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An unexpected course of the Meisenheimer reaction : aryl phosphates in the reaction of phosphoryl chloride with 2,3-diphenylquinoxaline-N_1-oxide.

J. Nasielski*, S. Heilporn, R. Nasielski-Hinkens and F. Geerts-Evrard
Université Libre de Bruxelles, Laboratoire de Chimie Organique,
Av. F.D. Roosevelt 50, B-1050 Bruxelles, Belgium.

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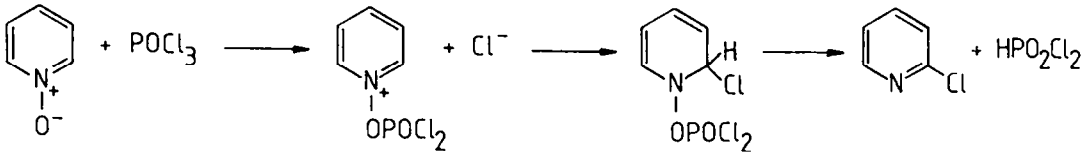
Summary. Contrary to what is observed with other π-deficient heteroaromatic N-oxides, the reaction of 2,3-diphenylquinoxaline-N_1-oxide with $OPCl_3$ gives only very poor yields of chlorinated quinoxalines. It is shown that the major product arises from an unprecedented attack by the nucleophilic oxygen atom of the reagent at a carbon atom of the homocycle of the O-phosphorylated N-oxide, leading ultimately to the corresponding mono- (or di-) aryl ester of phosphoric acid. Using a much smaller excess of $OPCl_3$ and dilution of the medium with an inert solvent strongly increase the yield of chlorination products.

It is suggested that, after the initial O-phosphorylation, phosphate formation might be the primary step in all the Meisenheimer reactions.

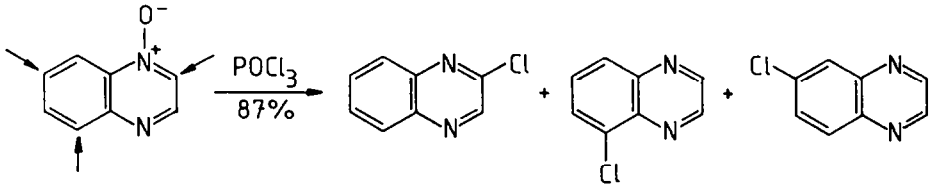
When pyridine-N-oxide I, or one of its derivatives, is heated with phosphoryl chloride, it gives the corresponding deoxygenated α- or γ-chloropyridine IV ; this transformation is referred to as the Meisenheimer reaction. The accepted sequence of events starts with the phosphorylation of the oxygen atom, leading to an N-substituted pyridinium ion II ; the chloride ion thus released attacks then α- or γ- with respect to the positively charged nitrogen atom and the



I II III IV

resulting σ complex III loses HPO_2Cl_2 in a concerted fashion[1], ultimately leading to the chloropyridine IV. Other acid chlorides, such as thionyl chloride, sulfuryl chloride, acetyl chloride or paratoluenesulfonyl chloride have been found suitable for this reaction[2], and also alcoholic HCl.

The regioselectivity of this transformation is very high, the chlorine atom being always found at a position ortho or para with respect to the nitrogen atom which was oxidized or, in the case of polycyclic aromatic systems, in a quasi para position[3], as illustrated by the behavior of quinoxaline-N_1-oxide V, where the chlorine atom has entered the ortho 2-position, or the quasi-para 7-position [1]. An intriguing observation is however the conspicuous absence of 5-chloro-quinoxaline VII, although it would correspond to attack on a position analogous

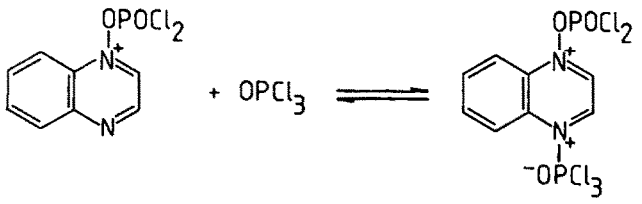


90 0 10

V VI VII VIII

to a naphthalene-type α position, which is well known to be more reactive than a β position such as 6- *[4,5]. This finding has led us to look for the reasons of this unexplained inertness of the 5-position.

