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(3) "The National Formulary," 13th ed., Mack Publishing Co., Easton, Pa., 1970, p. 882.
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# New Compounds: Anils

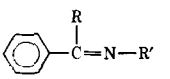
HEINO A. LUTS

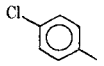
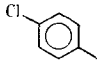
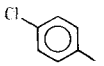
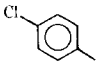
**Abstract** □ A series of new anils (ketimines) was synthesized by the condensation of a ketone with a desired amine.

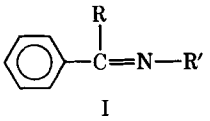
**Keyphrases** □ Anils, potential antianxiety agents—synthesis by condensation of ketone with amines, preliminary screening □ Ketimines, potential antianxiety agents—synthesis, preliminary pharmacological screening □ Antianxiety agents—synthesis of new anils, preliminary screening

In search for new compounds with CNS activity, a series of anils was prepared for pharmacological evaluation (I) (Table I). These compounds were synthesized by the condensation of a ketone with a desired amine according to the procedure described in the literature (1). Preliminary pharmacological studies indicate only insignificant antianxiety properties. The complete results will be published later.

**Table I**—Anils



| Number | R | R′ | Formula | Boiling Point | Molecular Weight | $n_D^{20}$ | Yield, % | Analysis, % Calc. | Found |
|---|---|---|---|---|---|---|---|---|---|
| I |  | —$CH_2CH_2N(CH_3)_2$ | $C_{17}H_{19}ClN_2$ | 180–184°/0.6 mm. | 286.78 | 1.5864 | 73 | C 71.19<br>H 6.68<br>Cl 12.37<br>N 9.77 | 70.84<br>6.70<br>12.77<br>9.41 |
| II |  | —$CH_2CH_2N(CH_2CH_3)_2$ | $C_{19}H_{23}ClN_2$ | 160–164°/0.5 mm. | 314.83 | 1.5735 | 57 | C 72.48<br>H 7.36<br>Cl 11.26<br>N 8.89 | 72.39<br>7.44<br>11.50<br>8.68 |
| III |  | —$CH_2CH_2CH_2N(CH_3)_2$ | $C_{18}H_{21}ClN_2$ | 182–1840°/0.6 mm. | 300.80 | 1.5790 | 73 | C 71.87<br>H 7.03<br>Cl 11.78<br>N 9.31 | 71.63<br>7.03<br>11.69<br>9.41 |
| IV |  | —$CH_2CH_2CH_2N(CH_2CH_3)_2$ | $C_{20}H_{25}ClN_2$ | 164–176°/0.6 mm. | 328.86 | 1.5678 | 58 | C 73.04<br>H 7.66<br>Cl 10.77<br>N 8.51 | 72.76<br>7.59<br>11.01<br>8.33 |
| V |  | —$CH_2CH_2N(CH_2CH_3)_2$ | $C_{18}H_{23}N_3$ | 182–183°/0.3 mm. | 280.37 | 1.5655 | 60 | C 77.10<br>H 7.91<br>N 14.99 | 77.03<br>8.28<br>14.98 |
| VI |  | —$CH_2CH_2CH_2N(CH_3)_2$ | $C_{17}H_{21}N_3$ | 168–170°/0.3 mm. | 267.35 | 1.5769 | 64 | C 76.37<br>H 7.91<br>N 15.72 | 76.63<br>7.68<br>15.51 |
| VII |  | —$CH_2CH_2CH_2N(CH_2CH_3)_2$ | $C_{19}H_{25}H_3$ | 176–177°/0.3 mm. | 295.41 | 1.5595 | 62 | C 77.24<br>H 8.53<br>N 14.22 | 76.94<br>8.40<br>14.21 |
| VIII |  | —$CH_2CH_2CH_2N(CH_3)_2$ | $C_{16}H_{20}N_2S$ | 176–182°/0.6 mm. | 272.39 | 1.5855 | 56 | C 71.28<br>H 7.74<br>N 9.78 | 71.42<br>7.52<br>9.62 |
| IX |  | —$CH_2CH_2N(CH_2CH_3)_2$ | $C_{17}H_{22}N_2S$ | 172°/0.4 mm. | 286.41 | 1.5836 | 55 | C 70.54<br>H 7.40<br>N 10.28 | 70.37<br>7.24<br>9.98 |
| X |  | —$CH_2CH_2CH_2N(CH_2CH_3)_2$ | $C_{18}H_{24}N_2S$ | 182°/0.3 mm. | 300.34 | 1.5714 | 53 | C 71.98<br>H 8.05<br>N 9.33 | 71.94<br>8.22<br>9.19 |



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 $\epsilon$ 4.79), 421 (log $\epsilon$ 4.58), and 442 (log $\epsilon$ 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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(1) For leading reference, see "The Actinomycins and Their Importance in the Treatment of Tumors in Animals and Man,"