The upper layer, consisting of an acetone solution of the iminodiester, was concentrated *in vacuo* and the residue was distilled; b.p. 109–110° (3.5 mm.), $n^{20}D$ 1.4364, d^{26}_4 1.0162, yield 175 g. (81%). The boiling point at 738 mm. was 248° (Heintz[19] reported 200–220° at atmospheric pressure for the compound prepared by a different method).

Anal. Calcd. for $C_{10}H_{19}NO_4$: C, 55.28; H, 8.82; N, 6.45. Found: C, 55.38; H, 8.86; N, 6.49.

The methiodide, prepared in the usual manner,[20] crystallized on cooling in Dry Ice. It was recrystallized from ethyl acetate, colorless needles, m.p. 62.5–64°.

Anal. Calcd. for $C_{11}H_{22}NO_4I$: C, 36.78; H, 6.17. Found: C, 36.86; H, 6.41.

N-Ethylhexamethylenimine (1-Ethylazacycloheptane).—Hexamethylenimine, as obtained[21] from ε-caprolactam, was converted by the usual alkylation procedure[22] with ethyl iodide to the N-ethyl compound in 66% yield, b.p. 90.5–91.5° (90 mm.), 153.5° (741 mm.), $n^{20}D$ 1.4571.

Anal. Calcd. for $C_8H_{17}N$: C, 75.52; H, 13.47; N, 11.01. Found: C, 75.56; H, 13.57; N, 11.21.

The picrate crystallized from ethanol as yellow needles, m.p. 173–173.5°.

Anal. Calcd. for $C_{14}H_{20}N_4O_7$: C, 47.19; H, 5.66; N, 15.72. Found: C, 47.49; H, 5.84; N, 15.72.

The methiodide crystallized from absolute ethanol as colorless leaflets, m.p. 244.5–245.5° dec.

Anal. Calcd. for $C_9H_{20}NI$: C, 40.16; H, 7.49; N, 5.20. Found: C, 40.29; H, 7.41; N, 5.17.

1-Ethyl-2-methylpiperidine.—α-Pipecoline was converted by treatment with ethyl iodide to the N-ethyl compound, b.p. 69° (50 mm.), 142° (744 mm.), $n^{20}D$ 1.4480 (reported[23,24] b.p. 148–149° (758 mm.), $n^{24.5}D$ 1.4480). The picrate crystallized as yellow platelets from ethanol, m.p. 189.5–190.5°.

Anal. Calcd. for $C_{14}H_{20}N_4O_7$: C, 47.19; H, 5.66; N, 15.72. Found: C, 47.47; H, 5.65; N, 15.50.

(19) W. Heintz, *Ann.*, **145**, 214 (1868).

(20) R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," 3rd edition, John Wiley and Sons, Inc., New York, N. Y., 1948, p. 180.

(21) L. Ruzicka, M. Kobelt, O. Häfliger and V. Prelog, *Helv. Chim. Acta*, **32**, 544 (1949).

(22) W. J. Hickinbottom, "Reactions of Organic Compounds," 2nd. Edition, Longmans, Green and Company, Inc., New York, N. Y., 1948, p. 299.

(23) W. Hohenemser and R. Wolffenstein, *Ber.*, **32**, 2520 (1899).

(24) A. Ladenburg, *Ann.*, **304**, 54 (1899).

The methiodide crystallized from ethyl acetate–ethanol as colorless granular crystals, m.p. 305° dec.

Anal. Calcd. for $C_9H_{20}NI$: C, 40.16; H, 7.49; N, 5.20. Found: C, 39.94; H, 7.33; N, 5.34.

1-Ethyl-2,5-dimethylpyrrole.—The procedure used was adapted from that for 2,5-dimethylpyrrole.[25] An application of the method used by Elderfield and Hageman[26] for 1-*n*-butyl-2,5-dimethylpyrrole gave a slightly better yield but the product was impure. A mixture of 57 g. (59.5 ml., 0.5 mole) of acetonylacetone and 22.5 g. (0.5 mole) of gaseous ethylamine dissolved in 50 ml. of water was shaken, with periodic cooling under the tap, until it no longer developed heat. The mixture was allowed to stand for 1 hour. The upper, oily layer was separated, the aqueous layer was extracted once with chloroform, and the extract was combined with the organic layer. After drying the solution and removing the chloroform, the product was distilled, b.p. 103.5–104.5° (45 mm.), 174° (739 mm.) (reported[27] 102° (79 mm.)), $n^{20}D$ 1.4884, yield 46.3 g. (75%).

