INVESTIGATION OF THE CHEMISTRY OF HETEROCYCLES

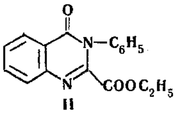
LI. REACTION OF ETHOXALYLANTHRANIL WITH AMINES

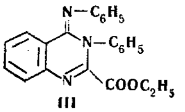
P. A. Petyunin, V. P. Chernykh,
G. P. Petyunin, and Yu. V. Kozhevnikov

UDC 547.856.1

The reaction of ethoxalylanthranil with aryl(heteryl)amines was studied, a method for obtaining 2-carbethoxy-3-R-substituted 4-quinazolones was developed, and the transformations of the latter were investigated.

Bogert and Gortner [2] isolated two substances by heating ethoxalylanthranil (I) with aniline: the one with mp 160° was assigned the 2-carbethoxy-3-phenyl-4-quinazolone (II) structure, while the other, with mp 290°, was assigned the 2-carbethoxy-3,4-diphenyl-4-imino-4-quinazolone (III) structure.


II


III

According to [3], I reacts with N-heterylhydrazines at the oxazine ring to form 2-carbethoxy-3-(N-heteryl)-substituted 4-quinazolones. Compound I has two electrophilic reaction centers – the C=O group (oxazine ring) and $COOC_2H_5$; the electrophilic properties of the C=O group are more strongly manifested since the acceptor effects of the ring nitrogen and the $COOC_2H_5$ group contribute to it.

This investigation is devoted to an elucidation of the character of the reaction of I with primary amines and to the development, on the basis of this reaction, of a method for obtaining quinazolone compounds. We repeated the experiments in [2] and found that the compound with mp 290° is really the anilide of 3-phenyl-4-quinazolone-2-carboxylic acid (XII, $R = R' = C_6H_5$), while that with mp 160° is a mixture of anilide XII and 2-carbethoxy-3-phenyl-4-quinazolone (V, $R = C_6H_5$). We have established that the reaction of I [2] with primary aryl(heteryl)amines in equimolecular ratios proceeds very readily on brief heating (30 min) in absolute dimethylformamide (DMF) and leads to the formation of 2-carbethoxy-3-R-substituted 4-quinazolones (V) (method A). The high dissolving capacity of DMF makes it possible to introduce amines with different natures and positions of the substituents into the reaction. The structure of V was proved by alternative synthesis: the arylides of N-ethoxalylanthranilic acid (VI, Table 1), obtained by the method in [4], were heated with phosphorus trichloride in toluene (method B). The IR spectra* of V ($R = 2\text{-}ClC_6H_4$) contain bands characteristic for the quinazolone ring: 1740 (ester C=O), 1695, 1600, 1480 (quinazolone ring [5]), 1310 and 1020 cm^{-1} (C–O–C). Preference should be given to method A with respect to the availability of the starting materials and the ease in carrying out the experiments. (See scheme, page 1474.)

According to [6], the reaction between acylanthranils and amines proceeds through a step involving the formation of arylides of N-acylanthranilic acids (in our case, through VI). However, the reaction between I and amines occurs in 30 min, while the conversion of VI to V requires 12 h (heating in diethyl oxalate or DMF). This indicates that the reaction between I and amines proceeds through a step involving the formation of a lactim (IV), which is instantly converted to V under the experimental conditions (150-180°).

---

*The measurements were made with a UR-10 spectrometer with LiF and NaCl prisms and KBr pellets.

Kharkov Pharmaceutical Institute. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 11, pp. 1575-1578, November, 1970. Original article submitted August 10, 1969.

© 1973 Consultants Bureau, a division of Plenum Publishing Corporation, 227 West 17th Street, New York, N. Y. 10011. All rights reserved. This article cannot be reproduced for any purpose whatsoever without permission of the publisher. A copy of this article is available from the publisher for $15.00.

