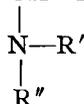


Aminoalcohols. XV. *p*-Aminopropadrine*

By WALTER H. HARTUNG and CARROLL P. FOSTER

INTRODUCED into clinical practice as "Ephetonal" without adequate pharmacological background (1) *p*-aminoephedrine (2) is reported to possess activity similar, in many respects, to its *p*-hydroxy isoster. It is well tolerated and differs from ephedrine in that it is appreciably less toxic (3), does not cause tachyphylaxis and apparently causes a rise in the blood sugar level (4). "Ephetonal" is apparently the only aromatic amino compound of the ephedrine type which has received any pharmacological attention, although other members are described. To *m*-aminoephedrine and *p*-aminonorephedrine are ascribed therapeutic properties which compare favorably with those of ephedrine (5). Other compounds are *p*-amino-*N*-methylephedrine and *p*-aminophenyl-1-methylamino-2-ethanol-1 (6).

According to the disclosures, the *p*-amino compounds were obtained by nitrating the aminoalcohol, $C_6H_5-CHOH-CH-R$, and



reducing. For example, from 20 Gm. norephedrine (propadrine) 6 to 7 Gm. *p*-nitronorephedrine may be expected; on reduction in the presence of palladium oxide, 1.5 Gm. of the dihydrochloride of *p*-aminonorephedrine is obtained; thus from 0.13 mole starting material is obtained a yield of 0.006 mole of final product (5a).

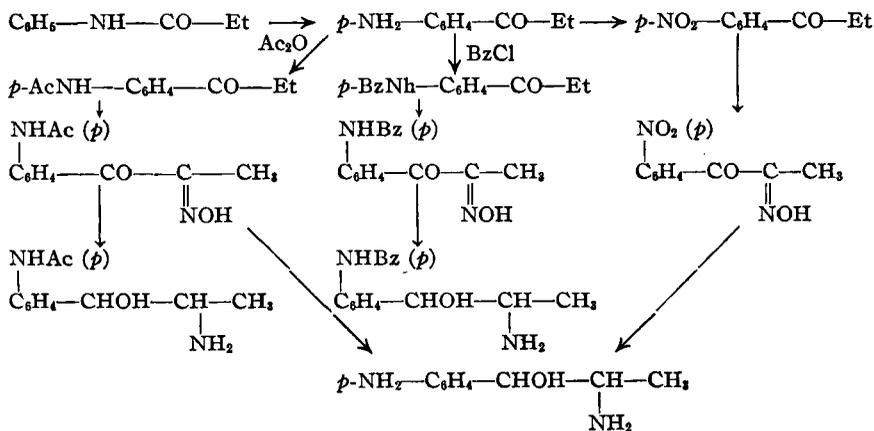
In view of the favorable physiological activity of *p*-aminoephedrine, as well as the

high activity of amino compounds in general, a study of the change produced in the biological properties of propadrine by the introduction of an amino group into the *p*-position of the molecule was undertaken. For this purpose, a new synthesis, starting with *p*-nitropropiofenone, was investigated. Unfortunately, this desirable ketone itself is difficult to obtain and, accordingly, a second method, starting with *p*-acylamino-propiofenone, was explored. Both ketones may be readily converted into their corresponding oximino intermediates, and these then may be reduced to the corresponding amino alcohols.

The reactions employed are indicated in Equation I.

Commanducci and Pescitelli (7) describe the nitration of propiofenone with "104 per cent" nitric acid at temperatures above 40° C., and they report the isolation of a product melting at 114°, which they called *p*-nitropropiofenone, but they give no further characterization of their product. Numerous experimental attempts in these Laboratories indicate that the conditions stated by the Italian workers are impossible, and it is now established that *p*-nitropropiofenone melts at 90–91° C. and not at 114°.

