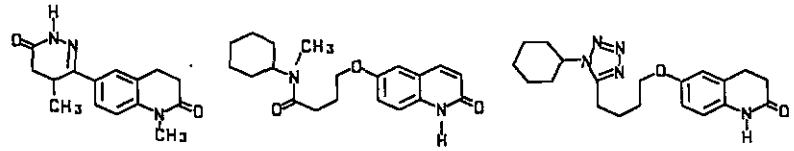
SYNTHESIS OF TRIAZOLO- AND TETRAZOLOQUINOLINE DERIVATIVES WITH ANTITHROMBOTIC ACTIVITY

Patrice Desos, Gilbert Schlewer*, and Camille Georges Wermuth

Département de Pharmacochimie Moléculaire, Centre de Neurochimie du CNRS, 6, rue Blaise Pascal, 67000 Strasbourg France

Abstract - *The syntheses of eight triazolo- or tetrazoloquinolines derived from Y-590, an antithrombotic agent, are reported with the objective to investigate the bioisosteric replacement of the quinolinone lactam function of Y-590 by a triazolic or tetrazolic ring system. The synthetic strategy employed involved either the formation of the triazolo-or tetrazoloquinoline followed by the introduction of the pyridazinone side-chain for the preparation of monotriazolo- or monotetrazoloquinolines, or the synthesis of a pyridazinonylquinolinone followed by the simultaneous creation of bis triazolic or tetrazolic fused rings.*

Various heterocyclic systems have been described for their potential to prevent the thrombus formation. Among these heterocyclic system are pyrimido[5,4-d]pyrimidines such as dipyridamole[1] and RX-RA 69[2], pyrimido[1,6-a]isoquinolines such as trequinsine[3,4], imidazo[2,1-b]quinazolin-2-ones such as anagrelide[5] and RO-15204[6], phthalazines such as phthalazinole[7], pyridazinones such as Y-590[8] or amipizone[9], and quinolinones such as cilostamide[10] and cilostazol[11]. Several molecular mechanisms of action have been hypothesized to account for this property. The best explanation advanced thus far correlates the antiaggregant effects of these compounds with their ability to increase cyclic AMP (cAMP) and, in some cases, cyclic GMP (cGMP) levels in blood platelets by inhibition of the corresponding phosphodiesterases[12]. Specifically phosphodiesterase inhibitors from the 2(*1H*)-quinolinone family, such as Y-590 **1**[8], cilostamide **2**[10], or cilostazol **3**[11] present interesting antithrombotic profiles insofar that both act with a relative selectivity on platelet phosphodiesterase and are orally active. Cilostazol is active at 10 mg/kg and is now in clinical testing. Y-590, although showing also a strong antihypertensive activity, possesses potent antithrombotic activity at doses as low as 0.1 mg/kg per os.



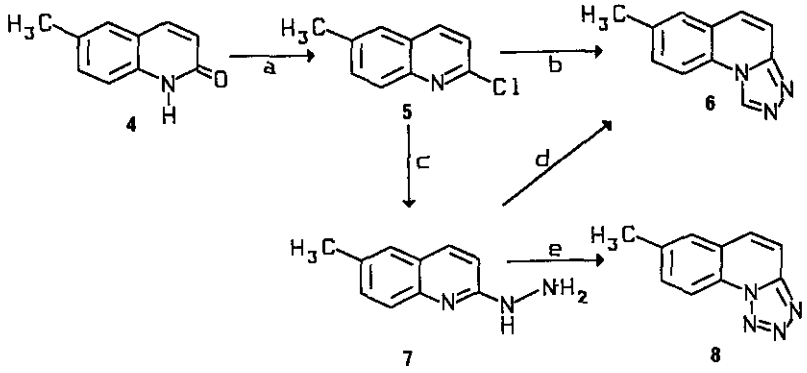
1 2 3

The objective of the present study was to investigate the bioisosteric replacement of the quinolinone lactam function found in Y-590 by a triazolic or tetrazolic ring system (Figure 1). An attempt was also made to replace both the quinolinone and the pyridazinone CONH groups of Y-590 by isosteric triazole or tetrazole rings. We describe below the synthesis of such fused heterocyclic systems.

Figure 1

Synthesis

The synthesis of the monotriazolic and monotetrazolic derivatives **16a, 16b, 17a, 17b, 31a,** and **31b** required the introduction of the triazolic or tetrazolic ring system in an early stage in the synthesis and the pyridazine ring was added later (Figures 2 and 3). The 6-methyl substituted 1,2,4-triazolo[4,3-a]quinoline 6 and tetrazolo[1,5-a]quinoline 8 were prepared by literature methods (Figure 2).



4 5 6 7 8

Figure 2 : a : $POCl_3$; b : $O=CHNHNH_2$; ç : NH_2NH_2. H_2O, n-butanol ; d: $HC(OEt)_3$; e : $NaNO_2$

Thus treatment of the 6-methyl-2(*1H*)-quinolinone 4[13,14] with phosphorus oxychloride yielded the 6-methyl-2-chloroquinoline 5 which was converted into the triazoloquinoline 6 by reaction with formylhydrazine or, with better yields, in two steps, by successive treatment with hydrazine hydrate and triethyl orthoformate. The tetrazolic analogue 8 was obtained from the hydrazinoquinoline 7 by treatment with sodium nitrite and acetic acid.

Mild oxidation of the benzylic methyl group of 6 or 8 using selenium oxide or ceric ammonium nitrate did not lead to the aldehyde 10. However this oxidation was easily achieved using chromium trioxide in acetic anhydride, and subsequent hydrolysis of the gem-diacetates 9 to give the aldehyde 10.

For the construction of the γ-keto ester side chain, an α-morpholinoacetonitrile anion was prepared starting from the formyl group and added to crotononitrile in accordance with a general method first described by Leete [16] and later developed by Albright and MacEvoy[17,18]. Thus the addition of morpholine in the presence of p-toluenesulfonic acid transforms 10 in a nonisolated imino derivative 11 which, after the addition of potassium cyanide, yields the α-morpholinoacetonitrile 12. Under alkaline conditions (Triton B) 12 forms a masked acyl anion which reacted through a Michael addition with crotononitrile to give the dinitrile 13. The hydrolysis of the dinitrile was conducted in two steps. The reaction with aqueous acetic acid regenerated the keto function 14, and a treatment with sulfuric acid (or hydrochloric acid) and ethanol led to the keto ester 15. The cyclization into the 3-pyridazinone 16 or into the 2-methyl-3-pyridazinone 17 was achieved by reaction of the keto ester 15 with hydrazine hydrate and methylhydrazine respectively[19]. Under the same conditions the treatment of the γ-keto ester 15 with phenylhydrazine led to the hydrazide 18 which was cyclized by heating in sulfuric acid to give 19 (Figure 3).

