, R^4 = -(CH)_4-$; d) $R^1, R^2 = R^3, R^4 = -(CH)_5-$;

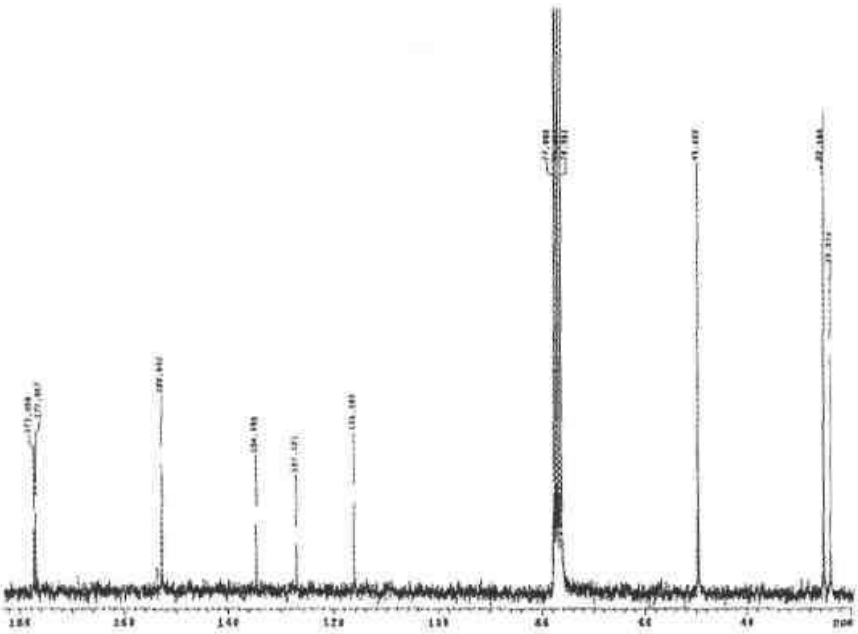
e) $R^1, R^2 = R^3, R^4 = -(CH)_zO(CH)_2-$; f) $R^1, R^2 = R^3, R^4 = -(CH)_6-$;

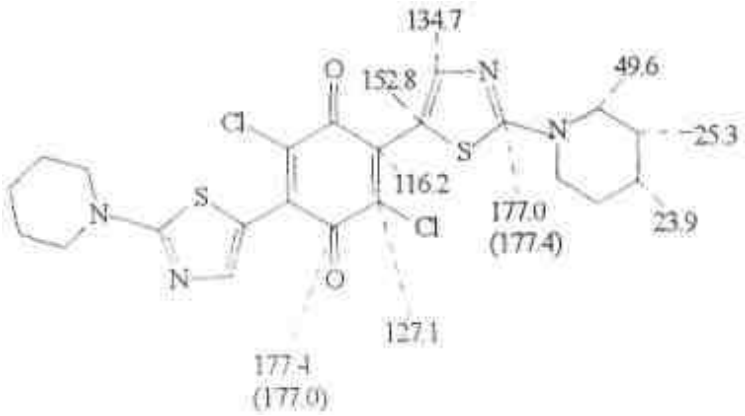
uz benzoflirāniem **4a,b** etanolā un oksidējot reakcijas produktus ar $FeCl_3$, ieguvām 2,5-bis(2-*N,N*-dimetilaminotiazol-5-il)- un 2,5-bis(2-piperidinotiazol-5-il)-3,6-dihlor-l,4-benzohinonus (**7a** un **d**). Pēc IS un ^{1}H-KMR spektriem šie hinoni ir pilnīgi identi ar savienojumiem, kas iegūti, izmantojot pirmo metodi.

2-Monoaizvietotu 3,5,6-trihlor-l,4-benzohinonu reakcijās ar nukleofīliem reaģentiem, otrais aizvietotājs visbiežāk stājas 5 vietā, ir arī izņēmumi, kad rodas 2,5- un 2,6-aizvietotu produktu maisījums. Simetriskas struktūras savienojuma - 2,5-bis(2-piperidinotiazol-5-il)-3,6-dihlor-l,4-benzohinona (**7d**) ^{13}C-KMR spektrā novēro (sk. 1. attēlu) 9 ^{13}C signālus. Tas apstiprina dialkilaminoetenilgrupas stāšanās 5 vietā (un nevis 6 vietā)

Simetriskā bistiazolilbenzohinona 7d ^{1}H-KMR spektrā novēro tiazola $C_{(4)}H$ signālu pie 8.76 m.d.(2H) un piperidīna cikla protonu signālus kā platus singletus pie 3.67 (8H, N-$CH_{2:}$) un 1,69 m.d. (12H, CH_2).Platie piperidīna CH_2 grupu protonu signāli

liecina par pipcridīna cikla inversiju. Bistiazolilbenzohinonu **7a-f** IS spektros novēro C=O grupu absorbcijas joslu 1643 - 1628 cm^{-1} intervālā. Bistiazolilbenzohinoni **7a-f** ir tumši zilas kristāliskas vielas ar augstām kušanas temperatūrām (>250° C ar sadalīšanos). Tie nedaudz, šķīst polāros organiskos šķīdinātājos (DMF, DMSO, CHCI3), veidojot zemu koncentrāciju intensīvi krāsotus šķīdumus.



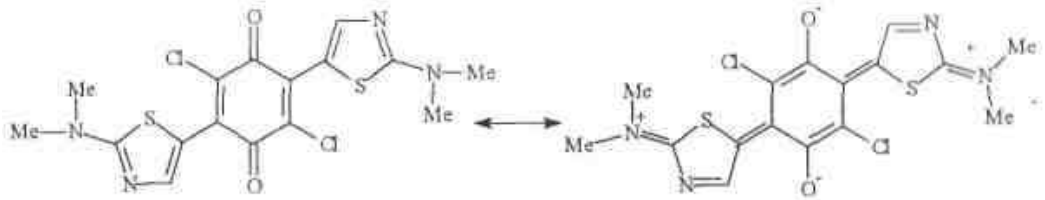


7d

l.att. 2.5-Bis(2-pipendinotiazol-5-il)-3,6-dihlor-l,4-benzohinona (117d) ^{13}C KMK spektrs $CDCl_3$ šķīdumā.

Bistiazolilbenzohinonu **7a-f** elektronu spektros novēro absorbcijas joslas pie 353- 363 nm un 562-610 mn. Divu savienojumu spektros novēro vēl vienu absorbcijas

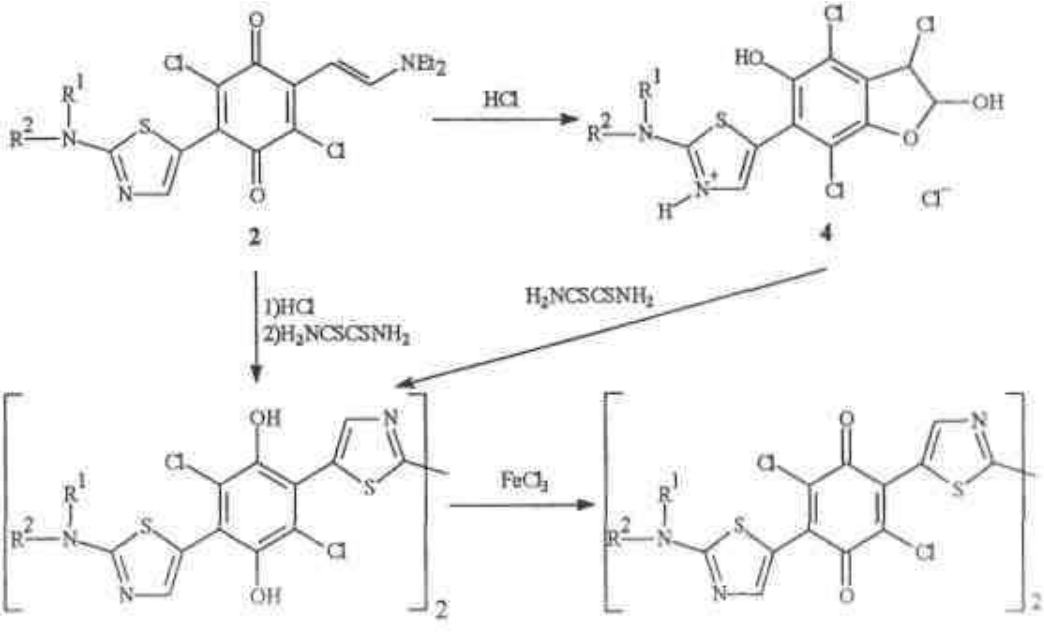
joslu pie 743 nm (**7a**) un 718 nm (**7d**). Savienojuma 7a gadījuma garo viļņu absorbcijas joslu var pierakstīt iekšmolekulāra lādiņa pārnesei, ko atspoguļo mezomērā struktūra **7B**.



7A **7B**

3. 5,5'-Bis[5-(2-*N*,*N*-dialkilaminotiazol-5-il)-3,6-dihlor-l,4-benzohinon-2-il]-2,2'-bitiazoli[4]

5,5'-Bis[5-(2-*N*,*N*-dialkilaminotiazol-5-il)-3,6-dihlor-l,4-benzohinon-2-il]-2,2'-bitiazolus (**9)** var sintezēt gan no benzofurāniem **4a,b,** gan arī tieši no vinilhinoniem **2a,b.** Sākumā ieguvām 5,5'-bis[4-(2-*N*,*N*-dialkilaminotiazol-5-il)-2,5-dihidroksi-3,6-dihlorfenil)-2,2'-bitiazolus (**8a,b**), iedarbojoties uz vinilhinoniem **2a,b** ar sālskābi un pēc tam ar ditioskābeņskābes diamīdu (rubeānskābi) acetonitrila šķīdumā.

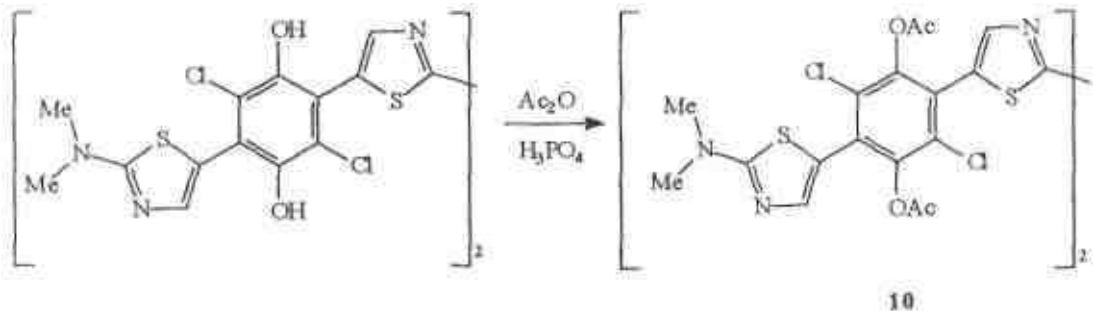


2 **4** **8** **9**

a) $R^1 = R^2 = Me$

b) $R^1, R^2 = -(CH_2)_5-$

Hidrohinonus **8a,b** ieguvām ar labiem iznākumiem (68 - 76%), ievērojot reaģentu molāro attiecību vinilhinons/rubeānskābe 2:1. Hidrohinona 8a H-KMR spektrā novēro divus tiazola cikla C($4_{(4)}$-H signālus pie 7,45 (2H) un 8,04 (2H, bitiazols)m.d. Hinoniltiazola **9b** elektronu spektrā novēro absorbcijas joslas garo viļņu rajonā pie 514 un 716 nm ($CHC1_3$ šķīdumā). Tetracetāta **10** ^{1}H-KMR spektrā novēro divus dažādu acetilgrupu signālus.



