Department of Chemical Research, Research Division, Hoffmann-La Roche Inc.

1-Phenyl-2-(α-hydroxyalkyl)-4(1H)-quinazolinones

J. Iacobelli, M. Uskokovic and W. Wenner

A recent report (7) from our laboratory describes the preparation of 2-(α-hydroxyalkyl)-4-quinazolinones, a group of compounds related to some naturally occuring alkaloids (8). The intermediates in this synthesis are 4,1-benzoxazepine-2,5(1*H*,3*H*)-diones (D) (1-6), which are prepared by cyclization of the corresponding N-(α-haloacyl)anthranilic acids (A). Originally, this cyclization was carried out in a sodium carbonate solution (1), but we could not repeat this procedure successfully. Many later attempts to promote the same reaction by employing different organic bases as reactants were also unsuccessful. Finally, this cyclization was accomplished by carrying out the reaction in a boiling dimethylformamide solution. This last method was applied in the cyclization of N-unsubstituted- and N-alkyl- (7), as well as N-phenyl-N-(α-haloacyl)-anthranilic acids. Thus, N-chloroacetyl-N-phenylanthranilic acid (III) and N-(α-bromopropionyl)-N-phenylanthranilic acid (VI) gave 1-phenyl-4,1-benzoxazepine-2,5(1*H*,3*H*)-dione (IV) and 3-methyl-1-phenyl-4,1-benzoxazepine-2,5(1*H*,3*H*)-dione (VII), respectively. It is probable that dimethylformamide acts in this reaction as a specific catalyst in addition to its function as the acceptor for the hydrogen halides formed (Chart 1).

CHART I

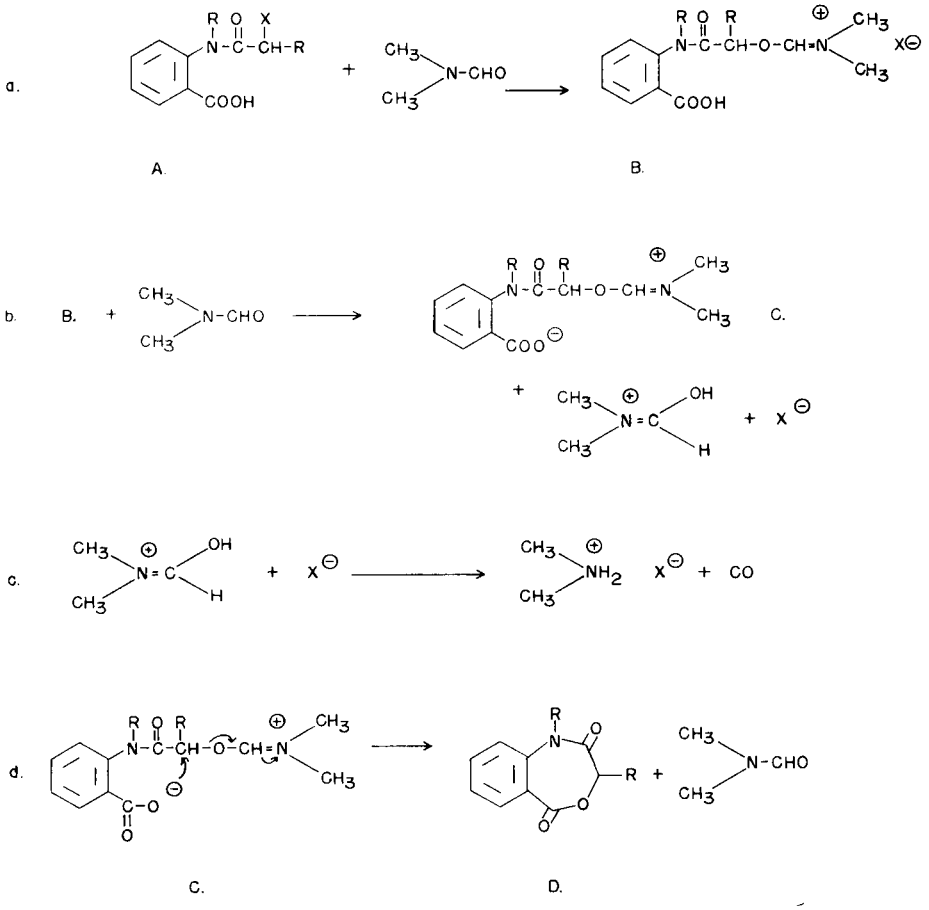
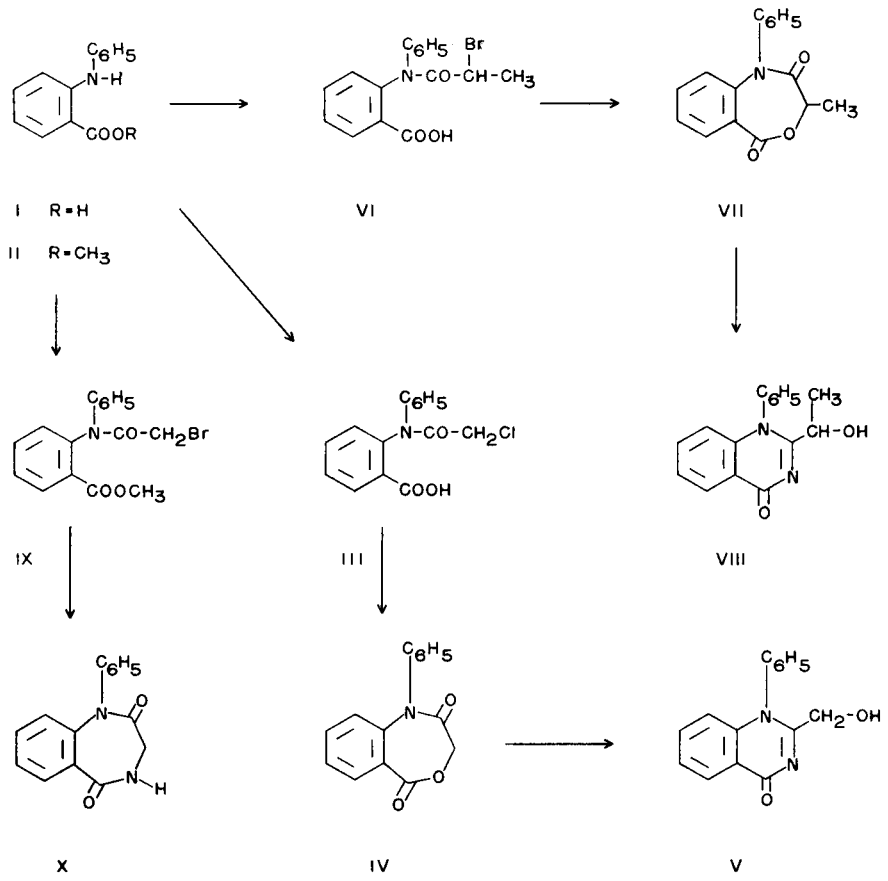


