

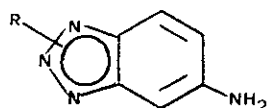
ADDITION REACTIONS OF 5-AMINOBENZOTRIAZOLES WITH
DIMETHYL ACETYLENEDICARBOXYLATE (DMAD). FORMATION OF
(Z/E) MICHAEL ADDUCTS, (BENZOTRIAZOL-5-YL)-2-PYRIDONES,
A TRIAZOLO-9,10-DIHYDROBENZO[b]AZEPINE AND A TRIAZOLO-
2-OXINDOLE

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Abstract-5-Aminobenzotriazoles (1a-d) reacted with DMAD to give the regioselective Michael adducts (Z)-(2a-d), accompanied with (benzotriazol-5-yl)-2-pyridones (3b-d), and in one case (2c) with the triazolo-9,10-dihydrobenzo[b]azepine (4). Cyclisation of the adducts (Z)-(2b-d) in Dowtherm gave the triazolo[4,5-f]-quinolinones (6b-d), which were converted into chloro derivatives (9b-d), in turn hydrolysed and decarboxylated to 9-chloro-1(2)-methyltriazolo[4,5-f]-quinolines (11c-d). Compound (1c) in refluxing acetonitrile with DMAD undergoes unusual cyclisation into triazolo-2-oxindole (5), then converted into 2-methyltriazolo[4,5-f]carbostyryl-9-carboxylate (17).

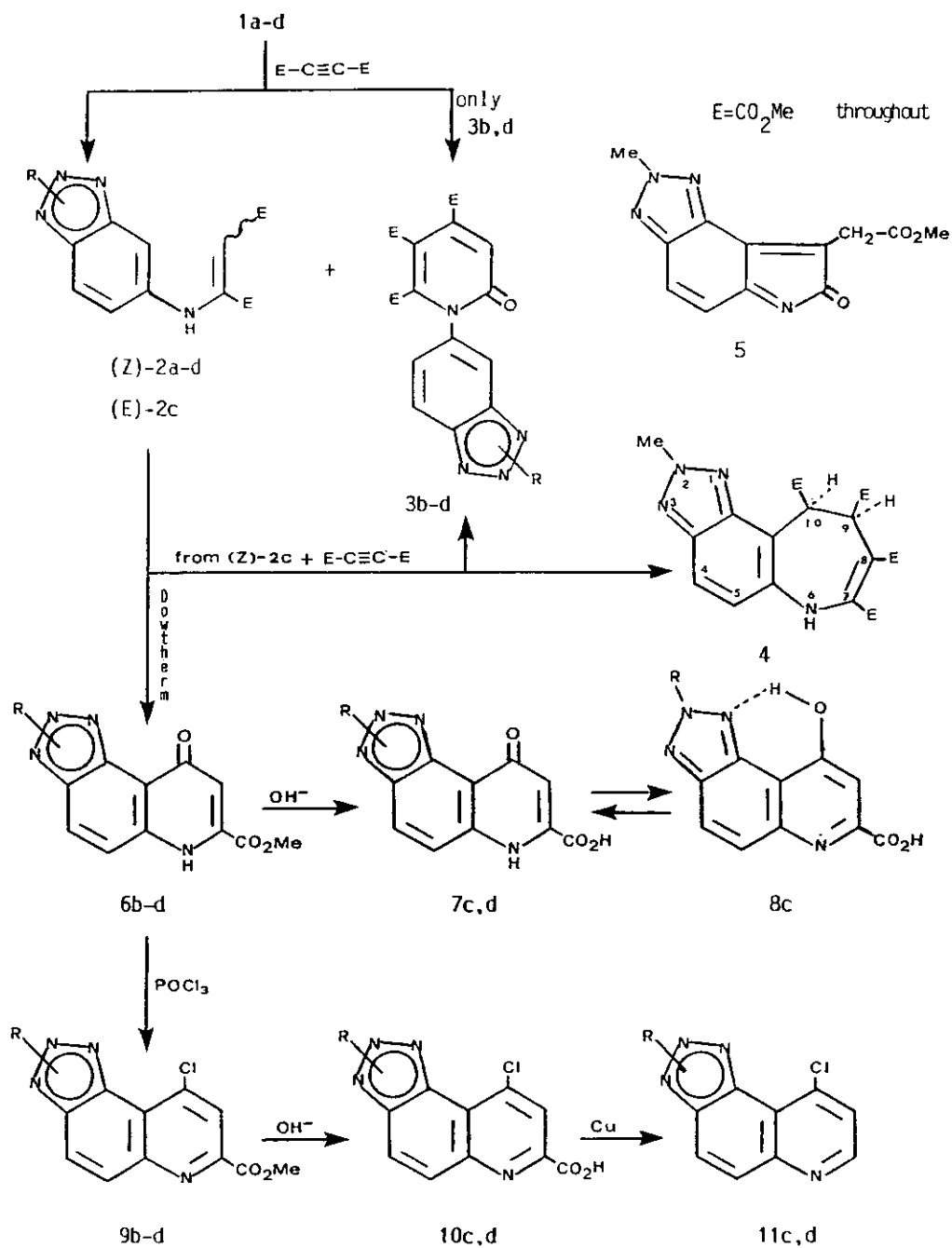
1,2,3-(1),(2),(3)*H*-Triazolo[4,5-*f*]quinolines are a new class of heterocycles of a certain pharmaceutical interest.¹ Some of these compounds were recently described by us as isosteric analogues of oxolinic acid and showed an encouraging *in vitro* antimicrobial activity against *Escherichia coli*.¹ The synthetic approach to these heterocycles was so far examined by the reaction of 5(6)-amino-1(2),(3)*H*-benzotriazoles with both β -keto esters and diethyl ethoxymethylenemalonate and proved to afford angular triazolo[4,5-*f*]quinoline.^{1,2} In continuation with this work, we have now investigated the addition reactions of the amines (1a-d) with DMAD as a variation of Gould-Jacobs method with the aim to obtain useful triazoloquinoline intermediates for the design of further bioactive molecules under development in our laboratory.³



