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STUDIES ON QUINAZOLINE CHEMISTRY. 4*. UNEXPECTED ROUTE OF ACYLATION OF ALKYL 2-(4,4-DIPHENYL-1,2,3,4-TETRAHYDRO-2-QUINAZOLINYLIDENE)ACETATES. MOLECULAR STRUCTURE OF METHYL 2-(4,4-DIPHENYL)-1,2,3,4-TETRAHYDRO-2-QUINAZOLINYLIDENE)-3-OXOBUTANOATE

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A study of the reaction of quinazoline derivatives with acid chlorides in the absence of acids has shown that alkyl 2-(4,4-diphenyl-1,2,3,4-tetrahydro-2-quinazolinylidene)acetates undergo C-acylation. The molecular structure of methyl 2-(4,4-diphenyl-1,2,3,4-tetrahydro-2-quinazolinylidene)-3-oxobutanoate has been investigated by X-ray analysis.

Keywords: tetrahydroquinazolinylideneacetates, acylation, mass spectrometry, molecular structure, prototropic tautomerism.

We have previously reported the reactions of *o*-aminophenyldiphenylcarbinol with different nitriles and perchloric acid [1, 2]. Under the given reaction conditions ethyl cyanoacetate gives ethyl 2-(4,4-diphenyl-1,2,3,4-tetrahydro-2-quinazolinylidene)acetate (**1b**) which exists as a mixture of *Z*- and *E*-isomers [2]. It was also noted that methylation of this compound occurs *via* N- and C-dimethylation with migration of the exocyclic multiple bond into the heterocycle to form the corresponding ethyl 2-(3-methyl-4,4-diphenyl-3,4-dihydro-2-quinazolinyl)propanoate.

In connection with such an unusual alkylation route where, in the presence of two amine nitrogen atoms, alkylation occurs at only one of these and the second alkylation is at the exocyclic multiple bond in α-position to the carboxylate group stimulated us to study the behavior of compounds **1a,b** towards an acylation reaction (i.e. in conditions exchanging a "soft" electrophile (R^+) for a hard one ($RC^+{=}O$)).

The reaction was carried out using a twofold excess of the carboxylic acid halide at room temperature in dry benzene [3] (Scheme 1).

Elemental analysis, ^1H NMR, and mass spectrometry showed that the products of monoacylation at an exocyclic C=C bond carbon atom **2a-g** were obtained in the reaction (Tables 1,2, and 6).

The ^1H NMR spectra of compounds **2a-g** (Table 2) were recorded in different solvents and showed a marked difference in the number and position of the NH proton signals. Hence in $CDCl_3$ solution there were four low field signals, each of intensity 0.5H, which points to the presence in solution of two geometric *Z*- and

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* For Communication 3 see [1].

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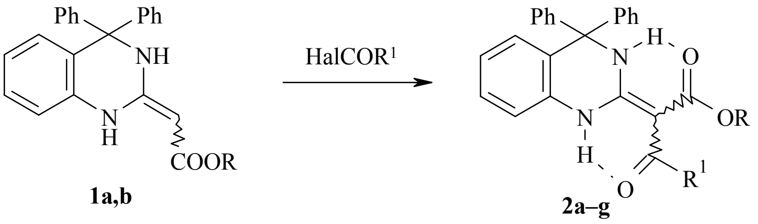
E-isomers in a ratio close to 1 : 1. The spectra recorded in $(CD_3)_2CO$ or DMSO-d_6 showed only two broad singlet signals for the NH protons, each of intensity 1H. Such a change in the nature of the spectra when crossing from a less to a more polar solvent can be explained by the existence of a dynamic equilibrium between isomeric forms as a result of a prototropic tautomerism of the type C $\rightleftarrows$ A $\rightleftharpoons$ B.

