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REACTIVITY OF 2-t-BUTYL-4,5-DIDEHYDROPYRIMIDINE AND ELECTRONIC STRUCTURE OF THE PARENT HETARYNE

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Abstract : 2-t-Butyl-4,5-didehydropyrimidine, generated by oxidation of 3-amino-5-t-butyl-3H-v-triazolo[4,5-d] pyrimidine, was allowed to react with a variety of reagents. Trapping experiments with furan and two tetracyclones gave the expected adducts in low to moderate yields. On treatment with anthracene and 1,3-cyclohexadiene, complex mixtures were obtained from which the adducts could not be isolated. Cycloaddition of phenyl azide to the intermediate yielded 3-phenyl-5-t-butyl-3H-v-triazolo[4,5-d]pyrimidine as the major product together with the unexpected 2-t-butyl-9H-pyrimido[4,5-b]indole in lesser amount. The structure of these two compounds was established by comparison with authentic specimens whose synthesis is described. Cycloaddition also occurred with 2,3,5-tri-O-benzoyl-β-D-ribofuranosyl azide to give an 8-azanucleoside in low yield. Oxidation of the precursor in ethanol gave solely 4-ethoxy-2-t-butylpyrimidine. Oxidation in the presence of iodine, in dichloromethane or benzene, afforded products arising from attack on the solvent, i.e. 4-chloro-5-iodo-2-t-butylpyrimidine and 5-iodo-4-phenyl-2-t-butylpyrimidine respectively. In addition, 5-iodo-2-t-butyl-4(3H)-pyrimidinone was obtained in both cases. Mechanisms for these reactions are proposed.
The electronic structure of 4,5-didehydropyrimidine has been calculated by an ab initio 3-21G quantum chemical method. Both the Molecular Electrostatic Potential and the Fukui function give a very reasonable account of the strong orientation effects observed in the additions to 2-t-butyl-4,5-didehydropyrimidine.

We have recently been concerned with the study of 2-t-butyl-4,5-didehydropyrimidine (2)[1], a highly reactive intermediate belonging to a group of hetarynes - the 4,5-didehydropyrimidines - whose existence was considered problematical. The purpose of the present paper is to give a complete account of the reactions in which 2-t-butyl-4,5-didehydropyrimidine (2) was involved and to discuss the results in the light of the electronic structure, computed by ab initio quantum chemical methods, of the unsubstituted intermediate.

ELECTRONIC STRUCTURE OF THE PARENT HETARYNE

Ab initio 3-21G [2] calculations on the charge distribution of 4,5-didehydropyrimidine were performed, using the geometry optimized with the same basis [3]. The Mulliken gross atomic populations [4] for the highly reactive triply bonded atoms were found equal to 5.697 electrons for C_4 and 6.010 electrons for C_5. These values show qualitative agreement with the earlier extended Hückel [5] results (3.55 and 4.44 valence electrons on C_4 and C_5 respectively) obtained by Hoffmann and co-workers [6] with an unoptimized benzene-type geometry and with our own STO-3G [7] results resting on a 3-21G geometry [1]. The $C_4^{\delta+}C_5^{\delta-}$ polarization is seen to be due

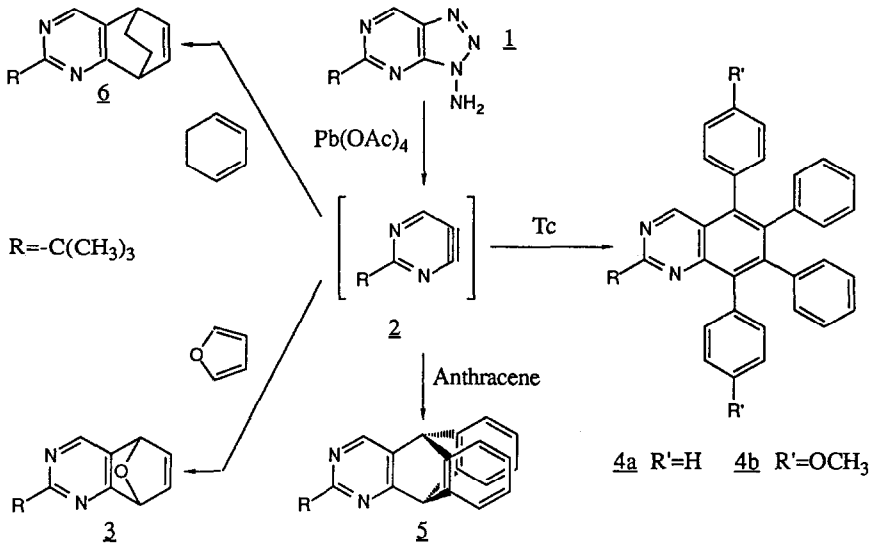
to a very important σ polarization ($q_4^\sigma = 4.672$ and $q_5^\sigma = 5.187$, q_i^σ denoting the σ-electron population at atom i), only partially (~ 40 %) compensated by the π polarization ($q_4^\pi = 1.025$ and $q_5^\pi = 0.822$) [8]. This σ polarization shows up in the HOMO which is essentially built up from three σ atomic orbitals on N_3, C_4 and C_5. It can trace its origin back to a σ conjugation phenomenon (ynamine-like delocalization of the nitrogen lone pair into the unusual σ component of the C_4C_5 triple bond - see scheme 3) which was invoked in Radom's paper [3] in order to explain the relatively short N_3C_4 bond (1.255 Å) and the large $N_3C_4C_5$ angle (146°).

REACTIVITY OF 2-t-BUTYL-4,5-DIDEHYDROPYRIMIDINE (2)

This hetaryne was easily generated from 3-amino-5-t-butyl-3H-v-triazolo[4,5-d]pyrimidine (1), which was chosen as a potential precursor for a variety of reasons [10]. Oxidation in dichloromethane solution with lead tetra-acetate, at room temperature, was instantaneous. These mild conditions offered the possibility of examining the behavior of the intermediate 2 toward some representative reagents as had been done with benzyne [11]. In none of the reactions described below was a 4,5-didehydropyrimidine dimer, i.e. a tetra-azabiphenylene, detected. This is in contrast to the known tendency of benzyne produced from 1-aminobenzotriazole to dimerise [12] but in accord with the behavior of didehydro-pyridines and -quinolines [13], generated by the method of Campbell and Rees [12].

