Reactions of 3,4-Disubstituted 4-Oxazolin-2-ones. I. A Novel Route to 1,3,5-Trisubstituted Hydantoins

MARCO F. SAETTONE

Institute of Pharmaceutical Chemistry, University of Pisa, Pisa, Italy

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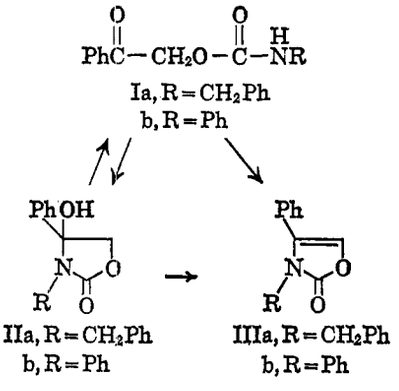
3,4-Diphenyl-4-oxazolin-2-one (IIIb), prepared by acid-catalyzed cyclization of phenacyl carbanilate (Ib), reacts with primary amines to give 5-hydroxyimidazolidin-2-one derivatives, which, after dehydration to the corresponding 4-imidazolin-2-ones, can be oxidized to 1,5-diphenylhydantoin derivatives. The reaction of IIIb with bromine gives a good yield of 5-bromo-3,4-diphenyl-4-oxazolin-2-one (XIIIb), which reacts with primary amines to give the same hydantoins obtained by the previously described route. The latter reaction was extended to 3-benzyl-4-phenyl-4-oxazolin-2-one (IIIa) with analogous results. The reaction of XIIIb with secondary amines leads to ring opening and formation of α-(N-carbamylanilino)phenylacetamide derivatives (XVIIa and b).

The preparation of 4-oxazolin-2-one derivatives (such as IIIa, Scheme I) by cyclization of N-substituted carbamates of α-hydroxy ketones has been occasionally reported in the literature.[1] Our interest in this reaction arose from the observation that phenacyl N-benzylcarbamate (Ia) was easily transformed, in the presence of base, into an isomeric compound to which the cyclic structure IIa was tentatively assigned.[2]

SCHEME I



The structure of 3-benzyl-4-hydroxy-4-phenyloxazolidin-2-one for IIa was confirmed by transformation to 3-benzyl-4-phenyl-4-oxazolin-2-one (IIIa), revealing a peculiar reactivity of the latter compound, which seemed in contrast with the alleged inertness of substituted 4-oxazolin-2-ones.[3] No serious attention has been given to the chemistry of 5-unsubstituted 4-oxazolin-2-ones, although the synthesis of at least one member of this series, 4-methyl-3-phenyl-4-oxazolin-2-one, has been reported in a number of recent papers.[4] The present article is concerned with a preliminary study of the chemistry of 3-benzyl-4-phenyl- (IIIa) and 3,4-diphenyl-4-oxazolin-2-one (IIIb).

Compound Ia was found to be very stable in ethanol solution. However, when small amounts of organic bases (benzylamine, triethylamine, pyridine, etc.) were added to the solution, Ia was transformed into a different compound to which, on the basis of analytical, spectral, and chemical evidence, was assigned the structure IIa. Treatment of IIa or Ia with acetic acid at reflux temperature produced the 4-oxazolin-2-one IIIa. When ethanol solutions of phenacyl carbanilate (Ib) were treated with bases, even at reflux temperature, no trace of 4-hydroxy-3,4-diphenyloxazolidin-2-one (IIb, analogous to IIa) could be detected in the mixture, Ib being quantitatively recovered. Treatment of Ib with acetic acid under reflux produced a good yield of 3,4-diphenyl-4-oxazolin-2-one (IIIb). The failure of Ib to cyclize to IIb might be ascribed in part to a steric effect, and in part to the lower nucleophilicity of the anion intermediate.[5]

The isolation of a 4-hydroxyoxazolidin-2-one (such as IIa) seems unprecedented. Easton, *et al.*,[1c] assumed the formation of similar compounds as intermediates in the synthesis of 4-oxazolin-2-ones, but did not report their isolation.

Treatment of IIIb[6] with aqueous methylamine at room temperature, or with benzylamine at reflux temperature, produced the 5-hydroxy-3,4-diphenylimidazolidin-2-ones VIIa and VIIb, respectively, (Scheme II). The reaction can be thought to proceed through ring opening to give the intermediates IV, V, and VI, and cyclization of VI to VII. This view is supported by the observation that solutions of VIIa and b, probably containing at equilibrium small amounts of the corresponding aldehydic tautomers VI, reduce Tollens reagent.

