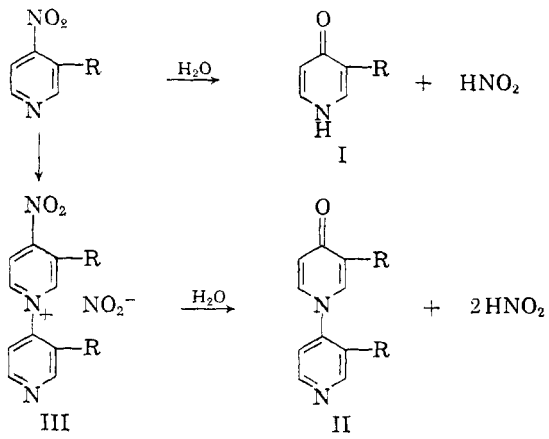

EXPERIMENTAL

*4-Hydroxy-3-picoline 1-oxide.* To a solution of 2.0 g. of potassium hydroxide in 20 ml. of water was added 2.0 g. of 4-chloro-3-picoline-1-oxide,[6] and the yellow solution was heated under reflux for 16 hr. Dilute hydrochloric acid (6*N*) was slowly added to *p*H 7 and the sodium silicate which separated was filtered and washed with water. The combined filtrates were acidified to *p*H 4 with hydrochloric acid and evaporated to dryness. Extraction of the residue with 100 ml. of absolute ethanol and evaporation of the ethanol extract yielded an amorphous tan solid which was triturated with cold ethanol. Filtration yielded 0.52 g. (30%) of 4-hydroxy-3-picoline-1-oxide, m.p. 215–216°. This material is reported to melt at 224°.[6]

*1-(3'-Methyl-4'-pyridyl)-3-methyl-4-pyridone* (II, R = —$CH_3$). The light yellow solid (1.87 g., m.p. 145–150° dec.) which had spontaneously precipitated from a sample of 10 g. of 4-nitro-3-picoline[3] on standing was collected by filtration and washed with ethanol. It was then dried, dissolved in 50 ml. of water and sodium carbonate added to *p*H 10. The resulting solution was evaporated to dryness under reduced pressure, the residue refluxed with 300 ml. of benzene for 30 min. and then filtered hot. Evaporation of the filtrates to dryness yielded 0.72 g. of a yellow solid, m.p. 165–175°. Sublimation at 140°/0.3 mm. removed a small amount of 3-methyl-4-pyridone, m.p. 91–94° (see below), and sublimation at 170°/0.3 mm. then yielded white crystals, m.p. 197–198°.

*Anal.* Calcd. for $C_{12}H_{12}N_2O$: C, 72.0; H, 6.0; N, 14.0. Found: C, 71.7; H, 6.1; N, 14.2.

*3-Methyl-4-pyridone* (I, R = —$CH_3$). Method A. The residue from the benzene extraction above was refluxed with chloroform and filtered hot. Evaporation of the chloroform filtrate to dryness yielded 0.27 g. of an oil which solidified on standing to a light yellow solid, m.p. 90°. Recrystallization from a mixture of ethanol, ether and petroleum ether (b.p. 40–60°) (1:5:25) gave light tan crystals, m.p. 92–94°.

*Anal.* Calcd. for $C_6H_7NO$: C, 66.0; H, 6.5; N, 12.8. Found: C, 66.1; H, 6.5; N, 12.6.

Method B. A solution of 0.25 g. of 4-hydroxy-3-picoline-1-oxide in 100 ml. of methanol was hydrogenated in the presence of 0.25 g. of 10% palladium-on-carbon catalyst and under 3 atm. of hydrogen at 43° for 8 hr. Removal of the catalyst by filtration and evaporation of the alcoholic filtrate gave a tan oil which solidified after extraction with boiling benzene; yield, 0.18 g. (82%), m.p. 92°. This material was identical in every respect with the product obtained by Method A above, as judged by a mixed melting point determination and comparison of infrared spectra.

*Nitric acid salt of 3-methyl-4-pyridone.* Method A. The yellow solid which had spontaneously precipitated from 4-nitro-3-picoline upon standing was collected by filtration, washed with ethanol and ether, and recrystallized from methanol. A product consisting of yellow crystals, m.p. 163° dec. and orange-yellow plates, m.p. 180° dec., was obtained. Hand separation of the crystals allowed the isolation in pure form of the plates, m.p. 180°d., which were recrystallized from methanol.