- a, R=H;
b, R=1-Me
c, R=2-Me
d, R=3-Me

1a-d

The amines (1a-d) add to DMAD according to a Michael addition (Scheme 1). This reaction is under kinetic control and, according to the amine employed under the conditions of Table 1, can be either highly regioselective or can lead to a mixture of (*Z*)/(*E*) isomers often accompanied with other products, the formation of which is indicative of the tendency to cyclise or to further add one extra mole of DMAD (Scheme 1 and Table 1). Thus, the amine (1a) gave a high yield (80%) of (*Z*)-2a when the reaction with DMAD was carried out in dry acetonitrile at room temperature, while 1c gave (*Z*)-2c either in ether or in absence of solvent and accompanied with a little amount of (*E*)-2c when this reaction was carried out in Dowtherm. Compounds (1b) and



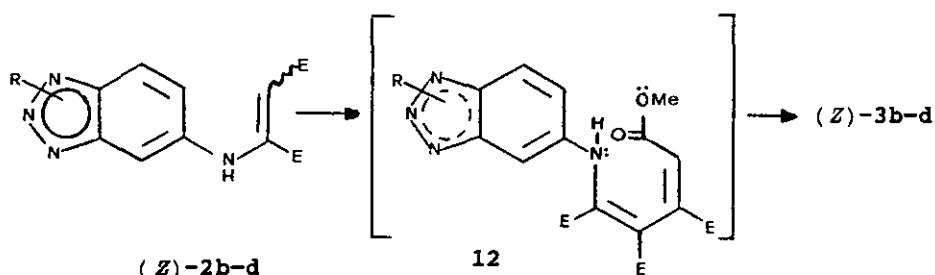
Scheme 1

Table 1. Products obtained in the reaction between the amines
(1a-d) and DMAD.

Compd + DMAD [Molar ratio]	Reaction time h	Solvent	Temp.	Method of purif.	Products isolated (Yield %)
1a [1:1.1]	20	a	room temperature	A	(Z)-2a (80)
1b [1:1]	20	a	reflux	A	(Z)-2b (65), 3b (3)
1c [1:1.5]	44	a	room temperature	A	(Z)-2c (79), 5 (11)
1c [1:1.1]	18	a	reflux	A	(Z)-2c (34), 5 (30)
1c [1:1.6]	72	b	room temperature	A	(Z)-2c (85)
1c [1:1.1]	0.5	c	reflux	B	(Z)-2c (21), (E)-2c (6), 1c (10)
1c [1:2.5]	110	-	room temperature	C	(Z)-2c (79), 1c (18)
1d [1:1.1]	72	a	room temperature	A	(Z)-2d (41), 3d (2)

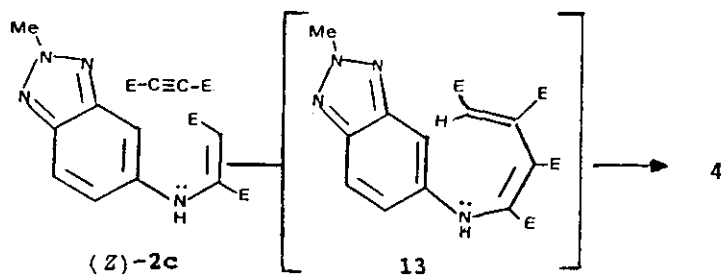
a=acetonitrile; b= ether; c=Dowtherm; -=no solvent.

(1d) with DMAD respectively gave the adducts (Z)-(2b) and (Z)-(2d) but accompanied with little amounts of the (benzotriazol-5-yl)-2-pyridones (3b,d). The formation of the 2-pyridones (3b,d) suggests that a certain amount of DMAD undergoes β -trans-addition to the initially formed enamino ester (2) to give the intermediate (12) which is induced to cyclise according to the mechanism depicted in Scheme 2.



Scheme 2

A good evidence for this is given by the results of the reaction of (Z)-2c with DMAD in refluxing acetonitrile which gave rise to 3c (78% yield) accompanied with the compound (4) (8% yield). The formation of 4 on the other hand would account for a moderate competitive cis-addition of DMAD to the enamino ester, *via* the intermediate (13) (Scheme 3) ending in the angular cyclisation product (4), when 1,3-hydrogen shift being promoted by the driving force to the aromatisation.

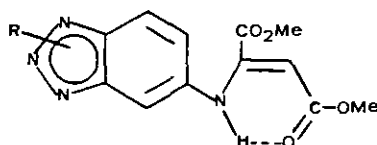


Scheme 3

The structure of **4** is supported by its spectroscopic and analytical data. Uv absorptions (341 and 277 nm) rather resemble those of the starting (*Z*)-**2c** thus indicating the lack of conjugation in the ring. The ^1H -nmr (200 MHz) spectrum shows an AB system for C-4 and C-5 protons ($J=9$ Hz), while the C-9 and C-10 protons resonate as two doublets ($J=3$ Hz) compatible with their *quasi* equivalence. COSY experiments confirm that the doublets are correlated and ^{13}C -DEPT spectrum clearly shows two upfield carbons (C-9 and C-10) as off-resonance doublets centered respectively at δ 48.51 and 46.46 which are in good accordance with the results obtained by Acheson *et al.*⁴ for similar structures. The formation of **4** is, to our knowledge, the first example of an aniline-like compound undergoing ring closure to an azepine, whereas in a similar case using 3,4-dimethoxyaniline and methyl propiolate the reaction led to quinoline derivatives.⁵ Formation of 2-pyridones has been observed by some of us in the reaction of β -enamino amides with DMAD in acetonitrile.⁶ Interestingly, the uv absorptions of **3b-d** are similar with those previously reported by us in the cited reference⁶ and the benzotriazolyl moiety on the pyridine ring does not seem to affect the chromophore due to the conjugation of pyridone ring. The addition reaction of **1c** with DMAD was also investigated varying the proportions of the reactants under the conditions of Table 1. In acetonitrile, at both room and reflux temperature, we were able to isolate the expected (*Z*)-**2c** along with the product (**5**) the structure demonstration of which will be discussed later. Ring closure of (*Z*)-**2a-d** in boiling Dowtherm gave compounds (**6b-d**) which do exist in quinolinone form (^{13}C -nmr evidence), while only **2a** failed to cyclise as a reverse Michael addition was taking place. However, their alkaline hydrolysis afforded the acids (**7c,d**) which in the case of **7c** shows in the ^1H -nmr spectrum

the existence of a keto-enolic equilibrium (3:1 ratio) stabilised by the hydrogen bonding as in 8c. Chlorination of 6b was difficult and gave a poor yield (20%) of 9b possibly because of the steric hindrance and this fact does not allow us to obtain sufficient material for further steps, while compounds (9c,d) were obtained respectively in 92 and 87% yields. Nor the alkaline saponification of 6b was successful. On the contrary the alkaline hydrolysis of the chloro derivatives (9c,d) gave the expected acids (10c,d) which underwent decarboxylation to 11c,d according to a described procedure.⁷ The assignments of the proposed structures came from the whole of analytical and spectroscopic data reported in the experimental section.