Dehydration of VIIa and b, carried out by heating under reflux acetic acid solutions of the compounds, produced the corresponding 4-imidazolin-2-ones VIIIa and b. These products on chromic acid oxidation gave 1-methyl- (IXa)[7] and 1-benzyl-3,4-diphenylhydantoin (IXb), respectively, whose structures were proved by independent syntheses. For this purpose, ethyl α-anilinophenylacetate[8] (X) was allowed to react with the appropriate amines to yield the amides XIa and XIb. Treatment of these with ethyl chlorocarbonate afforded the α-(N-carbethoxyanilino)phenylacetamides XIIa and XIIb, which, when heated above

(1) (a) K. V. Auwers and H. Mauss, *Biochem. Z.*, **192**, 200 (1928); (b) R. Gompper, *Ber.*, **89**, 1748 (1956); (c) N. R. Easton, D. R. Cassady, and R. D. Dillard, *J. Org. Chem.*, **27**, 2927 (1962).

(2) A. Da Settimo, M. F. Saettone, and C. Panichi, *Gazz. Chim. Ital.*, **95**, 624 (1965).

(3) See, *e.g.*, J. W. Cornforth in "Heterocyclic Compounds," Vol. 5, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1957, pp 376, 377.

(4) For a comprehensive survey on the preparation of this compound, see P. J. Stoffel and W. D. Dixon, *J. Org. Chem.*, **29**, 978 (1964).

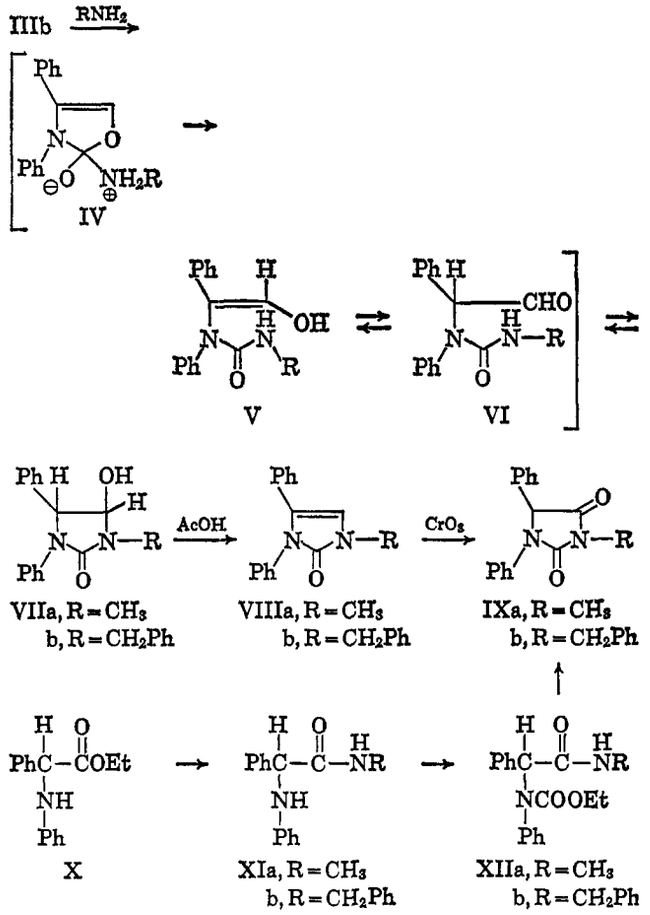
(5) Unpublished observations show indeed that phenacyl N-cyclohexylcarbamate, in which a similar steric (but not mesomeric) effect should be operative, does cyclize at a very slow but definite rate.

(6) This compound was preferred over IIIa for this set of reactions because of its simpler structure and greater ease of preparation. Analogous reactions of IIIa are currently being investigated.

(7) H. Aspelund, *Acta Acad. Aboensis, Math. Phys.*, **23**, No. 2 (1962); *Chem. Abstr.*, **59**, 2798 (1963).

(8) C. A. Bischoff, *Ber.*, **30**, 2303 (1897).

