[CONTRIBUTION FROM THE INSECTICIDE DIVISION, BUREAU OF CHEMISTRY AND SOILS]

THE PREPARATION OF SOME PYRROLIDINE DERIVATIVES[1,2]

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It is rather surprising that among the many synthetic and natural organic compounds which have been tested as contact insecticides, so few have been found to possess outstanding toxic action.

In the present state of our knowledge it would seem that of the natural products, the pyrethrins, rotenon (from derris) and nicotine are in a class by themselves. Whatever insecticidal action may be possessed by any other compound, either natural or synthetic, is in every case of a distinctly lower order, and it is not possible to arrange a list of compounds of progressively higher toxicity up to that of the order of the three mentioned. However, further study may yield results which will invalidate this generalization.

Owing to the work of Staudinger and Ruzicka[3] the chemical nature of the pyrethrins is well understood. They are both complicated esters containing a number of unsaturated bonds and asymmetric carbon atoms. As far as is known, even the slightest change in the complicated chemical structure of either lowers its specific action to a marked degree and generally destroys it altogether.

From what is known of tubotoxin, it seems probable that the same will hold true for that compound.

The investigations reported in this paper were undertaken to determine, if possible, whether the toxicity of nicotine is specific for the whole molecule or whether this effect is owing to some special grouping of its component parts.

From the formula for nicotine, which is β-pyridyl-α-N-methylpyrrolidine, it might be reasonable to assume that either the pyridine or the pyrrolidine group were responsible for its insecticidal property. Accordingly, a number of new substituted pyrrolidines were prepared and tested, besides a number of known ones, but none were found to possess toxicity approaching that of nicotine.

Substitution of the methyl or phenyl group in the α-position of the pyrrolidine molecule leads to comparatively inert compounds which do not show increased toxicity if they are in addition methylated on the

[1] A study of the insecticidal action of these compounds is being made in coöperation with Dr. C. H. Richardson, Deciduous Fruit Insect Investigations, Bureau of Entomology.

[2] Presented at the Insecticide Symposium, St. Louis meeting of the American Chemical Society, April, 1928.

[3] Staudinger and Ruzicka, *Helv. Chim. Acta*, **7**, 177–259, 377–458 (1924).

nitrogen. For instance, α-methyl, α,α-dimethyl[4] and α-phenylpyrrolidine, and their N-methyl derivatives were only slightly toxic.

The preparation of α-phenyl-N-methylpyrrolidine presented unusual difficulties. The action of methylamine on 1-phenyl-1,4-dibromobutane, $C_6H_5CHBr(CH_2)_2CH_2Br$, resulted in an unsaturated compound instead of the expected phenylmethylpyrrolidine. Although it was possible to prepare α-phenylpyrroline, attempts to reduce it were unsuccessful, nor was it possible to close the side chain of 1-phenyl-1-N-methylaminobutane by the method of Löffler.[5]

The compound was finally prepared from β-*p*-cresoxy-ethylbenzoylacetic ester by the following steps.

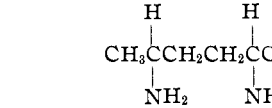
$$CH_3C_6H_4OCH_2CH_2CH(COC_6H_5)COOC_2H_5 \longrightarrow CH_3C_6H_4OCH_2CH_2CH_2COC_6H_5 \longrightarrow$$
$$CH_3C_6H_4O(CH_2)_3CNOHC_6H_5 \longrightarrow CH_3C_6H_4O(CH_2)_3CHNH_2C_6H_5 + HCl \longrightarrow$$
$$CH_3C_6H_4OH + Cl(CH_2)_3CHNH_2C_6H_5 \longrightarrow CH_2CH_2CH_2CHC_6H_5 + CH_3I \longrightarrow$$
$$\text{(NH bridge)}$$
$$CH_2CH_2CH_2CHC_6H_5$$
$$\text{(NCH}_3\text{ bridge)}$$

α-Methylpyrrolidine.—This derivative has been prepared and studied by Fenner and Tafel,[6] but it may be more conveniently obtained by the general method of Gabriel.[7]

β-*p*-Cresoxy-ethylacetoacetic Ester.—Fifty grams of acetoacetic ester (twice the theoretical quantity) was added to a solution of 4.5 g. of sodium in 75 cc. of alcohol, followed by 41 g. of β-*p*-cresoxy-ethyl bromide.[8] The solution was allowed to stand several hours and then was boiled for five hours under reflux. The alcohol was evaporated, the residue suspended in water and the insoluble oil extracted with ether. The ether solution, which was dried with calcium chloride, yielded about 70 g. of oil on evaporation.

