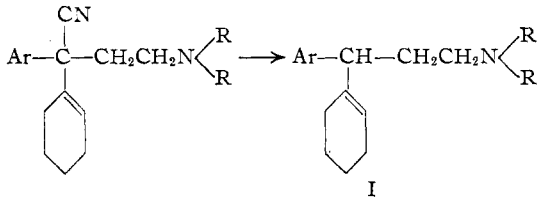
[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

The Preparation of Dimethyl-γ-cyclopentylidene-γ-phenylpropylamine and Related Compounds

BY MARY JACKMAN, C. BOLEN, F. C. NACHOD, B. F. TULLAR AND S. ARCHER

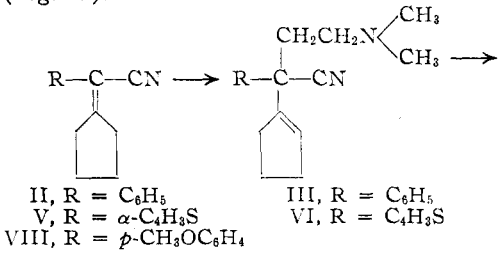
Some unpublished work in this laboratory[1] revealed that cleavage of α-aryl-α-Δ¹-cyclohexenyl-γ-dialkylaminobutyronitriles with excess sodium amide resulted in the formation of the amine, I, without migration of the double bond, thus



I

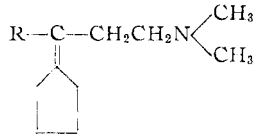
We wish to record at this time our experience with this reaction in the cyclopentenyl series.

Cyclopentanone condensed readily with phenylacetonitrile in sodium ethylate solution to yield α-cyclopentylidenephenylacetonitrile, II. When equimolar quantities were used the yield was only 30–40% but was increased to 65% when a four-fold excess of phenylacetonitrile was employed. The presence of a conjugated, semi-cyclic double bond in the molecule was indicated by a maximum at 258 mμ in the ultraviolet absorption spectrum (Fig. 1).



II, R = C_6H_5
V, R = α-C_4H_3S
VIII, R = p-$CH_3OC_6H_4$

III, R = C_6H_5
VI, R = C_4H_3S



IV, R = C_6H_5
VII, R = α-C_4H_3S

When this nitrile was alkylated with β-dimethylaminoethyl chloride with the aid of sodium amide the unsaturated nitrile, III, resulted.

When refluxed with excess sodium amide for thirty-six hours, III suffered loss of the cyano group. A liquid base was obtained which was separated from some unchanged nitrile by distillation. It was converted to the hydrochloride but in only 33% yield. This salt was the hydrochloride of IV.

The structure of the compound was proven in the following way. It showed an absorption peak of 246 mμ (Fig. 2), which indicated the presence of a double bond adjacent to the benzene ring. On oxidation with potassium permanganate cyclopentanone was obtained and characterized as its dibenzal derivative. These data are in accord with the structure, IV.

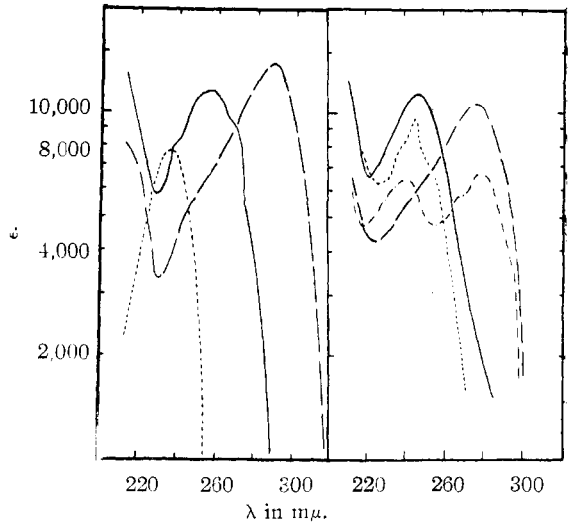
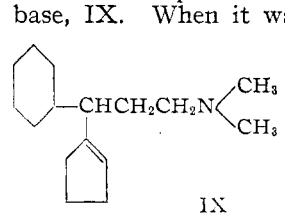


Fig. 1. Fig. 2.