Scheme 1



1a, 2a R = Me; **1b, 2b–g** R = Et; **2a,b** R^1 = Me, **c** R^1 = Ph, **d** R^1 = CH_2Cl,
e R^1 = 4-$O_2NC_6H_4$, **f** R^1 = 4-$MeOC_6H_4$, **g** R^1 = *n*-C_4H_9

The prototropic tautomerism (Scheme 2) provides the possibility of rotation relative to the exocyclic multiple bond which also leads to a dynamic *Z* – *E* isomerization [4, 5]. Such an isomerization has been observed in solution for 2-carbethoxy(acetyl)methylene-4-pyrimidinones in the study [6].

It appears that only one isomer is formed when crystallizing from solution to the solid phase. By X-ray analysis it was shown that for compound **2a** this is the *Z*-isomer (Figure 1, Tables 3-5).

As is evident from Figure 1, molecule **2a** has two intramolecular hydrogen bonds H(1)···O(3) and H(2)···O(1). For the hydrogen bond N(1)–H(1)···O(3) the parameters were: interatomic distances H(1)···O(3) and N(1)···O(3) 1.759 and 2.530 Å respectively, valence angles N(1)–H(1)···O(3) and H(1)···O(3)–C(12) 140.3 and 103.3° respectively.

TABLE 1. Characterictics of the Compounds Synthesized **2a-g**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	R_f*	IR spectrum, ν, cm^{-1} (NH, C=O, COOR)	Yield, %
		C	H	N				
2a	$C_{25}H_{22}N_2O_3$	75.28 75.36	5.72 5.56	6.88 7.03	160-162	0.30	3140, 1625, 1590	50
2b	$C_{26}H_{24}N_2O_3$	75.38 75.71	5.45 5.86	6.52 6.79	146-148	0.21	3160, 1650, 1620	57
2c	$C_{31}H_{26}N_2O_3$	78.50 78.46	5.35 5.52	5.72 5.90	158-160	0.81	3130, 1610, 1590	65
2d	$C_{26}H_{23}ClN_2O_3$	69.70 69.87	5.32 5.19	6.42 6.27	150-152	0.75	3140, 1610, 1580	60
2e*^{2}	$C_{31}H_{25}N_3O_5$	71.42 71.67	4.53 4.85	8.15 8.09	193-195	0.70	3120, 1610, 1590	62
2f	$C_{32}H_{28}N_2O_4$	76.35 76.17	5.71 5.59	5.43 5.55	173-174	0.65	3150, 1600, 1580	52
2g	$C_{29}H_{30}N_2O_3$	76.85 76.63	6.90 6.65	6.02 6.16	118-120	0.80	3120, 1680, 1590	55

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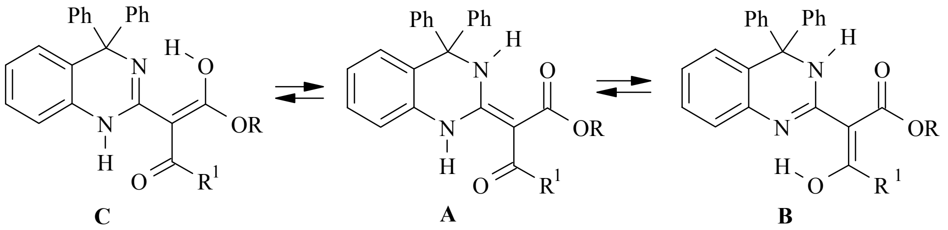
* UV-254 Silufol, benzene-ether, 4 : 1

*^{2} IR spectrum, ν, cm^{-1}: 1510, 1320 (NO_2).

Scheme 2



The parameters for the second hydrogen bond N(2)–H(2)···O(1) were: interatomic distances H(2)···O(1) and N(2)···O(1) 1.960 and 2.591 Å respectively, valence angles N(2)–H(2)···O(1) and H(2)···O(1)–C(10) 139.9 and 98.9° respectively.