CHART 2



Reaction of compounds IV and VII with ammonia gave 2-hydroxymethyl-1-phenyl-4(1*H*)-quinazolinone (V) and 2-(1-hydroxyethyl)-1-phenyl-4(1*H*)-quinazolinone (VIII), respectively. Most probably, these ring contractions consist of two steps. In the first step, the seven membered rings are opened by attack of ammonia on the carbonyl group of lactone moiety. In the second step, the resulting N-(α-hydroxyacyl)anthranylamides give quinazolinones by elimination of water. Similarly, it was expected that the reaction of N-bromoacetyl-N-phenylanthranilic acid methylester (IX) with ammonia would give 2-bromomethyl-1-phenyl-4(1*H*)-quinazolinone, or the products derived by a further substitution of bromine with ammonia. Contrary to this expectation, the product of this reaction was 1-phenyl-3*H*-1,4-benzodiazepine-2,5(1*H*,4*H*)-dione (X). This result shows that the substitution of the bromine atom by amino group in IX proceeds much faster than the formation of the amide by attack of ammonia on the ester part of molecule. Consequently, N-aminoacetyl-N-phenylanthranilic acid methyl ester so formed gives X by an intramolecular ring closure.

EXPERIMENTAL (10)

N-Chloroacetyl-N-phenylanthranilic acid (III) from I.

To a solution of 21.3 g. of N-phenylanthranilic acid (I) in 1.5 l. of anhydrous ether was added 9.6 g. of pyridine. The mixture was stirred and cooled to 0°. Then an ethereal solution of 13.4 g. of chloroacetyl chloride was added dropwise. When the addition was complete, the excess of pyridine was neutralized with an ethereal solution of hydrogen chloride. The pyridine hydrochloride was separated by filtration, and the filtrate was evaporated to dryness. The crystalline residue was recrystallized from ethanol to give a quantitative yield of III, m.p. 183-184°.