A hypothesis was presented before[1], based on the fact that the Meisenheimer reaction is run in $OPCl_3$, which is both the solvent and the reagent, i.e. a very electrophilic medium. With a large excess of $OPCl_3$, such as generally used, one might expect a strong complexation of the free N_4 nitrogen atom. The presence of



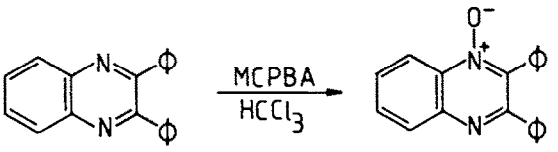
IX X

a very bulky group on N_4 would inhibit the attack of Cl^- at the hindered peri 5-position, thus diverting the reaction to the 6- (or 7-) carbon. We thus set out to try the same transformation on a quinoxaline-N-oxide which would be sufficiently hindered in order to inhibit the complexation of N_4 ; we selected 2,3-diphenylquinoxaline.

The Meisenheimer reaction of 2,3-diphenylquinoxaline-N_1-oxide has already been examined by Cheeseman in 1966[6] and was reported to give a yield of only 9% of 6-chloro-2,3-diphenylquinoxaline along with 6% of deoxygenation and large amounts of an untractable material.

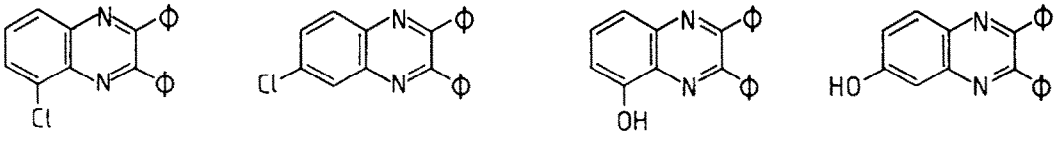
2,3-Diphenylquinoxaline-N_1-oxide and $OPCl_3$.

2,3-Diphenylquinoxaline-N_1-oxide XII was made by oxidizing 2,3-diphenylquinoxaline XI[7] with metachloroperbenzoic acid in chloroform with a 54% yield besides 40% of recovered starting material.



XI XII

For the purpose of identification, authentic samples of 5-chloro- (XIII)[6], 6-chloro- (XIV)[8], 5-hydroxy- (XV)[9] and 6-hydroxy-2,3-diphenylquinoxaline (XVI)[10] were synthesised by analogy with known procedures.

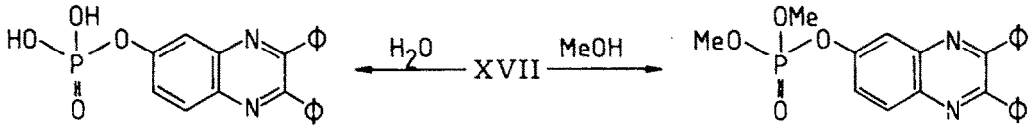


XIII XIV XV XVI

*Because of the symmetry of the quinoxaline skeleton, positions 2- and 3- are equivalent, as are positions 6- and 7-. A substituent entering position 7 of the N-oxide will thus be found at the 6 position of the deoxygenated quinoxaline.

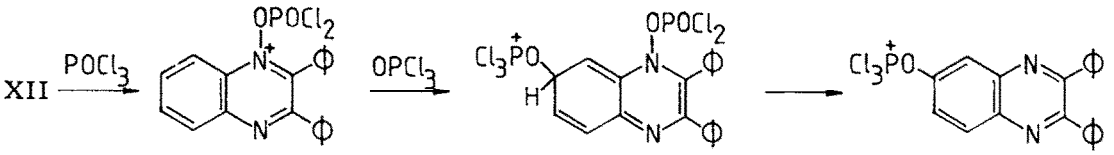
We first repeated Cheeseman's experiment and confirmed that with a tenfold excess of $OPCl_3$, only 11% of chlorodiphenylquinoxaline were formed after hydrolysis and isolation, together with large amounts of a pale-yellow sticky gum which proved impossible to purify neither by crystallisation nor by chromatography ; prolonged heating of this material in methanol gave small amounts of a readily purified compound which was identified, by comparison with an authentic sample, as 6-hydroxy-2,3-diphenylquinoxaline XVI. We diverge, however, from Cheeseman's results by finding that our chlorinated quinoxaline is actually a 1:4 mixture of 5- and 6-chloro-2,3-diphenylquinoxaline, XIII and XIV respectively, as shown by HPLC. The observation of a definite, though small amount of the 5-chloro compound was considered encouraging enough to engage in a deeper analysis of the system.

