The Reactions of Ethyl 3,4-Dihydro-4-quinazolylacetate and Its Derivatives with Cyclopentanone. An Attempt at the Synthesis of the 6,8-Diazasteroid System VII

Takao Yamazaki, Katsuhide Matoba, Atsuko Shirokawa

Faculty of Pharmaceutical Sciences, University of Toyama, Gofuku, Toyama 930, Japan

and

Raymond N. Castle

Department of Chemistry, Brigham Young University, Provo, Utah 84602

Received August 24, 1977

The reaction of ethyl 3,4-dihydro-4-quinazolylacetate (Ia) with cyclopentanone in the presence of trifluoroacetic acid gave mainly two decomposition products, carbostyril (VIII) and ethyl 2-aminocinnamate (IX). Two compounds which are suggested to have the 6,8-diazasteroid skeleton were also obtained in poor yield. Ethyl 3,4-dihydro-2-*p*-methoxyphenyl-4-quinazolylacetate (Ib), however, gave 2-*p*-methoxyphenylquinazoline (XII) as a decomposition product and did not condense with cyclopentanone. Furthermore, two ethyl 3,4-dihydroquinazolylacetates substituted at the 2-position with cyclohexyl (Ic) and methyl (Id) groups could not be converted to the expected diazasteroid system.

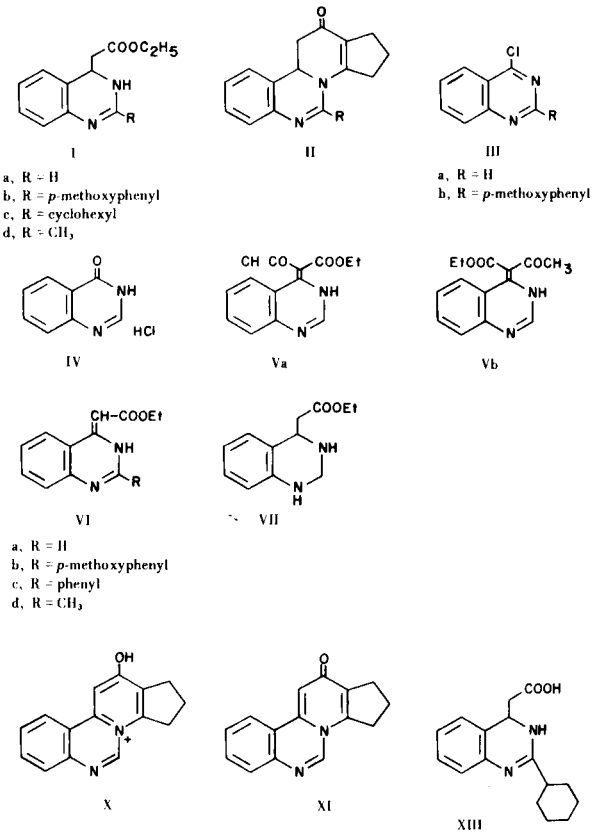
J. Heterocyclic Chem., **15**, 467 (1978)

In our laboratory, various diazasteroids have hitherto been synthesized (1). In this paper, we examined the chemical behavior of ethyl 3,4-dihydro-4-quinazolylacetate (Ia) and its 2-substituted derivatives (Ib-d) to apply them to the synthesis of the 6,8-diazasteroid systems (II).

At first, 4-chloroquinazoline (IIIa), a starting material to Ia, was synthesized as reported in the literature (2). However, since IIIa was very unstable toward moisture giving 4-quinazolone hydrochloride (IV), the method of its isolation was improved as follows: compound IIIa was extracted with *n*-hexane using a Soxhlet-extractor, from the powder obtained after the evaporation of an excess of phosphorus oxychloride from the reaction mixture. The chloride thus obtained was next treated with sodio ethyl acetoacetate in ether to give an isomeric mixture of the acetoacetylidene derivatives (Va and Vb) (3). From the nmr spectral data, it was shown that the ratio of Va to Vb was about 1 to 2, and the acetyl methyl group of Va appeared in lower field than that of Vb owing to the anisotropy of the benzene ring. This isomeric mixture was deacetylated with ethanolic trifluoroacetic acid as previously reported (4) to give ethyl 4-quinazolylacetate (VIa) *via* the trifluoroacetate salt. The melting point and the nmr spectrum of VIa were completely identical with those prepared *via* another route by Hayashi, *et al.*, (5).