In red fuming nitric acid phenyl ketones do not nitrate (8), and during the course of nitration with colorless fuming nitric acid, sp. gr. 1.48, a mixture of *o*- and *m*-nitropropiofenones may be obtained if the temperature of the reaction is kept low; but never has a trace of the *p*-isomer been



Equation I

* Received April 9, 1945, from the Research Laboratories, School of Pharmacy, University of Maryland, Baltimore.

isolated. As a rule it is not advisable to allow the temperature during nitration to

rise above 25° C., for then the reaction may easily get out of control, red fumes belch forth and the final product, in fair yields, is usually *m*-nitrobenzoic acid. In the light of these results, consistently duplicated, the use of a temperature above 40° C., as directed by Commanducci and Pescitelli, is incomprehensible.

p-Nitropropionophenone has now been synthesized, from *p*-aminopropionophenone, and characterized. Unfortunately the yields are low.

p-Aminopropionophenone is described by Kunckell (9) and by Derrick and Bornemann (10). These authors employed an adaptation of the Fries reaction, allowing propionyl chloride to react with acetanilide. Their conditions do not preclude contamination from *p*-aminoacetophenone derivatives, a fact which has been confirmed. A purer product is obtained if propionanilide is used. The yields of *p*-aminopropionophenone averaged somewhat less than one-third of theoretical.

The pharmacological properties of *p*-aminopropadrine are being studied by Dr. Karl Beyer of Sharp and Dohme, who will report in greater detail at another time. It may be mentioned at this time, however, that the compound does exhibit considerable parallelism with its isosteric *p*-hydroxypropadrine. It exhibits a high degree of circulatory activity and does not give rise to tachyphylaxis.

EXPERIMENTAL

***p*-Aminopropionophenone.**—The procedure, based on that of Kunckell (9) and of Derrick and Bornemann (10), but differing in details, found to give best consistent yields is as follows: In a 5-L., round-bottom, three-neck flask, equipped with sealed mechanical stirrer, dropping funnel, and reflux condenser (the upper end of which is attached to an HCl-absorption train), are placed 140 Gm. aniline (1.5 moles) and 1600 ml. carbon bisulfide. The flask is immersed in a water bath at 20–25° C.; to the rapidly stirred contents is slowly added 277.5 Gm. propionyl chloride (3 moles). The dropping funnel is now replaced with a funnel having a wide stem (suitable for addition of powder) through which 400 Gm. aluminum chloride (3 moles) is added, in approximately 15-Gm. portions and over the period of about an hour, to the rapidly agitated contents of the flask. During this reaction it is desirable to have the HCl-absorption train under slightly reduced pressure. The mixture is then stirred and heated on the water bath to gentle refluxing of the solvent until the evolution of HCl practically ceases (about five hours). The stirred mixture is then cooled on an ice bath and 100 ml. cold 10% HCl added dropwise, keeping the temperature below 30° C.; this is followed by sufficient ice and water to decompose the complex completely. The heterogeneous mixture is now filtered through a Büchner funnel; the small amount of solid material is *p*-propionylaminopropionophenone, which after recrystallization from hot water melts at 149–150° C.;

the filtrate, placed in a separatory funnel, separates into three layers.

The lowest layer is carbon bisulfide which, after volatilization, leaves an additional crop of 6 to 9 Gm. *p*-propionylaminopropionophenone. The middle or aqueous layer, when basified, liberates a solid weighing 1.5 to 3 Gm.; this is *p*-aminopropionophenone. The upper layer, primarily organic, is thick, orange-black in color, contains most of the product as free amine or its *N*-propionyl derivative; it is refluxed directly for several hours in 500 ml. 20% HCl. After hydrolysis is complete, decolorizing carbon is added to the hot acid solution followed by an equal volume of water; the solution is again brought to boiling and allowed to cool before filtering. The cold filtrate is basified and the liberated *p*-aminopropionophenone, weighing 30 to 37 Gm., is recrystallized from 40% ethanol. The combined yield is about 30%.

The purified *p*-aminopropionophenone appears as yellow crystals melting at 140° C. The hydrochloride melts at 198–199° C. The oxime melts at 153–154° C. Acetylation forms *p*-acetylaminopropionophenone melting at 172–173° C.; found N (Kjeldahl), 7.32% and 7.16%;¹ calculated N for C₁₁H₁₃O₂N, 7.29%; oxime of acetyl derivative melts at 156–157° C. (dec.).

p-Benzoylaminopropionophenone, formed in yields of 95%, melts at 187–188° C.; found N (Kjeldahl), 5.59% and 5.57%; calculated N for C₁₅H₁₅O₂N, 5.53%; the oxime melts at 164–165° C. (dec.).