The oil was distilled in a vacuum of 16 mm. The fraction boiling up to 130° con-

[4] The reduction of acetonylacetonedioxime prepared by the method of Paal (*Ber.*, **18**, 59 (1885)) under the same conditions as those used by Tafel in the case of the corresponding hydrazone (*Ber.*, **22**, 1860 (1889)), results in a mixture of dimethylpyrrolidine and 2,5-diaminopentane. The last compound shows no tendency to form the ring structure and can only be transformed into dimethylpyrrolidine by dry distillation of the hydrochloride. Since two dimethylpyrrolidines should exist according to theory, it would appear that the one represented by the space formula



might easily lose ammonia to form dimethylpyrrolidine, whereas if the position of one amino group were reversed, this reaction might not take place except under drastic conditions and would then result in an isomeric compound. A whole series of isomeric substituted pyrrolidines is possible with increase in the number of methyl groups, up to six optical pairs of tetramethylpyrrolidines, analogous to the hexitols in the sugar group.

[5] Löffler and Flügel, *Ber.*, **42**, 3431 (1909).

[6] Fenner and Tafel, *Ber.*, **31**, 909 (1898).

[7] Gabriel, *Ber.*, **24**, 3234 (1891).

[8] Weddige, *J. prakt. Chem.*, **24**, 242 (1881).

sisted mostly of acetoacetic ester. About 10 g. of a fraction boiling at 130–196° was obtained. The fraction boiling at 196–206° consisted of β-*p*-cresoxy-ethylacetoacetic ester. It was refractionated and yielded 25 g. of a product boiling at 202–204° (uncorr.).

Anal. Subs., 0.1874: CO_2, 0.4634; H_2O, 0.1212. Calcd. for $C_{15}H_{20}O_4$: C, 68.77; H, 7.43. Found: 67.43, 7.19.

γ-*p*-Cresoxypropylmethyl Ketone, $CH_3C_6H_4O(CH_2)_3COCH_3$.—Twelve grams of β-*p*-cresoxy-ethylacetoacetic ester was heated on the steam-bath with 2 g. of sodium hydroxide in 75 cc. of alcohol. Sodium bicarbonate separated out during the heating. The solution was diluted with water, acidified with acetic acid and the alcohol evaporated off. The separated oil was taken up in ether and the ether residue was distilled at 16 mm., yielding 6 g. of a fraction boiling at 163–180°. Several similar fractions were combined and the fraction boiling at 175–175° was collected. This material crystallized on standing and was freed from adhering oil by pressing between filter paper. It was easily soluble in all organic solvents and was analyzed without further purification.

Anal. Subs., 0.1560: CO_2, 0.4314; H_2O, 0.1163. Calcd. for $C_{12}H_{16}O_2$: C, 75.00; H, 8.33. Found: C, 75.42; H, 8.28.

The semicarbazone of the ketone prepared in the usual manner crystallized from alcohol in needles melting at 158°.

γ-*p*-Cresoxybutyric Acid.—The combined alkaline solutions from the saponification of 100 g. of β-*p*-cresoxy-ethylacetoacetic ester yielded 10 g. of γ-*p*-cresoxybutyric acid on acidification. It was recrystallized from 40% alcohol and melted at 84–85°.

Anal. Subs., 0.1630: CO_2, 0.4087; H_2O, 0.1035. Calcd. for $C_{11}H_{14}O_3$: C, 68.04; H, 7.21. Found: C, 68.37; H, 7.05.

γ-*p*-Cresoxypropylmethyl Ketoxime.—The oxime was obtained in good yield by warming 8 g. of the ketone dissolved in 75 cc. of an alcoholic solution of hydroxylamine prepared from 3 g. of the hydrochloride. After evaporation of the solvent, the residue crystallized to a solid cake. It was dissolved in ether, the solution was washed with water and dried with potassium carbonate and the solvent removed. The oxime may be recrystallized from petroleum ether or dilute alcohol and when pure melts at 54°.

