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DETERMINATION OF MASS SPECTRAL AND FRAGMENTATION PATTERN OF SOME CENTRALLY-ACTING 1,3-CYCLOHEXANDIONE DERIVATIVES

D. S. Ogunleye*

Department of Pharmaceutical and Medicinal Chemistry, Faculty of Pharmacy, Olabisi Onabanjo University, Sagamu. Nigeria.

Abstract
Many of the drugs currently used in clinical practice possess undesirable side effects, which make some patients less inclined to comply with recommended dosage regimen. Also, therapeutic failure has resulted from development of resistance by organisms to some drugs including antimalarials and antibiotics. There is need therefore, to find safer and effective alternatives devoid of the problems stated earlier. The cyclohexanediones are quite reactive and various workers have obtained several derivatives, which have been found to be biologically active with some possessing useful antimicrobial and herbicidal activities. The 1, 3-cyclohexanedion carboxylate and nine aryl- and arylalkylamino derivatives: ethyl 4-hydroxy-6-methyl-2-oxo-3-cyclohexene-1-carboxylate: ethyl 6-methyl-2-oxo-4-phenylamino-3-cyclohexene-1-carboxylate; ethyl 4-benzylamino 6-methyl-2-oxo-3-cyclohexene-1-carboxylate; ethyl 6-methyl-2-oxo-4-(2'-phenylethylamino)-3-cyclohexene-1-carboxylate; 6-methyl-2-oxo-4-phenylamino-3-cyclohexene-1-(N-phenyl)-carboxamide; 6-methyl-2-oxo-4-phenylamino-3-cyclohexene-1-(N-benzyl)-carboxamide; 4-benzylamino-6-methyl-2-oxo-3-cyclohexene-1-(N-benzyl) carboxamide; 4-benzylamino-6-methyl-2-oxo-3-cyclohexene-1-(N-2'-phenylethyl)-carboxamide; and 6-methyl-2-oxo-4-(2'-phenylethylamino)-3-cyclohexene-1-(N-benzyl)-carboxamide were synthesized. Phenyl, benzyl, phenylethyl, and their amino and carboxy derivatives fragment ions observed in the mass spectra of the corresponding compounds. Most of the compounds except those with phenylamino substituent at the 4-C caused reduction in activity of and sedation in chicks, indicating that they possessed central nervous system depressant properties. Thus they could be useful in the treatment of mental agitations and as muscle relaxants

Keywords: Cyclohexanediones; Mass spectra; Fragmentation pattern; C.N.S. depressant.

INTRODUCTION

Several of the drugs currently used in clinical practice possess undesirable side effects, which make some patients less inclined to comply with recommended dosage regimen. Also, therapeutic failure has resulted from development of resistance by organisms to some drugs including antimalarials and antibiotics.[1, 2]

Some 2-acyl derivatives of 1, 3-cyclohexanediones have been synthesized by reacting the enol acylate of the compounds with anhydrous aluminum chloride in dichloromethane.[3] Chlororesorcinols were prepared in 79-85% yield by treating cyclohexandiones with chlorine in dichloromethane at 0^{o}C via rearrangement and aromatisation of the dichlorocyclohexandiones.[4] The synthesis of 1, 3-cyclohexanedione carboxylate by

* Corresponding author. *E-mail address*: pharmdavid_2004@yahoo.com
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refluxing ethylcrotonate with ethyl acetoacetate in ethanolic sodium ethoxide has also been reported.[5] The report included aminoalkylation of the compound by refluxing with suitable amines in toluene. Another work has reported the synthesis of carboxamides from alkylamino derivatives of 1, 3-cyclohexanedione carboxylate.[6]

Cyclohexanediones have been reported to possess various biological activities A research reported that 2-butyryl-5- (3-cyclohexane-1-yl)-1, 3-cyclohexanedione after reaction with propoxyamine hydrochloride ($CH2=CHCH_2NH_2.HCl$) and anhydrous NaOAC in ethanol produced a 1,3-cyclohexanedione derivative which was useful against undesirable vegetation.[7] Some workers investigated the antimicrobial properties of *a*-dicarbonyl and related compounds and reported that 1, 2-cyclohexanediones were more effective against gram-positive bacteria and less against fungi and gram-negative bacteria than diacetyl. [8] Some 2-cyclohexylidenedithiolane derivatives found to protect mice against carbon tetrachloride-induced liver disorders were useful in the treatment of liver disorders in mice.[9] Also a 1, 3-cyclohexanedione and aryl and arylalkyl amino derivatives have been reported to block leptazole-induced seizures in chicks.[10] It is believed that this group of compounds could form veritable sources of new drugs to augment those currently used in clinical practice with better therapeutic advantage

