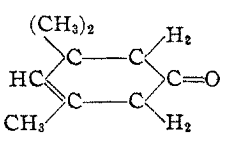
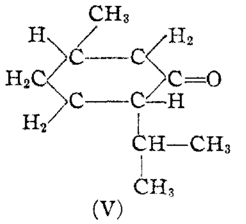


(III)

$K_{3500} = 0.117$



(V)

$K_{3390} = 0.126$

absorption for hydroxyl, either associated or unassociated. The carbonyl absorption is that of a normal ketone.

These data indicate that both the infrared and ultraviolet absorption spectra of the new compound are in accord with the keto structure (III).

Structure of the Semicarbazone Formed from Compounds (I) and (III).—Compounds (I) and (III) each yields a semicarbazone which melts at 186–187°.[1] Since these semicarbazones do not depress each other's melting points, they may be concluded to be identical. This conclusion is supported by their ultraviolet absorption curves (Fig. 3).

The chemical data do not warrant the assignment of a definite structure to the semicarbazone in question, but a comparison of its ultraviolet absorption curve with that of cyclohexanone semicarbazone (Fig. 3) suggests that the semicarbazone in question is derived from isophorone (I) rather than from its isomer (III). If such is the fact, then when the semicarbazone is formed from (III), the double bond is shifted, during the process of formation, from the β,γ to the α,β position.

Summary

1. Ultraviolet and infrared absorption spectra indicate that when isophorone is treated with methylmagnesium bromide in the presence of small amounts of ferric chloride, the double bond in the ring is shifted from the α,β to the β,γ position.

2. In the formation of the semicarbazone of $\Delta^{3,4}$-3,5,5-trimethylcyclohexenone, the double bond is shifted back to the α,β position and the semicarbazone of isophorone is obtained.

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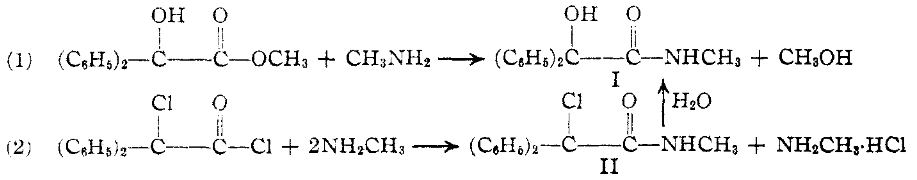
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF INDIANA UNIVERSITY]

Antispasmodics and Anticonvulsants. IV. N,N'-Substituted α-Aminodiphenylacetamides

BY JOHN H. BILLMAN, THELMA G. WARD[1] AND PHIL HARTER HIDY[2]

In an earlier publication[3] it was shown that certain α-aminodiphenylacetamides having identical radicals attached to both of the nitrogen atoms, possessed anticonvulsant as well as antispasmodic acitivity. It was decided, therefore, to synthesize a number of derivatives having dissimilar groups attached to the nitrogens by using α-chlorodiphenylacetyl chloride and two different amines.

The α-chlorine atom of an α-chloroacyl chloride is normally much less reactive than the chlorine atom attached to the carbonyl group. Klinger[4] has done some work which indicates that α-chlorodiphenylacetyl chloride when treated with two moles of aniline produces N-phenyl-α-chlorodiphenylacetamide. However, to verify this the following reactions were run



$$(1)\quad (C_6H_5)_2{-}\overset{OH}{\overset{|}{C}}{-}\overset{O}{\overset{\|}{C}}{-}OCH_3 + CH_3NH_2 \longrightarrow \underset{I}{(C_6H_5)_2\overset{OH}{\overset{|}{C}}{-}\overset{O}{\overset{\|}{C}}{-}NHCH_3} + CH_3OH$$

$$\uparrow H_2O$$

$$(2)\quad (C_6H_5)_2{-}\overset{Cl}{\overset{|}{C}}{-}\overset{O}{\overset{\|}{C}}{-}Cl + 2NH_2CH_3 \longrightarrow \underset{II}{(C_6H_5)_2{-}\overset{Cl}{\overset{|}{C}}{-}\overset{O}{\overset{\|}{C}}{-}NHCH_3} + NH_2CH_3{\cdot}HCl$$