Anal. Subs., 0.1647: CO_2, 0.4214; H_2O, 0.1214. Calcd. for $C_{12}H_{17}NO_2$: C, 69.57; H, 8.21. Found: C, 69.78; H, 8.18.

1-*p*-Cresoxy-4-amino-*n*-pentane, $CH_3C_6H_4O(CH_2)_3CHNH_2CH_3$.—Twenty-three grams of the oxime was dissolved in 300 cc. of 95% alcohol and reduced with 1000 g. of 2.5% sodium amalgam added in four portions of 250 g. each, followed by 25 cc. of glacial acetic acid over a period of four hours. The separated sodium acetate was filtered off and the solution diluted with 800 cc. of water and placed in a freezing mixture. About 14 g. of unchanged oxime was recovered by this treatment and was reduced again with sodium amalgam. The combined filtrates were concentrated to 150 cc. and extracted with ether. The ethereal solution yielded a small quantity of oxime. The aqueous solution was treated with sodium hydroxide, the separated oil taken up in ether and the ethereal solution dried with solid potassium hydroxide. About 10 g. of pure amine was obtained, boiling at 280–283° (uncorr.) at 760 mm.

Anal. Subs., 0.1570: CO_2, 0.4265; H_2O, 0.1355. Calcd. for $C_{12}H_{19}NO$: C, 74.61; H, 9.84. Found: C, 74.09; H, 9.59.

The amine combines with carbon dioxide from the air, forming a solid crystalline carbonate. The hydrochloride is also crystalline but somewhat hygroscopic.

α-Methylpyrrolidine.—Twenty grams of the hydrochloride was sealed in a glass tube with 70 cc. of aqueous hydrochloric acid, saturated at 0° and heated for fifteen hours at 100°. The contents of the tube presented two layers, the lighter one being *p*-cresol

which was removed by extraction with ether from the aqueous solution of the hydrochloride of 1-chloro-4-aminopentane. On evaporation the compound was left as a thick sirup.

The product was dissolved in a small quantity of water and the solution made strongly alkaline. On the addition of solid potassium hydroxide, the methylpyrrolidine separated as an oily layer, which was separated and further dehydrated with potassium hydroxide. The product distilled between 94 and 97°, which agrees fairly well with the figure given by Fenner and Tafel.[8] The yield was 8 g.

Anal. Subs., 0.1300: CO_2, 0.3340; H_2O, 0.1555. Calcd. for $C_5H_{11}N$: C, 70.58; H, 12.94. Found: C, 70.07; H, 13.29.

1-Phenyl-1-bromobutane and 1-Phenyl-1-methylaminobutane.—Twenty grams of phenylpropylcarbinol prepared by the method of Klages[9] was saturated with hydrobromic acid gas at 0°. In a few minutes the liquid became turbid and after standing overnight had separated into two layers. The oily layer was taken up in ether, and the excess hydrobromic acid was removed by washing with water. The ethereal solution was dried with calcium chloride and yielded 32 g. of residue. It was not analyzed. The bromo compound was dissolved in 50 cc. of methyl alcohol and poured into 160 cc. of a 25% methyl alcoholic solution of methylamine. After standing overnight, the solution was evaporated, leaving a mixture of oil and crystalline methylamine hydrobromide. It was dissolved in dilute hydrochloric acid and the solution was extracted with ether. The aqueous solution was made alkaline, and the separated oil was extracted with ether and dried with potassium carbonate. On evaporation it yielded 20 g. of oily residue, which boiled at 117–118° at 33 mm. (220° at 765 mm.).

Anal. Subs., 0.1378: CO_2, 0.4097; H_2O, 0.1258. Calcd. for $C_{11}H_{17}N$: C, 80.98; H, 10.43. Found: C, 81.22; H, 10.14.

The amine is insoluble in water, and it is probably owing to this property that efforts to close the side chain to the pyrrolidine ring by brominating on the nitrogen and eliminating the hydrobromic acid in accordance with the method of Löffler were unsuccessful.