The mass spectra behavior of a number of 1, 3-cyclohexanediones has been investigated.[11] The compounds were found to break down in a well-defined manner with pronounced peak at m/e 55 and that relative intensity of the fragments was highly dependent on the substituents in the 2- and 5-positions. The report also noted that the fragmentation process started with elimination of >C=O and C_2H_4 which reflected the ability of the 2-substituent to stabilize a double bond between the 2-C and that next to it; and that compounds with two enolizable carbonyl rings showed characteristic breakdown patterns due to the ease with which enolizable protons take part in rearrangement. Another report of the mass spectra of 1, 3-cyclohexanedione and its 2-, 4-, and 5-substituted derivatives indicated that the base peak arose mostly from an ion (m/e, 55+14n) carrying 20-50, 10-20, and 8-9% of the total ionic charge for the dimedones, 5-substituted dimmers and 2-chlorodimedones respectively.[12] The report also stated that in parent compounds with methyl subtituents and 5-monosubtituted isopropyl, butyl and pentyl groups, fragment ions resulted from a bond cleavages in the rings, but with longer alkyl groups in 2- and 4-positions fragmentation patterns depended on the position and size of substituents. It further explained that most patterns were rationalized from the diketo form through initial 1, 2- and 1, 6-bond cleavages, and that enol molecules appeared to yield mostly Retro-Diel Alder degradations and that in the 4-substituted cyclohexanedione and derivatives, the most important degradation was the McLafferty rearrangement.

The aims of this project therefore, are to synthesize 1, 3-cyclohexanedione carboxylate and some aryl- and arylalkylamino derivatives and determine the fragmentation patterns of such compounds from the mass spectra.

MATERIALS AND METHODS

All the synthetic work were carried out in our laboratory and all chemicals were obtained from Aldrich Chemical Co. Ltd., England. The reactions were monitored by thin layer chromatography using precoated sheets (Polygram SIL G/UV254, Camlab Cambridge) in chloroform: benzene (1:1) and

ultra violet spectroscopy (Unicam Sp 800 UV Spectrometer). Melting points were determined using by Gallenkamp (electrothermal) melting point apparatus. Mass spectra of the compounds were obtained from Mass Spectrometry Service, Chelsea College, London.

Ethyl 4-hydroxy-6-methyl-2-oxo-3-cyclohex ene-1- carboxylate (SI)

To a freshly prepared solution of sodium (9.2g, 0.4g-atom) in dry ethanol (200ml) was added ethyl acetoacetate (52g, 0.4mol) and the mixture was stirred on an ice-bath (15 min). Ethyl crotonate (45.6g, 0.4mol) was added drop wise and the mixture stirred at room temp. for a further 30 min. After refluxing (2 h) the reaction mixture was cooled during which and a white precipitate separated from the yellowish solution. The precipitate was filtered, dissolved in minimum amount of ice-cold water, acidified with sulphuric acid (2.5M, 70ml) and extracted with $CHCl_3$ (2 x 80 ml). The organic phase was washed with water to remove acid, dried (anhy. Na_2SO_4) and evaporated, and the residue crystallized from ethyl acetate to give ethyl 4-hydroxy-6-methyl-2-oxo-3-cyclohexene-1-carboxylate (SI) in 45% yield. It was recrystallised from ethyl acetate, m.p. 81-82^{o}C (lit. 81-82^{o}C). MS (m/z): 199 (M+1, 67%), 198 (M^+, 51%), 183 (M-CH_3, 56%), 170 (M-CO 22%), 153 (M-OC_2H_5 51%), 124 (24%), 115 (35%), 95 (25%), 84 (30%), 82 (25%), 69 (base peak, 100%), 55 (C_4H_7+ 23%) 41 (C_3H_3+, 25%).

Ethyl 6-methyl-2-oxo-4-phenylamino-3-cyc lohexene-1-carboxylate (S2)

A solution of ethyl 4-hydroxy-6-methyl-2-oxo-3-cyclohexene-1-carboxylate (14g, 0.07ml) and phenylamine (aniline, 6.58g, 0.07mol) in toluene (50ml) was refluxed (4 h) under a Dean-Stark water separator. About 1.26ml, (0.07mol) of water was collected. The reaction mixture was cooled and on standing at room temperature ethyl 6-methyl-2-oxo-4-phenylamino-3-cyclohexene-1-carboxylate precipitated out as white crystals and was filtered to give 68.7% yield. It was recrystallised from ethanol, m.p. 149-150^{o}C (lit. 148-149^{o}C). MS (m/z): 274(M+1,33%), 273(M+, 63%), 258(M-CH_3, 30%), 228 (M-OC_2 H5, 30%), 200(M-$COOC_2H_5$, 42%), 186(18%), 159(base peak, 100%), 158(50%), 130(42%). 92(PhNH+, 16%) 77(Ph+, 17%), 69(C_5H_5+, 12%), 41(C_3H_5+, 6%).