SCHEME II



their melting points, gave the hydantoins IXa[9] and IXb.

Conversion of the oxazole to the imidazole ring by reaction with ammonia or primary amines (*e.g.*, aniline) has been reported in the past by several authors.[10] Gabriel and Eschenbach[10d] were the first to report the transformation of oxazolidin-2-one into 1-phenylimidazolidin-2-one by treatment with aniline. The present conversion of a 4-oxazolin-2-one to 4-imidazolin-2-ones through 5-hydroxyimidazolidin-2-ones as intermediates appears, however, to differ substantially from previous literature examples. In the reaction of IIIb with amines, the choice of the amine proved to be critical: *e.g.*, a 5-hr reflux in aniline, isopropylamine, or *t*-butylamine resulted in total recovery of the starting material. The oxidation of 4,5-disubstituted 4-imidazolin-2-ones bearing aromatic groups in the 4 (or 5) position or in the 4 and 5 positions has been reported to yield N,N′-diacylated ureas.[11] In this connection, the oxidation of VIII to hydantoin derivatives appears of particular interest.[12]

(9) For an independent preparation of IXa, this standard hydantoin synthesis was preferred over the method of Aspelund,[7] involving the condensation of phenylglyoxal with N-phenyl-N′-methylurea.

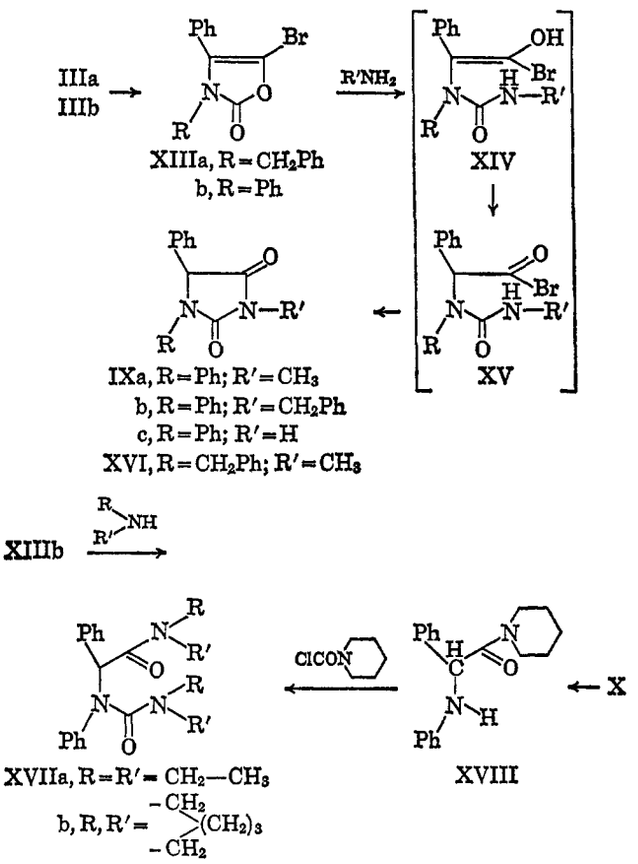
(10) (a) M. Lewy, *Ber.*, **21**, 2192 (1888); (b) F. R. Japp and T. S. Murray, *J. Chem. Soc.*, **63**, 469 (1893); (c) S. Minovici, *Ber.*, **29**, 2097 (1896); (d) S. Gabriel and G. Eschenbach, *ibid.*, **30**, 2494 (1897); (e) J. W. Cornforth and R. H. Cornforth, *J. Chem. Soc.*, 96 (1947); (f) J. W. Cornforth and H. T. Huang, *ibid.*, 1960 (1948); (g) J. W. Cornforth and E. Cookson, *ibid.*, 1085 (1952).

(11) (a) H. Biltz, *Ber.*, **41**, 1754 (1908); (b) *Ann.*, **368**, 156 (1909).

(12) Compound VIIIa showed a remarkable tendency toward autoxidation: *e.g.*, when an ethanol solution of the compound was allowed to evaporate at room temperature, conversion to the hydantoin IXa resulted in 28% yield.