Anal. Calcd. for $C_8H_{13}N$: C, 77.99; H, 10.63; N, 11.37. Found: C, 77.88; H, 10.71; N, 11.42.

1-Ethyl-2,5-dimethylpyrrolidine.—The pyrrole was hydrogenated according to the procedure of Elderfield and Hageman[26] to 1-ethyl-2,5-dimethylpyrrolidine, b.p. 131.5–132.5° (744 mm.), $n^{20}D$ 1.4332; d^{25}_4 0.8063, yield 19.4 g. (42%).

Anal. Calcd. for $C_8H_{17}N$: C, 75.52; H, 13.47; N, 11.01. Found: C, 75.37; H, 13.58; N, 11.27.

The picrate crystallized from ethanol as yellow leaflets, m.p. 195–197°.

Anal. Calcd. for $C_{14}H_{20}N_4O_7$: C, 47.19; H, 5.66; N, 15.72. Found: C, 47.36; H, 5.87; N, 15.64.

Since both *cis* and *trans* forms of 1-ethyl-2,5-dimethylpyrrolidine could be formed by this method of synthesis, it was not surprising that another picrate derivative was isolated, yellow leaflets from ethanol, m.p. 185.5–186°.

Anal. Found: C, 47.08; H, 5.77; N, 15.76.

A methiodide was obtained which crystallized from absolute ethanol as colorless platelets, m.p. 318–318.5° dec.

Anal. Calcd. for $C_9H_{20}NI$: C, 40.16; H, 7.49; H, 5.20. Found: C, 40.00; H, 7.46; N, 5.28.

(25) "Organic Syntheses," Coll. Vol. 2, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 219.

(26) R. C. Elderfield and H. A. Hageman, *J. Org. Chem.*, **14**, 605 (1949).

(27) S. J. Hazlewood, G. K. Hughes, F. Lions and co-workers, *J. Proc. Roy. Soc. N. S. Wales*, **71**, 92 (1937).

URBANA, ILLINOIS

[CONTRIBUTION FROM AVERY LABORATORY OF CHEMISTRY, UNIVERSITY OF NEBRASKA]

Ethylenimine Ketones. X. The Stereoisomerism of 1-Cyclohexyl-2-methyl-3-(*p*-phenylbenzoyl)-ethylenimine[1]

BY NORMAN H. CROMWELL AND RICHARD J. MOHRBACHER

RECEIVED JULY 27, 1953

To extend our studies of the hyperconjugating ability of three-rings with various other groups we have now synthesized and separated by chromatographic methods the *cis* and *trans* racemic forms of 1-cyclohexyl-2-methyl-3-(*p*-phenylbenzoyl)-ethylenimine from the reaction of α,β-dibromo-*p*-phenylbutyrophenone and cyclohexylamine. An examination of the diagnostic reactions of the *cis* and *trans* forms with phenylhydrazine, and an examination of the ultraviolet and infrared absorption spectra has led to the assignment of the *trans* configuration to the higher melting form and the *cis* configuration to the lower melting form in this series. The spectra studies indicate that the 2-methyl group in the *trans* form is able to interact electrically with the three-ring either inductively or possibly by a secondary hyperconjugation mode.

Six different pairs of *cis–trans* racemates of aryl aroyl ethylenimines have been obtained in previous investigations in this Laboratory from the reaction of a primary amine with an α,β-dibromoketone in dry benzene solution.[2] A detailed study of the diagnostic reactions of phenylhydrazine with the *cis–trans* isomeric pairs[2c,2d] and an examination of the ultraviolet and infrared spectra in these previous investigations was reported. It was concluded that the lower melting geometrical isomer which has its characteristic carbonyl absorption band at the lower frequency in both the ultraviolet and infrared ranges of the spectrum, and which reacts most readily with phenylhydrazine to pro-

(1) Presented at the 124th Meeting of the American Chemical Society, Chicago, Illinois, Sept., 1953.

(2) (a) N. H. Cromwell, *et al.*, THIS JOURNAL, **65**, 312 (1943); (b) *ibid.*, **71**, 708 (1949); (c) *ibid.*, **73**, 1044, 5929 (1951); (d) *J. Org. Chem.*, **17**, 414 (1952).

duce a 4-aminopyrazoline is the *trans* racemate. In the ultraviolet spectra the maximum absorption band to be associated with the aroyl grouping occurs with the greater intensity for the *trans* isomer in the six cases studied. The *cis* racemates produce the corresponding pyrazole in the phenylhydrazine reaction.

