Anal. Calcd. for $C_{15}H_{17}ON$: C, 79.26; H, 7.54. Found: C, 79.00; H, 7.62.

Clemmensen Reduction of 2-Piperidino-3-phenyl-2-cyclobutenone.—Zinc powder (250 g.) was treated with a solution of 25 g. of mercuric chloride in 250 ml. of water and 12.5 ml. of concentrated hydrochloric acid. The supernatant liquid was decanted and the solid washed with distilled water. A mixture of 250 ml. of water, 250 ml. of concentrated hydrochloric acid, 25 ml. of ethanol and 20 g. of 2-piperidino-3-phenyl-2-cyclobutenone was added to the amalgamated zinc. The reaction mixture was allowed to reflux for 75 min. and then was steam distilled. The distillate was extracted with ether; the organic layer was dried over magnesium sulfate and carefully distilled. Phenylcyclobutane (2.6 g., 22%) was obtained which was identified by comparison of its infrared spectrum with that of an authentic sample.

[CONTRIBUTION FROM THE LABORATORIES OF THE PHARMACEUTICAL RESEARCH DIVISION OF CIBA LTD.]

Nucleophilic Displacement Reactions of Some Halogen-substituted Phenylcyclobutenes and the Ring-opening Reaction of 2-Chloro-4-piperidino-3-phenyl-2-cyclobutenone

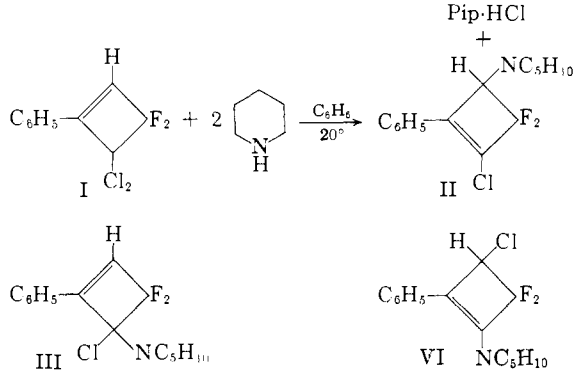
BY ERWIN F. JENNY AND JEAN DRUEY

RECEIVED NOVEMBER 6, 1959

Nucleophilic substitution reactions of 1,1-difluoro-2,2-dichloro-3-phenylcyclobutene, 1,1,2-trifluoro-2-chloro-3-phenylcyclobutene and 1,1-difluoro-2,4-dichloro-3-phenylcyclobutene with piperidine in benzene have been found to proceed with rearrangement. Hydrolysis of 1,1-difluoro-2-chloro-4-piperidino-3-phenyl-2-cyclobutene led to 2-chloro-4-piperidino-3-phenyl-2-cyclobutenone, which underwent a fast ring-opening reaction at room temperature with a vinyl ketene as the intermediate. The ketene added water to produce 2-chloro-3-phenyl-4-piperidino-3-butenoic acid, which, on warming *in vacuo*, eliminated a molecule of HCl to yield 3-phenyl-4-hydroxy-4-piperidino-2-butenoic acid lactone. The ultraviolet and infrared spectra of β-aminostyrenes are discussed.

Roberts and co-workers[1] have reported a simple way of synthesizing halogen-substituted phenylcyclobutenes and phenylcyclobutenones. The structural features and simplicity of the preparations prompted us to produce a wide variety of this type of compound for pharmacological and microbiological screening. The present paper will stress those of our findings that are of more immediate interest from a chemical point of view. In the few areas where our efforts overlapped with the work of Roberts and his group,[1c,1d] the results are in good agreement; mainly, however, our separate efforts proved to be complementary.

Nucleophilic Displacement Reaction of 1,1-Difluoro-2,2-dichloro-3-phenylcyclobutene (I) **with Piperidine in Benzene.**—1,1-Difluoro-2,2-dichloro-3-phenylcyclobutene (I) reacts very smoothly with piperidine in benzene to yield a new monopiperidino compound which was assigned structure II. It is completely inert in its reactivity both toward excess base and dilute mineral acid, a behavior which would hardly be expected of the two possible isomeric substitution products III and IV.[2] Compound III is most likely the highly reactive intermediate of a nucleophilic displacement described in the following section. The amino-styrene IV would supposedly hydrolyze under the influence of dilute hydrochloric acid. However, a hydrochloride (λ_{max} 260 mμ, ε 19,600, 95% ethanol) could be prepared of product II which hydrolyzed in water to give back unchanged the free base (λ_{max} 262 mμ, ε 19,900, 95% ethanol; 264 mμ, ε 19,700, CH_2Cl_2). Also, prolonged warming in an acid medium did not affect the substitution product. On the basis of these observations, combined with further evidence mentioned in the last section of this paper, the monopiperidino compound was assigned structure II.



The nucleophilic displacement reaction on the allylic *gem*-dichloride I obviously proceeded with rearrangement. Very probably we are dealing here with an SN2′ mechanism, a mode of substitution which had to be reckoned with, since it has been demonstrated by de la Mare and co-workers[3] that this type of substitution reaction is quite common with a number of open chain allylic *gem*-dihalides. With the stereochemical relationship between the entering and leaving group in SN2′ displacements having been established as *cis*,[4] it is possible to propose a conceivable mechanism for the nucleophilic attack of piperidine on compound I involving the cyclic transition state V.[5]

In this connection the fact may also be of interest that in 1,1,2-trifluoro-2-chloro-3-phenylcyclo-

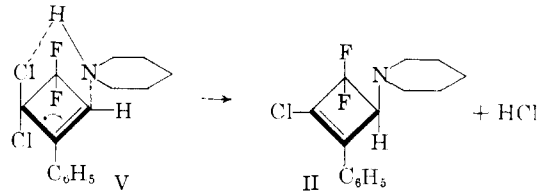
(1) (a) J. D. Roberts, G. B. Kline and H. E. Simmons, Jr., THIS JOURNAL, **75**, 4765 (1953). (b) E. J. Smutny and J. D. Roberts, *ibid.*, **77**, 3420 (1955) (c) Y. Kitahara, M. C. Caserio, F. Scardiglia and J. D. Roberts, *ibid.*, **82**, 3106 (1960) (d) M. C. Caserio, H. E. Simmons, Jr., A. E. Johnson and J. D. Roberts, *ibid.*, **82**, 3102 (1960).