Infrared spectrum (KBr): 2850, 2780, 2630, 2510 cm^{-1} (carboxyl group); 1680 cm^{-1} broad (=C=O groups).

Ultraviolet spectrum (2-propanol); λ infl. 221-222 (ε, 17,200); 250 (ε, 8,400); 290 mμ (ε, 1,800).

Anal. Calcd. for $C_{15}H_{12}ClNO_3$ (289.72): C, 62.18; H, 4.17; Cl, 12.24; N, 4.83. Found: C, 62.14; H, 4.21; Cl, 12.73; N, 4.80.

1-Phenyl-4,1-benzoxazepine-2,5(1*H*,3*H*)-dione (IV) from III.

A solution of 33 g. of III in 1 l. of dimethylformamide was refluxed for 4 hours and then evaporated *in vacuo*. The noncrystalline residue was dissolved in 500 ml. of methylene chloride, and this solution was washed with water, then with 10% sodium carbonate solution, and again with water, dried and evaporated to dryness. The crystalline residue was recrystallized from methanol. It gave 9.3 g. of IV, m.p. 136-138°.

Infrared spectrum ($CHCl_3$): 1734 cm^{-1} (lactone carbonyl); 1687 cm^{-1} (lactam carbonyl); 1355 and 1275 cm^{-1} (C-O-C group).

Ultraviolet spectrum (2-propanol): λ infl. 243-245 mμ (ε, 13,000); λ max 299-301 mμ (ε, 3,750).

Anal. Calcd. for $C_{15}H_{11}NO_3$ (253.21): C, 71.14; H, 4.37; N, 5.53. Found: C, 71.30; H, 4.16; N, 5.14.

2-(Hydroxymethyl)-1-phenyl-4(1*H*)-quinazolinone (V) from IV.

A solution of 12.6 g. of IV in 500 ml. of methanol was saturated with gaseous ammonia for 3 hours maintaining the temperature between 40-50°. The resulting reaction mixture was left for 3 days at room temperature, and then evaporated to dryness *in vacuo*. The infrared spectrum of the residue suggested that the major component was N-phenylanthranylamide, and only a very minor part consisted of the desired V. The latter compound was separated by crystallization from ethanol; 300 mg. of V, m.p. 203-208°, was obtained.

Infrared spectrum (KBr): 3260, 3240 and 1065 cm^{-1} (-OH group); 1626 cm^{-1} (=C=O); 1605 cm^{-1} (=C=N-); 1525 cm^{-1} (Ar-CO-N=C=).

Ultraviolet spectrum (2-propanol): λ max 229-230 (ε, 20,500); 275 (ε, 5,000); 304 (ε, 10,000); 315 mμ (ε, 8,500).

Anal. Calcd. for $C_{15}H_{12}N_2O_2$ (252.27): C, 71.41; H, 4.80; N, 11.11. Found: C, 71.59; H, 4.71; N, 11.15.

dl-3-Methyl-1-phenyl-4,1-benzoxazepine-2,5(1*H*,3*H*)-dione (VII) from I.

Forty-two and six-tenths g. of I was dissolved in 3 l. of anhydrous ether to which had been added 19.2 g. of pyridine. The solution was cooled to 0° and an ethereal solution of 51.8 g. of α-bromopropionyl bromide was added dropwise with stirring. When the addition was complete, the excess of pyridine was precipitated by the addition of ether saturated with hydrogen chloride gas. The pyridine salts were separated by filtration, and the filtrate was evaporated to dryness *in vacuo*. Although the infrared spectrum suggested a very pure product, the residue could not be crystallized. The product was then dissolved in 1 l. of dimethylformamide and refluxed for 4 hours. The solution was then evaporated and the residue dissolved in methylene chloride. The solution was washed with water, 10% sodium bicarbonate solution and again with water, dried and evaporated. The crystalline residue was recrystallized from methanol to give 39.5 g. of VII, m.p. 186-187.5°.

Infrared spectrum ($CHCl_3$): 1728 cm^{-1} (lactone carbonyl); 1700 cm^{-1} (lactam carbonyl); 1308 and 1248 cm^{-1} (C-O-C group).

Ultraviolet spectrum (2-propanol): λ infl. 220 (ε, 23,000); 235-237 mμ (ε, 13,000); λ max 320-321 mμ (ε, 3,200).