Fig. 1.—Absorption spectra in 95% ethanol of: ——, α-cyclopentylidenephenylacetonitrile; . . . . ., chloromethylthiophene; — —, α-cyclopentylidene-2-thienylacetonitrile.

Fig. 2.—Absorption spectra in 95% ethanol of: . . . . ., dimethyl γ-cyclopentylidene-γ-phenylpropylamine; ——, dimethyl γ-cyclopentylidene-γ-p-(methoxyphenyl)-propylamine; — —, dimethyl-γ-cyclopentylidene-γ-2-thienylpropylamine; — · — ·, γ-cyclopentylidene-γ-2-thienylpropylpiperidine.

The mother liquors from the above hydrochloride were concentrated and made basic. An oil separated which had the same boiling point as IV but the refractive index was considerably lower. No significant absorption peak in the ultraviolet was noted. A hydrochloride was prepared with some difficulty and proved to be different from the corresponding salts obtained from either IV or XI. The compound is undoubtedly the isomeric base, IX. When it was heated in



IX

(1) Jackman, Nachod and Archer, in press.

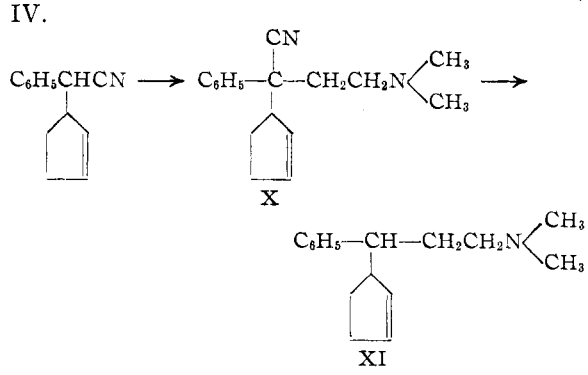
isopropyl alcohol solution with a slight excess of hydrobromic acid the hydrobromide of IV readily crystallized. Recycling of the unisomerized base led eventually to an 85% conversion to IV.

As neither α-thienylacetonitrile nor *p*-methoxyphenylacetonitrile was readily available, the unsaturated nitriles, V and VIII, were prepared from equimolar quantities of these substances and cyclopentanone. The yields were 40–45%. When α-cyclopentylidene-*p*-methoxyphenylacetonitrile was alkylated with dimethylaminoethyl chloride and the product then cleaved, a base was obtained which showed an absorption maximum at 246 mμ (Fig. 2). By analogy with IV it was assigned the cyclopentylidene structure. The corresponding reactions were carried out with II and β-piperidylethyl chloride. The base which was isolated as the hydrochloride did not exhibit any absorption maximum. It probably possessed the cyclopentenyl structure. In neither of the above instances were the mother liquors examined for the presence of isomeric compounds.

The nitrile, V, showed a maximum at 288 mμ rather than in the 240–260 mμ range. Thiophene[2,3] and chloromethylthiophene (Fig. 1) exhibited maxima in the 230–240 mμ range, while α-vinylthiophene showed a high peak at 272 mμ.[2] Since it was unlikely that the cyano group was responsible for this strong absorption it is our belief that the expression, V, accounts best for the absorption phenomenon. The base, VII, and the corresponding piperidyl derivative were prepared in the usual way. We did not look for any of the isomeric compounds but did succeed in isolating the hydrochloride of some unchanged nitrile, VI, while processing the cleavage reaction.

The salt of VII exhibited an intense maximum at 278 mμ and the corresponding piperidine compound showed two peaks, one at 238 mμ and the other at 271 mμ (Fig. 2). The maximum at the lower wave length was probably due to the thiophene ring and the cyclopentylidene structure was responsible for the peak at 278 mμ. It may be noted that the absorption maxima of II and V are 30 mμ apart which is almost precisely the difference between those of IV and VII (actually 32 mμ). The fact that these differences are almost identical and in the same direction lent support to the idea that both V and VII have double bonds conjugated with the thiophene ring.

