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PROTONATED 1,3-DIAZINES: NEW AND EFFECTIVE REAGENTS FOR AROMATIC ELECTROPHILIC SUBSTITUTION REACTIONS

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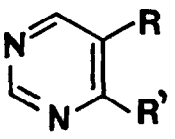
While looking for ways to prepare covalent conjugates between polycyclic aromatic hydrocarbons and purine or pyrimidine derivatives[1], we found that the parent systems **1** (R = R' = H; R = H, R' = CH_3; R = CH_3, R' = H), quinazoline **2**, and purine **3** (R = H or CH_3) can substitute hydrogen in many aromatic compounds, under surprisingly mild conditions.



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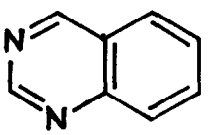

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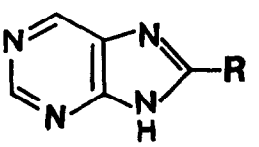

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This reaction proceeds when equimolar amounts of the reactants are treated in an inert solvent (like benzene, CS_2, $CHCl_3$) with an excess of trifluoroacetic acid. Other non-aqueous proton acids (e.g. formic acid, diflouroacetic acid, $HClO_4$ in glacial acetic acid, CF_3SO_3H) have proven less effective and / or convenient.

Depending on the reactivity of the educts taken, the reaction needs between 5 minutes at ambient temperature (example: resorcinol + quinazoline) and reflux for 12 hours (example: 9-methylanthracene + pyrimidine).

The yields range from 60 % to more than 90 %.

The reactivity of the heterocyclic compounds increases with the series:
purines < pyrimidines ≪ quinazoline
The following table summarizes some of our results:

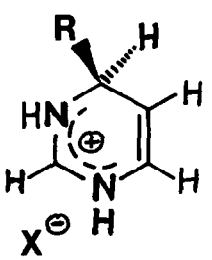
Reaction of 1,3-diazines with different aromatic hydrocarbons, in benzene:trifluoroacetic acid = 2:1

aromatic hydrocarbon	1.3 - diazine 1	2	3
9-methylanthracene	+	+	+
benzo[a]pyrene	+	+	+
benzo[e]pyrene	-	+	-
perylene	+	+	+
resorcinol	+2)	+2)	+
thiophene	+	+	-
indole	+	+	+

+ = product formed

- = no product formed

The products formed are salts of 4-arylsubstituted 3,4-dihydro-1,3-diazines, e.g. **4** and **5**, according to analytical and spectroscopical evidence[3]. Chemical evidence has up to now been obtained for several quinazoline-derivatives, e.g. **5**, which could be oxidized to the neutral 4-arylsubstituted quinazolines, e.g. **6**, by a known procedure reported specifically for the oxidation of 3,4-dihydroquinazolines[4)5)].



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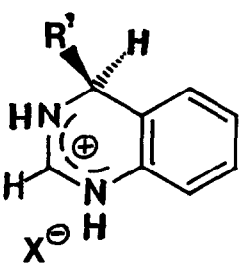

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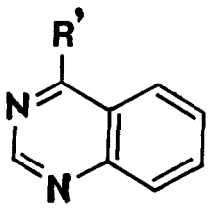
KOH/ $K_3Fe(CN)_6$ [43%]



6

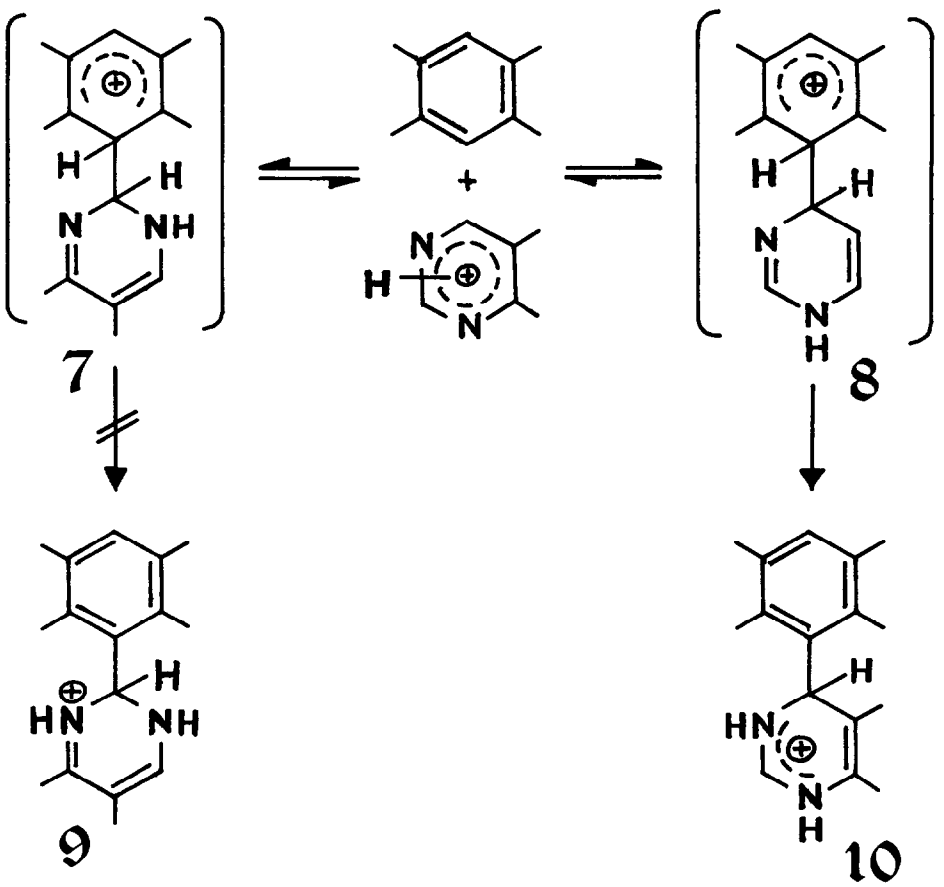
X = CF_3CO_2, Cl, Br, HCO_2, ClO_4, and picrates