On the assumption that the unknown major compound was an O-phosphorylated derivative of XVI, the latter was reacted with $OPCl_3$, the excess reagent removed and the residue was hydrolysed, giving a material which was similar to the unknown, including the IR spectrum. The possibility was thus considered that this compound is the mono-aryl ester of orthophosphoric acid XVIII originating from the hydrolysis of a still unspecified intermediate XVII and, in order to get a more easily purified product, the work-up of the reaction was performed with cold methanol rather than with water. This led to the isolation of the mixed ester XIX with a high yield, the overall material balance reaching now 70% or even more.



XVIII XIX

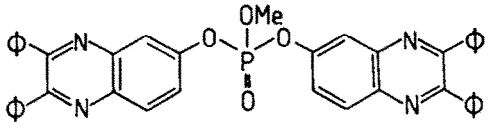
The origin and the structure of the postulated intermediate XVII may be visualised by assuming a nucleophilic attack by the oxygen atom of $OPCl_3$ at the quasi-para 7-position of the O-phosphorylated N_1-oxide XX followed by the



XX XVII

elimination of HPO_2Cl_2 ; hydrolysis or methanolysis of XVII then leads to the monoaryl ester XVIII or to the mixed ester XIX, respectively.

One other new compound was isolated from the medium ; its ^1H NMR spectrum is fully in agreement with that expected for the diaryl-monomethyl ester of phosphoric acid XIX'.



XIX'

It seems thus that the formation of the aryl phosphate or its derivatives requires an additional molecule of $OPCl_3$, competing with the attack by a chloride ion on the already phosphorylated N-oxide XX. A more dilute medium, the use of a smaller excess of $OPCl_3$, or the addition of an external source of chloride ions should then result in less phosphate formation and more chlorination. These hypotheses have been tested, and the results are summarized in Table 1.

The influence of dilution is illustrated by runs 2 and 3 as compared with 1 ; the addition of the inert solvent brings the concentration of $OPCl_3$ from neat down to 1.5 M, resulting in more than a doubling of the amount of chlorinated products (12 to 27%) and a corresponding drop in C-oxygenated compounds (81 to 68%). Experiments 4, 5 and 6 illustrate the second point : once the excess of $OPCl_3$ is fourfold or less, chlorinations are increased still further, and the amount of 5-chloroquinoxaline now reaches over 13% (run 6) while the oxygenated compounds account only for 40%, as compared with the original 81%. The presence of tetrabutylammonium chloride, which is soluble in this medium results in a dramatic increase in 6-chlorination, leaving the 5-chlorination essentially unaffected.

Expt n°	Conditions	Time (h)	5-Cl XIII	6-Cl XIV	6-ph XIX	diarph XIX'	6-OH XVI	deox XI	ΣCl	Σph+OH	yield
1	10 $OPCl_3$	0.5	2.2	9.9	68.0	11.8	1.0	7.2	12.1	80.8	85
2	10 $OPCl_3$ (a) + toluene	2.0	5.1	21.5	64.0	3.1	1.7	4.6	26.6	68.8	100
3	10 $OPCl_3$ (a) + benzene	17.0	5.5	22.0	48.0	14.4	4.6	5.4	27.5	67.0	73
4	4 $OPCl_3$ (a) + toluene	2.0	9.4	40.5	22.3	17.4	2.9	7.5	49.9	42.6	68
5	2 $OPCl_3$ + toluene	2.0	11.6	43.2	21.2	14.0	2.5	7.5	54.8	37.7	70
6	1 $OPCl_3$ + toluene	4.0	13.6	40.4	28.5	6.3	3.1	8.1	54.0	37.9	75
7	10 $OPCl_3$ (b) + toluene + $5Bu_4NCl$	6.0	2.7	60.1	11.7	12.4	6.8	9.5	62.8	30.9	95
8	10 $OPCl_3$ (a) + toluene	48.0	4.5	32.7	42.5	11.5	3.8	4.9	37.2	57.8	64

Table 1. Influence of experimental conditions on the product distribution in the Meisenheimer reaction. The conditions are: 50 mg of N-oxide XII, the number of mole-equivalents of $OPCl_3$ shown, and + toluene (or benzene) means that 1.5 ml of inert solvent has been added ; the mixture is then heated under reflux. The time (in hours) is that really required to witness the complete disappearance of the starting material, except in run 8. The amounts are given in percentage of total products ; the actual yields have to take into account the figures in the last column. When a reaction was run more than once in a given set of condition, it was found that the relative amounts of XIX, XXI and XVI showed a large scatter, but the sum was fairly constant, suggesting that their distribution strongly depends on the exact conditions of work-up. (a): average of two independent experiments. (b): average of four independent experiments.