The marked spasmolytic potency exhibited by the hydrochloride of IV (*vide infra*) prompted us to prepare an isomeric base in which the double bond was located in the cyclopentene ring. Phenylacetonitrile was alkylated with Δ^2-chlorocyclopentene in the presence of sodium amide.[4] Alkylation with β-dimethylaminoethyl chloride in the customary manner resulted in the formation of X which was isolated as the hydrochloride. Cleavage of the basic nitrile proceeded smoothly to give XI which differed markedly from IV and IX. The spasmolytic potency of this substance was much weaker than that of the isomeric base, IV.



All of the compounds reported in Table I were examined for their activity against spasms induced by acetylcholine and histamine and most of them were also tested as barium chloride antagonists. The most interesting compound from the pharmacological side was dimethyl-γ-cyclopentylidene-γ-phenylpropylamine which was sixty-six times as effective as papaverine in abolishing barium induced spasms. It was about one-tenth as active as atropine as an acetylcholine antagonist and almost as potent as Benadryl in relieving histamine spasms, *in vitro*.[5]

Experimental[6]

α-Cyclopentylidenephenylacetonitrile.—To a solution of one mole of sodium in 600 ml. of absolute ethanol cooled to −10° there was added 468 g. (4.0 moles) of phenylacetonitrile. To the stirred, cold mixture 84 g. (1.0 moles) of cyclopentanone was added dropwise. The solution was kept at −10° for five hours and then allowed to come to room temperature overnight. The whole was poured into ice-water and made acid to litmus. The organic layer was removed and combined with the ether which was used to wash the aqueous layer. After drying over sodium sulfate, the solution was distilled through a short column. The phenylacetonitrile was recovered at 65° (0.1 mm.) and the desired product boiled at 110–120° (0.1 mm.). It was added to two volumes of ligroin and filtered from the solid which separated (phenylacetamide). The filtrate was distilled and the required nitrile then boiled at 110–112° (0.1 mm.); wt. 120 g. (65.5%). It melted at 10.2°, $n^{25}D$ 1.5735.

Anal. Calcd. for $C_{13}H_{13}N$: N, 7.64. Found: N, 7.47.

When the phenylacetonitrile–cyclopentanone ratio was 1:1 the yield was 28%, 2:1, 37% and 3:1, 50%.

α-Cyclopentylidene-2-thienylacetonitrile.—To a solution of 16.5 g. of sodium in 430 ml. of absolute alcohol cooled to zero degrees, there was added 88.3 g. of 2-thienylacetonitrile. To the stirred, cold solution there was added dropwise 60.5 g. of cyclopentanone and the mixture then set aside at 5° for five days. At the end of this time it was poured onto ice and made acid to congo red. The oil was taken up in ether, washed with water and dried. On distillation there was obtained 49 g. (42%) of the desired nitrile, b. p. 143–150° (1.5 mm.). On standing the product crystallized. After recrystallization from ether–petroleum ether it melted at 46–48° (uncor.).

Anal. Calcd. for $C_{11}H_{12}NS$: S, 16.85. Found: S, 17.13.

(2) Smakula, *Z. physiol. Chem.*, **230**, 238 (1934).

(3) Kuhn and Dann, *Ann.*, **547**, 293 (1941).

(4) Buu-Hoï and Cagniant, *Comp. rend.*, **217**, 26 (1943).

(5) We are grateful to Dr. A. M. Lands of the Department of Pharmacology of this Institute for this information.

(6) Analyses were carried out under the supervision of Mr. M. E. Auerbach.