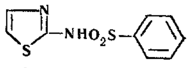
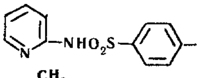
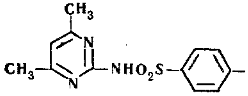
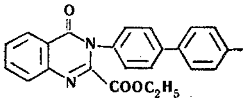
TABLE 1. Arylamides of N-Ethoxalylanthranilic Acid (VI)

R	Mp, °C*	Empirical formula	N, % found	N, % calc.	Yield, %
C_6H_5	160—161	$C_{17}H_{16}N_2O_4$	9,07	8,97	64,2
$3\text{-}CH_3C_6H_4$	171—172	$C_{18}H_{18}N_2O_4$	8,62	8,59	61,3
$3\text{-}BrC_6H_4$	185—186	$C_{17}H_{15}BrN_2O_4$	7,40	7,14	96,5
$4\text{-}BrC_6H_4$	220—222	$C_{17}H_{15}BrN_2O_4$	7,30	7,14	84,7
$4\text{-}CH_3OC_6H_4$	204—205	$C_{18}H_{18}N_2O_5$	8,20	8,18	97,0

---

*After recrystallization from ethanol.

TABLE 2. 3-R-Substituted 2-Carbethoxy-4-quinazolones

R	Method	Mp, °C*	Empirical formula	N, % found	N, % calc.	Yield, % A	Yield, % B
C_6H_5	A, B	108—109	$C_{17}H_{14}N_2O_3$	9,56	9,52	76,5	74,5
$2\text{-}CH_3C_6H_4$	A	91—92	$C_{18}H_{16}N_2O_3$	9,28	9,08	68,1	
$3\text{-}CH_3C_6H_4$	A,B	115—116	$C_{18}H_{16}N_2O_3$	9,00	9,08	68,7	71,1
$4\text{-}CH_3OC_6H_4$	A,B	125—126	$C_{18}H_{16}N_2O_4$	8,90	8,64	83,5	61,5
$4\text{-}C_2H_5OC_6H_4$	A	139—140	$C_{19}O_{18}N_2O_4$	8,43	8,29	96,2	
$3,4,5\text{-}(CH_3O)_3C_6H_2$	A	139—140	$C_{20}H_{20}N_2O_6$	7,51	7,29	51,8	
$2\text{-}ClC_6H_4$	A	119—120	$C_{17}H_{13}ClN_2O_3$	8,68	8,52	73.3	
$2\text{-}BrC_6H_4$	A	105—106	$C_{17}H_{13}BrN_2O_3$	7,55	7,50	77,5	
$3\text{-}BrC_6H_4$	A, B	143—144	$C_{17}H_{13}BrN_2O_3$	7,43	7,50	76,0	66,0
$4\text{-}BrC_6H_4$	A, B	184—185	$C_{17}H_{13}BrN_2O_3$	7,72	7,50	78,8	72,4
$2\text{-}Br\text{-}4,6\text{-}(CH_3)_2C_6H_2$	A	110—111	$C_{19}H_{17}BrN_2O_3$	7,31	6,98	67,3	
$3\text{-}HOOCC_6H_4$	A	217—218	$C_{18}H_{14}N_2O_5$	8,33	8,28	49,3	
$4\text{-}HOOCC_6H_4$	A	205—206	$C_{18}H_{14}N_2O_5$	8,57	8,28	51,8	
$4\text{-}C_2H_5OOCC_6H_4$	A	190—192 †	$C_{20}H_{18}N_2O_5$	7,95	7,66	63,7	
$3\text{-}O_2NC_6H_4$	A	181—182	$C_{17}H_{13}N_3O_5$	12,43	12,38	72,8	
$4\text{-}O_2NC_6H_4$	A	225—226	$C_{17}H_{13}N_3O_5$	12,27	12,38	44,5	
$\beta\text{-}C_{10}H_7$	A	125—126 †	$C_{21}H_{16}N_2O_3$	8,36	8,13	72,3	
$\alpha\text{-}C_{10}H_7$	A	151—152	$C_{21}H_{16}N_2O_3$	8,43	8,13	68,7	
$3\text{-}H_2NO_2SC_6H_4$	A	237—238	$C_{17}H_{15}N_3O_5S$	11,25	11,26	61,3	
$4\text{-}H_2NO_2SC_6H_4$	A	246—247 †	$C_{17}H_{15}N_3O_5S$	11,31	11,26	72,8	
$4\text{-}H_2NCONHO_2SC_6H_4$	A	194—195	$C_{18}H_{16}N_4O_6S$	13,59	13,46	56.4	
$4\text{-}n\text{-}C_4H_9NHCONHO_2SC_6H_4$	A	239—240 †	$C_{22}H_{24}N_4O_6S$	11,91	11,86	84,5	
	A	225 (dec.)	$C_{20}H_{16}N_4O_5S_2$	12,31	12,27	67,9	
	A	235—236 ‡	$C_{22}H_{18}N_4O_5S$	12,60	12,44	88,8	
	A	208 (dec.)	$C_{23}H_{21}N_5O_5S$	14,31	14,60	83,5	
	A	307 (dec.)	$C_{34}H_{26}N_4O_6$	9,89	9,55	79,4	
α-Pyridyl	A	216—218 ‡	$C_{16}H_{13}N_3O_3$	14,58	14,23	71,0	
4-Antipyrinyl	A	191—192	$C_{22}H_{20}N_4O_4$	13,98	13,99	92,1	