*Anal.* Calcd. for $C_6H_8N_2O_4$: C, 41.9; H, 4.7; N, 16.3. Found: C, 42.1; H, 4.6; N, 16.1.

The yellow crystals melting at 163° dec., appeared on the basis of microanalysis to be a mixture of the nitric acid salts of 3-methyl-4-pyridone and 1-(3'-methyl-4'-pyridyl)-3-methyl-4-pyridone. They were not further characterized.

Method B. Addition of 3.0 ml. of dilute nitric acid to 0.03 g. of 3-methyl-4-pyridone in water, followed by evaporation to dryness, yielded light yellow crystals, m.p. 180° dec., identical in every respect with the material prepared by Method A above.

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(6) A. R. Katritzky, *J. Chem. Soc.*, 2404 (1956).

## Preparation of 1-Phenyl-2-methyl-2-hydrazinopropane Hydrochloride and Its Isopropyl Derivative

B. VITHAL SHETTY

*Received December 19, 1960*

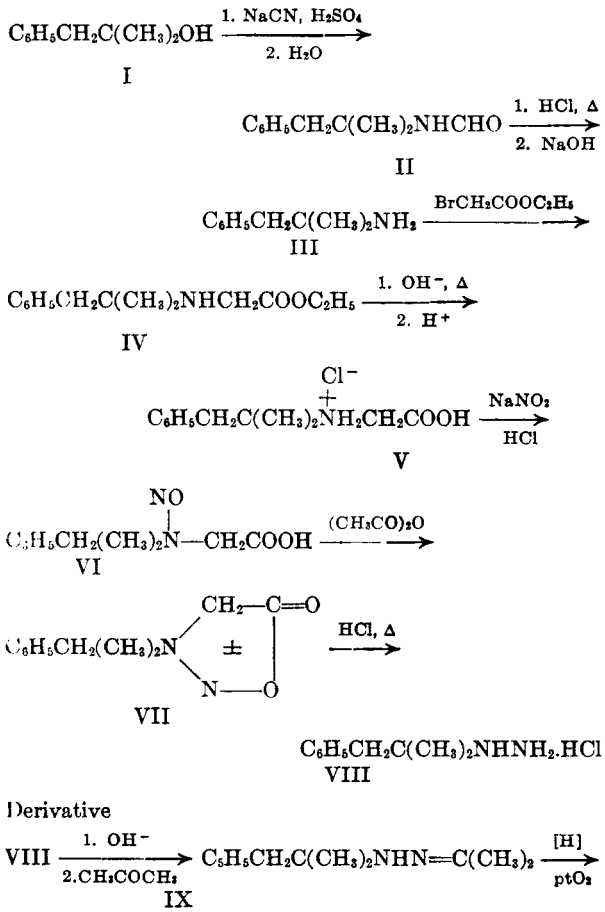
In view of the current interest in hydrazine derivatives of β-phenethylamine and the recent paper by Biel and co-workers[1] on the chemistry and structure activity relationships of aralkylhydrazines as central stimulants, we have prepared in our laboratory 1-phenyl-2-methyl-2-hydrazinopropane hydrochloride and *N*-(1-phenyl-2-*t*-butyl)-$N^1$-isopropylhydrazine hydrochloride to elucidate further the relationship between structure and pharmacological activity. The compounds were tested for hypotensive activity in dogs and cats. *N*-(1-Phenyl-2-*t*-butyl)-$N^1$-isopropylhydrazine hydrochloride produced only transient depressor responses in anesthetized dogs following intravenous injections of doses of 2 to 8 mg./kg. The compound, 1-phenyl-2-methyl-2-hydrazinopropane hydrochloride in doses up to 4.5 mg./kg. possesses intense vasopressor activity in anesthetized dogs.

*N*-Formyl-2-phenyl-*t*-butylamine (II) was prepared with slight modification of the procedure given by Ritter and Kalish.[2] We obtained the amide as a white solid with 92% yield. The authors[2] reported the amide as a viscous liquid and obtained 62% yield. The amide was hydrolyzed to the amine

(1) John H. Biel, Alexander E. Drukker, Thomas F. Mitchell, Edwin P. Sprengeler, Patrick A. Nuhfer, Alvin C. Conway, and A. Horita, *J. Am. Chem. Soc.*, **81**, 2805 (1959).