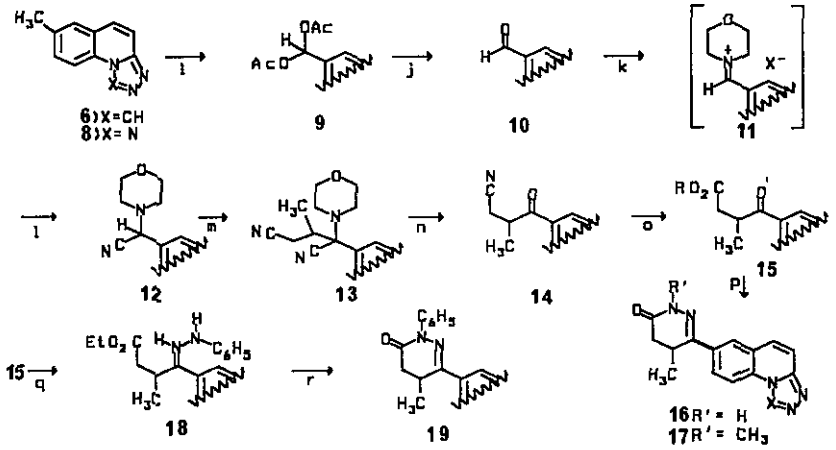


Figure 3 : i : CrO_3/Ac_2O ; j : H_3O^+ ; k : morpholine, TsOH ; l : KCN ; m : crotononitrile ; n : AcOH, H_2O ; o : H^+/EtOH ; p : NH_2NHR'; q : $NH_2NHC_6H_5$; r : H_3O+.

The strategy for the preparation of the bis triazolic and bis tetrazolic derivative **31a** and **31b** implies the simultaneous creation of the two fused triazolic rings (Figure 4).

The 3,4-dihydro-2(*1H*)-quinolinone **21** was prepared either by catalytic hydrogenation of the quinoline **20** in the presence of platinum oxide ; or more easily, by cyclization of the anilide of β-chloropropionic acid **22** which was itself prepared by condensation of aniline with β-chloropropionylchloride. The introduction of the ketocarboxylic acid side-chain was then achieved by a Friedel-Crafts acylation. Cyclization of this keto acid **23** with hydrazine hydrate yielded the dihydropyridazinone **24**. The simultaneous introduction of the two double bond into the pyridazinone and the quinolinone was not possible. We have always observed the formation of a mixture of partially dehydrogenated and unseparable compounds.

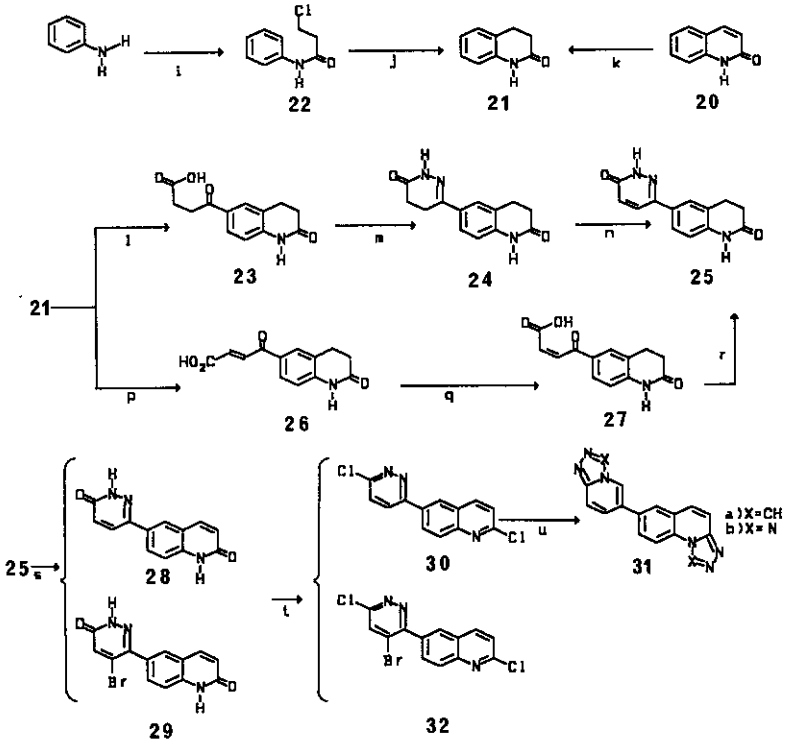


Figure 4 : i : $ClCOCH_2CH_2Cl$; j : $AlCl_3$; k : H_2, PtO_2 ; l : succinic anhydride ; m : NH_2NH_2, H_2O, n-butanol ; n : sodium m-nitrobenzenesulfonate ; p : maleic anhydride ; q : sodium sulfite ; r : NH_2NH_2, H_2O, n-butanol ; s : Br_2, AcOH ; t : $POCl_3$; u : cf figure 2 c,d,e.

Using sodium *m*-nitro-benzenesulfonate[20] a selective dehydrogenation into the pyridazinone **25** was observed.This compound **24** could also be obtained by replacing succinic anhydride by maleic anhydride in the initial Friedel-Crafts reaction. The unsaturated trans-keto-acid **26** was converted into its cis isomer **27** by treatment with sodium sulfite. Cyclization of **27** with hydrazine hydrate gave **24**. Treatment of **24** with bromine in acetic acid oxidized the quinolinone ring of **29**. As a side reaction product we always observed the formation of 8-bromoquinolinone **29**. Compounds **28** and **29** were not separable, but the mixture was directly treated with phosphorus oxychloride. The desired compound **30** was purified by column chromatography and transformed into the corresponding triazolic derivative **31** using the same procedure we have described above (Figure 4).

All the compounds prepared presented some antiaggregant activity. Particularly, compound **16a** was, in vitro, as potent as Y-590 (IC_{50} = 52 nM for Y-590 and 22 nM for compound **16a** on ADP induced aggregation). These results demonstrate the possible isosteries between the CONH group and the triazolic or tetrazolic heterocycles in this series.

AKNOWLEDGEMENTS

We thank Veronique Sonntag for technical help and Robert Kerr for his comments.