p-Propionylphenyldiazonium borofluoride is obtained in yields of 85% by treating *p*-aminopropionophenone with fluoboric acid according to the method of Starkey (11). The compound decomposes at 85° C., but like other diazonium borofluorides is quite stable at room temperature. Hydrolysis in boiling water yields *p*-hydroxypropionophenone, melting at 147–148° C.

p-Nitropropionophenone is obtained by replacing the diazonium group with the nitro group (11, 12). The yield, unfortunately, is rarely above 25%. The product, recrystallized from hot water and decolorized with charcoal, appears as pale yellow crystals, melting at 90–91° C. Found N (Kjeldahl), 7.72% and 7.75%; calculated N for C₉H₉O₂N, 7.82%. Oxidation with permanganate forms *p*-nitrobenzoic acid, melting at 240° C. The oxime, recrystallized from dilute ethanol, melts at 124° C. (dec.).²

Oximino ketones.—The synthesis of compounds of general formula Ar—CO—C—R and their use as



intermediates in preparing primary amino analogs of the ephedrine bases has been described (13). By following established procedures the oximinoketones listed in Table I were obtained. The slightly alkaline solutions of the oximino ketones, treated with hydroxylamine, formed excellent yields of the glyoximes, Ar—C—C—CH₃, which are also listed



in Table I. These glyoximes formed colored, insoluble chelates with ammoniacal solutions of nickel salts.

¹ Derrick and Bornemann (10) allowed propionyl chloride to react with acetanilide. When their directions are followed, a product melting at 165–168° C. is obtained, as they describe, which they call *p*-acetaminopropionophenone. Analysis of this product shows N (Kjeldahl) 6.87%; calculated N for C₁₂H₁₃CO—NH—C₂H₅—CO—C₂H₅, 7.33%; calculated N for C₁₂H₁₃CO—NH—C₂H₅—CO—C₂H₅, 6.82%.

Another possible product with Derrick and Bornemann's conditions is *p*-propionylaminopropionophenone. This compound, prepared in these Laboratories by E. C. Weinbach, melts at 131° C.

² The method of synthesis, combined with the analysis and oxidation, leaves no doubt about the identity of *p*-nitropropionophenone. As already indicated, the characterization by Commanducci and Pescitelli (7) is erroneous.

Reduction.—The catalytic hydrogenation of the α -oximinoethyl ketones was carried out in absolute ethanolic 2*N* HCl by means of palladium on charcoal (13, 14). Although reduction proceeded at ordinary pressures, the use of hydrogen at 10 to 20 atmospheres hastened the process and, as a rule, led to purer product.

***p*-Aminopropadrine.**—Three grams (0.015 mole) *p*-nitrophenyl α -oximinoethyl ketone and the catalyst (prepared from 3 gr. charcoal and 0.3 gr. PdCl₂) were suspended in 90 ml. absolute ethanolic 2*N* HCl, and the mixture shaken in an atmosphere of hydrogen at ordinary pressure; only five-sixths of the calculated hydrogen was taken up when reduction stopped completely. The catalyst was filtered out and the filtrate was evaporated to dryness in an evacuated desiccator over sulfuric acid, calcium chloride, and soda lime; the residue was gummy and hard to purify. This substance darkened on heating but did not melt below 300° C.; dissolved in water, it reduced Fehling's solution and on treatment with ammonia water color characteristic of pyrazine

two components, the dihydrochloride of *p*-aminopropadrine and the monohydrochloride of *p*-acetaminopropadrine; the latter being insoluble in cold absolute ethanol could be isolated by fractional crystallization. The hydrochloride of *p*-acetaminopropadrine melts at 236–237° C. (dec.). Found Cl, 14.77% and 14.92%; calculated Cl for C₁₁H₁₆O₂N₂·HCl, 14.50%. In some reduction experiments complete removal of the acetyl group was observed.

***p*-Benzoylaminopropadrine.**—*p*-Benzoylaminophenyl α -oximinoethyl ketone, reduced under conditions similar to those employed for the analogous *p*-acetamino compound, also stopped at the intermediate aminoketone stage; this did not melt below 340° C., reduced Fehling's solution, and with ammonium hydroxide gave the dihydropyrazine color reaction. Further reduction in dilute HCl formed pure *p*-benzoylaminopropadrine, which was isolated as the hydrochloride, nonfusible below 340° C. and stable toward Fehling's solution. Found Cl, 11.49% and 11.48%; calculated Cl for C₁₆H₁₈O₂N₂·HCl, 11.58%.