Treatment of IIIb with bromine afforded the 5-bromo derivative XIIIb, whose reaction with primary amines provided a simpler route to the 3-substituted 1,5-diphenylhydantoins described above. The reaction of the 5-bromo derivative (Scheme III), respectively, with methylamine, benzylamine, and ammonia gave, instead of the expected 5-amino-4-oxazolin-2-ones, the hydantoins IXa, IXb, and IXc[13] (83, 89, and 94% yield, respectively). Bromination of IIIa also gave a 5-bromo derivative (XIIIa), whose reaction with methylamine produced a good yield of 1-benzyl-3-methyl-5-phenylhydantoin (XVI). The scope and limitations of this reaction, which can be thought to proceed through the intermediates XIV and XV,[14] are currently being investigated in this laboratory. It might indeed provide an useful route to 1,3,5-trisubstituted hydantoins of potential pharmaceutical interest.

SCHEME III



Treatment of the bromo derivative XIIIb with secondary amines (respectively, diethylamine and piperidine) yielded the α-(N-carbamylanilino)phenylacetamide derivatives XVIIa and XVIIb. The structure of XVIIb was proven by reaction of ethyl α-anilinophenylacetate (X) with piperidine to give the piperidide XVIII. Treatment of XVIII with 1-piperidinecarbonyl chloride in the presence of base gave a product which was identical with XVIIb. Structure XVIIa rests on analytical and spectral data, and on the

(13) Prepared in 24% yield by a different method by G. Homberg [*Finska Kemistsamfundets Medd.*, **59**, 25 (1950); *Chem. Abstr.*, **46**, 8651 (1952)].

(14) This mechanism is to be preferred over an alternative one, involving substitution of the bromine by the amine to give a 5-amino-4-oxazolin-2-one derivative, and its rearrangement to the hydantoin.

similarity of the reacting species. The reaction of XIIIb with secondary amines should follow essentially the same path as the reaction with primary ones, *i.e.*, involving intermediates such as XIV and XV. In the latter case, however, intramolecular elimination of HBr is impossible, and reaction with a second mole of amine would give the open-chain compounds XVIIa and XVIIb.

Biological Activity.—All the new compounds described in the present paper were tested for central nervous activity in mice, and were found to be inactive at a dose of 300 mg/kg. Compound XIIa exhibited muscle relaxant activity. However, its minimal effective dose (75 mg/kg orally) indicated a level of activity not sufficient to warrant further investigation.

Experimental Section[15]

Phenacyl N-benzylcarbamate (Ia) was obtained in improved yield by using a slight modification of the procedure described in the previous paper.[2] A 20% solution of phosgene in toluene (25 ml, *ca.* 0.05 mole) was slowly added to a stirred solution of phenacyl alcohol[16] (6.12 g, 0.045 mole) in a mixture of benzene (25 ml) and dimethylaniline (10 ml), while cooling at 0°. To the stirred mixture was then added, without isolation of the intermediate chloroformate, a solution of benzylamine (10.7 g, 0.1 mole) in benzene (10 ml). Stirring at 0° was continued 1 hr, then the mixture was poured into water. The organic layer was separated, washed with 10% hydrochloric acid and water, dried (magnesium sulfate), and evaporated under reduced pressure to afford 7.75 g (64%) of Ia: mp 113–114° after recrystallization from benzene–petroleum ether; λ_{max} 242 mμ (ε 12,100, conjugated carbonyl group); λ 3.02 (NH), 5.88, 5.93 (CO) μ.

3-Benzyl-4-hydroxy-4-phenyloxazolidin-2-one (IIa).—A solution of Ia (5.4 g, 0.02 mole) in 95% ethanol containing a few drops of benzylamine or triethylamine (30 mg/ml) was allowed to stand at room temperature in an open flask for 3 days. The crystallized product (4.7 g, 87%) was collected and recrystallized from aqueous ethanol to yield pure IIa as colorless needles: mp 144–145°; λ 3.06 (OH), 5.77 (carbonyl group in five-membered ring) μ; no ultraviolet absorption in the 230–250-mμ region.

Anal. Calcd for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.55; H, 5.71; N, 4.96.

3-Benzyl-4-phenyl-4-oxazolin-2-one (IIIa).—A solution of IIa (2.69 g, 0.01 mole) in glacial acetic acid was refluxed for 2 hr. After removal of the solvent *in vacuo*, the oily residue was triturated with 10% sodium carbonate to yield crystalline IIIa (2.4 g, 95%), mp 59–61° after recrystallization from aqueous ethanol, λ 5.69 (CO) μ.

