New Compounds: Physiologically Active Amines and Amine Salts

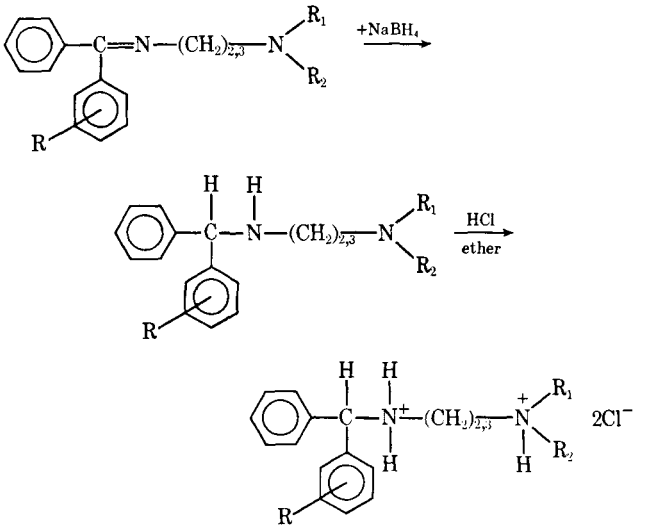
HEINO A. LUTS*▲ and JEROME F. GRATTAN†

Abstract □ A group of compounds having the amine moiety were synthesized from anils and subjected to preliminary pharmacological studies.

Keyphrases □ Amines, active—synthesized from anils □ Anils—used for synthesis of active amines and amine salts □ CNS agents, potential—conversion of anils to active amines and amine salts

The authors previously described the synthesis and activity of some centrally active anils (1). These compounds now have been converted to a series of secondary and tertiary amines (Table I) and amine salts (Table II) in the hope that their CNS activity will be superior to that of the anils. Pharmacological data, to be published at a later date, indicate that the activity is enhanced by the conversion.

Conversion of the anils to the amines was accomplished by sodium borohydride reduction and then acidified as illustrated in Scheme I.



Scheme I

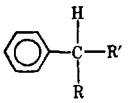


Table I—Substituted Diamines

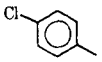
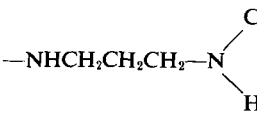
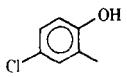
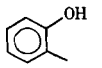
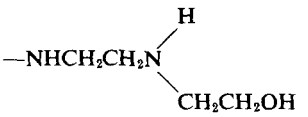
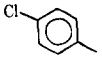
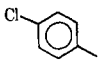
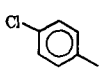
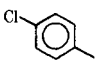
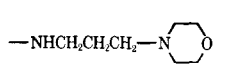
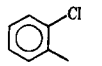
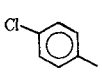
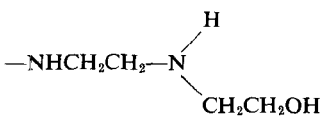
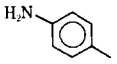
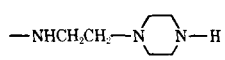
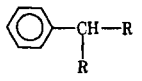
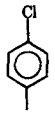
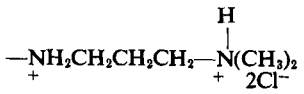
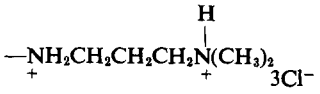
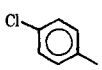
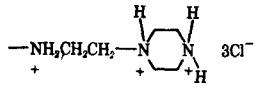
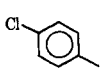
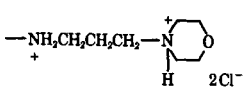
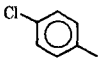
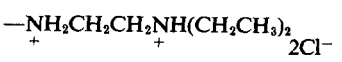
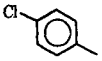
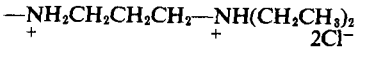
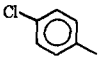
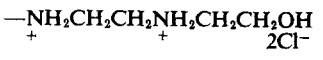
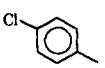
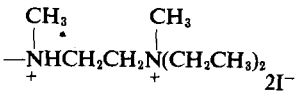
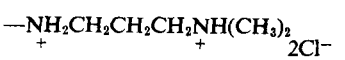
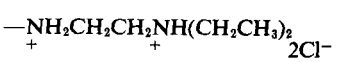
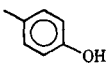
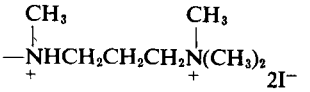
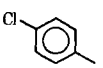
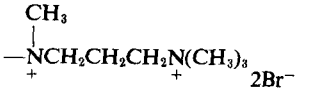
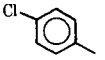
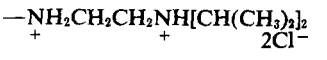
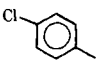
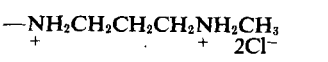
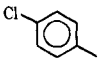
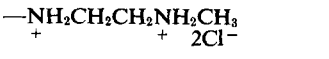
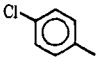
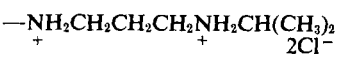
Number	R	R′	Formula	Boiling Point	Molecular Weight	Analysis, % N— Calc.	Found
1			$C_{17}H_{21}ClN_2$	173–174°/0.5 mm.	288.82	9.73	10.04
2		—NHCH$_2$CH$_2$CH$_2$—N(CH$_3$)$_2$	$C_{18}H_{23}ClN_2O$	180–181°/0.5 mm.	318.85	8.79	8.93
3			$C_{17}H_{22}N_2O_2$	170–190°/0.35 mm.	286.38	9.78	9.61
4		—NHCH$_2$CH$_2$—N(CH$_2$CH$_3$)$_2$	$C_{19}H_{25}ClN_2$	171–172°/0.5 mm.	316.87	8.84	8.70
5		—NHCH$_2$CH$_2$CH$_2$—N(CH$_3$)$_2$	$C_{18}H_{23}ClN_2$	174–175°/0.5 mm.	302.84	9.25	9.05
6		—NHCH$_2$CH$_2$CH$_2$—N(CH$_2$CH$_3$)$_2$	$C_{20}H_{27}ClN_2$	178–181°/0.5 mm.	330.90	8.47	8.66
7			$C_{20}H_{25}ClN_2O$	226–232°/0.14 mm.	344.89	8.12	7.90
8		—NHCH$_2$CH$_2$CH$_2$—N(CH$_3$)$_2$	$C_{18}H_{23}ClN_2$	184–192°/0.5 mm.	302.85	9.25	9.35
9			$C_{17}H_{21}ClN_2O$	210–215°/0.35 mm.	304.82	9.19	9.01
10			$C_{19}H_{26}N_4$	160–165°/0.6 mm.	310.445	18.05	17.90