We have adopted the symbolism of *bent-bonds*,[2d] as first suggested by Coulson and Moffitt[3] for cyclopropane, in our pictorial description and discussion of the bonding orbitals of the ethylenimine ring. When atoms with π-bonding electrons (carbon atoms of the benzene ring or carbonyl group) are attached to the carbon atoms of a bent-bond ring (*i.e.*, ethylenimine) some overlapping and interaction is to be expected as represented in the diagram in a previous paper.[2d]

The purpose of the present study was to obtain stereoisomers of ethylenimine ketones with an alkyl group, such as the methyl group, in the 2-position on the ring instead of an aryl group which has occurred in this position in all previous isomeric pairs which have been studied. As in the previous investigations it was the further purpose of our studies to relate the stereochemical configurations of the new series to their absorption spectra and behavior with phenylhydrazine.

p-Phenylcrotonophenone (I) was prepared by a Friedel–Crafts reaction from biphenyl and crotonoyl chloride using *sym*-tetrachloroethane as a solvent. Decomposition of the reaction mixture with ice and hydrochloric acid produced a mixture of the desired unsaturated ketone and the corresponding aldol, β-hydroxy-*p*-phenylbutyrophenone (II). A chromatographic separation of the crude products indicated a mixture of about 56% *p*-phenylcrotonophenone (I) and 44% β-hydroxy-*p*-phenylbutyrophenone (II). The aldol was readily converted to the α,β-unsaturated ketone by distillation under vacuum.

The aldol product II gave a 97% yield of β-chloro-*p*-phenylbutyrophenone (IV) when treated with dry hydrogen chloride in benzene solution. For comparison of spectra purposes *p*-phenylbutyrophenone (III) was prepared by a catalytic hydrogenation of the α,β-unsaturated ketone I.

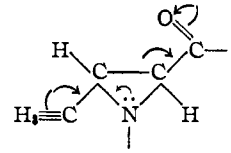
The aldol-α,β-unsaturated ketone mixture gave a good yield of the desired α,β-dibromo-*p*-phenylbutyrophenone on reaction with bromine in carbon tetrachloride solution. Cyclohexylamine reacted with this dibromide to give the expected ethylenimine ketone, 1-cyclohexyl-2-methyl-3-(*p*-phenylbenzoyl)-ethylenimine in good yield. This crude product was separated by chromatographing into about 33% of a high melting form (VA) and 59% of a low melting form (VB). The high melting form (VA) was also obtained from a reaction mixture containing *p*-phenylcrotonophenone, iodine and cyclohexylamine, following the method of Southwick and Christman.[4] In agreement with their results we found only one product to be present in the reaction mixture. Since the racemates isolated by Southwick and Christman were identical with compounds to which we have assigned *trans* structures, it seemed probable that the 1-cyclohexyl-2-methyl-3-(*p*-phenylbenzoyl)-ethylenimine obtained from the present reaction was also the *trans* form VA in spite of the fact that in this series it is the higher melting of the two racemates.

The higher melting ethylenimine ketone VA was found to react with phenylhydrazine to give mainly 1-phenyl-3-*p*-xenyl-4-cyclohexylamino-5-methylpyrazoline. A 16% yield of 1-phenyl-3-*p*-xenyl-5-methylpyrazole was also obtained from this reaction mixture. The low melting isomer VB produced only the pyrazole under the same conditions.

An examination of the ultraviolet absorption spectra of VA and VB showed that the higher melting isomer VA has its maximum at a lower frequency (longer wave length) and at a higher intensity than the lower melting form VB, see Table I. Also the intense band to be associated with the carbonyl stretching vibration in the infrared was found at the lower frequency for the higher melting racemate VA, see Table I. Consequently, on the basis of the results from the reactions of these isomers with phenylhydrazine as well as because of the results from the spectra studies, the high melting racemate VA is assigned the *trans* structure, while the lower melting isomer VB is assigned the *cis* configuration in this series.

The ultraviolet and infrared spectra of the parent α,β-unsaturated ketone I, and of the parent saturated ketone III were determined for comparison purposes, see Table I. The ultraviolet absorption spectra of the aldol II, of the pyrazoline VI and the pyrazole VII are also reported, see Table I. The ultraviolet and infrared spectra of 1-cyclohexyl-2-(*p*-phenylbenzoyl)-ethylenimine have been redetermined and found to differ somewhat with the results reported previously,[2c,2d] see Table I.