An analogous treatment of Ia gave IIIa in 67% yield.

Anal. Calcd for $C_{16}H_{13}NO_2$: C, 76.47; H, 5.22; N, 5.57. Found: C, 76.32; H, 5.06; N, 5.61.

Phenacyl Carbanilate (Ib).—A mixture of phenacyl alcohol (13.6 g, 0.1 mole) and phenyl isocyanate (11.9 g, 0.1 mole) in a 250-ml erlenmeyer flask fitted with an air condenser, was rapidly heated on a hot plate until a vigorous reaction had started, then was allowed to cool slowly. The solid reaction product was collected, washed thoroughly with petroleum ether, dried (24.5 g, 96%), and recrystallized from ethanol to yield pure Ib: mp 149–150°; λ_{max} 250 mμ (ε 21,000); λ 3.01 (NH), 5.79, 5.92 (CO) μ.

Anal. Calcd for $C_{15}H_{13}NO_3$: C, 70.58; H, 5.13; N, 5.49. Found: C, 70.63; H, 5.11; N, 5.69.

The compound was recovered unchanged in quantitative yield after a 5-hr reflux in a 20% solution of triethylamine in ethanol.

3,4-Diphenyl-4-oxazolin-2-one (IIIb).—A solution of Ib (8.5 g, 0.033 mole) in 25 ml of glacial acetic acid was refluxed for 8 hr. The solvent was then removed *in vacuo* and the residue (6.55 g, 83%) was crystallized from ethanol to yield pure IIIb as colorless needles, mp 128–130°, λ 5.69 (CO) μ.

Anal. Calcd for $C_{15}H_{11}NO_2$: C, 75.93; H, 4.67; N, 5.90. Found: C, 76.15; H, 4.73; N, 6.01.

5-Hydroxy-1-methyl-3,4-diphenylimidazolidin-2-one (VIIa).—A suspension of finely powdered IIIb (4.75 g, 0.02 mole) in 40% aqueous methylamine (80 ml) was magnetically stirred, at room temperature, for 40 hr, then was poured into water (200 ml). The solid product was collected (4.70 g, 88%) and recrystallized from aqueous ethanol to give pure VIIa as colorless prisms: mp 156–158°; λ 2.99 (OH), 5.96 (CO) μ.

Anal. Calcd for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44. Found: C, 71.65; H, 6.08; N, 10.63.

1-Benzyl-5-hydroxy-3,4-diphenylimidazolin-2-one (VIIb).—A solution of IIIb (4.75 g, 0.02 mole) in benzylamine (10 g) was refluxed for 5 hr, then was poured into 200 ml of water. The crude reaction product was collected, washed with a little amount of ethanol, and recrystallized from ethyl acetate–petroleum ether to afford 5.3 g (77%) of VIIb: mp 185–186°; λ 2.97 (OH), 5.90 (CO) μ.

Anal. Calcd for $C_{22}H_{20}N_2O_2$: C, 76.72; H, 5.85; N, 8.13. Found: C, 76.57; H, 5.98; N, 8.00.

Ethanol solutions of both VIIa and VIIb reduced rapidly Tollens reagent[17] after slight warming on the water bath.

1-Methyl-3,4-diphenyl-4-imidazolin-2-one (VIIIa).—A solution of VIIa (1.34 g, 5.0 mmoles) in glacial acetic acid (15 ml) was heated at 100° for 1 hr. The solvent was then removed *in vacuo* and the residue was taken up in ether. Evaporation of the ethereal extract, previously washed with 10% sodium carbonate and water and dried (magnesium sulfate), afforded 1.12 g (89%) of VIIIa, mp 132–134° after recrystallization from benzene–petroleum ether,[18] λ 5.92 (CO) μ.

Anal. Calcd for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.19. Found: C, 76.80; H, 5.78; N, 11.03.

1-Benzyl-3,4-diphenyl-4-imidazolin-2-one (VIIIb).—A solution of VIIb (3.44 g, 0.01 mole) in 15 ml of glacial acetic acid was refluxed for 10 hr. The solvent was then eliminated *in vacuo* and the residue (2.55 g, 78%) was crystallized from ethyl acetate to afford pure VIIIb: mp 126–128°; λ 5.89, 5.94 (CO) μ.