10

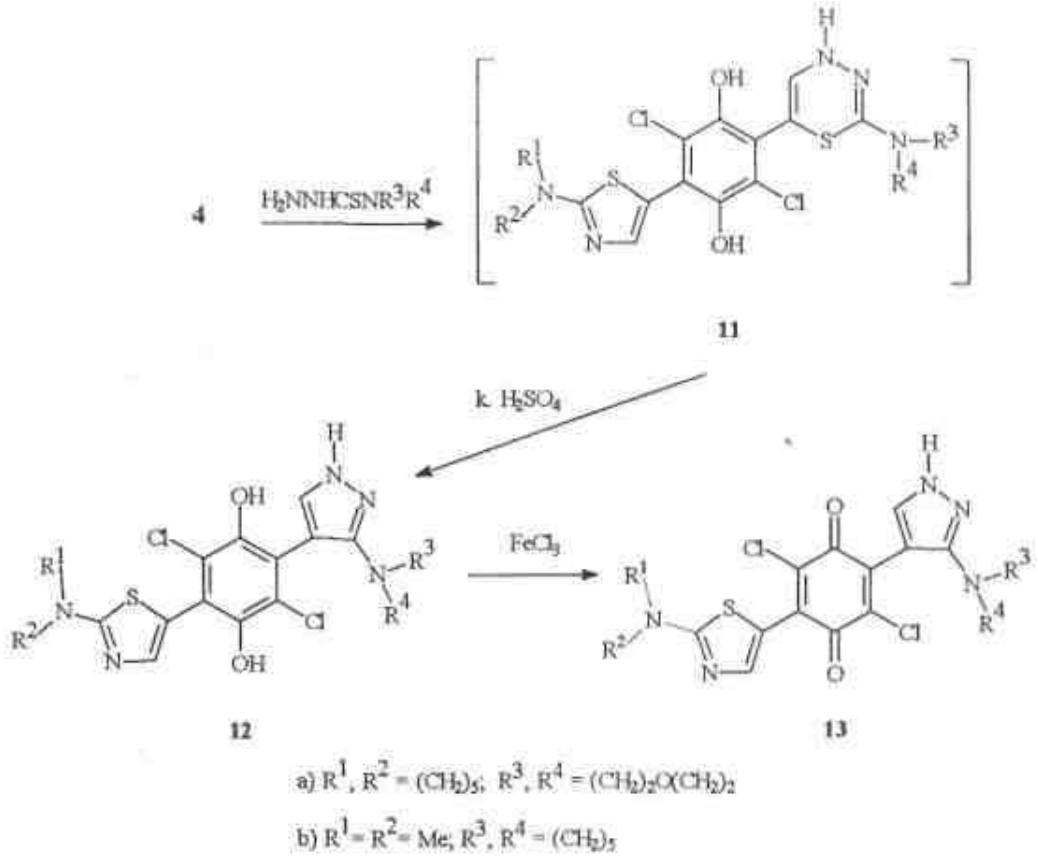
4. 2-(3-7V,7V-Dialkilaminopirazolm-4-il)-5-(2-N,N-dialkilarninotiazol-5-il)-3,6-dihlor-l,4-benzohinoni [2]

2-(3-*N*,*N*-Dialkilaminopirazol-4-il)-5-(2-*N*,*N*-dialkilaminotiazol-5-il)-3,6-dihlor-hidrohinonus (**12**) ieguvām, karsējot dihidrofurānu **4** un attiecīgos 4,4-dialkiltiosemikarbazīdus etanolā konc. sērskābes klātbūtnē. Ņemot vērā literatūras datus, varam uzskatīt, kā benzofurāna 4 un 4,4-dialkiltiosemikarbazīda reakcijā vispirms veidojas savienojums **11.** Šim savienojumam ir *4H*-l,3,4-tiadiazīna cikls, kuram notiek tiadiazīna cikla sašaurināšanās ar sēra atoma ekstrūziju.

$^!$H KMR spektros redzam signālu, kas atbilst tiazola C(4)-H protonam, pie 7,87 (**12a**) un 7,98 **(12b)** m.d. Pirazola $C_{(5)}$-H signālus novēro attiecīgi pie 7,43 (**12a**) un 7,47 (**12b**)m.d. IS spektros redzama plata OH grupu absorbcijas josla rajonā 3390-3000 cm^{-1}.

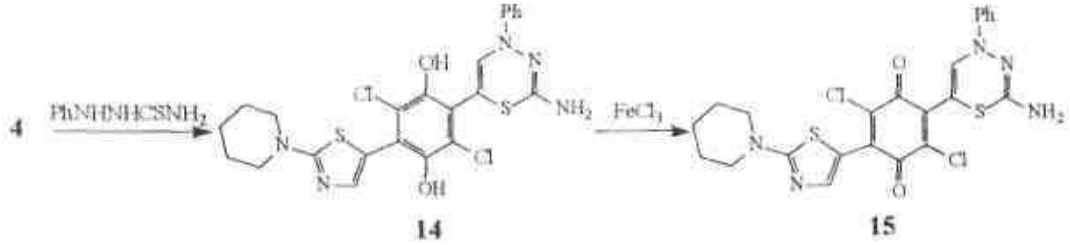
Pēc oksidēšanas ar $FeCl_3$ ūdens/DMF šķīdumā ieguvām 2-(3-*N*,*N*-dialkilaminopirazol-4-il)-5-(2-N,N-dialkilaminotiazol-5-il)-3,6-dihlor-l,4-benzohinonus (**13**). Benzohinoni **13** ir tumši zilas kristāliskas vielas, kūst virs 250° C. Oksidēšanas reakcijas norit lēnāk un ar zemākiem iznākumiem salīdzinot ar benzohinoniem 7. Tiazola$C_{(4)}$ - H protona signāls [8,64 m.d. (**13a)**; 8,49 m.d. (**13b**)] nobīdās uz vājākiem laukiem vairāk, neka pirazola $C_{(5)}$ - H protona [7,87 m.d. (**13a**); 7,94 m.d. (**13b**)]

signāls salīdzinot ar savienojumiem **12.** Savienojuma **13a** elektronu spektrā novēro absorbcijas joslas pie 344 (lg s = 4,10) un 640 (3,65) nm.



5. 2-(2-Amino-4-fenil-*4H*-l,3,4-tiadiazīn-6-il)-5-(2-piperidinotiazoI-5-il)-3,6-dlhlor-l,4-benzohinons [2]

2-(2-Amino-4-fenil-*4H*-l,3,4-tiadiazīn-6-il)-5-(2-piperidinotiazol-5-il)-3,6-dihlorhidrohinonu (**14**) ieguvām, karsējot benzofurānu **4b** un 1-feniltiosemikarbazīdu etanolā. Pirmajā stadijā veidojas sēra alkilēšanas produkts, kurš, saskaņā ar literatūras datiem, pēc karsēšanas etanolā ciklizējas par tiadiazīnu. Hidrohinons **14** ir balta kristāliska viela, (>250° C). ^{1}H KMR spektrā novēro tiadiazina $C_{(5)}$ - H singletu pie 8,11 m.d., tiazola $C_{(5)}$ - H singletu pie 7,29 m.d. OH grupu protonu signālus novērojām kā platus singletus pie 5,78 m.d



14 **15**

Hidrohinona **14** oksidēšana ar $FeC_{(3)}$ ūdens/ DMF šķīdumu notiek viegli un ar augstiem iznākumiem. Benzohinons 15 ir tumši violeta kristāliska viela. Tās ^{1}H-KMR novēro $C_{(5)}$ - H tiadiazīna protona signālu pie 8,90 m.d., $C_{(4)}$ - H tiazola protona signālu - pie 8,73 m.d. Elektronu spektrā novēro absorbcijas joslas pie 403 nm (lg £ = 4,18) un pie 715 nm (lg e = 3,70). 6-(Trihlor-l,4-benzohinonil)-2-amino-4-fenil-*4H*-l,3,4-tiadiazīna UV spektrā garo viļņu absorbcijas josla parādījās pie daudz īsākiem viļņiem — 482 nm (lg £ = 3,93).

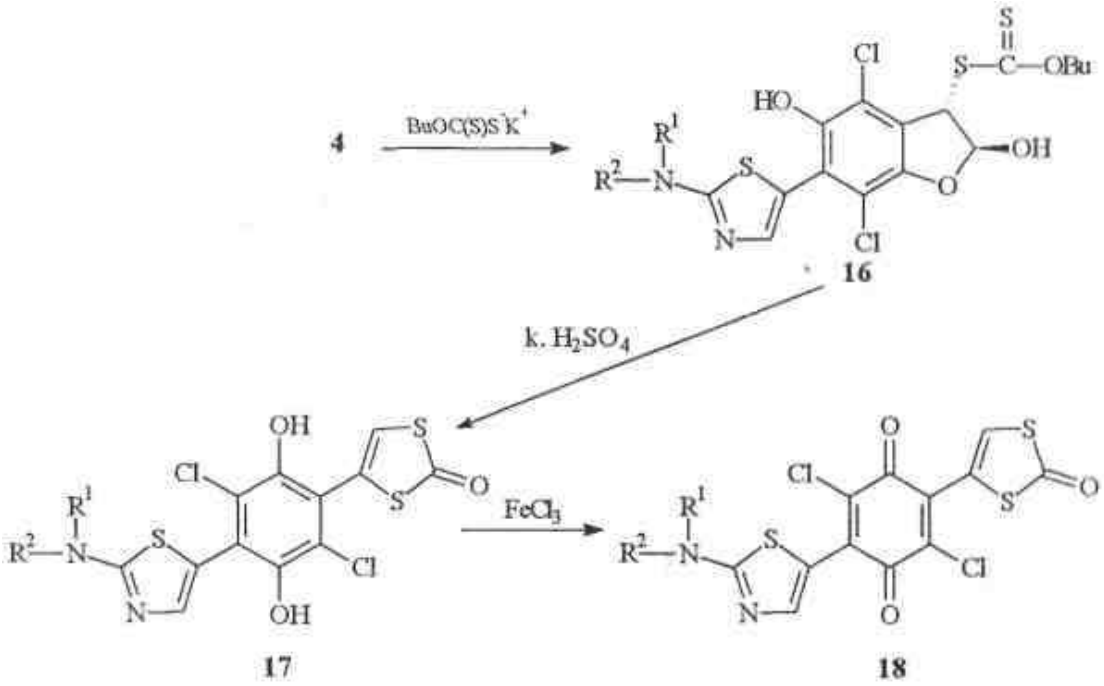
6. 2-(2-*N,N*-Dialkilaminotiazol-5-il)-5-(1,3-ditiol-2-on-4-il)-3,6-dihlor-l,4-benzohinoni [2]

Salīdzinoši daudz ir publikāciju par l,3-ditiol-2-onu iegūšanas metodēm sakarā ar to izmantošanu tetratiafulvalēnu sintēzē. Lai konstruētu l,3-ditiol-2-ona ciklu bieži izmanto fi-ketoditioestera ciklizāciju ar stiprām minerālskābēm (H_2SO_4, $HClO_4$).