Ethyl 4-benzylamino-6-methyl-2-oxo-3-cy clo hexene-1-carboxylate (S3)

A similar technique as described for (S2) using a solution of ethyl 4-hydroxy-6-methyl-2-oxo-3-cyclohexene-3-cyclohexene-1-carboxylate (5.62g, 0.0284mol) and benzylamine (3.046g, 0.0284mol) gave ethyl 4-benzylamino-6-methyl-2-oxo-3-cyclohexene-1-carboxylate (S3) in 75% yield. It was recrystallised from ethanol, m.p. 125-126^{o}C (lit. 125-126^{o}C). MS (m/z): 288(M+1, 66%), 287(M+, 78%), 272(M-CH_3, 35%), 258 (M-CH_2CH_3, 4%), 242 (M-OC_2H_5, 33%), 214 (M-$COOCH_2H_5$, 42%), 1886(13%), 172(25%), 172(25%), 145 (36%). 144(93%), 91(base peak, CH_2Ph+, 100%, 77(Ph+, 4%), 69(10%), 65(C_5H_5+, 15%), 41(C_3H_5+, 7%).

Ethyl 6-methyl-2-oxo-4-(2'-phenylethylam ino)-3-cyclohexene-1-carboxylate (S4).

A similar technique as described for (S2) using a solution of ethyl 4-hydroxy-6-methyl-2-oxo-3-cyclohexene-1- carboxylate (5.61g, 0.0283mol) and 2'-phenylethylamine (3.433g, 0.0283mol) gave ethyl 6-methyl-2-oxo-4-(2"-phenylethylamino)-3-cyclohexene-1-carboxylate (S4) in 74% yield. It was recrystallised from ethanol, m.p 134.5-135.5^{o}C (lit. 134-35^{o}C). MS (m/z): 302(M+1, 40%), 301(M+, 78%), 286(M-CH_3, 20%), 256

(M-OC_2H_5, 30%), 228 (M-$COOC_2H_5$, 21%), 210(34%), 187(22%), 164(22%), 136(31%), 105(CH_2CH_2Ph, 39%), 104(base peak, 100%), 96(29%), 91 (CH_2Ph+, 18%), 77(Ph+, 10%), 69(21%), 67(21%), 65 (C_5H_5+, 6%), 41(C_3H_5+, 9%).

6-methyl-2-oxo-4-phenylamino-3-cyclo hexene-1-(N-phenyl)-carboxamide (S5).

A solution of ethyl 6-methyl-2-oxo-4-phenylamino-3-clohexene-1-carboxylate (1.044g, 0.0038mol) and phenylamine (1.0066g, 0.0115mol) in toluene (50ml) was refluxed (6h) under a Dean-Stark water separator. The ethanol produced was separated. The reaction mixture was then allowed to cool to room temperature and on standing, 6-methyl-2-oxo-4-phenylamino-3-cyclohexene-1-(N-phenyl)-carboxamide (S5) precipitated out as white crystals which was filtered to give 44% yield. It was recrystallized from ethanol, m.p. 226-227^oC (lit. 226 – 227^oC). MS (m/z): 322(M+2, 15%), 321(M+1, 54%), 202(14%), 201(M-CONHPh+H, 80%), 200(46%), 199(24%), 187(18%), 186(M-CONHPh-Ch_3+H, base peak, 100%), 93($PhNH_2$+, 9%), 92 (PhNH+, 6%) 69(9%), 41(C_3H_5+, 5%).

6-methyl-2-oxo-4-phenylamino-3-cyclo hexene-1-(N-benzyl)-carboxamide (S6).