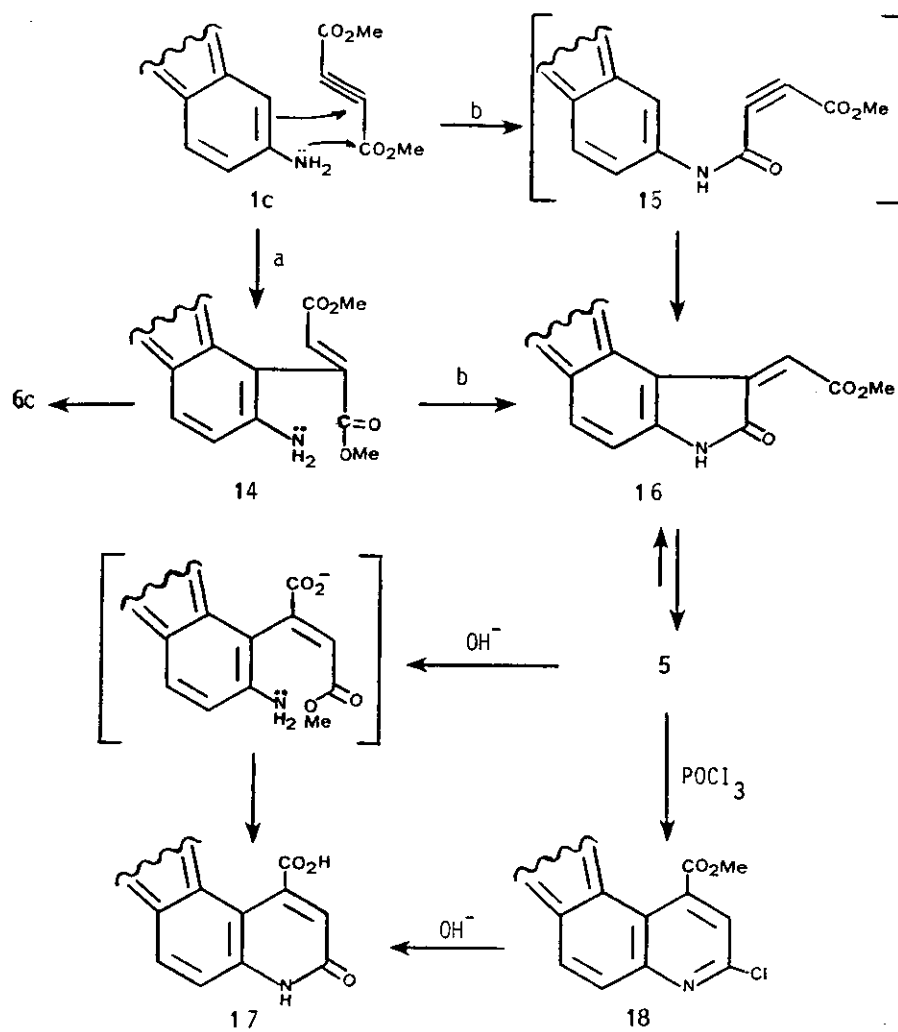
Uv spectra of the aminobutenedioates (Z)-(2a-d) exhibited strong maxima absorptions for the 326-334 nm chromophore due to the enamino ester conjugation in accordance with previous observations,⁸ while in the case of the isomer (E)-2c the intensity of the maximum at the highest wavelength (343 nm) was lower than that at 279 nm. This fact would well account for the suggestion that compounds (Z)-(2a-d) do exist in the hydrogen bonded conformation as it is clearly deduced by the chemical shift of the N-H group (*vide infra*).



(Z)-2a-d

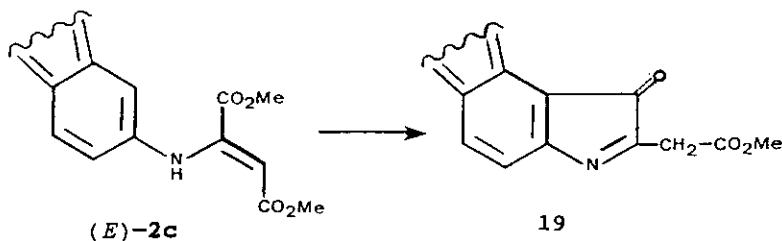
In addition uv spectra of 2-pyridones showed a chromophore identical to that earlier reported by some of us,⁶ while compounds (9b-d) at the usual dilution show uv spectra where the highest wavelength absorptions, due to the fine structure of the triazoloquinoline ring are hardly detectable. These uv spectra run in a more concentrated solution clearly show fine maxima at 326 and 312 nm.

The structure of 5 was achieved on the basis of elemental analysis, spectral evidences and chemical behavior. The infrared spectrum showed two NH absorptions at 3320 and 3200 cm^{-1} , an ester carbonyl at 1730 cm^{-1} and another absorption band at 1670 cm^{-1} which is consistent with a five membered ring C=O in an oxindole system.⁹ The ^1H -nmr spectrum showed a singlet at δ 10.54, due to the NH proton with the same integral of the singlet at δ 6.20 for the (Z)-exo-cyclic olefinic H-9⁸ in 16. These two protons were in 1:2 ratio with each part of the AB system ($J=16$ Hz) due to the non equivalent exo-cyclic methylene in 5. ^{13}C -Nmr spectrum confirmed N-C=O resonance at 173.39 δ and an off-resonance triplet for the CH_2 signal. The formation of 5 under the above-mentioned mild conditions seems to indicate that a competitive reaction had taken place between 1c and DMAD via the possible routes a and b depicted in Scheme 4. Route a involves a β -attack to enamine as postulated in other cases¹⁰ to give compound (14) which can undergo ring closure to the triazoloquinoline (6c) or to the oxindole (16). The latter mainly exists in equilibrium with its tautomer (5) (0.5:1 ratio) (^1H -nmr evidence), perhaps because of its better stability in the indolenine form. Route b simply postulates an amide formation then undergoing oxindole cyclisation through the more activated carbon on the double bond. Compound (5) was not stable in either acidic or alkaline medium. When treated with POCl_3 it transforms into the chlorotriazoloquinoline (18), a structural isomer of 9c with an almost coincident uv spectrum, while its alkaline hydrolysis gave the acid (17) also obtained from the saponification of (18) thus confirming the lability of chlorine in *alfa* to the nitrogen of the quinoline ring. Compound (17) possesses the same chromophore found in the 2-methyl(2H)-9-phenyltriazolo[4,5-h]carbostyrl and an identical chemical shift for C-7 proton.² Examples of an oxindole ring expansion into carbostyrl derivatives are well documented in the literature¹¹ and