Benzofurānu 4a,b reakcijā ar kālija *O*-butilksantogenātu ieguvām hlora atoma aizvietošanas produktus - *O*-butil S-[6-(*N,N*-dialkilaminotiazol-5-il)-4,7-dihlor-2,5-dihidroksi-2,3-dihidrobenzo[**b**]furān-3-il]ksantogenātus **(16a,b**). Mēs noskaidrojām, ka benzofurāna **4** reakcijā ar sēru saturošiem bifunkcionāliem reaģentiem notiek hlora atoma nukleofīlā aizvietošana ar sēra atomu, starpprodukta reciklizācija un heterocikliska savienojuma veidošanās. Tas notiek, ja hlora atoms aizvietojas ar sēra atomu, kuram bija divkārša saite ar oglekli. Gadījumā, ja saite veidojas starp benzofurāna $C_{(3)}$ - atomu un negatīvi lādētu ksantogenāta sēra atomu, aizvietošanas produktu varām izdalīt individuālā veidā.

Ksantogenāta 16a ^{1}H KMR spektrā novēro $C_{(5)}$ - OH grupas protona signālu pie 9,43 m.d. (1H), $C_{(2)}$- OH grupas protona signāls sašķeļas dupletā un parādās pie 8,18 m.d. (^3J - 6 Hz), tiazola $C_{(4)}$ - H signāls redzams pie 7,23 m.d. (1H), $C_{(2)}$ - H signālu

novērojām kā dupletu dupletu ar divām spinu mijiedarbības konstantēm - viena (^3J = 6 Hz) atbilst mijiedarbībai ar OH grupu, otra atbilst mijiedarbībai ar $C_{(3)}$ - H protonu. Šajā gadījumā mēs ieguvām aizvietošanās produktu tikai vienā *trans-konfigurācijā* (^3J < 0,5 Hz).



Karsējot ksantogenātu **16a** konc. sērskābē pie 60° C ieguvām *2-(2-N,N*-dimetilaminotiazol-5-il)-5-(l,3-ditiol-2-on-4-il)-3,6-dihlorhidrohinonu **(17a).** Var uzskatīt, kā reakcijas gaitā sākumā notiek $C_{(2)}$ - OH grupas protonēšana un pēc ūdens molekulas atšķelšanās notiek iekšmolekulāra reciklizācija (furāna cikla atvēršanās un 1,3-ditiola cikla saslēgšanās).Pēc butoksigrupas hidrolīzes veidojas hidrohinons **17.** ^{1}H KMR spektrā novērojām hidroksilgrupu signālus kā platus singletus pie 9,27 m.d. (2H), tiazola $C_{(4)}$ - H signālu pie 7,43 m.d., l,3-ditiol-2-ona $C_{(5)}$ - H signālu pie 7,23 m.d. Oksidējot hidrohinonus **17** ar dzelzs trihlorīda šķīdumu DMF/$H_2$0, ieguvām *2-(2-N,N*-dialkilaminotiazol-5-il)-5-(l,3-ditiol-2-on-4-il)-3,6-dihlor-l,4-benzohinonus **(18a,b).** Benzohinoni **18a,b** ir tumši zilas kristāliskas vielas (K.p.> 240 C, ar sadalīšanos).

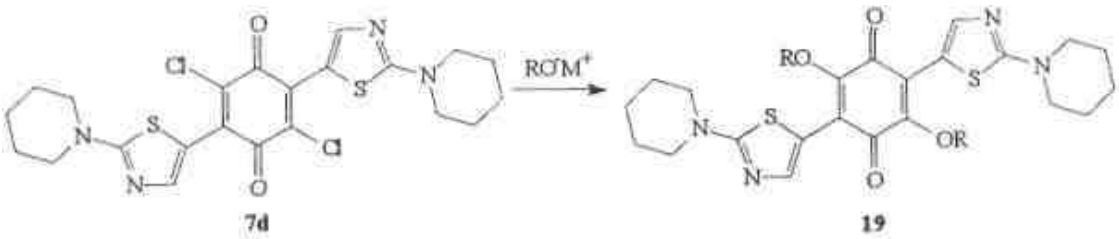
^{1}H KMR spekļros novērojām tiazola $C_{(4)}$ - H signālu pie 8,72 m.d. **(18a)** un 8,69 m.d. **(18b),** l,3-ditiol-2-ona $C_{(5)}$-H signāli ir pie 7,23 (18a) un 7,27 **(18b).** Benzohinona

18a elektronu spektra novēro absorbcijas joslas garo viļņu rajona pie 480 (lg ε = 3,57) un 683 nm (lg ε = 3,80, $CHCl_3$ šķīdumā).

7. 2,5-Bis(2-piperidinotiazol-5-il)- 3,6-dihlor-l,4-benzohinona hlora atomu nukleofilā aizvietošana [5]

Ar nolūku noskaidrot mūsu bistiazolilbenzohinonu īpašības mēs pētījām bistiazolilbenzohinona **7d** reakcijas ar nukleofīliem reaģentiem.

Benzohinona **7d** un nātrija metanolāta reakcijā veidojās 2,5-bis(2-piperidīnotiazol-5-il)-3,6-dimetoksi-l,4-benzohinons **(19a).** Ja izmantojām absolūtu (bezūdens) metanolu, reakcijas iznākums bija 91%. Dimetoksihinona **19a** ^{1}H KMR spektrā novēro metoksigrupu signālu pie 4,01m.d. (6H), tiazola $C_{(4)}$ - H signāls, salīdzinot ar hinonu **7d**, nobīdās stiprāko lauku virzienā par 0,35 m.d. (8,41 m.d.). IS spektrā novērojām C =O valences svārstību absorbcijas joslu pie 1632 cm^{-1}. Elektronu spektrā garo viļņu rajonā novēro tikai vienu absorbcijas joslu pie 537 nm (lg ε= 4,25).

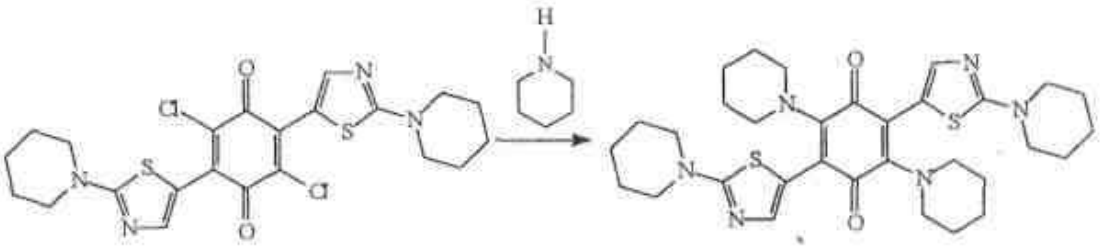


a) M = Na, R = Me
b) M = K, R = Et

Karsējot bistiazolilbenzohinonu **7d** ar trīskāršu kālija etanolāta pārākumu, ieguvām 2,5-bis(2-piperidīnotiazol-5-il)-3,6-dietoksi-l,4-benzohinonu **(19b).** Hlora atomu aizvietošana ar etoksigrupām notiek grūtāk un ar zemāku iznākumu. ^{1}H KMR spektrā novēro etoksigrupu signālus pie 1,38 m.d. (6H) un 4,27 m.d. (4H). Tiazola $C_{(4)}$-H signāls ir pie 8,36 m.d. IS spektrā novēro C = O grupu absorbcijas joslu piel632 cm^{-1}. Elektronu spektrā garo viļņu rajonā parādās absorbcijas josla pie 530 nm (lg ε= 4,07).

Lai ievadītu hidroksilgrupas 3 un 6 vietās mums bija divi ceļi. Pirmais -apmainīt hlora atomus ar hidroksilgrupām bāziskā vidē. Mēs mēģinājām dažādus šķīdinātājus (MeOH, EtOH, DMF, acetonitrilu, dioksānu, sulfolānu) un reaģentus (KOH, NaOH, KOH/$CSCO_3$, LiOH), dažādus reakcijas apstākļus (maisījām istabas

temperatūrā, karsējām), bet izdalīt dihidroksiproduktu neizdevās. Otrais variants - hidrolizēt metoksigrupas 3 un 6 vietās, bet veiksmīgi realizēt hidrolīzi arī neizdevās. Ar mērķi aizvietot hlora atomus ar piperidīnogrupām mēs maisījām tiazolibenzohinonu 7d piperidīnā 8 stundas. Uzņemtajā produktā ^{1}H KMR spektrā visi signāli bija stipri paplašināti, tajā skaitā arī TMS signāls.



7d 20

3,6-Bispiperidīnobenzohinona 20 ^{1}H KMR spektra signālu raksturs liecina par to, ka gala produkts satur nelielu daudzumu dipolāra anjon-radikāļa. ^{1}'H KMR spektrā novērojam $C_{(4)}$ - H signālu pie 8,58 m.d. (2H) un platus piperidīnā protonu signālus. Piperidīnu metilēngrupu protonu signāli redzami pie 1,42 (12H) un 1,69 m.d. (12H), metilēngrupas saistītas ar piperidīnā slāpekļa atomu parādās pie 2,96 (8H) un 3,36 (8H).

SECINĀJUMI

1. Veikto pētījumu rezultātā izstrādāta ērta, vispārēja preparatīva metode, lai sintezētu kā simetriskus, tā asimetriskus 2,5-bisheteroaril-3,6-dihlor-l,4-benzohinonus ar sēru un/vai slāpekli saturošu heterociklu fragmentiem.

2. Iegūti jaunie 2,5-bisheteroarilaizvietotie 1,4-benzohinoni ar vienādiem heterocikla fragmentiem - (2,5-bis(2-*N*,*N*-dialkilaminotiazol-5-il)-3,6-dihlor-l,4-benzohinoni), kā arī ar dažādiem heterociklu fragmentiem (ar pirazola, *4H*-1,3,4-tiadizīna vai 1,3-ditiol-2-ona fragmentiem molekulas 5-vietā) un 5,5'-bis[5-(2-*N*,*N*-dialkilaminotiazol-5-il)-3,6-dihlor-l,4-benzohinon-2-il]-2,2’-bitiazoli.

3. Ar ^{13}C KMR metodi pierādīts, ka 2-(2-*N*,*N*-dialkilaminotiazol-5-il)-3,5,6-trihlor-l,4-benzohinona molekulā hlora atoma aizvietošana ar *N*,*N*-dialkilaminoetenilgrupu notiek 5-vietā, līdz ar to pēc tālākām pārvērtībām gala rezultātā veidojas tikai viens no iespējamiem regioizomēriem - 2,5-bisheteroarilaizvietots 3,6-dihlor-l,4-benzohinons.

4. Noskaidrots, ka 2-(2-*N*,*N*-dialkilaminotiazol-5-il)-5-(2-A^{r},A^{r}-dietilarninoetenil)-3,6-dihlor-l,4-benzohinona un sālskābes reakcijas rezultātā veidojas universāli sintoni - 6-(2-*N*,*N*-dialkilaminotiazol-5-il)-2,5-dihidroksi-3,4,7-trihlor-2,3-dihidro-benzo[*b*]furāni. Izdalot šos savienojumus, ir iespējams iegūt 2,5-bisheteroarilaizvietotus 1,4-benzohinonus gan ar vienādu, gan ar dažādu heterociklu fragmentiem.