A similar technique as described for (S5) using a solution of ethyl 6-methyl-2-oxo-4-phenylamino-3-cyclohexene-1-carboxylate (0.995g, 0.00036mol) and benzylamine (1.17g, 0.011mol) gave 6-methyl-2-oxo-4-phenylamino-3-cyclohexene-1- (N-benzyl)-carboxamide (S6) in 75% yield. It was recrystallized from ethanol, m.p. 185-186.5^oC (lit. 185-186^o C). MS (m/z): 336(M+2, 19%), 335(M+1, 64%), 201(M-$CONHCH_2Ph$+H, 33%), 200(M-$CONHCH_2Ph$ base peak, 100%), 199(58%), 186(M-$CONHCH_2Ph$-CH_3, 42%)159(17%), 158(12%), 130(10%), 93(NH_2Ph+, 6%) 92(NHPh+, 8%), 91(CH_2Ph+, 18%), 77(Ph+, 6%), 69(5%), 65(C_5H_5+, 3%), 41(C_3H_5+, 2%).

4-Benzylamino-6-methyl-2-oxo-3-cyclo hexene-1-(N-phenyl)-carboxamide (S7).

A similar technique, as described for (S5) using a solution of ethyl 4-benzylamino-6-methyl-2-oxo-3-cyclohexene-1-carboxylate (1.888g, 0.0066mol) and phenylamine (1.838g, 0.0197mol) gave 4-benzylamino-6-methyl-2-oxo-3-cyclohexene-1-(N-phenyl)-carboxamide (S7) in 34% yield. It was recrystallized from ethanol, m.p. 189-190^oC (lit. 189-191^OC). MS (m/z): 335(M+1, 10%), 334(M+, 34%), 242 (M-NHPh, 4%), 215(M-CONHPh+H, 90%), 214(M-CONHPh, 28%), 200 (M-CONHPh-CH_3+H, base peak, 100%), 144(10%), 92(NHPh+, 7%) 91(CH_2Ph+, 65%), 69(8%), 65(C_5H_5+, 6%), 41(C_3H_5+, 4%).

4-Benzylamino-6-methyl-2-oxo-3-cyclo hexe-1-(N-benzyl)-carboxamide (S8).

A similar technique, as described for (S5) using a solution of ethyl 4-benzylamino-6-methyl-2-oxo-3-cyclohexene-1-carboxylate (1.624g, 0.0057mol) and benzylamino (1.82g, 0.0171mol) gave 4-benzylamino-6-methyl-2-oxo-3-cyclohexene-1-(N-benzyl)-carboxamide (S8) in 46% yield. It was recrystallized from ethanol, m.p. 179-180^oC (lit. 179-180^oC). MS (m/z): 350(M+2, 28%), 349(M+1, 79%), 348 (M+, 3%), 334(N-$CONHCH_2Ph$ base peak, 100%), 213(44%), 200 (N-$CONHCH_2Ph$-Ch_3+H, 44%), 173(16%), 145 (8%), 144 (30%), 124 (M-$CONHCH_2Ph$ - CH_2Ph+H, 17%), 106 ($PhCh_2NH$+, 8%), 91($PhCH_2$+, 78%), 65 (C_5H_5+, 7%), 41(C_3H_5+, 3%).

4-Benzylamino-6-methyl-2-oxo-3-cyclohex ene-1-(N-2'-phenylethyl)-carboxamide (S9)

A similar technique, as described for (S5) using a solution of ethyl 4-benzylamio-6-methyl-2-oxo-3-cyclohexene-1-carboxylate (1.448g, 0.005mol) and 2'-phenylethylamine (1.83g, 0.015mol) gave 4-benylamino-6-methyl-2-oxo-3-cyclohexene-1-(N-2'-phenylethyl)- carboxamide (S9) in 76% yield. It was recrystallized from ethanol, m.p. 184-185^{o}C (lit184 – 185^{o}C). MS (m/z): 364(M+2,26%), 363(M+1, 72%), 362 (M+, 3%), 348(M-CH_3+H, 10%), 272(M-CH_2Ph+H, 46%), 243(M-$NHCH_2CH_2Ph$+H, 11%), 242(M-$NHCH_2Ph$-CH_3, 63%), 215(M-$CONHCH_2CH_2Ph$, 28%), 214 (base peak, 100%), 200(M-$CONHCH_2CH_2Ph$-CH_3, 31%), 173(15%), 144 (25%), 124(17%), 105 ($NHCH_2Ph$+, 9%), 91 CH_2Ph+, 73%) 65 (C_5H_5+, 6%), 41 (C_3H_5+).

6-methyl-2-oxo-4-(2'-phenylethylamino)-3-cyclohexene-1-(N-benzyl)-carboxamide (S10).