The result of reduction of VIa was remarkably different from that of the reduction of its hydrochloride: the product from VIa hydrochloride was ethyl 3,4-dihydro-4-quinazolylacetate (Ia) only, while from VIa, a mixture of Ia and ethyl 1,2,3,4-tetrahydro-4-quinazolylacetate (VII) was obtained. In the latter case, the ratio of Ia to VII was about 1 to 3. It was interesting that these results were different from those obtained using ethyl 2-substituted-4-quinazolylacetates, as mentioned below (4,6). Compounds Ia and VII were separated easily by silica gel column chromatography. The picrates of Ia and VII melted at 145-147° and 164-166°, respectively, and the elemental analyses were consistent with each structure.

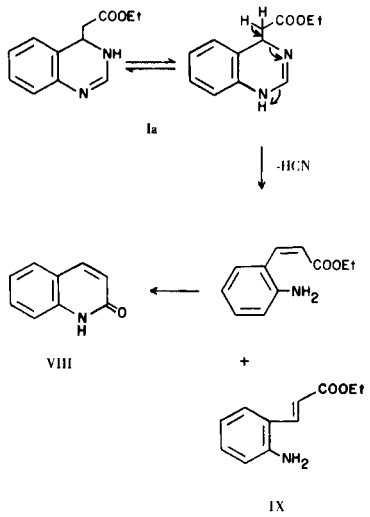
Chart 1



Compound Ia was treated with cyclopentanone in the presence of trifluoroacetic acid (7). The major products were carbostyril (VIII) and ethyl 2-aminocinnamate (IX). Compound VIII was identified with an authentic sample. Compound IX exhibited a carbonyl band at 1690 cm^{-1}

in the ir spectrum and signals of the AB type (J = 15.8 Hz) at δ 6.30 and 7.77 ppm in the nmr spectrum, with a parent peak at m/e 191 in the mass spectrum. A proposed mechanism of the formation of these unexpected products from Ia is shown in Chart 2, where the electron shift from the active methylene group toward the quinazoline ring decomposes the ring skeleton.

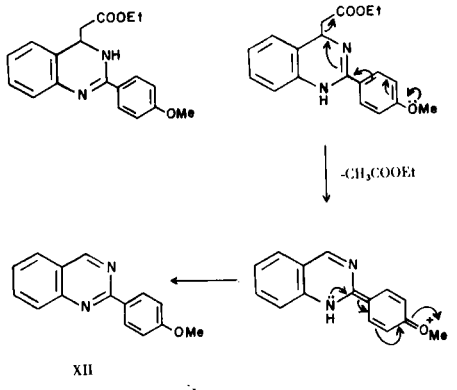
Chart 2



By further treatment of the crude reaction product with ethylene glycol, two minor products were obtained. One was isolated as yellow needles which melted at 250-252° and exhibited a carbonyl band at 1680 cm^{-1} in the ir spectrum, with a parent peak at m/e 238 and the base peak at m/e 237 (X) in the mass spectrum. Another was isolated as brown needles which melted at 304-306° and exhibited a carbonyl band at 1650 cm^{-1} in the ir spectrum, and a parent peak at m/e 236 (base peak) in the mass spectrum. It was suggested that the former and the latter were 6,8-diazagona-1,3,5(10),6,13-pentaen-12-one (II, R = H) and 6,8-diazagona-1,3,5(10),6,9(11),13-hexaen-12-one (XI), respectively. Unfortunately we could not obtain a sufficient amount of these compounds for elemental analyses and nmr spectral measurements in spite of repeated trials. From VII, the condensed product was not isolated, but a large amount of starting material was recovered along with a small amount of VIII.