(2) (a) C. T. Mason, C. W. R. Wade and H. W. Pouncy, Jr., *ibid.*, **76**, 2255 (1954); (b) P. Ballinger, P. B. D. de la Mare, G. Kohnstam and B. M. Pratt, *J. Chem. Soc.*, 3641 (1955).

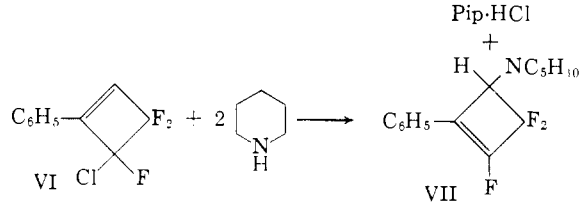
(3) P. B. D. de la Mare and C. A. Vernon, *ibid.*, 3325, 3331, 3628 (1952); P. B. D. de la Mare, E. D. Hughes, P. C. Merriman, L. Pichat and C. A. Vernon, *ibid.*, 2563 (1958); for further references on SN2′ see footnotes 1c and 1d.

(4) W. G. Young, I. D. Webb and H. L. Goering, THIS JOURNAL, **73**, 1076 (1951); G. Stork and W. N. White, *ibid.*, **75**, 4119 (1953); **78**, 4609 (1956).

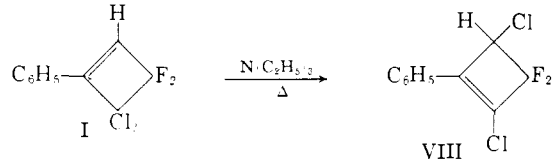
(5) A. G. Catchpole, E. D. Hughes and C. K. Ingold, *J. Chem. Soc.*, 8 (1948).



butene (VI) the more reactive chloride is displaced by piperidine in an SN2′ reaction to yield VII.



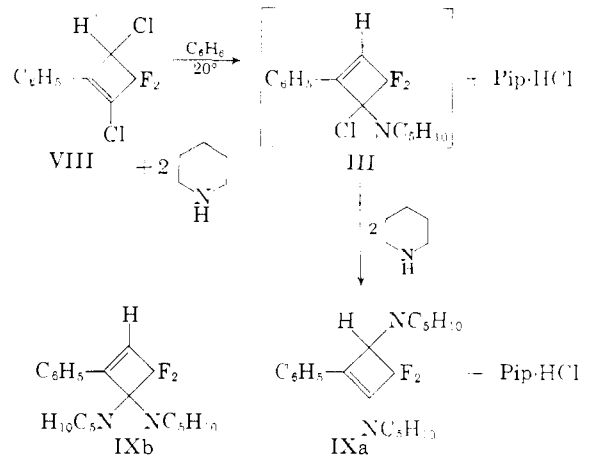
Nucleophilic Displacement Reaction of 1,1-Difluoro-2,4-dichloro-3-phenylcyclobutene (VIII) with Piperidine in Benzene.—1,1-Difluoro-2,2-dichloro-3-phenylcyclobutene (I) can be isomerized easily to the isomeric 2,4-dichloro compound VIII, as was reported by Roberts and co-workers[1a]



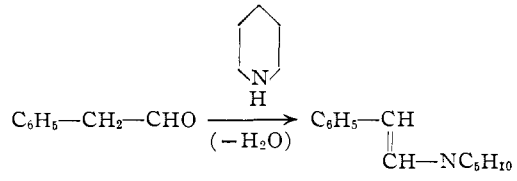
If equimolar quantities of piperidine and 2,4-dichloro compound VIII are allowed to react with each other, a disubstitution product (IX), piperidine hydrochloride and starting material VIII are obtained in the ratio 1:2:3. The formation of a dipiperidino-cyclobutene derivative and the absence of any monosubstitution product strongly indicate that the loss of the first chlorine atom proceeds by an SN2′ mechanism, since the alternative SN2 formulation would lead to the stable monopiperidino compound II. This result is somewhat surprising since the allylic chlorine is easily accessible for the usual SN2 type displacement and the point of attack at the double bond is substituted by a chlorine atom.[6] The intermediate III which is proposed for this displacement reaction would be expected to react more rapidly with piperidine than does the starting material VIII.[2]

Compound IX is an almost colorless oil which turns red on standing. It can be converted into a crystalline monohydrochloride in anhydrous ethyl acetate. The assignment of structure IXa rather than IXb is based on evidence obtained from ultraviolet, infrared and nuclear magnetic resonance spectra.

(*a*) *Ultraviolet evidence:* From styrene (λ_{max} 246 mμ)[7] to a phenylcyclobutene of type I, the ultraviolet absorption maximum moves upwards by about 5–10 mμ. Introduction of a chlorine at the double bond to generate compounds like VIII causes the absorption maximum to increase by another 5–10 mμ. If, however, a nitrogen atom is adjacent to a conjugated system, a considerable shift of the UV absorption band toward longer wave



lengths may occur. Thus, 1-diethylaminobutadiene absorbs at 281 mμ (ϵ 24,000) whereas unsubstituted butadiene has its absorption maximum at 217 mμ (ϵ 21,000).[8] With these increments in mind, one would expect the β-aminostyrene compound IXa to absorb above 300 mμ and compound IXb at or a little below 255 mμ. In fact, a methylene chloride solution of the disubstitution product shows an ultraviolet absorption band at 309 mμ (ϵ 11,000) with no absorption below this wave length. Since we could not find any information in the literature pertaining to physical properties of β-aminostyrenes, we prepared β-piperidinostyrene from phenylacetaldehyde and piperidine in the presence of a catalytic amount of *p*-toluenesulfonic acid



As expected, the ultraviolet absorption spectrum of β-piperidinostyrene in methylene chloride showed only one band at 305 mμ (ϵ 14,700), a fact which strongly supports structure IXa for IX.

