# DIAZABICYCLOALKANES WITH BRIDGEHEAD NITROGEN ATOMS.

## 27.* SYNTHESIS OF PHENAZINO[1',2'-b]- AND PHENAZINO[2',3'-b]-1,4-DIAZABICYCLO[2.2.2]OCTENES

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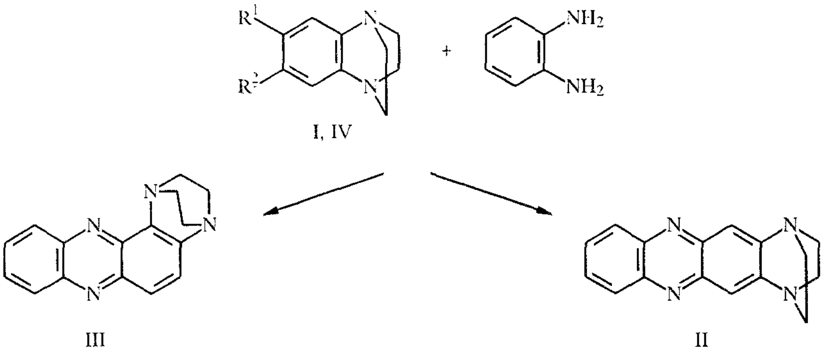
*Reaction of 4'-iodo- and 4',5'-diiodobenzo[b]-1,4-diazabicyclo[2.2.2]octenes with o-phenylenediamine under Ullmann condensation conditions gives a mixture of phenazino[1',2'-b]- and phenazino[2',3'-b]-1,4-diazabicyclo-[2.2.2]octenes or only the latter, depending upon the grade of copper.*

Oligonucleotides containing an interchelating phenazine residue at one end and an alkylating agent residue at the other have been used to modify nucleic acids [2].

In this regard there has been interest in combining in one molecule a phenazine fragment and a 1,4-diazabicyclooctane, quaternary salts of which possess alkylating properties [3].

This problem was resolved using an Ullmann condensation between o-phenylenediamine and 3'-,4'- or 4',5'-halo-substituted benzo[b]-1,4-diazabicyclo[2.2.2]octene. Ullmann condensation [4] of 4',5'-diiodobenzo[b]-1,4-diazobicyclo[2.2.2]octene (I) with o-phenylenediamine gave two products (II and III) with similar $R_f$ and UV spectra virtually identical to that of phenazine.

The mass spectra of both compounds shows a molecular ion peak with mass 262 and intense peaks at M-28 and M-29, characteristic of compounds containing a diazabicyclic fragment [5]. The PMR spectrum of II shows a singlet signal (intensity 2H) at 7.95 ppm, the remaining aryl protons giving two symmetrical multiplets characteristic of phenazine. The aliphatic protons give a multiplet corresponding to 8H. The spectrum of III shows two doublets at 7.75 and 8.19 ppm (both 1H) with J = 8.5 Hz but not showing a meta coupling constant. The remaining aryl protons give a complex set of signals (see Experimental). The aliphatic protons give two multiplets with intensity 8H.



I $R^1=R^2=I$; IV $R^1=I$, $R^2=H$

Based on these data and on elemental analysis, compound II can be assigned the structure phenazino[2',3'-b]-1,4-diazabicyclo[2.2.2]octene and III the isomeric phenazino[1',2'-b]-1,4-diazabicyclo[2.2.2]octene.

The ratio of isomers II and III varies from 3:1 to 10:1 and depends on the grade of copper catalyst. Hence, use of freshly activated finely dispersed copper prepared as in [4] gives only II, whereas old or ignited copper powder gives up to 7% of III (overall yield of II and III in both cases is about 30%).

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*For Communication 26 see [1].

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TABLE 1. Physical Parameters for Compounds

| Compound | Empirical formula | $R_f$ | mp, °C | $\lambda_{max}$ (log ε) | Yield, % |
|---|---|---|---|---|---|
| II | $C_{16}H_{14}N_4$ | 0,30 | 240...241* | 210 (4,47), 250 (5,09), 362 (4,22) | 24 |
| III | $C_{16}H_{14}N_4$ | 0,46 | 171...173* | 208 (4,35), 251 (4,95), 362 (4,07) | 7 |
| VI | $C_{16}H_{16}N_4O_2$ | 0,28 | 146...148 | 263 (4,18), 421 (3,88) | 80 |
| VII | $C_{16}H_{16}N_4O_2$ | 0,21 | 168...170 | 288 (4,14), 425 (3,16) | 37 |

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*From hexane.

