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α-DIMETHYLAMINOMETHYLENE DERIVATIVES OF SUCCINIMIDE AND GLUTARIMIDE IN THE FISCHER REACTION

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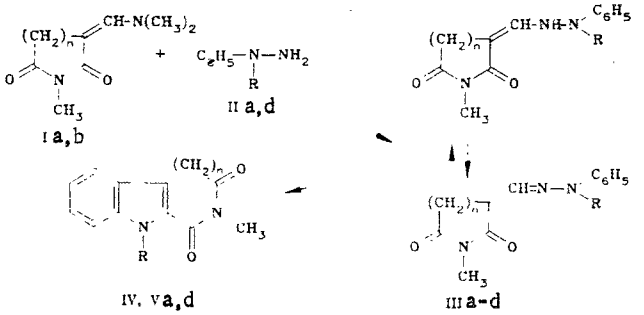
A study has been made of the behavior of α-dimethylaminomethylene derivatives of succinic and glutaric acid N-methylimides when reacted with different arylhydrazines under the conditions of the Fischer reaction.

It has been shown previously [1, 2] that the interaction of α-formylbutyrolactams with arylhydrazines in the Fischer reaction is accompanied by an intramolecular rearrangement and this leads to the formation of 1-oxo-1,2,3,4-tetrahydro-β-carbolines.

It was of interest to study the possibility of this rearrangement occurring for other heterocyclic aldehydes or their enamines.

In the present work a study was made of the reaction of α-dimethylaminomethylene derivatives of succinic and glutaric acid N-methylimides I with arylhydrazines II.



Ia, IV n=1; Ib, V n=2; II—V **a** R=$CH_2C_6H_5$, **b** R=C_6H_5, **c** R=CH_3, **d** R=H

It is known that in the Vilsmeier reaction N-substituted succinimides, unlike γ-lactams [3], do not give dimethylaminomethylene derivatives but undergo aromatization and are converted to α,α'-dichloro-β,β'-diformylpyrroles [4]. Consequently, we obtained the necessary enamines Ia, b by the action of bis(dimethylamino)methoxymethane on the N-methylimides of succinic [5] and glutaric acid.

When enamines Ia, b are reacted with arylhydrazines in aqueous 2-propanol in the presenc of hydrochloric acid (the conditions for obtaining 1-oxo-1,2,3,4-tetrahydro-β-carbolines), the reaction stops at the stage where hydrazones III are formed. For example, the α,α-diphen hydrazone of α-formyl-N-methylsuccinimide IIIb was separated and it consisted of a mixture of at least two isomers with a markedly different chromatographic mobility on Silufol. Howev separation of them chromatographically turned out to be impossible as in solution in the presence of adsorbents or acids both isomers are quite rapidly interconverted with the formation of an equilibrium mixture. On standing, crystals of a pure isomer with the lower R_f value precipitate out from a concentrated benzene or chloroform solution of the mixture of isomers. Separation of the second isomer in a pure form was not achieved.

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Evidently these isomers are hydrazone and enehydrazine forms, and the crystalline tautomer should be assigned the enehydrazine structure. In its IR spectrum there is an intense band in the region 3385 cm^{-1} from NH bond vibrations, and in the region of double bond stretc ing vibrations three absorption bands are observed at 1750, 1700, and 1640 cm^{-1}. The first two bands should be attributed to vibrations from the imide carbonyl groups and the latter to C=C bond vibrations. In the IR spectrum of the mixture of isomers there is an additional high-frequency carbonyl absorption band (1780 cm^{-1}), indicating the presence of the less conjugated hydrazone structure in the mixture [6].

The UV spectra also confirm the assignments made. The crystalline tautomer as the more conjugated enehydrazine system has an absorption maximum at longer wavelength (288 nm). In the absorption spectrum ofthe mixture of isomers, together with this maximum there is a shoulder at shorter wavelength (270 nm) corresponding to the absorption from the less-conjugated hydrazone form.

In the PMR spectrum of the pure enehydrazine, a singlet from the methyl group appears at 2.79 ppm. In the spectrum of the equilibrium mixture of IIIb isomers, two singlets are observed at 2.79 and 2.85 ppm, corresponding to the methyl groups of enehydrazine and hydrazone. A comparison of the relative intensity of these signals shows that in the equilibrium mixture the enehydrazine and hydrazone forms are present in the ratio 2:1. Cyclization of such hydrazones to give the expected β-carbolines IVa-d was achieved only under quite severe conditions – by boiling in glacial acetic acid saturated with dry HCl. Under these conditions the initially formed hydrazones IIIa-d cyclize to 1,3-dioxo-1,2,3,4-tetrahydro-β-carbolines, which were very unstable in solution (in due course turning an intense green color).