Conjugation between the amine nitrogen atoms and carbonyl groups were revealed through a marked distortion of interatomic distances in the system of formal double and single bonds containing these atoms. Hence the formal double bonds C(1)–C(9) and C(12)–O(3) were strongly lengthened: bond C(1)–C(9) to

TABLE 2. ^1H NMR Spectra of Compounds **2a-g**

Compound	Solvent	Chemical shifts, δ, ppm.	SSCC, *J*, Hz
2a	$CDCl_3$	2.45 (3H, s, CH_3CO); 3.80 (3H, s, CH_3OCO); 6.85 (1H, d, H-8); 7.18 (13H, m, H_{arom}); 10.90, 12.00, 13.10, 14.05 (2H, four s, 2NH)	$^3J_{7,8}$ = 8.0
	$(CD_3)_2CO$	2.30 (3H, s, CH_3CO); 3.75 (3H, s, CH_3OCO); 7.05 (4H, m, C_6H_4); 7.40 (10H, m, $2C_6H_5$); 12.20, 12.85 (2H, two br. s, 2NH)	—
2b	$CDCl_3$	1.42 (3H, t, CH_3); 2.50 (3H, s, CH_3CO); 4.25 (2H, q, CH_2); 6.75 (1H, d, H-8); 7.20 (13H, m, H_{arom}); 10.95, 12.00, 13.10, 14.00 (2H, two br. s, 2NH)	$^3J_{7,8}$ = 8.0, $^3J_{CH_2CH_3}$ = 7.5
	$(CD_3)_2CO$	1.20 (3H, t, CH_3), 2.25 (3H, s, CH_3CO); 4.15 (2H, q, CH_2); 6.90 (4H, m, C_6H_4); 7.22 (10H, m, two C_6H_5); 11.95, 12.80 (2H, four s, 2NH)	$^3J_{CH_2CH_3}$ = 7.0
2c	$CDCl_3$	0.65 (3H, t, CH_3), 3.80 (2H, q, CH_2); 6.77 (1H, d, H-8); 7.30 (18H, m, H_{arom}); 10.55, 11.53, 12.15, 13.20 (2H, four s, 2NH)	$^3J_{CH_2CH_3}$ = 6.4, $^3J_{7,8}$ = 7.2
2d	$CDCl_3$	1.40 (3H, t, CH_3), 4.30 (2H, q, CH_2); 4.72 (2H, s, CH_2Cl); 6.75 (1H, d, H-8); 7.20 (13H, m, H_{arom}); 10.95, 12.00, 12.65, 13.60 (2H, four s, 2NH)	$^3J_{CH_2CH_3}$ = 7.0
2e	DMCO-d_6	0.57 (3H, t, CH_3); 3.78 (2H, q, CH_2); 6.77 (1H, d, H-8); 7.20 (1H, t, H-6); 7.30 (11H, m, two C_6H_5+ + H-7); 7.35 (1H, d, H-5); 7.60 (2H, d, H_B); 8.25 (2H, d, H_A); 11.55, 12.10 (2H, two s, 2NH)	$^3J_{CH_2CH_3}$ = 7.0, $^3J_{7,8}$ = 7.2, $^3J_{5,6}$ = 7.5, $^3J_{AB}$ = 9.0
2f	DMCO-d_6	0.68 (3H, t, CH_3); 3.78 (3H, s, OCH_3); 3.82 (2H, q, CH_2); 6.72 (1H, d, H-8); 6.92 (2H, d, $2H_B$); 7.10 (2H, d, $2H_A$); 7.18 (1H, t, H-6); 7.25 (11H, m, two C_6H_5 + H-7); 7.30 (1H, d, H-5); 11.40, 11.90 (2H, two br. s, 2NH)	$^3J_{CH_2CH_3}$ = 6.5, $^3J_{7,8}$ = 7.7, $^3J_{5,6}$ = 7.6, $^3J_{AB}$ = 8.0
2g	DMCO-d_6	0.90 (3H, t, CH_3); 1.30 (5H, m, γ-CH_2 + CH_3); 1.51 (2H, t, β-CH_2); 2.75 (2H, t, α-CH_2); 4.20 (2H, q, CH_2); 6.70 (1H, d, H-8); 7.15 (1H, t, H-6); 7.25 (1H, d, H-5); 7.30 (11H, m, two C_6H_5 + H-7); 12.10, 12.55 (2H, two br. s, 2NH)	$^3J_{CH_2CH_3}$ = 6.8, $^3J_{7,8}$ = 7.5, $^3J_{5,6}$=7.7, $^3J_{CH_2CH_3}$ = 6.0

