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THE CHEMICAL SIMULATION OF THE "ATP-IMIDAZOLE" CYCLE

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ABSTRACT : The synthetic strategy inherent in the "ATP-Imidazole" cycle and centred around the vicinal disposition of $-NH_2$ and $-CONH_2$ functions, has been demonstrated with anthranilamide (2) and 1-benzyl-5-aminoimidazole-4-carboxamide (1) as regeneratable carriers involving specifically N-alkylated quinazolin-4-ones, hypoxanthines and adenines, as key intermediates. The isolation and characterization of the enamine (22) coupled with other observations has made it possible to rationalize the pathways involved in these cyclic operations. The practical utility of the synthetic strategy using regeneratable carriers has been illustrated with the synthesis of a range of 1,5-disubstituted imidazoles. Whilst pathways leading to specific N-alkylation in the Natural cycle and in simulation studies are comparable, the subsequent events take place in a reverse order, primarily because of the divergence in the hydrolytic profile of the alkylated substrates. The action of dilute alkali on 3-alkylated quinazolin-4-ones leads to 2-3 rather than 3-4 bond rupture. Endeavours to promote the latter path, by blocking the 2 position gave unexpected results. 2-Methyl-3-phenacyl quinazolin-4-one gave with dilute alkali the novel aromatic tricyclic system (32) from trans-annular cyclization. On the other hand, the 2-blocked 3-benzamido quinazolin-4-ones (33) and (34) gave triazoles (35) and (36) arising from the desired 3-4 rupture followed by cyclization initiated by the resulting amidine unit. 2-Phenyl-3-benzamidoquinazolin-4-one (34) with distilled water at 200°C gave a number of products which have been identified and their formation explained.

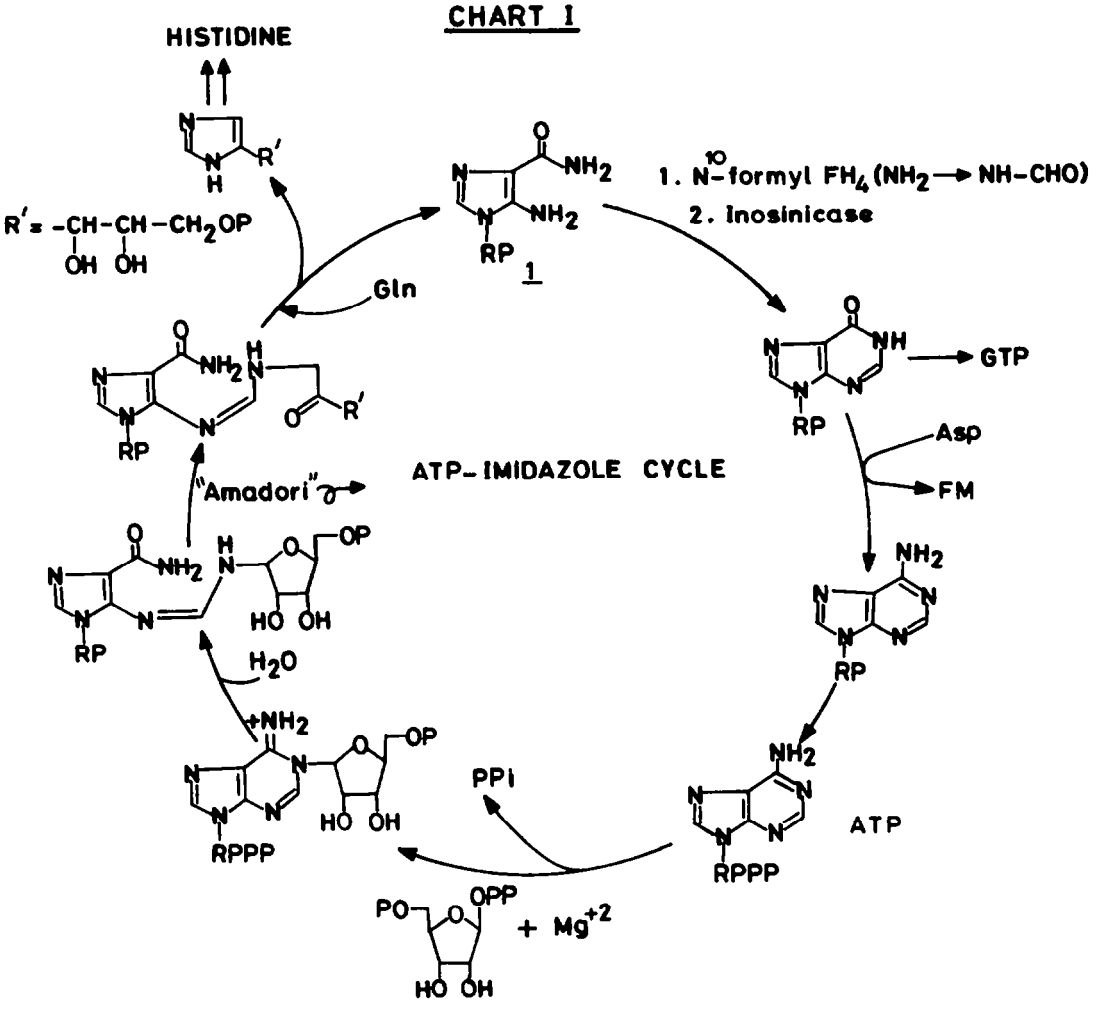
An attractive facet of the art in organic synthesis would be the creation of structures on a carrier molecule[1] which can be re-cycled. Such a strategy -although used by Nature for the biosynthesis of compounds vitally associated with life processes[2] -has been neither exploited nor systematically explored thus far. A unique example of this strategy in Nature is the ATP-Imidazole cycle wherein a derived imidazole is grown on a mobile carrier imidazole via a cyclic pathway that is linked to the biosynthesis of the purine code bases ATP and GTP as well as to the imidazole amino acid histidine[3] (Chart I).

The chemical simulation of the ATP-Imidazole cycle[4] was initially carried out on a model which possessed the operating part of the cycle, namely, the vicinal disposition of the $-NH_2$ and $-CONH_2$ units and substituting the more reactive imidazole moiety with a phenyl ring. Thus, all early experiments made use of anthranilamide rather than the N-substituted-5-aminoimidazole-4-carboxamide as the carrier molecule.

Anthranilamide (2) was readily converted to quinazolin-4-one (4) by treatment with dimethylacetal of DMF and then to an array of 3-substituted quinazolin-4-ones. All endeavours to rupture these specifically at the 4-oxo location, that would lead to the release of the -COOH function and which is the pathway that is established for the ATP-Imidazole cycle (Chart I) did not succeed, but gave frequently products arising from re-arrangements(vide infra). The alternative strategy involving cyclization followed by rupture proved successful[5].

Specific alkylation of quinazolin-4-one (4) was achieved by treatment of the conjugate base, generated with 1 eq. of KOH, with phenacyl bromide in ethanol to give 3-phenacyl quinazolin-4-one (6, mp 159°C, 40%)[6]. By a similar procedure, 3-acetonylquinazolin-4-one (7, mp 158°C, 50%) was prepared using bromoacetone. Compound (6) proceeded through the cycle (Chart II) on reflux for 12h with benzylamine (4 eq.) and p-TsOH (2 eq.) leading to the derived product 1-benzyl-5-phenylimidazole (8, mp 111°C, 69%) and anthranilbenzylamide (10, mp 123°C, 71%). The latter was transformed to anthranilamide (2) in 85% yields by treatment with methanesulfonic acid. Thus, the sequence of events outlined in Chart II represents synthesis of an imidazole on anthranilamide as the carrier molecule. In an analogous manner, 3-acetonylquinazolin-4-one (7) was transformed to 1-benzyl-5-methylimidazole (9, 55%, mp 99°C, overall yield from anthranilamide 23.6%) and the amide (10) (45%).