Discussion

The dilution experiments strongly suggest that the chlorinations are intramolecular whereas the formation of phosphates is intermolecular. It is, however, difficult to give a satisfactory picture for the intramolecular attack by a chloride species: i) a direct transfer within the O-phosphorylated N-oxide XX, even having an additional chlorine atom attached to phosphorus, is unbelievable in view of the excessive strains which would be involved, ii) a transfer occurring in a more complex structure containing an additional molecule of $OPCl_3$ is ruled out by the observation that decreasing the amount of $OPCl_3$ increases chlorination. The least improbable picture would thus be that of a tight ion pair made during the formation of XX, which would collapse to a σ complex similar to III, or dissociate ; once dissociated, the most probable fate of XX is then the attack by $OPCl_3$.

The involvement of an ion-pair is further strengthened by noticing that dilution with a solvent of low dielectric constant (toluene, $\varepsilon = 2$) inhibits the dissociation to ions, as compared with neat $OPCl_3$ ($\varepsilon = 13$) and, in addition to the concentration effect, contributes to increase the amount of intramolecular chlorinations.

This hypothesis also throws some light on the 5- to 6- ratio of chlorination products ; it may indeed be assumed that the very first intermediate formed in the reaction is the O-phosphorylated compound XXI, still containing its original three chlorine atoms, which then ionizes to the ion pair XXII. The attachment of Cl^- to the 7-position of the O-phosphorylated diphenylquinoxaline-N_1-oxide involves less geometrical rearrangement since this carbon atom is closer to the reacting $OPOCl_3$ moiety than carbon atom 5. Application of the principle of least motion thus leads to predict that the 6-chloroquinoxaline should be more abundant than the 5-isomer, resulting in the observed 4:1 ratio. This effect cooperates with the aforementioned steric inhibition due to the coordination of N_4 with $OPCl_3$, although steric effects are usually less efficient in intramolecular processes than in intermolecular reactions ; some coordination is to be assumed, considering the regiospecificity of phosphate formation (see below).

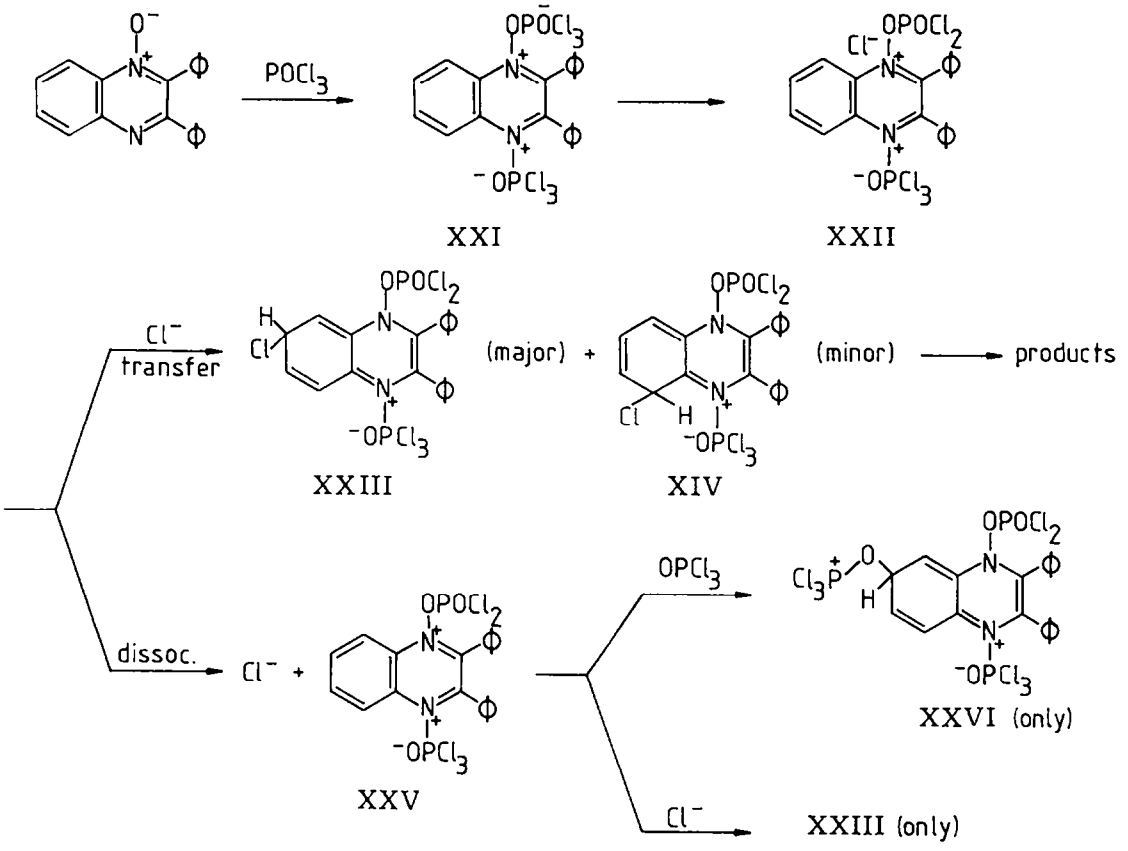
Experiments 4 to 6 prove that phosphate formation is due to $OPCl_3$ and not to some partially hydrolysed form, since any contribution of HPO_2Cl_2 should be more important when there is less $OPCl_3$ whereas the contrary is observed.