1.437(2) and C(12)–O(3) to 1.245(2) Å (in the conjugated C=C–C=O system the standard value for the C=C bond is 1.36 ± 0.01 and for the C=O bond 1.215 ± 0.005 Å [7]). As a result of the conjugation the interatomic distances N(1)–C(1) and N(2)–C(1) were shortened to 1.340(2) and 1.334(2) Å (standard N–C (*sp*^{2}) bond length 1.43 ± 0.01 Å [7]). Attention is also drawn to the difference in the interatomic distances N(1)–C(4) and N(1)–C(1), a marked decrease in the N(1)–C(1) bond length pointing to a shift of the unshared electron pair on the N(1) atom into the conjugated C=C–C=O system.

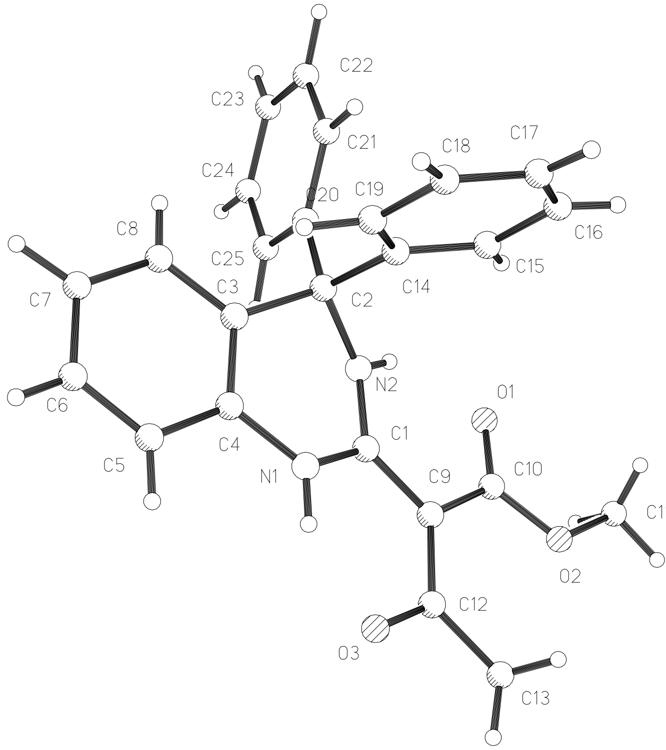


Figure 1. Projection of the spatial model of methyl 2-(4,4-diphenyl-1,2,3,4-tetrahydro-2-quinazolinylidene)-3-oxobutanoate (**2a**).

TABLE 3. Basic Bond Lengths (*d*) in the Molecule of Compound **2a**

Bond	*d*, Å	Bond	*d*, Å
O(1)–C(10)	1.224(2)	C(2)–C(14)	1.544(3)
O(2)–C(10)	1.333(2)	C(3)–C(8)	1.381(3)
O(2)–C(11)	1.448(3)	C(3)–C(4)	1.385(3)
O(3)–C(12)	1.245(2)	C(4)–C(5)	1.382(3)
N(1)–C(1)	1.340(2)	C(5)–C(6)	1.373(3)
N(1)–C(4)	1.407(3)	C(6)–C(7)	1.374(4)
N(2)–C(1)	1.334(2)	C(7)–C(8)	1.385(3)
N(2)–C(2)	1.464(2)	C(9)–C(12)	1.443(3)
C(1)–C(9)	1.437(3)	C(9)–C(10)	1.447(3)
C(2)–C(3)	1.513(3)	C(12)–C(13)	1.500(3)
C(2)–C(20)	1.530(3)		