TABLE I.—ARYL α -OXIMINOETHYL KETONES

$ \begin{array}{c} p\text{-R}-\text{C}_6\text{H}_4 \\ \\ \text{CO}-\text{C}-\text{CH}_3 \\ \\ \text{NOH} \end{array} $	Yield, %	M. P., ° C.	Analyses for N Glyoxime			
			Molecular Formula	% Found	% Calcd.	M. P. (dec.)
R = NO ₂	70	132–133	C ₉ H ₈ O ₄ N ₂	13.35 13.32	13.46	197
—NHCOCH ₃	75	219	C ₁₁ H ₁₂ O ₂ N ₂	12.69 12.75	12.72	225
—NHCOC ₆ H ₅	75	209 (dec.)	C ₁₆ H ₁₄ O ₂ N ₂	9.84 9.81	9.93	245

formation developed. Since this behavior is quite characteristic for α -amino ketones, it is believed that the product was the dihydrochloride of *p*-aminophenyl α -aminoethyl ketone. Found Cl (Volhard), 29.6% and 29.7%; calculated Cl for C₉H₁₂ON₂·2HCl, 29.9%.

When the reduction was repeated at 15 atmospheres pressure, the reaction was complete in little more than an hour. The product, isolated as described above for the aminoketone above, did not reduce Fehling's solution, gave no evidence of dihydropyrazine formation, and melted at 192–193° C. (dec.). Oberlin (5) describes the dihydrochloride of *p*-aminonorephedrine as melting at 192–193° C. (dec.). Found Cl (Volhard), 29.62% and 29.60%; calculated Cl for C₉H₁₄ON₂·2HCl, 29.71%.

***p*-Acetaminopropadrine.**—Seven grams (0.033 mole) *p*-acetaminophenyl α -oximinoethyl ketone and catalyst suspended in 100 ml. absolute 2*N* ethanolic HCl was reduced at an initial pressure of 15 atmospheres hydrogen; reduction proceeded smoothly until two-thirds the calculated H₂ was taken up (forty-eight minutes) and then stopped. The product, isolated as described above, represented a yield of 97% of the aminoketone hydrochloride, $p\text{-CH}_2\text{CONH}-\text{C}_6\text{H}_4-\text{CO}-\underset{\text{NH}_2\cdot\text{HCl}}{\text{CH}}-\text{CH}_3$, melting at

257–258° C. (dec.). On treatment with ammonium hydroxide, the product gave color reactions characteristic for pyrazine formation.

The aminoketone hydrochloride was dissolved in 100 ml. 3.5% HCl and reduced further with fresh catalyst, initial hydrogen pressure 6½ atmospheres. In half an hour the calculated H₂ was taken up and further reduction ceased. The product, after removal of the solvent as described above, consisted of

Hydrolysis of *p*-acylaminopropadrines.—In view of the fact that appreciable amounts of *p*-aminopropadrine formed during the reduction of *p*-acetaminophenyl α -aminoethyl ketone, involving removal of the acyl group, no difficulty was anticipated in hydrolyzing the *p*-acylaminopropadrine derivatives. However, side reactions, the nature of which has not been established, interfere and none of the desired product has thus far been obtained or isolated in this manner.

Half-gram *p*-acetaminopropadrine hydrochloride refluxed gently in 30 ml. 20% HCl for ninety minutes yielded yellow crystals melting 160° C. (dec.), which by the Volhard method showed the presence of 26.1% Cl; it is not unlikely that the product is impure dihydrochloride of *p*-aminophenyl-1-amino-2-chloro-1-propane, $p\text{-NH}_2-\text{C}_6\text{H}_4-\text{CHCl}-\text{CH}(\text{NH}_2)-\text{CH}_2\cdot 2\text{HCl}$, calculated available Cl, 27.5%; that is, the alcoholic hydroxyl group may have been replaced by a Cl atom.