Reactions with 1,3-dienes (Scheme 1)

The existence of 2-t-butyl-4,5-didehydropyrimidine (2) was first indicated by trapping with furan [14]. When the oxidation was performed in the presence of a large excess of furan, the yield of the cycloadduct 3 was fairly good (nearly 50 %). It was reduced to 9 % when a threefold molar excess was used as in the experiments carried out with three other dienes under similar conditions. 2,3,4,5-Tetraphenylcyclopentadienone (tetracyclone, Tc) gave 5,6,7,8-tetraphenyl-2-t-butylquinazoline (4a) in 24 % yield. The related 2,5-di-(p-methoxyphenyl)-3,4-diphenyl-cyclopentadienone was found to be somewhat less effective (16 % of 4b). The



SCHEME 1

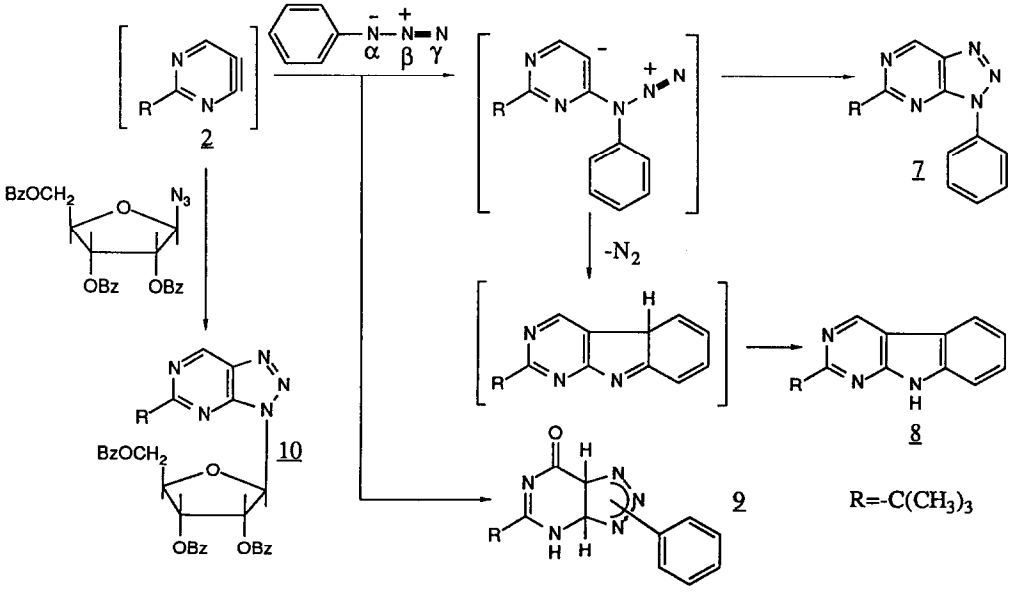
reaction with anthracene was disappointing. A complex mixture was obtained in which, after preparative layer chromatography, trace amounts of the 1,3-diazatriptycene 5 could be detected by mass spectrometry ($M^{+\cdot}$ at m/z 312). Finally, 1,3-cyclo-hexadiene, used in excess, gave a mixture of derivatives from which 2-t-butyl-5,8-dihydro-5,8-ethanoquinazoline (6) could not be isolated. Its presence was inferred from a mass spectrum which showed, in addition to the parent peak at m/z 214 (70 %), important fragmentation peaks at m/z 199 (52 %, loss of a methyl group), 186 (43 %, loss of ethylene), and 171 (base peak, $[186\text{-}CH_3]^+$).

Apparently the yields reported here (tetracyclone > disubstituted tetracyclone > furan > anthracene) parallel those obtained for the reactions of benzyne, generated in the same way [11]. However, they are much lower. This could be due (a) to the lower stability of the hetaryne 2 in which a nitrogen lone pair is adjacent to the triple bond [6] and (b) to the highly polarized nature of this bond which decreases orbital control [13,15]. On the other hand, compared with the analogous reactions of 2,3-didehydro-pyridine and -quinoline [16], the trapping experiment of the intermediate 2 with tetracyclone is more satisfactory (24 % yield instead of 4 % and 2 % respectively).

Reactions with two 1,3-dipoles (scheme 2)

1,3-Dipolar cycloadditions involving hetarynes have received only a minimum of attention. Four 1,3-dipolar species were allowed to react with 3,4-didehydropyridine [17]. The adducts were obtained in low yield in one case, in moderate yield in another.

Oxidation of the precursor 1 in the presence of a large excess of phenyl azide gave three compounds which were separated by preparative layer chromatography. The first was 3-phenyl-5-t-butyl-3H-v-triazolo[4,5-d] pyrimidine (7) (43 % yield) whose structure was established by comparison with an authentic sample. The l-phenyl isomer was not found. The second compound (19 % yield) was obtained as an unexpected by-product. It was shown to be 2-t-butyl-9H-pyrimido[4,5-b]indole (8) by an independent procedure. The third compound was isolated in minute amounts. Its high-resolution mass spectrum gave the molecular ion at m/z 271.1429 ($C_{14}H_{17}N_5O$ requires 271.1433) and showed sequentially loss of a C_4H_9 group, N_2 and CO. From examination of the IR and ^1H NMR spectra (see experimental section), it was not possible to completely identify the structure. The formula 9 as indicated in the scheme is considered strictly tentative. By contrast, addition of phenyl azide to benzyne, generated oxidatively, gave only 1-phenylbenzotriazole in 45 % yield [11].



SCHEME 2

The authentic sample of 3-phenyl-5-t-butyl-3H-v-triazolo[4,5-d]pyrimidine (7) was prepared from 4-chloro-5-nitro-2-t-butylpyrimidine [10]. Treatment with aniline yielded 4-anilino-5-nitro-2-t-butylpyrimidine. Catalytic reduction of the latter afforded 5-amino-4-anilino-2-t-butylpyrimidine which was converted without purification into the triazolo-pyrimidine 7 by reaction with nitrous acid. At this stage, papers by Boyer, Higashino and co-workers [18,19] suggested a photochemical route to the pyrimido-indole 8 which proved to be satisfactory. Irradiation of compound 7 in methanol with UV light produced 2-t-butyl-9H-pyrimido[4,5-b]indole (8) in 39 % yield.