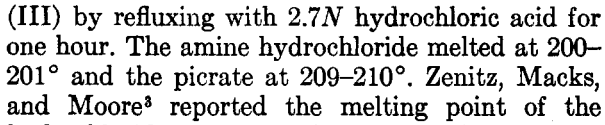
(2) John J. Ritter and Joseph Kalish, *J. Am. Chem. Soc.*, **70**, 4050 (1948).

(III) by refluxing with 2.7*N* hydrochloric acid for one hour. The amine hydrochloride melted at 200–201° and the picrate at 209–210°. Zenitz, Macks, and Moore[3] reported the melting point of the hydrochloride as 200–201°, Ritter and Kalish[2] as 198–198.5°, and Shelton and Van Campen[4] as 195–196°. The amine (III) was treated with ethyl bromoacetate and the reaction product (IV) was hydrolyzed to V. This was isolated by careful adjustment of *p*H, but one could proceed with the next step without isolation. The nitroso derivative (VI) was obtained in good yield and it was treated with acetic anhydride to give the sydnone (VII). On treating it with concentrated hydrochloric acid and heating it on a steam bath, the reaction mixture formed an oily layer. It was cooled in an ice bath and saturated with dry hydrogen chloride. The solid was removed by filtration and the process was repeated a few times to give the compound (VIII). The yield was rather low and this may be due to olefin formation. The reaction between the hydrazino compound (VIII) as a base and acetone started to take place within a few minutes at room temperature. The Schiff base (IX), thus obtained, was readily reduced to the isopropyl derivative (X).




(3) Bernard L. Zenitz, Elizabeth B. Macks, and Maurice L. Moore, *J. Am. Chem. Soc.*, 70, 955 (1948).

(4) Robert L. Shelton and Marcus G. Van Camphen, Jr., U. S. Pat. 2,408,345 (Sept., 1946).




## EXPERIMENTAL[5]

*N-Formyl-2-phenyl-t-butylamine* (II). To 830 ml. of glacia acetic acid, cooled in an ice bath, 377.0 g. (7.69 moles) of sodium cyanide was added with vigorous stirring, and controlling the temperature below 20°. This was followed by the addition of a solution of 900 cc. of sulfuric acid in 830 cc. of glacial acetic acid. The cooling bath was removed and 1000.0 g. (6.65 moles) of $\alpha,\alpha$-dimethylphenylethyl alcohol was added portion-wise, with stirring, during 10 min. The stirring was continued for 15 min. during which time the temperature gradually rose to 55°. The reaction mixture was heated to 75° and maintained at this temperature for 0.5 hr. Then it was allowed to stand at room temperature for 2 hr. Ten liters of water was added to the reaction mixture and neutralized with solid sodium bicarbonate. The solid product separated in the top layer. It was extracted with ether, dried and concentrated. The product was recrystallized from cyclohexane with activated carbon giving 1080.0 g. (92%) of white crystals, m.p. 63–64°.

*Anal.* Calcd. for $C_{11}H_{15}NO$: C, 74.58; H, 8.47; N, 7.91. Found: C, 74.96; H, 8.32; N, 7.84.

*2-Phenyl-t-butylamine* (III). The formamide (II) was hydrolyzed by heating with 2.7*N* hydrochloric acid for 1 hr. and the salt thus obtained was converted to the base by treating with dilute sodium hydroxide solution. The amine hydrochloride melted at 200–201° in agreement with Zenitz, Macks, and Moore[3] and the picrate at 109–110°.

*Ethyl ester of N-($\alpha,\alpha$-dimethyl-$\beta$-phenethyl)glycine* (IV). A solution of 196.0 g. (1.32 moles) of $\alpha,\alpha$-dimethyl-$\beta$-phenethylamine (III), 108.0 g. (0.64 mole) of ethylbromoacetate and 780 cc. of benzene was refluxed for 5 hr., cooled, and filtered. From the filtrate, the solvent was removed under reduced pressure. The crude product weighed 165.0 g. and was used as such without further purification.