---

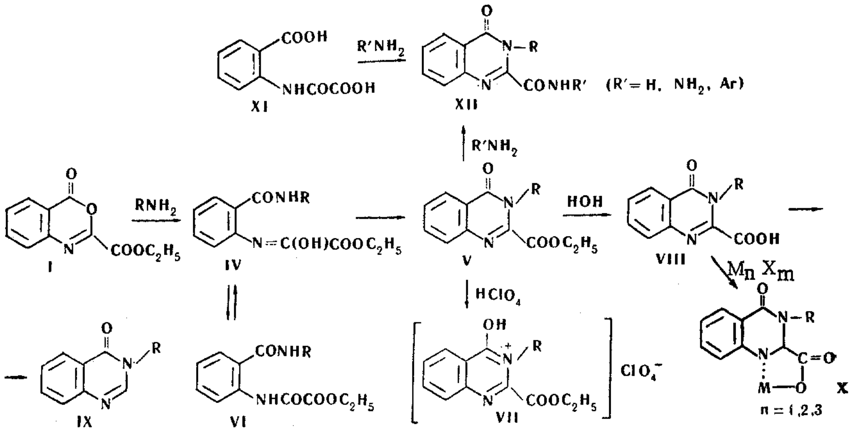
*Crystallization solvent.

†Aqueous DMF.

‡Aqueous acetic acid; ethanol was used for the rest.

Quinazolones V (Table 2) are crystalline substances that are insoluble in water; they give perchlorates [VII (R = $2\text{-}ClC_6H_4$)] with perchloric acid in acetic anhydride. A confirmation of the structure may be the fact that a band at 3350-3550 cm^{-1}, which can be related to the OH group (compare with the structure of pyridone salts [7]), is displayed in the IR spectrum of VII, as compared with V (R = $2\text{-}ClC_6H_4$).

Quinazolones V are readily saponified to form 3-R-substituted 4-quinazolone-2-carboxylic acids (VIII). The ammonium salts of the latter give crystalline precipitates (X) with many cations (Ag^{+1}, Ba^{+2}, Pb^{+2}, Zn^{+2}, Cu^{+2}, Hg^{+2}, Fe^{+2}, Cd^{+2}, Sn^{+2}, Al^{+3}, Fe^{+3}, Bi^{+3}, Cr^{+3}, Sb^{+3}).