A similar techniques, as described for (S5) using a solution of ethyl 6-methyl-2-oxo-4-(2'phenylethylamino)-3-cyclohexene-1-carboxylate (1.625g, 0.0054mol) and benzylamine (1.734g, 0.0162mol) gave 6-methyl-2-oxo-4-(2' phenylethylamino)-3-cyclohexene-1-(N-benzyl)-carboxamide (S10) in 54% yield. It was recrystallized from ethanol, m.p. 165-166.5^{o}C (lit. 165-166^{o}C). MS (m/z): 363(M+1,28%), 362(M+, 82%), 347(M-Ch_3, 14%), 271(M-CH_2Ph, 7%), 228(M-$CONHCH_2$ PH, base peak, 100%, 214(M-$CONHCH_2Ph$-CH_3+H, 40%), 136(43%), 122 ($NH_3CH_2CH_2Ph$, 10%), 106($NHCH_2Ph$, 9%), 105 (CH_2CH_2Ph, 32%), 104(35%), 92(CH_3Ph+, 5%), 91 (CH_2Ph+, 46%), 77(Ph+, 6%), 65(C_5H_5+, 5%), 41(C_3H_5+, 4%).

Effect of Compounds on Central Nervous System

Male chicks, 3-5 day-old, kept singly in specially constructed transparent multipurpose observation box with a hinged cover on top, were used to determine the effect of the compounds on the central nervous system. Solutions of the compounds were made in 5% ethanolic normal saline. The chicks were administered the compounds at doses of 10, 50 and 100mg/kg, intraperitoneally and observed for 1h in the box. All experiments were performed in as quiet an environment as possible, during which animals had access to food and water. In all cases, control experiments were run concurrently for ease of direct comparison and animals received 0.2ml of the solvent; this volume representing the maximum injected into any chick used in the whole experiment.

RESULTS AND DISCUSSION:

The mechanism of reaction in the synthesis of 1, 3-cyclohexanediones carboxylate is reported to involve a 3-step reaction while the aminoalkylation reaction to obtain the aryl- or arylalkylamino derivatives was a 2-step substitution reaction involving replacement of the 4-C oxygen preferentially over the ester group at 1-C with the amino group in a molar ratio of 1:1 above 100^{o}C and the subsequent generation of a molecule of water. The aryl- and arylalkylamino derivatives of the 1,3 cyclohexanedione carboxylates were refluxed with the corresponding amines in a 1:1 molar ratio for 6h in toluene to obtain the carboxamides. The carboxamide can also be prepared from 1, 3-cyclohexandione carboxylate by addition of excess amines, in which case the 4-C and side chains will have the same aryl- or arylalkylamino group (Scheme 1).

The mass spectra of the various compounds showed informative and distinctive fragmentation pattern and gave quite

conclusive picture of the overall structure of each compound and its molecular weight. The fragmentation pattern is quite unique, and S1 seemed to produce many more pronounced fragments than the aryl- and arylalkylamino derivatives. The fragmentation pattern is presented in Scheme 2.

Elimination of methyl (M-15) was common to all the compounds. For the carboxylates there was an initial elimination of ethyl (M – 29, though weak) followed by ethoxy (M – 45) and then carboethoxy (M – 73) fragments from the compounds (Scheme 3). The fragments eliminated in the carboxamides included the following: phenyl (m/z 77) phenylamine (m/z 92) and phenylcarboxamide (PhNHCO, m/z 120) from S5 (M+ 320) and S7 (M+ 334); phenyl, benzyl (m/z 91), benzylamine (m/z 106) and benzylcarboxamide ($PhCH_2NHCO$, m/z 134) from S6 (M+ 336), S8 (M+ 350) and S10 (M+ 364); and phenylethylcarboxamide ($PhCH_2CH_2NHCO$, m/z 148) from S9 (M+ 362) were observed in the spectra of the respective compounds (Scheme 3). The phenyl ring fragment ion was observed in the spectra of all the compounds except S1 while the benzyl ($PhCH_2$) fragment was found in the spectra of all compounds except S1, S2 and S5. Also, the phenylamine fragment ion was common occurrence in spectra of S2, S5 and S6; while benzylamine ion was common in the spectra of S3, S6, S8, S9 and S10.

