Amino Alcohols. XVII.* Arylethanolamines†

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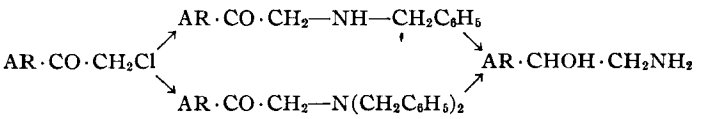
Aracyl chlorides, $Ar \cdot CO \cdot CH_2Cl$, were allowed to react with benzylamine or dibenzylamine to form aracylamines. These were then subjected to hydrogenolytic debenzylation, yielding primary aracylamines, $Ar—CO—CH_2—NH_2$; continued catalytic reduction, without previous isolation of the amino ketone, formed the corresponding arylethanolamines.

ARYLPROPANOLAMINES and arylethanolamines possess the optimum structure necessary for the production of pressor activity (1). The changes in pharmacodynamic activity produced in phenylpropanolamine by the introduction of various substituents into the phenyl nucleus have been extensively studied. In order to determine with greater certainty whether these modifications may be ascribed solely to the substituent under investigation, the effect of its presence in phenylethanolamine should also be investigated.

Many of the arylpropanolamines, $AR \cdot CHOH \cdot CH(CH_3) \cdot NH_2$, were prepared by the straightforward catalytic hydrogenation of the readily available oximinoketones of structure, $AR \cdot CO \cdot C(CH_3):NOH$ (2). Oximinoketones of structure, $AR \cdot CO \cdot CH:NOH$, may be converted with almost equal facility into the corresponding arylethanolamines, $AR \cdot CHOH \cdot CH_2NH_2$ (2, 3) but regrettably these desirable intermediates cannot be obtained by the methods so useful for the preparation of the higher homologs. Arylglyoxolohydroxamyl chlorides, $AR \cdot CO \cdot C:NOH$ (with Cl), are available (4), but as yet the problem of their consistent reduction to the desired amino alcohols is still unsolved.

In continuing the quest for a satisfactory procedure by which the arylethanolamines may be synthesized, the catalytic hydrogenolysis of benzylamines (5, 6) was studied. Aracyl halides, $AR \cdot CO \cdot CH_2X$, were condensed with benzylamine or dibenzylamine; the benzyl groups were removed catalytically, and the carbonyl group was reduced to the carbinol in the same reaction.

This method promises to be useful wherever it is possible to prepare the necessary aracyl halide.



EXPERIMENTAL

Preparation of Aracyl Chlorides

Phenacyl chloride was prepared by the Friedel-Crafts reaction, in a yield of 75%, by the action of chloroacetyl chloride on benzene.

p-Hydroxyphenacyl chloride was prepared by a Friedel-Crafts reaction on anisole according to the following method (3):

In a 2-liter, three-neck, round-bottom flask fitted with a reflux condenser connected to a HCl absorption trap, a sealed mechanical stirrer, and a small powder funnel were placed 60.5 cc. (0.55 mole) anisole, 48.2 cc. (0.63 mole) chloroacetyl chloride, and 1000 cc. ligroin (E.K. Co., practical). The reaction flask was immersed in a bath of water (40–45°) and during the course of forty-five minutes, 90.0 Gm. (0.675 mole) anhydrous aluminum chloride was added to the rapidly stirred mixture. After all of the $AlCl_3$ had been added, the mixture was heated in the water bath for an hour; stirring of the reactants and removal of the HCl being continued. The temperature of the bath was then raised to 50–55° and during the course of an hour a second portion of 90.0 Gm. anhydrous aluminum chloride was added. Then the bath was heated to boiling and the solvent recovered under reduced pressure (waterpump) during the course of one and one-half to two hours, the condenser remaining in the reflux position. When practically all of the ligroin had been removed, the reaction mixture was allowed to stand at room temperature for one hour and the aluminum complex decomposed by the addition of crushed ice followed by 500 cc. concentrated hydrochloric acid, during which, vigorous stirring of the reaction mix-

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ture was maintained. The dark purple, tarry mixture thus obtained was allowed to stand overnight and then extracted with six 300-cc. portions of ether. The ethereal extracts were combined, washed with 200 cc. of cold water, 250 cc. of a 5% solution of $(NH_4)_2CO_3$ and then with six portions (400 cc. each) of a 10% Na_2CO_3 solution to remove the *p*-hydroxyphenacyl chloride. The alkaline extracts were then treated individually with excess concentrated hydrochloric acid to precipitate the crude product. The precipitated product thus obtained was allowed to stand overnight in the refrigerator; it was then filtered off and dried with suction. Recrystallization from 80% ethanol with the addition of 3.0 Gm. of charcoal yielded 30.0 Gm. (31.6%) of *p*-hydroxyphenacyl chloride; m. p. 147–148° (dec.).