TABLE 4. Basic Valence Angles (φ) in the Molecule of Compound **2a**

Angle	φ, deg	Angle	φ, deg
C(10)–O(2)–C(11)	116.1(2)	C(12)–C(9)–C(10)	124.4(2)
C(1)–N(1)–C(4)	122.20(19)	O(1)–C(10)–O(2)	119.2(2)
C(1)–N(2)–C(2)	122.98(18)	O(1)–C(10)–C(9)	125.5(2)
N(2)–C(1)–N(1)	115.58(19)	O(2)–C(10)–C(9)	115.3(2)
N(2)–C(1)–C(9)	123.59(19)	O(3)–C(12)–C(9)	121.9(2)
N(1)–C(1)–C(9)	120.83(19)	O(3)–C(12)–C(13)	115.1(2)
N(2)–C(2)–C(3)	105.82(16)	C(9)–C(12)–C(13)	123.0(2)
N(2)–C(2)–C(20)	108.30(16)	C(19)–C(14)–C(15)	118.6(2)
C(3)–C(2)–C(20)	111.43(17)	C(19)–C(14)–C(2)	122.4(2)
N(2)–C(2)–C(14)	109.02(16)	C(15)–C(14)–C(2)	119.0(2)
C(3)–C(2)–C(14)	110.88(16)	C(14)–C(15)–C(16)	120.1(3)
C(20)–C(2)–C(14)	111.19(16)	C(17)–C(16)–C(15)	120.2(3)
C(8)–C(3)–C(4)	118.4(2)	C(18)–C(17)–C(16)	120.4(3)
C(8)–C(3)–C(2)	123.9(2)	C(17)–C(18)–C(19)	120.2(3)
C(4)–C(3)–C(2)	117.58(19)	C(14)–C(19)–C(18)	120.6(3)
C(5)–C(4)–C(3)	121.1(2)	C(25)–C(20)–C(21)	118.3(2)
C(5)–C(4)–N(1)	120.0(2)	C(25)–C(20)–C(2)	119.6(2)
C(3)–C(4)–N(1)	118.89(18)	C(21)–C(20)–C(2)	122.0(2)
C(6)–C(5)–C(4)	119.0(2)	C(22)–C(21)–C(20)	120.5(2)
C(5)–C(6)–C(7)	121.3(3)	C(23)–C(22)–C(21)	120.7(3)
C(6)–C(7)–C(8)	118.8(3)	C(22)–C(23)–C(24)	119.7(3)
C(3)–C(8)–C(7)	121.3(2)	C(23)–C(24)–C(25)	120.1(3)
C(1)–C(9)–C(12)	119.18(19)	C(20)–C(25)–C(24)	120.5(2)
C(1)–C(9)–C(10)	116.34(19)		