Anal. Calcd. for $C_{16}H_{13}NO_3$ (267.28): C, 71.90; H, 4.90; N, 5.24. Found: C, 72.04; H, 4.76; N, 5.23.

dl-2-(1-Hydroxyethyl)-1-phenyl-4(1*H*)-quinazolinone (VIII) from VII.

A suspension of 13.4 g. of VII in 500 ml. of methanol was saturated with gaseous ammonia at a temperature between 40-50°. The resulting solution was left standing at room temperature for 4 days. It was then evaporated to dryness and the crystalline residue recrystallized from water to give 5.2 g. of VIII, m.p. 169-170°. Here also, the infrared spectrum of the crude product showed that the major component was N-phenylanthranylamide.

Infrared spectrum ($CHCl_3$): 3530-3470 cm^{-1} (broad) and 1042 cm^{-1} (-OH group); 1656 and 1652 cm^{-1} (=C=O); 1606 cm^{-1} (=C=N-); 1536 cm^{-1} (Ar-CO-N=C=).

Ultraviolet spectrum (2-propanol): λ max 230 (ε, 19,750); 267-268 (ε, 4,750); 277 (ε, 5,250); 303 (ε, 10,000); 314-315 mμ (ε, 9,000).

Anal. Calcd. for $C_{16}H_{14}N_2O_2$ (266.30): C, 72.16; H, 5.30; N, 10.52. Found: C, 71.85; H, 5.28; N, 10.49.

1-Phenyl-3*H*-1,4-benzodiazepine-2,5(1*H*,4*H*)-dione (X) from II.

A solution of 48 g. of N-phenylanthranilic acid methyl ester (II) in 2 l. of anhydrous ether was stirred and cooled to 0°. To the mixture was added first 17 ml. of pyridine and then dropwise 43 g. of bromoacetyl bromide, dissolved in 100 ml. of anhydrous ether. Pyridine hydrobromide precipitated and was separated by filtration. The filtrate was evaporated to dryness. The remaining sirupy bromoacetyl derivative IX was dissolved in 2 l. of methanol; this solution was saturated with gaseous ammonia and allowed to stand for 48 hours at room temperature. After dilution with a large excess of water, the mixture was extracted with methylene chloride, the extract washed with water, dried and evaporated. The crystalline residue was recrystallized twice from methylene chloride-ether, yielding 23 g. of X, m.p. 221-224°.

Infrared spectrum ($CHCl_3$): 3400 cm^{-1} (=N-H); 1692 and 1668 cm^{-1} (=C=O); 1604 cm^{-1} (phenyl).

Ultraviolet spectrum (2-propanol): λ max 212-215 (ε, 28,000); 292-294 mμ (ε, 4,200); λ infl. 241-242 mμ (ε, 14,800).

Anal. Calcd. for $C_{15}H_{12}N_2O_2$ (252.112): C, 71.41; H, 4.80; N, 11.11. Found: C, 71.09; H, 4.70; N, 11.29.

On the basis of the infrared spectrum, the mother liquors consisted mostly of N-phenylanthranylamide.

REFERENCES

(1) J. D. Riedel, *Riedel's Ber.*, 13, (1912), (*Chem. Zentr.*, I, 1773 (1912)).

(2) C. M. Bean, J. Kenyon and H. Phillips, *J. Chem. Soc.*, 303 (1936).

(3) J. L. Everett, J. J. Roberts and W. C. J. Ross, *ibid.*, 2386 (1953).

(4) A. Kiprianov, *Ukrain. Khem. Zhur.*, 1, 644 (1925).

(5) F. Micheel and W. Busse, *Chem. Ber.*, 91, 985 (1958).

(6) E. Testa, I. Fontanella and M. Bovara, *Il Farmaco*, 18, 815 (1963).

(7) M. Uskoković, J. Iacobelli and W. Wenner, *J. Org. Chem.*, 29, 582 (1964).

(8) D. R. Mehta, J. S. Naravane and D. M. Desai, *ibid.*, 28, 445 (1963); W. L. F. Armarego, "Advances in Heterocyclic Chemistry" by A. R. Katritzky, Ed., Academic Press, New York, N. Y., 1963, pp. 253-309.

(9) M. Uskoković, J. Iacobelli and W. Wenner, *J. Org. Chem.*, 27, 3606 (1962).

(10) All melting points are uncorrected. Elemental microanalyses were performed by Dr. A. Steyermark. Ultraviolet spectra were taken on a Cary Model 14M spectrophotometer. Infrared spectra were taken on a Perkin-Elmer Model 21 spectrophotometer.

Received March 1, 1965 Nutley, New Jersey