1,3-Dioxo-1,2,3,4,5,10-hexahydroazepino[3,4-b]indoles (Va-d) are obtained in a similar manner from N-methyl-α-dimethylaminomethyleneglutarimide.

In the IR spectra of the dioxocarbolines IVa-d and dioxoacepinoindoles Va-d synthesized, the amide fragment appears as a doublet band from symmetric and antisymmetric carbonyl group vibrations in the regions 1745-1690 and 1675-1635 cm^{-1}, respectively. Also, the higher-frequency band has a lower intensity, which is characteristic of cyclic compounds containing a CO–NH–CO group [7].

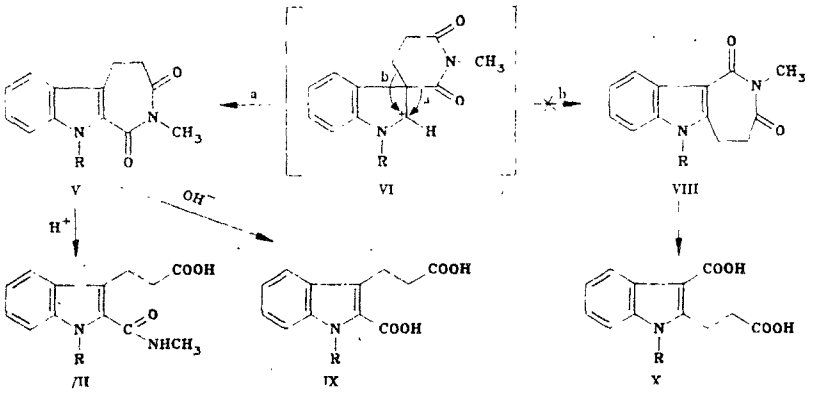
In the PMR spectra of compounds IV and Va-d, a singlet with chemical shift 3.1-3.4 ppm from the methyl group at the 2-position is observed. For azepinoindoles Va-d the protons of the two methylene groups in the azepine ring appear as a multiplet in the region 2.9-3.3 ppm. The protons of the methylene group in 1,3-dioxocarbolines IVa-d give a singlet at lower field at 4.0-4.1 ppm, which is in agreement with the data given in [8] for an analogous compound with an α-phenylethyl substituent at the 2-position. The signal from the 9-CH_3 group appears in the same region.

In the UV spectra two absorption maxima in the regions 239-243 and 288-316 nm are displayed by all compounds IV and Va-d.

It follows from the data of the mass spectra of compounds IVd and Va, c that the molecular ion has a high stability (relative intensity of peak >80%) and its main fragmentation pathways are connected with the breakup of the imide ring. The most intense peaks in the mass spectra of the compounds investigated correspond to the ions $[M - CO]^+$, $[M - CONCH_3]^+$, and $[M - CON(CH_3)CO]^+$.

When α-substituted phenylhydrazines were used, in certain cases together with the main reaction products IVa and Va,c, carboline IVd and azepinoindole Vd, which are not substituted on the indole nitrogen atom, were also isolated. The dealkylated products IVd and Vd were obtained in small quantities (7-13%).

Increasing the time of reaction between N-methyl-α-dimethylaminomethyleneglutarimide and α-benzylphenylhydrazine in order to increase the yield only led to partial hydrolysis of azepinoindole Va obtained, with the process involving opening of the imide ring. As a result, the N-methylamide of 1-benzyl-3-(2-carboxyethyl)-2-indolylcarboxylic acid was isolated from the reaction mixture in small yield (3%). It was established subsequently that 10-benzyl-1,3-dioxo-1,2,3,4,5,10-hexahydroazepino[3,4-b]-indole is completely converted to amide VII (R = $CH_2C_6H_5$) on boiling for a short time in a mixture of acetic and concentrate hydrochloric acids. The structure of the amide obtained has been established by mass spectrometry. The presence in the spectrum of peaks from the $[M - CONHCH_3]^+$ and $[M - CH_2COOH]^+$



ions and the absence of $[M - COOH]^+$ and $[M - CH_2CONHCH_3]^+$ definitely indicate that in the dicarboxylic acid monoamide VII the free carboxyl group is contained in the aliphatic side chain, while the amide group is directly attached to the indole ring.