Anal. Calcd for $C_{22}H_{18}N_2O$: C, 80.95; H, 5.56; N, 8.58. Found: C, 80.79; H, 5.61; N, 8.40.

1-Methyl-3,4-diphenylhydantoin (IXa). A. From VIIIa.—To a solution of VIIIa (250 mg, 1.0 mmole) in 2 ml of glacial acetic acid was added 2 ml (1.0 mmole) of a 5% solution of chromium trioxide in acetic acid. The mixture was heated 20 min on a water bath, then was poured into 80 ml of 10% sodium carbonate and extracted with ether. Evaporation of the dried (magnesium sulfate) ethereal extract gave a residue which was crystallized from ethanol to yield 110 mg (41%) of IXa: mp 185–186° (lit.[7] mp 182–183°); λ 5.67 (w), 5.89 (s) (CO) μ.

Spontaneous evaporation of an ethanol solution of VIIIa (100 mg/4 ml) at room temperature resulted in formation of a residue which, upon crystallization from ethanol, afforded 30 mg (28%) of IXa, identical with the previously obtained material.

B. From X.—A suspension of α-anilinophenylacetate hydrobromide[9] (X, 5.0 g, 0.015 mole) in 40% methylamine (7 ml) was allowed to stand at room temperature, with occasional swirling, for 12 days. Water (100 ml) was then added and the solid product was collected. Recrystallization from benzene afforded 2.3 g (64%) of **α-anilinophenylacetic acid methylamide (XIa)**: mp 115–117°;[19] λ 3.01 (NH), 6.02 (CO) μ.

Anal. Calcd for $C_{15}H_{16}N_2O$: C, 74.97; H, 6.71; N, 11.66. Found: C, 75.09; H, 6.86; N, 11.61.

To a warm solution of XIa (1.2 g, 5.0 mmoles) in dry dimethylaniline (3 ml) was added 0.6 ml (0.68 g, 6.3 mmoles) of ethyl chlorocarbonate. The mixture was heated at 90° for 2 hr, then was poured into 50 ml of 10% hydrochloric acid. The solid was

(15) Melting points (Kofler apparatus) are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Infracord Model 137 spectrophotometer on Nujol mulls; ultraviolet spectra were determined on a Beckman Model DU spectrophotometer in 95% ethanol. Microanalyses were carried out by the Microanalytical Laboratory of the University of Padova, Italy. Identity of compounds was verified by mixture melting point and comparison of infrared spectra. Petroleum ether refers to the fraction of boiling range 60–80°.

(16) Prepared in 75% yield from phenacyl chloride by the potassium formate method described by P. L. Julian, *et al.* [*J. Am. Chem. Soc.*, **67**, 1203 (1945)] for the synthesis of α-hydroxy-β-phenylpropiophenone. I. A. Kaye, *et al.* [*ibid.*, **75**, 746 (1953)], prepared phenacyl alcohol from phenacyl bromide by the same method in 72% yield.

(17) Prepared according to R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1956, p 162.

(18) It is recommended to avoid keeping the compound in solution for a long time, because of its facile oxidability to the hydantoin IXa (see footnote 12).

(19) Aspelund[7] reported for this compound, which he obtained on alkaline hydrolysis of IXa, mp 129–130°.

collected (1.14 g, 73%) and recrystallized from ethyl acetate to give **α-(N-carbethoxyanilino)phenylacetic acid methylamide (XIIa)**: mp 150–152°; λ 3.02 (NH), 5.93, 6.01 (CO) μ.

Anal. Calcd for $C_{18}H_{20}N_2O_3$: C, 69.21; H, 6.45; N, 8.97. Found: C, 69.03; H, 6.60; N, 9.09.

A sample of XIIa (1.0 g, 3.2 mmoles) was heated for 2 hr in a sublimator at 200° and 20 mm. The residue (800 mg, 94%) was recrystallized from ethanol to give pure IXa, identical with the previously obtained material.

C. From XIIIb.—To a solution of IIIb (2.37 g, 0.01 mole) in 20 ml of chloroform was slowly added 26.5 ml (0.01 mole) of a 6% solution of bromine in chloroform. The flask was allowed to stand under a fume hood until the copious evolution of hydrogen bromide had almost ceased, then the solvent was distilled and the residue was taken up in benzene (charcoal). Addition of petroleum ether to the solution caused crystallization of **5-bromo-3,4-diphenyl-4-oxazolin-2-one (XIIIb**, 2.62 g, 83%), mp 163–164° after recrystallization from the same solvent mixture, λ 5.69 (CO) μ.