As mentioned above, ethyl 2-unsubstituted 3,4-dihydroquinazolylacetate decomposed rather than give enamine formation. Therefore, we next tried to prepare the 6,8-diazasteroid system having a substituent, the *p*-methoxyphenyl group, in the 7-position. The *p*-methoxyphenyl group is an electron releasing group and should shift the electron current toward the quinazoline ring away from the active methylene group in ethyl 3,4-dihydro-2-*p*-methoxyphenyl-4-quinazolylacetate (Ib). Ethyl 2-*p*-methoxyphenyl-4-quinazolylacetate (VIb) was prepared similar to VIa. 2-*p*-Methoxyphenyl-4-chloroquinazoline (IIIb), a starting material to VIb, was very stable compared with the 2-unsubstituted analogue (IIIa), and did not react with sodio ethyl acetoacetate in ether. The reaction could be completed only by carrying it out in xylene. The product in this case was VIb, which exhibited a signal at δ 5.38 ppm in the nmr spectrum, due to the vinyl proton of the enamino ester moiety. The reduction of the double bond of this enamino ester was carried out in a similar fashion as in the case of VIa. In this case, however, the catalytic reduction product was the dihydro compound, Ib, which exhibited a signal at δ 5.07 ppm due to the benzyl methine proton in the nmr spectrum and whose picrate melted at 136-139°. Unfortunately Ib thus obtained failed to react with cyclopentanone. The reason for this failure was believed to be due to steric hindrance of the *p*-methoxyphenyl group. Furthermore, Ib also decomposed on heating to afford 2-*p*-methoxyphenylquinazoline (XII) which exhibited a signal at δ 9.35 ppm due to the proton at the 4-position in the nmr spectrum. A proposed mechanism is shown in Chart 3, where the cleavage of ethyl acetate takes place by the strong electron releasing ability of the *p*-methoxyphenyl group.

Chart 3



Next the authors examined the correlation between steric repulsion and electron releasing ability. Thus, we tried to prepare ethyl 3,4-dihydro-4-quinazolylacetate substituted with a phenyl group at the 2-position. Ethyl 2-phenyl-4-quinazolylacetate (VIc) was synthesized in the usual manner. The catalytic reduction of VIc was accompanied by the hydrogenation of the phenyl group at the 2-position, and gave in quantitative yield ethyl 3,4-dihydro-2-cyclohexyl-4-quinazolylacetate (Ic). Therefore, although we were unsuccessful in our original purpose, the condensation reaction with cyclopentanone proved successful. The only crystalline compound obtained was 3,4-dihydro-2-cyclohexylquinazolylacetic acid (XIII).

We then turned our attention to the preparation of ethyl 3,4-dihydro-2-methyl-4-quinazolylacetate (Id), which also could be easily synthesized after the manner mentioned above. In this case, however, the attempt to condense Id with cyclopentanone also was unsuccessful under several sets of conditions. Thus ethyl 3,4-dihydro-

2-substituted-4-quinazolylacetates, which were synthesized with the intent of avoiding the decomposition of the quinazoline ring, did not condense with cyclopentanone in all cases tried. The reason may be due to the localization of a double bond at the 2,3-position rather than the 1,2-position in ethyl dihydro-2-substituted-4-quinazolylacetates. This problem may be solved by further investigation.

EXPERIMENTAL

All the melting points and boiling points are uncorrected. Infrared (ir) spectra were determined using a Hitachi Grating Infrared 215 Spectrophotometer with absorptions given in cm^{-1}. Nmr spectra were recorded on JEOL C-60H Spectrometer using TMS as the internal standard. The chemical shifts and coupling constants (J) are described in δ and Hz, respectively. Mass spectra were measured with a JEOL TMS-01SG (75 eV, direct inlet system) Spectrometer. Uv spectra were obtained in ethanol by using a Hitachi Model EPS-2T Spectrometer.

4-Quinazolone Hydrochloride (IV).

By recrystallization from ethanol, 4-chloroquinazoline (IIIa) (2) was converted into IV, m.p. 194° (As the temperature was elevated, fine needles appeared which melted at 222-224°, and which were identical with 4-quinazolone as shown by the ir and the melting point).

Anal. Calcd. for $C_8H_7ClON_2$: C, 52.56; H, 3.54; N, 15.34. Found: C, 52.39; H, 3.30; N, 15.30.

4-Quinazolone was treated with 10% ethanolic hydrochloric acid to give the same salt as obtained above.

Ethyl 4-Quinazolylacetoacetate (Va and Vb).

To a suspension of sodio ethyl acetoacetate (8.1 g., 53 mmoles) in absolute ether (200 ml.), IIIa (8.8 g., 53 mmoles) in absolute ether (100 ml.) was added dropwise. The mixture was then refluxed for about 30 hours. The residue obtained after the evaporation of solvent was dissolved in water (80-90 ml.) and acidified with 10% hydrochloric acid to give yellow crystals (14.6 g.), which were recrystallized from ethanol, m.p. 77-85° (quantitative yield); ir (nujol): ν C=O 1720, ν 1620, 1575; nmr (carbon tetrachloride): 1.06 (t, J = 8, $-CH_2-CH_3$ of Vb), 1.24 (t, J = 8, $-CH_2-CH_3$ of Va), 1.80 (s, $-CO-CH_3$ of Vb), 2.28 (s, $-CO-CH_3$ of Va), 4.08 (q, J = 8, $-O-CH_2-$ of Vb), 4.22 (q, J = 8, $-O-CH_2-$ of Va), 8.93 (s, vinylic H of Vb), 9.20 (s, vinylic H of Va).