A careful comparison (see Table I) of the absorption spectra of the isomeric 1-cyclohexyl-2-methyl-3-(*p*-phenylbenzoyl)-ethylenimine isomers, (VA) and (VB), with the parent α,β-unsaturated ketone I, the parent saturated ketone III, and with the spectra of other ethylenimine ketones previously studied[2] suggests that the 2-methyl group in the *trans* form VA is able to interact with the three-ring. This may represent the first evidence for the existence of a secondary, σ–σ bond hyperconjugation of this type.



Introduction of the N-cyclohexylimino grouping into the *p*-phenylbutyrophenone structure to form the *trans*-1-cyclohexyl-2-methyl-3-(*p*-phenylbenzoyl)-ethylenimine causes a shift in the ultraviolet spectrum from λ 275 mμ (ϵ 23,900) to λ 284 mμ (ϵ 27,520), and in the infrared (Nujol mull) carbonyl stretching vibration from 1680 to 1660 cm.$^{-1}$. In the case of the *cis*-1-cyclohexyl-2-methyl-3-(*p*-phenylbenzoyl)-ethylenimine the shifts were considerably less; for the ultraviolet spectrum to λ 279 mμ (ϵ 24,720) and for the infrared (Nujol mull)

(3) C. A. Coulson and W. E. Moffitt, *Phil. Mag.*, [7] **40**, 1 (1949).

(4) P. L. Southwick and D. R. Christman, THIS JOURNAL, **74**, 1886 (1952).

TABLE I

SUMMARY OF ABSORPTION SPECTRA OF BIPHENYL COMPOUNDS

Structure	Molar concn. × 10^5	Ultraviolet max.[a] λ, mμ	ε × 10^{-3}	Infrared bands 1700–1600 cm.$^{-1}$[b] Band	Nujol mull	CCl_4 sol. Wave no.	Approx. % abs.
$CH_3CH_2CH_2COC_6H_4$—C_6H_5-*p*	5.0	275	23.90	C=O	1680	1687	78
				Phenyl	1610		
CH_3CH=$CHCOC_6H_4$—C_6H-*p*[c]	5.0	277	23.94	C=O	1666	1671	74
						1655–1660	46
				C=C	1617	1627	77
				Phenyl	1605		
C_6H_5—$CH_2CH_2COC_6H_4$—C_6H_5-*p*	0.94	276	25.16[d]	C=O	1679	1690	77
				Phenyl	1609		
C_6H_5—CH=$CHCOC_6H_4$—C_6H_5-*p*[c]	0.53	310	32.63[d]	C=O	1658	1668	69
						1650–1655	36
				C=C	1605	1615	79
				Phenyl	1595		
1-Cyclohexyl-3-(*p*-phenylbenzoyl)-ethylenimine	5.0	280	24.44	C=O	1675	1685	52
						1665	48
				Phenyl	1612		
2-methyl, *cis* (VB)	5.0	279	24.72	C=O	1677	1688	58
						1660	34
				Phenyl	1608		
trans (VA)	5.0	284	27.52	C=O	1660	1667	64
				Phenyl	1608		
2-phenyl, *cis*	0.65	280	23.92[d]	C=O	1684	1690	65
						1668	32
				Phenyl	1609		
trans	0.71	286	30.26[d]	C=O	1655	1668	70
				Phenyl	1607		
$CH_3CH(OH)CH_2COC_6H_4C_6H_5$-*p* (II)	5.0	281	24.20	....	..	....	..
1-Phenyl-3-(*p*-xenyl)-5-methylpyrazole (VII)	5.0	289	31.66	....	..	....	..
1-Phenyl-3-(*p*-xenyl)-4-cyclohexyl-5-methylpyrazoline (VI)	5.0	260	20.58	....	..	....	..
		377	29.36	....	..	....	..