Interestingly, some experimental results seem to indicate that the pyrimido-indole 8 did not derive from compound 7 after the cycloaddition was complete. The same yields were indeed obtained in the absence of light, and neither acetic acid or lead di- and tetra-acetate caused the conversion of the triazolo-pyrimidine 7 into 8.

The sequence shown in scheme 2 is proposed to explain the reaction products 7 and 8. Since the triple bond is very polarized, 2-t-butyl-4,5-didehydropyrimidine (2) would be more susceptible to ionic addition than to concerted cycloaddition [13,15]. More precisely, taking into account that 3-21G calculations on phenyl azide (using a standard geometry [20], except for the two N N distances [21]) led to electronic populations of N_α, N_β and N_γ of 7.418, 6.966 and 6.948 respectively (in qualitative agreement with our earlier STO-3G calculations [1]), we think that the predominant interaction between the hetaryne 2 and the reactant would be C_4-N_α. This could produce a doubly charged species which could collapse either by ring closure to form compound 7 or by elimination of nitrogen. In the latter case, simultaneous or stepwise attack on the phenyl group, followed by a proton shift, could then lead to the pyrimido-indole 8.

We next examined the feasibility of using the hetaryne 2 for the synthesis of an 8-azanucleoside. Garcia-Munoz and co-workers [22] reported earlier that benzyne, generated by aprotic diazotization of anthranilic acid, reacts more or less successfully with glucopyranosyl- and galactopyranosyl azides to give 1-glycosyl-benzotriazoles. When 3-amino-5-t-butyl-3H-v-triazolo[4,5-d]pyrimidine (1) was oxidized in the presence of three equivalents of 2,3,5-tri-O-benzoyl-β-D-ribofuranosyl azide, the adduct 10 was obtained, albeit in low yield. Its structure was supported by mass and ^{1}H NMR data, the point of attachment of the glycosyl portion being presumably the 3-position by analogy to the results described above. The proton absorptions for the carbohydrate moiety were all shifted downfield, compared with the proton absorptions for the starting azide (from 5.67 to 6.94, 5.58 to 6.60, 5.83 to 6.50 ppm for $H_{1'}$, $H_{2'}$, $H_{3'}$ respectively, to a lesser extent for $H_{4'}$ and $H_{5'}$).On the other hand, the nucleoside 10 was assigned the β configuration since it should possess the same stereochemistry as the azido sugar.

Reaction with a nucleophile (scheme 3)

From earlier semi-empirical theoretical works [6,9] as well as from our own ab initio results concerning the polarity of the C_4C_5 triple bond, it was concluded that 4,5-didehydropyrimidine should undergo preferential nucleophilic attack at the 4- rather than the 5-position. Up to now, there was no clear-cut experimental evidence on this point [23].

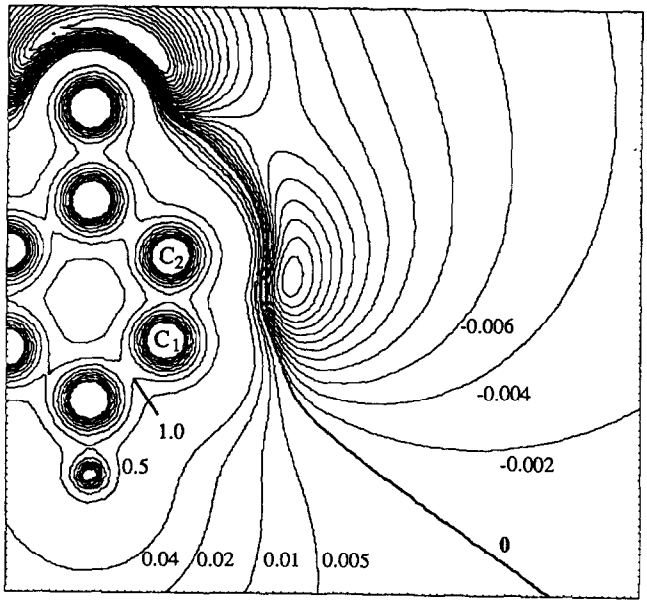
The generation of 2-t-butyl-4,5-didehydropyrimidine (2) by the oxidative method provided the opportunity of investigating its reactivity toward a weak nucleophile. Thus, experiments were carried out in a 4:1 mixture of ethanol and dichloromethane. 4-Ethoxy-2-t-butylpyrimidine (11) was isolated in significant amounts. It was identified by its ^{1}H NMR spectrum. The 2,5-disubstituted pyrimidine was not detected. This result clearly demonstrates that the electrophilic site of the hetaryne 2 is located at carbon 4.

In comparison with unsymmetrically substituted benzynes, such as 3- and 4- fluoro-benzynes, a higher regioselectivity was thus found. Indeed, both fluorobenzynes led to two isomers upon nucleophilic reactions, the meta/ortho ratio in the former being systematically larger than the para/meta ratio in the latter [25]. The regioselectivity sequence 4-fluorobenzyne < 3-fluorobenzyne < 2-t-butyl-4,5-didehydropyrimidine (2) suggested an increasing dissymmetry in the triple bond.