5. Noskaidrots, ka 6-(2-*N*,*N*-dialkilaminotiazol-5-il)-2,5-dihidroksi-3,4,7-trihlor-2,3-dihidrobenzo[*b*]furāna reakcijas ar bifunkcionāliem nukleofiliem reaģentiem, atkarībā no reaģenta struktūras, norit divējādi: pēc hlora atoma aizvietošanas 3 vietā tūlīt seko reciklizācijas reakcija un veidojas 2,5-bisheteroaril-3,6-dihlorhidrohinoni (ar tiourīnvielām, rubeānskābi. 4,4-dialkiltiosemikarbazīdiem un 1-feniltiosemikarbazīdu) vai arī iespējams izolēt hlora atoma nukleofiās aizvietošanās produktu un pēc tam to ciklizēt konc. sērskābē (ar kālija *O*-butilksantogenātu).

RĪGAS TEHNISKĀ UNIVERSITĀTE
RIGA TECHNICAL UNIVERSITY

MATERIĀLZINĀTNES UN LIETIŠĶĀS ĶĪMIJAS FAKULTĀTE
FACULTY OF MATERIAL SCIENCE AND APPLIED CHEMISTRY

Nelli BATENKO

2,5-BISHETEROARILAIZVIETOTU l,4-BENZOHINONU SINTĒZE

SYNTHESIS OF 2,5-BISHETEROARYL SUBSTITUTED 1,4-BENZOQUINONES

Summary of doctoral thesis

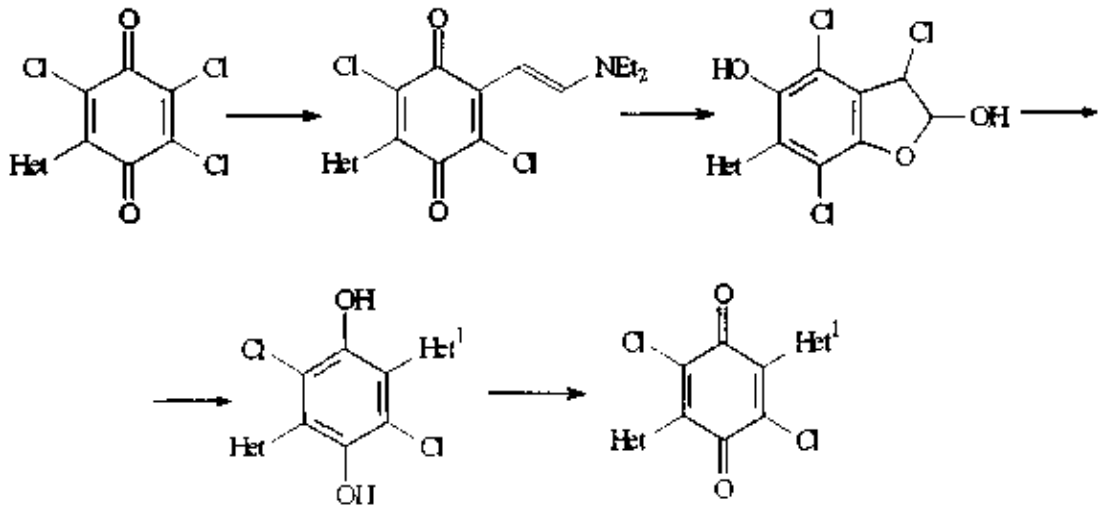
ZINĀTNISKIE VADĪTĀJI:
SUPERVISORS:
Dr. habil. chem. profesors Raimonds Valters
Dr. chem. Gatis Karlivāns

Rīga 2005

Introduction

The number of publications concerning synthesis and properties of quinone derivatives has considerably increased during the last years. Compounds containing quinone group exhibit numerous biological (antitumor, antifungal, antiparasitic, antidiabetic and anti-HIV) activities. Quinone derivatives have a great potential as molecular electronic devices and nonlinear optical materials (many of them have found an application as electron accepting component in the synthesis of ion-radical salts and charge transfer complexes). The chemistry of quinones is largely dependent on the nature of subsfituents on the quinonic ring. Heteroarylsubstituted quinones that integrate two different subunits - quinone and heterocycle - could open access to novel molecules and materials possessing interesting properties. It is important to note that general and efficient synthetic methods that allow easy preparation of structurally diverse heteroaryl-substituted quinones are rare [1].

The aim of present work was the elaboration of a general method for the synthesis of bisheteroarylsubstituted 1,4-benzoquinones (with similar or different heterocycles) applying the synthesis strategy developed at our department (RTU, Faculty of Material Science and Applied Chemistry, R. Valters, G. Karlivans, M. Utinans, J. Gulbis) for monoheteroarylsubstituted 1,4-benzoquinones. As an extension of these studies, we investigated possibilities to synthesize bisheteroarylsubstituted 1,4-benzoquinones on the basis of trichloroheteroarylsubstituted 1,4-benzoquinone using following strategy:

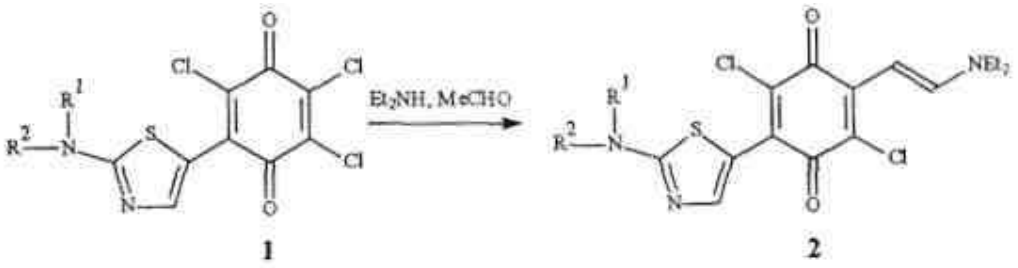


Our interest was focused on the synthesis of 6-(2-*N*,*N*-dialkylaminothiazol-5-yl)-3,5,6-trichloro-2,5-dihydroxy-2,3-dihydrobenzo[*b*]furans which were transformed into 2,5-bisheteroarvlsubstituted 1,4-benzoquinones using the recyclization reactions with sulfur

containing bifunctional reagents. In our work we also investigated reactions of 2,5-bis(2-piperidinothiazol-5-yl)-3,6-dichloro-l,4-benzoquinone with nucleophilic reagents.

1. 6-(2-*N*,*N*-Dialkylaminothiazol-5-yl)- 3,4,7-trichloro-2,5-dihydroxy-2,3-dihydrobenzo[*b*]furans [2]

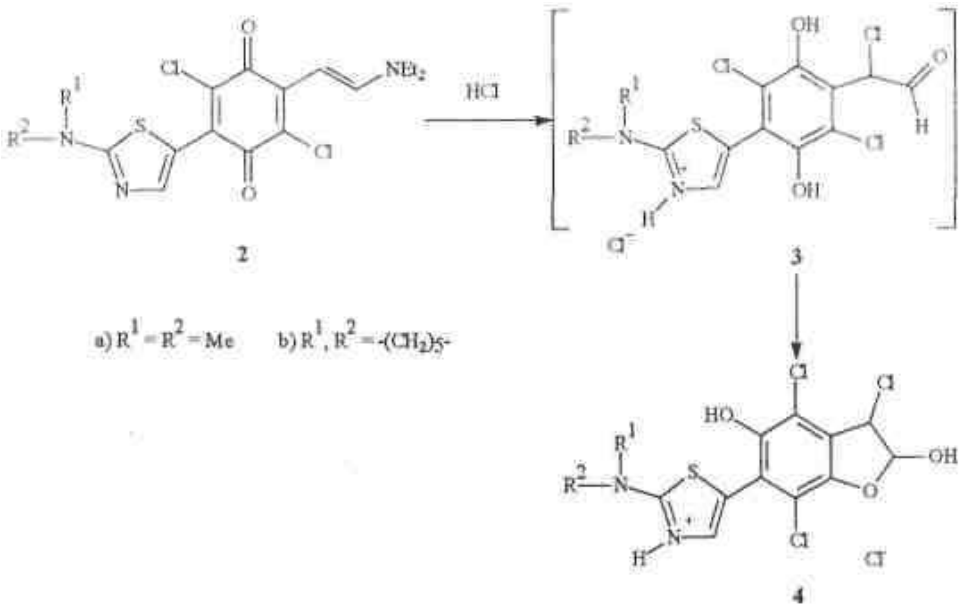
Initial investigations focused on the reactions of the easily obtainable *2-(2-N,N*-dialkylammothiazol-5-yl)-3,5,6-trichloro-l,4-benzoquinones with diethyl amine and acetaldehyde. The reaction proceeds *via* formation of an enamine, which reacts with the compound 1. 2-(2-*N*,*N*-Dalkylaminothiazol-5-yl)-5-(2-*N*,*N*-diethylamino-ethenyl)-3,6-dichloro-l,4-benzoquinones (2a-e) were formed as the substitution products of chlorine atom in position 5.



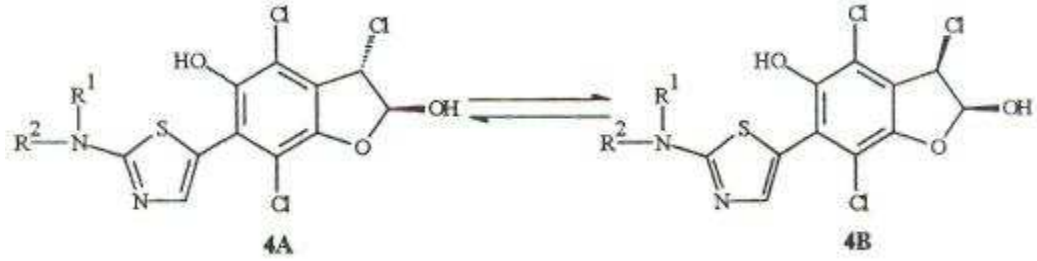
a) $R^1 = R^2 = Me$; b) $R^1, R^2 = -(CH_2)_4-$; c) $R^1, R^2 = -(CH_2)_5-$ d) $R^1, R^2 = -(CH_2)_6-$; e) $R^1, R^2 = -(CH_2)_2O(CH_2)_2-$

The quinones **2a-e** are deeply colored crystalline compounds (mp > 250°). The vinylic protons of the products appear in the ^{1}H-NMR spectra as two doublets, at 8 = 5.56-5.64 and at 8 = 8.36-8.44 ppm. The coupling constants are ^3J = 13-14 Hz which proves that the ethenyl group is in the *E* configuration. The electronic absorption spectra of the compounds **2a-e** show bands around 350 and 557-566 nm. The yield of compounds 2a-e was 90-95%, but desired product was not isolated in the case of unsubstituted amino group ($R^1 = R^2 = H$).