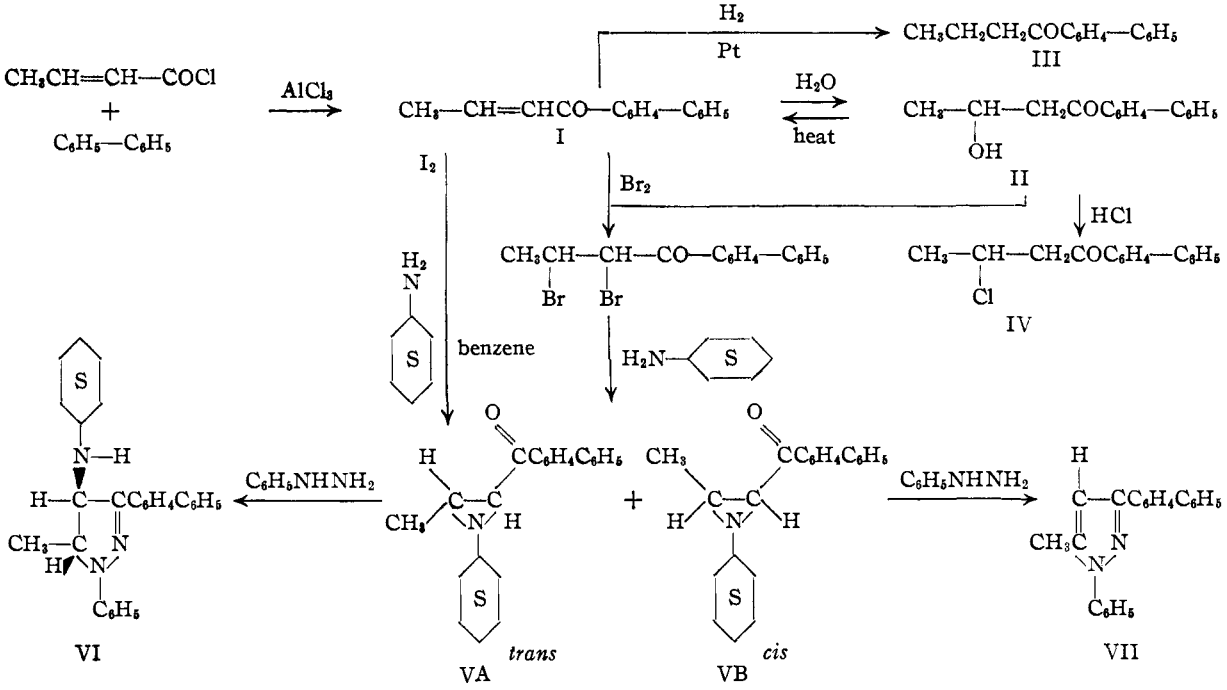
[a] Ultraviolet determinations were made at about 25° using 2,2,4-trimethylpentane solutions and a Beckman model DU photoelectric quartz spectrophotometer employing 10-mm. silica cells. [b] All infrared determinations were made by Prof. C. W. Rook, Infrared Spectroscopy Laboratory, University of Nebraska, with a Perkin–Elmer recording instrument Model 21. For the Nujol mull studies the entire spectra from 650–4000 cm.$^{-1}$ were recorded although only the bands from 1600–1700 cm.$^{-1}$ are given here. The CCl_4 solution studies were done with 0.6% solutions using a 1.0-mm. NaCl cell between 1800 and 1600 cm.$^{-1}$. It seems probable that the double C=O bands observed with the CCl_4 solutions for the two α,β-unsaturated ketones, the two *cis*-tri-substituted ethylenimines and the di-substituted ethylenimine are the consequence of rotational isomerism resulting from rotation of the three-ring carbon to carbonyl carbon bond. This interesting phenomenon must be investigated further using various solvents and temperatures before a complete discussion is warranted. [c] These are probably the *trans* forms. [d] These results have been reported previously, see ref. 2d.

carbonyl stretching vibration to 1677 cm.$^{-1}$. The ultraviolet spectrum, λ 280 mμ (ε 24,400) and the infrared (Nujol mull) carbonyl stretching vibration at 1675 cm.$^{-1}$ for 1-cyclohexyl-2-(*p*-phenylbenzoyl)-ethylenimine were nearly identical with the results obtained with the *cis*-1-cyclohexyl-2-methyl-3-(*p*-phenylbenzoyl)-ethylenimine. A comparison of the ultraviolet spectrum, λ 277 mμ (ε 23,940) and of the infrared (Nujol mull) carbonyl stretching vibration at 1666 cm.$^{-1}$ for *p*-phenylcrotonophenone (*trans* ?) with the values described above for *trans*-1-cyclohexyl-2-methyl-3-(*p*-phenylbenzoyl)-ethylenimine, indicates that the N-cyclohexylimino grouping introduces more unsaturation into the *p*-phenylbutyrophenone parent structure causing a greater polarization of the carbonyl group than does the presence of a carbon to carbon double bond.