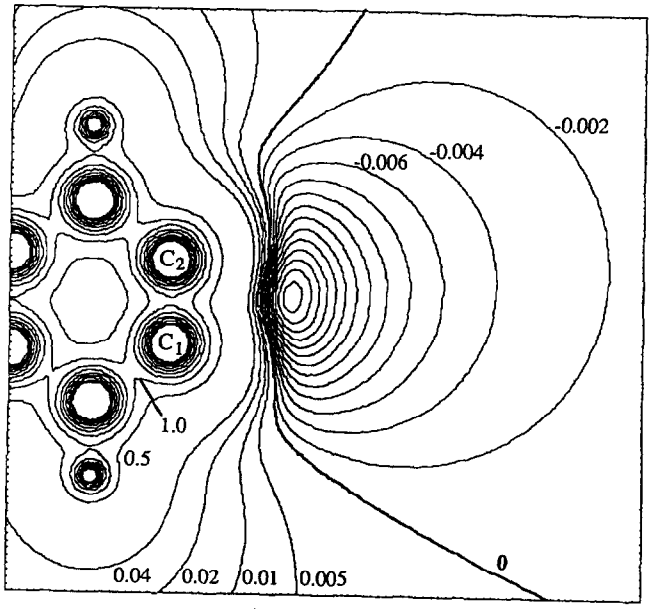
This hypothesis was investigated by a calculation of the Molecular Electrostatic Potential [26] in the triple bond region of the molecular plane. The calculations were again performed at a 3-21G level, starting from completely optimized 3-21G structures (the salient features for the 3- and 4-fluoro-benzynes are the C_1C_2

distance (1.2264 Å and 1.2242 Å) and the valence angles at C_1 (122.0° and 126.6°) and C_2 (131.9° and 128.1° respectively); for benzyne, the values are 1.2250 Å and 127.4°)[27].

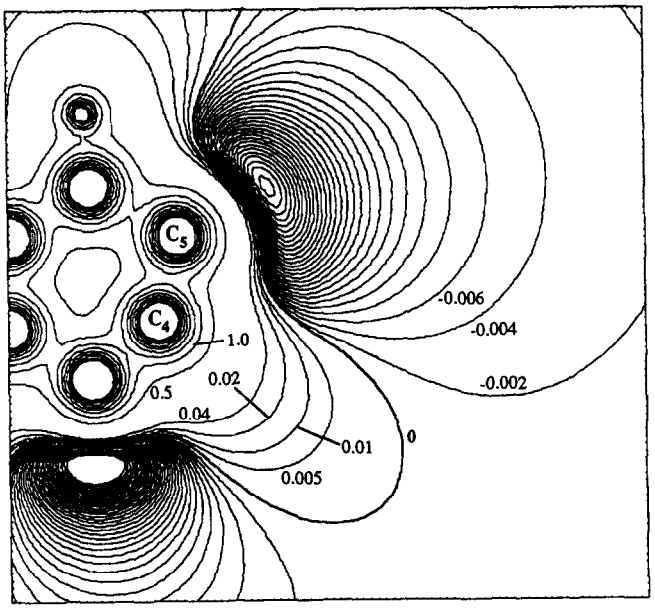
Fig.1. Molecular Electrostatic Potential in the molecular plane of 3-fluorobenzyne (a), 4-fluorobenzyne (b) and 4,5-didehydropyrimidine (c). Contour values in a.u.



(a)



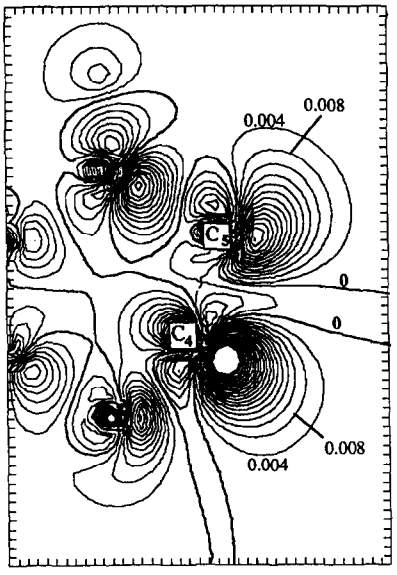
(b)



(c)

The results in figure 1 show that in 4-fluorobenzyne the region of negative potential values is only slightly distorted toward C_2, promoting C_1 for nucleophilic attack, whereas in 3-fluorobenzyne this trend is much more pronounced, in accordance with the experimental data [25]. In the parent hetaryne, a highly dissymmetric potential was found in the C_4C_5 region, even showing a sign inversion which leads to a large positive region around C_4. Thus, nucleophilic attack at this position is strongly favored.

Fig.2. Fukui function $f^+(\underline{r})$ in the molecular plane for 4,5-didehydropyrimidine. Contour values in a.u.

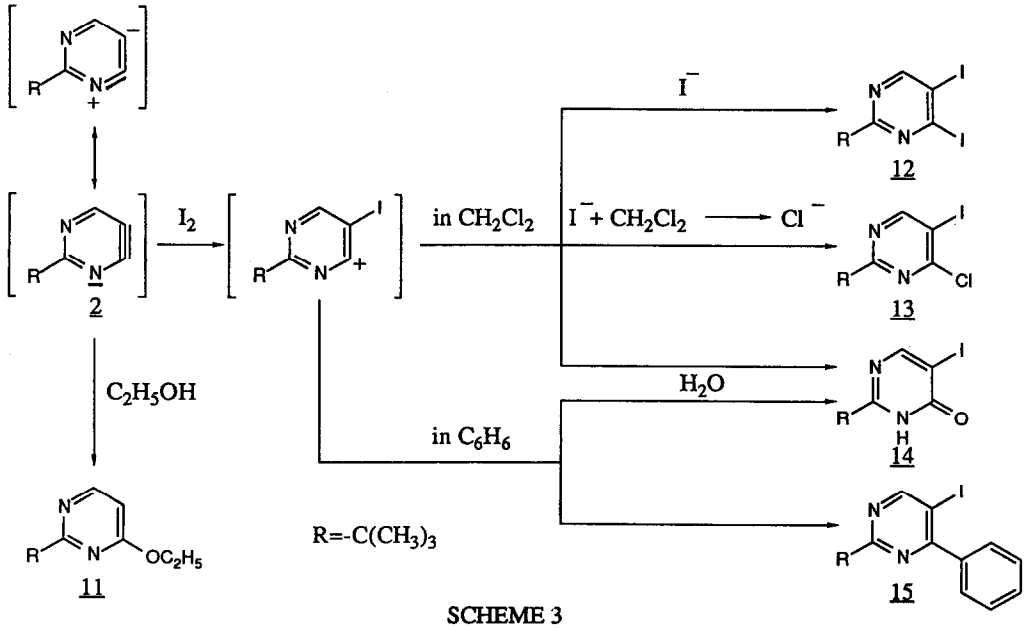


It is interesting to compare this result with that obtained via a recently developed reactivity function based on density functional theory [28], namely the Fukui function (in the case considered f^+) [29]. Two of the present authors obtained promising results [30,31] with this technique, among others on the orientation of electrophilic attack on substituted benzenes [31]. Figure 2 shows the Fukui function f^+ for 4,5-didehydropyrimidine in the molecular plane. Again, a highly dissymmetric pattern was found in the C_4C_5 region, the much larger positive values around C_4 strongly favoring nucleophilic attack at this position. Further research in this direction however needs to be done in order to reach definitive conclusions.