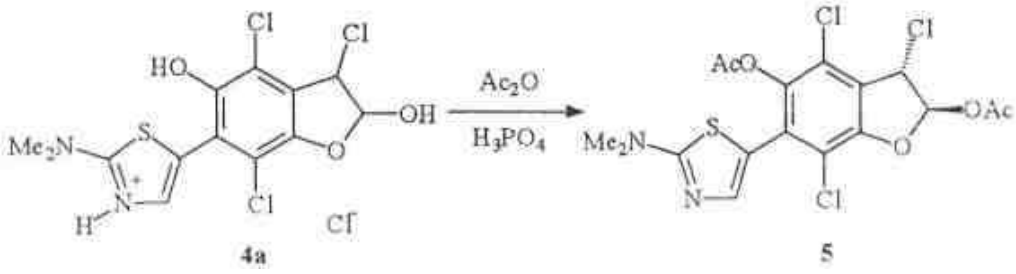
To introduce the second heterocycle moiety, quinones 2a-e could be transformed into 6-(2-*N*,*N*-dialkylaminothiazol-5-yl)-3,4,7-trichloro-2,5-dihydroxy-2,3-dihydro-benzo[*b*]furans **(4a,b).** The enamine hydrolysis with HC1 gave benzofurans **4a,b**. Benzofurans **4a, b** were isolated from the reaction mixture as hydrochlorides. A plausible mechanism for acid-induced conversation of enamines 2a,c to benzofurans 4a,b involves cyclization of the a-chloroacetaldehyde intermediate 3.



The ^{1}H NMR spectrum obtained for benzofuran 4a shows two doublets at 8_H 6.11 ($C_{(2)}$-H) and 5.67 ($C_{(3)}$-H) ppm with coupling constant ^3J = 4.89 Hz (4B) and two intensive doublets at $\delta 5_H$ 6.02 ($C_{(2)}$-H) and 5.40 ($C_{(3)}$-H) ppm with coupling constant $^3J \sim 0.5$ Hz **(4A)**. The spectroscopic data prove that the compounds **4a,b** exist as mixtures of the 2H, 3H *cis-trans* stereoisomers (for **4a** *cis/trans* ratio 16:84, for **4b** -36:64, both in DMSO-d_6).



An intermediate, a-chloroaldehyde **3**, was assumed to be involved in the conversions **4A/4B** but was not detected.

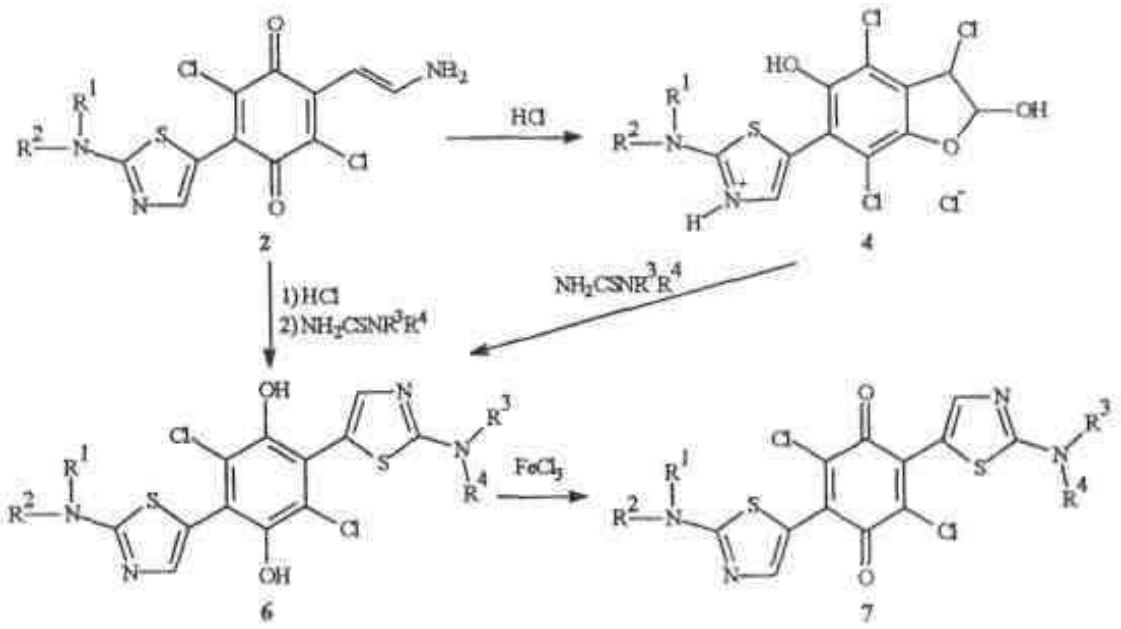


The treatment of benzofuran 4a with acetic anhydride in the presence of catalytic amount of orthophosphoric acid led to acylation of both hydroxy groups yielding

2,5-diacetoxy-6-(2-*N*,*N*-dimethylaminothiazol-5-yl)-3,4,7-trichloro-2,3-dihydro-benzo[*b*]furan (5). The $Q_{(2)}$-H and $C_{(2)}$-H protons of the compound 5 appear in the ^{1}HNMR spectrum as singlets at 6H 6.85 and 5.87 ppm. The coupling constant is $^3J < 0.5$ Hz, which proves that the 2,3-substituents are in the *trans*-configuration. It seemed reasonable to assume that formation of *trans*-isomer is preferable.

2. 2,5-Bis(2-*N*,*N*-dialkylaminothlazol-5-yl)-3,6-dichloro-l,4-benzoquinones [2,3]

Two procedures have been used to prepare 2,5-bis(2-*N*,*N*-dialkylaminothiazol-5-yl)-3,6-dichloro-l,4-benzoquinones (7). In the first procedure, 2-(2-*N*,*N*-dialkylaminothiazol-5-yl)-5-(2-*N*,*N*-diethylaminoethenyl)-3,6-dichloro-l,4-benzo-quinones **(2a-e)** were reacted with variously substituted thioureas in the presence of hydrochloric acid. In the second procedure, 6-(2-*N*,*N*-dialkylaminothiazol-5-yl)-3,4,7-trichloro-2,5-dihydroxy-2,3-dihydrobenzo[*b*]furans **(4a,b)** were reacted with substituted thioureas.



a) $R^1 = R^2 = R^3 = R^4 =$ Me; b) $R^1, R^2 =$ -(CH)$_5$-, $R^3 = R^4 =$ H;
c) $R^1, R^2 =$ -(CH)$_5$-, $R^3, R^4 =$ -(CH)$_4$-; d) $R^1, R^2 = R^3, R^4 =$ -(CH)$_5$-;
e) $R^1, R^2 = R^3, R^4 =$ -(CH)$_2$O(CH)$_2$-; f) $R^1, R^2 = R^3, R^4 =$ -(CH)$_6$-;

In the beginning, all benzoquinones **7a-f** were synthesized by the first procedure. In this case the reaction proceeds *via* formation of initial intermediate benzofuran 4, nucleophilic substitution of a chlorine atom with sulfur at the position 3 and recyclization (dihydrobenzofuran ring opening with subsequent cyclization to the thiazole ring). Thus, the 2,5-bis(2-*N*,*N*-dialkylaminothiazol-5-yl)-3,6-dichlorohydroquinones **(6a-f)** were formed. The hydroquinones **6a-f** were directly used for the following oxidation reaction due to their ability to be readily oxidized in air to the corresponding 1,4-benzoquinones. This is indicated by the presence of the C=0 group absorption band (1640, 1630 cm^{-1} respectively) in the IR spectra (compounds **6a** and 6d). The electronic absorption spectrum of the **6d** shows the band typical for heteroarylsubstituted 1,4-benzoquinones (582 nm). The 2,5-bis(2-*N*,*N*-dialkylaminothiazol-5-yl)-3,6-dichloro-l,4-benzoquinones **(7a-f)** were obtained in high yields by oxidation of **6a-f** with ferric chloride in aqueous DMF. 2,5-Bis(2-*N*,*N*-dimethylaminothiazol-5-yl)- and 2,5-bis(2-piperidinothiazol-5-yl)-3,6-dichlorohydroquinones **(6a** and **6d)** have been prepared by the second procedure in the reaction of benzofurans **4a,b** with *N*,*N*-dimethyl- and *N*,*N*-pentamethylenthioureas in the ethanol. Hydroquinones **6a,d** were converted into the corresponding 1,4-benzoquinones by oxidation with $FeCl_3$. The ^{1}H NMR and IS spectral characteristics of the compounds 7a and 7d are identical to the data of the compounds **7a,d** obtained by the first method.

It is known, that the predominant direction of nucleophilic substitution of two halogen atoms in the chloranil is 2,5-disubstitution. But in some cases reaction with nucleophilic reagents give mixture of 2,5- and 2,6-substituted regioisomers. C NMR spectrum of symmetrical 2,5-bis(2-piperidinothiazol-5-yl)-3,6-dichloro-l,4-benzoquinone (**7d**), as expected, showed nine ^{13}C signals (Fig. 1) that confirm the 2,5-position of the heterocycles on the benzoquinone ring. The thiazol's protons of the benzoquinone **7d** are observed in the H NMR spectrum at 8.76 ppm (2H), the piperidine cycle protons appear as broad singlets at 3.67 (8H, N-CH2) and 1.69 (12H, CH_2) ppm, which indicate the piperidine cycle inversion. In the IR spectra typical C=O group absorptions appear in the region of 1643-1628 cm^{-1}. The benzoquinones **7a-f** are intensely blue colored, they are poorly soluble in organic solvents (DMF, DMSO, $CHC1_3$), and give deeply colored solutions at low concentrations. When heated above > 250° C, they gradually decompose.

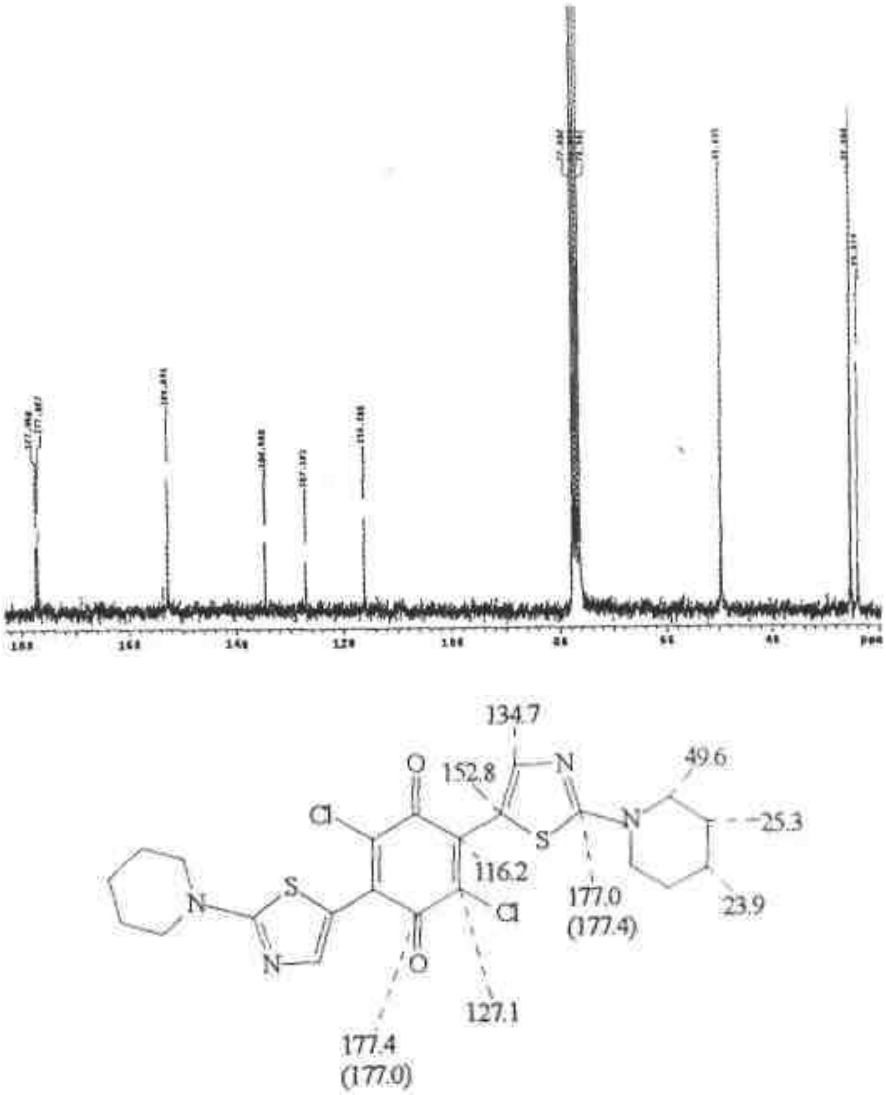
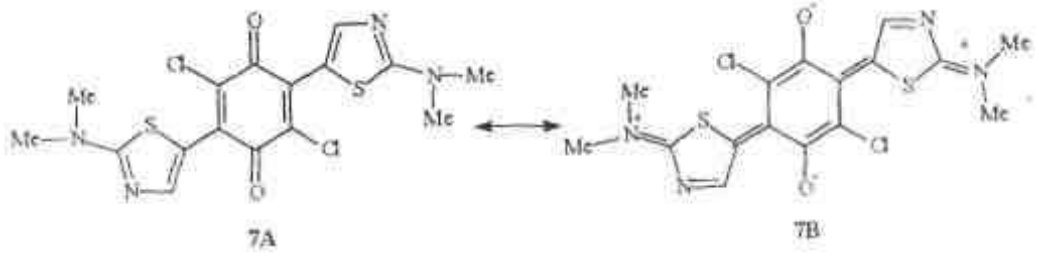