Acids VIII, owing to the acceptor effect of the quinazolone ring, are very readily decarboxylated (even during crystallization) to form 3-R-substituted 4-quinazolones (IX).

Quinazolones V readily undergo ammonolysis, amination, and hydrazinolysis to form the corresponding products of substitution of the $COOC_2H_5$ group (XII). The structure of the latter was proved by alternative synthesis in the case of the anilide of 3-phenyl-4-quinazolone-2-carboxylic acid (XII, R = R' = C_6H_5); this was effected by heating N-ethoxalylanthranilic acid (XI) with aniline and phosphorus oxychloride in toluene.

Thus I is a strong electrophilic reagent that first reacts at the quinazolone ring with primary amines and then at the $COOC_2H_5$ group to form V and XII, respectively.

EXPERIMENTAL

2-Carbethoxy-3-aryl(heteryl)-4-quinazolone. A. A mixture of 0.01 mole of I and 0.01 mole of amine in 3 ml of DMF was refluxed for 30 min (3 h in the case of p-nitroaniline), poured into 15 ml of water, and the precipitate was filtered and crystallized.

B. Phosphorus trichloride (0.01 mole) was added to a solution of 0.01 mole of VI in 40 ml of absolute toluene, the mixture was refluxed for 1 h, cooled, and the resulting precipitate was treated as in the previous experiment. The identity of the products was established by a mixed melting-point determination.

2-Carbethoxy-3-phenyl-4-quinazolone (V, R = C_6H_5). A solution of 2.3 g of VI (R = C_6H_5) in 9 ml of diethyl oxalate (or DMF) was refluxed for 12 h, the excess solvent was removed in vacuo, and the residue was crystallized to give 1.9 g (87.9%) of product.

N-Ethoxyanthranilic Acid (XI). This was obtained in 83.7% yield by saponification of ethyl N-ethoxyanthranilate [8]. The product was obtained in the form of needles (from water) with mp 240° (decomp.). Found %: N 7.12. $C_9H_7NO_5$. Calculated %: N 6.95.

Anilide of 3-Phenyl-4-quinazolone-2-carboxylic Acid (XII, R = R' = C_6H_5). A. Compound V (R = C_6H_5) (0.5 g) and 1.5 g of aniline were refluxed for 4 h, 10 ml of water was added, and the mixture was acidified with hydrochloric acid. The precipitate was filtered and crystallized from DMF to give needles with mp 290°.

B. A mixture of 1.05 g of XI, 0.93 g of aniline, and 2.3 g of phosphorus oxychloride in 50 ml of toluene was refluxed for 4 h. The toluene was then steam distilled, and the residue was crystallized from DMF to give a product with mp 290°.

C. The compound was obtained by the Bogert method [2] by refluxing I with excess aniline and had mp 290°. Found %: N 12.29. $C_{21}H_{15}N_3O_2$. Calculated %: N 12.31.

No melting-point depressions were observed for mixtures of all of the samples.

Amide of 3-(4-Sulfamoylphenyl)-4-quinazolone-2-carboxylic Acid (XII, R = 4-$H_2NO_2SC_6H_4$, R' = H). A solution of 1 g of V (R = 4-$H_2NO_2SC_6H_4$) in 5 ml of DMF was saturated with gaseous ammonia, and the mixture was hermetically sealed and held at room temperature for 24 h. The mixture was the diluted with 25 mole of water and acidified with hydrochloric acid. The precipitate was filtered and crystallized from ethanol to give 0.8 g (85.3%) of needles with mp 253-255°. Found %: N 16.44. $C_{15}H_{12}N_4O_4S$. Calculated %: N 16.28.