TABLE I

SUBSTITUTED CYCLOPENTENYL AND CYCLOPENTYLIDENEPROPYLAMINE HYDROCHLORIDES

Hydrochloride of	M. p., °C. (cor.)	Solvent	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	Chlorine Calcd.	Chlorine Found
Dimethyl-γ-cyclopentylidene-γ-phenylpropylamine	204.4–207.8	Isopropyl alc.	72.29	72.22	9.10	9.15			13.34	13.06
γ-Δ¹-Cyclopentenyl-γ-phenylpropylpiperidine	227 d.	Alcohol ether	74.60	74.69	9.24	9.23	4.58	4.47	11.59	11.60
Dimethyl-γ-cyclopentylidene-γ-*p*-methoxyphenylpropylamine	185.6–186.6	Ethyl acetate	69.01	69.12	8.86	8.65	4.74	4.83		
Dimethyl-γ-cyclopentylidene-γ-2-thienylpropylamine	200.4–203.5	Alcohol ether	61.85	62.14	8.16	8.26	5.15	5.30		
γ-Cyclopentylidene-γ-2-thienylpropylpiperidine	166–168.5	Ethyl acetate	65.46	65.38	8.40	8.30	4.49	4.29		
α-Δ²-Cyclopentenyl-γ-dimethylamino-α-phenylbutyronitrile	214.4–216.4	Isopropyl alc.	70.20	70.04	7.97	7.74			12.19	11.99
Dimethyl-γ-Δ²-cyclopentenyl-γ-phenylpropylamine	128.8–131.8	Ethyl acetate	72.29	72.17	9.10	8.99			13.34	13.12
Dimethyl-γ-Δ²-cyclopentenyl-γ-phenylpropylamine methiodide	171–173.6	Water	54.99	54.93	7.06	7.10			34.18[a]	33.73

[a] Iodine analysis.

Cyclopentylidene-*p*-methoxyphenylacetonitrile.—When an equivalent amount of *p*-methoxyphenylacetonitrile was substituted for 2-thienylacetonitrile, the corresponding unsaturated nitrile was obtained in approximately the same yield; m. p. 64–66° after recrystallization from dilute ethanol.

Anal. Calcd. for $C_{14}H_{15}NO$: C, 79.00; H, 7.06; N, 6.57. Found: C, 79.03; H, 7.06; N, 6.34.

γ-Dimethylamino-α-Δ¹-cyclopentyl-α-phenylbutyronitrile.—A mixture of 940 ml. of benzene and 108 g. of sodium amide was placed in a two-liter flask equipped with a stirrer and efficient condenser. The nitrile, II (183 g.) was added in a thin stream and the mixture which had warmed spontaneously to 42° was heated to reflux and then allowed to cool to 50°. Then 162 g. of dimethylaminoethyl chloride was added portionwise. After about one-half hour the evolution of ammonia became vigorous and the source of heat was then removed for a short time. The mixture was refluxed for six hours and cooled. Excess sodium amide was destroyed with alcohol and the mixture was poured into water. The benzene solution was separated and extracted with 5% hydrochloric acid. The acid washings were shaken with benzene, separated and then made alkaline. The oil that separated was collected with ether and then dried. Distillation afforded a small forerun, b. p. 98–100° (0.1 mm.), which was IV and a main fraction, b. p. 128–130° (0.1 mm.), $n^{25}D$ 1.5293. It weighed 165 g. (65%). It was not purified further but used directly in the next step.

Dimethyl γ-Cyclopentylidene-γ-phenylpropylamine.—A mixture of 254 g. of the nitrile, III, 105 g. of sodium amide and one liter of dry xylene was heated under reflux for thirty-six hours. The product was isolated by essentially the same procedure as used for the nitrile, III, described above. The main fraction, b. p. 98–100° (0.1 mm.), $n^{25}D$ 1.5268, weighed 191 g. The yield of mixed bases was 83%. About 15 g. of unchanged nitrile was recovered.

For conversion to the hydrochloride, one mole (229 g.) of the above mixture was dissolved in one liter of acetone at 5° and treated with a slight excess of concentrated hydrochloric acid. The salt of dimethyl γ-cyclopentylidene-γ-phenylpropylamine separated immediately, wt. 79 g. (33%). The product thus obtained was recrystallized from isopropyl alcohol. It melted at 204.4–207.8°. A portion of the hydrochloride was converted to the base in the usual way. It boiled at 98–100° (0.1 mm.), $n^{25}D$ 1.5328.

In the preparation of the other bases listed in Table I the intermediate γ-dialkylamino-α-cyclopentyl-α-arylbutyronitriles were not distilled but used directly in the cleavage reaction.

γ-Dimethyl-α-Δ¹-cyclopentenyl-α-thienylbutyronitrile Hydrochloride.—Some of the starting nitrile co-distilled with the base, VII. When this mixture was treated with alcoholic hydrogen chloride in ether, a mixture of salts was obtained. It was leached with ethyl acetate. This cooled extract deposited a salt which on further recrystallization melted at 194–195.8° (cor.). Analysis indicated that it was the hydrochloride of VI.