Fig.l. ^{13}C NMR spectral data ($CDC1_3$) of compound **7d.**

The electronic absorption spectra of the benzoquinones 7a-f show bands around 353-363nm and at 562-610 nm. The UV spectra of two compounds **7a** and **7d** show a further absorption maximum at 743 and 718 nm, respectively.

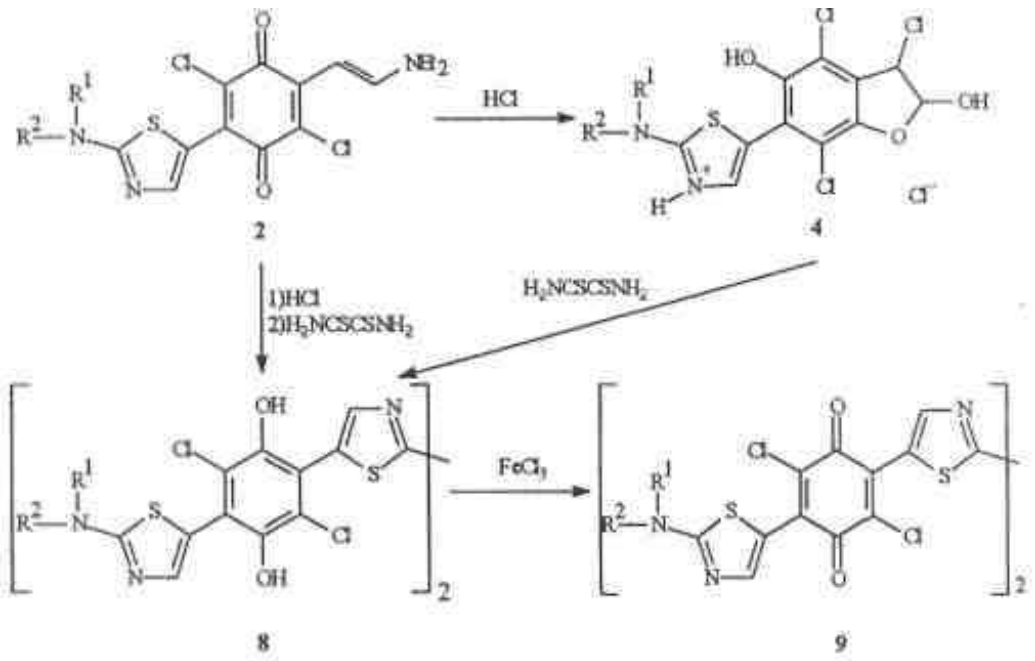


7A 7B

These bands correspond to intramolecular electron transfer from the donor heterocyclic moiety to the acceptor quinonic moiety of the molecule. For compound 7a, intramolecular charge transfer can exist in the mesomeric form **7B**.

3. 5,5'-Bis [5-(2-*N*,*N*-dialkylaminothiazol-5-yI)-3,6-dichloro-l,4-benzoquinon-2-yl]-2,2'-bithiazole [4]

Both compounds **2** and **4** could be useful for the synthesis of 5,5'-bis[5-(2-*N*,*N*-dialkylaminothiazol-5-yl)-3,6-dichloro-l,4-benzoquinon-2-yl]-2,2'-bithiazole (9). Benzoquinones **2a,c** were chosen as initial candidates for the synthesis of **9a,b**. We found that treatment of **2a,c** with HC1 in MeCN and the following reaction with rubeanic acid (dithiooxalic diamide) lead to the formation of corresponding 5,5'-bis[4-(2-*N*,*N*-dialkylaminothiazol-5-yl)-3,6-dichloro-2,5-dihydroxyphenyl]-2,2'-bithiazoles (**8a,b**).

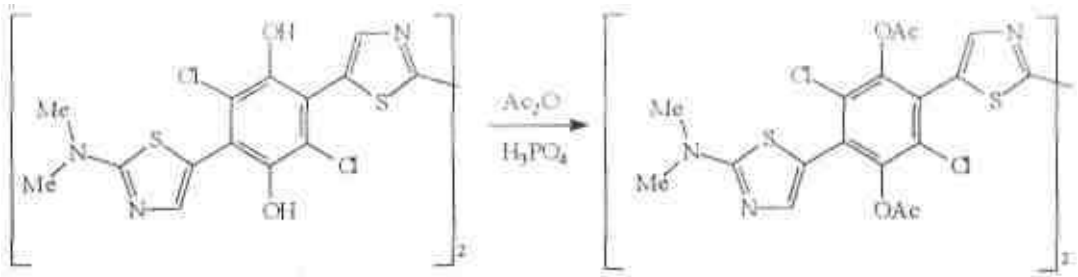


a) $R^1 = R^2 = Me$

b) $R^1, R^2 = -(CH_2)_5-$

The hydroquinones **8a,b** were obtained in good yields using 2 mol of benzoquinone **2a** or **2c** per mole of rubeanic acid. The ^{1}H NMR spectrum of hydroquinone **8a** indicated the presence of two different thiazole rings: two $C_{(4)}$-H proton singlets appear: at 7.45 (2H, dialkylaminothiazole) and 8.04 (2H, bithiazole) ppm. The

electronic absorption spectrum of the benzoquinone 9b shows bands at 514 and 716 mm ($CHC1_3$).



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In the ^{1}H NMR spectrum of the compound 10 the presence of two different acyl groups is observed. The spectral data of acyl product confirm the structure of its precursor - hydroquinone **8a.**

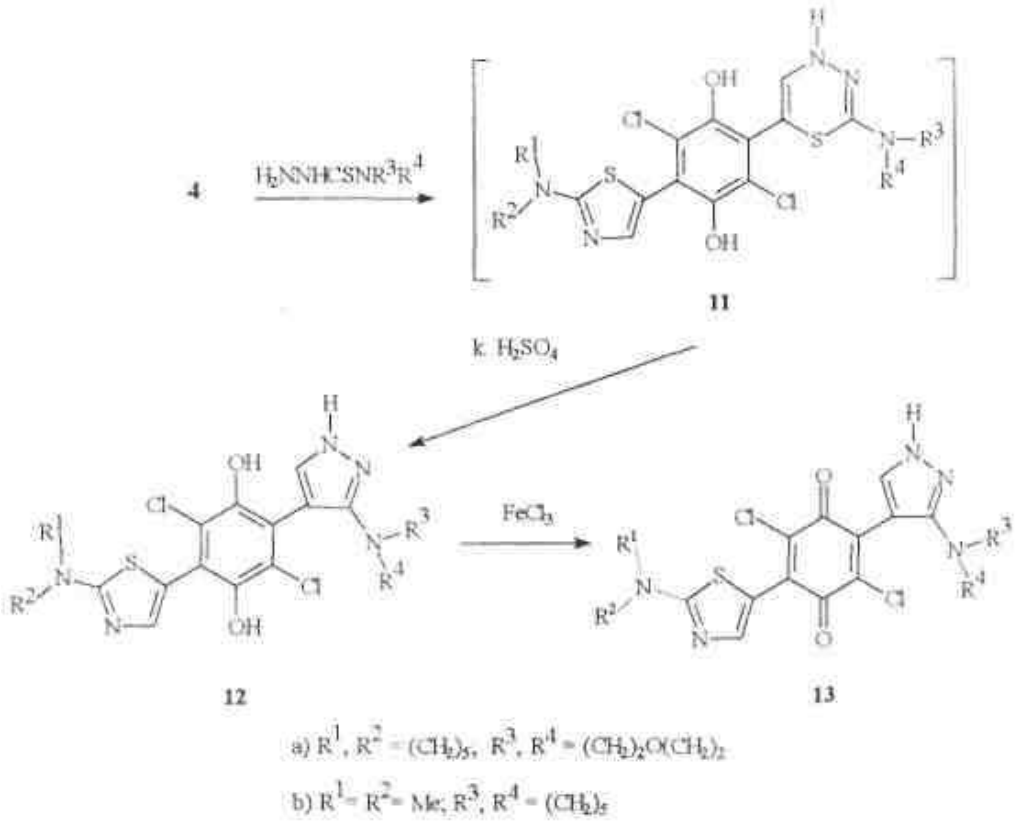
4. 2-(3-*N*,*N*-DialkyIaminopyrazol-4-yl)-5-(2-*N*,*N*-ialkylaminothiazol-5-yl)-3,6-dichloro-l,4-benzoquinones [2]

2-(3-*N*,*N*-Dialkylaminopyrazol-4-yl)-5-(2-*N*,*N*-dialkylaminothiazol-5-yl)-3,6-dichlorohydroquinones (12) were formed by heating of dihydrofurans 4 with the corresponding 4,4-dialkylthiosemicarbazide in the presence of sulfuric acid. It is suggested that the pyrazole system is formed *via* the intermediate 1,3,4-thiadiazine **11** which readily undergoes extrusion of a sulfur atom with the formation of a pyrazole ring.

The chemical shift of the thiazole $C_{(4)}$-H proton appeared at 7.87 **(12a)** and 7.98 **(12b)** ppm, the pyrazole $C_{(5)}$-H protons singlet shows at 7.43 **(12a)** and 7.47 **(12b)** ppm. In the IR spectra, the typical OH group band appears in the region 3390-3000 cm^{-1}.