Other β-aminostyrenes described later in this paper (compounds XIX, XXVIII and XXIX) do not fit into this pattern. The conjugation of these compounds is disturbed to a considerable extent by steric hindrance. Their ultraviolet spectra (λ_{max} 250 mμ; ϵ 8,000) show that the nitrogen atoms are no longer in a favorable position for their unshared electron pairs to participate with the π-electrons of the styrene systems. The presence or absence of this type of conjugation manifested itself in catalytic hydrogenation experiments: the double bond of the sterically hindered enamines XIX, XXVIII and XXIX could be hydrogenated very easily, whereas compounds IX and β-piperidinostyrene with their extended conjugation showed almost complete resistance to catalytic hydrogenation.

(*b*) *Infrared evidence:* During this study it became apparent that most of the investigated β-aminostyrenes show an infrared band around 6.0–

(6) For main references see footnotes in 1c.

(7) Compare also Table I in 1c.

(8) K. Bowden, E. A. Braude, E. R. H. Jones and B. C. L. Weedon *J. Chem. Soc.*, **45**, 945, 948 (1946).

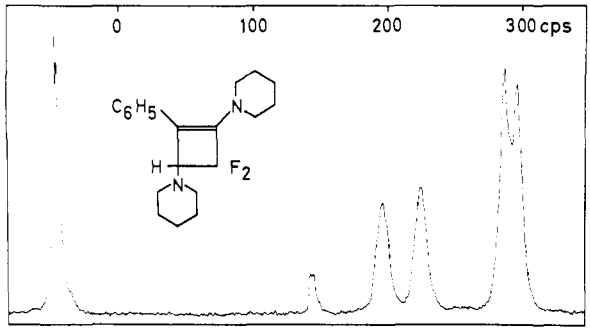


Fig. 1.—Proton magnetic resonance spectrum of 1,1-difluoro-2,4-dipiperidino-3-phenylcyclobutene (IXb). The spectrum of a 0.2-molar solution of IXb in carbon tetrachloride was recorded with a Varian Associates High Resolution Spectrometer V-4300 C at 60 mc. and 12-in. magnet equipped with Super Stabilizer, using a precision external annular cell (Wilmod Glass Co., Landisville, New Jersey) with pure benzene taken as zero of reference.

6.1 microns with a very high extinction. This absorption can be attributed to the conjugated double bond. Since the disubstitution product of VIII with piperidine shows an extremely strong band in that region also, structure IXa is again favored over structure IXb.

(*c*) *N.m.r. evidence:* The proton magnetic resonance spectrum, which was recorded and interpreted by Dr. René F. Zürcher of our Physics Department, allowed us to make an unequivocal choice between the structures IXa and IXb.

Compound IXa has five phenyl hydrogens, one allylic hydrogen on the four-membered ring, and, on the non-equivalent piperidine rings, two groups of four α- and two groups of six β,γ-methylene hydrogens each. Spin-spin interaction with the two non-equivalent fluorines would be expected to split the n.m.r. absorption band of the allylic proton into four peaks.

Compound IXb has five phenyl hydrogens, one vinyl hydrogen on the four-membered ring, and, on the two equivalent piperidine rings, eight coinciding α- and twelve β- and γ-methylene hydrogens. The two equivalent fluorines would be expected to split the n.m.r. absorption band of the vinyl hydrogen into a 1:2:1-triplet.

TABLE I

PROTON N.M.R. ABSORPTION OF 1,1-DIFLUORO-2,4-DIPIPERIDINO-3-PHENYLCYCLOBUTENE (IXa)

	Cps.[a]	Ppm.
C_6H_5	−48, −46	δ = −0.80, −0.77
Allylic H	145	2.42
α-CH_2 in piperidine rings	197, 226	3.28, 3.77
β- and γ-CH_2	289, 298	4.82, 4.97

[a] The shift values were determined by the audio-frequency side band method and are precise to within 2 cps. The sign of the shift is chosen to be positive when the resonance falls at a higher applied field than the reference. No correction was made for the bulk susceptibility differences.

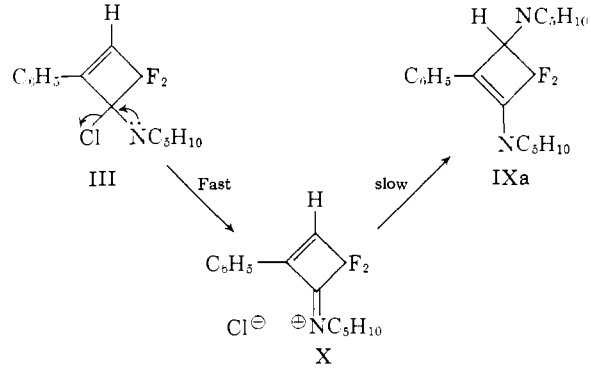
As can be seen from Fig. 1 and 2 and Table I the n.m.r. absorption spectrum of the difluorodipiperidinophenylcyclobutene shows five phenylprotons in the form of two unresolved peaks at −48 and −46 cps., one allylic proton with a band at 145 cps., two peaks at 197 and 226 cps. representing two

Fig. 2.—Fine structure of the allylic proton of compound IXb; $J_1 \cong 2.5$ cps., $J_2 \cong 1.0$ cps.

groups of four α-methylene protons each, and two peaks at 289 and 298 cps. totalling twelve β- and γ-methylene protons. The band at 197 cps. is tentatively assigned to the piperidino group at the double bond. The band of the allylic proton at 145 cps. is split into four peaks (Fig. 2), because of the mentioned spin–spin interaction with the two non-equivalent fluorines of compound IXa. The allylic proton couples with the *cis* and *trans* fluorine nuclei with two different spin coupling constants: $J_1 \cong$ 2.5 cps. and $J_2 \cong$ 1.0 cps. This splitting pattern and the position of the chemical shift clearly show that the ring proton cannot be attached to the double bond.