This observation is taken with the absence of such a reaction in any other solvents with similar reflux temperatures. We therefore propose that, after substitution of one iodine in I by o-phenylenediamine, we are dealing with two parallel reactions corresponding to Ullmann condensation to give isomer II and to a condensation characteristic of 2-aminodiphenylamines occurring under similar conditions [6].

As a check we have treated 4'-iodobenzo[b]-1,4-diazabicyclo[2.2.2]octene (IV) with o-phenylenediamine under the same conditions. A mixture of isomers II and III was obtained in the ratio 4:1 to 5:1. The grade of catalyst influenced the overall isomer yield (20-25%) but did not affect their ratio.

Attempts to synthesize pure III by carrying out this reaction with 3'-iodobenzo[b]-1,4-diazabicyclo[2.2.2]octene (V) were unsuccessful due to tarring.

Since one of the most used preparations of phenazines is the intramolecular cyclization of o-nitrodiphenylamine in the presence of lead or iron oxalate [7, 8] we have treated IV and V with o-nitroaniline to give 4'-(o-nitroanilino)-benzo[b]-1,4-diazabicyclo[2.2.2]octene (VI) and 3'-(o-nitroanilino)-benzo[b]-1,4-diazabicyclo[2.2.2]octene (VII), respectively. When using freshly activated copper the yield of VI reached 80%, but for VII it did not exceed 37%. When preparing VI, two further products (I and II, overall yield 1-3%) are seen, but not in VII.

Attempts to carry out the cyclization of VI and VII in the presence of lead or iron oxalate gives for VII extensive tarring of the reaction mixture and for VI only 3-7% of isomer II and 1-2% of isomer III. These results are probably associated with the severe conditions used.

## EXPERIMENTAL

IR spectra were recorded on a Specord M-80 instrument for KBr tablets, UV spectra on a Specord M-40 using ethanol solvent, and PMR spectra on a Bruker WP-200 (200 MHz) instrument using HMDS internal standard. Mass spectra were taken on an MS-8200 (Finnigan MAT). Thin-layer chromatography was performed on Armsorb TSK UV 254 plates in the system chloroform—ethanol (20:1). Preparative HPLC was carried out on a Laboratoni Pristroj Praha chromatograph on Silosorb-600 5-micron sorbent with chloroform eluent.

All of the compounds obtained gave correct elemental analytical data. The remaining parameters are given in Table 1. 4',5'-Diiodo- and 4'-iodobenzo[b]-1,4-diazabicyclo[2.2.2]octene was obtained by the method in [5] and 3'-iodobenzo[b]-1,4-diazabicyclo[2.2.2]octene by the method in [9].

**Phenazino[2',3'-b]-1,4-diazabicyclo[2.2.2]octene (II, $C_{16}H_{14}N_4$) and Phenazino[1',2'-b]-1,4-diazabicyclo[2.2.2]octene (III, $C_{16}H_{14}N_4$).** A mixture of 4',5'-diiodobenzo[b]-1,4-diazabicyclo[2.2.2]octene (0.2 g, 0.5 mmole), o-phenylenediamine (0.07 g, 0.52 mmole), Cu (0.06 g, 1.0 mmole), CuI (0.08 g, 0.5 mmole), and $K_2CO_3$ (0.14 g, 1 mmole) were suspended in nitrobenzene (10 ml) and refluxed for 2 h. The mixture was filtered and the nitrobenzene evaporated in vacuo. The residue was refluxed with ether (30 ml). The ether was evaporated and the residue chromatographed on a 1.5 × 50 cm column. Compounds II and III were found in the fractions giving TLC spots with $R_f$ 0.30 and 0.46 respectively. The yield of II was 0.05 g (24%) and of III 0.01 g (7%). PMR spectra (200 MHz in $CDCl_3$): for compound II, 8.15-8.26 (2H, m, 5',8' arom.), 7.95 (2H, s, 1',4' arom.), 7.71-7.82 (2H, m, 6',7' arom.), 2.88-3.44 ppm (8H, sym m, —$CH_2$—); for compound III, 8.53-8.48 (1H, m, 8' arom.), 8.20-8.25 (1H, m, 5' arom.), 8.17 (1H, d, 3' arom.), 7.80-7.85 (2H, m, 6',7' arom.), 7.75 (1H, d, 4' arom.), 3.30-3.52 (4H, m, —$CH_2$—), 2.38-3.12 ppm (4H, m, —$CH_2$—).