A second attempt was made to prepare α-phenyl-N-methylpyrrolidine through the following steps

$$C_6H_5CHOHCH_2CH{=}CH_2 + 2HBr \longrightarrow C_6H_5CHBr(CH_2)_2CH_2Br + NH_2CH_3 \longrightarrow C_6H_5\underbrace{CH(CH_2)_2CH_2N}CH_3$$

It resulted, however, in an isomeric, open-chain unsaturated compound.

1-Phenyl-1,4-dibromobutane.—Twenty grams of allylphenylcarbinol[10] was saturated in direct sunlight in a quartz flask with hydrobromic acid gas. In two hours the reaction was complete and no more gas was absorbed. The product was taken up in ether, washed with ice water and the solution dried with calcium chloride. The residue weighed 36.5 g., which is close to the theoretical yield. The product could not be distilled. Thirty-two grams of the crude product was added in small portions to 200 cc. of a 25% methyl alcoholic solution of methylamine.

After standing overnight, the solvent and excess amine were removed by evaporation and the residue was dissolved in dilute hydrochloric acid and extracted with ether. The aqueous solution yielded an oily product, which was taken up in ether, and the solution was dried with solid potassium hydroxide. The ether residue consisted of 17 g. of oil, which when twice distilled at 770 mm. yielded 10 g. of product, boiling at 209–216°.

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[9] Klages, *Ber.*, **37**, 2312 (1904).

[10] Klemenko, *J. Russ. Phys.-Chem. Soc.*, **43**, 212 (1911).

The analysis agrees for $C_{11}H_{15}N$, but its reactions indicate that it is unsaturated, and its properties do not agree with those of α-phenyl-N-methylpyrrolidine, which was finally prepared by another procedure.

Anal. Subs., 0.1202: CO_2, 0.3595; H_2O, 0.0980. Calcd. for $C_{11}H_{15}N$: C, 81.99; H, 9.31. Found: C, 81.56; H, 9.05.

The compound should be represented by one of the three formulas $C_6H_5CH{=}CH{-}CH_2CH_2NHCH_3$, $C_6H_5CHNCH_3CH_2CH{=}CH_2$ or $C_6H_5CH{=}CHCH(NHCH_3)CH_3$.

Benzoyltrimethylene.—This compound was prepared from benzoylacetic ester[11] and ethylene bromide according to the method of Perkin[12] slightly modified. The method consists in heating the ester in alcoholic solution under pressure with half the theoretical quantities of ethylene bromide and sodium ethylate. The only change made was to repeat this treatment with one-half the original quantities of bromide and sodium ethylate, which resulted in a better yield. Benzoyltrimethylene bromide was prepared according to the Perkin directions.[12]

α-Phenyl-N-methylpyrroline.—Seventeen grams of benzoyltrimethylene bromide was added to about 75 cc. of 25% methyl alcoholic methylamine. After evaporation of the solvent, the oily residue was extracted with dilute hydrochloric acid. The insoluble portion was extracted with ether and the solution dried and evaporated, yielding about 8 g. of product, boiling at 136–139° at 34 mm. and at 239–246° at 760 mm. It contained no nitrogen. The analysis and boiling point indicate that it was regenerated benzoyltrimethylene.

Anal. Subs., 0.1735: CO_2, 0.5201; H_2O, 0.1105. Calcd. for $C_{10}H_{10}O$: C, 82.19; H, 6.85. Found: C, 81.84; H, 7.09.

Perkin[12] refers to the action of silver nitrate and sodium ethylate on benzoyltrimethylene bromide and states that the resulting compound is probably 3-benzoyl-*n*-propyl alcohol. He did not analyze his product, but we have found that any base will regenerate the benzoyltrimethylene from the bromide. The acid solution referred to above was treated with sodium hydroxide, the separated oil was taken up in ether and the solution was dried with potassium carbonate and evaporated. The residue boiled at 134–139° at 34 mm. The analysis agreed for phenylmethylpyrroline.

Anal. Subs., 0.1427: CO_2, 0.4327; H_2O, 0.1021. Calcd. for $C_{11}H_{13}N$: C, 83.01; H, 8.17. Found: C, 82.69; H, 7.96.