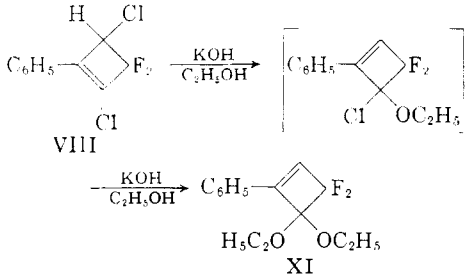
The evidence adduced from the nuclear magnetic resonance data unequivocally demonstrates, therefore, that the disubstitution product of VIII with piperidine must be assigned structure IXa.

When the substitution reaction of VIII to IXa is followed spectrophotometrically in methylene chloride a band develops at 276 mμ (highest ϵ observed so far is 10,000), which then vanishes. This finding seems to indicate that the transition from the highly reactive intermediate III to the final product is not a simple SN2′ reaction but a two-step process with the intermediate X absorbing at 276 mμ



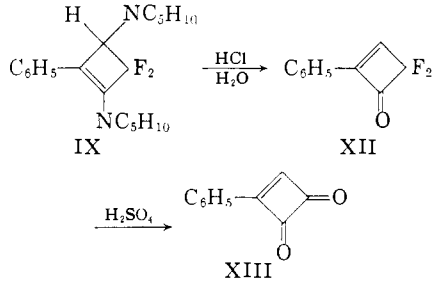
The interesting facet of such an SN1 mechanism of substitution and rearrangement (in fact, an SN1′ reaction) is that the ionization step is fast, because it is accelerated by the unshared electron pair of the nitrogen atom and leads to a relatively stable ion-pair X. This process is then followed by the final and slow step wherein the carbimonium cation X reacts with the nucleophile to yield the rearranged product IXa.

The course of this reaction is an interesting contrast to the findings of Roberts and co-workers,[1]

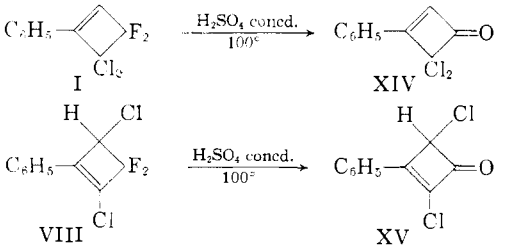


who obtained the *gem*-diether XI from the reaction of VIII with potassium hydroxide in ethanol

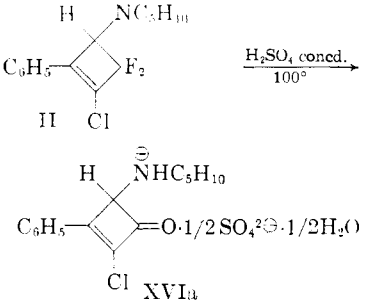
Treatment of IXa with warm dilute hydrochloric acid led to the formation of 4,4-difluoro-2-phenylcyclobutenone (XII) (λ_{max} 261 mμ, ϵ 15,000, 95% ethanol), a compound which was independently obtained by Roberts and co-workers,[1c] through hydrolysis of the diether grouping of compound XI. Hydrolysis of XII with hot concentrated sulfuric acid yielded phenylcyclobutadienoquinone (XIII), which had been prepared by Smutny and Roberts[1b] by a different route.



Hydrolysis of 1,1-Difluoro-2-chloro-4-piperidino-3-phenyl-2-cyclobutene (II) with Concentrated Sulfuric Acid at 100°.—The customary chemical inertness of the fluorine atoms in organic molecules is fortunately not so pronounced in fluorine-substituted phenylcyclobutenes of the type discussed in this paper. Roberts and co-workers[1a] have developed a useful process by which the fluorines can be removed from the four-membered ring. Compounds I and VIII lose their *gem*-difluoride grouping in concentrated sulfuric acid at 100° and give the corresponding ketones XIV and XV in good yields

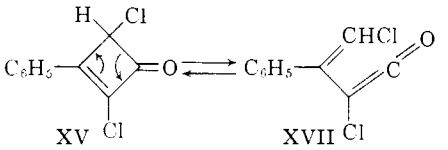


This hydrolysis reaction was applied to the monopiperidino compound II, whereby the corresponding ketone could be isolated in the form of a colorless, crystalline salt-hydrate XVI. It was recrystallized from water with considerable loss, and organic solvents decomposed the compound instantaneously. Its infrared absorption at 5.6 μ in Nujol or potassium bromide indicated the presence of a carbonyl group and the ultraviolet spectrum in water showed an absorption band at 284 mμ (ϵ 15,300), whose extinction coefficient must be regarded as a minimal value because of partial decomposition of the salt-hydrate in water. These data tally well with the expected structure for ketone salt (XVIa, free base = XVIb).

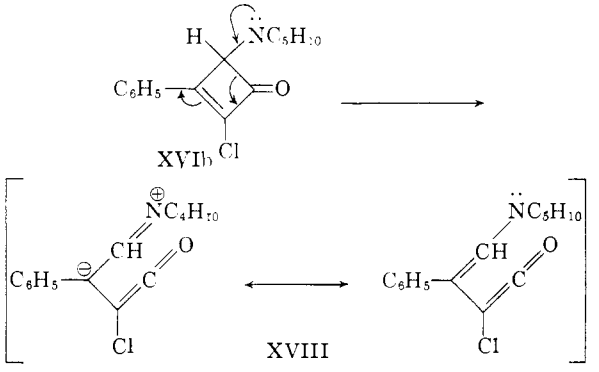


The behavior of XVIa when it came into contact with organic solvents was rather surprising. In the process of wetting the colorless crystals with solvents such as methylene chloride, benzene, diethyl ether or ethanol, the surface of the solid and the organic liquid phase turned yellow instantaneously. The infrared spectrum of such a solution, with methylene chloride as the solvent, again showed a band at 5.6 μ with an additional one, although slightly stronger, at 5.7 μ. After about 2 hours both bands had merged into one weak and broad absorption band between 5.7–5.8 μ.