The favorable influence of tetrabutylammonium chloride is very selective: only 6-chlorination is considerably increased (experiment 7). We interpret this as evidence for an exclusively intramolecular origin of the 5-chloroquinoxaline, while chlorination in position 7 can originate both from an intramolecular process and from the intermolecular attack of Cl^-, either directly on one of the doubly phosphorylated ions XXI, XXII or XXV, or on the activated phosphoric ester derivative XVII. The fact that intermolecular addition of Cl^- avoids the 5-position suggest that the two phenyl groups are not sufficient to completely inhibit complexation at N-4.

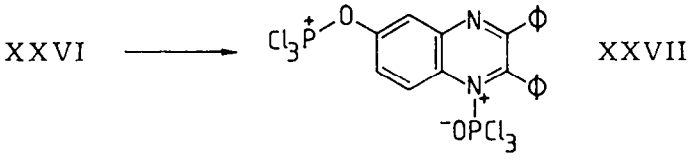
It is also interesting to notice that, as mentioned before, the presence of the phenyl groups in the 2- and 3-positions appreciably enhances chlorination in 5- compared to the unsubstituted system, lending thus support to the hypothesis [1] that the absence of 5-chlorination in the latter case is due to the full attachment of $OPCl_3$ to the N_4 nitrogen atom, resulting thus in a strong inhibition at the 5-position due to the steric hindrance associated with the bulky $OPCl_3$ group. It is thus seen that the presence of a bulky group in the 3-position may have an influence on the remote carbocycle through indirect steric effects ; the obvious extrapolation to 2,3-di-t-butylquinoxaline-N_1-oxide is,

however, hampered by the tedious synthesis[11] of this interesting compound. Also noteworthy in this connection is the absence of C-5 phosphate, strengthening thus the idea that 5-chlorination occurs mainly through an intramolecular pathway.

Our results thus suggest the following overall scheme for the Meisenheimer reaction on 2,3-diphenylquinoxaline-N_1-oxide :



Ion XXVI is the only regio-isomer formed because of the presence of the hindering group on N_4. It will eventually lose the elements of HPO_2Cl_2, giving XXVII which will remain as such until work-up or, in the presence of Cl^-, slowly evolve to 6-chloro-2,3-diphenylquinoxaline.



We now wish to discuss what we consider as the most intriguing of our findings. The yields of Meisenheimer reactions are usually fair to high and, to the best of our knowledge, there is no previous report on mono-aryl ester of phosphoric acid formation in the standard conditions ; one may thus wonder whether phosphoric ester formation is restricted to 2,3-diphenylquinoxaline-N_1-oxide. We discard this idea on the basis that there is no compelling reason why it should be so, and we rather look for another explanation. We start by observing that Meisenheimer reactions are always performed on heterocyclic N-oxides which have at least one α- or γ-position available for substitution in the heterocycle and, should there be any prior phosphate formation leading to an