Hydrazide of 3-(4-Phenetyl)-4-quinazolone-2-carboxylic Acid (XII, $R = 4\text{-}C_2H_5OC_6H_4$, $R' = NH_2$). A solution of 1.69 g of V ($R = 4\text{-}C_2H_5OC_6H_4$) in 8 ml of ethanol and 0.3 g of hydrazine hydrate was heated for 7 h. The mixture was cooled, and the precipitate was filtered and crystallized from ethanol to give needles with mp 195-196°. The yield was 1.3 g (80.2%). Found %: N 17.09. $C_{17}H_{16}N_4O_3$. Calculated %: N 17.28.

Perchlorate of 3-(2-Chlorophenyl)-2-carbethoxy-4-quinazolone (VII, $R = 2\text{-}ClC_6H_4$). A solution (1 ml) of 72% perchloric acid in acetic anhydride (1 : 1) was added to a hot solution of 1 g of V ($R = 2\text{-}ClC_6H_4$) in 5 ml of acetic anhydride. After 1 h the precipitate was filtered and washed with ether to give 1.2 g (92.3%) of plates with mp 205° (decomp. with sparking). IR spectrum: 3350-3550 (OH), 1740 (ester C=O), 1690, 1600, and 1480 (quinazolone ring [5]), 1305 and 1020 (C–O–C), 1150, 1120, and 1090 cm^{-1} (ClO_4^- [9]).

3-(4-Antipyrinyl)-4-quinazolone-2-carboxylic Acid (VIII, R = 4-Antipyrinyl). Compound V (R = 4-antipyrinyl) (1 g) was treated for 3 min with 5 ml of 10% sodium hydroxide, and the mixture was filtered and acidified to pH 5 with hydrochloric acid. The precipitate was filtered, washed with water, and air-dried to give 0.75 g (80%) of a product with mp 196° (decomp.). Found %: N 14.96. $C_{20}H_{16}N_4O_4$. Calculated %: N 14.88.

Ammonium Salt of VIII. This was isolated by dissolving the acid in concentrated ammonium hydroxide with subsequent evaporation of the solution to one-third of the original volume.

3-(4-Sulfamoylphenyl)-4-quinazolone (IX, $R = 4\text{-}H_2NO_2SC_6H_4$). Compound V ($R = 4\text{-}H_2NO_2SC_6H_4$) (4 g) was dissolved in 10 ml of 10% sodium hydroxide, and the solution was filtered and acidified with hydrochloric acid to pH 5. The precipitate was filtered and crystallized from DMF–ethanol to give 3.2 g (75.3%) of plates with mp 275°. Found %: N 14.25. $C_{14}H_{11}N_3O_3S$. Calculated %: N 13.96.

3-(4-Anisyl)-4-Quinazolone (IX, $R = 4\text{-}CH_3OC_6H_4$). This was similarly obtained in 53.4% yield from V ($R = 4\text{-}CH_3OC_6H_4$) in the form of needles (from aqueous ethanol) with mp 195°. Found %: N 11.04. $C_{15}H_{12}N_2O_2$. Calculated %: N 11.09.

LITERATURE CITED

1. P. A. Petyunin and P. A. Bezuglyi, Khim. Geterotsikl. Soedin., 954 (1970).
2. M. T. Bogert and R. A. Gortner, J. Am. Chem. Soc., 32, 119 (1910).
3. German Patent No. 1,196,203 (1966); Ref. Zh. Khim., 20N, 273 (1967).
4. P. A. Petyunin, V. S. Shklyaev, and A. S. Pesis, Zh. Obshch. Khim., 27, 1554 (1957).
5. H. Culbertson, I. C. Decius, and B. E. Christensen, J. Am. Chem. Soc., 74, 4834 (1952).
6. D. T. Zentmyer and E. C. Wagner, J. Org. Chem., 14, 967 (1949).
7. Physical Methods in the Chemistry of Heterocyclic Compounds [in Russian], Khimiya, Moscow-Leningrad (1966), p. 562.
8. B. R. Baker and P. I. Almaula, J. Org. Chem., 27, 4672 (1962).
9. A. Cross, Introduction to Practical Infrared Spectroscopy [Russian translation], IL, Moscow (1961), p. 106.