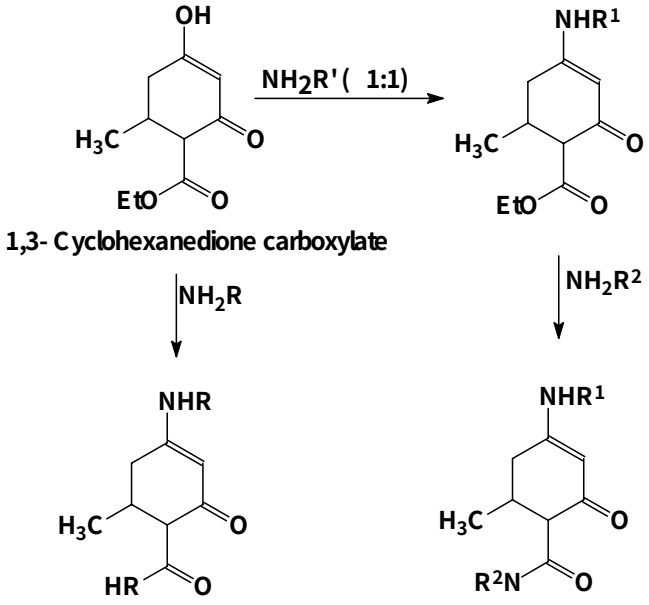
Cylohexenyl systems have been reported to undergo a typically Retro-Diel-Alder fragmentation on electron impact with the diene system appearing as the charged fragment in the spectrum.[13] Thus for carboxylates (S1, S2, S3 and S4) the pattern in Scheme 2 and for carboxamides (S5, S6, S7, S8, S9 and S10 the pattern in Scheme 3 were very likely. The m/z 114, 84, 69 and 41 occurred in the mass spectrum of S1 in 3, 30, 100 and 25% abundance respectively. The corresponding values of m/z, 84 in S2, S3 and S4 were 159 (100%), 173(72%) and 187(22%) respectively, implying decreased stability with increased alkyl chain length while the abundance for m/z, 114 in S2, S3 and S4 were 0.6, 0.2, and 0% respectively. The first generation species could lose CO to give another one, m/z, 56 (16%), 131(15%), 145(36%) and 159(6%) for S1, S2, S3 and S4 respectively. Again the fragment m/z 69 and 41 were observed in spectra of all the compounds to varying abundances. The species, m/z 114 was also found to be generally unstable in the carboxamides. Generally, esters undergo primary single bond cleavage processes to generate positively charged carbonyl and carboxylate ions. For this type of competition between losses of two or more radicals in 70 eV spectra, the loss of the larger radical is usually dominant.[13] Thus, in the carboxamides, though the ethoxy radical is lost, the loss of carboethoxy is more dominant. It should be noted that all the compounds gave m/z 41 ($C_3H_5^+$) a saturated carbonium ions, which is what is left of the cyclohexanedione nucleus at the end of fragmentation. Compounds containing the benzyl group yield $C_7H_7^+$ (m/z, 91) and its subsequent product, $C_5H_5^+$ (m/z, 65); and these values were observed in the spectra of all the compounds that were proposed to have the benzyl group in this work. The structure of the various compounds is given in Scheme 4.

Pharmacological Studies

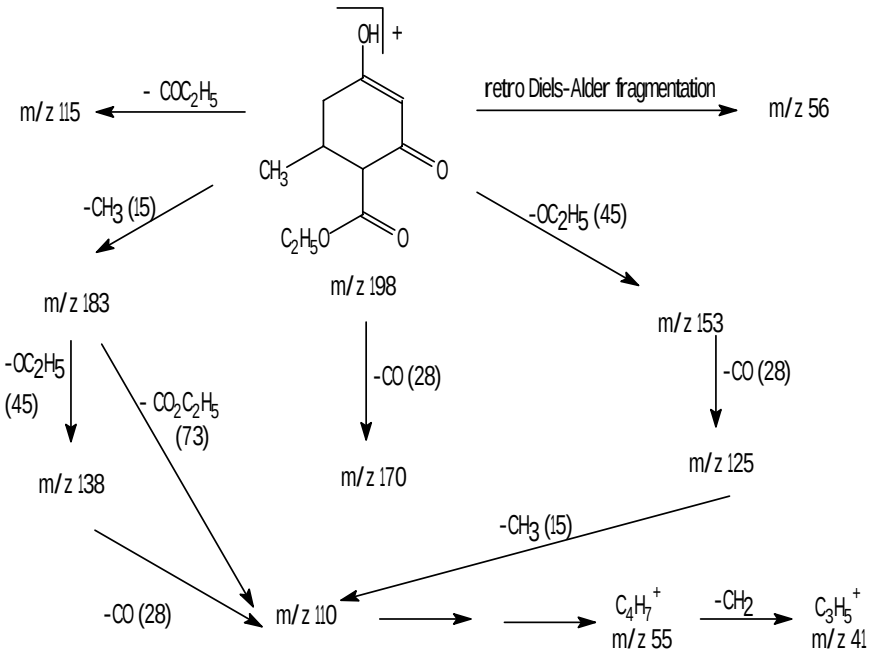
Effect of the compounds on the central nervous system (CNS) in chicks is presented in Table 1. Marked CNS depression was caused by S1, which has a hydroxyl group at 4-C. Substitution of the 4-hydroxy group with aryl, and arylalkyl amino groups gave compounds with varying degrees of CNS depressant activity, depending on the nature of the substituents. The chicks administered