The infrared studies, especially those with the carbon tetrachloride solutions, indicate that for the *trans*-ethylenimine ketone structures the enhancement of the polarity of the carbonyl group in the ground state is about the same whether a methyl (wave no. 1667 cm.$^{-1}$) or a phenyl (wave no. 1668 cm.$^{-1}$) group is introduced into the 3-position of 1-cyclohexyl-2-(*p*-phenylbenzoyl)-ethylenimine (wave no. 1685 cm.$^{-1}$). In the *cis* configurations, such as VB, both the methyl (wave no. 1688 cm.$^{-1}$) and the phenyl (wave no. 1690 cm.$^{-1}$) group appear to inhibit the orbital overlap of the carbonyl group π-orbital with the bent-bond orbital of the three-ring in the ground state, the phenyl group being somewhat more effective in this respect. The ultraviolet absorption spectra studies show the phenyl group (λ 286 mμ, ε 30,260) to be somewhat more effective than the methyl group (λ 284 mμ, ε 27,520) in extending the conjugation of the excited state of the *trans* tri-substituted ethylenimine, but neither group has any effect on the *cis* structures. A comparison of the effect of a cyclohexyl group with those produced by the methyl and phenyl groups on the absorption spectra of these tri-substituted ethylenimines may help us to distinguish between inductive and resonance effects.

Acknowledgment.—The work described here was done under a grant to one of us from the

REACTION CHART



National Science Foundation, Research Grant NSF-G-57.

Experimental[5]

***p*-Phenylcrotonophenone and β-Hydroxy-*p*-phenylbutyrophenone.**—A 55-g. (0.53 mole) sample of crotonoyl chloride and 77 g. (0.5 mole) of biphenyl were dissolved in 300 ml. of *sym*-tetrachloroethane and the solution cooled to 0°. To the cooled stirred solution 73.5 g. (0.55 mole) of anhydrous aluminum chloride was added slowly over a period of one hour. The solution was warmed to 50° and stirring continued for 1.5 hours. The reaction mixture was poured onto a mixture of ice and concd. hydrochloric acid. The organic layer was dried and the solvent removed at 40° under vacuum. Petroleum ether (b.p. 30–60°) was added to the residue to precipitate 87 g. of crude product, m.p. 65–95°. Further recrystallization from petroleum ether narrowed the melting range to 72–95°. Distillation at a pressure of about 0.6 mm. of 13.5 g. of the crude product in a solids distillation flask produced 11.4 g. of a pale yellow solid which was recrystallized from petroleum ether (b.p. 60–68°) to give long, colorless needles, m.p. 99–100°.

Anal. Calcd. for $C_{16}H_{14}O$: C, 86.46; H, 6.35. Found: C, 86.59; H, 6.43.

Chromatographic separation of 4 g. of the crude acylation product, m.p. 75–87°, was carried out on activated alumina using dry benzene to place the material on the column and a 1–100 abs. alcohol–benzene solution to develop the column. The alcohol concentration of the eluent was gradually increased to 5–100 abs. alcohol–benzene. The first eluates contained the *p*-phenylcrotonophenone (I), m.p. 98–100°, wt. 1.76 g. (48%). The later eluates contained the β-hydroxy-*p*-phenylbutyrophenone (II), m.p. 116.5–118°, wt. 1.6 g. (44%).

Anal. Calcd. for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71. Found for (II): C, 80.07; H, 6.69.

β-Chloro-*p*-phenylbutyrophenone.—A 0.099-g. (0.00042 mole) sample of II was dissolved in 10 ml. of dry benzene and treated with dry hydrogen chloride gas. The solution was evaporated to dryness *in vacuo* with gentle warming. The residue was recrystallized from petroleum ether (b.p. 60–68°) to give β-chloro-*p*-phenylbutyrophenone (IV), wt. 0.105 g. (97% yield), m.p. 103–104°.

Anal. Calcd. for $C_{16}H_{15}ClO$: C, 74.27; H, 5.84; Cl, 13.70. Found for (IV): C, 74.67; H, 6.17; Cl, 13.32.

(5) Microanalyses were determined by the Clark Microanalytical Laboratory, Urbana, Illinois.

A sample of the mixed acylation product estimated to contain about 56% *p*-phenylcrotonophenone and 44% β-hydroxy-*p*-phenylbutyrophenone was treated with dry hydrogen chloride under the same conditions as above to produce an 86% yield of β-chloro-*p*-phenylbutyrophenone.

***p*-Phenylbutyrophenone.**—A 2-g. sample of I produced 1.5 g. (73% yield) of *p*-phenylbutyrophenone (III) using PtO_2 catalyst in abs. alcohol with 45 lb. pressure of hydrogen; recrystallized from abs. alcohol, m.p. 96–97°.[6]

α,β-Dibromo-*p*-phenylbutyrophenone.—An 86-g. sample of the mixed acylation product (m.p. 65–95°) was treated with 61.9 g. of bromine in 210 ml. of carbon tetrachloride at 10–20°. The bromine color was rapidly destroyed during the addition. Concentration of the reaction mixture produced 113 g. of crude product. Recrystallization from a mixture of benzene and petroleum ether gave colorless needles, m.p. 171–172°.