EXPERIMENTAL SECTION

Melting points were obtained on a calibrated hot stage apparatus and are uncorrected. ^{1}H-Nmr spectra were recorded on a Bruker WP 60 spectrometer or a Bruker 200AC instrument using the δ scale with reference to tetramethylsilane.

6-Methyl-2-chloroquinoline 5

A mixture of 13 g (0.16 mol) of 6-methyl-2(*1H*)-quinolinone[13,14] and 150 ml of phosphorus oxychloride was stirred for 17 h at 60°C. After evaporation of the excess of phosphorus oxychloride under reduced pressure the residue was cooled in an ice bath and then hydrolyzed by addition of crushed ice. The precipitate was filtered, washed with water and dried over magnesium sulfate. The yield of 6-methyl-2-chloroquinoline **5** after recrystallization from methanol was 12g (85%). mp 115.2-115.5°C. Anal. Calcd for $C_{10}H_8ClN$: C, 67.61 ; H, 4.53 ; N, 7.88. Found : C, 67.66 ; H, 4.22 ; N, 7.89. ^{1}H-Nmr (d_6 acetone) : 2.51 (s, 3H,-CH_3), 7.42 (d, J = 8.7, 1H, Ar), 7 50-8.00 (AB system + s, J =8.2, 3H, Ar), 8.20 (d, J = 8.7, 1H, Ar).

7-Methyl-1,2,4-triazolo[4,3-a]quinoline 6

Method A : Starting from 6-methyl-2-chloroquinoline **5**

A mixture of 8.0 g (0.048 mol) of 5 and 5.4 g (0.096 mol) of formylhydrazine in 80 ml of n-butanol was heated at 110 °C for 15 h. After evaporation of the solvent to dryness the residue was partitioned between water and dichloromethane. The product was purified by column chromatography on silica gel using a mixture of ethyl acetate - dichloromethane - methanol : 6-3-1 as eluent. The yield of 6 was 4.9 g (57%). mp 194.5°C ; Anal. Calcd for $C_{11}H_9N_3$: C, 72.11 ; H, 4.95 ; N, 22.93. Found : C, 72.62 ; H, 4.77 ; N, 22.92. ^{1}H-Nmr ($CDCl_3$): 2.50 (s, 3H, $-CH_3$), 7.00-7.90 (m, 5H, Ar), 9.06 (s, 1H, -N-CH=N-).

Method B : Starting from 6-methyl-2-hydrazinoquinoline 7

To a solution of 15 g (0.086 mol) of 7 (see below) in 200 ml of n-butanol, 14 g (0.09 mol) of triethyl orthoformate was added and the mixture was stirred at 100°C for 5 h. After evaporation of the solvents the residue was poured into water, filtered, washed with acetone and dried over magnesium sulfate. The yield of triazole 6 was 15 g (95%).

6-Methyl-2-hydrazinoquinoline 7

A suspension of 10 g (0.056 mol) of 5 in 100 ml of hydrazine hydrate was heated at 110°C for 15 h. After cooling to room temperature the mixture was poured into 200 ml water. The solid was filtered, washed with water and dried over magnesium sulfate. After recrystallization from chloroform and hexane the yield of compound 7 was 7.4 g (76%). mp 144°C. Anal. Calcd for $C_{10}H_{11}N_3$: C, 69.34 ; H, 6.40, N, 24.27. Found : C, 69.55 ; H, 6.57 ; N, 24.40. ^{1}H-Nmr ($CDCl_3$): 2.43(s, 3H, $-CH_3$), 4.00 (broad s, exchangeable with D_2O, 1H, NH), 6.00 (broad s, exchangeable with D_2O, 2H, NH_2), 6.69 (d, J = 8.2, 1H, Ar), 7.10-7.80 (m, 4H, Ar).

Methyltetrazolo[1,5-a]quinoline 8

To a stirred solution of 50 g (0.289 mol) of hydrazino derivative 7 in 500 ml of 2N acetic acid a solution of 20.0 g (0.318 mol) of sodium nitrite in 200 ml of water was added. After 1 h stirring at room temperature the precipitate was filtered, washed with water and dried at 80°C. After recrystallization from methanol the yield of compound 8 was 45 g (84%). mp 162.7°C. Anal. Calcd for $C_{10}H_8N_4$: C, 65.20 ; H, 4.38 ; N, 30.42. Found : C, 65.38 ; H, 4.49 ; N, 30.35. ^{1}H-Nmr ($CDCl_3$): 2.61 (s, 3H, $-CH_3$), 7.30-7.60 (m, 4H, Ar), 8.55 (d, J = 8.3, 1H, Ar).

7-Diacetyloxymethyl-1,2,4-triazolo[4,3-a]quinoline 9a

To an ice cooled flask containing 15.0 g (0.082 mol) of 6 in 65 ml of acetic anhydride, 18 ml of concentrated sulfuric acid was added dropwise with continuous stirring. Then a cooled solution of 22.8 g of chromium trioxide in 120 ml of acetic anhydride was carefully added. After stirring at 0°C for 2 h and at room temperature overnight, the mixture was poured into

1 l of cold water and extacted with dichloromethane. The organic layer was washed with a saturated solution of aqueous sodium bicarbonate, water and brine, dried over magnesium sulfate and the solvents removed under reduced pressure. The yield of compound **11a** was 11.5 g (45%). mp 201°C. ^{1}H-Nmr ($CDCl_3$) : 2.17 (s, 6H, -CH_3), 7.50-7.80 (m, 5H, Ar), 7.97 (s, 1H, -$CH(OAc)_2$), 9.28 (s, 1H, N=CH-N).

7-Diacetyloxymethyltetrazolo[1,5-a]quinoline 9b

The same procedure as for **11a** was used, starting from **8**. Yield 58%. mp 157°C. ^{1}H-Nmr ($CDCl_3$) : 2.15 (s, 6H, -CH_3), 7.70-8.30 (m, 6H, Ar + $CH(OAc)_2$).

7-Formyl-1,2,4-triazolo[4,3-a]quinoline 10a

A mixture of 11.5 g (0.040 mol) of **11a** in 20 ml of water, 20 ml of ethanol and 1 ml of concentrated sulfuric acid was refluxed for 1 h. After evaporation under reduced pressure, the residue was poured into 100 ml of water and extracted with dichloromethane. The organic layer was dried over magnesium sulfate and the solvents removed. For analytical purposes a small part of the product was recrystallized from dimethylformamide. The yield of the aldehyde **10a** was 73%. mp >300°C. Anal. Calcd for $C_{11}H_7N_3O$: C, 67.00 ; H, 3.57 ; N, 21.31. Found : C, 66.95 ; H, 3.68 ; N, 21.60. ^{1}H-Nmr ($CDCl_3$) : 7.67(d, J = 9.0, 2H), 8.17 (s, 1H), 8.30 (d, J = 9.0, 2H), 9.25 (s, 1H, N-CH=N), 10.11 (s, 1H, CHO).