Anal. Calcd. for $C_{14}H_{14}O_3N_2$: C, 65.10; H, 5.46; N, 10.85. Found: C, 65.02; H, 5.48; N, 10.61.

Ethyl 4-Quinazolylacetate (VIa).

An ethanolic solution of the isomeric mixture of V (7.7 g.) and trifluoroacetic acid (25 ml.) was refluxed for 3 hours. The residue obtained after the evaporation of the solvent was poured into water (70 ml.) to give yellow crystals; VIa trifluoroacetate, m.p. 130-160° sublim. (recrystallized from ethanol); ir (nujol): ν C=O 1680; nmr (deuteriochloroform-trifluoroacetic acid): 1.57 (3H, t, $-CH_3$), 4.37 (2H, q, $-O-CH_2-$), 6.12 (1H, s, vinylic H), 7.40-8.10 (4H, m, aromatic H), 8.50-8.77 (1H, d, -N=CH-N<), 13.40 (1H, br.s, >NH).

Anal. Calcd. for $C_{14}H_{13}F_3O_4N_2$: C, 50.91; H, 3.94; N, 8.48. Found: C, 50.71; H, 3.75; N, 8.38.

An aqueous solution of the trifluoroacetic acid salt was basified with 10% sodium carbonate to give white needles; VIa: 2.3 g. (yield 35.7%), m.p. 91-95° (5); ir (nujol): ν C=O 1644; nmr (deuteriochloroform): 1.30 (3H, t, $-CH_3$), 4.19 (2H, q, $-O-CH_2-$), 5.47 (1H, s, vinylic H), 7.0-8.1 (5H, m, aromatic H), 14.1 (1H, br.s, >NH); VIa-picrate: m.p. 220-222° (recrystallized from ethanol); ir (nujol): ν C=O 1638, ν 1550.

Anal. Calcd. for $C_{18}H_{15}O_9N_5$: C, 48.54; H, 3.40; N, 15.73. Found: C, 48.74; H, 3.12; N, 15.93.

Compound VIa Hydrochloride.

This compound had m.p. 181-185° (recrystallized from ethanol).

Anal. Calcd. for $C_{12}H_{13}ClO_2N_2$: C, 57.03; H, 5.15; N, 11.09. Found: C, 57.18; H, 5.19; N, 11.20.

Ethyl 3,4-Dihydro-4-quinazolylacetate (Ia).

An ethanolic solution of VIa-hydrochloride (3 g.) was hydrogenated over Adam's catalyst (0.5 g.) in ethanol (100 ml.) under a pressure of 80 atmospheres. After the uptake of hydrogen ceased, the reaction mixture was filtered, concentrated *in vacuo* to give a viscous oily residue, which was dissolved in water and basified (*p*H 9-10) with sodium carbonate and then extracted with chloroform. The chloroform layer was washed with water and dried over anhydrous magnesium sulfate. After the evaporation of solvent, the residue was micro-distilled, $b.p._5$ < 180°, 1.8 g. (yield 71.2%); ir (film): ν C=O 1730, ν C=N 1660, ν C=C 1620, 1600; nmr (carbon tetrachloride): 1.27 (3H, t, J = 6.5, $-CH_3$), 2.33-3.27 (2H, m, $-CH_2-CO-$), 4.17 (2H, q, J = 6.5, $-O-CH_2-$), 5.10 (1H, d, J = 6, >CH-N<), 6.50-7.83 (5H, m, aromatic H and vinylic H).

Anal. Calcd. for $C_{12}H_{14}O_2N_2$: C, 66.03; H, 6.47; N, 12.84. Found: C, 66.19; H, 6.50; N, 12.73.

Compound Ia Picrate.

This compound had m.p. 145-147° (recrystallized from ethanol); ir (nujol): ν C=O 1713, ν C=N 1640.

Anal. Calcd. for $C_{18}H_{17}O_9N_5$: C, 48.32; H, 3.83; N, 15.66. Found: C, 48.36; H, 3.61; N, 15.55.

Ethyl 1,2,3,4-Tetrahydro-4-quinazolylacetate (VII).