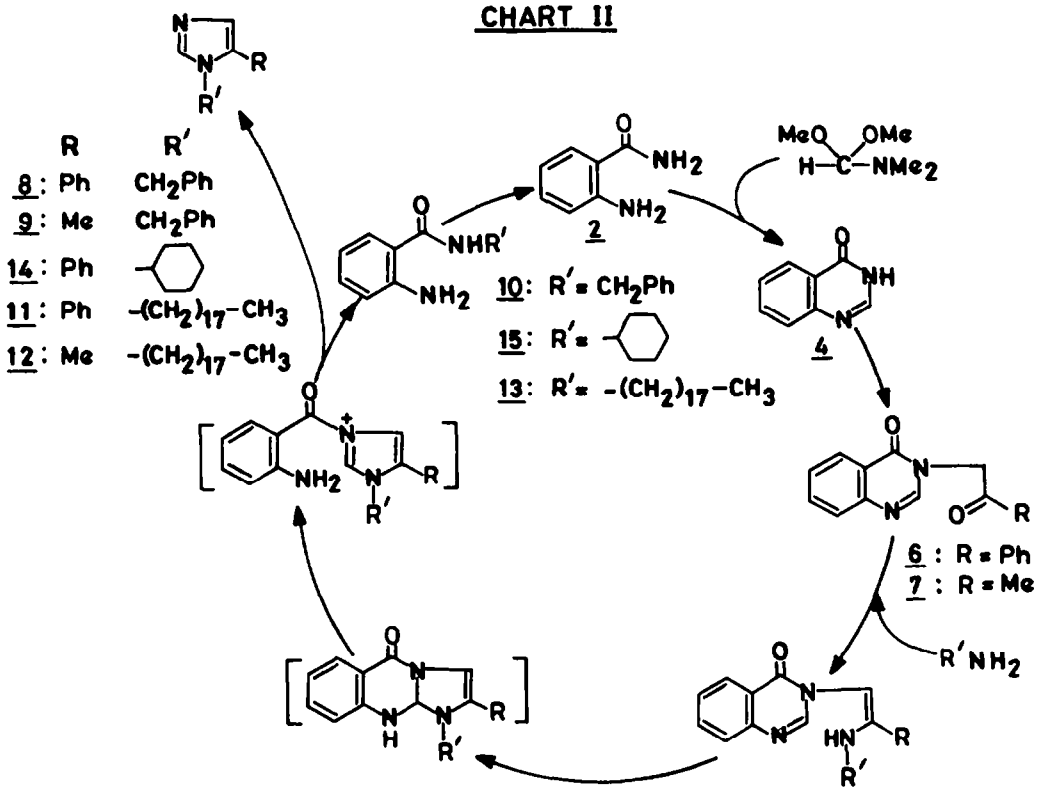
CHART I



The selective formation of specifically 5-substituted N-protected imidazoles by the carrier molecule strategy provides the best route to such compounds[7]. For example, the hitherto recommended procedure for the preparation of 1-benzyl-5-methylimidazole (9) is : D-fructose → 4 (5)-hydroxymethylimidazole → 1-benzyl-4-hydroxymethylimidazole + 1-benzyl-5-hydroxymethylimidazole, chromatographic separation of the desired 5-isomer, halogenation with $SOCl_2$ and reduction ($Pd/C/H_2$) (overall yield of (9) from fructose <2%). The (9) thus obtained was identical in all respects to that prepared *via* the cyclic operation (Chart II).

The general utility of such a cyclic strategy for the preparation of 1-protected-5-substituted imidazoles as well as for a variety of 1-substituted imidazoles has been further established. Thus, the reaction of (6) with octadecylamine gave the derived product, 1-octadecyl-5-phenylimidazole (11, 32%) and anthraniloctadecylamide (13, 35%) (Chart II). In an analogous manner, compound (7) when processed through the cycle gave 1-octadecyl-5-methylimidazole (12, 18%) and 31% of (13). The novel lipids (11) and (12) are of interest since, they carry the biologically important imidazole unit. Micellar systems involving either (11) or (12) are therefore expected to show novel catalytic profile in imidazole mediated reactions.

CHART II



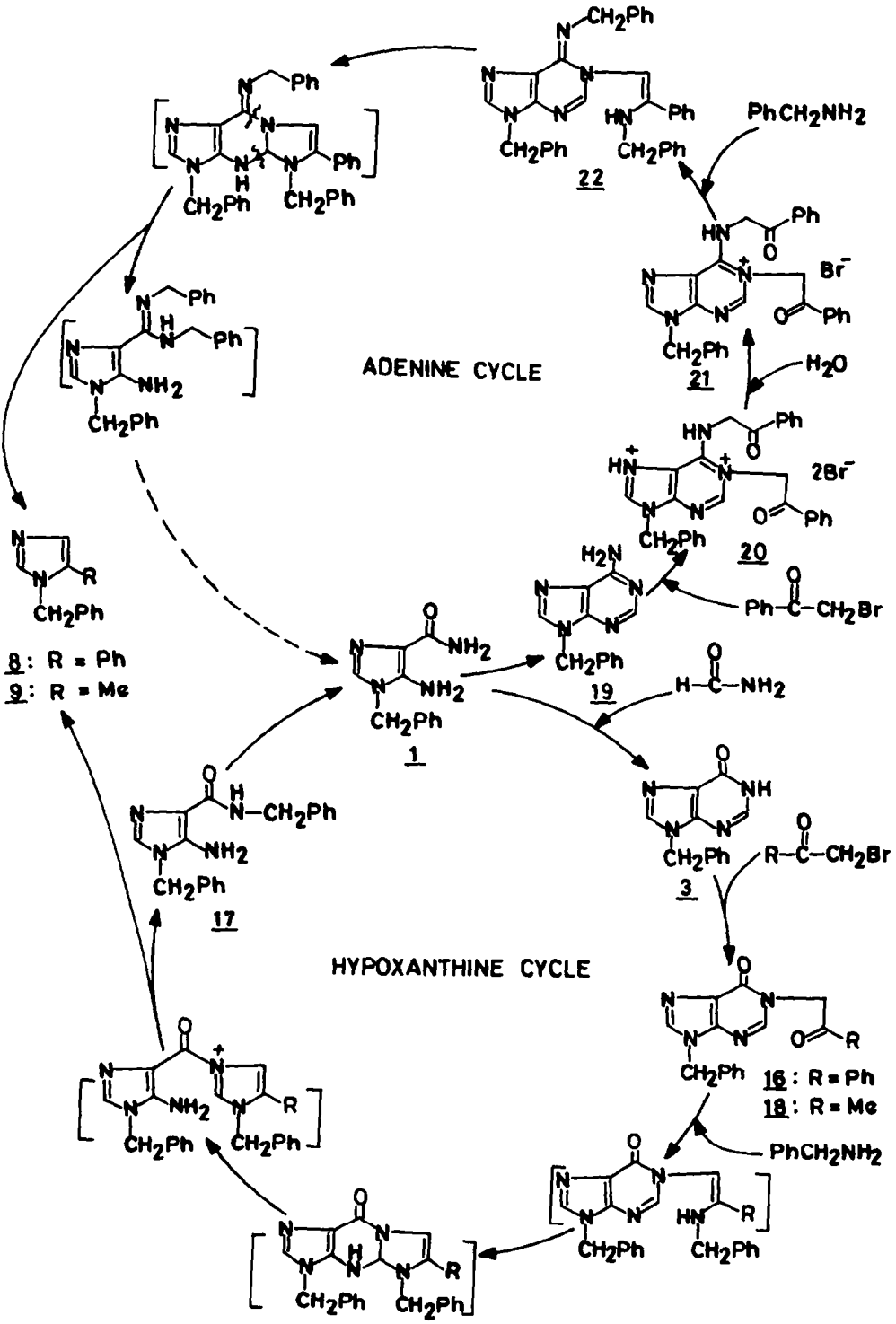
1-Cyclohexyl-5-phenylimidazole (14, 70%) and anthranilcyclohexylamide (15, 65%) were obtained when (6) was processed through the cycle with cyclohexylamine (Chart II).