Reaction with an electrophile (scheme 3)

Bromine has been shown to add in high yield to benzyne generated from 1-aminobenzotriazole [11]. When the hetaryne 2 was allowed to react with a slight excess of iodine, in dichloromethane, two products were obtained after separation by preparative layer chromatography. The minor product was isolated in 24 % yield. It was identified as 5-iodo-2-t-butyl-4(3H)-pyrimidinone (14) by its spectral data and by comparison with authentic material. The latter was prepared from 2-t-butyl-4(3H)-pyrimidinone by treatment with N-iodosuccinimide in refluxing chloroform [32].

The major product of the reaction was obtained as an oil. Its mass spectrum showed a small parent peak at m/z 388 (3 %) due to the expected diiodo derivative 12 and, very surprisingly, a greater parent peak at m/z 296 (35 %) (plus an isotopic peak at m/z 298, 12 %) strongly indicative of a chloro-iodo-2-t-butylpyrimidine. In the ^1H NMR spectrum, the two dihalogeno-compounds could also be well discerned by the difference in the chemical shifts of the 6-position protons (8.67 and 8.86 ppm respectively). The ratio was 5:95. The yields calculated therefrom were 2 and 38 %. An attempted separation by H.P.L.C. was not completely satisfactory. The major band was shown by mass spectrometry to contain the chloro-iodo derivative. Finally, with boiling aqueous sodium hydroxide, the oily mixture was converted into 5-iodo-2-t-butyl-4(3H)-pyrimidinone (14), thus proving that the expected substitution pattern 13 was correct. Products derived from attack on chlorinated solvents were observed earlier when benzenediazonium-2-carboxylate was decomposed in the presence of iodine [33].



SCHEME 3

In order to avoid participation in the reaction by dichloromethane, the use of dry benzene was investigated. A substantial yield (40 %) of 5-iodo-4-phenyl-2-t-butylpyrimidine (15) was obtained in this case together with the pyrimidinone 14 (43 %). The structure of the former was established spectroscopically. The reaction gave no detectable amount of the diiodo derivative 12.

These results may be understood on the basis that electrophilic attack by iodine on 2-t-butyl-4,5-didehydropyrimidine (2) occurs entirely at carbon 5. This is in accord with the important delocalization of the adjacent nitrogen lone pair into the unusual σ bond and with the MEP plot (figure 1c). The resulting pyrimidinium cation would then react with any nucleophile present in the mixture, e.g. iodide ions, chloride ions presumed to be derived from dichloromethane by nucleophilic displacement, traces of water or benzene.

In conclusion, taken as a whole, the results described here provide convincing evidence for the generation of a 4,5-didehydropyrimidine intermediate and throw some light on its reactivity in cycloaddition and polar reactions.

COMPUTATIONAL DETAILS

The SCF and MEP calculations were carried out with the program GAMESS [34]. The Fukui function f^+ was calculated as described in references [30] and [31] via a finite difference approach as

$$f^+(\underline{r}) \approx \rho_{N+1}(\underline{r}) - \rho_N(\underline{r})$$

where $\rho_M(\underline{r})$ represents the electron density of a given point $\underline{r}$ for the neutral system (M = N) and the corresponding anion (M = N+1), these values being obtained again via GAMESS. A program DIFF [30] was used for subtracting the densities of the neutral system and the corresponding anion and transferring the data to the graphical output program CONTOUR [35] also used for the MEP plots.

EXPERIMENTAL

Melting points were taken on a Reichert "Thermopan" microscope and are uncorrected. Mass spectra were obtained on a V.G. Micromass 7070 F spectrometer. ^{1}H NMR spectra were determined on a Bruker VM 250 instrument (chemical shifts are quoted in ppm downfield from internal tetramethylsilane).

Oxidations

(a) Reaction with furan. To 30 mg (0.156 mmoles) of 3-amino-5-t-butyl-3H-v-triazolo[4,5-d]pyrimidine dissolved in a mixture of anhydrous furan (3 ml) and dichloromethane (0.5 ml) were added in portions, with vigorous stirring, 81 mg (0.183 mmoles) of lead tetra-acetate. There was immediate evolution of nitrogen. After a few minutes, the reaction mixture was evaporated to dryness and the residue triturated with dichloromethane. The lead diacetate was filtered off and the dark yellow filtrate chromatographied on a preparative plate (Silica gel 60, 8:2 hexane - ethyl acetate). The only large band present (Rf 0.6) was pale yellow after being observed at 254 nm. It was removed and swirled with ether. The adsorbent was eliminated by centrifugation and the supernatant filtered through a Millipore Millex HV-13 filter. Evaporation of the solvent gave 15 mg (47 %) of 2-t-butyl-5,8-dihydro-5,8-epoxyquinazoline (3). Sublimation at 60°/1 Torr (the "cold finger" was cooled to -25°) afforded white crystals, m.p. 92-94°. MS m/z 202.1110 ($C_{12}H_{14}N_2O$ requires 202.1106). ^{1}H NMR ($CDCl_3$) δ 1.38 (9H, s, $C(CH_3)_3$), 5.59 (1H, m, H_8), 5.84 (1H, dd, J 0.8 and J 1.9 Hz, H_5) 7.07 (2H, m, H_6 and H_7) and 8.30 (1H, d, J_{4-8} 0.5 Hz, H_4) ppm.