An ethanolic solution of VIa (1 g.) was hydrogenated over Adam's catalyst (0.3 g.) under a pressure of 120 atmospheres. After the uptake of hydrogen ceased, the reaction mixture was worked up as mentioned in the preparation of Ia. The reaction product was purified by silica gel column chromatography. From the fractions eluted with benzene, ether, and chloroform-ethanol (9:1), recovered VIa (0.2 g.), VII (0.6 g.) (yield 59.3%), and Ia (0.2 g.) were obtained, respectively. Compound VII was micro-distilled, $b.p._3$ <180°; ir (film): ν C=O 1732; nmr (carbon tetrachloride): 1.20 (3H, t, J = 7, $-CH_3$), 2.63 (2H, d.like, J = 7, $-CH_2-CO-$), 3.25 (2H, br.s, 2x >NH), 3.80-4.50 (5H, m, $-O-CH_2-$, >N-CH_2-N<, and >CH-N<), 6.18-7.27 (4H, m, aromatic H).

Compound VII Picrate.

This compound had m.p. 164-166° (recrystallized from ethanol); ir (nujol): ν C=O 1720, ν C=C 1610.

Anal. Calcd. for $C_{18}H_{19}O_9N_5$: C, 48.11; H, 4.26; N, 15.59. Found: C, 48.38; H, 3.97; N, 15.36.

Reaction of Ia with Cyclopentanone.

A solution of Ia (1.0 g.) in toluene was treated for 10 hours with cyclopentanone (1 g.) and trifluoroacetic acid (0.1 ml.) using equipment with a Dean-Stark water separator. The reaction mixture was washed with 10% sodium bicarbonate solution and saturated sodium chloride solution. The dried solvent was evaporated *in vacuo* and the residue was fractionated by silica gel column chromatography. Cyclopentanone, ethyl *trans*-2-aminocinnamate (IX), unidentifiable enamino ester, carbostyril (VIII) and Ia were eluted with hexane, benzene, ether, chloroform, and chloroform-ethanol (9:1), respectively. Compound IX was micro-

distilled, b.p.$_1$ < 150°, 0.2 g. (yield 18.1%), m.p. 60-62°; ir (nujol): ν NH 3490, 3385, ν C=O 1690, ν C=C 1620; nmr (deuteriochloroform): 1.32 (3H, t, $-CH_3$), 3.95 (2H, br.s, $-NH_2$), 4.23 (2H, q, $-CH_2-$), 6.30 and 7.77 (each 1H, AB type, J = 15.8, vinylic H); ms: m/e 191 (M^+).

Anal. Calcd. for $C_{14}H_{13}O_2N_2$: C, 69.09; H, 6.85; N, 7.33. Found: C, 69.05; H, 6.70; N, 7.62.

Compound VIII.

This compound had m.p. 200-201°, 0.15 g. (yield 22.6%); ir (nujol): ν C=O 1655, ν C=C 1638; nmr (trifluoroacetic acid): 8.16-7.50 (4H, m, aromatic H), 8.57 and 7.27 (each 1H, AB type, J = 8.5, vinylic H). It was identical with an authentic sample. In a sealed tube, the crude unidentifiable enaminoester (0.2 g.) was heated with ethylene glycol (3 ml.) at 170-180° for 15 hours. After it was cooled, the reaction mixture was poured into water to give a precipitate, which was filtered and dried. It was then fractionated by silica gel column chromatography. From the fraction eluted with benzene, 6,8-diazagona-1,3,5(10),6,13-penten-12-one (II, R = H) was obtained, m.p. 250-252° (recrystallized from chloroform), 20 mg. (yield 1.8%); ir (chloroform): ν C=O 1680, ν C=N 1620; uv (ethanol): λ max (ϵ) 233 (35,100), 284 (10,100), 360 (6,400); ms: m/e 238 (M^+, 32.0%), 237 ($(M-1)^+$, base peak x), 119 (M^{++} (doubly charged ion), 73.2%). From the fraction eluted with ether, 6,8-diazagona-1,3,5(10),6,9(11),13-hexan-12-one (XI) was obtained, m.p. 304-306° (recrystallized from benzene); 15 mg. (yield 1.4%); ir (nujol): ν C=O 1650, ν C=N 1620; uv (ethanol): λ max (ϵ) 218 (27,100), 272 (16,300), 318 (7,200); ms: m/e 236 (M^+, base peak), 235 ($(M-1)^+$, 63.8%).

2-*p*-Methoxyphenyl-4-chloroquinazoline (IIIb).