R = 1,3-dihydroxybenzene(4)-, **R'** = anthracene(9)-

DISCUSSION:

Protonation of 1,3-diazines leads to formation of azacarbenium ions, whose positive charge should be localized predominantly at the nitrogen atom sites. According to former reports[6], such azacarbenium ions should demonstrate very little or no "carbenium ion character". On the grounds of the experimental results reported here, we suggest this statement to be revised, at least for the special systems of the 1,3-diazines **1**, **2**, and **3**.

Calculations[7] have demonstrated that C-2 should be the most electrophilic carbon site in protonated 1,3-diazines. But attack from this position would lead - via σ-complex **7** -finally to chemically unstable (and mainly unknown)[8] 1,2-dihydro-1,3-diazines **9**. If, on the other hand, C-4 attacks electrophilically the aromatic compound, σ-complex **8** is formed which can rearrange by intramolecular proton shift to a highly resonance-stabilized[9] (cyclic) amidinium salt **10**:



Detailed work, dealing with the different classes of compounds involved, is in progress and will be reported elsewhere.

Acknowledgment: I thank Professor Manfred Wilk, Frankfurt, for his support of this work, and Professor Felix Bergmann, Jerusalem, for an opportunity to discuss it.

NOTES AND REFERENCES:

1) W.Girke, M.Wilk, in: Chemical Carcinogenesis, Part A, p 183-195 Ed. by P.Ts'o, J.DiPaolo, Marcel Dekker Inc., New York, 1974

2) 4,6-disubstituted resorcinols are also formed. Disubstitution was not observed with purine.

3) Analytical details, in proof of structures 4, 5, and 6:

a) 4-(2,4-dihydroxy-1-phenyl)3,4-dihydropyrimidinium chloride 4:
$C_{10}H_{11}ClO_2N_2$ calc. C 53.0, H 4.9, N 12.4, found C 52.6, H 4.4, N 12.0
^{1}H-NMR (C_3D_6O): (from int. TMS) δ = 5.24(dd, J= 3+8 Hz, 1H), 5.66(d, J=3Hz,1H), 6.42(d, J=8Hz, 2H), 6.56(s, 1H), 7.06(d, J=8Hz, 1H), 8.12(s, 1H) (OH an NH at lower field).

b) 4-anthryl-3.4-dihydroquinazolinium trifluoroacetate 5:
$C_{24}H_{17}F_3N_2O_2$ calc. C 68.3, H 4.0, N 6.6, found C 68.7, H 4.1, N 6.4
MS: $(M - CF_3CO_2H)^+$, calc. 308.1313, found: 308.1302
^{1}H-NMR (DMSO): δ = 6.28(d, 1H), 6.78(dd or t?, 1H), 7.0 - 8.4(several multiplets, 11H), 8.54(s, 1H), 8.62(s, 1H)

c) 4-anthryl-quinazoline 6:
$C_{22}H_{14}N_2$ calc. C 86.3, H 4.6, N 9.2 found: C 86.4, H.4.5, N 9.4
MS: $(M - H)^+$, calc. 305.1079, found: 305.1071
^{1}H-NMR ($CDCl_3$+CF_3CO_2H): δ = 7.1 - 7.6 (m, 8H), 7.8 - 8.2(m, 3H), 8.38 (d, 1H), 8.66(s, 1H), 9.73(s, 1H)

4) S.Gabriel, Berichte 36, 800 (1903)

5) T.Higashino, Yakugaku Zasshi 80, 245 (1960), cf. C.A. 54, 13125 (1960)

6) F.Scott, R.Butler, in: Carbonium Ions, Vol. IV pp 1669, and literature cited therein. Ed. by G.Olah, P.Schleyer, Wiley-Interscience, New York 1973.

7) R.Pugmire, D.Grant, J. Am. Chem. Soc. 90, 697 (1968)

8) R.Elderfield, Ed., "Heterocyclic Compounds", Vol. 6, pp 367 J.Wiley & Sons, Inc., New York 1957
W.Armarego, in: Advances in Heterocyclic Chemistry, Vol. I, pp 281 Ed. by A. Katritzky, Acad. Press, New York 1963

9) G.Häflinger, in: The Chemistry of Amidines and Imidates Ed. by S.Patai, J.Wiley & Sons, 1975