The cyclic operations with anthranilamide (Chart II) illustrate that aspect of the ATP-Imidazole cycle which involves the directed synthesis of an imidazole using a soluble regeneratable carrier. An aesthetically more pleasing aspect of the ATP-Imidazole cycle is the generation of a derived imidazole from an imidazole carrier. We have accomplished this starting from 1-benzyl-5-aminoimidazole-4-carboxamide (1) (Chart III).

1-Benzyl-5-aminoimidazole-4-carboxamide (1) was transformed with formamide to 9-benzyl hypoxanthine (3, 87%)[8]. Specific alkylation[6] of (3) with phenacyl bromide gave 1-phenacyl-9-benzylhypoxanthine (16, 82%). Compound (16) with benzylamine (4 eq.) and p-TsOH (3 eq.) in refluxing xylene for 12h gave the derived product 1-benzyl-5-phenylimidazole (8, 36%) and 1-benzyl-5-aminoimidazole-4-carboxylic-acid benzylamide (17, 33%). Compound (17) with neat MsOH at 125-130°C for 3h gave the carrier (1) (80%) which was available to initiate the second cycle[9].

Compound (1) in an analogous manner, was transformed, via (3) to the corresponding 1-acetonyl-9-benzylhypoxanthine (18) (66%) with bromoacetone and then processed through the cycle to the derived product, 1-benzyl-5-methylimidazole (9, 30%) and (17), (26%), (Chart III).

CHART III


ADENINE CYCLE
HYPOXANTHINE CYCLE
22
21
20
19
1
3
17
8: R = Ph
9: R = Me
16: R = Ph
18: R = Me
PhCH2NH2
H2O
2Br⁻
Br⁻
H-C-NH2
Ph-C-CH2Br
R-C-CH2Br

The derived product (9) was transformed to dl-histidine by sequence, SeO_2 oxidation, $NaBH_4$ reduction, deprotection ($Pd/C/H_2$), treatment with $SOCl_2$, alkylation with NaC(NHAc) $(CO_2Et)_2$ and hydrolysis.

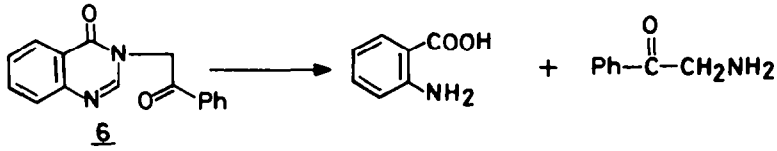
The above cyclic strategy leading to derived imidazoles has also been illustrated with adenine, an actual participant in the ATP-Imidazole cycle (Chart I). The reaction of 9-benzyladenine (19) [10] with phenacyl bromide in dry DMF at rt. gave the bis-salt (20). Interestingly, during model studies, when (19) was treated with benzylbromide in a similar manner, only the 1-alkylated salt was obtained. Compound (20) with hot water -- conditions under which the model system 1,9-dibenzyladenine hydrobromide hydrolyses to the neutral 6-imino-1,9-dibenzyladenine -- gave the monohydrobromide (21) (Chart III).

Compound (21) on reflux in xylene for 4h with benzylamine (4 eq.) gave the derived product 1-benzyl-5-phenylimidazole (8, 38%). In addition, there was obtained a crystalline compound for which, based on spectral and analytical data, structure (22) (mp 136-138°C, 28%) has been assigned.

Most gratifyingly, compound (22) on reflux in xylene with benzylamine (4 eq.) and p-TsOH (1 eq.) for 12h gave an excellent (88%) yield of the derived product 1-benzyl-5-phenylimidazole (8), thus supporting the earlier[4] rationalization that such cyclic operations proceed via key enamine intermediates. As expected, (21) on reflux in dry xylene with benzylamine (4 eq.) and p-TsOH (2 eq.) for 12 h gave directly the derived product (8) (71%); none of the intermediate (22) could be detected. Similarly, (21) was transformed with cyclohexylamine to the derived product 1-cyclohexyl-5-phenylimidazole (14, 50%). It appears therefore that p-TsOH promotes the rapid conversion of (22) to (8)[11,12]. An integrated picture of the present endeavours relating to the generation of derived imidazoles from the carrier imidazole (1) involving hypoxanthine and adenine is presented in Chart III[13].

A comparison of events established for the ATP-Imidazole cycle (Chart I) with that accomplished in the biomimetic studies (Charts II and III) shows that whilst pathways leading to specific N-alkylation are similar, the protocols pertaining to subsequent events are in reverse order. Although the hydrolytic rupture of the 1-6 purine bond of the Natural cycle was accomplished in biomimetic studies, the subsequent events have defied simulation endeavours thus far.

The reaction of 3-phenacylquinazolin-4-one (6) in refluxing 0.4 N aq. NaOH gave anthranilic acid (45%) and 3-amino-2,4-diphenylpyrrole (27, 37%), from dimerization of the resulting ω-amino acetophenone[14].



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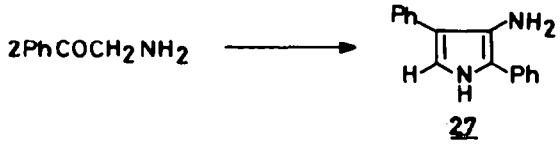

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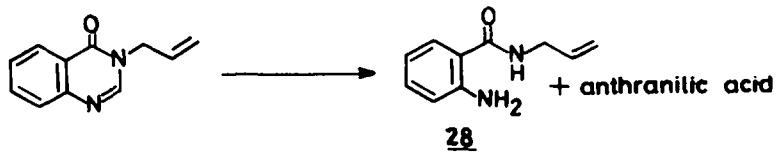
The isolation of anthranilallylamide (28) and anthranilbenzhydrazide (29) on treatment of, respectively, 3-allylquinazolin-4-one and 3-benzamidoquinazolin-4-one with dilute alkali shows that the 2-3 bond is cleaved initially[3c].