Scheme 4

the behavior of 5 seems to fall in this case. Although a similar cyclisation starting from the (*E*)-2c could give compound (19), an isomer of 5, it is our opinion that despite the obtained spectroscopic data would match well with this structure, its transformation into carbostyryl derivative (17) is difficult to occur unless a possible rearrangement may have occurred.



Scheme 5

At the present stage we can conclude that this evenience is unlikely since (*E*)-2c was isolated in very low yield (6%) only when the reaction was carried out in boiling Dowtherm, while in the other examined cases we observed that a cyclisation into pyridone was preferred.

EXPERIMENTAL

Melting points are uncorrected and were taken on a Kofler apparatus. Uv spectra were recorded in nm (log ϵ) for ethanolic solutions with a Perkin-Elmer Lambda 5 spectrophotometer. Ir spectra are for nujol mulls and were made by a Perkin-Elmer 781 infrared spectrophotometer. ^1H -Nmr spectral data were obtained by a Perkin-Elmer Hitachi R-24A (60 MHz) or a Varian XL-200 (200 MHz) instruments using TMS as internal standard. ^{13}C -Nmr spectral data were measured with a Varian XL-200 spectrometer. Elemental analyses were performed at the Laboratorio di

Microanalisi, Dipartimento di Scienze Farmaceutiche, University of Padua-Italy.

Materials: Column chromatography was carried out using silica gel 60 (230-400 mesh), and flash chromatography was performed with Merck silica gel 60 (70-230 mesh). Acetonitrile used in the reactions was dried over Woelm basic alumina. Amines (1a-d) were prepared according to a described procedure.²

Addition reaction of amines (1a-d) with DMAD. General procedure:

Method A.--- A mixture of the appropriate amine and DMAD, in the molar ratio shown in Table 1, in dry acetonitrile (30-70 ml), or alternative solvent as indicated, was stirred at room temperature or refluxed for the time shown in Table 1. After evaporation of the solvent, the residue was chromatographed through silica gel column eluting with ether. In the case of 1b the separation of the reaction products was accomplished by fractional recrystallisation and further purification of the residue obtained on evaporation of the mother liquors by column chromatography.

(Z)-(2a); mp 132-134°C (from ether). Anal. Calcd for $C_{12}H_{12}N_4O_4$: C, 52.17; H, 4.38; N, 20.28. Found : C, 52.05; H, 4.54; N, 19.90.

Ir: $\nu_{\max}$ 3300, 3200-2500, 1740, 1670, 1620 cm^{-1} . Uv: $\lambda_{\max}$ 326 (4.45), 272 sh (4.22), 222 inf (4.49) nm. ^1H-Nmr ($CDCl_3$): δ 9.58 (1H, s, NH, collapses with D_2O), 7.70 (1H, d, $J=9$ Hz, H-7), 7.15 (1H, d, $J=2$, H-4), 6.84 (1H, dd, $J=9$ and 2 Hz, H-6), 5.40 (1H, s, olefinic H), 3.68 and 3.62 (3H, s, COOMe).

(Z)-(2b); mp 98-100°C (from chloroform). Anal. Calcd for $C_{13}H_{14}N_4O_4$: C, 53.79; H, 4.86; N, 19.30. Found : C, 53.42; H, 4.77; N, 19.73.

Ir : $\nu_{\max}$ 3450-3200 broad, 1730, 1660, 1620, 1610 cm^{-1} . Uv: $\lambda_{\max}$ 329(4.15), 264 (3.93) nm. $^1\text{H-Nmr}$ (CDCl_3): δ 9.55(1H, br s, NH, collapses with D_2O), 7.32 (1H, d, $J=2$ Hz, H-4), 7.30 (1H, d, $J=9$ Hz, H-7), 6.98 (1H, dd, $J=9$ and 2 Hz, H-6), 5.38 (1H, s, olefinic H), 4.15(3H, s, N-Me), 3.65 and 3.59 (3H, s, COOMe).

(Z)-(2c); mp 85-87°C (by trituration with ether). Anal. Calcd for $\text{C}_{13}\text{H}_{14}\text{N}_4\text{O}_4$: C, 53.79; H, 4.86; N, 19.30. Found C, 53.98; H, 4.93; N, 19.12. Ir: $\nu_{\max}$ 3250, 1725, 1660, 1610 cm^{-1} . Uv: $\lambda_{\max}$ 334 (4.53), 281 (4.34), 212 sh (4.56) nm. $^1\text{H-Nmr}$ (CDCl_3): δ 9.62 (1H, s, NH, collapses with D_2O), 7.72 (1H, d, $J=9$ Hz, H-7), 7.20 (1H, d, $J=2$ Hz, H-4), 7.00 (1H, dd, $J=9$ and 2 Hz, H-6), 5.45 (1H, s, olefinic H), 4.45 (3H, s, N-Me), 3.73 and 3.68 (3H, s, COOMe).