7-Formyltetrazolo[1,5-a]quinoline 10b

The same procedure as for **10a** was used, starting from **11b**. Yield 80%. mp 254°C. Anal. Calcd for $C_{10}H_5N_4O$: C, 60.60 ; H, 3.05 ; N, 28.27. Found : C, 60.70 ; H, 3.02 ; N, 28.44. ^{1}H-Nmr (d_6 DMSO) : 8.32 (AB system $\Delta\delta$ = 0.53 ppm, J = 9.7, 2H, H_9 and H_{10}), 8.42 (dd, J = 8.7, 1.5, 1H, H_6), 8.80 (d, J = 8.7, 1H, H_5), 8.80 (d, J = 1.5, 1H, H_8), 10.25 (s, 1H, CHO).

7-(1-Morpholino-1-cyanomethyl)-1,2,4-triazolo[4,3-a]quinoline 12a

A solution of 2.8 g (0.015 mol) p-toluene sulfonic acid, 1.42 g (0.016 mol) of morpholine and 2.5 g (0.008 mol) of **10a** in 30 ml of THF was stirred for 1 h at reflux. The solution was cooled to room temperature and 0.89 g (0.014 mol) of potassium cyanide dissolved in 2.5 ml of water was added. After 3 h stirring at 65°C, the mixture was allowed to cool, the solvent was evaporated under reduced pressure and 200 ml of water was added. The product was extracted with dichloromethane. The organic layer was washed with a saturated solution of sodium hydrogenosulfite, with water and brine. After drying over magnesium sulfate and evaporation of the solvent 2.8 g (73%) of **12a** were obtained. mp 257.5°C. Anal. Calcd for $C_{16}H_{15}N_5O$, 1/2 H_2O : C, 63.56 ; H, 5.33 ; N, 23.16. Found : C, 63.76 ; H, 5.04 ; N, 23.13. ^{1}H-Nmr ($CDCl_3$, 200 MHz) : 2.40-2.60 (m, 4H, CH_2-N-CH_2), 3.60-3.80 (m, 4H, CH_2-O -CH_2), 5.01 (s, 1H, NC-CH -

-N), 7.64 (d, J = 9.6, 1H, H_{10}), 7.77 (d, J = 9.6, 1H, H_9), 7.90 (dd, J = 8.6, J = 1.8, 1H, H_6), 8.00-8.20 (m, 2H, H_5, H_8), 9.30 (s, 1H, N-C<u>H</u>-CN).

7-(1-Morpholino-1-cyanomethyl)tetrazolo[1,5a]quinoline 12b

The same procedure as for **12a** was used starting from **10b**. The yield after recrystallization from ethanol was 83%. mp 176.3°C. Anal. Calcd for $C_{15}H_{14}N_6O$: C, 61.21 ; H, 4.79 ; N, 28.56. Found : C, 61.10 ; H, 4.82 ; N, 28.47. ^{1}H-Nmr ($CDCl_3$) : 2.40-2.60 (m, 4H, CH_2-N-CH_2), 3.60-3.80 (m, 4H, CH_2-O-CH_2), 5.24 (s, 1H, NC-C<u>H</u>-N), 7.80-8.30 (m, 4H, Ar), 8.68 (d, J = 9.7, 1H, Ar).

7-(1,3-Dicyano-2-methyl-1-morpholinopropyl)-1,2,4-triazolo[4,3-a]quinoline 13a

To a stirred 5.4g (0.0184 mol) of **12a** (fine powder), 12.3 g (0.184 mol) of crotononitrile was added. The mixture was stirred for 10 min more, then 0.5 ml of Triton B was added, provoking an exothermic reaction. This mixture was stirred at room temperature for 3 h. The product was purified by column chromatography on silica gel with a mixture of dichloromethane - ethyl acetate - methanol : 5-4-1 as eluent. The yield of the quinoline **14a** was 5.7 g (86%) of **13a**. mp 236.0°C. Anal. Calcd for $C_{20}H_{20}N_6O$: C,66.65 ; H, 5.59 ; N, 23.32. Found : C, 66.69 ; H, 5.47 ; N, 23.30. ^{1}H-Nmr ($CDCl_3$), 1.12 and 1.21 (2d, J = 6.7, 3H, diastereomeric CH_3), 2.10-2.20 (m, 1H, CH_2-C<u>H</u>, -CH_3), 2.40-2.80 (m, 6H, CH_2-N-CH_2 and CH_2-CN), 3.60-3.90 (m, 4H, CH_2-O-CH_2), 7.50-8.00 (m, 5H, Ar), 9.25 (s, 1H, N-C<u>H</u>=N).

7-(1,3-Dicyano-2-methyl-1-morpholinopropyl)tetrazolo[1,5-a]quinoline 13b

The same procedure as for **13a** was used starting from **12b**. Recrystallization from ethanol. Yield : 88%. mp 115.9°C. Anal. Calcd for $C_{19}H_{19}N_7O$: C, 63.14 ; H, 5.30 ; N, 27.13. Found : C, 63.03 ; H, 5.46 ; N, 26.85. ^{1}H-Nmr ($CDCl_3$) : 1.15 (2d, J = 7.5, 3H, diastereomeric CH_3), 2.10-2.30 (m, 1H, CH_2,-C<u>H</u>-CH_3), 2.40-2.90 (m, 6H, CH_2-N-CH_2 and CH_2-CN), 3.85 (t, J = 4.5, 4H, CH_2-O-CH_2), 7.90-8.40 (m, 4H, Ar), 8.85 (d, J = 9.7, 1H, Ar).

7-(3-Cyano-2-methylpropionyl)-1,2,4-triazolo[4,3-a]quinoline 14a

A solution of 5.5 g (0.015 mol) of **13a** in 45 ml of 75% acetic acid was stirred for 5 h at room temperature. After evaporation to dryness under reduced pressure 30 ml of water were added. This mixture was stirred 10 min and the white powder was filtered. The yield of compound **14a** was 3.5 g (87%). mp 243.1°C. Anal. Calcd for $C_{15}H_{12}N_4O$: C, 68.16 ; H, 4.58 ; N, 21.20. Found : C, 68.33 ; H, 4.72 ; N, 21.30. ^{1}H-Nmr (d_6 DMSO) : 1.30 (d, J = 7.2, 3H, CH_3), 2.85 (d, J = 7.2, 2H, CH_2-CN), 4.01 (q, J = 7.2, 1H, CO-C<u>H</u>-CH_3), 7.60-8.70 (m, 5H, Ar), 9.75 (s, 1H, N-C<u>H</u>=N).