The compound could not be made to absorb hydrogen in the presence of a platinum catalyst nor were any other attempts to reduce it successful.

β-*p*-Cresoxyethylbenzoylacetic Ester, $CH_3C_6H_4OCH_2CH_2CH(COC_6H_5)COOC_2H_5$.—One hundred and seven grams of benzoylacetic ester and 60 g. of *p*-cresoxy-ethylene bromide (one-half of the equivalent quantity) were dissolved in an absolute alcoholic solution of sodium ethylate prepared from 150 cc. of absolute alcohol and 6.4 g. of sodium. After boiling for six hours under reflux, the solvent was removed, water added and the reaction products were dissolved in ether. The ethereal solution was washed with water and dried with calcium chloride, yielding 145 g. of oily product on evaporation. It was subjected to fractional distillation in vacuum. The fraction boiling below 260° (8 mm.) was discarded. About 40 g. of product distilling at 240–250° consisted of impure *p*-cresoxyethylenebenzoylacetic ester. There was some decomposition during distillation and the compound could not be prepared absolutely pure. It was again distilled for analysis.

Anal. Subs., 0.1575: CO_2, 0.4353; H_2O, 0.0823. Calcd. for $C_{20}H_{22}O_4$: C, 73.62; H, 6.75. Found: C, 74.73; H, 5.80.

[11] Claisen, *Ann.*, **291**, 70 (1896).

[12] Perkin, *J. Chem. Soc.*, **47**, 836 (1885).

γ-*p*-Cresoxypropylphenyl Ketone, $CH_3C_6H_4O(CH_2)_3OCC_6H_5$.—The ketone cleavage of the ester was carried out by heating with slightly more than the calculated quantity of alcoholic potassium hydroxide for four hours on the steam-bath. The product remaining after evaporation of the solvent was an oil, which was dissolved in ether, and the solution was dried and evaporated. The product was fractionated at 8 mm. The major portion boiled at 250–260° with slight decomposition. The distillate crystallized at once and, after removal of adhering oil by pressing between filter paper, it was recrystallized from about 5 parts of 95% alcohol. It crystallizes in large prisms which melt at 63°. The yield was from 40 to 50% of the weight of the ester employed.

In subsequent operations the ester was not distilled, the fractions boiling below 200° at 32 mm. being removed and the crude ester saponified. The ketone may also be obtained from the crude ester by saponification and distilling off the products boiling under 200° and allowing the undistilled material to crystallize. Analysis of the pure ketone gave the following results.

Anal. Subs., 0.2021: CO_2, 0.5965; H_2O, 0.1269. Calcd. for $C_{17}H_{18}O_2$: C, 80.31; H, 7.08. Found: C, 80.49; H, 6.97.

γ-*p*-Cresoxypropylphenyl Ketoxime.—Five grams of ketone was dissolved in an alcoholic solution of hydroxylamine prepared from 1.5 g. of hydroxylamine hydrochloride and 0.5 g. of sodium. After the solution was heated for one hour on the steam-bath, the solvent was removed, leaving a sirupy product which crystallized to a solid cake. It crystallized from petroleum ether in long prisms, melting at 75°. The yield was quantitative.

Anal. Subs., 0.1617: CO_2, 0.4462; H_2O, 0.1012. Calcd. for $C_{17}H_{19}NO_2$: C, 75.47; H, 7.06. Found: C, 75.27; H, 6.88.

1-*p*-Cresoxy-4-amino-4-phenylbutane Hydrochloride, $CH_3C_6H_4O(CH_2)_3CH(NH_2\cdot HCl)C_6H_5$.—Twenty-five grams of oxime was dissolved in 500 cc. of 95% alcohol and reduced with 1800 g. of 2.5% sodium amalgam which was added in portions of about 250 g. each, followed by the addition of 25 cc. of glacial acetic acid over a period of three hours. The temperature was kept below 40° during the reaction.

The sodium acetate was filtered off and washed with alcohol, and the alcoholic solutions were concentrated on the steam-bath to 150 cc. An oily substance, probably the acetate of the amine, separated out and was extracted with ether.