Anal. Calcd. for $C_{15}H_{20}N_2S{\cdot}HCl$: C, 60.68; H, 7.13; N, 9.44. Found: C, 60.62; H, 6.68; N, 9.19.

Dimethyl-γ-Δ¹-cyclopentenyl-γ-phenylpropylamine.—The filtrate from the preparation of IV was concentrated to dryness and the residue dissolved in water. The solution was made alkaline and the oil taken up in ether and dried. The base was distilled. It boiled at 90° (0.09 mm.), $n^{25}D$ 1.5238. It formed a hydrochloride which was recrystallized from alcohol–ether, m. p. 115–117°.

Anal. Calcd. for $C_{16}H_{23}N{\cdot}HCl$: N, 5.27. Found: N, 5.32.

Isomerization of Dimethyl-γ-Δ¹-cyclopentenyl-γ-phenylpropylamine.—One hundred grams of the above base was dissolved in 300 ml. of isopropyl alcohol and 55 ml. of 48% hydrobromic acid and refluxed for three hours. The solvents were removed *in vacuo*. The residue was dissolved in 300 ml. of isopropyl alcohol and the solution allowed to cool. There deposited 61 g. (45%) of the hydrobromide of IV, m. p. 181–183°. The filtrate was taken to dryness and redissolved in isopropyl alcohol. On cooling a further quantity of the salt separated. After repeating this operation twice more there was obtained 115 g. (85%) of the hydrobromide.

Anal. Calcd. for $C_{16}H_{23}N{\cdot}HBr$: N, 4.52. Found: N, 4.46.

The salt was converted to the base and then to the hydrochloride which proved to be identical with the corresponding salt prepared from IV.

Δ²-Cyclopentenylphenylacetonitrile.—One hundred grams of phenylacetonitrile was added to a stirred mixture of 40 g. of sodium amide and 250 ml. of dry toluene over a period of one hour, keeping the temperature below 30°. Then 87.7 g. of freshly distilled Δ²-chlorocyclopentene was added dropwise at such a rate that the temperature did not rise above 30°. The mixture was left overnight and then treated with ethanol and then with water. The toluene layer was washed with water, dried and distilled. The fraction, b. p. 146–151° (8 mm.) was collected as the desired nitrile (wt. 86 g., 55%). A portion was redistilled for analysis; b. p. 153–155° (11 mm.).

Anal. Calcd. for $C_{13}H_{13}N$: C, 85.21; H, 7.15; N, 7.64. Found: C, 85.47; H, 7.06; N, 7.65.

The nitrile was alkylated in the usual way with β-dimethylaminoethyl chloride. The crude alkylated nitrile was converted directly to the hydrochloride without distillation.

For conversion to the cleavage product, XI, the nitrile, X, was treated in the manner described above. From 29 g. of Δ^2-cyclopentenylphenylacetonitrile there was obtained 23.5 g. of dimethyl-γ-Δ^2-cyclopentenyl-γ-phenylpropylamine, b. p. 116–117° (1.0 mm.).

Oxidation of Dimethyl-γ-cyclopentylidene-γ-phenylpropylamine Hydrochloride.—Two grams of the salt dissolved in 30 ml. of water was stirred as a solution of 6.5 g. of potassium permanganate in 200 ml. of water was added in a thin stream. After one-half hour of stirring the mixture was steam-distilled. To the first 20 ml. of distillate there was added 10 ml. of ethanol, six drops of benzaldehyde and two drops of 10% sodium hydroxide solution. The mixture was shaken vigorously by hand for a few minutes and the yellow solid which formed was collected on a filter. After crystallization from ethanol the yellow needles of dibenzalcyclopentanone melted at 185–186° (uncor.) undepressed by admixture with an authentic specimen.

Summary

1. Condensation of cyclopentane with phenylacetonitrile, *p*-methoxyphenylacetonitrile and 2-thienylacetonitrile gave the corresponding cyclopentylidene arylacetonitriles.

2. Alkylation of the above nitriles with dimethylaminoethyl chloride, followed by removal of the cyano group with sodium amide yielded dimethyl - γ - cyclopentylidene - γ - arylpropylamines.