Anal. Calcd for $C_{15}H_{10}BrNO_2$: C, 56.95; H, 3.16; N, 4.43. Found: C, 57.02; H, 3.28; N, 4.62.

A suspension of XIIIb (1.58 g, 5.0 mmoles) in 15 ml of aqueous 40% methylamine was magnetically stirred, at room temperature, for 3 days, then was poured into water (100 ml). The solid product (1.2 g, 90%) was collected and recrystallized from ethanol to give pure IXa, identical with the previously obtained material.

Anal. Calcd for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30; N, 10.52. Found: C, 72.03; H, 5.34; N, 10.64.

1-Benzyl-3,4-diphenylhydantoin (IXb). A. From VIIIb.—To a solution of VIIIb (652 mg, 2.0 mmoles) in glacial acetic acid (5 ml) was added 4 ml (2.0 mmoles) of a 5% solution of chromium trioxide in acetic acid. The mixture was heated on a water bath for 30 min, then was poured into water (100 ml) and extracted with ether. The ethereal extract was washed with 10% sodium carbonate and water, dried (magnesium sulfate), and evaporated to give a residue, which was triturated with a small amount of ethanol to yield crystalline IXb (250 mg, 36.5%): mp 186–188°; λ 5.67 (w), 5.88 (s) (CO) μ.

B. From X.—A mixture of ethyl α-anilinophenylacetate hydrobromide (X, 5.0 g, 0.015 mole) and benzylamine (10 g) was heated at 100° for 10 hr. After elimination of the excess benzylamine *in vacuo*, the residue crystallized on trituration with water. The crude product was recrystallized from ethanol to yield 3.05 g (64%) of **α-anilinophenylacetic acid benzylamide (XIb)**: mp 149–150°; λ 3.04 (NH), 6.03 (CO) μ.

Anal. Calcd for $C_{21}H_{20}N_2O$: C, 79.71; H, 6.37; N, 8.85. Found: C, 79.67; H, 6.50; N, 8.71.

To a solution of XIb (6.3 g, 0.02 mole) in diethylaniline (20 ml) was added 2.4 ml (2.7 g, 0.025 mole) of ethyl chlorocarbonate. The mixture was heated at 90° for 3 hr, then was poured into 10% hydrochloric acid (150 ml). The solid was collected (5.2 g, 67%) and recrystallized from ethyl acetate to give **α-(N-carbethoxyanilino)phenylacetic acid benzylamide (XIIb)**: mp 138–140°; λ 2.99 (NH), 5.91, 6.02 (CO) μ.

Anal. Calcd for $C_{24}H_{24}N_2O_3$: C, 74.20; H, 6.23; N, 7.21. Found: C, 73.99; H, 6.37; N, 7.08.

A sample of XIIb (1.55 g, 4.0 mmoles) was heated for 2 hr in a sublimator at 260° and 25 mm. The partly sublimed residue was recrystallized from ethanol to yield 0.96 g (70%) of IXb, identical with the previously obtained material.

C. From XIIIb.—A mixture of XIIIb (1.58 g, 5.0 mmoles), benzylamine (2.0 g), and water (1.0 ml) was heated at 100° for 5 hr, then was poured into water (100 ml). The solid product was collected, washed with water, and recrystallized from ethanol to yield 1.42 g (83%) of IXb, identical with the previously obtained material.

Anal. Calcd for $C_{22}H_{18}N_2O_2$: C, 77.17; H, 5.30; N, 8.18. Found: C, 76.98; H, 5.40; N, 8.06.

3,4-Diphenylhydantoin (IXc).—A solution of XIIIb (1.58 g, 5.0 mmoles) in a mixture of chloroform (30 ml) and ethanol (60 ml) was saturated with gaseous ammonia, then was allowed to stand at room temperature for 6 days. After addition of chloroform (70 ml) the mixture was extracted several times with 10% sodium hydroxide. Acidification of the alkaline extract caused precipitation of IXc (1.10 g, 87%): mp 205–206° (lit.[12,20] mp 204–206°) after recrystallization from ethanol; λ 2.64 (w), 2.83 (s) (CO) μ.