intermediate such as XVII, this would undergo a facile substitution of phosphoryl by chloride at the very position which is activated by the electron-attracting heteroatom ; no phosphorylation product at these positions will be expected on isolation. When there is a possibility of reaction in an adjacent homocycle, the competition will always favor the heterocycle, which means that the amount of phosphate formation similar to the one observed here will result in small amounts of material which may well be lost because of its solubility in water. The present system combines the impossibility of heterocycle reaction with the hydrophobicity of the two additional phenyl groups ; these two characteristics cooperate to yield a large quantity on an insoluble compound which was thus easy to observe. Our previous results with 6-nitroquinoxaline-N_1-oxide lead to a similar conclusion: it was found that this N-oxide gave an unexpectedly high proportion (over 93%) of halogenation in the homocycle when treated with $OPCl_3$ [1] but, interestingly, the positions quasi-para to the N-oxide group are just those positions which are activated by the nitro group and, should any attack by $OPCl_3$ occur there, it would also rapidly result in chlorination by intermolecular substitution. An attractive overall picture thus emerges for the mechanism of the Meisenheimer reaction:after attachment of $OPCl_3$ to the N-oxide oxygen atom, there is a competition between an intramolecular chlorine transfer and an intermolecular phosphorylation; when phosphorylation occurs at an activated position, it ultimately gives way to chlorination products, and in the other cases, the phosphorylation product will be isolable. This last point is illustrated by experiment 8 which is identical with experiment 2, except that the reaction medium was refluxed for 48 hours instead of 2 with the hope that the phosphorylated intermediate would be transformed into the corresponding chloride; the data clearly show the sluggishness of this potential substitution reaction: the increase in chlorination is small, but the overall yield drops to 64%.

A last point, which has not yet been elucidated, is that of small and variable amounts (5 to 10%) of the deoxygenation product XI. Our results show that it is unrelated to the presence of the inert solvent.

Experimental

^1H NMR spectra were recorded on a Brüker VM 250 instrument at 250 MHz with internal TMS. Mass spectra were obtained with a VG Micromass 7070F spectrometer. HPLC analyses were performed with a Waters Associates apparatus, using a UV detector. Melting points, measured on a Reichert hot stage microscope, are uncorrected.

2,3-Diphenylquinoxaline-N_1-oxide XII.

3.0 g (10,6 mmol) of 2,3-diphenylquinoxaline [7] and 2.0 g (11,6 mmol) of freshly purified metachloroperbenzoic acid are dissolved in 100 mL of chloroform and kept at 50°C during 18 h. After being extracted three times with saturated aqueous sodium hydrogen carbonate and dried over magnesium sulphate, the organic phase was evaporated to dryness under reduced pressure. The crude solid (3.15 g) was chromatographed through alumina with toluene and gave successively 1.2 g (4.2 mmol) of starting material, 1.7 g (5.7 mmol, 54 %) of 2,3-diphenylquinoxaline-N_1-oxide and 19 mg (0.06 mmol) of 2,3-diphenylquinoxaline-N_1,N_4-dioxide. Recrystallisation of the mono-oxide from ethanol afforded white needles, MP 205-207°C, lit [12] : 196°C. MS: $M^{\cdot +}$ at m/z = 298. ^1H NMR ($CDCl_3$) : δ = 8.65 (ddd, H_8), 8.20 (ddd, H_5), 7.84 (ddd, H_7), 7.76 (ddd, H_6) and 7.41-7.22 (m, 10H, 2x C_6H_5) ppm, with $J_{5,6}$ = 8.8, $J_{5,7}$ = 1.3, $J_{5,8}$ = 0.7, $J_{6,7}$ = 6.9, $J_{6,8}$ = 1.4 and $J_{7,8}$ = 8.5 Hz.

5-Chloro-2,3-diphenylquinoxaline, XIII

This was prepared following Cheeseman's procedure[6] with a 93% yield. MP: 158-160°C, lit.[6]: 158-159°C. MS: $M^{\cdot+}$ at m/z = 316-318. ^1H NMR ($CDCl_3$) ; the three proton system of the quinoxaline homocycle was analysed as an ABX system : δ = 8.09 (dd, H_8), 7.86 (dd, H_6) and 7.67 ppm (dd, H_7) with $J_{6,7}$ = 7.6, $J_{6,8}$ = 1.3 and $J_{7,8}$ = 8.5 Hz ; also 7.25-7.63 ppm (10H, m, 2x C_6H_5).