3. Cleavage of γ-dimethylamino-α-Δ^1-cyclopentenyl-α-phenylbutyronitrile gave a mixture of cyclopentylidene and cyclopentenyl bases. The latter was isomerized to the former with the aid of hydrobromic acid.

4. Alkylation of cyclopentylidenephenylacetonitrile with β-piperidylethyl chloride gave a basic nitrile which was cleaved to the non-conjugated γ-Δ^1-cyclopentenyl-γ-phenylpropylpiperidine.

5. Alkylation of Δ^2-cyclopentenylphenylacetonitrile with β-dimethylaminoethyl chloride gave α-Δ^2-cyclopentenyl-γ-dimethylamino - α - phenylbutyronitrile which suffered cleavage of the cyano group when treated with sodium amide to give dimethyl - γ - Δ^2 - cyclopentenyl - γ - phenylpropylamine.

6. The ultraviolet absorption spectra of some cyclopentylidenearylacetonitriles and γ-cyclopentylidene-γ-arylpropylamines in ethanol solution were recorded.

RENSSELAER, N. Y. RECEIVED OCTOBER 15, 1948

[CONTRIBUTION FROM LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY]

Pteroic Acid Derivatives. III. Pteroyl-γ-glutamylglutamic Acid and Pteroyl-γ-glutamyl-γ-glutamylglutamic Acid

BY J. H. BOOTHE, J. SEMB, C. W. WALLER, R. B. ANGIER, J. H. MOWAT, B. L. HUTCHINGS, E. L. R. STOKSTAD AND Y. SUBBAROW

In a previous communication[1] the preparation of pteroyl-γ-glutamylglutamic acid and pteroyl-γ-glutamyl-γ-glutamylglutamic acid was described. The pteroyl tripeptide showed the same biological activity when assayed against *S. faecalis* R. and *L. casei* as did the fermentation *L. casei* factor. Although this first method of synthesis indicated the probable position of the peptide linkages in the fermentation *L. casei* factor, it left much to be desired as a preparative method for large-scale work.

It was thought that it would be desirable to find a method in which the *p*-nitrobenzoyl group could be used instead of the carbobenzoxy group to protect the amino group of glutamic acid. When attempts were made to form the anhydride of *p*-nitrobenzoylglutamic acid analogous to carbobenzoxyglutamic anhydride,[2] the product was found to be completely racemized. Therefore, other methods were investigated.

The method reported here utilizes the γ-monoester of glutamic acid which was prepared by the method of Bergmann and Zervas.[3] The γ-ethyl glutamate (I) was *p*-nitrobenzoylated in a solution of sodium bicarbonate by treating with *p*-nitrobenzoyl chloride. The γ-ethyl *p*-nitrobenzoylglutamate (II) was converted to the hydrazide (III) by use of hydrazine hydrate and then to the azide (IV) by treating with nitrous acid. This azide then reacted with diethyl glutamate in ethyl acetate according to previously described methods[4,5,6] to yield the diester of the *p*-nitrobenzoyl dipeptide (VI).

It was later found that the azide would also react with γ-ethyl glutamate or glutamic acid in an aqueous sodium bicarbonate solution to yield the *p*-nitrobenzoyl dipeptide as the monoester (VIII) or as the triacid (V). The *p*-nitrobenzoyl-γ-glutamylglutamic acid (V) was reduced to the corresponding *p*-amino compound and converted to the pteroyl derivative as previously described.[1,7] In order to characterize the *p*-aminobenzoyl dipeptide, it was esterified and isolated as the triethyl ester.

The *p*-nitrobenzoyl tripeptide was prepared by

(1) Boothe, *et al.*, THIS JOURNAL, **70**, 1099 (1948).
(2) Bergmann and Zervas, *Ber.*, **65**, 1192 (1932).
(3) Bergmann and Zervas, *Z. physik. Chem.*, **221**, 53 (1933).
(4) Fruton and Bergmann, *J. Biol. Chem.*, **127**, 637 (1939).
(5) Fruton, *ibid.*, **146**, 463 (1942).
(6) Plentl and Page, *ibid.*, **163**, 59 (1946).
(7) Waller, *et al.*, THIS JOURNAL, **70**, 19 (1948).