3-Benzyl-5-bromo-4-phenyl-4-oxazolin-2-one (XIIIa).—To a solution of IIIa (1.0 g, 4.0 mmoles) in chloroform (20 ml) was slowly added, with stirring, 10.7 ml (4.0 mmoles) of a 6% solution of bromine in chloroform. After the evolution of hydrogen bromide had subsided, the solvent was removed and the residue was crystallized from benzene–petroleum ether (charcoal) to yield 1.16 g (88%) of XIIIa as colorless needles, mp 104–105°, λ 5.63 (CO) μ.

Anal. Calcd for $C_{16}H_{12}BrNO_2$: C, 58.20; H, 3.64; N, 4.24. Found: C, 58.39; H, 3.73; N, 4.39.

1-Benzyl-3-methyl-5-phenylhydantoin (XVI).—A suspension of XIIIa (0.66 g, 2.0 mmoles) in 40% methylamine (15 ml) was magnetically stirred, at room temperature, for 3 days, then was poured into water (150 ml). The solid product was collected, washed with water, dried (0.5 g, 89%), and recrystallized from ethanol to give pure XVI: mp 120–121°; λ 5.69 (w), 5.88 (s) (CO) μ.

Anal. Calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.79; H, 5.79; N, 10.07.

N,N-Diethyl α-(N-Diethylcarbamylanilino)phenylacetamide (XVIIa).—A suspension of XIIIb (1.58 g, 5.0 mmoles) in 30% aqueous diethylamine (15 ml) was heated on a water bath for 8 hr, then was poured into water (100 ml). The solid was collected and crystallized from aqueous ethanol to give 1.55 g (81%) of XVIIa as colorless plates, mp 85–87° after a further crystallization from petroleum ether, λ 6.05 (CO) μ.

Anal. Calcd for $C_{23}H_{31}N_3O_2$: C, 72.41; H, 8.19; N, 11.02. Found: C, 72.64; H, 8.31; N, 11.06.

N,N-Pentamethylene α-(N-Pentamethylenecarbamylanilino)-phenylacetamide (XVIIb). A. From XIIIb.—A solution of XIIIb (1.58 g, 5.0 mmoles) in piperidine (10 ml) was heated on a water bath for 5 hr, then was poured into water (100 ml). The semisolid product which separated was triturated with ethanol to afford crude XVIIb, mp 130–135°. Recrystallization from benzene–petroleum ether gave 1.74 g (85%) of the pure product, mp 137–139°, λ 6.11 (CO) μ.

B. From X.—A mixture of ethyl α-anilinophenylacetate hydrobromide (X, 5.0 g, 0.015 mole) and piperidine (20 g) was refluxed for 3 days, then was poured into water (200 ml). The solid was collected and crystallized from ethanol to give 800 mg (18%) of **α-anilinophenylacetic acid piperidide (XVIII)**: mp 168–170°; λ 2.97 (NH), 6.14 (CO) μ. The mother liquors of XVIII yielded on concentration 2.0 g of unreacted ethyl α-anilinophenylacetate.

Anal. Calcd for $C_{19}H_{22}N_2O$: C, 77.52; H, 7.53; N, 9.52. Found: C, 77.37; H, 7.71; N, 9.49.

A mixture of XVIII (0.59 g, 2.0 mmoles), 1-piperidinecarbonyl chloride[21] (0.59 g, 4.0 mmoles), and anhydrous pyridine (0.6 g) was heated at 150° until the solid was completely dissolved, then at 100° for 6 hr. The solution was then poured into 10% hydrochloric acid (50 ml) and the semisolid product which separated was taken up in ether. The ethereal solution was washed several times with 10% hydrochloric acid and water, dried (magnesium sulfate), and evaporated to give a residue, which was crystallized from benzene–petroleum ether to afford 200 mg (25%) of XVIIb, identical with the previously obtained material.

Anal. Calcd for $C_{25}H_{31}N_3O_2$: C, 74.04; H, 7.71; N, 10.36. Found: C, 74.15; H, 7.85; N, 10.52.

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(20) E. Testa and R. Ettorre, *Arch. Pharm.*, **290**, 532 (1957).

(21) Prepared according to W. J. Rost, *J. Am. Pharm. Assoc., Sci. Ed.*, **46**, 290 (1957).