The diphenylacetic acid derivatives (I) formed in reactions (1) and (2) were found to be identical. Both products melted at 146–147° and gave no depression in melting point when fused together. This temperature is approximately 60° below the melting point of the isomeric α-methylaminodiphenylacetic acid.[5] Neither product was soluble in alkali or hydrochloric acid. Thus the structure of Compound II is established. These results along with the fact that the α-chloroacetamides were obtained in yields of better than seventy per cent. confirm the order and relative ease of replacement of the chlorine atoms in α-chlorodiphenylacetyl chloride. It is this appreciable difference in reactivity which made possible the synthesis of α-aminodiphenylacetamides, with unlike radicals attached to each nitrogen atom, according to the reactions

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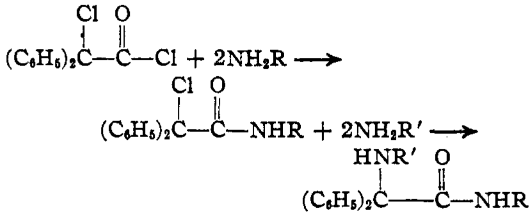
[1] Submitted to the Faculty of the Graduate School in partial fulfillment of the requirements for the degree, Doctor of Philosophy, in the Department of Chemistry, Indiana University.

[2] Eli Lilly Fellow.

[3] Billman and Hidy, THIS JOURNAL, **65**, 760 (1943).

[4] Klinger, *Ann.*, **389**, 255 (1912).

[5] Biltz and Seydel, *Ann.*, **391**, 227 (1912).

(3) 

$$(C_6H_5)_2\overset{\overset{\displaystyle Cl}{|}}{C}-\overset{\overset{\displaystyle O}{\|}}{C}-Cl + 2NH_2R \longrightarrow (C_6H_5)_2\overset{\overset{\displaystyle Cl}{|}}{C}-\overset{\overset{\displaystyle O}{\|}}{C}-NHR + 2NH_2R' \longrightarrow (C_6H_5)_2\overset{\overset{\displaystyle HNR'}{|}}{C}-\overset{\overset{\displaystyle O}{\|}}{C}-NHR$$

The N-substituted α-chlorodiphenylacetamides which were isolated and characterized are listed in Table I.

TABLE I

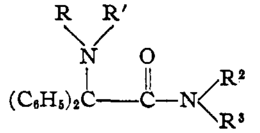
N-SUBSTITUTED α-CHLORODIPHENYLACETAMIDES

Amine used	M. p. of amide, °C.	Yield, %	Nitrogen, % Calcd.	Nitrogen, % Found
Methylamine	94.0–95.0	>70	5.42	5.48
Ethylamine	95.5–96.0	87.5	5.14	5.23
n-Propylamine	68.5–69.0	73.5	4.88	5.07
p-Phenetidine	76.0–77.0	77.5	3.84	3.94

The N,N'-substituted α-aminodiphenylacetamides prepared are listed in Table II.

TABLE II

N,N'-SUBSTITUTED α-AMINODIPHENYLACETAMIDES



$$(C_6H_5)_2\overset{\overset{\displaystyle RR'N}{|}}{C}-\overset{\overset{\displaystyle O}{\|}}{C}-N\begin{matrix}R^2\\R^3\end{matrix}$$

Amines used $RR'NH$	Amines used R^2R^3NH	M. p. of amide, °C. (uncor.)	Nitrogen, % Calcd.	Nitrogen, % Found
p-Phenetidine	Ammonia	167.5–168	8.08	8.06
Ammonia	*p*-Phenetidine	138	8.08	7.96
Diethylamine	Ethylamine	134.5–135	9.03	9.32
Diethylamine	*p*-Phenetidine	55	6.88	6.96
n-Propylamine	*p*-Phenetidine	118	7.29	7.22
n-Butylamine	*p*-Phenetidine	78	6.83	6.96
Di-*n*-butylamine	*p*-Phenetidine	110	6.27	6.11
Cyclohexylamine	*p*-Phenetidine	160 (dec.)	6.54	6.20

The pharmacological tests which have been run on these compounds indicate that they do not differ greatly in antispasmodic or anticonvulsant activity from the α-aminodiphenylacetamides having identical groups attached to both nitrogen atoms.