6-Chloro-2,3-diphenylquinoxaline, XIV

Was made following C.V. Deliwala, S. Rajagopalan method[8] ; yield 78%. MP: 122-123°C, lit.[7]: 123-125°C. MS: $M^{\cdot+}$ at m/z = 316-318. ^1H NMR ($CDCl_3$) ; the three proton system of the quinoxaline homocycle can be analysed as an AMX system: δ = 8.17 (d, H_5), 8.10 (d, H_8) and 7.70 ppm (dd, H_7), with $J_{5,7}$ = 2.3 and $J_{7,8}$ = 8.8 Hz ; also 7.35-7.50 ppm (10H, m, 2x C_6H_5).

7-Amino-5 methoxy-2,3-diphenylquinoxaline

2 g (9.4 mmol) of 2-methoxy-4,6-dinitroaniline[13] in 120 mL of ethanol-dioxane (1:1) were hydrogenated in the presence of 10% Pd/C at room temperature and under 1 atm. After the absorption of the calculated amount of hydrogen (1.4 L), the suspension was rapidly filtered through Celite directly into a solution of benzil (1.98 g, 9.4 mmol) in 20 mL ethanol. The mixture was kept at 50°C for 30 min and concentrated to dryness under reduced pressure. The resulting brown solid was dissolved in chloroform, adsorbed on cellulose and chromatographed through alumina with chloroform. Recrystallisation from aqueous methanol gave 2.03 g (6.2 mmol, 66%) of white needles ; MP: 251-253°C. MS: m/z = 327 ($M^{\cdot+}$), 311 ($M-NH_2$).

5-Hydroxy-2,3-diphenylquinoxaline, XV

7-Amino-5-methoxy-2,3-diphenylquinoxaline (1.8 g, 5.5 mmol) was introduced in 35 mL of 10M H_2SO_4 containing 0.1 mL of phosphinic acid and a piece of copper turning ; the mixture was kept below 0°C, while a solution of 22 mg of $NaNO_2$ in 0.11 mL water was added dropwise. The mixture was kept at 0°C for 7 h, and at 4°C for one night, diluted with water, neutralised and extracted with chloroform. The organic phase was dried over magnesium sulphate, evaporated to dryness and the residue was eluted through alumina with chloroform ; recrystallisation from ethanol afforded 725 mg (2.3 mmol, 42%) of 5-methoxy-2,3-diphenylquinoxaline, MP: 194-196°C, lit.[8]: 190°C. MS: m/z = 312 ($M^{\cdot+}$).

This was demethylated with constant-boiling HBr according to Lane and Williams[9]. Recrystallisation from ethanol gave 484 mg (1.6 mmol, 84%) of orange needles of 5-hydroxy-2,3-diphenylquinoxaline. MP: 134-137°C ; lit.[8]: 133-134°C. MS: m/z = 298 ($M^{\cdot+}$) ^1H NMR ($CDCl_3$): the three protons of the quinoxaline homocycle were analysed as an ABX three-spin system ; δ = 7.70 (dd, H_8), 7.68 (dd, H_7) and 7.22 ppm (dd, H_6) with $J_{6,7}$ = 7.8, $J_{6,8}$ = 1.2 and $J_{7,8}$ = 8.6 Hz ; also 7.53-7.33 ppm (m, 10H, 2x C_6H_5).

6-Hydroxy-2,3-diphenylquinoxaline, XVI

4-Amino-3-nitrophenol[10] (405 mg, 2.6 mmol) was hydrogenated in 20 mL ethanol in the presence of 10% Pd/C at room temperature. After 40 min, the suspension was filtered, benzil (550 mg, 2.6 mmol) was added to the filtrate and the solution refluxed for 6 h. Concentration and filtration gave 408 mg, (1,4 mmol, 53%) of green 6-hydroxy-2,3-diphenylquinoxaline which was recrystallised from ethanol-water (8:2) ; MP: 262-264°C. MS: m/z = 298 ($M^{\cdot+}$). ^1H NMR ($CDCl_3$): δ = 8.05 (d, H_8), 7.43 (d, H_5), and 7.36-7.26 ppm (m, 11H, H_7 and 2x C_6H_5), with $J_{5,7}$ = 2.7 and $J_{7,8}$ = 9.1.

[5-(2,3-diphenyl)-quinoxalyl] dimethyl phosphate.