(b) Reaction with tetracyclone. The oxidation was carried out in a similar way to that described in (a). 180 mg (0.468 mmoles) of tetracyclone and 5 ml of dichloromethane were used. Separation was performed by preparative layer chromatography (Silica gel 60, 7:3 benzene - petroleum ether, two developments). The product

(Rf 0.4), located below the wide band due to the unreacted tetracyclone (Rf 0.6), appeared as a yellow fluorescent band when observed at 350 nm. It was extracted for 6 hr with anhydrous benzene in a Soxhlet apparatus. Evaporation of the solvent gave 18 mg (24 %) of 5,6,7,8-tetraphenyl-2-t-butylquinazoline (4a) as a pale yellow solid which was recrystallized with difficulty from ethanol to yield white crystals, remelt m.p. 269-271°. MS m/z 490.2401 ($C_{36}H_{30}N_2$ requires 490.2409). ^1H NMR ($CDCl_3$) δ 1.35 (9H, s, $C(CH_3)_3$), 6.82-6.89 and 7.19-7.22 (8H and 12H, m, 4 C_6H_5), 9.15 (1H, s, H_4) ppm.

(c) Reaction with 2,5-di-(p-methoxyphenyl)-3,4-diphenylcyclopentadienone. The procedure described in (b) was repeated in the presence of 207 mg (0.466 mmoles) of the diene [36]. Separation (99:1 benzene - ethyl acetate), followed by extraction of the white fluorescent band (Rf 0.25) gave 14 mg (16 %) of 5,8-di-(p-methoxyphenyl)-6,7-diphenyl-2-t-butylquinazoline (4b). Recrystallization of this material from 7:3 ethanol - hexane yielded white crystals, remelt m.p. 232-235°. MS m/z 550.2605 ($C_{38}H_{34}N_2O_2$ requires 550.2620). ^1H NMR ($CDCl_3$) δ 1.37 (9H, s, $C(CH_3)_3$), 3.77 (6H, s, 2 OCH_3), 6.74 (2H, d, J 8.8 Hz, 2H ortho to OCH_3), 6.74-6.85 (6H, m, 2H ortho to OCH_3 and 4H of 2 C_6H_5), 6.86-6.95 (6H, m, 6H of 2 C_6H_5), 7.08 (2H, d, J 8.7 Hz, 2H meta to OCH_3), 7.14 (2H, d, J 8.7 Hz, 2H meta to OCH_3) and 9.17 (1H, s, H_4) ppm.

(d) Reaction with phenyl azide. 20 mg (0.104 mmoles) of 3-amino-5-t-butyl-3H-v-triazolo [4,5-d]pyrimidine dissolved in a mixture of anhydrous phenyl azide (1 ml) and dichloromethane (1 ml) were treated portionwise, with vigorous stirring, with 72 mg (0.162 mmoles) of lead tetra-acetate. Gas evolution was instantaneous. A few minutes later, the dichloromethane was evaporated with a stream of nitrogen. The bright yellow residue was applied to a Sep-Pak cartridge which was eluted with hexane until all the excess of phenyl azide has been moved out. The other components were eluted with chloroform and then separated by preparative layer chromatography (alumina, 3:1 hexane - dichloromethane). Three bands were obtained and each one extracted with chloroform. The largest band (Rf 0.5-0.8) afforded 11.5 mg (43 %) of 3-phenyl-5-t-butyl-3H-v-triazolo[4,5-d]pyrimidine (7) which was recrystallized from 3:1 ethanol - water. m.p. 126-127°. MS m/z 253.1323 ($C_{14}H_{15}N_5$ requires 253.1327). This product was identical with that made by the method described below. The second band (Rf 0.35), much fainter, yielded 2 mg (7 %) of a compound of unestablished structure (9). m.p. 117-121°. MS m/z 271.1429 (8 %, $C_{14}H_{17}N_5O$ requires 271.1433). Important fragments at 214 (63 %, M-C_4H_9), 186.0665 (10 %, 214-N_2, $C_{10}H_8N_3O$ requires 186.0667), 158.0718 (13 %, 186-CO,$C_9H_8N_3$ requires 158.0718), 77 (19 %), 57 (56 %) and 28 (100 %). IR (KBr) ν_{max} 3290, 2920, 1690, 1635 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.37 (9H, s, $C(CH_3)_3$), 5.54 (1H, d, J 9 Hz), 7.47-7.56 (2H, m), 7.56-7.64 (4H, m) and 10.99 (1H, broad signal) ppm. The third band (Rf 0.25), which appeared as a violet fluorescent zone when examined under UV light (254 nm), gave 4.5 mg (19 %) of 2-t-butyl-9H-pyrimido[4,5-b]indole (8). This material was recrystallized from 95:5 petroleum ether - ethanol. m.p. 194-195°. It was identical with a sample obtained by photolysis (see below).

(e) Reaction with 2,3,5-tri-O-benzoyl-β-D-ribofuranosyl azide. The procedure described in (b) was repeated in the presence of 228 mg (0.468 mmoles) of the glycosyl azide [37]. Separation (Silica gel 60, 9:1 benzene - ethyl acetate), removal of the band (Rf 0.45) located below the wide zone (Rf 0.65) due to the excess of the azide, extraction with acetone and evaporation of the solvent yielded 15 mg (15 %) of 3-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-5-t-butyl-3H-v-triazolo[4,5-d]pyrimidine (10) as a yellow syrup. MS m/z 621.2230 ($C_{34}H_{31}N_5O_7$ requires 621.2223). ^1H NMR ($CDCl_3$) δ 1.51 (9H, s, $C(CH_3)_3$), 4.68 (1H, dd, $J_{5'a-5'b}$ 12 Hz, $J_{4'-5'a}$ 5.8 Hz, $H_{5'a}$), 4.83 (1H, dd, $J_{5'a-5'b}$ 12 Hz, $J_{4'-5'b}$ 4.3 Hz, $H_{5'b}$), 4.96 (1H, ddd, $J_{3'-4'}$ 6.6 Hz, 2 $J_{4'-5'}$ 5.8 and 4.3 Hz, $H_{4'}$), 6.50 (1H, dd, $J_{3'-4'}$ 6.6 Hz, $J_{2'-3'}$ 5.5 Hz, $H_{3'}$), 6.60 (1H, dd, $J_{2'-3'}$ 5.5 Hz, $J_{1'-2'}$ 2.8 Hz, $H_{2'}$) 6.94 (1H, d, $J_{1'-2'}$ 2.8 Hz, $H_{1'}$), 7.34-7.43 (6H, m, H_{meta}), 7.49-7.60 (3H, m, H_{para}), 7.95-8.00 (6H, m, H_{ortho}) and 9.51 (1H, s, H_7) ppm.