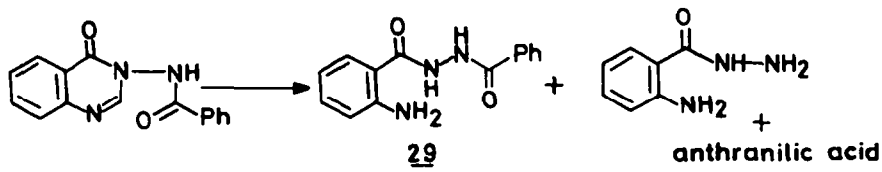
The preference for 2-3 bond rupture was absent when the 2 location was blocked by substitution. The reaction of 2-methyl-3-phenacylquinazolin-4-one (30)[15] with dilute alkali gave the tricyclic compound (31) (97%) which, as could be expected, readily underwent aromatization to give (32).



28

The facile(30) to(32) change illustrates the overwhelming control exerted by the conjugate base of the 2-substituent and provides an excellent method for the synthesis of novel systems of the type (32).

2-Methyl-3-benzamidoquinazolin-4-one (33), having a poor nucleophilic acceptor ligand at 3-location, gave none of the tricyclic compound related to (31) on treatment with dilute alkali. Instead, the triazole (35) arising from the desired 3-4 bond cleavage followed by unwanted cyclization initiated by the resulting amidine unit, was isolated in 35% yields. 2-Phenyl-3-benzamidoquinazolin-4-one (34) gave, in a similar manner, the triazole (36).



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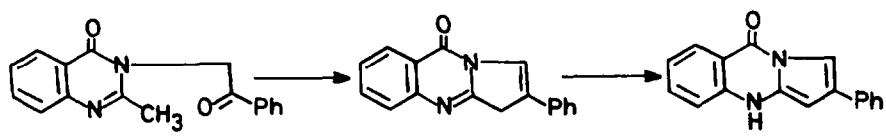
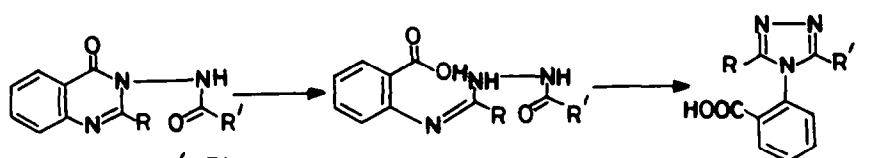


30 31 32

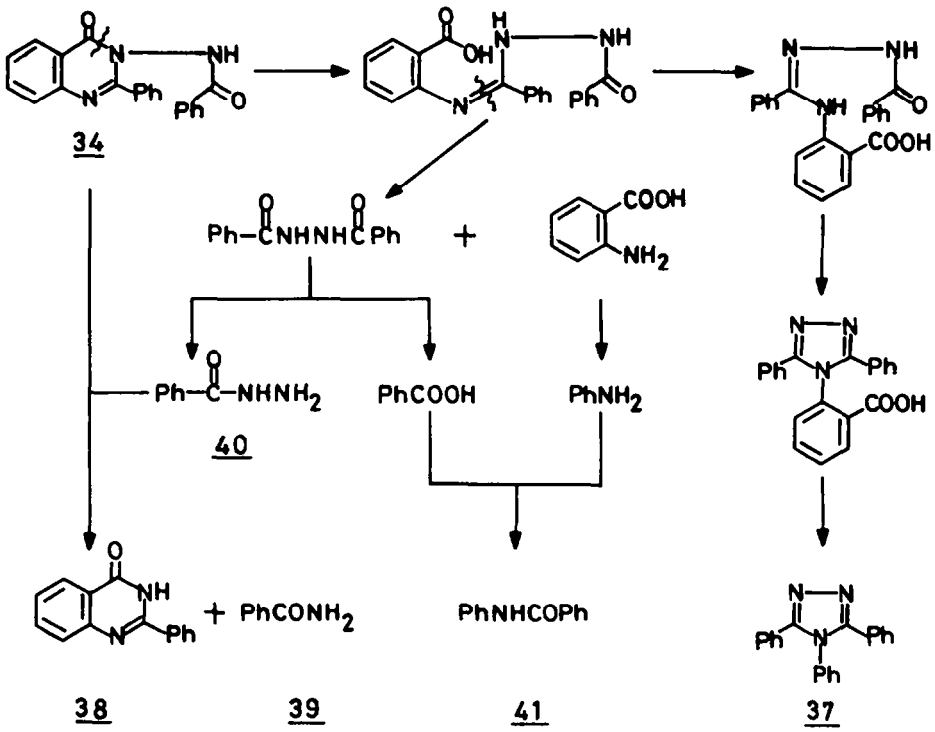
The 1-6 bond in purine in the ATP-Imidazole cycle is cleaved with water. Most experiments to simulate this with suitable models failed. The exception was 2-phenyl-3-benzamidoquinazolin-4-one (34), which on reaction with distilled water at 200°C for 12h gave 3,4,5-triphenyl (1,2,4) triazole (37, 8%), 2-phenylquinazolin-4-one (38, 8%), benzamide (39, 19%) benzhydrazide (40, 15%) and benzanilide (41, 41%). The formation of these products, best understood on the basis of the expected 3-4 bond cleavage, is rationalized in Chart IV.



33 : R = Me ; R′ = Ph
34 : R = R′ = Ph

35 : R = Me ; R′ = Ph
36 : R = R′ = Ph

CHART IV



Acknowledgements

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EXPERIMENTAL[16]

I. The reaction of quinazolin-4-one (4) with phenacyl bromide : Preparation of 3-phenacylquinazolin-4-one (6) :

Phenacyl bromide (7.96g, 40 mmol) was added to a solution of the potassium salt of (4)[17] in MeOH -- prepared from 0.58M KOH in dry MeOH (100 ml) and (4) (5.84g, 40 mmol) -- and the solution left stirred at rt. overnight, filtered, the filtrate evaporated and the residue chromatographed on a short column of silica gel. Elution with PhH:EtOAc :: 70 : 30 gave (6) as colourless prisms, mp 159°C, yield 4.2g (70%) (Found : C, 72.80 ; H, 4.39 ; N, 10.82 ; Calc. for $C_{16}H_{12}N_2O_2$; C, 72.72 ; H, 4.54 ; N, 10.60%) ; IR : ν_{max} (KBr) cm^{-1} 1690, 1665, 1595 ; NMR : δ ($CDCl_3$) 5.45 (s, 2H), 7.35-8.45 (m, 10H) ; m/z : 264 (M^+), 159 (M^+ -PhCO).

II. The reaction of quinazolin-4-one (4) with bromoacetone : Preparation of 3-acetonylquinazolin-4-one (7) :

The reaction of bromoacetone (6g, 43 mmol) with the potassium salt of (4) in MeOH -- prepared from 0.53 M KOH (100 ml) and (4) (5.84g, 40 mmol) -- as described in Experiment I, gave 4g (50%) of (7); colourless needles, mp 158°C (lit.[18] mp 159°C) (Found : C, 65.80 ; H, 5.25 ; N, 13.77 ; Calc. for $C_{11}H_{10}N_2O_2$: C, 65.35 ; H, 4.95 ; N, 13.86%), IR : ν_{max} (KBr) cm^{-1} 1720, 1675, 1610 ; NMR : δ ($CDCl_3$) 2.35 (s, 3H), 4.85 (s, 2H), 7.3-8.4 (m, 5H) ; m/z : 202 (M^+), 159 (M^+ -$COCH_3$).