7-(3-Cyano-2-methylpropionyl)tetrazolo[1,5-a]quinoline 14b

The same procedure as for **14a** was used starting from **13b**. Recrystallization from acetic acid. Yield : 76%. mp 192.2°C. Anal. Calcd for $C_{14}H_{11}N_5O$: C, 63.38 ; H, 4.18 ; N, 26.40. Found, C, 62.82 ; H, 4.23 ; N, 26.28. ^{1}H-Nmr ($CDCl_3$): 1.42 (d, J = 7.5, 3H, CH_3), 2.85 (d, J = 7.2, 2H, $-CH_2-CN$), 4.00-4.30 (m, 1H, -CO-CH), 8.10-9.10 (m,5H, Ar)

7-(3-Carbethoxy-2-methylpropionyl)1,2,4-triazolo[4,3-a]quinoline 15a

A solution of 2.0 g (0.0064 mol) of keto nitrile **14a** in 4 ml of concentrated HCl and 2 ml of ethanol was stirred under reflux. After evaporation of the solvents under reduced pressure 30 ml of ethanol were added and the solution was refluxed for 10 h. After cooling, the insoluble material was filtered off. The filtrate was evaporated to dryness and dichloromethane (150 ml) was added. The solution was washed with water and brine and dried over magnesium sulfate. The crude product was purified by chromatography on silca gel eluted with a mixture of ethyl acetate - methanol : 8-2. The yield of compound **15a** was 1.7 g (85%). ^{1}H-Nmr ($CDCl_3$) : 1.20 (d, J = 7.2, 3H, CH-CH_3), 1.32 (t, J = 7.5, 3H, OCH_2CH_3), 2.30-3.30 (m, 3H, CH_2CO and CH-CO), 4.12 (q, J = 7.0, 2H, O-CH_2), 7.20-7.90 (m, 5H, Ar), 9.15 (s, 1H, N-CH=N).

7-(3-Carboxy-2-methylpropionyl)tetrazolo[1,5-a]quinoline 15b

A solution of 2.0 (0.0075 mol) of keto nitrile **14b** in 20 ml of water and 10 ml of concentrated sulfuric acid was stirred under reflux for 4 h. Water (100 ml) was added and the mixture was extracted with dichloromethane. The organic layer was washed with water and brine, and dried over magnesium sulfate. The yield of the keto acid **15b** was 1.8 g (88%). An analytical sample was recrystallized from acetic acid. mp 165.8°C. Anal. Calcd for $C_{14}H_{12}N_4O_3$, 1/3 AcOH : C, 57.88 ; H, 4.41 ; N, 18.40. Found C, 57.73 ; H, 4.46 ; N, 18.28. ^{1}H-Nmr (d_6 DMSO) : 1.20 (d, J = 7.2, 3H, CH_3), 2.80-3.00 (m, 3H, CH_3-CH-CH_2), 7.90-9.00 (m, 5H, Ar).

7-(2,3,4,5-Tetrahydro-5-methyl-3-oxopyridazin-6-yl))-1,2,4-triazolo[4,3-a]quinoline 16a

To a solution of quinoline **15a** (1.7 g, 0.0054 mol) in 20 ml of n-butanol, a solution of 0.30 g (0.0059 mol) hydrazine hydrate diluted in 5 ml of n-butanol was slowly added. The solution was heated under a gentle reflux for 15 min. After cooling, the yellow powder was filtered. This powder was stirred for 0.5 h in water, filtered again, washed with water and dried over magnesium sulfate. The yield of compound **16a** was 1.14 g (75%). mp 291°C. Anal. Calcd for $C_{15}H_{13}N_5O$: C, 65.50 ; H, 4.69 ; N, 25.08. Found : C, 64.76 ; H, 4.52 ; N, 24.94. ^{1}H-Nmr (d_6 DMSO, 200MHz) : 1.15 (d, J = 7.5, CH-CH_3), 2.60-2.80 (m, 2H, CH-CH_2), 3.50-3.70 (m, 1H, CH_2 -CH-CH_3), 7.83 (AB system, $\Delta\delta$ = 0.13 ppm, J = 9.6, 2H, H_9, H_{10}), 8.20 (dd, J = 8.8, 2.1, 1H, H_6), 8.41 (d, J = 2.1, 1H, H_8), 8.48 (d, J = 8.8, 1H, H_5), 9.99 (s, 1H, N-CH=N), 11.14

(broad s, 1H, exchangeable with D_2O, NH).

7-(2,3,4,5-Tetrahydro-5-methyl-3-oxopyridazin-6-yl)tetrazolo[1,5-a]quinoline 16b

The same procedure as above for compound **16a** was used, starting with **16b**. Recrystallization from DMF. Yield 78%. mp 270.3°C. Anal. Calcd for $C_{14}H_{12}N_6O$: C, 59.99 ; H, 4.32 ; N, 29.99. Found : C, 60.33, H, 4.17 ; N, 30.14. ^{1}H-Nmr (d_6 DMSO, 200MHz) : 1.17 (d, J = 7.2, 3H, CH_3), 2.83 (d, J = 6.6, 2H, CH_2-CH), 3.50-3.60 (m, 1H, CH-CH_3), 8.14 (d, J = 9.4, 1H, H_5), 8.37 (d, J = 9.2, 1H, H_6), 8.41 (d, J = 8.4, 1H, H_{10}), 8.64 (s, 1H, H_8), 8.66 (d, J = 8.5, 1H, H_9), 11.23 (s, 1H, exchangeable with D_2O NH).