We are deeply grateful to Eli Lilly and Company for the grant which made this work possible and to Drs. H. M. Lee, C. E. Powell and E. E. Swanson of the same company who ran the pharmacological tests.

Experimental

α-Chlorodiphenylacetyl Chloride.—Prepared from benzilic acid and phosphorus pentachloride as previously described.[3]

N-Ethyl-α-chlorodiphenylacetamide.—To 10 g. of α-chlorodiphenylacetyl chloride dissolved in 75 ml. of ice-cold dry ether was added two mole equivalents of gaseous ethylamine. The solution was then allowed to warm up to and remain at room temperature for five hours. The ethylamine hydrochloride was filtered off and washed with two 25-ml. portions of dry ether. The combined washings and filtrate were extracted with dilute hydrochloric acid to remove any excess amine. The ether solution was dried over anhydrous sodium sulfate and then evaporated to dryness under reduced pressure. Recrystallization of the residue from ether and petroleum ether gave 9 g. (87.5% yield) of N-ethyl-α-chlorodiphenylacetamide melting at 95.5–96°.

The α-chlorodiphenylacetamides listed in Table I were prepared by a procedure similar to the one above.

N-Ethyl-α-diethylaminodiphenylacetamide.—To a 125-ml. flask fitted with a reflux condenser was added 9 g. of ethyl-α-chlorodiphenylacetamide and 4.8 g. of diethylamine. A mercury trap was attached to the outlet of the condenser and the solution then refluxed for twelve hours. The mixture was treated with 100 ml. of ether, warmed, and filtered to remove the diethylamine hydrochloride. The filtrate was extracted with small portions of 0.1 *N* hydrochloric acid until the extractions proved to be acid to litmus. The acid extracts were then neutralized with sodium carbonate and extracted with two 50-ml. portions of ether. The brown semi-crystalline product remaining was removed, washed with water and recrystallized from methyl alcohol to yield 3.7 g. (36%) of a white solid melting at 134.5–135°.

The compounds listed in Table II were prepared by a procedure similar to that used for synthesizing N-ethyl-α-diethylaminodiphenylacetamide. When high boiling amines were used, no mercury seal was attached to the condenser.

N-Methylbenzilamide (I) was prepared by the following two methods:

Method 1.—Methyl benzilate was prepared from benzilic acid, methyl alcohol and sulfuric acid similar to the method described by Acree.[6] The ester was dissolved in ether and tested with gaseous methylamine in a flask fitted with a dry ice-cooled condenser to the top of which was attached a mercury seal. The mixture was refluxed for six hours, poured into water and the insoluble portion recrystallized from methyl alcohol. The product melted at 146–147°.

Method 2.—N-Methyl-α-chlorodiphenylacetamide was prepared the same way as the corresponding ethylamide described above. One gram of the methylamide was refluxed with 25 ml. of water for two and one-half hours. Upon cooling the pale yellow oil solidified to a white crystalline mass. Recrystallization from methyl alcohol yielded a white solid melting at 146–147° which when fused with the amide produced by method (1) also melted at 146–147°.

Summary

1. It has been proved that the chlorine atom attached to the carbonyl group in α-chlorodiphenylacetyl chloride is more readily replaced by an amine than is the α-chlorine atom.

2. A number of new α-chlorodiphenylacetamides have been isolated and characterized.

3. Eight N-alkyl α-aminodiphenylacetamides of a new type have been prepared.

BLOOMINGTON, IND. RECEIVED OCTOBER 23, 1944

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[6] Acree, *Ber.*, **37**, 2765 (1904).