The possibility that the rapidly decomposing compound was the free base of ketone XVIb could be verified by trapping the first intermediate of this reaction. A few years ago one of us and Roberts[9] reported on the mechanism of racemization of optically active 2,4-dichloro-3-phenylcyclobutenone (XV). It could be shown that the racemization reaction involves a reversible formation of (1-phenyl-2-chloroethenyl)-chloroketene (XVII). This thermal ring-opening reaction in chloroform or glacial acetic acid at 100° proceeded with a half-life of about 1 hour.



It is assumed that this type of mechanism also operates in the decomposition reaction of the free base XVIb, giving the vinyl ketene XVIII as the first intermediate

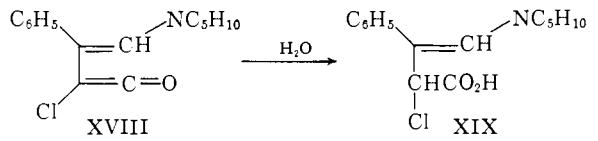


(9) E. F. Jenny and J. D. Roberts, THIS JOURNAL, 78, 2005 (1956).

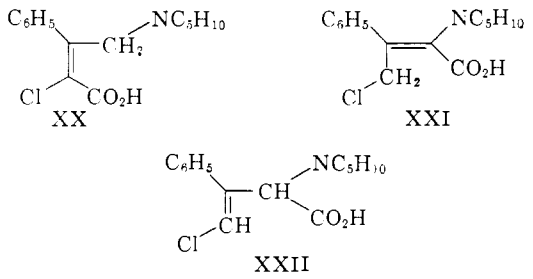
It is interesting to note that the transition from XV to XVIb causes the ring-opening reaction to be faster by several powers of ten, the half-life of the free base XVIb being about 30 minutes at 20°. Its salt, in which the free electron pair of the nitrogen atom is blocked by a proton, is stable at room temperature. The corresponding 2,2-dichloro-ketone XIV does not undergo this thermal ring-opening reaction at all within the investigated temperature range up to 100°.

The fast decomposition of salt XVIa in anhydrous organic solvents is probably due to its partial hydrolysis, which is enhanced by the low basicity of the free base XVIb. Thus generated, it will enter into the organic phase and undergo thermal ring opening. The infrared absorption bands at 5.7–5.8 μ of such a solution can probably be ascribed to the intermediate XVIII and some of its reaction products.

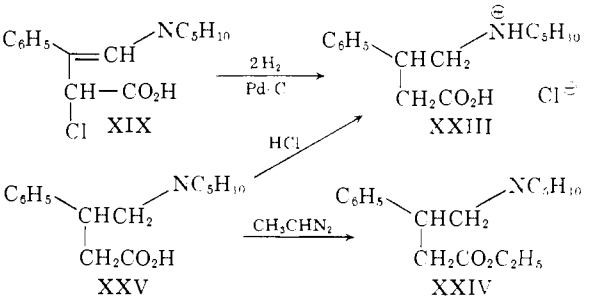
As mentioned earlier, intermediate XVIII can easily be trapped and converted into a relatively stable compound. A solution of the free base XVIb in ether, which is saturated with water, will deposit the crystalline β,γ-unsaturated acid XIX, which arises from addition of one molecule of water to the ketene grouping of the ring-opening product XVIII

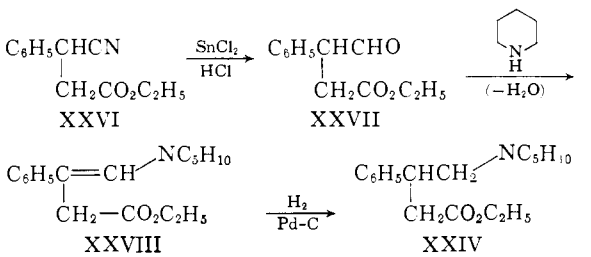


Since the ultraviolet spectrum of XIX in 95% ethanol or water showed only one absorption band at 254 mμ (ε 8,000) or 248 mμ (ε 7,150), respectively, the isomeric cinnamic acid derivatives XX and XXI were excluded as unlikely structures for the open-chain acid.[10] The ultraviolet evidence also rules out structure XXII (and XX) since the spectrum indicates that the nitrogen atom of the open-chain acid is adjacent to a double bond.

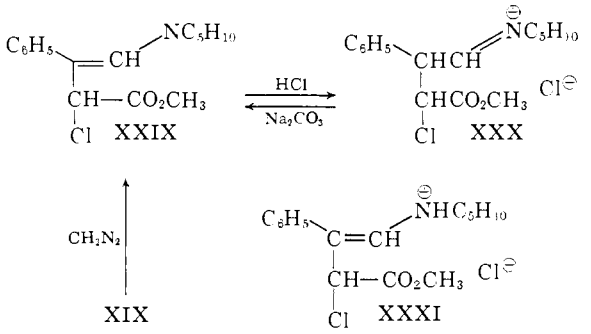


An unequivocal synthesis of the skeletal framework of XIX made it possible to exclude with certainty structures XXI and XXII. Acid XIX was hydrogenated over palladium to the hydrochloride XXIII. The ethyl ester XXIV of the corresponding free γ-amino acid XXV proved to be identical with an authentic sample of ethyl 3-phenyl-4-piperidinobutyrate as shown by infrared spectra. Compound XXIV was obtained by reducing ethyl β-phenyl-β-cyanopropionate (XXVI)[11] to the aldehyde XXVII,[12] which was converted quantitatively into the corresponding enamine XXVIII (λ_{max} 250 mμ, ε 8,000, hexane) by treating it with piperidine in benzene in the presence of a catalytic amount of *p*-toluenesulfonic acid. The aminostyrene was hydrogenated in anhydrous ethyl acetate to the desired ethyl 3-phenyl-4-piperidinobutyrate (XXIV)





Acid XIX can be esterified easily with diazomethane to the corresponding methyl ester XXIX, which is convertible into a crystalline hydrochloride XXX. Aqueous sodium carbonate decomposes XXX to give back the free base XXIX in quantitative yield.