(Z)-(2d); mp 108-110°C (from chloroform-ether). Anal. Calcd for $\text{C}_{13}\text{H}_{14}\text{N}_4\text{O}_4$: C, 53.79; H, 4.86; N, 19.30. Found: C, 53.59; H, 4.83; N, 19.42. Ir: $\nu_{\max}$ 3270, 1740, 1680, 1600 cm^{-1} . Uv: $\lambda_{\max}$ 331 (4.18), 273 (3.84), 226 (4.14) nm. $^1\text{H-Nmr}$ (CDCl_3): δ 10.45 (1H, s, NH collapses with D_2O), 8.25 (1H, d, $J=9$, H-7), 7.22 (1H, dd, $J=9$ and 2 Hz, H-6), 7.20 (1H, d, $J=2$ Hz, H-4), 5.75 (1H, s, olefinic H), 4.38 (3H, s, N-Me), 3.90 and 3.82 (3H, s, COOMe).

(3b); mp 226-227°C (by trituration with acetone). Anal. Calcd for $\text{C}_{18}\text{H}_{16}\text{N}_4\text{O}_7$: C, 54.00; H, 4.03; N, 14.00. Found: C, 53.87; H, 3.95; N, 13.92. Ir: $\nu_{\max}$ 1740, 1680, 1610 cm^{-1} . Uv: $\lambda_{\max}$ 334 (3.74), 261 (4.30), 207 (4.68) nm. $^1\text{H-Nmr}$ ($\text{DMSO}-d_6$): δ 7.96 (1H, d, $J=2$ Hz, H-4'), 7.81 (1H, d, $J=9$ Hz, H-7'), 7.48 (1H, dd, $J=9$ and 2 Hz, H-6'), 6.73 (1H, s, H-3), 4.32 (3H, s, N-Me), 3.72, 3.62 and 3.25 (3H, s, COOMe).

(3d); mp 231-233°C (by trituration with acetone). Anal. Calcd for $C_{18}H_{16}N_4O_7$: C, 54.00; H, 4.03; N, 14.00. Found: 53.87; H, 4.08, N, 13.83. Ir: $\nu_{\max}$ 1730, 1680, 1600 cm^{-1} . Uv: $\lambda_{\max}$ 320 (3.65), 288 sh (3.82), 260 (4.24), 206 (4.64) nm. $^1\text{H-Nmr}$ ($\text{CDCl}_3 + \text{DMSO-d}_6$): δ 7.85 (1H, d, $J=9$ Hz, H-7'), 7.65 (1H, d, $J=2$ Hz, H-4'), 7.02 (1H, dd, $J=9$ and 2 Hz, H-6'), 6.67 (1H, s, H-3), 4.02 (3H, s, N-Me), 3.60, 3.49 and 3.10 (3H, s, COOMe).

(5); mp > 320°C (from dimethyl sulfoxide). Anal. Calcd for $C_{12}H_{10}N_4O_3 + 1.25 \text{ H}_2\text{O}$: C, 51.33; H, 4.27; N, 19.96. Found: C, 51.32; H, 4.33; N, 19.96. Ir: $\nu_{\max}$ 3350, 1730, 1670, 1610, 1580 cm^{-1} . Uv: $\lambda_{\max}$ 315 (4.20), 289 (4.21), 229 (4.66) nm. $^1\text{H-Nmr}$ (DMSO-d_6) (200 MHz): δ 10.54 (0.5 H, s, NH collapses with D_2O), 7.85 (1H, d, $J_{4,5}=8$ Hz, H-4), 7.13 (1H, d, $J=8$ Hz, H-5), 6.20 (0.5 H, s, olefinic H-9), 4.41 (3H, s, N-Me), 3.73 (3H, s, COOMe), 3.11 (1H, d, $J_{a,b}=16$ Hz, H-9a), 2.70 (1H, d, $J=16$ Hz, H-9b). $^{13}\text{C-Nmr}$ (DMSO-d_6) (50 MHz): δ 173.39 (C=O), 167.23 (C=O), 141.23 (s, C-3a), 140.99 (s, C-8b), 119 (d, C-4), 118.55 (d, C-5), 109.10 (s, C-5a), 72.02 (s, C-8), 52.60 (q, OMe), 43.10 (q, N-Me), 42.45 (t, CH_2).

Method B.— A mixture of reactants as indicated in Table 1 was heated, under stirring, in Dowtherm at 250-260°C for 30 min. After cooling, the reaction mixture was taken up with hexane (80 ml) and stirred until a solid was formed. This, after filtration, was chromatographed on silica gel eluting in the order with ether to give (Z)-2c (21% yield), identical with a sample described above, and then with a mixture of ether and increasing amounts of acetone to give 1c (10%) and (E)-2c (6%).

(E)-(2c); mp 191-192 °C (by trituration with ether). Anal. Calcd for $C_{13}H_{14}N_4O_4$: C, 53.79; H, 4.86; N, 19.30. Found: C, 53.68; H, 4.98; N, 19.10. Ir: $\nu_{\max}$ 3320, 1740, 1720, 1700, 1640, 1615 cm^{-1} . Uv: $\lambda_{\max}$ 343, 279, 207 nm. 1H -Nmr ($CDCl_3$): δ 7.55 (1H, d, $J=9$ Hz, H-7), 6.82 (1H, d, $J=2$ Hz, H-4), 6.80 (1H, dd, $J=9$ and 2 Hz, H-6), 4.52 (1H, s, olefinic H), 4.40 (1H, s, N-Me), 3.78 and 3.68 (3H, s, COOMe), (NH obscured by the ester's resonances).

Method C.--- A mixture of reactants under the conditions of Table 1 was stirred and then flash chromatographed on silica gel column eluting with ether. The first fractions gave compound (Z)-(2c) identical with the above sample and the starting amine (1c) (8%).