^{1}H NMR ($CDCl_3$) of 2,3,5-tri-O-benzoyl-β-D-ribofuranosyl azide (a somewhat less resolved spectrum is described in the literature [38]) : δ 4.56 (1H, dd, $J_{5a\text{-}5b}$ 13.2 Hz, $J_{4\text{-}5a}$ 5.5 Hz, H_{5a}), 4.73-4.80 (2H, m, H_4 and H_{5b}), 5.58 (1H, dd, $J_{2\text{-}3}$ 4.8 Hz, $J_{1\text{-}2}$ 1.6 Hz, H_2), 5.67 (1H, d, $J_{1\text{-}2}$ 1.6 Hz, H_1), 5.83 (1H, dd, $J_{3\text{-}4}$ 5.5 Hz, $J_{2\text{-}3}$ 4.8 Hz, H_3), 7.30-7.61 (9H, m, H_{meta} and H_{para}) and 7.87-8.11 (6H, m, H_{ortho}) ppm.

(f) Reaction with ethanol. The oxidation was carried out in a similar way to that described in (a). 6 ml of anhydrous ethanol and 1.5 ml of dichloromethane were used. Preparative layer chromatography (Silica gel 60, 9:1 hexane - ethyl acetate), extraction of the only important band (Rf 0.8) with acetone and careful evaporation of the solvent with a stream of nitrogen afforded 14 mg (50 %) of 4 ethoxy-2-t-butylpyrimidine (11) as a rather volatile yellow oil. MS m/z 180.1268 ($C_{10}H_{16}N_2O$ requires 180.1262). ^{1}H NMR ($CDCl_3$) δ 1.37 (9H, s, $C(CH_3)_3$), 1.39 (3H, t, J 7.1 Hz, CH_3), 4.43 (2H, q, J 7.1 Hz, CH_2), 6.47 (1H, d, $J_{5\text{-}6}$ 5.8 Hz, H_5) and 8.36 (1H, d, $J_{5\text{-}6}$ 5.8 Hz, H_6) ppm.

(g) Reaction with iodine. 20 mg (0.104 mmoles) of 3-amino-5-t-butyl-3H-v-triazolo[4,5-d]pyrimidine and 32 mg (0.126 mmoles) of iodine dissolved in 6 ml of dry dichloromethane or benzene were treated as usual with 54 mg (0.122 mmoles) of lead tetra-acetate. Preparative layer chromatography (Silica gel 60, 98:2 hexane - ethyl acetate) gave two major bands which were removed and extracted with dichloromethane.

Reaction in dichloromethane. The top band (Rf 0.85) afforded 13 mg of a 95:5 oily mixture of 4-chloro-5-iodo- and 4,5-diiodo-2-t-butylpyrimidines (13 and 12). Yields 39 % and 2 % respectively. MS m/z 296 (35 %, $M^{+\cdot}$), 298 (12 %) (chloro-iodo derivative) and 388 (3 %, $M^{+\cdot}$) (diiodo derivative). Fragment peaks at m/z 281 (100 %, $[M\text{-}CH_3]^+$), 283 (33 %, $[298\text{-}CH_3]^+$) and 373 (3 %, $[M\text{-}CH_3]^+$). ^{1}H NMR ($CDCl_3$) δ 1.38 (9H, s, $C(CH_3)_3$) and 8.86 (1H, s, H_6) ppm (chloro-iodo derivative), 1.35 (9H, s, $C(CH_3)_3$) and 8.67 (1H, s, H_6) ppm (diiodo derivative). The ratio of the two compounds amounted to 95:5. The lower band (Rf 0.4) yielded 7 mg (24 %) of 5-iodo-2-t-butyl-4(3H)-pyrimidinone (14) which was recrystallized from 1:1 ethanol - water. m.p. 205-206°. MS m/z 277.9914 ($C_8H_{11}IN_2O$ requires 277.9918). IR (KBr) ν_{max} 1642 cm^{-1}. This product was identical with that prepared by iodination of 2-t-butyl-4(3H)-pyrimidinone (see below).

Reaction in benzene. The top band (Rf 0.6) gave 14 mg (40 %) of 5-iodo-4-phenyl-2-t-butylpyrimidine (15) as a whitish solid which was sublimed at 50°/0.05 Torr. m.p. 77°. MS m/z 338.0277 ($C_{14}H_{15}IN_2$ requires 338.0281). ^{1}H NMR ($CDCl_3$) δ 1.42 (9H, s, $C(CH_3)_3$), 7.46-7.49 and 7.75-7.79 (3H and 2H, m, C_6H_5), 9.02 (1H, s, H_6) ppm. The bottom band (Rf 0.3) yielded 12.5 mg (43 %) of 5-iodo-2-t-butyl-4(3H)-pyrimidinone (14).

Alkaline hydrolysis. 6 mg of the mixture of 4-chloro-5-iodo- and 4,5-diiodo-2-t-butylpyrimidines (13 and 12) were treated with 1 ml of a 0.1 M sodium hydroxide solution. After one night at room temperature, the reaction mixture was heated under reflux for 3 hr. The resulting solution was then made acid with concentrated hydrochloric acid and extracted with dichloromethane. The combined organic layers were dried over magnesium sulfate, filtered and evaporated to give 5.5 mg of 5-iodo-2-t-butyl-4(3H)-pyrimidinone (14), m.p. 205-206°.