Anal. Calcd. for $C_{16}H_{14}Br_2O$: C, 50.29; H, 3.69. Found: C, 50.17; H, 3.43.

1-Cyclohexyl-2-methyl-3-(*p*-phenylbenzoyl)-ethylenimine, High Melting.—Following the procedure of Southwick and Christman[3] for an analogous synthesis, a solution of 11.4 g. (0.045 mole) of iodine in 100 ml. of dry benzene was added slowly to a solution of 10 g. (0.045 mole) of *p*-phenylcrotonophenone and 17.9 g. (0.180 mole) of cyclohexylamine in 25 ml. of benzene. The crude product isolated from the reaction mixture weighed 9.2 g. (64% yield). Recrystallization from petroleum ether gave colorless needles VA, m.p. 141.5–142°.

Anal. Calcd. for $C_{22}H_{25}NO$: C, 82.72; H, 7.89; N, 4.39. Found: C, 83.11; H, 7.83; N, 4.55.

Reaction of α,β-Dibromo-*p*-phenylbutyrophenone with Cyclohexylamine.—To a suspension of 8.3 g. (0.022 mole) of α,β-dibromo-*p*-phenylbutyrophenone in 55 ml. of dry benzene was added 6.5 g. (0.066 mole) of cyclohexylamine. The reaction mixture was stirred at 10–30° for six hours and allowed to stand in the ice chest for 18 hours. The precipitated cyclohexylamine hydrobromide was removed by filtration and well washed with benzene, the washings being added to the filtrate. Evaporation of the filtrate gave 5.9 g. (85% yield), m.p. 109–122°, of the crude 1-cyclohexyl-2-methyl-3-(*p*-phenylbenzoyl)-ethylenimine.

A chromatographic separation of 3 g. of the above crude product was carried out on a column of activated alumina. The material was added to the column in a solution of dry benzene. The column was developed with a 1–100 abs. alcohol–benzene solution and eluted with a 2–100 mixture

(6) L. M. Long and H. R. Henze, THIS JOURNAL, **63**, 1939 (1941).

of the same solvents. The first eluates contained the higher melting, more insoluble isomer while the later fractions contained the lower melting, more soluble form. Ultraviolet spectra maxima were determined for several of the fractions. No indication of the presence of more than two compounds was found. From the chromatographic separation 1.7 g. (59% of total material recovered) of low melting VB, m.p. 127–128°, λ_{max}, 2790 Å., and 0.95 g. (33% of total material recovered) of high melting VA, m.p. 141–142°, λ_{max}, 2840 Å., and 0.25 g. of a mixed fraction, m.p. 110–135°, resulted. The total recovery of material from the chromatographic separation was 2.9 g. (97%).

Anal. Calcd. for $C_{22}H_{25}NO$: C, 82.72; H, 7.89; N, 4.39. Found for (VB): C, 82.88; H, 7.62; N, 4.64.

Reaction of Ethylenimine Ketones with Phenylhydrazine.—A 1.90-g. (0.006 mole) sample of VA was dissolved in 25 ml. of 40–60 abs. alcohol–chloroform solution, cooled and treated with 0.75 g. (0.012 mole) of glacial acetic acid and 0.75 g. (0.006 mole) of phenylhydrazine. Almost immediately the solution began to show the characteristic blue fluorescence of the aminopyrazolines.[2c] After standing at room temperature for 14 hours, isolation of the products produced 0.3 g. (16% yield) of 1-phenyl-3-(*p*-xenyl)-5-methylpyrazole (VII), m.p. 128–129.5°, as colorless plates, recrystallized from abs. alcohol; and 0.88 g. (40% yield) of 1-phenyl-3-(*p*-xenyl)-4-cyclohexylamino-5-methylpyrazoline (VI), m.p. 158.5–159.5°, as yellow-green hexagonal plates, recrystallized from benzene and petroleum ether (b.p. 60–68°). The product VI gave positive Knoor and Raiford pyrazoline tests.[7] The solid compound and solutions as dilute as 0.5×10^{-4} *M* showed a strong blue fluorescence when exposed to ultraviolet light.

Anal. Calcd. for $C_{28}H_{31}N_3$ (VI): C, 82.11; H, 7.63; N, 10.30. Found: C, 82.04; H, 7.63; N, 10.20. Calcd. for $C_{22}H_{18}N_2$ (VII): C, 85.13; H, 5.84; N, 9.03. Found: C, 84.87; H, 5.82; N, 9.19.