7-(2,3,4,5-Tetrahydro-2,5-dimethyl-3-oxopyridazin-6-yl)-1,2,4-triazolo[4,3-a]quinoline 17a

The keto ester **15a** 1.3 g (0.0041 mol) was dissolved in 30 ml of ethanol. Methylhydrazine 0.38 g, (0.0082 mol), diluted in 5 ml of ethanol, was added and the mixture was stirred under reflux for 12 h and evaporated to dryness. Some water was added and the product was extracted with dichloromethane. The organic layer was washed with water and brine and dried over magnesium sulfate. After evaporation of the solvent, the product was purified on silica gel column chromatography with a mixture of dichloromethane - ethyl acetate - methanol : 5-4-1 as eluent. The yield of compound **17a** was 0.85 g (65%). mp 184°C. Anal. Calcd for $C_{16}H_{15}N_5O$, 2/3 H_2O : C, 62.94 ; H, 5.17 ; N, 22.94. Found : C, 63.13 ; H, 5.27 ; N, 23.33. ^{1}H-Nmr (d_6 DMSO) : 1.25 (d, J = 7.2, 3H,CH-CH_3), 2.70 (d, J = 6.3, 2H, CH_2-CO), 3.10-3.20 (m, 1H, CH-CH_3), 3.52 (s, 3H, N-CH_3), 8.10-8.40 (m, 5H, Ar), 9.39 (s, 1H, N-CH=N).

7-(2,3,4,5-Tetrahydro-2,5-dimethyl-3-oxopyridazin-6-yl)tetrazolo[1,5-a]quinoline 17b

The same procedure as for **17a** was used, starting with **16b**. Recrystallization from DMF. Yield: 83%. mp 228.9°C. Anal. Calcd for $C_{15}H_{14}N_6O$: C, 61.28 ; H, 4.79 ; N, 28.56. Found : C, 61.40 ; H, 4.79 ; N, 28.80. ^{1}H-Nmr (d_6 DMSO): 1.10 (d, J = 7.5, 3H, CH_3), 2.75 (d, J = 7.0, 2H, CH_2-CH), 3.37 (s, 3H, N-CH_3), 3.70-3.80 (m, 1H, CH_3-CH-CH_2), 8.00-8.80 (m, 5H, Ar).

7-(3-Carbethoxy-2-methyl-1-phenylhydrazonopropyl)-1,2,4-triazolo[4,3-a]quinoline 18a

A solution of 0.6 g (0.0019 mol) of keto ester **15a**, 5 ml of n-butanol and 0.31 g (0.0028 mol) of freshly distilled phenylhydrazine was refluxed for 15 h. After cooling to room temperature the precipitate was filtered, washed with ethanol and dried under reduced pressure. The yield of phenylhydrazone **18a** was 0.45 g (66%). mp 212°C. Anal. Calcd for $C_{23}H_{23}N_5O$: C, 68.80 ; H, 5.77 ; N, 17.45. Found : C, 69.09 ; H, 5.85 ; N, 17.26. ^{1}H-Nmr ($CDCl_3$) : 1.15 (d, J = 7.5, 3H, CH-CH_3), 1.32 (t, J = 7.5, 3H, O-CH_2-CH_3), 2.3-3.3 (m, 3H, CH-CH_3, CH_2CO_2), 4.10 (q, J = 7.0, 2H, O-CH_2), 6.80-8.10 (m, 11H, Ar, NH), 9.20 (s, 1H, N-CH=N).

7-(3-Carboxy-2-methyl-1-phenylhydrazonopropyl)tetrazolo[1,5-a]quinoline 18b

The same procedure as above was used starting with 15b. Recrystallization from acetic acid. Yield 81%. mp 230.8°C. Anal. Calcd for $C_{20}H_{18}N_6O$: C, 64.15 ; H, 4.85 ; N, 22.45. Found : C, 64.12 ; H, 4.96 ; N, 22.28. ^{1}H-Nmr (d_6 DMSO, 200MHz) : 1.19 (d, J = 7.4, 3H, CH_3), 2.76 (d, J = 6.6, 2H, CH_3-CH-CH_2), 3.60-3.90 (m, 1H, CH_3-CH-CH_2), 6.60-7.20 (m, 6H, C_6H_5 + NH), 8.10-8.90 (m, 4H), 10.00 (s,1H, CO_2H).

7-(2,3,4,5-Tetrahydro-5-methyl-2-phenyl-3-oxopyridazin-6-yl)-triazolo[4,3-a]quinoline 19a

A suspension of 300 mg (0.00075 mol) of 18a, and 4 drops of concentrated sulfuric acid in 6 ml of ethanol was heated at 90°C for 12 h and then cooled to room temperature. After recrystallization from acetone the yield was 200mg (80%) of pure 19a. mp 255.9°C. Anal. Calcd for $C_{21}H_{17}N_5O$: C, 70.97 ; H, 4.82 ; N, 19.71. Found : C, 70.83 ; H, 4.83 ; N, 19.60. ^{1}H-Nmr (d_6 DMSO) : 1.44 (d, J = 7.5, 3H, CH-CH_3), 2.60-2.80 (m, 2H, CH_3CH-CH_2), 3.60-3.70 (m, 1H, CH_3CH-CH_2), 7.30-7.70 (m, 5H, C_6H_5), 8.00-8.70 (m, 5H, Ar), 9.27 (s, 1H, N-CH=N).

7-(2,3,4,5-Tetrahydro-5-methyl-2-phenyl-3-oxopyridazin-6-yl)tetrazolo[1,5-a]quinoline 19b

The same procedure as for 19a was used starting from 18b. Recrystallization from ethanol. Yield: 81%. mp 230.8°C. Anal. Calcd for $C_{20}H_{16}N_6O$: C, 67.40 ; H, 4.53 ; N, 23.58. Found : C,67.60 ; H, 4.48 ; N, 23.81. ^{1}H-Nmr ($CDCl_3$, 200 MHz) : 1.43 (d, J = 7.4, 3H, CH_3), 2.76 (dd, J = 16.8, 2.0, 2H, CH_3-CH-CH_2), 3.60-3.80 (m, 1H, CH_3-CH-CH_2), 7.30-7.60 (m, 5H, C_6H_5), 7.95 (AB system, $\Delta\delta$ = 0.23 ppm, J = 9.4, 2H, H_5, H_6), 8.30-8.40 (m, 2H, H_8, H_{10}), 8.73 (d, J = 8.4, 1H, H_9).

3,4-Dihydro-6-succinoyl-2(*1H*)quinolinone 23

In a flask equipped with a mechanical stirrer, 82.7 g (0.62 mol) of $AlCl_3$ were introduced. With the help of a dropping funnel 14 ml of DMF were slowly added very exothermic reaction. Then a mixture of 9.11 g (0.062 mol) 3,4-dihydro-2(*1H*)quinolinone 21 and 6.2 g (0.062 mol) succinic anhydride (fine powder) was added in small portions. The mixture was stirred and heated at 70°C for 2 h. The reaction mixture was poured onto crushed ice in small portions. After 15 min standing, the precipitate was filtered off to recover the unreacted 21. The filtrate was acidified with 1N HCland left standing overnight. The precipitate was filtered and dissolved in an alkaline solution (NaOH 1N). This solution was reacidified and the crystals filtered again, washed with water and dried under reduced pressure. The yield of compound 23 was 12.6 g (83%). mp 236°C. ^{1}H-Nmr (d_6 DMSO) : 2.80-2.90 (m, 4H), 3.00-3.20 (m, 4H), 6.94 (d, J = 8.0, 1H, H_8), 7.70-7.80 (m, 2H, H_5, H_7), 10.43 (s, exchangeable with D_2O, 1H, NH quinolinone), 12.15 (broad s, exchangeable with D_2O, 1H, NH pyridazinone).