2-*p*-Methoxyphenyl-4-quinazolone (7) (44.5 g., 177 mmoles) and phosphorus pentoxide (94.0 g., 443 mmoles) were dissolved in phosphorus oxychloride (250 ml.) by warming and the mixture was refluxed at 110-120° for 10 hours. The residue after the evaporation of phosphorus oxychloride was poured onto ice-water and then extracted with ether. The ether layer was washed with 10% sodium bicarbonate solution, saturated sodium chloride solution, and dried. The solvent was evaporated to give pale yellow crystalline compound IIIb: 30 g. (yield 65%), m.p. 123-124° (recrystallized from ether); ir (nujol): 1610, 1570; nmr (carbon tetrachloride): 3.85 (3H, s, $-OCH_3$), 6.83-8.55 (8H, m, aromatic H).

Anal. Calcd. for $C_{15}H_{11}ClON_2$: C, 66.54; H, 4.07; N, 10.35. Found: C, 66.75; H, 4.18; N, 10.12.

Ethyl 2-*p*-Methoxyphenyl-4-quinazolylacetate (VIb).

To a solution of absolute xylene (20 ml.) of IIIb (6 g., 22 mmoles), sodio ethyl acetoacetate (4.6 g., 33 mmoles) and ethyl acetoacetate (0.2 g., 1.5 mmoles) were added. After the mixture was refluxed for 20 hours, benzene (50 ml.) was added. The organic layer was washed with saturated sodium chloride solution and dried over anhydrous magnesium sulfate. The concentrated mixture was fractionated by silica gel column chromatography. From the fraction eluted with benzene, a yellow crystalline substance was obtained, VIb: 4.3 g. (yield 59%); m.p. 124-128° (recrystallized from benzene); ir (nujol): ν C=O 1640; nmr (carbon tetrachloride): 1.30 (3H, t, J = 6, $-CH_3$), 3.87 (3H, s, $-OCH_3$), 4.16 (2H, q, J = 6.5, $-O-CH_2-$), 5.38 (1H, s, vinylic H), 6.83-8.13 (8H, m, aromatic H).

Anal. Calcd. for $C_{19}H_{18}O_3N_2$: C, 70.79; H, 5.63; N, 8.69. Found: C, 70.74; H, 5.88; N, 8.58.

Compound VIb Hydrochloride.

This compound had m.p. 95° (recrystallized from ethanol, brown needles).

Ethyl 3,4-Dihydro-2-*p*-methoxyphenyl-4-quinazolylacetate (Ib).

An ethanolic suspension of VIb hydrochloride (5.2 g.) was hydrogenated over Adam's catalyst (0.3 g.) under a pressure of 3 atmospheres. After the uptake of hydrogen ceased, the reaction mixture was filtered and concentrated *in vacuo* to give a viscous oily residue, which was dissolved in water and basified (*p*H 9-10) with 10% sodium bicarbonate solution and then extracted with chloroform. The chloroform layer was washed with water and dried over anhydrous magnesium sulfate. The crude crystalline substance (5 g.) obtained after the evaporation of solvent was recrystallized from benzene, Ib (2.1 g. (yield 40.2%) white needles); m.p. 121-122°; ir (nujol): ν C=O 1725, ν C=N 1620, 1595; nmr (deuteriochloroform): 1.30 (3H, t, J = 7, $-CH_3$), 2.30-3.13 (2H, m, $-CH_2-CO-$), 3.83 (3H, s, $-OCH_3$), 4.20 (2H, q, J = 7, $-CH_2-$), 5.07 (1H, d.d, J = 9, 4, $-CH<$), 6.82-7.85 (8H, m, aromatic H); uv (ethanol): λ max 315, 257 nm.

Compound Ib Picrate.

This compound was yellow needles, m.p. 136-139° (recrystallized from ether).

Anal. Calcd. for $C_{25}H_{25}O_6N_7$: C, 54.25; H, 4.16; N, 12.66. Found: C, 54.42; H, 4.15; N, 12.44.

2-*p*-Methoxyquinazoline (XII).

A solution of Ib (265 mg.) in ethylene glycol (10 ml.) was heated at 180° in a sealed tube for 15 hours. The reaction mixture was poured into water and extracted with chloroform. The chloroform layer was washed with saturated sodium chloride solution. The dried solvent was evaporated *in vacuo* and the brown black residue was purified by silica gel column chromatography. With benzene, a crystalline substance was eluted and recrystallized from ethanol, XII: 200 mg. (yield, quantitative), m.p. 91-93° (Lit. (8) 95-96°); ir (nujol): ν 1630, 1610, 1597; nmr (carbon tetrachloride): 3.90 (3H, s, $-OCH_3$), 6.95-8.73 (8H, m, aromatic H), 9.35 (1H, s, H at 4-position).