An identical experiment with the lower melting ethylenimine ketone VB produced an 88% yield of the pyrazole (VII), m.p. 128.5–129.5°. The solid compound but not dilute solutions of the pyrazole showed a blue fluorescence when exposed to ultraviolet light.

(7) L. C. Raiford and W. J. Peterson, *J. Org. Chem.*, **1**, 544 (1937).

LINCOLN, NEBRASKA

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF PARKE, DAVIS & CO.]

Anticonvulsants. IV. An Investigation of α-(Substituted phenyl)-succinimides

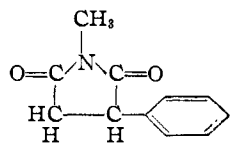
BY C. A. MILLER AND LOREN M. LONG

RECEIVED JULY 20, 1953

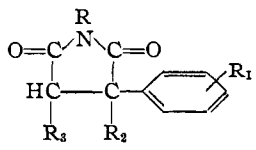
Thirty-three α-phenylsuccinimides containing a substituent on the phenyl group have been prepared and tested for anticonvulsant activity. Many compounds of this group effectively suppress metrazol and/or electrically-induced convulsions in laboratory animals. Clinical evaluation of a number of these products is in progress.

In the first paper[1] of this series a number of α-phenylsuccinimides were shown to possess a high degree of anticonvulsant activity.[2] Subsequently, a clinical study proved several of these to be effective anti-epileptic agents. N-Methyl-α-phenylsuccinimide (Milontin)[3] I is particularly efficacious in the treatment[4,5] of petit mal epilepsy and is relatively non-toxic.

Consequently, the study of this type of compound was extended by the synthesis of a group of α,β-substituted phenylsuccinimides[6] and alkylsuccinimides.[7] Many of these derivatives exhibited considerable activity[2] against metrazol-induced convulsions, and a few showed an appreciable activity against electrically-induced convulsions. None of the alkylsuccinimides was effective in the latter tests.



I



II

R, R_2, R_3 = H, Alkyl
R_1 = Hal, CH_3, OH, CH_3O–

The present paper is concerned with the synthesis and anticonvulsant properties of a series of succinimides, illustrated by II, which contain a substituent on the phenyl group.

The method of synthesis which has been discussed previously[1,6,7] employs the condensation of the appropriate aldehyde[8] or ketone[9,10] with ethyl cyanoacetate. The α-cyanocinnamate thus formed is converted by means of potassium cyanide to the α,β-dicyanopropionate which is subsequently hydrolyzed to the succinic acid with concentrated hydrochloric acid or a mixture of hydrochloric and acetic acids. In one case the dicyano ester was methylated before hydrolysis. Conversion of succinic acid to the imide was effected by distillation of the amine salt. The pertinent data are given in Table I.

Anticonvulsant Activity.—The succinimides were tested for their anticonvulsant activity by a method[11] described earlier. As with the previously tested substituted succinimides, many of the compounds of the present series were effective in suppressing metrazol-induced convulsions. In a few cases the activity exhibited against electrically-induced convulsions was interesting; however, to date none of the compounds examined have approached the activity shown by 5,5-diphenylhydantoin (Dilantin).[12] A number of these com-

(1) C. A. Miller and L. M. Long, THIS JOURNAL, **73**, 4895 (1951).
(2) G. Chen, C. Ensor, R. Portman and A. C. Bratton, *J. Pharmacol. Exp. Therap.*, **103**, 54 (1951).
(3) Parke, Davis & Co. trademark for N-methyl-α-phenylsuccinimide.
(4) F. T. Zimmerman, *Arch. Neurol. Psychiat.*, **66**, 156 (1951).
(5) J. G. Millichap, *Lancet*, **2**, 907 (1952).
(6) C. A. Miller, H. I. Scholl and L. M. Long, THIS JOURNAL, **73**, 5608 (1951).
(7) C. A. Miller and L. M. Long, *ibid.*, **75**, 373 (1953).
(8) A. Lapworth and J. A. McRae, *J. Chem. Soc.*, **121**, 2741 (1922).
(9) A. C. Cope, C. M. Hoffman, C. Wyckoff and E. Hardenbergh, THIS JOURNAL, **63**, 3452 (1941).
(10) E. J. Cragoe, C. M. Robb and J. M. Sprague, *J. Org. Chem.*, **15**, 381 (1950).
(11) G. Chen and C. R. Ensor, *Arch. Neur. Psychiat.*, **63**, 56 (1950).
(12) Parke, Davis and Co. registered trademark for 5,5-diphenylhydantoin.