Table II—Substituted Diamine Salts



Number	R	R′	Formula	Melting Point	Analysis, % Calc.	Found
1			$C_{18}H_{25}Cl_3N_2$	98–99°	N 7.45 C 28.30	7.62 28.19
2			$C_{17}H_{26}Cl_3N_3$	154°	N 11.10 C 28.07	11.01 27.92
3			$C_{19}H_{26}Cl_4N_3$	182–186°	N 12.66 C 10.68	12.53 10.51
4			$C_{20}H_{26}Cl_3N_2O$	170–172°	N 6.72 C 25.52	6.68 25.45
5			$C_{19}H_{26}Cl_3N_2$	118–120°	N 7.21 C 27.36	7.30 27.24
6			$C_{20}H_{29}Cl_3N_2$	129–131°	N 6.94 C 26.43	6.88 26.26
7			$C_{17}H_{23}Cl_3N_2O$	241°	N 7.41 C 28.16	7.29 28.03
8			$C_{21}H_{31}ClI_2N_2$	167°	N 4.66 C 5.90	4.54 5.72
9			$C_{18}H_{26}Cl_2ON_2$	148–150°	N 4.08 C 20.61	3.89 20.43
10			$C_{17}H_{24}Cl_2N_2O_2$	113–115°	N 7.80 C 19.73	7.69 19.56
11			$C_{19}H_{28}Cl_2N_2O$	110–112°	N 7.38 C 11.64	7.46 11.78
12			$C_{20}H_{30}I_2N_2O$	88–90°	N 4.50 C 11.40	4.37 11.54
13			$C_{20}H_{29}Br_2ClN_2$	90–92°	N 5.69 C 7.20	5.53 7.39
14			$C_{21}H_{31}Cl_3N_2$	162–163°	N 6.70 C 25.45	6.75 25.29
15			$C_{17}H_{23}Cl_3N_2$	225–227°	N 7.74 C 29.40	7.56 29.32
16			$C_{16}H_{21}Cl_3N_2$	230–231°	N 8.06 C 30.59	7.89 30.64
17			$C_{19}H_{27}Cl_3N_2$	182–183°	N 7.19 C 27.29	7.10 27.18

EXPERIMENTAL[1]

One-tenth mole of anil in 50 ml. of methanol was reduced with 0.15 mole (5.6 g.) of sodium borohydride (2). The mixture was refluxed for 30 min., the methanol was removed by distillation, 50 ml. of water was added, and the mixture was cooled. The oily reaction mixture was then extracted twice with 50-ml. portions of ether. The extracts were combined, dried over anhydrous calcium sulfate, and acidified with anhydrous hydrogen chloride. The crystals were collected, washed with dry ether, and recrystallized from an ethanol–ether mixture.