**4'-(o-Nitroanilino)-benzo[b]-1,4-diazabicyclo[2.2.2]octene (VI, $C_{16}H_{16}N_4O_2$).** Obtained similarly to II and III from 4'-iodobenzo[b]-1,4-diazabicyclo[2.2.2]octene (0.29 g, 0.05 mmole) and o-nitroaniline (0.15 g, 0.52 mmole). The product was filtered, the nitrobenzene evaporated in vacuo, and the residue refluxed with decane (15 ml). The hot solution was filtered and cooled to give orange cubic crystals of VI (0.12 g, 80%). PMR spectrum (90 MHz in acetone-$D_6$): 9.44 (1H, s, 3′ arom.), 8.16 (1H, d, 3″ arom.), 7.49 (1H, t, 5″ arom.), 7.14-7.28 (3H, m, arom.), 6.85 (1H, t, 4″ arom.), 2.63-3.18 ppm (8H, sym m, $—CH_2—$).

**3′-(o-Nitroanilino)-benzo[b]-1,4-diazabicyclo[2.2.2]octene (VII, $C_{16}H_{16}N_4O_2$).** Obtained similarly to II and III from 3′-iodobenzo[b]-1,4-diazabicyclo[2.2.2]octene (0.29 g, 0.5 mmole) and o-nitroaniline (0.15 g, 0.52 mmole). The product was filtered, the nitrobenzene evaporated in vacuo, and the residue refluxed with ether (50 ml). The solution was filtered, the ether evaporated, and the residue chromatographed on a 1.5 × 50 cm column isolating the orange fraction with $R_f$ 0.21. Recrystallization from decane gave orange cubic crystals of VII (0.05 g, 37%). PMR spectrum (90 MHz in acetone-$D_6$): 7.80 (1H, d, 3″ arom.), 7.48 (1H, t, 5″ arom.), 7.07-7.15 (2H, m, arom.), 6.80-6.91 (3H, m, arom.), 2.95-3.06 (2H, m, $—CH_2—$), 2.41-2.71 ppm (6H, m, $—CH_2—$).

## REFERENCES

1. S. O. Doronina, A. A. Gall', and G. V. Shishkin, *Khim. Geterotsikl. Soedin.*, No. 8, 1091 (1992).
2. V. F. Zarytova, I. V. Kutyavin, M. A. Podyminogin, V. N. Sil'nikov, and G. V. Shishkin, *Bioorg. Khim.*, **13**, 1212 (1987).
3. N. P. Luk'yanchuk, V. N. Sil'nikov, and G. V. Shishkin, *Khim. Geterotsikl. Soedin.*, No. 8, 1106 (1989).
4. N. S. Vul'fson, *Preparative Organic Chemistry,* Goskhimizdat, Moscow (1959), p. 739.
5. A. A. Gall' and G. V. Shishkin, *Khim. Geterotsikl. Soedin.*, No. 9, 1239 (1986).
6. B. M. Mikhailov and A. N. Blokhina, *Izv. Akad. Nauk SSSR, Ser. Khim.*, No. 3, 304 (1950).
7. H. C. Waterman and D. L. Vivian, *J. Org. Chem.*, **14**, 289 (1949).
8. D. L. Vivian, G. Y. Greenberg, and J. L. Hartwell, *J. Org. Chem.*, **16**, 1 (1951).
9. A. A. Gall', A. S. Trachum, V. A. Romantsev, and G. V. Shishkin, *Khim. Geterotsikl. Soedin.*, No. 6, 798 (1991).