Compound XII Picrate.

This compound had m.p. 163-166° (Lit. (8) 161-162°).

Ethyl 2-Phenyl-4-quinazolylacetate (VIc).

A suspension of 4-chloro-2-phenylquinazoline (2) (IIIc) (21 g., 87 mmoles), sodio ethyl acetoacetate (20 g., 130 mmoles), and ethyl acetoacetate (2 g., 13 mmoles) in xylene (150 ml.) was refluxed for 20 hours. The reaction mixture was poured into water and the aqueous layer was extracted with benzene. The combined organic layer was dried over anhydrous magnesium sulfate and the solvent was distilled off to give a crystalline substance, which was recrystallized from ether, VIc: (yield 80%), m.p. 120°; ir (nujol): ν C=O 1650, ν C=N 1625; nmr (carbon tetrachloride): 1.40 (3H, t, J = 7.0, $-CH_3$), 4.27 (2H, q, J = 7, $-CH_2-O-$), 5.53 (1H, s, vinylic H), 6.7-8.8 (9H, m, aromatic H).

Anal. Calcd. for $C_{18}H_{16}O_2N_2$: C, 73.97; H, 5.48; N, 9.59. Found: C, 74.03; H, 5.34; N, 9.48.

Compound VIc Hydrochloride.

This compound had m.p. 113-115° (recrystallized from ethanol).

Anal. Calcd. for $C_{18}H_{17}ClO_2N_2$: C, 65.75; H, 5.18; N, 8.52. Found: C, 65.52; H, 5.15; N, 8.41.

Ethyl 3,4-Dihydro-2-cyclohexyl-4-quinazolylacetate (Ic).

An ethanolic solution of VIc hydrochloride (2.2 g.) was hydrogenated over Adam's catalyst (0.5 g.) under the pressure of 4 atmospheres for 5 hours. The solution was filtered and concentrated *in vacuo*. The residue basified with ammonia water was extracted with chloroform. The dried solvent was distilled to

give crude Ic, b.p.$_3$ 180° (yield, quantitative); ir (film): ν C=O 1740, 1670-1635, 1590; nmr (carbon tetrachloride): 1.30 (3H, t, J = 6.5, -CH_3), 1.3-2.3 (11H, m, cyclohexyl H), 2.5-2.8 (2H, m, -CH_2-CO-), 4.20 (2H, q, J = 6.5, -CH_2-O-), 4.95 (1H, q, J = 8, 4, >CH-N<), 5.76 (1H, br.s, >NH), 6.7-7.4 (4H, m, aromatic H); ms: m/e 300 (M^+, 50%), 213 ((M-CH_2-COOEt)$^+$, base peak).

Anal. Calcd. for $C_{18}H_{24}O_2N_2$: C, 72.00; H, 8.00; N, 9.33. Found: C, 72.25; H, 8.20; N, 9.07.

Ic *p*-Nitrobenzoate.

This compound was an oil; nmr (carbon tetrachloride): 2.57 (2H, J = 7, -CH_2-CO-), 5.78 (1H, t, J = 7.5, >CH-N<), 7.60 and 8.27 (each 2H, AB type, J = 8, aromatic H).

Reaction with Ic and Cyclopentanone.

A mixture of Ic, cyclopentanone and a catalytic amount of trifluoroacetic acid was treated in a sealed tube or refluxed overnight in xylene. In both cases, the only crystalline compound obtained from the fraction eluted with acetone in silica gel column chromatography was 3,4-dihydro-2-cyclohexyl-4-quinazolylacetic acid (XIII), m.p. 215° (recrystallized from acetone-ethanol); ir (nujol): ν NH 3180, ν C=O 1740, ν 1660, 1600; nmr (trifluoroacetic acid): 1.2-2.3 (11H, m, cyclohexyl H), 3.20 (2H, d, J = 5, -CH_2-CO-), 5.5 (2H, br.s, >CH-N< + >NH), 7.1-7.7 (4H, m, aromatic H), 8.23 (1H, br.s, -OH); ms: m/e 272 (M^+, 70%), 213 ((M-CH_2-COOH)$^+$, base peak).