On being shaken with 75 cc. of 15% hydrochloric acid, the ether solution became filled with a mass of white crystals of the hydrochloride of the base. The aqueous solution was made alkaline with sodium hydroxide and extracted with ether. The ether was evaporated, leaving an oil which also crystallized when treated with dilute hydrochloric acid. The combined yield was 20 g. of the hydrochloride. It was crystallized from hot water, from which it separated in long needles. The nitrate is also difficultly soluble in water and crystallizes in plates.

Anal. Subs., 0.1616: CO_2, 0.4145; H_2O, 0.1100. Subs., 0.1215: AgCl, 0.0595. Calcd. for $C_{17}H_{22}NOCl$: C, 70.22; H, 7.57; Cl, 11.87. Found: C, 69.95; H, 7.56; Cl, 11.68.

1-Phenyl-1-amino-4-chlorobutane Hydrochloride.—Twenty-two grams of *p*-cresoxy-aminophenylbutane hydrochloride was heated in a sealed tube with 150 cc. of aqueous hydrochloric acid saturated at 0° for twenty hours. The separated cresol was removed with ether and the aqueous solution concentrated on the steam-bath. The compound crystallized on evaporation. A part was recrystallized for analysis from about 5 parts of hot water. It melted with decomposition at 200–205°. The yield was 13 g.

Anal. Subs., 0.1340: AgCl, 0.1749. Calcd. for $C_{10}H_{15}NCl_2$: Cl, 31.65. Found: 31.06.

α-Phenylpyrrolidine.—Twelve grams of phenylaminochlorobutane hydrochloride was dissolved in water and a strong solution of potassium hydroxide added. The oil which separated reacted suddenly with evolution of heat to form α-phenylpyrrolidine. The product was extracted with ether and the solution dried with solid potassium hydroxide. The ether residue boiled at 236–238° (uncorr.) at 757 mm. The yield was 8 g.

Anal. Subs., 0.1400: CO_2, 0.4155; H, 0.1154. Calcd. for $C_{10}H_{13}N$: C, 81.63; H, 8.84. Found: C, 80.94; H, 9.15.

α-Phenyl-N-methylpyrrolidine.—Four grams of α-phenylpyrrolidine was dissolved in 25 cc. of methyl alcohol containing 4 g. of methyl iodide. After twelve hours the solvent was evaporated and the residue treated with strong potassium hydroxide solution. Most of the oil was soluble in ether but a part remained undissolved. The ethereal solution was dried with solid potassium hydroxide and the ether evaporated, leaving 2.6 g. of base, which distilled at 760 mm. at 225–227° (uncorr.). The yield of pure product was 2.2 g.

Anal. Subs., 0.1460: CO_2, 0.4374; H_2O, 0.1161. Subs., 0.1560: N, 11.2 cc. at 29° and 762 mm. Calcd. for $C_{11}H_{15}N$: C, 81.99; H, 9.31; N, 8.69. Found: C, 81.71; H, 8.83; N, 8.23.

Summary

A number of pyrrolidine derivatives have been prepared with reference to their chemical relation to nicotine and tested as contact insecticides.

Methods are described for the preparation of α-methyl- and α-phenylpyrrolidine and α-phenylpyrroline and their N-methyl derivatives. The various intermediary compounds and the results of several unsuccessful attempts to prepare substituted pyrrolidines are described in the experimental part.

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[CONTRIBUTION FROM THE INSECTICIDE DIVISION, BUREAU OF CHEMISTRY AND SOILS]

THE PREPARATION AND PROPERTIES OF SOME NEW DERIVATIVES OF PYRIDINE[1,2]

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In a previous article it was pointed out that whereas nicotine, which is β-pyridyl-α-N-methylpyrrolidine, stands out as one of the few known organic compounds possessing insecticidal properties of a very high order, none of the several other substituted pyrrolidines which have been tested approach it in toxicity.

It is natural to inquire whether or not the pyrrolidine group is essential to the specific toxic effect of nicotine on insects and whether or not some

[1] A study of the insecticidal action of these compounds is being made in coöperation with Dr. C. H. Richardson, Deciduous Fruit Insect Investigations, Bureau of Entomology.

[2] Presented at the Insecticide Symposium, St. Louis meeting of the American Chemical Society, April, 1928.