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

REFERENCES

(1) H. A. Luts, *J. Pharm. Sci.*, **60**, 1903(1971).

(2) H. A. Luts, W. Zucarello, and J. F. Grattan, *ibid.*, **54**, 460 (1965).

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New Compounds: Resolution of *d,l*-α-Benzamido-4-hydroxy-3-methoxydihydrocinnamic Acid, a Precursor of *l*-3,4-Dihydroxyphenylalanine

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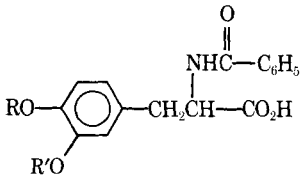
Abstract □ *d,l*-α-Benzamido-4-hydroxy-3-methoxydihydrocinnamic acid was resolved using dehydroabietylamine, and the *l*-salt thus obtained was converted to *l*-3,4-dihydroxyphenylalanine.

Keyphrases □ *d,l*-α-Benzamido-4-hydroxy-3-methoxydihydrocinnamic acid—resolution using dehydroabietylamine □ *l*-3,4-Dihydroxyphenylalanine—resolution of a precursor, *d,l*-α-benzamido-4-hydroxy-3-methoxydihydrocinnamic acid, using dehydroabietylamine □ Dehydroabietylamine—used to resolve *d,l*-α-benzamido-4-hydroxy-3-methoxydihydrocinnamic acid, a precursor of *l*-3,4-dihydroxyphenylalanine

The recent interest in *l*-3,4-dihydroxyphenylalanine (I) for the treatment of Parkinson's disease prompted an investigation into the synthesis of this amino acid. Although *d,l*-α-benzamido-3-hydroxy-4-methoxydihydrocinnamic acid (II) had been resolved using cinchonine (1), resolution of the isomeric amino acid III, derived from vanillin in the azlactone synthesis, apparently had not been previously reported[1].

Resolution of III was not achieved with cinchonine but was readily effected in excellent yield in the present work with dehydroabietylamine (IV). The optically active amine IV, previously isolated from commercial Amine D, is a relatively inexpensive, nontoxic agent and has been employed in the resolution of racemic α-phenoxypropionic acid and racemic α-benzyloxycarbonylaminophenylacetic acid (2).



II: R = CH_3, R′ = H
III: R = H, R′ = CH_3

Treatment of the resolved *l*-salt of III with dilute hydrochloric acid followed by refluxing 48% HBr yielded I. Thus, this resolution of racemic II afforded I in high optical purity and good yield without lengthy fractional crystallization.

EXPERIMENTAL[2]

Resolution of *d,l*-α-Benzamido-4-hydroxy-3-methoxydihydrocinnamic Acid (III)—Dehydroabietylamine (IV) (57 g., 0.20 mole) was dissolved in 450 ml. boiling methanol, and a small amount of mechanical impurity was removed by filtration. The solution was heated to boiling, and a solution of III (3) (63 g., 0.20 mole) in 160 ml. boiling methanol was added. The solution was boiled, and 113 ml. of boiling water was added (to turbidity). The mixture was allowed to cool gradually to room temperature and was stored at room temperature for 18 hr. The product was washed with two 125-ml. portions of methanol–water (4:1), air dried, and then dried at 60° to give 51 g. (83%) of the product, m.p. 223–224°; $[\alpha]_D^{25}$ +50.30° (concentration 1.91%, methanol). The analytical sample was obtained after three recrystallizations from methanol–water (4:1); $[\alpha]_D^{25°}$ +53.50° (concentration 1.97%, methanol).

Anal.—Calc. for $C_{17}H_{17}NO_5 \cdot C_{20}H_{31}N$: C, 73.87; H, 8.44; N, 4.66. Found: C, 73.97; H, 8.05; N, 4.66.

***l*-3,4-Dihydroxyphenylalanine (I)**—A 3-ml. portion of concentrated hydrochloric acid was added to a mixture of 3.85 g. (0.0064 mole) of the resolved salt of IV and III, 40 ml. water, and 40 ml. ethyl acetate. The organic layer was separated, and the aqueous

[1] After this work was completed, resolution of III using dehydroabietylamine was reported; A. Kaiser, M. Scheer, W. Haeusermann, and L. Marti, German pat. 1,964,420; through *Chem. Abstr.*, 74, 3864y (1971).

[2] Melting points were taken in a Mel-Temp apparatus in open capillary tubes and are uncorrected. The optical rotation measurements were determined on a Perkin-Elmer 141 polarimeter. The amino acid analysis was conducted on a Phoenix Precision Instruments amino acid analyzer, using a 50-cm. 2-Å column at 50° and pH 5.29, with Pierce *d,l*-3,4-dihydroxyphenylamine, Puriss. grade, employed as the standard.