TABLE 5. Dihedral Angles (θ) in the Molecule of Compound **2a**

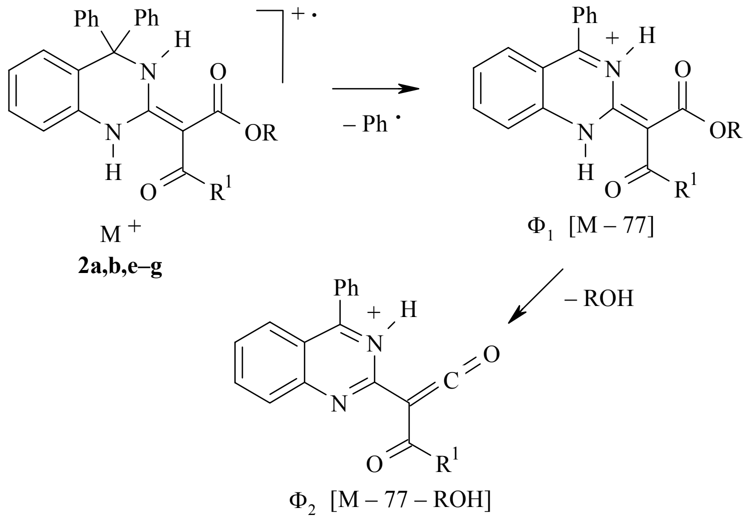
Angle	θ, deg	Angle	θ, deg
N(1)–C(4)–C(3)–C(2)	5.8 (2)	N(2)–C(1)–C(9)–C(10)	5.4 (2)
C(4)–C(3)–C(2)–N(2)	33.8 (2)	N(1)–C(1)–C(9)–C(12)	1.6 (2)
C(3)–C(2)–N(2)–C(1)	47.3 (2)	C(1)–C(9)–C(10)–O(1)	12.9 (2)
C(2)–N(2)–C(1)–N(1)	27.3 (2)	C(1)–C(9)–C(12)–O(3)	1.8 (2)
N(2)–C(1)–N(1)–C(4)	9.0 (2)	C(1)–C(9)–C(12)–C(13)	166.2 (2)
C(1)–N(1)–C(4)–C(3)	19.0 (2)	C(9)–C(10)–O(2)–C(11)	177.5 (2)

The strictly conjugated system of the β,β-diamino-α,α-dicarbonyl group is virtually planar, the dihedral angles for N(1)–C(1)–C(9)–C(12) and N(2)–C(1)–C(9)–C(10) being 1.6 and 5.4° (see Table 5) and stabilized by the two hydrogen bonds reported above. The formation of such a conjugated system is likely the driving force for acylation at the multiple bond.

The six-membered heterocyclic fragment of the molecule has a distorted *twist boat* conformation. Calculation of the ring folding parameters carried out according to [8] for C(1)–N(1)–C(4)–C(3)–C(2)–N(2) gave the following values: $S = 0.449$; $\theta = 59.03^{\circ}$, $\Psi = 18.97$. Atoms N(1) and C(2) deviate by 0.145 and 0.494 Å correspondingly from the plane of the remaining four atoms of the "*boat bottom*" (mean deviation not greater than 0.05 Å). The dihedral angles between the "*boat bottom*" and "*boat walls*" C(1)–N(1)–C(4) and N(2)–C(2)–C(3) are 4.9 and 33.7° respectively.

The spatial position of the three phenyl substituents on the sp^3-hybridized C(2) atom are very reminiscent of the conformation of triphenylmethane as a distorted *propeller*. The phenyl rings C(3)·C(8), C(14)···C(19), and C(20)···C(25) are twisted to the same side of the corresponding planes N(2)–C(2)–C(*i*) (*i* = 3, 14, or 20) by 32.2, 46.6, and 43.1°.

Scheme 3



A characteristic feature of the electron impact mass spectra of the synthesized compound **2a-b,e-g** is the successive fission from the molecular ion of a phenyl radical and a molecule of the corresponding alcohol (Scheme 3). Further fission of the Φ_2 cation is determined by the nature of the substituent R^1. In the spectra of all of the compounds investigated there are also quite strong peaks (12-79%) associated with the acyl cation $R^1–C^+=O$.

TABLE 6. Electron Impact Mass Spectra of Compounds **2a,b,e-g**

Com-pound	*m/z* (*I*, %) of maximum				
	$M^{+\cdot}$	Φ_1^+	Φ_2^+	$R^1–C^+=O$	Other characteristic ions
2a	398 (12)	321 (5)	289 (100)	43 (50)	247 (28) [Φ_2–42], 205 (5) [Φ_2–42–42], 77 (45)
2b	412 (38)	335 (15)	289 (100)	43 (20)	247 (26) [Φ_2–42], 205 (5) [Φ_2–42–42], 77 (30)
2e	519 (24)	442 (5)	396 (100)	150 (23)	104 (44) [C_7H_4O], 77 (30)
2f	504 (43)	427 (5)	381 (100)	135 (79)	92 (7), 77 (20)
2g	454 (60)	377 (6)	331 (61)	85 (12)	412 (15) [M–42], 370 (100) [M–42–42], 289 (30) [Φ_2–42], 247 (99) [Φ_2–42–42], 77 (27)