Compound XXIX absorbs at 242 mμ (ε 7,650) or 248 mμ (ε 8,000) in hexane or 95% ethanol, respectively. A solution of its hydrochloride in acetonitrile shows an absorption band at 270 mμ (ε 7,600). Structure XXX is preferred to the isomeric enammonium structure XXXI on account of the fact that enammonium salts have a styrene-like ultraviolet spectrum.[13] The absorption at 270 mμ may be due to a partial hydrolysis of the enimmonium salt with traces of water in the solvent and subsequent elimination of HCl leading to a cinnamic acid derivative. The same phenomenon is observed when the free acid XIX is treated with

(10) This argument should also be valid in case of a *cis*-relationship between the phenyl and carboxyl group.

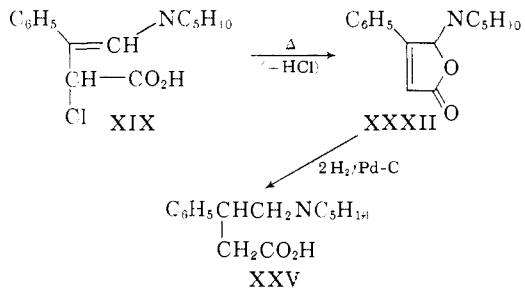
(11) C. F. H. Allen and H. B. Johnson, *Org. Syntheses*, **30**, 84 (1950).

(12) G. Swain, A. R. Todd and W. S. Waring, *J. Chem. Soc.*, 548 (1944).

(13) G. Opitz, H. Hellmann and H. W. Schubert, *Ann.*, **623**, 112, 117 (1959).

concentrated hydrochloric acid. Such a solution absorbs at 280 mμ (ε 7,350). The infrared spectrum did not enable us to distinguish between the two structures XXX and XXXI, since the ester-hydrochloride showed no bands at the wave lengths where NH—, C≡C— or C=N— groups usually absorb.[13]

A rather interesting reaction occurred when the free acid XIX was heated to 80° *in vacuo*. The long needles turned into a colorless powder, and the elemental analysis indicated the loss of one molecule of hydrogen chloride. Compound XXXII showed an ultraviolet absorption spectrum like that of cinnamic acid (215 and 276 mμ, ε 15,500 and 19,200, 95% ethanol). The spectrum was not changed on the addition of mineral acid.



The structure was established by catalytic hydrogenation, which led to the previously mentioned 3-phenyl-4-piperidinobutyric acid (XXV).

The γ-amino lactone is perfectly stable toward dilute aqueous mineral acid. It can be extracted from the reaction mixture with 2*N* hydrochloric acid and recovered quantitatively after prolonged heating of the acid solution. Phthalids which are substituted by a basic nitrogen in the 3-position are stable in hot water.[14] The authors do not, however, mention anything about the stability of these closely related compounds toward aqueous acids.

Acknowledgment.—We thank Drs. Marjorie C. Caserio and John D. Roberts for having sent us their manuscripts[1c,1d] prior to their publication, and Dr. René F. Zürcher of our Physics Department for recording and interpreting the n.m.r. spectrum.

Experimental[15]

1,1-Difluoro-2-chloro-4-piperidino-3-phenyl-2-cyclobutene (II).—To a solution of 11.0 g. of 1,1-difluoro-2,2-dichloro-3-phenylcyclobutene (I) in 30 ml. of anhydrous benzene was added dropwise a solution of 10 ml. of anhydrous piperidine in 25 ml. of anhydrous benzene. The reaction mixture was heated to 50° for 15 minutes. The precipitated piperidine hydrochloride (5.6 g.) was then removed by filtration. The filtrate was evaporated at 40° *in vacuo*. The crystalline residue of 12.8 g. of essentially pure II was recrystallized from acetonitrile and gave a product of m.p. 48–51°.

Anal. Calcd. for $C_{15}H_{16}NClF_2$: C, 63.49; H, 5.68; N, 4.94; Cl, 12.50. Found: C, 63.48; H, 5.58; N, 4.98; Cl, 12.53.

A solution of this compound in anhydrous ethyl acetate was treated with 4*N* HCl in anhydrous ethyl acetate. The hydrochloride thus obtained was recrystallized from anhydrous ethyl acetate and gave a product of m.p. 157–158°.

Anal. Calcd. for $C_{15}H_{17}NCl_2F_2$: C, 56.26; H, 5.35; N, 4.37; Cl, 22.15. Found: C, 56.16; H, 5.49; N, 4.65; Cl, 21.90.

2-Chloro-4-piperidinium-3-phenyl-2-cyclobutenone Sulfate (XVIa).—Concentrated sulfuric acid (27 ml.) was heated on a steam-cone in a flask equipped with a mechanical stirrer, and then 22.0 g. of 1,1-difluoro-2-chloro-4-piperidino-3-phenyl-2-cyclobutene (II) was added in one portion. Hydrogen fluoride evolution began at once. The mixture was heated and stirred for 10 minutes and then immediately cooled down to room temperature. Ice was added and the slowly separating crystals (24.0 g.) collected by filtration. They were washed with and recrystallized from water, whereby colorless needles were obtained, m.p. 70–72°.

Anal. Calcd. for $C_{30}H_{36}O_7N_2Cl_2S$: C, 56.34; H, 5.67; O, 17.51; N, 4.38; Cl, 11.09; S, 5.01. Found: C, 56.2; H, 5.8; O, 17.5; N, 4.1; Cl, 11.1; S, 5.1.

2-Chloro-3-phenyl-4-piperidino-3-butenoic Acid (XIX).—A solution of sulfate XVIa in water was shaken with ether. The yellow ether layer was extracted twice with 2*N* sodium carbonate, then saturated with water and allowed to stand at room temperature. After about 2 hr., long colorless needles of acid XIX had deposited, m.p. 144–147° dec.