3,4-Dihydroxyphenacyl chloride was prepared according to the method of Levin (4).

Condensation of Aracyl Chlorides with Amines

ω-Benzylaminoacetophenone Hydrochloride.—In a 250-cc., glass-stoppered Erlenmeyer flask was placed 21.4 Gm. (0.2 mole) of benzylamine in 150 cc. of dry ether; then 15.0 Gm. (0.1 mole) of phenacyl chloride was added in small portions with shaking. After standing overnight the precipitated benzylamine hydrochloride was filtered off and washed with 25 cc. of dry ether. Absolute ethanolic hydrogen chloride was added to the filtrate to precipitate the amino ketone hydrochloride. The resulting precipitate was recrystallized from absolute ethanol and ether and 19.0 Gm. (72.75%) of white crystals, m. p. 215–219° (red effervescent melt), were obtained; this agreed with the reported melting point for ω-benzylaminoacetophenone hydrochloride (7).

ω-Dibenzylamino-*p*-hydroxyacetophenone Hydrochloride.—In a 500-cc., three-neck, round-bottom flask provided with a sealed mechanical stirrer, a reflux condenser, and a dropping funnel was placed 6.0 Gm. (0.04 mole) of *p*-hydroxyphenacyl chloride in 75 cc. of absolute ethanol. The stirrer was set in motion and the mixture warmed on a water bath until the *p*-hydroxyphenacyl chloride dissolved with the formation of a light tan color. Then 16.0 Gm. (0.08 mole) of dibenzylamine was added through the dropping funnel in 0.5-cc. portions. After the first addition of dibenzylamine the color changed to dark red and the mixture warmed up moderately, but not enough to cause the ethanol to reflux. The reaction mixture was then refluxed on a water bath for four hours, after which the mixture was allowed to stand overnight. The precipitated dibenzylamine hydrochloride was filtered off and the ethanol was completely removed under reduced pressure. The residue was taken up in 150 cc. of warm ether and the ethereal solution was washed with water to remove any trace of dibenzylamine hydrochloride. The ether was removed and an uncrystallizable oil was obtained; the oil was taken up in hot chloroform and filtered through a filter paper wet with chloroform to remove the water present. The chloroformic solution was cooled and absolute ethanolic hydrogen chloride added to precipitate the amino ketone hydrochloride. The resulting precipitate was recrystallized from absolute ethanol and ether and 11.5 Gm. (77.25%) of white crystals, m. p. 239–241° (dec.), were obtained.

Anal.—Calcd. for $C_{22}H_{22}O_2NCl$: N, 3.82%. Found (Kjeldahl): N, 3.79%; 3.81%.

ω-Dibenzylamino-3,4-dihydroxyacetophenone Hydrochloride.—In a 500-cc., three-neck, round-bottom flask provided with a sealed mechanical stirrer, a reflux condenser, and a dropping funnel was placed 18.6 Gm. (0.1 mole) of 3,4-dihydroxyphenacyl chloride in 100 cc. of absolute ethanol. The stirrer was set in motion and the mixture warmed on a water bath until the ketone had dissolved with the formation of a light purple color. Then 39.4 Gm. (0.2 mole) of dibenzylamine was added through the dropping funnel in 0.5-cc. portions. After the first addition of dibenzylamine the color changed to dark brown and the mixture warmed up moderately, but not enough to cause the ethanol to reflux. The reaction mixture was then refluxed on the water bath for six hours, after which the mixture was allowed to stand overnight. The precipitated dibenzylamine hydrochloride was filtered off and the ethanol was removed under reduced pressure. The residue was taken up in 200 cc. of warm ether and the ethereal solution was washed with water to remove any trace of dibenzylamine hydrochloride. The ether was removed and the crude product recrystallized from dilute ethanol. Thirty-two grams (92.25%) of white crystals, m. p. 165° (dec.), were obtained.

Anal.—Calcd. for $C_{22}H_{21}O_3N$: N, 4.03%. Found (Kjeldahl): N, 3.92%; 3.94%.

The free base was dissolved in absolute ethanol and absolute ethanolic hydrogen chloride was added to precipitate the ω-dibenzylamino-3,4-dihydroxyacetophenone hydrochloride, m. p. 203–205° (dec).

Attempts to prepare the monobenzylamino derivative were unsuccessful. Dakin (8) ascribed the failure of benzylamine and 3,4-dihydroxyphenacyl chloride to react as expected to the presence of the phenolic hydroxyl groups.