Freshly distilled phosphoryl chloride (1 mL) containing 67 mg (0.2 mmol) of 5-hydroxy-2,3-diphenylquinoxaline was refluxed for 18 h, then cooled and poured into 50 mL of ice-cold methanol. The medium was then made alkaline with aqueous ammonia, and evaporated to dryness. The white residue was suspended in water and extracted with chloroform ; this was washed with saturated aqueous sodium hydrogen carbonate, dried over magnesium sulphate and evaporated to dryness. The crude solid, dissolved in a minimal amount of chloroform, was chromatographed through silicagel with hexane-ethyl acetate (7:3). Recrystallisation from hexane-benzene yielded 55 mg (0.1 mmol, 60 %) of white 5-(2,3-diphenyl)-quinoxalyl dimethyl phosphate. MP: 131-132°C. MS: m/z = 406 ($M^{\cdot+}$), 375 ($M^{\cdot+}-CH_3O$). ^1H NMR ($CDCl_3$): δ = 8.02 (ddd, H_8), 7.71 (ddd, H_7), 7.65 (ddd, H_6), 7.57-7.26 (m, 10H, 2x C_6H_5) and 3.96 ppm (d, 6H, 2x OCH_3) with $J_{6,7}$ = 7.8, $J_{6,8}$ = 1.2, $J_{7,8}$ = 8.5, $J_{H6,P}$ = 1.7, $J_{H8,P}$ = 1.2, $J_{H7,P}$ = 0.3 and $J_{H_3C,P}$ = 11.3 Hz, from the analysis of the ABMX four-spin system. Analysis : $C_{22}H_{19}N_2O_4P$ (MW = 406.38) requires : C: 65.0 ; H: 4.7 ; N: 6.9% Found: C:64.8 ; H: 4.7 ; N: 6.9 %.

[6-(2,3-diphenyl)-quinoxalyl] dimethyl phosphate XIX

Freshly distilled phosphorus oxychloride (10 mL) containing 300 mg (10^{-3} mmol) 2,3-diphenylquinoxaline-N_1-oxide was refluxed for 30 min ; the excess reagent was then removed under reduced pressure and the residue added to cold methanol. The medium was made alkaline with aqueous ammonia, the methanol stripped off and the residue dissolved in chloroform ; the organic layer was washed with water, extracted with three portions of saturated aqueous sodium hydrogen carbonate, dried over magnesium sulphate and evaporated to dryness. The resulting crude solid was dissolved in a minimal amount of chloroform and eluted through silicagel with hexane-ethyl acetate (7:3), affording 325 mg of the phosphate ester, and small amounts of 5- and 6-chloro-2,3-diphenylquinoxaline and the deoxygenated precursor 2,3-diphenylquinoxaline. Recrystallisation of the ester from hexane-chloroform gave 275 mg (0.68 mmol, 68%) of 6-(2,3-diphenyl)-quinoxalyl dimethyl phosphate XIX as white needles ; MP: 171-172°C. MS: m/z = 406 ($M^{\cdot+}$), 297 ($M^{\cdot+}-OP(OMe)_2$) : ^1H NMR ($CDCl_3$): δ = 8.17 (d, H_8), 7.99 (dd, H_5), 7.66 (dd, H_7), 7.5-7.3 (m, 10H, 2x C_6H_5) and 3.93 (d, 6H, 2x OCH_3) ppm, with $J_{5,7}$ = 2.5, $J_{7,8}$ = 9.2, $J_{H5,P}$ = 1.3, $J_{H7,P}$ = 0.7 and $J_{H_3C,P}$ = 11.4 Hz, from the analysis of the AMXα four-spin system. Analysis : $C_{22}H_{19}N_2O_4P$ (MW = 406.38) requires C: 65.0, H: 4.7, N: 6.9%. Found: C: 65.0 ; H: 4.7 ; N: 6.8 %.

Meisenheimer reactions

The following exemplifies the general procedure which was used: 50 mg of 2,3-diphenylquinoxaline-N_1-oxide dissolved in the amounts of $OPCl_3$ and other addends were refluxed for the time stated in Table 1. After cooling, the mixture was poured in 100 mL cold methanol, made alkaline with aqueous ammonia, and evaporated under reduced pressure. The residue was suspended in water, extracted with two portions of chloroform, the organic layer washed free of acid with water and three times with saturated aqueous sodium hydrogen carbonate, dried over magnesium sulphate, and evaporated to dryness. The components of the resulting mixture were determined by HPLC after standardisation with authentic samples ; column: RoSIL C18-HL-D (Altech RSL) 5 µ, 25 cm x 4.6 mm ID, elution with methanol-water 8:2.

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