Concentrated sulfuric acid (27 ml.) was heated on a steam cone in a flask equipped with a mechanical stirrer, and then 22.0 g. of 1,1-difluoro-2-chloro-4-piperidino-3-phenyl-2-cyclobutene (II) was added in one portion. Hydrogen fluoride evolution began at once. The mixture was heated and stirred for 10 minutes and then immediately cooled to room temperature. Ice was added and the solution neutralized with solid, anhydrous sodium carbonate. The reaction mixture was immediately extracted with ether. The ethereal solution of the free base XVIb was saturated with water and left standing overnight at room temperature. The deposited crystals of acid XIX were filtered off and recrystallized from water; 8.0 g., m.p. 148–150° dec.

Anal. Calcd. for $C_{15}H_{18}O_2NCl$: C, 64.39; H, 6.48; O, 11.44; N, 5.01; Cl, 12.67. Found: C, 64.39; H, 6.53; O, 11.31; N, 5.08; Cl, 12.88.

Methyl 2-Chloro-3-phenyl-4-piperidino-3-butenoate (XXIX).—Acid XIX (2.8 g.) in 50 ml. of methanol was esterified with 40 ml. of a 1 *M* ethereal diazomethane solution. The residue of the evaporated solution crystallized below 25°. It was dissolved in anhydrous ethyl acetate and treated with a solution of HCl in anhydrous ethyl acetate. The hydrochloride XXX separated in colorless crystals which were recrystallized from alcohol–ethyl acetate; m.p. 150° dec.

Anal. Calcd. for $C_{16}H_{21}O_2NCl_2$: C, 58.18; H, 6.41; O, 9.69; Cl, 21.47. Found: C, 58.17; H, 6.50; O, 9.80; Cl, 21.41.

The hydrochloride could be converted quantitatively into the free base XXIX with 2*N* sodium carbonate solution.

Lactone of 3-Phenyl-4-hydroxy-4-piperidino-2-butenoic Acid (XXXII).—A sample (1 g.) of XIX was heated to 80–90° under reduced pressure (0.02 mm.), whereby the colorless lactone XXXII sublimed to the cooler parts of the flask, m.p. 123–125°. At temperatures above 100° a black oil was formed from which the lactone could be extracted with aqueous hydrochloric acid. The acid solution was neutralized with 2 *N* sodium carbonate, and the precipitated lactone isolated by filtration. It was recrystallized from petroleum ether; m.p. 123–125°.

Anal. Calcd. for $C_{15}H_{17}O_2N$: C, 74.05; H, 7.04; O, 13.15; N, 5.76. Found: C, 73.98; H, 7.07; O, 13.46; N, 5.52.

An acidic aqueous solution of XXXII was kept at 50–60° for 2 hours. The lactone could be recovered unchanged after this treatment. With sodium hydroxide, piperidine was split off immediately.

Hydrochloride of 3-Phenyl-4-piperidinobutyric Acid (XXIII).—Acid XIX (1.40 g.) was dissolved in 95% ethanol (70 ml.) and hydrogenated at room temperature and atmospheric pressure in the presence of 10% palladium-on-charcoal (150 mg). Two moles of hydrogen per mole of XIX was absorbed. The catalyst was separated by filtration and the filtrate evaporated to dryness at 40° *in vacuo*. The solid residue (1.4 g. of essentially pure XXIII) was recrystallized from anhydrous alcohol and yielded colorless crystals, m.p. 210–214°. The infrared spectrum of XXIII in Nujol was identical with the one of the hydrochloride of compound XXV.

(14) D. D. Wheeler, D. C. Young and D. S. Erley, *J. Org. Chem.*, **22**, 547 (1957).

(15) We are indebted to Mr. Peter Schäublin for assistance in the experimental work. Melting and boiling points are not corrected. Analyses are by Dr. H. Gysel and W. Padowetz of our Analytical Department.

Anal. Calcd. for $C_{15}H_{22}O_2NCl$: O, 11.28; N, 4.94; Cl, 12.49. Found: O, 10.95; N, 4.93; Cl, 12.64.

3-Phenyl-4-piperidinobutyric Acid (XXV).—Lactone XXXII (1.0 g.) was dissolved in 95% ethanol (50 ml.) and hydrogenated at room temperature and atmospheric pressure in the presence of 10% palladium-on-charcoal (100 mg). Two moles of hydrogen per mole of XXXII was absorbed. The catalyst was separated by filtration, and the filtrate evaporated to dryness at 40° *in vacuo*. The solid residue (0.9 g. of essentially pure XXV) was recrystallized from ethyl acetate and yielded colorless, extremely water-soluble crystals, m.p. 154–157°.

Anal. Calcd. for $C_{15}H_{21}O_2N$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.70; H, 8.68; N, 5.49.

A hydrochloride was obtained by treating a solution of XXV in anhydrous ethyl acetate with 4 *N* HCl in anhydrous ethyl acetate, and recrystallizing the precipitate from anhydrous alcohol, m.p. 210–214°. Its infrared spectrum in Nujol proved to be identical with the one of compound XXIII. Mixed m.p. of the two hydrochlorides was without depression.

Ethyl 3-Phenyl-4-piperidinobutyrate (XXVII). (a) From XXV.—Acid XXV (0.5 g.) was dissolved in ethanol (10 ml.) and treated with 30 ml. of a 1 *M* ethereal diazoethane solution. The oily residue of the evaporated solution was dissolved in methylene chloride. The infrared spectrum of this solution was identical with the one of compound XXVII prepared as described under (b).

(b) **From XXVII.**—A solution of 4.50 g. of ethyl β-formyldihydrocinnamoate,[12] 1.89 g. of piperidine and a catalytic amount of *p*-toluenesulfonic acid in 20 ml. of anhydrous benzene was boiled for 2.5 hr. in an open flask. The evaporating benzene was replaced every 10 minutes by anhydrous benzene. The reaction mixture was then evaporated *in vacuo* and yielded 5.6 g. of enamine XXVIII as a yellow oil.

Crude XXVIII (0.5 g.) was dissolved in anhydrous ethyl acetate (25 ml.) and hydrogenated at room temperature and atmospheric pressure in the presence of 10% palladium-on-charcoal (100 mg.); 1 mole of hydrogen per mole of XXVIII was absorbed rapidly. The catalyst was separated by filtration, and the filtrate evaporated *in vacuo*. The infrared spectrum of the oily residue in methylene chloride was identical with the one of compound XXIV prepared as described under (a).