Anal. Calcd. for $C_{16}H_{20}O_2N_2$ + 1.9 H_2O: C, 62.74; H, 7.78; N, 9.15. Found: C, 62.94; H, 7.67; N, 9.10.

Ethyl 2-Methyl-4-quinazolylacetate (VId).

A mixture of 4-chloro-2-methylquinazoline (IIId) (9) (5.5 g., 31 mmoles), sodio ethyl acetoacetate (7.1 g., 46 mmoles), and ethyl acetoacetate (1 g.) in toluene (100 ml.) was refluxed for 24 hours. The reaction mixture was worked up as usual. To an ethanolic solution of the residue was added ethanolic hydrochloric acid to give yellow VId hydrochloride, which was recrystallized from ethanol, m.p. 208-210°.

Anal. Calcd. for $C_{13}H_{15}ClO_2N_2$: C, 58.54; H, 5.63; N, 10.51. Found: C, 58.30; H, 5.51; N, 10.35.

Its hydrochloride in water was neutralized with sodium bicarbonate and extracted with ether. Crude VId obtained after the evaporation of dried solvent was recrystallized from *n*-hexane, yield 5.1 g. (71.5%), m.p. 42-43°; ir (nujol): ν NH 3370, ν C=O 1660, ν C=N 1623; nmr (carbon tetrachloride): 1.30 (3H, t, J = 7.5, -CH_2-*CH_3*), 2.40 (3H, s, vinylic CH_3), 4.13 (2H, q, J = 7.5, -O-CH_2-), 5.30 (1H, s, vinylic H), 7.0-7.9 (4H, m, aromatic H).

2-Methyl-4-quinazolone Hydrochloride.

Upon standing for about 1 week in a refrigerator, 4-chloro-2-methylquinazoline (IIId) turned to methyl-4-quinazolone hydrochloride, m.p. 240° sublim. (recrystallized from ethanol); ir (nujol): ν C=O 1720, 1690.

Anal. Calcd. for $C_9H_9ClON_2$: C, 54.96; H, 4.58; N, 14.25. Found: C, 54.93; H, 4.58; N, 14.02.

Ethyl 3,4-Dihydro-2-methyl-4-quinazolylacetate (Id).

In the usual manner (4 atmospheres, 20 hours), VId hydrochloride was hydrogenated, (yield, quantitative); ir (film): ν C=O 1740; nmr (carbon tetrachloride): 1.27 (3H, t, J = 8, -CH_2-*CH_3*), 2.07 (3H, s, vinylic CH_3), 2.3-3.1 (2H, m, -CH_2-CO-), 4.20 (2H, q, J = 8, -O-CH_2-), 5.06 (1H, q, J = 8, 5, >CH-N<), 6.45 (1H, br.s, >NH), 6.8-7.4 (4H, m, aromatic H).

Id Picrate.

This compound had m.p. 175-176° (recrystallized from ethanol).

Anal. Calcd. for $C_{19}H_{19}O_9N_5$: C, 49.46; H, 4.12; N, 15.18. Found: C, 49.33; H, 4.19; N, 14.98.

Acknowledgment.

We are indebted to Mr. S. Honma for his assistance in a part of the experimental work.

REFERENCES AND NOTES

(1) T. Yamazaki, M. Nagata, K. Matoba, H. Takahata and R. N. Castle, *J. Heterocyclic Chem.*, **14**, 469 (1977).

(2) M. M. Endicott, E. Wick, M. L. Mercury and M. L. Sherrill, *J. Am. Chem. Soc.*, **68**, 1299 (1946).

(3) R. C. Elderfield and I. Serlin, *J. Org. Chem.*, **16**, 1669 (1951).

(4) T. Yamazaki, K. Matoba, M. Yajima, M. Nagata and R. N. Castle, *J. Heterocyclic Chem.*, **12**, 973 (1975).

(5) T. Higashino, H. Ito and E. Hayashi, *Chem. Pharm. Bull.*, **20**, 1550 (1972).

(6) T. Yamazaki, K. Matoba, K. Isomura, M. Nagata and R. N. Castle, *J. Heterocyclic Chem.*, **11**, 503 (1974).

(7) V. S. Patel and S. R. Patel, *J. Indian Chem. Soc.*, **42**, 531 (1965).

(8) M. Lora-Tamayo, R. Madronero and G. G. Munoz, *Chem. Ber.*, **94**, 208 (1961).

(9) H. C. Scarborough, B. C. Lawes, J. L. Minielli and J. L. Compton, *J. Org. Chem.*, **27**, 957 (1962).