III. The reaction of 3-phenacylquinazolin-4-one (6) with benzylamine : Isolation of the derived imidazole (8) and the modified carrier (10) :

A stirred mixture of (6) (0.528g, 2 mmol), benzylamine (0.856g, 8 mmol), anhyd. p-TsOH (0.76g, 4 mmol) and dry xylene (50 ml) was refluxed for 12h, cooled, solvents evaporated and the residue chromatographed on silica gel. Elution with PhH : EtOAc :: 80 : 20 gave 0.31g (69%) of anthranilbenzylamide (10) mp 123°C (lit.[19] mp. 123°C) ; IR : ν_{max} (KBr) cm^{-1} 3480, 3360, 3310, 1630 ; NMR : δ ($CDCl_3$) 4.55 (d, 2H), 5.25 (br, 2H), 6.5-7.5 (m, 10H).

Further elution with PhH : EtOAc :: 60 : 40 gave 0.33g (71%) of the derived product, 1-benzyl-5-phenylimidazole (8) as colourless needles from benzene mp. 111°C (Found : C, 81.80 ; H, 6.06 ; N, 11.80 ; Calc. for $C_{16}H_{14}N_2$: C, 82.05 ; H, 5.98 ; N, 11.97%) ; NMR : δ ($CDCl_3$) 5.1 (s, 2H), 6.7-7.9 (m, 12H) ; m/z : 234 (M^+).

IV. The reaction of 3-acetonylquinazolin-4-one (7) with benzylamine : Isolation of the derived imidazole (9) and the modified carrier (10) :

The reaction of (7) (0.606g, 3 mmol) with benzylamine (1.28g, 12 mmol) and anhyd. p-TsOH (1.14g, 6.6 mmol) in dry xylene (50 ml) when carried out exactly as described in Experiment III, gave 0.3g (45%) of anthranilbenzylamide (10) and 0.284g (55%) of the derived product 1-benzyl-5-methylimidazole (9) mp. 99°C (Found : C, 76.39 ; H, 6.62 ; N, 16.57 ; Calc. for $C_{11}H_{12}N_2$: C, 76.74 ; H, 6.97 ; N, 16.28%) ; NMR : δ ($CDCl_3$) 2.1 (s, 3H), 5.05 (s, 2H), 6.85-8.2 (m, 7H) ; m/z : 172 (M^+).

V. The reaction of anthranilbenzylamide (10) with methanesulfonic acid : Regeneration of the carrier (2):

A stirred mixture of (10) (0.363g, 1.6 mmol), MsOH (1.54g, 16 mmol) and dry xylene (15 ml) was refluxed for 10h, solvents evaporated, neutralized with aq. ammonia, extracted with $CHCl_3$ (3x20 ml), dried and evaporated. The residue on chromatography over a short column of silica gel and elution with PhH : EtOAc :: 50 : 50 gave 0.185g (84%) of anthranilamide (2) mp. 110°C (lit. mp. 110°C).

VI. The reaction of 3-phenacylquinazolin-4-one (6) with octadecylamine : Isolation of derived product 1-octadecyl-5-phenylimidazole (11) and anthraniloctadecylamide (13) :

A stirred mixture of (6) (0.528g, 2 mmol), octadecylamine (2.152g, 8 mmol), anhyd. p-TsOH (0.95g, 5 mmol) and dry xylene (40 ml) was refluxed for 18h, solvents evaporated and the residue chromatographed on silica gel. Elution with PhH : EtOAc :: 80 : 20 gave 0.27g (35%) of (13) ; colourless crystals, mp. 86-87°C ; IR : ν_{max} (KBr) 3500, 3400, 3330, 1640, 1590, 1550 ; NMR : δ($CDCl_3$) 0.63-1.73 (m, 35H), 3.33 (m, 2H), 5.2 (s, 2H), 6.05 (br, 1H), 6.43-7.43 (m, 4H) ; m/z : 388 (M^+). Further elution with PhH : EtOAc :: 70 : 30 afforded derived product (11) (0.26g, 33%) as a low melting solid ; NMR : δ($CDCl_3$) 0.6-1.75 (m, 35H), 3.95 (t, 2H), 6.95-7.85 (m+s, 7H) ; m/z : 396 (M^+).

VII. The reaction of 3-acetonylquinazolin-4-one (7) with octadecylamine : Isolation of the derived product 1-octadecyl-5-methylimidazole (12) and amide (13) :

The reaction of 3-acetonylquinazolin-4-one (7) (1g, 5 mmol) and octadecylamine (4g, 15 mmol) promoted by anhyd. p-TsOH (1.9g, 10 mmol) in dry xylene (40 ml) when carried out precisely as described in Experiment VI gave 0.612g (31%) of anthraniloctadecylamide (13) mp. 86-87°C and 0.296g (18%) of the derived imidazole (12), as a low melting solid ; NMR : δ($CDCl_3$) 0.65-1.85 (m, 35H), 2.27 (s, 3H), 3.80 (t, 2H), 7.25 (s, 1H), 7.35 (s, 1H) ; m/z : 334 (M^+).

VIII. The reaction of 3-phenacylquinazolin-4-one (6) with cyclohexylamine : Isolation of the derived product 1-cyclohexyl-5-phenylimidazole (14) and anthranilcyclohexylamide (15) :

The reaction of (6) (0.528g, 2 mmol) and cyclohexylamine (0.792g, 8 mmol) promoted by anhyd. p-TsOH (0.76g, 4.4 mmol) in dry xylene (50 ml) when carried out precisely as described in Experiment III gave 0.115g (65%) of anthranilcyclohexylamide mp. 154°C (lit.[19] mp. 154°C) ; IR : ν_{max} (KBr) cm^{-1} 3470, 3360, 3290, 1620 ; NMR : δ($CDCl_3$) 0.6-2.3 (m, 10H), 3.85 (br, 1H), 5.5 (br, 2H), 5.9 (br, 1H), 6.4-7.3 (m, 4H) and 0.14g (70%) of the derived product 1-cyclohexyl-5-phenylimidazole, colourless thick liquid bp 180°C/0.1 torr (Found : C, 79.35 ; H, 7.48 ; N, 12.40 : Calc. for $C_{15}H_{18}N_2$: C, 79.65 ; H, 7.96 ; N, 12.38% ; NMR : δ ($CDCl_3$) 1-2.35 (m, 10H), 3.85 (br, 1H), 7.35 (br, 7H) ; m/z : 226 (M^+). In this experiment 0.296 g of starting material was recovered.

IX. The reaction of 9-benzylhypoxanthine with phenacyl bromide : Preparation of 1-phenacyl-9-benzylhypoxanthine (16) :

Phenacyl bromide (1.86g, 9 mmol) was added to a solution of the potassium salt of 9-benzylhypoxanthine in MeOH -- prepared from 0.14 M KOH in dry MeOH (50 ml) and 9-benzylhypoxanthine (1.06g, 4.6 mmol) -- the reaction mixture left stirred at rt. overnight, filtered, the filtrate evaporated and the residue chromatographed on silica gel. Elution with $CHCl_3$: MeOH :: 96 : 4 gave 1.3g (82%) of (16) as colourless prisms, mp. 201°C (Found : C, 69.32 ; H, 4.15 ; N, 16.61 ; Calc. for $C_{20}H_{16}N_4O_2$: C, 69.76 ; H, 4.65 ; N, 16.28%) ; IR : ν_{max} (KBr) cm^{-1} 1700, 1610, 1590 ; NMR : δ ($CDCl_3$) 5.3 (s, 2H), 5.5 (s, 2H), 7.2-8.2 (m, 12H) ; m/z : 344 (M^+), 239 (M^+-PhCO).