Synthesis of 5-iodo-2-t-butyl-4(3H)-pyrimidinone [39]

A solution of 0.478 g (3.14 mmoles) of 2-t-butyl-4(3H)-pyrimidinone [10] and 0.744 g (3.31 mmoles) of N-iodosuccinimide in 60 ml of chloroform was heated under reflux for 1hr. Iodine was then removed from the solution by washing with three portions of 2 % aqueous sodium dithionate. The organic layer was dried over magnesium sulfate, filtered and evaporated under reduced pressure. The crude iodo derivative was recrystallized from 1:1 ethanol - water to give colorless platelets, m.p. 204-205°. Yield 0.275 g (31.5 %). ^{1}H NMR ($CDCl_3$) δ 1.42 (9H, s, $C(CH_3)_3$), 8.42 (1H, s, H_6) and 12.35 (1H, broad signal, NH) ppm.

Synthesis of 3-phenyl-5-t-butyl-3H-v-triazolo[4,5-d]pyrimidine

(a) 4-Anilino-5-nitro-2-t-butylpyrimidine. The ethereal solution of 4-chloro-5-nitro-2-t-butylpyrimidine [10], obtained from 0.6 g (3.05 mmoles) of 5-nitro-2-t-butyl-4(3H)-pyrimidinone, was concentrated to ca. 5 ml

and cooled in an ice bath. 1.4 ml (15 mmoles) of aniline dissolved in 14 ml of anhydrous ether were then added dropwise with vigorous stirring. The reaction mixture was allowed to warm to room temperature, kept overnight, washed three times with 2 % aqueous hydrochloric acid and once with water. The ether layer was dried over magnesium sulfate, filtered and evaporated to dryness to give 0.642 g (78 %) of crude product. Recrystallization from 3:1 ethanol - water (24 ml per g) yielded bright yellow needles, m.p. 115-116°. MS m/z 272 ($M^{+\cdot}$). ^1H NMR ($CDCl_3$) δ 1.39 (9H, s, $C(CH_3)_3$), 7.22-7.25 (1H, m, H_{para}), 7.38-7.44 (2H, m, H_{meta}), 7.70-7.73 (2H, m, H_{ortho}), 9.29 (1H, s, H_6) and 10.15 (1H, broad signal, NH) ppm. Anal. Calcd. for $C_{14}H_{16}N_4O_2$: C 61.75; H 5.92; N 20.57. Found : C 61.87; H 5.99; N 20.31.

(b) 5-Amino-4-anilino-2-t-butylpyrimidine. A solution of 0.1 g (0.367 mmoles) of 4 -anilino-5-nitro-2-t-butylpyrimidine in 25 ml of ethanol was hydrogenated in the presence of 0.03 g of 5 % palladium on charcoal catalyst until 26.5 ml (1.1 mmole) of gas were taken up. The reduction mixture was filtered through Celite and the collected catalyst washed well with ethanol. The filtrate was evaporated to dryness and the residue recrystallized from hexane (165 ml per g) to give 0.089 g (100 %) of a colorless solid, m.p. 140-142°. MS m/z 242 ($M^{+\cdot}$). ^1H NMR ($CDCl_3$) δ 1.38 (9H, s, $C(CH_3)_3$), 3.0 (2H, broad signal, NH_2), 6.99 (1H, broad signal, NH), 7.00-7.07 (1H, m, H_{para}), 7.31-7.37 (2H, m, H_{meta}), 7.70-7.74 (2H, m, H_{ortho}) and 7.95 (1H, s, H_6) ppm.

(c) 3-Phenyl-5-t-butyl-3H-v-triazolo[4,5-d]pyrimidine. 0.5 g (1.84 mmoles) of 4-anilino-5-nitro-2-t-butylpyrimidine was hydrogenated by the method described above. The ethanol filtrate was concentrated until some solid separated. 5.52 ml of 1 M hydrochloric acid was added, and the mixture stirred and cooled to 0°. The precipitate was dissolved by adding a minimum volume of ethanol. 0.14 g (2.02 mmoles) of sodium nitrite dissolved in a small volume of water was then added. After 1 hr, the reaction mixture was allowed to warm to room temperature and set aside overnight. A minimum volume of water was finally added and the grayish white precipitate that deposited was collected. There was obtained 0.428 g (92 %) of 3-phenyl-5-t-butyl-3H-v-triazolo[4,5-d]pyrimidine (7). Recrystallization from 3:1 ethanol - water (26 ml per g) gave colorless needles, m.p. 126-127°. MS m/z 253 ($M^{+\cdot}$). ^1H NMR ($CDCl_3$) δ 1.53 (9H, s, $C(CH_3)_3$), 7.44-7.51 (1H, m, H_{para}), 7.58-7.65 (2H, m, H_{meta}), 8.36-8.41 (2H, m, H_{ortho}) and 9.56 (1H, s, H_7) ppm. UV (CH_3OH) λ_{max} 204, 236 nm; log ε 4.31, 4.28; λ_{min} 212 nm; log ε 4.03. Anal. Calcd. for $C_{14}H_{15}N_5$: C 66.38; H 5.97; N 27.65. Found : C 66.49; H 6.04; N 27.28.

Synthesis of 2-t-butyl-9H-pyrimido[4,5-b]indole

A solution of 0.1 g (0.395 mmoles) of 3-phenyl-5-t-butyl-3H-v-triazolo[4,5-d]pyrimidine in 230 ml of methanol was irradiated with a low-pressure Hanau mercury arc for 6 hr. The solvent was then removed under reduced pressure. The residual orange gum was adsorbed onto microcrystalline cellulose and chromatographed on alumina (Alox). Elution with 6:4 hexane - dichloromethane gave 0.035 g (39 %) of a white solid which was recrystallized from 95:5 petroleum ether - ethanol (55 ml per g) to yield colorless needles, m.p. 193.5-195°. MS m/z 225.1266 ($C_{14}H_{15}N_3$ requires 225.1266). ^1H NMR ($CDCl_3$) δ 1.51 (9H, s, $C(CH_3)_3$), 7.29-7.49 (3H, m, H_6, H_7, H_8), 8.05-8.09 (1H, m, H_5), 8.89 (1H, broad signal, NH) and 9.27 (1H, d, $J_{4,9}$ 0.8 Hz, H_4) ppm. UV (CH_3OH) λ_{max} 212, 230, 254, 290 nm; log ε 4.48, 4.41, 4.44, 4.11; λ_{min} 222, 242, 270; log ε 4.33, 4.28, 3.87.

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