Reaction of (Z)-2c with DMAD

i-- A mixture of a large excess of DMAD (1.47 g, 10.34 mmol) and (Z)-2c (1 g, 3.44 mmol) in dry acetonitrile (30 ml) was refluxed for 120 h. After evaporation of the solvent, the residue was taken up with ether and the solid formed was separated to give 2-methyl-7,8,9,10-tetramethoxycarbonyl-2H-triazolo-6H-9,10-dihydrobenzo[b]azepine (4)

(0.12 g, 8% yield); mp 204-206 °C (from ether). Anal. Calcd for $C_{19}H_{18}N_4O_8 \cdot H_2O$: C, 50.89; H, 4.50; N, 12.50. Found: C, 50.52; H, 4.61; N, 12.54. Ir: $\nu_{\max}$ 3325, 1725, 1715 cm^{-1} . Uv: $\lambda_{\max}$ 341 (4.09), 277 (4.28), 212 (4.32) nm. 1H -Nmr ($CDCl_3$ +DMSO- d_6): δ 9.05 (1H, br s, NH, collapses with D_2O), 7.39 (1H, d, $J=9$ Hz, H-4), 7.02 (1H, d, $J=9$ Hz, H-5), 4.66 (1H, d, $J=3$ Hz, H-9), 4.56 (1H, d, $J=3$ Hz, H-10), 4.31 (3H, s, N-Me), 3.78, 3.64, 3.58 and 3.29 (3H, s, COOMe). ^{13}C -Nmr ($CDCl_3$) (50 MHz): δ 171.22 (s, C=O), 170.45 (s, C=O), 168.32 (s, C=O), 166.60 (s, C=O), 144.21 (s, C-10b), 141.18 (s, C-3a), 138.04 (s, C-5a), 135.99 (s, C-10a), 122.12 (d, C-4), 117.63 (d, C-5), 112.67 (s, C-7), 106.16 (s, C-8), 53.59 (q, O-Me), 52.44 (q, O-Me), 52.30 (q, O-Me),

52.20 (q, O-Me), 48.51 (d, C-9), 46.46 (d, C-10), 43.21 (q, N-Me). The mother liquors evaporated *in vacuo* gave a residue which was chromatographed on silica gel column using ether as eluent to give trimethyl 1-(2-methyl-2H-benzotriazol-5-yl)pyridin-2-one-4,5,6-tricarboxylate (3c) (1.06 g, 78% yield) mp 134-136°C (from ether). Anal. Calcd for $C_{18}H_{16}N_4O_7 + 0.5 H_2O$: C, 52.81; H, 4.19; N, 13.69. Found: C, 52.64; H, 3.86; N, 13.72. Ir: ν_{max} 1750, 1730, 1670 cm^{-1} . Uv: λ_{max} 316 (4.06), 267 (4.61), 208 (4.98) nm. 1H -Nmr ($CDCl_3$): δ 7.77 (1H, d, J=9 Hz, H-7'), 7.60 (1H, d, J=2 Hz, H-4'), 7.08 (1H, dd, J=9 and 2 Hz, H-6'), 6.70 (1H, s, H-3), 4.40 (3H, s, N-Me), 3.81, 3.70 and 3.37 (3H, s, COOMe). The further fractions obtained eluting the column with a 7:3 mixture of ether-acetone, gave on evaporation a little amount (0.15 g, 15% yield) of the starting (Z)-2c.

ii-- In an other experiment a mixture of (Z)-2c (1.3 g, 4.5 mmol) and DMAD (2.04 g, 18 mmol) was stirred at room temperature for 180 h. After distillation of the excess of DMAD *in vacuo*, the oily residue was chromatographed on silica gel, eluting the column with ether to give in the order (Z)-2c (0.12 g, 9% yield), 3c (1.5 g, 84% yield) and 4 (0.07 g, 4% yield).

Cyclisation of dimethyl N-(1(2)(3)-R-1H(2H),(3H)-benzotriazol-5-yl)aminobutenedioates (Z)-(2a-d) into quinolinones (6b-d). *General procedure:* A stated amount of the appropriate ester (2a-d) (2.4 - 10.5 mmol) dissolved in boiling diphenyl ether (25-50 ml) was refluxed for 30 min. After cooling, the reaction mixture was triturated with hexane (100 ml) and stirred for an additional 30 min. The precipitate formed (6b-d) was collected and recrystallised as indicated below.

(Z)-(2a) gave the starting amine (1a) in 40% of yield.

(Z)-(2d) yielded 6b (75% yield), mp 238-240°C (from ethanol). Anal. Calcd for $C_{12}H_{10}N_4O_3$: C, 55.81; H, 3.90; N, 21.70. Found: C, 56.01; H, 3.75; N, 21.45. Ir: $\nu_{\max}$ 3300, 1700, 1630, 1600, 1585 cm^{-1} . Uv: $\lambda_{\max}$: 329 (3.65), 315 (3.70), 304 (3.63), 254 (4.33), 216 (4.12) nm. $^1\text{H-Nmr}$ ($\text{CDCl}_3 + \text{DMSO-d}_6$) (200 MHz): δ 8.15 (1H, d, $J=9$ Hz, H-4), 8.10 (1H, s, NH, exchange with D_2O), 7.97 (1H, d, $J=9$ Hz, H-5), 6.89 (1H, s, H-8), 4.84 (3H, s, N-Me), 4.03 (3H, s, COOMe).

(Z)-(2c) gave (6c) (88% yield), mp 279-281 °C (from dimethyl sulfoxide). Anal. Calcd for $C_{12}H_{10}N_4O_3$: C, 55.81; H, 3.90; N, 21.70. Found: C, 55.62; H, 3.83; N 21.62. Ir: $\nu_{\max}$ 3420, 1740 cm^{-1} . Uv: $\lambda_{\max}$ 310 infl (4.07), 256 (4.69), 216 (4.48) nm. $^1\text{H-Nmr}$ (DMSO-d_6): δ 8.15 (1H, d, $J=9$ Hz, H-4), 7.85 (1H, d, $J=9$ Hz, H-5), 7.25 (1H, s, H-8), 4.55 (3H, s, N-Me), 4.00 (3H, s, COOMe), 3.50 (1H, br s, NH, exchange with D_2O).

(Z)-(2b) afforded (6d) (95% yield); mp 280-282°C (from dimethyl formamide). Anal. Calcd for $C_{12}H_{10}N_4O_3$: C, 55.81; H, 3.90; N, 21.70. Found: C, 55.44; H, 3.86; N, 22.07. Ir: $\nu_{\max}$ 3500-3300 br, 1730, 1620 cm^{-1} . Uv: $\lambda_{\max}$ 342 infl (3.79), 332 (3.82), 324 infl (3.73), 256 (4.43), 218 (4.24), nm. $^1\text{H-Nmr}$ ($\text{DMSO-d}_6 + \text{d-TFA}$) (200 MHz): δ 8.51 (2H, at, $J=9$ Hz, H-4+H-5), 7.91 (1H, s, H-8), 4.50 (3H, s, N-Me), 4.15 (3H, s, COOMe).