X. The reaction of 1-phenacyl-9-benzylhypoxanthine (16) with benzylamine : Isolation of the derived imidazole (8) and the modified carrier imidazole (17) :

A stirred mixture of (16) (0.344g, 1 mmol), benzylamine (0.428g, 4 mmol), anhyd. p-TsOH (0.57g, 3 mmol) and dry xylene (30 ml) was refluxed for 12h, cooled, solvents evaporated and the residue chromatographed on silica gel. Elution with PhH : EtOAc :: 50 : 50 gave 0.084 g (36%) of the derived product 1-benzyl-5-phenylimidazole (8) mp. 111°C ; further elution with PhH : EtOAc :: 40 : 60 afforded 0.1g (33%) of 1-benzyl-5-aminoimidazole-4-carboxylic acid benzylamide (17) ; colourless prisms, mp. 159-160°C (lit.[20] mp. 161°C) ; IR : ν_{max} (KBr) cm^{-1} 3400, 3300, 1630 ; NMR : δ ($CDCl_3$) 4.45 (d, 2H, + D_2O s), 4.7 (br, 2H, exch. D_2O), 4.8 (s, 2H), 6.8-7.7 (m, 12H) ; m/z : 306 (M^+).

XI. The reaction of 9-benzylhypoxanthine with bromoacetone : Preparation of 1-acetonyl-9-benzylhypoxanthine (18) :

The reaction of bromoacetone (1.3g, 9 mmol) with the potassium salt of 9-benzylhypoxanthine in MeOH -- prepared from 0.14 M KOH in dry MeOH (50 ml) and 9-benzylhypoxanthine (1.06 g, 4.6 mmol) -- done precisely as described in Experiment IX gave 0.83 g (66%) of (18) ; colourless needles, mp. 155-158°C (Found : C, 64.10 ; H, 5.30 ; N, 19.35 ; Calc. for $C_{15}H_{14}N_4O_2$: C, 63.83 ; H, 4.96 ; N, 19.86%) ;

IR : ν_{max} (KBr) cm^{-1} 1715 (br), 1580 ; NMR : δ ($CDCl_3$) 2.25 (s, 3H), 4.95 (s, 2H), 5.3 (s, 2H), 7.3 (s, 5H), 7.75 (s, 1H), 7.95 (s, 1H) ; m/z : 282 (M^+), 239 (M^+-$COCH_3$).

XII. The reaction of 1-acetonyl-9-benzylhypoxanthine (18) with benzylamine : Isolation of the derived imidazole (9) and the modified carrier imidazole (17) :

A stirred mixture of (18) (0.282g, 1 mmol), benzylamine (0.428g, 4 mmol), anhyd. p-TsOH (0.57g, 3 mmol) and dry xylene (30 ml) was refluxed for 12h, solvents evaporated and the residue chromatographed on silica gel. Elution with PhH : EtOAc : 50 : 50 gave 0.050 g (30%) of the derived product 1-benzyl-5-methylimidazole (9) mp. 99°C. Further elution with PhH : EtOAc :: 40 : 60 gave 0.079g (26%) of (17) as colourless prisms, mp. 161°C.

XIII. The reaction of 1-benzyl-5-aminoimidazole-4-carboxylic acid benzylamide (17) with methane sulfonic acid : Regeneration of carrier, 1-benzyl-5-aminoimidazole-4-carboxamide (1) :

A stirred mixture of (17) (0.28g, 0.9 mmol) and MsOH (1.5 ml, excess) was held at 125-130°C for 3h, cooled, added to cold water (~ 10 ml), neutralised with aq. ammonia, filtered, washed with cold water and dried. Crystallization from ethanol gave 0.176g (88%) of (1) ; colourless prisms mp. 256°C (lit.[8] mp. 257°C).

XIV. The transformation of the derived product 1-benzyl-5-methylimidazole (9) to dl-histidine : 1-Benzyl-5-formylimidazole :

A mixture of (9) (0.172g, 1 mmol), SeO_2 (0.120g, 1.2 mmol) and glacial AcOH (5 ml) was refluxed for 10h, evaporated and the residue chromatographed on silica gel. Elution with EtOAc : MeOH :: 80 : 20 gave 0.066g (35.4%) of 1-benzyl-5-formylimidazole which was used as such in the following experiment. IR : ν_{max} (neat) cm^{-1} 1690 (-CHO).

1-Benzyl-5-hydroxymethylimidazole :

A solution of the above aldehyde in dry MeOH (10 ml) was admixed with $NaBH_4$ (0.100g, 2.38 mmol), left stirred at rt. for 5h, evaporated and chromatographed on silica gel. Elution with EtOAc : MeOH : 80 : 20 gave 0.041g (61%) of 1-benzyl-5-hydroxymethylimidazole mp. 134°C (lit.[21] mp. 134-135°C) identical to an authentic sample prepared from D-fructose[21] ; NMR : δ ($CDCl_3$) 4.46 (s, 2H), 4.7 (s, 1H), 5.14 (s, 2H), 6.61-7.91 (m, 7H).

5-Hydroxymethylimidazole :

The deprotection was achieved in quantitative yields by hydrogenation over Pd/C ; Picrate mp. 202-203°C (lit.[22], mp. 203°C).

dl-Histidine :

5-hydroxymethylimidazole was transformed to dl-histidine by known procedures[23,24]. The amino acid thus obtained was identical in all respects to an authentic sample.

XV. The reaction of 9-benzyladenine (19) with phenacyl bromide : Preparation of the bis-alkylated salt (20) :

A stirred solution of (19)[10] (2.25g, 10 mmol) and phenacyl bromide (3g, 15 mmol) in dry DMF (50 ml) was left stirred overnight at rt., evaporated, the residue washed with dry ether (3 x 20 ml) and crystallized from abs. MeOH to give 2.218g (35%) of (20) ; colourless prisms, mp. 219-223°C (Found : C, 54.40 ; H, 4.42 ; N, 10.82 ; Calc. for $C_{28}H_{25}N_5O_2Br_2$: C, 53.93 ; H, 4.01 ; N, 11.23%) ; IR : ν_{max} (KBr) cm^{-1} 3420, 3060, 1690, 1630, 1600.

XVI. Hydrolysis of the bis-salt (20) : Preparation of the mono-salt (21) :

A suspension of the bis-salt (20) (1.2g, 1.93 mmol) in water (90 ml) was left immersed in boiling water for 0.25h, cooled, filtered and crystallized from MeOH to give 0.96g (92%) of the mono-salt (21) ; colourless needles, mp. 225-228°C (Found : C, 62.04; H, 4.22; N, 12.93%; Calc. for $C_{28}H_{24}N_5O_2Br$: C, 61.99; H, 4.43; N, 12.91%); IR : ν_{max} (KBr) cm^{-1} 3460, 3020, 1710, 1660, 1600 ; ^1H NMR : δ (DMSO-d_6) : 5.05 (s, 2H), 5.7 (s, 2H), 6.4-7.1 (m, 16H), 7.35 (d, J=8Hz, 2H), 7.91 (s, 1H), 8.75 (s, 1H) ; ^{13}C NMR : δ (DMSO-d_6) : 190.8 (carbonyl), 145.5, 136.0, 134.7, 134.5, 133.9, 133.8, 131.6, 129.1, 128.9, 128.7, 128.3, 125.6, 114.1, 109.59, 55.7 (-CH_2), 49.1 (-CH_2).