with the compounds remained stationary with or without crying and in some cases dosed off. In the control experiments the normal activity characteristic of chicks continued. The phenaylamino substituent gave compounds that lacked the depressant activity, as in 6-methyl-2-oxo-4-phenylamino-3-cyclohexene-1-carboxylate (S2). However at same position, substitution with benzylamino group gave compounds with enhanced activity, while with 2'-phenylethylamino group gave a compound with reduced activity as in 4-benzylamino-6-methyl-2-oxo-2-cyclohexene-1-carboxylate (S3) and 6-methyl-2-oxo-4-(2'-phenylethyl amino)-3-cyclohexene-1-carboxylate (S4) respectively. Thus, it appeared that optimum activity was achieved with methylene bridge between the amino and the aromatic groups on the 4-C position side chain of the cyclohexanedione. Increase or decrease in the alkyl chain length from methylene led to reduction or abolishing of activity respectively. Both S5 and S6 at 10, 50 and 100mg/kg did not produce any appreciable effect on the normal activities of the chicks. However, S7, S8 and S9 produced a dose-dependent depression characterized by inactivity to drowsiness in the animals and this effect progressed to sleep at very high doses. Low dose of S10 (10mg/ml) did not seem to affect the behavior of the animals, but at higher doses depression, characterized by less activities, was observed.

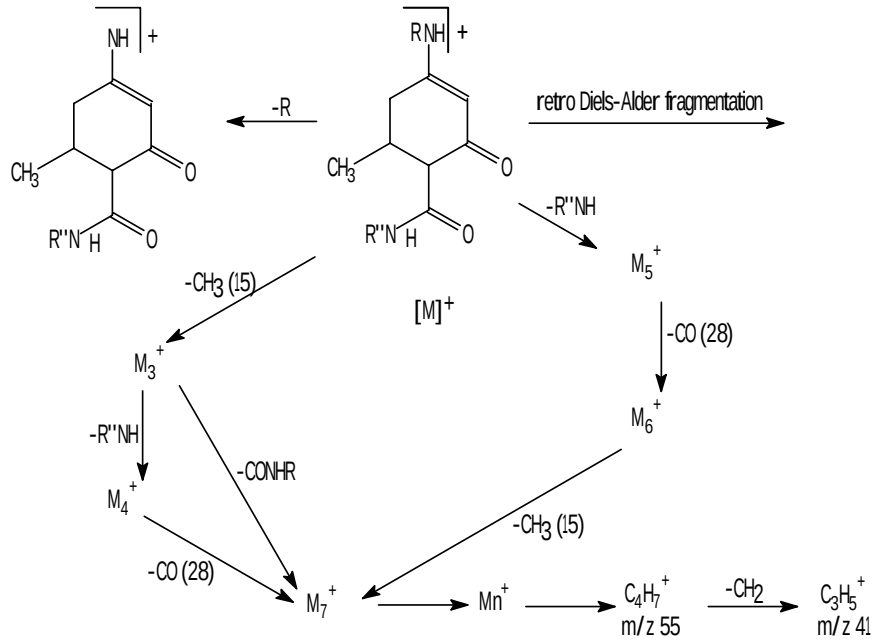
Scheme 1. Aminoalkylation of 1,3-cyclohexanedione carboxylate



Scheme 2: Major fragmentation pattern of ethyl-4-hydroxy-6-methyl-2 oxo-cyclohexene carboxylate.

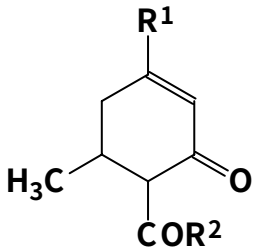


Scheme 3. Major fragmentation pattern of carboxamide derivatives of 1,3-hexanedione



$M^+ – M^+n$ = Fragment molecules
R, R" = Phenyl, Benzyl, Phenylethyl groups

Scheme 4. General Structure of 1,3 Cyclohexandione and Derivatives



Compound	R^1	R^2
S1	OH	OC_2H_5
S2	NHPh	OC_2H_5
S3	$NHCH_2Ph$	OC_2H_5
S4	$NHCH_2CH_2Ph$	OC_2H_5
S5	NHPh	NHPh
S6	NHPh	$NHCH_2Ph$
S7	$NHCH_2Ph$	NHPh
S8	$NHCH_2Ph$	$NHCH_2Ph$
S9	$NHCH_2Ph$	$NHCH_2CH_2Ph$
S10	$NHCH_2CH_2Ph$	$NHCH_2Ph$

Table 1: Effect of some 1,3-cyclohexenedione derivatives on behavioral activities of young chicks.