Hydrolysis of the esters (6c-d) into the acids (7c-d) and of (5) and (18) into the acid (17)

General procedure: i- A suspension of the ester [(0.45 g, 1.74 mmol) of 6c and (4.96 g, 19.2 mmol) of 6d] in 1M NaOH aqueous solution (~ 30 ml) was stirred under reflux for 2 h. After cooling, on acidification with

conc. HCl solution a precipitate was obtained and filtered off. The acids were then recrystallized as indicated. Analytical and spectroscopic data are reported as follows:

(7c) (76% yield); mp 293-295 °C (from dimethyl sulfoxide). Anal. Calcd for $C_{11}H_8N_4O_3 + 1.25 H_2O$: C, 49.53; H, 3.97; N, 21.01. Found: C, 49.36; H, 3.68; N, 20.95. Ir: ν_{max} 3400, 1710, 1640, 1600 cm^{-1} . Uv: λ_{max} 336, 323, 308, 276, 264, 256 nm . 1H -Nmr (DMSO- d_6): δ 8.20 (1H, d, J=9 Hz, H-4), 8.01 (1H, d, J=9 Hz, H-5), 7.06 (1H, s, H-8), 4.53 (3H, s, N-Me), 4.16 (1H, br s, OH).

(8c) 1H -Nmr (DMSO- d_6) (200 MHz): δ 8.12 (1H, d, J=9 Hz, H-4), 7.51 (1H, d, J=9 Hz, H-5), 6.65 (1H, s, H-8), 4.66 (3H, s, N-Me).

(7d) (84% yield); mp >300°C (from dimethylformamide-water). Anal. Calcd for $C_{11}H_8N_4O_3 + 0.5 H_2O$: C, 52.17; H, 3.82; N, 22.13. Found: C, 51.87; H, 3.83; N, 22.16. Ir: ν_{max} 3460 br, 1670, 1600, 1550 cm^{-1} . Uv: λ_{max} 339, 326, 288, 253, 215 nm . 1H -Nmr (DMSO- d_6 +d-TFA) (200 MHz): δ 8.52 (1H, d, J=9 Hz, H-4), 8.39 (1H, d, J=9 Hz, H-5), 7.94 (1H, s, H-8), 4.48 (3H, s, N-Me).

ii- In an identical manner as above from compound (5) (1.7 g, 6.58 mmol) was obtained the acid (17) (1.45 g, 90% yield), mp 371-373°C¹² (from dimethyl sulfoxide). Anal. Calcd for $C_{11}H_8N_4O_3 + 0.5 H_2O$: C, 52.17; H, 3.58; N, 22.13. Found: C, 52.28; H, 3.26; N, 21.93. Ir: ν_{max} 3400 br, 1700, 1660 cm^{-1} . Uv: λ_{max} 352, 339, 324, 303, 281, 260 nm (4.81), 224 nm . 1H -Nmr [200 MHz] (DMSO- d_6): δ 12.42 (1H, br s, OH which collapses with D_2O), 8.08 (1H, d, J=9.2 Hz, H-4), 7.46 (1H, d, J=9.2 Hz, H-5), 6.61 (1H, s, H-8), 4.44 (3H, s, N-Me). ^{13}C -Nmr [50 MHz] ($CDCl_3$ +d-TFA): δ 170.43 (NH-C=O), 164.17 (C=O), 143.29 (s, C-9),

141.33 (s, C-3a), 138.72 (s, C-9b), 138.09 (s, C-5a), 124.22 (d, C-8), 119.55 (d, C-4), 118.23 (d, C-5), 107.57 (s, C-9a), 43.52 (q, N-Me).

iii- Operating under the same conditions as above from compound (18) (1 g, 3.61 mmol) was obtained the acid (17) (0.85 g, 96% yield) identical (mp,ir,uv,¹H-Nmr) to an authentic sample described above.

Chlorination of the esters (6b-d) and (5)

General procedure: A mixture of 6b-d (1.43-10 mmol) and POCl₃ (2-14 ml, 21.45-150 mmol) was stirred at 100-110 °C for 2 h. After cooling, the mixture was poured onto a mixture of crushed ice and water (30-80 ml) and stirred for 1 h. The solid formed was filtered off, thoroughly washed with water to give the chloro esters (9b-d). Analytical and spectroscopic data are reported as follows:

(9b) (20% yield); mp 201-203 °C (from chloroform). Anal. Calcd for C₁₂H₉N₄O₂Cl: C, 52.09; H, 3.28; N, 20.25; Cl, 12.81. Found: C, 51.83; H, 3.36; N, 19.99; Cl, 13.08. Ir: $\nu_{\max}$ 1750, 1565 cm⁻¹. Uv: $\lambda_{\max}$ 261 nm. ¹H-Nmr (CDCl₃): δ 8.39 (1H, s, H-8), 8.35 (1H, d, J_{4,5}=9 Hz, H-4), 8.22 (1H, d, J=9 Hz, H-5), 4.85 (3H, s, N-Me), 4.10 (3H, s, COOMe).

(9c) (92% yield); mp 243-244 °C (from chloroform). Anal. Calcd for C₁₂H₉N₄O₂Cl: C, 52.09; H, 3.28; N, 20.25; Cl, 12.81. Found: C, 51.70; H, 3.19; -N, 20.35; Cl, 13.16. Ir: $\nu_{\max}$ 1720 cm⁻¹. Uv: $\lambda_{\max}$ 320 sh, 280 sh, 262, 220 nm. ¹H-Nmr (DMSO-d₆): δ 8.71 (1H, s, H-8), 8.64 (1H, d, J_{4,5}=9 Hz, H-4), 8.40 (1H, d, J=9 Hz, H-5), 4.75 (3H, s, N-Me), 4.19 (3H, s, COOMe). In CDCl₃ the AB system appears as a singlet located at δ 8.90.

(9d) (87% yield); mp 258-260 °C (from chloroform). Anal. Calcd for $C_{12}H_9N_4O_2Cl$: C, 52.09; H, 3.28; N, 20.25; Cl, 12.81. Found: C, 51.89; H, 3.33; N, 20.38; Cl, 12.96. Ir: $\nu_{\max}$ 1720, 1590 cm^{-1} . Uv: $\lambda_{\max}$ 325, 312, 280 inf, 256 nm. 1H -Nmr ($CDCl_3$ +d-TFA): δ 8.10 (1H, s, H-8), 8.02 (1H, d, $J_{4,5}=9$ Hz, H-4), 7.85 (1H, d, $J=9$ Hz, H-5), 4.25 (3H, s, N-Me), 3.80 (3H, s, COOMe).