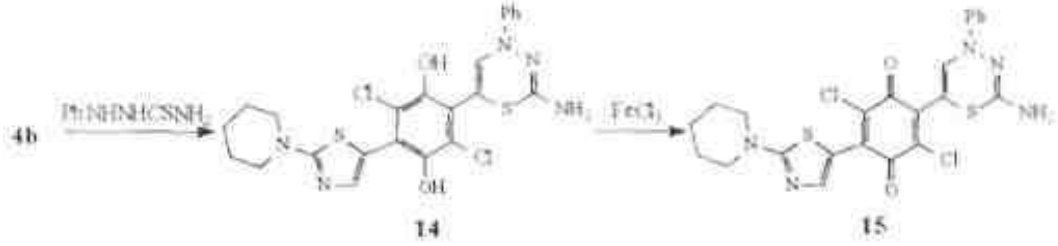
After subsequent oxidation with aqueous ferric chloride hydroquinones **12a,b** yield the 2-(3-*N*,*N*-dialkylaminopyrazol-4-yl)-5-(2-*N*,*N*-dialkylaminothiazol-5-yl)-3.6-dich!oro-1.4-benzoquinones **(13)**. This oxidation reaction was longer and yields were not as good as in the case of benzoquinones **7a-f**. The thiazol's protons of the benzoquinones **13** are observed in the ^{1} H NMR spectra at 8.64 **(13a)** and 8.49 **(13b)**

ppm. the pyrazole $C_{(5)}$-H protons appear at 7.87 (**13a**) and 7.94 (**13b**) ppm. The UV spectrum of 13a showed absorption bands at 344 (lg ε 4.10) and 640 (lg ε - 3.65) nm.



5. 2-(2-Amino-4-phenyl-*4H*-l,3,4-thladiazin-6-yl)-5-(2-piperidinothiazol-5-yl)-3,6-dichloro-l,4-benzoquinone [2]

Our investigation showed that reaction of benzofuran **4b** with 1-phenylthiosemicarbazide in refluxing ethanol lead to the 2-(2-amino-4-phenyl-*4H*-l,3,4-thiadiazin-6-yl)-5-(2-piperidinothiazol-5-yl)-3,6-dichlorohydroquinone (**14**). This reaction mechanism involves formation of a sulfur alkylation's product at the initial stage and a subsequent cyclisation to the thiadiazine ring at the final stage. Hydroquinone 14 is a white crystalline compound (mp > 250° C). The heterocyclic protons in the ^{1}H NMR spectrum appear as singlets at 8.11 (thiadiazine $Q_{(5)}$-H) and 7.29 (thiazole $C_{(4)}$-H) ppm. The OH group signal was observed as a broad singlet at 5.78 ppm.



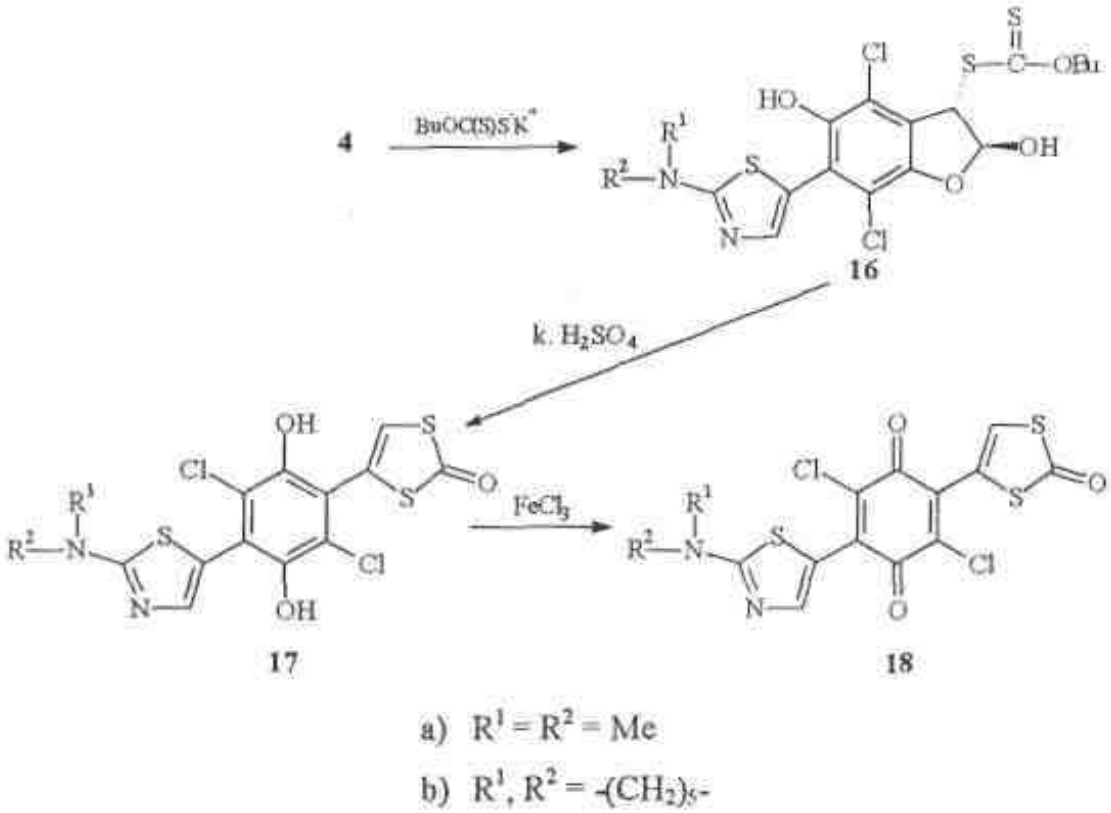
$FeCl_3$ (H_2O/DMF) could easily oxidize hydroquinone **14** to the corresponding benzoquinone **15** with high yield. Benzoquinone **15** is a purple crystalline compound. In this case the heterocyclic protons in the ^{1}H NMR spectrum appear at 8.90 (thiadiazine $C_{(5)}$-H) and 8.73 (thiazole $C_{(4)}$-H) ppm. The electronic absorption spectrum of the benzoquinone **15** shows the expected absorption bands at 403 nm (lg ε= 4.18) and at715 nm (lg ε = 3.70) nm. In the UV spectrum of 6-(trichloro-l,4-benzoquinonyl)-2-amino-4-phenyi-*4H*-l,3,4-thiadiazine only one absorption band appear in this region (482 nm, lg ε = 3.93).

6. 2-(2-*N*,*N*-Dialkylaminothiazol-5-yl)-5-(l,3-dithlol-2-on-4-yl)-3,6-dichloro-l,4-benzoquinones [2]

Much attention was devoted to the synthesis of the l,3-dithiol-2-ones because they have been extensively used as intermediates in the synthesis of tetrathiafulvalenes. In most cases the l,3-dithiol-2-one ring could be formed by cyclization of a β-ketodithioester with strong mineral acid (H_2SO_4, $HClO_4$).

Treatment of benzofurans **4a,b** with potassium O-butylxanthate gave chlorine atom substitution products - xanthates **16a,b.** We have established that the reaction of benzofuran **4a,b** with sulfur containing bifunctional compounds proceeds *via* substitution of chlorine atom in position 3 in the first stage and further opening of the dihydrobenzofuran ring with subsequent cyclization to the corresponding heterocycle. It is noteworthy that this sequence occurs if substitution proceeds with a bifunctional reagent containing double bond C=S. The intermediate substitution product could be isolated only in the case when the reagent contains negatively charged sulfur atom (potassium *O*-butylxanthate). In the ^{1}H NMR spectrum of xanthate **16a** the $C_{(5)}$-OH group proton appeared at 9.43 ppm, the $C_{(2)}$-OH group proton showed as doublet at 8.18 (^3J = 6 Hz) ppm, the thiazole $C_{(4)}$ -H singlet was observed at 7.23 ppm. The $C_{(2)}$-H proton appeared as a doublet of doublets with two

coupling constants: ^3J = 6 Hz (coupling with OH group) and ^{3} < 0.5 Hz (coupling with $C_{(3)}$-H proton). The coupling constant ^3J < 0.5 Hz proves that the xanthate **16a** exists as *trans* stereoisomer.

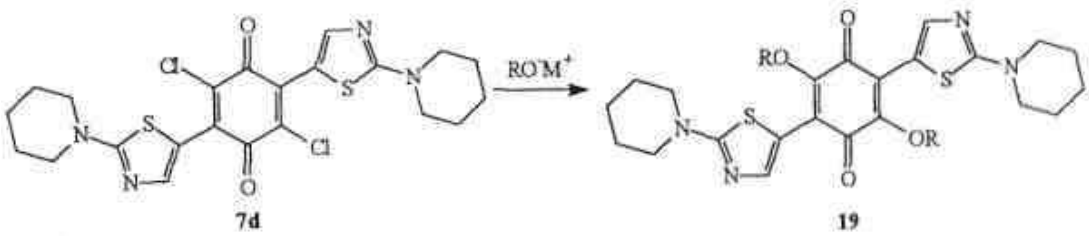


Xanthates **16** could be directly converted into hydroquinones **17** by heating in concentrated sulfuric acid. The probable mechanism seems to be the proton addition to the $C_{(2)}$-OH group, recyclization (furan ring opening and formation of the 1,3-dithiol-2-one ring) with removal of the butoxy group and formation of hydroquinones **17**. In the ^{1}H NMR spectrum of hydroquinone **17a** OH group signal appeared as a broad singlet at 9.27 (2H) ppm, heterocyclic protons were observed at 7.43 (thiazole $C_{(4)}$-H) and 7.23 ppm (l,3-dirhiol-2-one $C_{(5)}$-H). After treatment with $FeCl_3$ (H_20/DMF) at room temperature hydroquinones 17 gave 2-(2-*N*,*N*-dialkylamino1hiazol-5-yl)-5-(l,3-dithiol-2-on-4-yl)-3,6-dichloro-l,4-benzoquinones (**18**) in good yield. Benzoquinones **18** are dark blue crystalline compounds (mp > 250° C). In the ^{1}H NMR spectra of benzoquinones **18** thiazole $C_{(4)}$-H signals were observed at 8.72 (**18a**) and 8.69 (**18b**) ppm, l,3-dithiol-2-one signals appeared at 7.23 (**18a**) and 7.27 (**18b**) ppm. Electronic absorption spectrum of **18a** showed bands at 480 (lg ε=3.57) and 683 nm (lg ε =3.80)

7. Nucleophilic substitution of chlorine atoms in 2,5-bis(2-piperidino-thiazol-5-yl)-3,6-dichloro-l,4-benzoquinones [5]

Our interest in heteroarylsubstituted quinones led us to study their reactions with nucleophilic reagents.

Treatment of benzoquinone **7d** with 2.5 equivalent of MeONa in dry methanol at room temperature resulted in a substitution of both chlorine atoms yielding 2,5-bis(2-piperidinothiazol-5-yl)-3,6-dimethoxy-l,4-benzoquinone **(19a,** 91%). The proton NMR spectrum of **19a** confirmed that two methoxy groups were present (5 4.01 ppm (6H)). In this spectrum a shift of the thiazole proton from 8.76 (**7d**) to 8.41 ppm **(19a)** was observed. In the IR spectrum typical quinonic absorption appears at 1632 cm^{-1}. The electronic absorption spectrum of **19a** shows only one charge transfer band at 537 run (lg ε = 4.25)



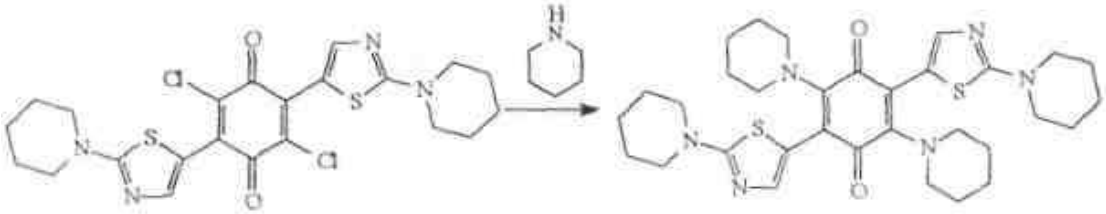
7d 19

c) M = Na, R = Me
d) M = K, R = Et

The reaction of benzoquinone **7d** with excess EtOK at reflux resulted in 2,5-bis(2-piperidinothiazol-5-yl)-3,6-diethoxy-l,4-benzoquinone **(19b)** in 48% yield. The above results indicate that benzoquinone **19a** would be formed more easily than compound **19b.** In ^{1}H NMR spectrum of **19b** the proton at $C_{(4)}$ of the thiazole has the chemical shift of 8.36 ppm, ethoxy group signals appear at 1.38 (6H) and 4.27 (4H) ppm. In the UV spectrum of the **19b** the charge transfer band appears at 530 nm (lgε = 4.07).

