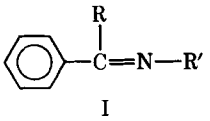

I

EXPERIMENTAL[1]

One-tenth mole of ketone and 0.1 mole of the desired amine were mixed with 100 ml. of xylene, fitted with a water separator, and refluxed for 20 hr. or more until no more water formed. After the theoretical amount of water was separated and the solvent was removed, the product was isolated by distillation under reduced vacuum.

[1] All melting points were taken on a Thermolyne apparatus and are not corrected.

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New Compounds: Synthesis of Dimethyl *N,N'*-Bis(2-amino-3-oxophenoxazine-4,6-dimethyl-1,9-dicarbonyl)-*dl*-dialaninate

M. T. WU* and R. E. LYLE

Abstract □ Dimethyl *N,N'*-bis(2-amino-3-oxophenoxazine-4,6-dimethyl-1,9-dicarbonyl)-*dl*-dialaninate was synthesized from *N*-(3-benzyloxy-4-methyl-2-nitrobenzoyl)-*dl*-alanine methyl ester.

Keyphrases □ Dimethyl *N,N'*-bis(2-amino-3-oxophenoxazine-4,6-dimethyl-1,9-dicarbonyl)-*dl*-dialaninate—synthesis □ Phenoxazine ring system analogs—synthesis of dimethyl *N,N'*-bis(2-amino-3-oxophenoxazine-4,6-dimethyl-1,9-dicarbonyl)-*dl*-dialaninate

The extreme potency of the antibiotic actinomycin has generated considerable interest in the chemistry and pharmacology of this natural product (1). Actinomycin has been shown to be a complex amide of a substituted phenoxazinedicarboxylic acid and a cyclic pentapeptide. Because of interest in heteroaroylamino acids (2), it seemed desirable to prepare some simple analogs of phenoxazine ring systems (3). Accordingly, dimethyl *N,N'*-bis(2-amino-3-oxophenoxazine-4,6-dimethyl-1,9-dicarbonyl)-*dl*-dialaninate (II) was synthesized by hydrogenation of *N*-(3-benzyloxy-4-methyl-2-nitrobenzoyl)-*dl*-alanine methyl ester (I), followed by oxidation with *p*-benzoquinone.

EXPERIMENTAL[1]

N-(3-Benzyloxy-4-methyl-2-nitrobenzoyl)-*dl*-alanine Methyl Ester (I)—3-Benzyloxy-4-methyl-2-nitrobenzoic acid (4), 5.75 g. (0.02 mole), was suspended in 20 ml. of dry benzene and heated under gentle reflux with thionyl chloride (12 ml.) for 1.5 hr. The resulting solution was concentrated under reduced pressure to remove the excess thionyl chloride, and the residual acid chloride was then redissolved in dry benzene (100 ml.). *dl*-Alanine methyl ester dihydrochloride, 3.52 g. (0.02 mole), was added, and the mixture was heated under reflux for 15 hr.; then any undissolved material was separated from the hot solution. The filtrate was diluted with *n*-hexane. The solids which separated on cooling were recrystallized from 95% ethanol to give 3.74 g. (50%) of *N*-(3-benzyloxy-4-methyl-2-nitrobenzoyl)-*dl*-alanine methyl ester (I), m.p. 148–150°; $\nu_{max.}$ 3380 (NH), 1740 (ester CO), 1660 (amide CO), 1530 and 1370 (NO_2), and 780 and 745 cm.$^{-1}$ (substituted benzene).

Anal.—Calc. for $C_{19}H_{20}N_2O_6$: C, 61.28; H, 5.41. Found: C, 61.44; H, 5.71.

Dimethyl *N,N'*-Bis(2-amino-3-oxophenoxazine-4,6-dimethyl-1,9-dicarbonyl)-*dl*-dialaninate (II)—*N*-(3-Benzyloxy-4-methyl-2-nitrobenzoyl)-*dl*-alanine methyl ester (I), 2.98 g. (0.008 mole), was dissolved in 200 ml. of hot ethyl acetate and hydrogenated over 1 g. of palladium-on-charcoal (5%) at room temperature for 19 hr. The catalyst was removed by filtration, and the colorless filtrate was evaporated in a rotary evaporator. The intermediate *o*-aminophenol was redissolved in absolute alcohol (100 ml.). A solution of 2.59 g. (0.024 mole) of *p*-benzoquinone in 50 ml. of absolute alcohol was added. The mixture, exposed to the atmosphere, was stirred for 1 hr., and the red solid (1.62 g., 80%) was separated by filtration. The analytical sample was obtained from chloroform by means of a soxhlet extractor to give bright-red crystals, m.p. > 260°; $\nu_{max.}$ 3400 and 3250 (NH, NH_2), 1730 and 1700 (ester and quinone CO), 1660 (amide CO), and 740 and 725 cm.$^{-1}$ (substituted benzene); $\lambda_{max.\ (nm.)}^{abs.\ EtOH}$ 238 (log ϵ 4.79), 421 (log ϵ 4.58), and 442 (log ϵ 4.59).