EXPERIMENTAL

IR spectra were recorded on a Specord IR-75 instrument at room temperature using vaseline oil. ^{1}H NMR spectra were taken on Tesla BS-467 (60 MHz) and Bruker DRX 500 (500 MHz) instruments using TMS as internal standard. Mass spectra were obtained on a Varian CH-6 instrument with direct introduction of the sample into the ion source and an electron ionization energy of 70 eV. TLC was performed on Silufol UV-254 plates and revealed using iodine vapor.

X-Ray Analysis of Compound 2a. Colorless crystals of compound **2a** of composition $C_{25}H_{22}N_2O_3{\cdot}0.5C_2H_5OH$ were obtained by multicrystallization from ethanol and are triclinic. At 18ºC: $a = 8.915(2)$, $b = 11.299(2)$, $c = 12.549(3)$ Å, $\alpha = 69.40(3)$, $\beta = 73.81(3)$, $\gamma = 68.81(3)^\circ$, $V = 1086.5(4)$ Å^3, $d_{calc} = 1.287$ g/cm^3. Space group P-1, $Z = 2$. The X-ray analysis was carried out on a CAD-4, four circle, automatic diffractometer (graphite monochromator, MoKα radiation, $\theta/2\theta$ scanning from 1.76 to $\theta_{max} = 25^\circ$). Crystal size 0.23×0.21×0.12 mm. 3812 Reflections were obtained with $I > 3\sigma(I)$. The structure was solved by a direct method using the SHELXTL program package [9] and refined in the anisotropic approximation (isotropic for hydrogen atoms) to difference factors of $R_1 = 0.0315$ and $wR_2 = 0.0728$. The atomic coordinates have been placed in the Cambridge structural data bank (reference CCDC 620810).

Methyl 2-(4,4-Diphenyl-1,2,3,4-tetrahydro-2-quinazolinylidene)acetate (1a) was prepared according to method [2]. Mp 179-181ºC (ethanol). IR spectrum, ν, cm^{-1}: 3280 (NH), 1615 (C=C), 1660 ($COOCH_3$). ^{1}H NMR spectrum (DMSO-d$_6$), δ, ppm: 3.50 (3H, s, CH_3); 4.20, 4.38, 9.47, 9.75 (four signals with intensity 0.5H each, 2NH); 6.60 (1H, m, H-8); 6.85 and 6.90 (1H, two signals with intensity 0.5H each, =CH-); 7.20 (13H, m, H$_{arom}$). Found, %: C 77.25; H 5.41; N 7.52. $C_{23}H_{20}N_2O_2$. M$^{+\cdot}$ 356. Calculated, %: C 77.53; H 5.62; N 7.86. M 356.50.

Ethyl 2-(4,4-Diphenyl-1,2,3,4-tetrahydro-2-quinazolinylidene)-3-oxobutanoate (2b). Na_2CO_3 (0.5 g) was added with stirring to a solution of the ethyl ester **1b** (0.65 g, 1.7 mmol) and acetyl bromide (0.42 g, 3.4 mmol) in dry benzene (7 ml). The mixture was stirred vigorously for 2.5 h at room temperature. At the end of the reaction (TLC monitoring) the inorganic salt was filtered off, washed with benzene, and the filtrate was evaporated. The product obtained was purified by column chromatography (L 40/100 grade silica gel, benzene eluent). Yield 0.4 g (57%).

Compound 2a was prepared similarly from the methyl acetate **1a**.

Compounds 2c-g were prepared by the scheme given above using acid chlorides as acylating agents.

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