3,4-Dihydro-6-(2,3,4,5-tetrahydro-3-oxopyridazin-6-yl)-2-(1H)-quinolinone 24

A solution of 1.8 g (0.0072 mol) of keto acid **23** and 0.40 g (0.0081 mol) hydrazine hydrate in 50 ml of n-butanol was heated at reflux for 10 h. The hot suspension was filtered, and the residue was washed with ethanol and dried under reduced pressure. The yield of compound **25** was 1.45 g (82%), mp >300°C. ^{1}H-Nmr (d_6 DMSO): 2.80-2.90 (m, 4H), 3.00-3.40 (m, and water) 10.30 (s, exchangeable with D_2O, 1H, NH quinolinone), 10.85 (s, exchangeable with D_2O, 1H, NH pyridazinone).

3,4-Dihydro-6-(4,5-dihydro-3-oxopyridzin-6-yl)-2-(*1H*)-quinolinone 25 starting from 24

Sodium *m*-nitrobenzenesulfonate (13.9 g, 0.069 mol) was added to a solution of **24** (10 g (0.041 mol) in 320 ml of water containing 8.2 g (0.21 mol) sodium hydroxide. This solution was stirred at 100°C for 16 h, then filtered througt a Celite pad. The filtrate was acidified to pH 1 with HCl and filtered again. The crystalline powder obtained was washed *with water and ethanol* and dried under reduced pressure. The yield of **26** was 8.3 g (84%). mp >300°C. ^{1}H-Nmr (d_6 DMSO) : 2.85 (t, J = 7.5, 2H, CH_2-CO), 3.10-3.40 (m, 2H, CH_2-CH_2-CO), 6.90-7.10 (m, 2H, H_8, $H_{4'}$), 7.60-7.80 (m, 2H, H_5, H_7), 7.95 (d, J = 8.0, 1H, $H_{5'}$), 10.30 (s, *exchangeable with D_2O, 1H, NH quinolinone*), 13.11 (s, exchangeable with D_2O, 1H, NH pyridazinone).

3,4-Dihydro-6-(4,5-dihydro-3-oxopyridazin-6-yl)-2-(*1H*)-quinolinone 25 starting from 26

A solution of 30 g (0.12 mol) of keto acid **27** *(see below) in 450 ml of water containing* 31 g (0.24 mol) of sodium sulfite was stirred at 70°C for 30 mn. After cooling to room temperature to the solution acidified to pH 1 with concentrated HCl, 9.2 g (0.183 mol) of hydrazine hydrate was added and the mixture stirred at 100°C for 5 h. The precipitate was filtered, washed with water and ethanol and dried under reduced pressure. 21 g (76%) of pyridazinone **25** were obtained.

6-(3-Trans-carboxyacryloyl)-3,4-dihydro-2(*1H*)-quinolinone 26

The same procedure as for **23** was used but using maleic anhydride. Yield 77%. mp >300°C. ^{1}H-Nmr (d_6 DMSO) : 2.99 (t, J = 8.0, 2H, CH_2-CH_2-CO), 3.3-3.5 (t and water), 6.66 (d, J = 15.5, 1H, HC=CH-CO_2H), 6.96 (d, J = 8.1, 1H, H_8), 7.7-8.0 (m, 3H, HC=CH-CO_2H, H_5, H_7), 9.20 (broad s, exchangeable with D_2O, NH), 10.55 (broad s, exchangeable with D_2O, CO_2H).

6-(2,3-Dihydro-3-oxopyridazin-6-yl)-2(*1H*)-quinolinone 28

To a hot solution (90°C) of 10 g (0.044 mol) of pyridazinone **25** in 330 ml of acetic acid , 5 ml of bromine (0.22 mol) were slowly added. The heating was continued for 5 h. The precipitate was filtered, washed with water and ethanol and dried under reduced pressure. A mixture

of **28** and **29** was obtained. The two compounds could not be separated. The mixture was used as such for the next step.

6-(3-Chloropyridazin-6-yl)-2-chloroquinoline 30

A mixture of 9.2 g of **28** and **29** in 200 ml of of phosphorus oxychloride was stirred at 70°C for 4h. After evaporation to dryness, the residue was triturated with crushed ice, filtered, and washed a few time with water. A continuous extraction with dichloromethane for 12 h afforded a mixture of products which were purified using a column chromatography on silica gel eluted with a mixture of dichloromethane - ethyl acetate : 95 - 5. The first compound eluted was 6-(3-chloropyridazin-6-yl)-2-chloro-8-bromoquinoline **30**. Rf(silica gel, CH_2Cl_2) : 0.75. Yield : 9%. mp 266°C. Anal. Calcd for $C_{13}H_6BrCl_2N_3$: C,43.98 ; H, 1.70 ; N, 11.84 ; Br, 22.51. Found · C, 43.99 ; H, 1.40 ; N, 11.97 ; Br, 22.87. ^{1}H-Nmr ($CDCl_3$, 200 MHz) : 7.52 (d, J = 8.5, 1H, H_3), 7.59 (d, J = 9.0, 1H, $H_{4'}$), 7.98 (d, J = 8.9, 1H, $H_{5'}$), 8.23 (d, J = 8 5, 1H, H_4), 8.53 (d, J = 1.9, 1H, H_5), 8.75 (d, J = 1.9, 1H, H_7). The second product eluted was the expected dichloride **30**. Rf (silica gel, CH_2Cl_2-AcOEt : 95-5): 0.30. Yield: 22%. *mp* >300°C. Anal. Calcd for $C_{13}H_7Cl_2N_3$: C, 56.54 ; H, 2.55 ; N, 15.22. Found : C, 56.03 ; H, 2.68 ; N, 14.91. ^{1}H-Nmr ($CDCl_3$, 200 MHz): 7.48 (d, J = 9.1, 1H, H_3), 7 63 (d, J = 10.1, 1H, $H_{4'}$), 7.96 (d, J = 9.1, 1H, $H_{5'}$), 8.19 (AB system, $\Delta\delta$ = 0.07 ppm, J = 9.6, 2H, H_6, H_7), 8.36 (dd, J = 9.1, J = 1.9, 1H, H_4), 8.56 (d, J = 1.9, 1H, H_5).