Anal.—Calc. for $C_{24}H_{26}N_4O_8$: C, 57.82; H, 5.26. Found: C, 57.56; H, 5.21.

[1] All melting points are uncorrected. Analyses were obtained from Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. UV spectra were obtained with a Perkin-Elmer spectracord in absolute ethanol solution. IR spectra were obtained on a Perkin-Elmer infracord determined as mulls in series 11–14 Halocarbon oil from 4000 to 1300 cm.$^{-1}$ and in mineral oil from 650 to 1300 cm.$^{-1}$.

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COMMUNICATIONS

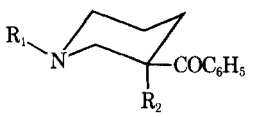
Novel Behavior of *N*-Methyl-3-benzoyl-3-hydroxypiperidine under Conditions of Von Braun Demethylation

Keyphrases □ *N*-Methyl-3-benzoyl-3-hydroxypiperidine—novel behavior, Von Braun demethylation □ *N*-Methylethanolamines, tertiary—Von Braun demethylation, novel reaction with cyanogen bromide □ Von Braun demethylation—novel reaction of tertiary *N*-methylethanolamines with cyanogen bromide

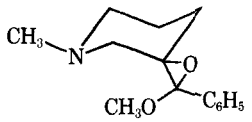
Sir:

The Von Braun demethylation (1, 2) effected by treatment of tertiary *N*-methylethanolamines with CNBr has been successful with Compounds I–IV (2) but has failed in the conversion of V to VI (2). The unusual behavior of similarly constituted tertiary *N*-methylethanolamines (3–5) is borne out, if only in a negative sense, by the work of others (6, 7) who described the demethylation of 14-acetoxycodeinone (VII) and 14-acetoxydihydrocodeinone (VIII) but not of the 14-hydroxy analogs (IX and X) from which they were prepared. The nature of the impediment by the hydroxyl group is suggested by studies of other investigators (8–10) on alkyl cyanates, by previous studies in these laboratories on epoxy ether (IV) formation from I (13–15) and on the chemistry of the hydroxyl group in V, IX, and X (3–5), and by the character of the reaction mixture and products obtained by treatment of V with CNBr.

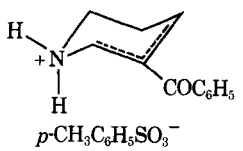
Under the usual reaction conditions, V (8 g.) afforded a benzene-insoluble, water-soluble plastic mass. The IR spectrum exhibited bands at 2218 (CN) and 1675 cm.$^{-1}$ (C=O, ketone) as well as a band at 3470 cm.$^{-1}$, characteristic of but weaker than the expected absorption for the OH group of V. The acid-washed, benzene-soluble fraction of the reaction mixture (<1 g.) exhibited bands at 2218 (CN) and 1680 cm.$^{-1}$ (C=O, ketone) but no band in the 3500-cm.$^{-1}$ region. This oil exhibited a positive Beilstein test for halogen. Following hydrolysis in concentrated HCl, water and exces acid were removed *in vacuo*. The residue was dissolved in water. The solution was washed with chloroform, alkalized with sodium carbonate, and extracted again with chloroform. Evaporation of the extract afforded



I: $R_1 = CH_3$, $R_2 = Cl$
II: $R_1 = CH_3$, $R_2 = O_2CCH_3$
III: $R_1 = CH_3$, $R_2 = OCH_3$
V: $R_1 = CH_3$, $R_2 = OH$
VI: $R_1 = CN$, $R_2 = OH$
XII: $R_1 = H$, $R_2 = OH$
XIII: $R_1 = CH_3$, $R_2 = OCN$
XIV: $R_1 = CH_3$, $R_2 = Br$
XV: $R_1 = CN$, $R_2 = OCN$
XVI: $R_1 = CN$, $R_2 = Br$
XVII: $R_1 = H$, $R_2 = Br$

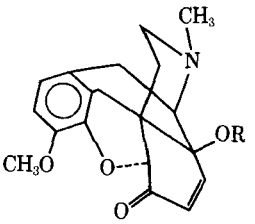


IV

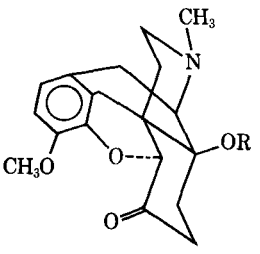


p-$CH_3C_6H_5SO_3^-$

XI



VII: R = $OCCH_3$
IX: R = H



VIII: R = $OCCH_3$
X: R = H