Catalytic Reduction of Benzylamino Ketones

Preparation of Catalyst.—The palladium-charcoal catalyst was prepared in sodium acetate solution by a modification of the general procedure employed in these Laboratories (9, 10).

ω-Aminoacetophenone Hydrochloride and Phenylethanolamine Hydrochloride.—The hydrogenation of ω-benzylaminoacetophenone hydrochloride in absolute ethanol stopped when the N-benzyl group was removed. When water was employed as a solvent, the benzyl group was removed and the carbonyl group was reduced to the secondary alcohol. These results are in harmony with previous observations that amino ketones are more easily reduced to amino alcohols in aqueous solution (11),

and would seem to indicate that hydrogenolysis of N-benzyl groups proceed more easily than reduction of the carbonyl group.

To 6.53 Gm. (0.025 mole) of ω-benzylaminoacetophenone hydrochloride, dissolved in 100 cc. of absolute ethanol, was added 3.0 Gm. of catalyst. The reduction mixture was shaken at room temperature under 100 lb. pressure for three hours when one mole of hydrogen had been absorbed. The catalyst was filtered off and the ethanol removed under reduced pressure. On recrystallization of the crude product from absolute ethanol and ether 3.75 Gm. (88.2%) of white crystals, m. p. 182° (dec.), were obtained. The product reduced Fehlings solution and formed an N-benzoyl derivative, m. p. 123–124° (12), thus indicating the product obtained was ω-aminoacetophenone hydrochloride.

These reduction conditions were repeated, except that distilled water was used instead of absolute ethanol. After one hour 2 moles of hydrogen had been absorbed. The product, isolated as described above, was recrystallized from absolute ethanol and ether, weighed 3.8 Gm., representing a yield of 87.7%, m. p. 211–212°; it formed an N-benzoyl derivative m. p. 145–146° (13), thus confirming the formation of phenylethanolamine hydrochloride.

p-Hydroxyphenylethanolamine Hydrochloride.—To 4.6 Gm. (0.0125 mole) of ω-dibenzylamino-*p*-hydroxyacetophenone hydrochloride, dissolved in 100 cc. of 95% ethanol, was added 3.0 Gm. of catalyst. The reduction mixture was shaken at room temperature under 150 lb. pressure for one hour when 3 moles of hydrogen had been absorbed. The catalyst was filtered off and the ethanol removed under reduced pressure. On recrystallization of the crude product from absolute ethanol and ether, 2.0 Gm. (85.8%) of greyish white crystals, decomposing at 168–170° in an effervescent melt, were obtained. The product formed a dibenzoyl derivative, m. p. 210° (14).

ω-Amino-3,4-dihydroxyacetophenone and 3,4-Dihydroxyphenylethanolamine Hydrochloride.—For the reduction of ω-dibenzylamino-3,4-dihydroxy acetophenone hydrochloride to the amino alcohol a higher ratio of catalyst was required. When the usual ratio of catalyst to ketone was employed, only the N-benzyl groups were removed.

To 4.0 Gm. (0.011 mole) of ω-dibenzylamino-3,4-dihydroxyacetophenone hydrochloride, suspended in 75 cc. of distilled water, was added 3.0 Gm. of catalyst. The reduction mixture was shaken at room temperature under 150 lb. pressure for one and one-half hours when 3 moles of hydrogen had been absorbed. The catalyst was filtered off and the solution evaporated to dryness over concentrated H_2SO_4, soda lime, and anhydrous $CaCl_2$ in an evacuated desiccator. An attempt was made to recrystallize the crude product from absolute ethanol and ether, but the material was too hygroscopic. The partially purified product was dried over P_2O_5 and 2.0 Gm. (88.5%) of tan crystals, m. p. 137° (dec.), were obtained. This evidence agrees with the melting point reported for 3,4-dihydroxyphenylethanolamine hydrochloride (15).

When the reduction was repeated using 9.5 Gm. (0.025 mole) of dibenzylamino ketone with the same amount of catalyst, only 2 moles of hydrogen were taken up in five hours. After removal of the catalyst the solution was concentrated over concentrated H_2SO_4, soda lime, and anhydrous $CaCl_2$ in an evacuated desiccator, to approximately one-tenth of the original volume. The concentrated solution was throughly chilled and 28% ammonia was added drop by drop until the solution was just neutral. The crude product was filtered off and washed throughly with cold water and ethanol. The product was dried over P_2O_5 and 3.5 Gm. (85.0%) of pinkish white crystals, m. p. 235° (dec.), were obtained. This evidence agrees with the melting point reported for ω-amino-3,4-dihydroxyacetophenone (16).