(18) (93% yield); mp 190-191°C (from acetone). Anal. Calcd for $C_{12}H_9N_4O_3Cl$: C, 52.09; H, 3.28; N, 20.25; Cl, 12.81. Found: C, 52.38; H, 3.13; N, 20.36; Cl, 12.75. Ir: $\nu_{\max}$ 1730, 1580, 1550 cm^{-1} . Uv: $\lambda_{\max}$ 284 sh (4.34), 264 (5.04), 236 sh (4.47), 222 (4.41) nm. 1H -Nmr (200 MHz) ($CDCl_3$ +d-TFA): δ 8.38 (1H, d, $J=9.4$ Hz, H-4), 8.11 (1H, d, $J=9.4$ Hz, H-5), 7.88 (1H, s, H-8), 4.65 (3H, s, N-Me), 4.23 (3H, s, COOMe). ^{13}C -Nmr (50 MHz) ($CDCl_3$ +d-TFA): δ 166.42 (C=O), 148.34 (s, C-7), 145.05 (s, C-9), 143.58 (s, C-3a), 142.97 (s, C-5a), 137.99 (s, C-9b), 127.78 (d, C-8), 122.43 (d, C-5), 121.59 (d, C-4), 117.14 (s, C-9a), 55.10 (q, O-Me), 43.85 (q, N-Me).

Hydrolysis of the chloro esters (9c-d) into the acids (10c-d). *General procedure:* In a identical manner as for the above mentioned cases of 6c-d, the esters (9c-d) (1.74 mmol) were hydrolysed in alkaline medium (30 ml of 1M NaOH aqueous solution) which was eventually decolourized with charcoal and filtered. The mother liquors were made acidic with conc. HCl solution and the precipitates were collected and washed with water. The acids were solids and were recrystallized as indicated. Analytical and spectroscopic data are reported as follows:

(10c) (92% yield); mp 239-240°C (from dimethyl sulfoxide-water). Anal. Calcd for $C_{11}H_7N_4O_2Cl$: C, 50.30; H, 2.69; N, 21.33; Cl, 13.50. Found: C, 50.12; H, 2.53; N, 21.00; Cl, 13.30. Ir: $\nu_{\max}$ 1700, 1660, 1580 cm^{-1} .

Uv: $\lambda_{\max}$ 325, 312, 280 nm , 260, 231 nm . $^1\text{H-Nmr}$ (200 MHz) (DMSO-d_6): δ 8.20 (1H, s, H-8), 8.15 (1H, d, $J_{4,5}=9$ Hz, H-4), 7.85 (1H, d, $J=9$ Hz, H-5), 4.57 (3H, s, N-Me), 4.30 (1H, br s, COOH).

(10d) (89% yield); mp 254-256 $^{\circ}\text{C}$ (from dimethyl sulfoxide-water). Anal. Calcd for $\text{C}_{11}\text{H}_7\text{N}_4\text{O}_2\text{Cl}$: C, 50.30; H, 2.69; N, 21.33; Cl, 13.50. Found: C, 50.30; H, 2.58; N, 21.47; Cl, 13.61. Ir: $\nu_{\max}$ 1755, 1590 cm^{-1} . Uv: $\lambda_{\max}$ 325, 312, 280 nm , 256 nm . $^1\text{H-Nmr}$ (200 MHz) (DMSO-d_6): δ 8.10 (1H, s, H-8), 8.05 (1H, d, $J_{4,5}=9$ Hz, H-4), 7.90 (1H, d, $J=9$ Hz, H-5), 6.00 (1H, br s, COOH), 4.35 (3H, s, N-Me).

Decarboxylation of the acids (10c-d) to chloroquinolines (11c-d).

General procedure: Compound [(10c or 10d)] (6.7-7.58 mmol) was added in small portions to a suspension of copper (1-1.1 g, 17.8--19.6 mmol) in refluxing Dowtherm (30-60 g). After 1h the hot mixture was filtered to remove the insoluble copper and, once cooled, then diluted with light petroleum (bp 40-60 $^{\circ}\text{C}$). The chloroquinolines (11c-d) separated as solids. Analytical and spectroscopic data are reported as follows:

(11c) (60% yield); mp 188-189 $^{\circ}\text{C}$ (from chloroform). Anal. Calcd for $\text{C}_{10}\text{H}_7\text{N}_4\text{Cl}$: C, 54.93; H, 3.23; N, 25.63; Cl, 16.22. Found: C, 55.04; H, 3.18; N, 25.39; Cl, 16.33. Ir: $\nu_{\max}$ 1580 cm^{-1} . Uv: $\lambda_{\max}$ 322, 308, 289 nm , 255, 225 nm . $^1\text{H-Nmr}$ (200 MHz) (CDCl_3): δ 8.65 (1H, d, $J_{7,8}=6$ Hz, H-7), 7.92 (1H, d, $J_{4,5}=9$ Hz, H-4), 7.75 (1H, d, $J=9$ Hz, H-5), 7.45 (1H, d, $J=6$ Hz, H-8), 4.48 (3H, s, N-Me).

(11d) (62% yield); mp 218-220 $^{\circ}\text{C}$ (from chloroform). Anal. Calcd for $\text{C}_{10}\text{H}_7\text{N}_4\text{Cl}$: C, 54.93; H, 3.23; N, 25.63; Cl, 16.22. Found: C, 54.92; H, 3.13; N, 25.80; Cl, 16.54. Ir: $\nu_{\max}$ 1590 cm^{-1} . Uv: $\lambda_{\max}$ 323, 308, 282, 274, 222 nm . $^1\text{H-Nmr}$ (200 MHz) ($\text{CDCl}_3+\text{DMSO-d}_6$): δ 8.68 (1H, d, $J_{7,8}=6$

Hz, H-7), 7.95 (1H, d, $J_{4,5}=9$ Hz, H-4), 7.70 (1H, d, $J=9$ Hz, H-5), 7.57 (1H, d, $J=6$ Hz, H-8), 4.35 (3H, s, N-Me).

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