XVII. The reaction of the bis-alkylated mono-salt (21) with benzylamine : Isolation of the key enamine intermediate (22) and derived product 1-benzyl-5-phenylimidazole (8) :

A mixture of (21) (0.9g, 1.66 mmol), benzylamine (1.2 ml, 11.2 mmol) and dry xylene (30 ml) was refluxed for 4h, evaporated and chromatographed on silica gel. Elution with PhH : EtOAc :: 65:35 gave 0.25g (28%) of the enamine (22) ; colourless crystals mp. 136-138°C (Found : C, 78.20; H, 5.43 ; Calc. for $C_{34}H_{30}N_6$: C, 78.16 ; H, 5.74%) ; IR : ν_{max} (KBr) cm^{-1} 3240, 1630 ; NMR : δ($CDCl_3$) 3.7 (m,2H + D_2O), 4.22 (s, 2H), 4.75 (s, 1H), 4.85 (s, 1H), 5.2 (m, 1H, exch. with D_2O), 7.2-8.0 (m, 23 H) ; m/z : 522 (M^+). Further elution with PhH : EtOAc :: 55 : 45 gave 0.153g (38%) of the derived product (8) mp. 111°C.

XVIII. The reaction of (22) with benzylamine : Demonstration of the intermediacy of (22) in the formation of the derived product (8) :

A mixture of (22) (0.25g, 0.478 mmol), benzylamine (0.2g, 1.9 mmol), anhyd. p-TsOH (0.108g, 0.57 mmol) and dry xylene (30 ml) was refluxed for 6h, evaporated and chromatographed on silica gel. Elution with PhH : EtOAc :: 60 : 40 gave 0.098g (88%) of the derived product 1-benzyl-5-phenylimidazole (8), mp. 110-111°C.

XIX. The reaction of (21) with benzylamine and p-TsOH : The direct transformation to the derived imidazole (8) :

A mixture of (21) (0.238g, 0.45 mmol), benzylamine (0.2g, 1.8 mmol), anhyd. p-TsOH (0.17g, 0.9 mmol) and dry xylene (20 ml) was refluxed for 12h, evaporated and chromatographed on silica gel. Elution with PhH : EtOAc :: 60 : 40 gave 0.07g (72%) of the derived imidazole (8) mp. 111°C.

XX. The reaction of (21) with cyclohexylamine and p-TsOH : Isolation of the derived product 1-cyclohexyl-5-phenylimidazole (14) :

A mixture of (21) (0.450g, 0.83 mmol) cyclohexylamine (0.520g, 5.25 mmol), anhyd. p-TsOH (0.300g, 1.57 mmol) and dry xylene (30 ml) was refluxed for 18h, evaporated and chromatographed on silica gel. Elution with PhH : EtOAc :: 70 : 30 gave 0.091g (49%) of (14) whose properties were identical to the sample obtained from Experiment VIII.

XXI. The reaction of 3-phenacylquinazolin-4-one (6) with aqueous alkali : Isolation of 3-amino-2,4-diphenylpyrrole (27) and anthranilic acid :

A suspension of (6) (0.310g, 1.17 mmol) in aq. NaOH (0.6 N, 30 ml) was refluxed for 16h, cooled, extracted with ethyl acetate (3 x 25 ml), dried, evaporated and the residue on crystallization from ethanol gave greenish yellow needles of (27) ; 0.103g (37%), mp. 180-181°C (lit.[25] mp 178-179°C) ; IR : ν_{max} (KBr) cm^{-1} 3430, 3240, 1615 ; NMR : δ ($CDCl_3$) 3.67 (br, 2H, exch. D_2O), 6.6 (d, J=3Hz, 1H), 6.87-8.1 (m, 11H) ; m/z : 234 (M^+).

The aqueous layer was adjusted to pH ~ 7 with 2N H_2SO_4, extracted with CH_2Cl_2 (3 x 20 ml), dried, evaporated and the residue on crystallization from benzene gave 0.073 g (45%) of anthranilic acid mp 144°C (lit. mp 144-146°C).

XXII. The reaction of 2-methylquinazolin-4-one with phenacyl bromide : Preparation of 2-methyl-3-phenacylquinazolin-4-one (30) :

Phenacyl bromide (12.13g, 61 mmol) was added to a solution of the potassium salt of 2-methylquinazolin-4-one -prepared from 2- methylquinazolin-4-one[26] (10.66g, 66.6 mmol) and 1M KOH in dry ethanol (95 ml) — left stirred at rt. overnight, filtered, the filtrate evaporated and the residue chromatographed on silica gel. Elution with PhH : EtOAc :: 90 : 10 gave compound, mp 135°C which was identified as a mixture of epoxides resulting from the base promoted Darzen' s type condensation of phenacyl bromide[15] ; yield 2g (21%).

Further elution with PhH : EtOAc :: 70 : 30 gave 4.5g (24%) of (30) mp 164°C (Found : C, 73.10 ; H, 4.71; N, 9.97 ; Calc. for $C_{17}H_{14}N_2O_2$: C, 73.38; H, 5.03; N, 10.07%) ; IR : ν_{max} (KBr) cm^{-1} 1670, 1590 ; NMR : δ ($CDCl_3$) 2.46 (s, 3H), 5.39 (s, 2H), 7.26-8.36 (m, 9H) ; m/z : 278 (M^+).

XXIII. The reaction of 2-methyl-3-phenacylquinazolin-4-one (30) with aqueous alkali : Isolation of the tricyclic compound (31) :

A suspension of (30) (0.826 g, 2.97 mmol) in aq. NaOH (0.75N, 40 ml) was refluxed for 14 h, cooled, acidified with 2N H_2SO_4 (pH ~ 3), extracted with CH_2Cl_2 (3 x 20 ml), dried and evaporated to give 0.746 g (97%) of (31), mp 205-206°C ; IR : ν_{max} (KBr) cm^{-1} 1665 ; NMR : δ ($CDCl_3$) 5.05 (d, J=0.5 Hz, 2H, allylic coupling), 6.9 (t, J=0.5Hz, 1H), 7.3-8.4 (m, 9H) ; m/z : 260 (M^+).

XXIV. Thermal aromatization of (31) : Isolation of the aromatic tricyclic system (32) :

Crystallization of (31) either from hot CH_2Cl_2 or from hot benzene led to quantitative isomerization to the aromatic compound (32), mp 185°C ; IR : ν_{max} (KBr) cm^{-1} 3400 (br), 1660 ; NMR : δ ($CDCl_3$) 7.26-8.44 (m, ar).

XXV. The reaction of 2-methyl-3-benzamidoquinazolin-4-one (33) with aqueous alkali : Isolation of 4-(o-carboxyphenyl)-3-phenyl-5-methyl(1,2,4) triazole (35) :

A suspension of (33)[27] (3.5 g, 13 mmol) in aq. NaOH (1N, 50 ml) was refluxed for 12h, cooled, extracted with ethyl acetate (5 x 50 ml) to remove 0.6 g of unchanged (33) the aqueous layer acidified with 2N H_2SO_4, filtered, dried and crystallized from hot MeOH to give 1.2g (34%) of (35), mp 245-246°C. Compound (35)[4] gave with CH_2N_2, in quantitative yields, the methyl ester, mp 159-161°C (Found : C, 70.04; H, 4.89 ; N, 13.86 ; Calc. for $C_{17}H_{15}N_3O_2$: C, 69.62; H, 5.12; N, 14.33%) ; IR : ν_{max} (KBr) cm^{-1} 1720; NMR : δ($CDCl_3$) 2.3 (s, 3H), 3.6 (s, 3H), 7.2-8.2 (m, 9H) ; m/z 293 (M^+), 234 (M^+ -COOMe).