SUMMARY

The possibility of synthesizing arylethanolamines by hydrogenolytic debenzylation of suitable intermediates was examined. Aracyl chlorides were allowed to react with benzylamine or dibenzylamine to form, in good yields, compounds of general structure $AR \cdot CO \cdot CH_2—NH—CH_2C_6H_5$ or $AR \cdot CO \cdot CH_2—N(CH_2C_6H_5)_2$. The dibenzolamino derivative is more satisfactory for phenolic aracyl chlorides. Evidence indicates that with palladinized charcoal catalyst, the benzyl groups are more easily removed than is the carbonyl group reduced to carbinol.

The following intermediate benzylamino ketones were prepared and described:

1. ω-benzylaminoacetophenone hydrochloride.
2. ω-dibenzylamino-*p*-hydroxyacetophenone hydrochloride.
3. ω-dibenzylamino-3,4-dihydroxyacetophenone hydrochloride and converted into the corresponding arylethanolamines, *viz.*:
4. Phenylethanolamine hydrochloride.
5. *p*-Hydroxyphenylethaolamine hydrochloride.
6. 3,4-Dihydroxyphenylethanolamine hydrochloride.

REFERENCES

(1) Hartung, W. H., *Ind. Eng. Chem., Ind. Ed.*, **37**, 126 (1945).
(2) Hartung, W. H., *et al.*, *J. Am. Chem. Soc.*, **51**, 2262 (1929); **52**, 3317(1930); **53**, 4149(1931); **57**, 1091(1935).
(3) Levin, N., Thesis, University of Maryland (1942).
(4) Levin, N., and Hartung, W. H., *J. Org. Chem.*, **7**, 408(1942).
(5) Birkoter, L., *Ber.*, **75B**, 429(1942).
(6) Baltzly, R., and Buck, J. S., *J. Am. Chem. Soc.*, **65**, 1984(1943).
(7) Gabriel, S., *Ber.*, **47**, 1346(1914).
(8) Dakin, H. D., *Proc. Roy. Soc.*, **76B**, 498(1905).
(9) Levin, N., Graham, B. E., and Koloff, H. G., *J. Org. Chem.*, **9**, 380(1944).
(10) Iwamoto, H. K., and Hartung, W. H., *ibid.*, **9**, 513 (1944).
(11) Hartung, W. H., *J. Am. Chem. Soc.*, **53**, 2248(1931).
(12) Pictet, A., and Gams, A., *Ber.*, **43**, 2387(1910).
(13) Kolshorn, E., *ibid.*, **37**, 2484(1904).
(14) Mannich, C., and Thiele, E., *Arch. Pharm.*, **253**, 194 (1915).
(15) Beilstein, "Organische Chemie," ed. **4**, Vol. XIII, p. 830.
(16) Tutin, F., *J. Chem. Soc.*, **97**, 2520(1911).

Pyrethrum Culture Investigations in Nebraska*,†

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The results of an investigation with Pyrethrum concerned with spacing, yield, and potency of plots of this plant under experimental cultivation in the several altitude ranges of the state are presented.

THE RENEWED interest in the growing of pyrethrum in the western hemisphere and the possible adaptability of the plant as a crop to the several altitude ranges and irrigated areas of the state prompted the present study. In normal times the requirements of pyrethrum are largely obtained from Dalmatia, Japan, Kenya, and Brazil. Commercial exploitation of the plant as a crop in the United States is limited, although considerable cultivation is in progress of development in Central and South American countries.

The present paper presents the results of a limited investigation of plantings of one seed source of pyrethrum (*Chrysanthemum cinerariaefolium* Vis.) obtained from the Division of Drug and Related Plants of the United States Department of Agriculture. The original work was inaugurated in 1942. Seedlings obtained from flats sown in the first week in February were transplanted into the field in early June in the several years of plantings. Replicated plots were established at the Scottsbluff Field Station in a spacing and yield study under irrigation. There were four replicated five-row plots of each of a six-inch, twelve-inch, eighteen-inch and twenty-four-inch spacing in rows eighteen feet long, the rows thirty inches apart. The field was uniform with respect to fertility and physical conditions. All other data were obtained from nonreplicated plots.

The harvesting of the flowers was done by hand. The middle row of the replicated plots was used to furnish yield data and the flowers collected were used for the assay determinations. Plants selected at random from the nonreplicated plots furnished the material used to assay these plots. These results (Table I) and other data are presented. The assay procedure (1) was conducted within three months of the harvest date and the average of three determinations is recorded.

The acre yields are calculated, based on full stands. Actual stands in the plots were lower. There was little winter killing, the

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