*N-($\alpha,\alpha$-Dimethyl-$\beta$-phenethyl)glycine hydrochloride* (V). Ethyl ester of *N*-($\alpha,\alpha$-dimethyl-$\beta$-phenethyl)glycine, 84.6 g. (0.36 mole), and 63.0 g. of sodium hydroxide dissolved in 740 cc. of water were mixed and refluxed for 1 hr. The mixture was cooled, washed with ether, and the solid was removed by filtration. This was dissolved in a minimum amount of water, acidified with dilute hydrochloric acid (*p*H 2) and concentrated to one-half its volume. On cooling, the solid which precipitated out, was removed by filtration. It was recrystallized twice from absolute methanol giving 35.0 g. (40%) of white crystals, m.p. 214–215°.

*Anal.* Calcd. for $C_{12}H_{18}ClNO_2$: C, 59.38; H, 7.06; N, 5.77, Cl, 14.61. Found: C, 59.18; H, 7.27; N, 5.61; Cl, 14.80.

*N-Nitroso-N-($\alpha,\alpha$-dimethyl-$\beta$-phenethyl)glycine* (VI). *N*-($\alpha,\alpha$-Dimethyl-$\beta$-phenethyl)glycine hydrochloride, 30.0 g. (0.123 mole), was dissolved in 300 cc. of water, acidified to *p*H 2 with concentrated hydrochloric acid and cooled. With stirring, 17.0 g. (0.24 mole) of sodium nitrite dissolved in 50 cc. of water was added drop-wise during 0.5 hr. The stirring was continued for 1.5 hr. and the product was removed by filtration. It was recrystallized from methanol and water giving 28.0 g. (97%) of white crystals, m.p. 144–145°.

*N-2-Phenyl-t-butyl-sydnone* (VII). A mixture of 75.0 g. (0.32 mole) of *N*-nitroso-*N*-($\alpha,\alpha$-dimethyl-$\beta$-phenethyl)glycine and 327.0 g. of acetic anhydride was stirred, while heating on a steam bath, for 3 hr. It was filtered while hot and the filtrate was concentrated under reduced pressure. The solid

(5) Melting points were taken in Thomas-Hoover capillary melting point apparatus and are uncorrected. Analyses are by Clark Micoranalytical Laboratory, Urbana, Ill.

product was recrystallized from acetone giving 50.0 g. (71%) of white crystals, m.p. 108–110°.

*Anal.* Calcd. for $C_{12}H_{18}N_2O_2$: C, 66.05; H, 6.42; N, 12.84. Found: C, 66.67; H, 6.43; N, 12.78.

*1-Phenyl-2-methyl-2-hydrazinopropane hydrochloride* (VIII). Fifty grams (0.22 mole) of *N*-2-phenyl-*t*-butylsydnone was treated with 100 cc. of concd. hydrochloric acid and heated on a steam bath for 15 min. It was cooled on an ice bath and saturated with dry hydrogen chloride. The solid was removed by filtration and the process was repeated twice. The product was recrystallized from absolute methanol and ether giving 10.0 g. (22%) of white crystals—m.p. 139–141°.

*Anal.* Calcd. for $C_{10}H_{17}N_2Cl$: C, 59.85; H, 8.47; N, 13.96; Cl, 17.70. Found: C, 59.11; H, 8.49; N, 14.12; Cl, 17.62.

*N-(1-Phenyl-2-t-butyl)-N¹-isopropylhydrazine hydrochloride* (XI). 1-Phenyl-2-methyl-2-hydrazinopropane, 1.2 g. (0.007 mole), and 0.4 g. (0.006 mole) of acetone were mixed and allowed to stand at room temperature for 5 hr. The turbid solution was dissolved in ether, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residual oil was dissolved in 25 cc. of absolute ethanol and hydrogenated using platinum dioxide as the catalyst at 60 lbs. pressure. The hydrogenation was completed in 1 hr. It was filtered, cooled on an ice bath and saturated with dry hydrogen chloride. The solvent was removed *in vacuo* and the solid was recrystallized from absolute methanol and ether giving 0.5 g. (28%) of white crystals, m.p. 143–145°.