XXVI. The reaction of 2-phenyl-3-benzamidoquinazolin-4-one (34) with aqueous alkali : Isolation of 4-(o-carboxyphenyl)-3,5-diphenyl(1,2,4) triazole (36) :

A suspension of (34)[28] (1.2g, 3 mmol) in aq. NaOH (1N, 25 ml) was refluxed for 12h, the clear solution cooled, the precipitated sodium salt collected, acidified with 2N H_2SO_4 (~ 30 ml), left stirred overnight, filtered and crystallized from hot methanol to give 0.6g (50%) of (36), mp 319-320°C. Compound (36) was transformed with CH_2N_2, in quantitative yields to the methyl ester, mp 208-210°C (Found : C, 73.90; H, 5.04; N, 11.90; Calc. for $C_{22}H_{17}N_3O_2$: C, 74.37; H, 4.79; N, 11.83%) ; IR : ν_{max} (KBr) cm^{-1} 1720 ; NMR : δ($CDCl_3$) 3.55 (s, 3H), 7.2-8.0 (m, 14H); m/z : 355 (M^+), 295 (M^+-COOMe).

XXVII. The reaction of 2-phenyl-3-benzamidoquinazolin-4-one (34) with distilled water at 200°C : Isolation

of 3,4,5-triphenyltriazole (37), 2-phenylquinazolin-4-one (38), benzamide (39), benzhydrazide (40) and benzanilide (41) :

A suspension of (34) (0.3 g, 0.9 mmol) in distilled water (3 ml) was sealed and held at 200°C for 12h. Five such batches so processed were cooled, cautiously opened, extracted with ethyl acetate, evaporated and chromatographed.

Eluent			Compound	Yield (%)	(mp)	lit. mp	m/z
PhH	:	EtOAc					
95	:	5	(41)	0.35g (41)	163-164°C	162-164°C	197(M^+)
90	:	10	(39)	0.1g (19)	126-128°C	128-129°C	122$(M+1)^+$
60	:	40	(38)	0.08g (8)	229°C	223°C[29]	-
50	:	50	(37)	0.1g (8)	296-297°C	299°C[30]	297(M^+)
10	:	90	(40)	0.09g (15)	110-112°C	112°C	136(M^+)

REFERENCES AND NOTES

1. This description is appropriate for several cyclic operations and permits the variation with reference to the nature of the carriers. We thank the referee for suggesting this terminology.
2. The cyclic strategy used in Nature for important life processes such as Calvin cycle, Krebs cycle, Urea cycle and the ATP-Imidazole cycle must have evolved over a period of time. These highlight the best practice of organic synthesis in terms of artistry and versatility.
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5. The first successful simulation was achieved with 3-(o-aminophenyl)quinazolin-4-one (5; mp 140°C) — prepared from (4) and o-phenylenediamine — in reflux in aq. 1N NaOH for 1.5 hr leading to the derived product benzimidazole (73%) and the carrier anthranilic acid (79%).
6. The site of such alkylations has been established by extensive studies carried out on the model system (ref. 4).
7. In spite of the continuing interest in imidazoles (see M.R. Grimmett in Advances in Heterocyclic Chemistry, Ed. A.R. Katrizky and A.J. Boulton, Vol. 27, p. 242, Academic Press, 1980), the procedures for the synthesis of N-protected 5-substituted imidazoles are scarce and the pathways cumbersome.
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9. Blank experiments have clearly established that the amides (10) and (17) do not arise from trivial fragmentation of, respectively, either (6), (7) or (16), (18).
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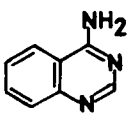
11. Compound (22) on reflux in xylene with only p-TsOH failed to give derived imidazoles.
12. An aspect that has thus far eluded solution is the characterization of the compound arising from separation of the derived imidazole. In the case of earlier cycles this was not a problem. The envisaged compound here (Chart III, Adenine Cycle) is endowed with so many basic and reactive nitrogens. It is not surprising therefore that the fraction after separation of the derived product was found to be complex.
13. Whilst derived products could be obtained from 9-benzyladenine (19), the related model namely, 4-aminoquinazoline (23) failed.



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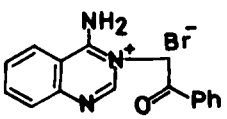

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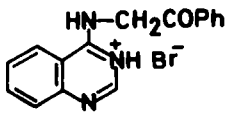

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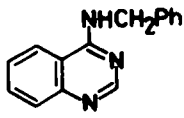

26

Alkylation of (23) with 1.5 eq. of phenacyl bromide in DMF at rt. gave the 3-monoalkylated salt (24, 65%). Treatment of (24) with hot water, under conditions for (20) → (21) change, resulted in Dimroth rearrangement (D.J. Brown in Mechanisms of Molecular Migrations Ed. B.S. Thyagarajan, Wiley, New York 1968, Vol.1, p. 209; M. Wahren, Z. Chem. 9, 241 (1969)) leading to the isomeric salt (25), which on treatment with benzylamine (4 eq.) and p-TsOH (2 eq.) in refluxing xylene for 12h gave 4-benzylamino quinazoline (26, 56%). The structure of (26) was established by comparison with an authentic sample.

14. In support of this, 3 N-(2',2'diethoxyethyl)quinazolin-4-one under similar alkaline conditions gave 1-amino-2, 2-diethoxy ethane in 83% yields.

15. The apparently straight forward preparation of 2-methyl-3-phenacylquinazolin-4-one (30), by the reported procedure (A.P. Bhaduri, L.M. Khanna and M.L. Dhar, Indian J. Chem., 2, 159 (1964)) involving alkylation of the conjugate base of 2-methylquinazolin-4-one with phenacyl bromide, was, in the event, beset with unexpected complications. The reaction gave a compound mp 135-136°C, in agreement with that reported for (30) and a more polar compound mp 164°C. Further studies established that the compound with mp 164°C was in fact the desired (30) and that the substance with mp 135-136°C resulted from a base promoted Darzen type condensation of phenacyl bromide (C.L. Stevens, R.J. Church and V.J. Traynelis, J. Org. Chem., 19, 522 (1954) ; J. A. Berson, J. Am. Chem. Soc., 74, 5175 (1952) ; J.F. Wright and L.M. Minsk, J. Am. Chem. Soc., 75, 98 (1953)).

16. MPs are not corrected. IR spectra were recorded in a PE 580 instrument as KBr discs. NMR spectra was obtained on a 10-15% solution in $CDCl_3$ or DMSO (d_6) on a FT R-600 instrument. The chemical shifts are recorded in ppm with TMS at 0.00 as internal standard. Mass spectra were obtained on a Jeol instrument. Silica gel (Acme) was used for TLC and column chromatography (100-200 mesh). Reactions were monitored wherever possible by TLC. The organic extracts were invariably dried over anhydrous $MgSO_4$ and solvents evaporated in vacuo.

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