6-(3-Hydrazinopyridazin-6-yl)-2-hydrazinoquinoline 32

A suspension of 1.36 g (0.0049 mol) of **30** in 17 ml of hydrazine hydrate was stirred at 100°C for 15 h. Water (100 ml) was added. The precipitate was filtered, washed with water and some acetone. The yield of the hydrazino derivative was 1.2 g (92%). mp 280°C. ^{1}H-Nmr (d_6 DMSO): 4.50 (very broad s, 6H, $NHNH_2$), 6.89 (d, J = 9.0, 1H), 7.12 (d, J = 9.4, 1H), 7.62 (d, J = 8.8, 1H), 7.80-8.00 (m, 2H), 8.10-8.30 (m, 2H).

7-Triazolo[4,3-b]pyridazin-6-yl)triazolo[4,3-a]quinoline 31a

A solution of 600 mg (0.0024 mol) of dihydrazino derivative **32** and 730 mg (0.0049 mol) of ethyl orthoformate in 10 ml of n-butanol was heated at 90°C for 10h. After evaporation of the n-butanol, water was added to precipitate the product which was collected by filtration and dried under reduced pressure. Recrystallization from DMF. The yield was 430 mg (67%). mp >300°C. Anal. Calcd for $C_{15}H_9N_7$ · C, 62.71 ; H, 3.16. Found : C, 61.32 ; H, 3.45. ^{1}H-Nmr (d_6 DMSO, 200 MHz) : 7.64 (AB system, $\Delta\delta$ = 0.12 ppm, J = 8.6, 2H, $H_{6'}$, $H_{7'}$), 7.96 (d, J = 9.6, 1H, H_{10}), 8.49 (AB part of an ABX system, J_{AB} = 8.8, J_{AX}=2.0, 2H, H_5, H_6), 8.65 (d, J = 8.8, 1H, H_9), 8.82 (d, J = 2.3, 1H, H_8), 9.40 (s, 1H, H_3), 9.76 (s, 1H, $H_{3'}$).

7-(Tetrazolo[1,5-b]pyridazin-6-yl)tetrazolo[1,5-a]quinoline 31b

A solution of 600 mg (0.0024 mol) of dihydrazino derivative **32** in 12 ml of 4N acetic acid was stirred and a solution of 460 mg (0.0067 mol) of sodium nitrite dissolved in 5 ml of water were slowly added. The mixture was stirred at room temperature for 2 h and crystal was filtered. The crystal was washed with water and dried under reduced pressure. The product was purified by column chromatography on silica gel with a mixture of dichloromethane - ethyl acetate - methanol : 5-4-1 as eluent. Recrystallization from DMF. Yield : 420 mg (64%) of **32b**. mp 151°C. Anal. Calcd for $C_{13}H_7N_9$, 1/4 DMF : C, 53.69 ; H, 2.87 ; N, 42.14. Found : C, 53.65 ; H, 2.44 ; N, 42.04. ^{1}H-Nmr (d_6 DMSO, 200 MHz) : 8.17 (d, J = 8.3, 1H, H_{10}), 8.40 (d, J = 8.3, 1H, H_9), 8.59 (d, J = 8.3, 1H, $H_{8'}$), 8.75 (AB system, J = 10.0, 2H, H_5, H_6), 9.00 (d, J = 8.3, 1H, $H_{7'}$), 9.11 (s, 1H, H_8).

REFERENCES

1. F. Mac Elroy, and B.B. Philip, Life Science, 1975, 17, 1479.
2. C. Machleidt, P. Rose, and U. Mittmann, Tromb. Res., 1985, 37, 595.
3. D. Ruppert, and K.U. Weithmann, Life Sciences, 1982, 31, 2037.
4. B. Lal, A.N. Dodadwalla, N.K. Dadkar, A. D'Sa, and N.J. De Sousa, J. Med. Chem., 1984, 28, 1470.
5. J. S. Fleming, and J.P. Buyniski, Thromb. Res., 1979, 15, 373.
6. R. Muggli, T.B. Tschopp, E. Mittelholzer, and R. Baumgartner, J. Pharmacol. Exp. Therap., 1985, 235, 212.
7. M. Hagiwara, T. Endo, T. Kanayama, and H. Hidaka, J. Pharmacol. Exp. Therap., 1979, 211, 26.
8. H. Mikashima, T. Nakao, and K. Goto, Thromb. Res., 1983, 31, 599.
9. M. Thyes, H. D. Lehmann, J. Gries, H. Konig, R. Kretzschmar, J Kunze, R. Lebkucher, and D. Lenke, J. Med. Chem., 1983, 26, 800.
10. T. Nishi, F. Tabusa, T. Tanaka, H. Ueda, T. Shimizu, T. Kanbe, Y. Kimura, and K. Nakagawa, Chem. Pharm. Bull., 1983, 31 852.
11. T. Nishi, F. Tabusa, T. Tanaka, T. Schimizu, T. Kanbe, Y. Kimura, and K. Nakagawa, Chem. Pharm. Bull., 1983, 31, 1151.
12. J.P. Cazenave, M.L. Wiesel, and S. Hemmendinger, Agents and Actions, 1984, 15, 24.
13. K.H. Johnston, R.M. Luker, and G.H. Williams, J. Chem. Soc. Perkin I, 1972, 1648.
14. J. Cologne, and R. Chambard, Bull. Soc. Chim. France, 1953, II, 982.

15. A. Vogel, "Textbook of Practical Organic Chemistry", Fourth Edition, Longman, London and New-York, 1978, 766.

16. E. Leete, M.P. Chendekel, and G.B. Bodem, J. Org. Chem., 1972, 37, 4465.

17. J.D. Albright, F.J. Mac Evoy, and D.B. Morvan, J. Heterocyclic Chem., 1978, 15, 881.

18. F.J. Mac Evoy, and J.D. Albright, J. Org. Chem., 1979, 44, 4597.

19. C.G. Wermuth, and A. Exinger, Agressologie, 1972, 13, 285.

20. J.D. Albright, D.B. Moran, W.B. Wright Jr., J.B. Collins, B. Beer, A.S. Lippa, and E.N. Greenblatt, J. Med. Chem., 1981, 24, 592.

Received, 24th September, 1988