*Anal.* Calcd. for $C_{13}H_{13}N_2Cl$: C, 64.32; H, 9.48; N, 11.54; Cl, 14.63. Found: C, 64.61; H, 9.59; N, 11.50; Cl, 14.60.

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## Chemistry of Aryl Isocyanates. The Influence of Metal Carboxylates on the Aryl Isocyanate–Ethyl Carbanilate Reaction

I. C. KOGON

*Received October 5, 1960*

In previous work it was shown that, at elevated temperature, aryl isocyanates and substituted ethyl carbanilates react slowly,[1,2] to form an equilibrium mixture of the starting materials and ethyl $\alpha,\gamma$-diarylallophanate. It has now been found that metal carboxylates will catalyze this reaction at room temperature to give ethyl $\alpha,\gamma$-diarylallophanate, Table I, in good yield. The yield of product is dependent upon the metal carboxylate and, as the data in Table I show, lead and cobalt carboxylates are the best catalysts for this reaction.

The use of these metal derivatives was extended to substituted aryl isocyanates and carbanilates to form substituted diarylallophanates (I).

$$R{-}C_6H_4NHCN(C_6H_4R')COOR'' \quad (I)$$
$$\|$$
$$O$$

where
R = H, *o*-$CH_3$, *p*-Cl, *p*-$CH_3$
R′ = H, *p*-$CH_3$, *m*-$OCH_3$
R″ = $C_2H_5$, $C_6H_5$

The reaction does not proceed when ethyl carbanilate or phenyl isocyanate are replaced by ethyl carbamate or ethyl isocyanate respectively.

At room temperature the metal carboxylates except the zinc derivative slowly catalyze the formation of triphenyl isocyanurate from phenyl isocyanate. Lead and cobalt derivatives are the most active catalysts. To verify that trimerization of phenyl isocyanate is considerably slower than allophanate formation when lead or cobalt carboxylates are used as catalysts, equimolar quantities of phenyl isocyanate and ethyl carbanilate were reacted at room temperature in the presence of a small quantity of cobalt 2-ethylhexanoate. A 95.5% yield of ethyl $\alpha,\gamma$-diphenylallophanate and 0.84% of triphenyl isocyanurate was obtained.

### EXPERIMENTAL[3]

*Preparation of ethyl α,γ-diphenylallophanate.* To a solution consisting of 11.9 g. (0.1 mole) of phenyl isocyanate and 16.5 g. (0.1 mole) of ethyl carbanilate was added 0.15 g. of cobalt 2-ethylhexanoate in mineral spirits. After 6 hr. the purple reaction mixture solidified. To the solid was added 100 ml. of hot petroleum ether (b.p. 30–60°) and the solution filtered rapidly. A white crystalline product weighing 0.1 g. (0.84%) and melting at 277–278° was obtained. A mixture melting point with an authentic sample of triphenyl isocyanurate, m.p. 278°, gave no depression. The filtrate was then evaporated to dryness and the residue recrystallized from ethyl alcohol. There was obtained a white crystalline solid weighing 27.1 g. (95.5%), m.p. 92–94°. A mixture melting point with an authentic sample of ethyl $\alpha,\gamma$-diphenylallophanate, m.p. 94° gave no depression, m.p. 92–94° The following compounds were prepared in a similar manner using cobalt 2-ethylhexanoate in mineral spirits.

*Ethyl-α,o-methoxyphenyl-γ-phenylallophanate*, yield (51%), m.p. 95°. The infrared spectrum exhibited a twin carbonyl band at 5.92 and 5.94 μ.

*Anal.* Calcd. for $C_{17}H_{18}N_2O_4$: N, 8.6. Found: 8.9.

*Ethyl-α,p-chlorophenyl-γ,p-tolylallophanate*, yield (66%), m.p. 96°. The infrared spectrum exhibited a twin carbonyl band at 5.82 and 5.95 μ.

*Anal.* Calcd. for $C_{17}H_{17}N_2O_3Cl$: N, 8.4 Found: 8.5.

(1) I. C. Kogon, *J. Am. Chem. Soc.*, 78, 4911 (1956).
(2) I. C. Kogon, *J. Org. Chem.*, 24, 83 (1959).

(3) All melting points were determined in a Fischer-Herschberg apparatus and are uncorrected.