Gentle refluxing in dilute HCl had little effect on *p*-benzoylaminopropadrine; usually the starting material was largely recovered unchanged, contaminated with only small amounts of yellow crystals which could not be identified as the desired hydrolytic product. More drastic conditions gave unchanged material, some benzoic acid but nothing that could be identified as *p*-aminopropadrine. The use of concentrated HCl gave unchanged *p*-benzoylaminopropadrine, larger amounts of benzoic acid, and a resinous fraction from which no *p*-aminopropadrine could be isolated. *p*-Benzoylaminopropadrine was not affected by refluxing with a solution of sodium bicarbonate.³

³ It is not presumed that there is any similarity, but this resistance of the benzoyl group to hydrolysis calls to mind Abel's difficulty [Abel, *Bull. Johns Hopkins Hosp.*, 12, 337 (1901)] in hydrolyzing completely his polybenzoyl derivative of epinephrine.

SUMMARY

1. The synthesis of *p*-aminopropiophenone and its acylated derivatives is described.

2. *p*-Nitropropiophenone has been synthesized and characterized.

3. *p*-Nitro-, *p*-acetamino- and *p*-benzoylaminopropiophenone have been converted into their corresponding α -oximinoethyl ketones, which have been catalytically reduced to *p*-amino-, *p*-acetamino- and *p*-benzoylaminopropadrine.

4. The attempts to hydrolyze *p*-acetaminopropadrine and *p*-benzoylaminopropadrine to *p*-aminopropadrine proved unsuccessful.

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A Synthesis of *p*-Aminophenylalanine*

By ALBERT M. MATTOCKS and WALTER H. HARTUNG

A new synthesis of *p*-aminophenylalanine from *p*-nitrophenylpyruvic acid is described. Unsuccessful attempts at nitrosation of *p*-nitrobenzylmalonic ester and *p*-nitrobenzylacetoacetic ester are recorded.

p-Aminophenylalanine has not been found in nature, nor is it an amino acid that might be suspected to occur in the animal body; however, being a nitrogen analog of tyrosine, it might be metabolized in a manner similar to that of tyrosine and yet produce a different physiological action. Such action seems probable, since Selinger (1) found that *p*-aminoephedrine is chemically and physiologically isosteric with *p*-hydroxyephedrine. Hence, in order that *p*-aminophenylalanine might be available for physiological studies, its synthesis was undertaken.

Erlenmeyer and Lipp (2) nitrated phenylalanine, and isolated the *p*-nitro compound which they reduced to obtain *p*-aminophenylalanine. Friedländer (3) prepared *p*-aminophenylalanine by reduction of *p*-nitrophenyl- α -nitroacrylic acid. Takayama and Tubuku (4), in a study of the nitration of phenylalanine, obtained *p*-nitrophenylalanine in 53 per cent yield, but they did not reduce the compound.

In the present investigation *p*-nitrotoluene was condensed with ethyl oxalate to yield ethyl *p*-nitrophenylpyruvic acid, and the keto ester was converted into a corresponding α -oximino ester by condensation with hydroxylamine. Simultaneous catalytic reduction of the oximino and nitro groups produced the ethyl ester of *p*-aminophenylalanine. Attempts to prepare α -oximino- β -keto- β -(*p*-nitrophenyl)-propionic acid from appropriately substituted malonic and acetoacetic esters, according to the procedures developed by Barry (5) were unsuccessful.

EXPERIMENTAL

Nitrosation Experiments.—*p*-Nitrobenzylmalonic ester, prepared according to the procedure of Reissert (6) and by direct nitration of benzylmalonic ester, was treated with isopropyl nitrite in the presence of sodium ethoxide and also with isopropyl nitrite in the presence of hydrochloric acid, but nitrosation did not proceed in either case. Mixtures of products giving no consistent results on Kjeldahl analysis were obtained by these methods. Similar results were obtained by nitrosation experiments on *p*-nitrobenzylacetoacetic ester.

***p*-Nitrophenylpyruvic Acid Ethyl Ester.**—*p*-Nitrotoluene was condensed with ethyl oxalate in the presence of sodium ethoxide according to the procedure of Wislicenus and Schulz (7), except that the red sodium salt of the quinoid form was removed from the solution as such and used in this form.

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