Prompted by the idea of preparing 2,5-bis(2-piperidinothiazol-5-yl)-3,6-dihydroxy-1,4-benzoquinone, we undertook a study of the chlorine atoms' substitution by hydroxy groups in basic media. We examined different solvents (MeOH, EtOH, DMF, MeCN, dioxane, sulfolane), reagents (KOH, NaOH, KOH/$CsCO_3$, LiOH) and

reaction conditions (stirring at room temperature, heating, refluxing), but the desired dihydroxy product was not isolated Attempts to hydrolyze methoxy groups at positions 3 and 6 were not successful. Next, we studied the reaction of benzoquinone **7d** with piperidine. In this case the nucleophilic substitution of chlorine atoms took place, but the obtained benzoquinone **20** obviously contains a small amount of a dipolar anion radical which causes broadening of all lines in ^{1}H NMR spectrum.



7d 20

The ^{1}H NMR spectrum exihibited a broad singlet at 8.58 ppm (thiazole $C_{(4)}$-H, 2H) and broad signals of piperidine protons at 2.96 (8H) and 3.36 (8H) ppm (for the CH_2 adjacent to the nitrogen atoms), and at 1.42(12H)and 1.69 (12H) ppm.

CONCLUSIONS

1 A new, general and efficient svntlietic method for the synthesis of symmetrical and asymmetrical 2,5-bisheteroaryl-3,6-dichloro-l,4-benzoquinones with sulfur and/or nitrogen containing heterocycles has been elaborated.

2. A series of new 2,5-bisheteroarylsubstituted 1,4-benzoquinones with similar (2,5-bis(2-*N*,*N*-dialkylaminothiazol-5-yl)-3,6-dichloro-l,4-benzoquinones) and different (with pyrazole, *4H*-1,3,4-thiadiazine or l,3-dithiol-2-one ring at the position 5 of benzoquinone) heterocycle fragments has been synthesized, 5,5'-Bis[5-(2-*N*,*N*-dialkylaminothiazol-5-yl)-3,6-dichloro-l,4-benzoquinon-2-yl]-2,2'-bithiazoles also have been obtained.

3. It was confirmed by the ^{13}C NMR method that the chlorine atom substitution in 2-(2-*N*,*N*-dialkylaminomiazol-5-yl)-3,5,6-trichloro-l,4-benzoquinone with *N*,*N*-dialkylaminoethenyl group proceeds at position 5 of benzoquinone and further only one (2,5-bisheteroarylsubstituted 1,4-benzoquinone) of the two possible regioisomers was obtained.

4. Reaction of 2-(2-*N*,*N*-dialkylaminothiazol-5-yl)-5-(2-*N*,*N*-diemylaminoetheiryl)-3,6-dichloro-l,4-benzoquinones and hydrochloric acid led to the formation of universal synthones - 6-(2-*N*,*N*-dialkylaminothiazol-5-yl)-3,4,7-trichloro-2,5-dihydroxy-2,3-dihydrobenzo[*b*]furans. Obtaining of this synthone was a key step in the synthesis of 2,5-bisheteroarylsubstituted 1,4-benzoquinones with similar and different heterocycle fragments.

5. Reactions of 6-(2-*N*,*N*-dialkylaminothiazol-5-yl)-3,4,7-trichloro-2,5-dihydroxy-2,3-dihydrobenzo[*b*]furans with bifunctional nucleophilic reagents could proceed by two routes depending on the nature of the reagents. In the first case (reaction with thioureas, rubeanic acid, 4.4-dialkylthiosemicarbazides and 1-phenylthiosemicarbazide) the substitution of chlorine atom at the position 3 followed by recyclization reaction leading to 2,5-bisheteroaryl-3,6-dichlorohydroquinones. In the second case (reaction with potassium *O*-

butylxanthate) an intermediate substitution product could be isolated and the subsequent cyclization proceeded under acidic conditions.

6. The reactions of 6-(2-*N*,*N*-dialkylaminothiazol-5-yl)-3,4,7-trichloro-2,5-dihydroxy-2,3-dihydrobezo[*b*]furans with 4,4-dialkylthiosemicarbazides proceeded *via* the intermediate *4H*-l,3,4-thiadizine derivatives which undergo extrusion of a sulfur atom with the formation of 2-(3-*N*,*N*-dialkylaminopyrazol-4-yl)-5-(2-*N*,*N*-dialkylaminothiazol-5-yl)-3,6-dichlorohydroquinones.

7. In the reaction of 2,5-bis(2-piperidinothiazol-5-yl)-3,6-dichloro-l,4-benzo-quinones with nucleophilic reagents (sodium methoxide, potassium ethoxide and piperidine) corresponding chlorine atoms' substitution products were obtained.

8. ^{1}H NMR, ^{13}C NMR, IR and UV data confirmed the structures of the obtained compounds. The electronic absorption spectra of 2,5-bisheteroarylsubstituted 1,4-benzoquinones show bands in the region between 480-743 nm. This absorption indicates the presence of intramolecular charge transfer between the electron donating heterocycles and the electron accepting benzoquinone moiety.

9. The results of our investigations have been reported at 7 international conferences and 5 articles have been published.

The results of this thesis have been presented in the following papers (1-5) **and abstracts of conferences** (6-14)**:**

1. II. Г. Батенко, Г. А. Карливан, Р. Э. Валтер. Методы синтеза гетероарилзамещенных 1,4-бензо- и 1,4-нафтохинонов (обзор). АТС, с. 803-833 *(2005);* N. G. Batenko, G. Karlivans, R. Valters. Methods for the synthesis of heteroaryl-substituted 1,4-benzo- and 1,4-naphthoquinones (review). *Chem. Heterocycl. Comp.*, p. 691-717(2005).

2. N. G. Batenko, G. A. Karlivans, R. E. Valters. A new method for the synthesis of 2,5-bisheteroaryl-3,6-dichloro-l,4-benzoquinones. *Heterocycles,* 65, p.1569-1576 (2005).

3. Н. Г. Батенко, Р. Э. Валтер, Г. А. Карливан. Синтез 2,5-бис(2-аминотиазол-5-ил)-3,6-дихлор-1,4-бензохинонов. *ХТС,* с. 835-839 (2000).

4. N.G.Batenko, R.Valters, and G.Karlivans. Synthesis of 2,5-bis(2-aminothiazol-5-yl)-3,6-dichloro-1,4-benzoquinones. *Chem. Heterocycl.Comp.,* p. 733-737 (2000).N.Batenko, R.Valters, and G.Karlivans. Synthesis of 2,2'-bi[5-(2-*N*,*N*-dialkylaniinothiazole-5-yl)-3,6-dichloro-l,4-benzoquinone-2-yl]thiazoles. *RTU Zinātniskie raksti. Sērija 1. Materiālzinātne un lietišķā ķīmija.* RTU, Rīga, 7.sējums, 99. - 102. 1pp. (2003)

5. N.Batenko, R.Yalters, and G.Karlivans. Nucleophilic substitution of chlorine atoms in 2,5-dichloro-3,6-bis(2-piperidinothiazol-5-yl)-l,4-benzoquinone. *RTU Zinātniskie raksti. Sērija 1. Materiālzinātne un lietišķā ķīmija.* RTU, Rīga, 3.sējums,166. - 169. lpp. (2001).

6. R.Valters, N.Batenko, and G.Karlivans. Synthesis of bis(2-aminothiazol-5-yl)-3,6-dicloro-l,4-benzoquinones. *18th International Symposium on the Organic Chemistry of Sulfur,* Abstracts, Florence, Italy, July 13-18, 1998, P. 232.

7. R.Valters, G.Karlivans. J.Gulbis, and N.Batenko. Synthesis of trichloro-1,4-benzoquinonylsubstituted heterocycles and related compounds. *17th International Congress of Heterocyclic Chemistry,* Abstracts, Institute of Organic Chemistry Vienna University of Technology, Vienna, August 1 6, 1999, PO-279.

8. Н.Батенко, Р.Валтерс, Г.Карливанс. Синтез 2,5-бис(2-аминотиазол-5-ил)-3,6-дихлоро-1,4-бензохинонов. *Вторая международная конференция молодых ученых. Материалы конференции. Актуальные тенденции в органическом синтезе на пороге новой эры.* Санкт-Петербург, Россия, Июнь 28-30, 1999, С. 50

9. N.Batenko, R.Valters, and G.Karlivans. Synthesis of Dihetarylsubstituted 1,4-benzoquinones (In Latvian). *Abstract Book of 40. Student Scientific and Technical Conference of Riga Technical University*, Riga, 26. - 30. April, 1999, P. 13.

10. N.Batenko, R.Valters, and G.Karlivans. Reactions of 2,5-bis (2-aminothiazol-5-yl)-3,6-dichloro-l,4-benzoquinones with nucleophile reagents (In Russian). Abstract Book. *Studentu mokslines konferencijos. CHEMIJA 1R CHEMINE TECHNOLOGIJA.* Kauno tehnologijos universitetas. Kaunas. Technologija. 2000, P. 279.

11. N.Batenko, RValters, and G.Karlivans. Nucleophilic substitution of chlorine atoms in 2,5-dichloro-3,6-bis(2-N,Ndialkylaminothiazol-5-yl)-l,4-benzoquinones. *Third Youth School-Conference on Organic Synthesis "Organic synthesis in the New Century",* Abstracts of Papers, Saint-Petersburg, Russia, June 24-27, 2002, P. 68.

12. R.Valters, J.Gulbis, N.Batenko, and G.Karlivans, Synthesis of trichloro-1,4-benzoquinonylsubstituted 3-dialkylaminothiazoline-2-thiones and related heterocycles. *20th International Symposium on the Organic Chemistry of Sulfur*, Book of Abstracts, Northern Arizona University, Flagstaff, Arizona, July 14-19, 2002, PR 1.

13. N.Batenko, R.Valters, G.Karlivans. Synthesis of 5-(2-N,N-diaikylaminothiazole-5-yl)-3,6-dichloro-l,4-benzoquinonylsubstituted 2,2'-bithiazoles (In Latvian) Abstract Book of RTU 44th International Scientific Conference. Riga, October 9-11, 2003, P. 60.

14. R. E. Valters, N. G. Batenko, G A. Karlivans. A new method for the synthesis of 2,5-bisheteroaryl-3,6-dichloro-l,4-benzoquinones, *20th International Congress Heterocyclic Chemistry,* Book of Abstracts, University of Palermo, Italy, July 31-August 5, 2005,