Compound	Dose (mg/kg)		
	10	50	100
S1	+	++	+++
S2	-	-	-
S3	+	++	+++
S4	-	+	+++
S5	-	-	-
S6	-	-	-
S7	+	+	+++
S8	+	+	++
S9	+	+	++
S10	-	+	++

Key: - No observable effect; + Reduced activity; + Central nervous system depression; ++ Marked c.n.s. depression; +++ Sedation

CONCLUSION

The type and nature of fragments observed in the mass spectra of each compound completely agreed with arrangement of the chemical groups as in the structure proposed for the corresponding compounds synthesized. From the mass spectra data, the molecular weights of the compounds were deduced. The fragmentation pattern of the series was unique and definite. Preliminary pharmacological investigation indicated that 1, 3-cyclohexandione carboxylate and the 4-benzylamino derivatives could be developed as potential central nervous system depressants with possible safer therapeutic index in the treatment of mental agitation and other states of hyperactivity.

REFERENCES

1. Doberstyn BE, Resistance of Plasmodium falciparum. Experimental. 40: 1311-1317.
2. Franklin, TJ. Bacterial (1994) Resistance to Antibiotics. In: Pharmaceutical Microbiology, 5th Ed. Hugo WB and Russell AD, (eds), Blackwell Scientific Publications, London: 208-230.
3. Lakhvich FR, Budai SI, Khlebnikova TS. (1979) From Otkrytiya, Izobret. Prom. Obraztsy, Tovarnye Znaki. 16; 115-15. CA, 91:1404304p (1979)
4. Schamp N, Verha R, and De Buyck L. (1974). Two-step Synthesis of 2-chlororesorcinolsfrom 1, 3 cyclohexanediones. Meded Fac. Land Boumenta. Rijksimiv Gent. 39 (4): 1645-48.
5. Ogunleye DS, Edafiogho I, and Husseini IM (2003). Synthesis and Spectra Analysis of 1,3-cyclohexandione Carboxylate and Derivatives. Nigerian Journal of Pharmaceutical Research, 2; 38-43.
6. Ogunleye, D. S. Edafiogbo I, and Husseini, I. M.(2002). Synthesis and Spectral Analysis of 1, 3-cyclohexanedione Carboxamides. Tropical J. Pharm. Res. In press.
7. Jahn D, Becker R, Goetz N, Wuerzer B. (1981) Cyclohexane-1, 3-dione derivatives and their use against undesirable vegetation. Eur. Pat. Appl. Ep 70, 495 (cl. CO7C83/06 26 Jan. 1983.DE. Appl. 3, 128, 960, 22 Jul. 981, 36.
8. Jay JM, Rivers GM, Boisrevt WE (1983). Antimicrobial properties of a-dicarbonyl related compounds. J. Food Prot., 46(4): 325-29.
9. Hiraga K, Golo M, Inuoe k, Uchida M (1989). 2-cyclohexyllidine dithiolanes for treatment of liver disorders. Jpn. Kokai Tokkyo Koho Jp. 01, 242, 580 (89,242,580) Cl. (07D 339/06) 27 Sept., Appl. 88/68,713, 23 Mai 1988; 13.
10. Ogunleye DS, Husseini IM and Ogunleye TO (2002). 1, 3-cyclohexandione Carboxylate and some Enaminone Derivatives as Potential Anticonvulsant Agents. Nigerian Journal of Pharmaceutical Research, 1: 78-81.
11 Mattson Ove. H (1968). Mass Spectra of some Cyclic B-diketones. Acta Chem. Scand. 22 (8): 2479-92.
12. Vanderwalle M, Schamp N, and de Wilde H. (1967). Studies in Organic Mass Spectrometry. Fragmentation of 2-alkyl 1,3 cyclohexandiones. Bull. Soc. Chem., Belges. 76 (1-2): 111-22.
13. Williams DH, Fleming I (1980) Spectroscopic Methods in Organic Chemistry, 3rd Ed. McGraw-Hill Book Coy. (UK) Ltd, London, 1-9.