1,1,2-Trifluoro-3-phenyl-4-piperidino-2-cyclobutene (VII).—To a solution of 10.9 g. of 1,1,2-trifluoro-2-chloro-3-phenylcyclobutene (VI) in 30 ml. of anhydrous benzene was added dropwise a solution of 10 ml. of anhydrous piperidine in 20 ml. of anhydrous benzene. The reaction mixture was heated to 50° for 30 minutes. The precipitated piperidine hydrochloride (6.05 g) was then removed by filtration. The filtrate was evaporated at 40° *in vacuo*. The residue (13.0 g. of essentially pure VII) crystallized after standing overnight. It was recrystallized from methanol and yielded colorless VII, m.p. 40–42°.

Anal. Calcd. for $C_{15}H_{16}NF_3$: C, 67.40; H, 6.03; N, 5.24. Found: C, 67.15; H, 5.78; N, 5.27.

1,1-Difluoro-2,4-dipiperidino-3-phenylcyclobutene (IX).—To a solution of 99.0 g. of 1,1-difluoro-2,4-dichloro-3-phenylcyclobutene (VIII) in 270 ml. of anhydrous benzene was added dropwise a solution of 225 ml. of anhydrous piperidine in 225 ml. of anhydrous benzene. The reaction mixture was then kept at 60° for 60 minutes. The precipitated piperidine hydrochloride (97.0 g.) was removed by filtration. The filtrate was evaporated at 45° *in vacuo*, whereby 143 g. of IX was obtained in form of a yellow oil. A sample of this oil was dissolved in anhydrous ethyl acetate, and a solution of HCl in the same solvent added. The colorless monohydrochloride thus obtained was recrystallized from chloroform–ethyl acetate, m.p. 158–160°. During this process piperidine hydrochloride would occasionally crystallize with the hydrochloride IX.

Anal. Calcd. for $C_{20}H_{27}N_2ClF_2$: C, 65.12; H, 7.38; N, 7.59; Cl, 9.61. Found: C, 64.10; H, 7.52; N, 7.65; Cl, 9.91.

4,4-Difluoro-2-phenylcyclobutenone (XII).—Crude hydrochloride IX (3.2 g.) was suspended in 30 ml. of 2 *N* hydrochloric acid and kept at 70° for 45 minutes. The reaction mixture was cooled to room temperature, whereby the separated oil solidified. It was crystallized from chloroform–pentane and yielded 1.1 g. of colorless crystals, m.p. 83–86°, which easily sublime at 0.03 mm. and 40°.

Anal. Calcd. for $C_{10}H_6OF_2$: C, 66.67; H, 3.36. Found: C, 66.06; H, 3.67.

Phenylcyclobutadienoquinone (XIII).[1b]—4,4-Difluoro-2-phenylcyclobutenone (XII) (200 mg.) was stirred with concentrated sulfuric acid (2 ml.) at 100°. Ice was added to the reaction mixture after 3 minutes. The precipitate was collected by filtration and recrystallized from acetone. The yellow crystals, m.p. 152°, gave no depression with an authentic sample of phenylcyclobutadienoquinone.

β-Piperidinostyrene.[16]—A solution of 9.2 g. of phenylacetaldehyde in 25 ml. of anhydrous benzene, a small crystal of *p*-toluenesulfonic acid and a solution of 7.0 g. of anhydrous piperidine were mixed. The solution turned hot and turbid instantaneously. It was boiled for 2 hr. in an open flask. The evaporating benzene which removed the eliminated water was replaced from time to time by anhydrous benzene. The reaction mixture was then evaporated *in vacuo* and yielded 15.9 g. of β-piperidinostyrene as a yellow oil. It was distilled under reduced pressure and yielded 7.5 g. of a yellow, low-melting solid, b.p. 95–100° at 0.02 mm.

Anal. Calcd. for $C_{13}H_{17}N$: C, 83.37; H, 9.15; N, 7.48. Found: C, 83.17; H, 9.20; N, 7.35.

The infrared spectrum of the product showed an extremely strong double bond absorption band at 6.1 μ.

(16) C. Mannich and H. Davidsen, *Ber.*, **69**, 2106 (1936).

BASEL, SWITZERLAND

[CONTRIBUTION FROM THE WM. H. NICHOLS CHEMICAL LABORATORY, NEW YORK UNIVERSITY]

The Arylation of Cycloheptatriene

BY KARL WEISS AND SISTER MARIE LALANDE, C.S.J.

RECEIVED JULY 31, 1959

Phenyl-, *p*-chlorophenyl- and *p*-nitrophenylcycloheptatriene have been prepared by the direct arylation of cycloheptatriene under the conditions of the Meerwein reaction. The reaction was accompanied by the formation of cycloheptatrienylacetone. On the basis of spectral data and an analysis of the pertinent aspects of another synthesis of phenylcycloheptatriene, structures are proposed for the arylcycloheptatrienes obtained.

Interest in the radical chemistry of cyclic polyolefins has prompted us to investigate the arylation of cycloheptatriene, formally written as Ia, but preferably considered to be planar and pseudo-aromatic.[1] The copper salt-catalyzed decomposition of diazonium salts in aqueous acetone (Meerwein reaction) was chosen as the radical source[2] since this system does not readily initiate the polymerization of olefins. The reaction of radicals with Ia can proceed in two ways, (i) by hydrogen abstraction from the methylene group and (ii) by

(1) (a) W. von E. Doering, G. Laber, R. Vonderwahl, N. F. Chamberlain and R. B. Williams, THIS JOURNAL, **78**, 5448 (1956); (b) E. W. Abel, M. A. Bennett and G. Wilkinson, *Proc. Chem. Soc.*, 152 (1958).

(2) (a) J. K. Kochi, THIS JOURNAL, **79**, 2942 (1957); (b) S. C. Dickerman, K. Weiss and A. K. Ingberman, *ibid.*, **80**, 1904 (1958).