For the proposed intermediate structure VI there are two routes for rearrangement – a and b – that are theoretically possible; these can result in the formation of the isomeric compounds V and VIII. In order to select the rearrangement route and substantiate the structure of the compounds obtained, we undertook the alkaline hydrolysis of azepinoindole Vd so as to obtain one of the dicarboxylic acids IX or X depicted. As a result of hydrolysis only acid IX (R = H) was obtained, which indicates that route a is realized and, consequently, it is V and VII that are formed.

EXPERIMENTAL

IR spectra were recorded on a UR-20 instrument in KBr pellets or in CH_2Cl_2 solution; UV spectra were recorded in 2-propanol on a Hitachi EPS-3T instrument; PMR spectra were recorded on Bruker WM (200 MHz) and Varian FT 80-A (80 MHz) instruments in $CDCl_3$ and $(CD_3)_2CO$, with TMS as internal standard. Mass spectra were obtained on a Varian MAT-311A instrument. Chromatographic mobility of the compounds was determined on Silufol UV-254 plates; development was carried out using UV light or iodine vapor.

Bis(dimethylamino)methoxymethane was obtained according to the method in [9]. N-Methylsuccinimide was obtained with a yield of 97% by methylation of N-sodium succinimide with methyl iodide [10]. N-Methylglutarimide was obtained by heating the methylammonium salt of glutaric acid [11].

N-Methyl-α-dimethylaminomethylenesuccinimide (Ia). 6.10 g (0.05 mole) of bis(dimethylamino)methoxymethane was added to 5.65 g (0.05 mole) of N-methylsuccinimide and the mixture was heated for 2 h at 110°C on an oil bath. The dimethylamine and methyl alcohol formed were removed under vacuum. The crystalline residue was washed with absolute ether. Yield was 6.5 g (75%) of white crystals, mp 174°C, Rf 0.60 (acetone). IR spectrum (KBr): 1710, 1655 (C=O), 1600 cm^{-1} (C=C). UV spectrum, λ_{max} (log ε): 305 nm (4.49). PMR spectrum ($CDCl_3$, 80 MHz): 7.11 (1H, broad s, CH=C); 3.42 (2H, broad s, CH_2); 3.00 [6H, s, $N(CH_3)_2$]; 2.95 ppm (3H, s, N–CH_3). Gave a green color with $FeCl_3$. According to the data of [5], mp 172°C.

N-Methyl-α-dimethylaminomethyleneglutarimide (Ib). This was obtained in a similar manner to compound Ia from N-methylglutarimide. Yield 58%, mp 107°C, Rf 0.50 (benzene–acetone, 1:1). IR spectrum (KBr): 1685, 1650 (C=O), 1570 cm^{-1} (C=C). UV spectrum, λ_{max} (log ε): 217 (4.33), 320 nm (4.60). PMR spectrum ($CDCl_3$, 200 MHz): 7.78 (1H, s, CH=C); 3.15 (3H, s, N–CH_3); 3.09 [6H, s, $N(CH_3)_2$]; 2.78 (2H, t, J = 7.5 Hz, CH_2C=O); 2.56 ppm (2H, t, J = 7.5 Hz, CH_2C=C). Found, %: C 59.8, H 7.8. $C_9H_{14}N_2O_2$. Calculated, %: C 59.4, H 7.8. Gave a green color with $FeCl_3$.

N,N-Diphenylhydrazone of α-Formyl-N-methylsuccinimide (IIIb). 1.1 g (5 mmole) of α,α-diphenylhydrazine hydrochloride and 0.84 g (5 mmole) of N-methyl-α-dimethylaminomethylenesuccinimide were dissolved on heating in 10 ml of glacial acetic acid and the mixture was left overnight. The acetic acid was evaporated under vacuum, and the residue was dissolved in 50 ml of chloroform, washed with water (2 × 15 ml), dried over $MgSO_4$, and the solvent was evaporated under vacuum. 1.5 g of a vitreous substance was obtained, being a mixture of two isomers. The yield was quantitative, Rf 0.15; 0.50 (benzene–ether, 3:1). IR spectrum (CH_2Cl_2): 3385 (NH), 1780, 1750, 1700 (C=O), 1640 cm^{-1} (C=C). UV spectrum, λ_{max} (log ε):

TABLE 1. Properties of 1,3-Dioxo-1,2,3,4-tetrahydro-β-carbolines (IV) and 1,3-Dioxo-1,2,3,4,5,10-hexahydroazepino[3,4-b]-indoles (V)

Compound	mp,* °C	R_f†	Found, %		Empirical formula	Calculated, %		Yield, %
			C	H		C	H	
IVa	201	0,72	75,0	5,3	$C_{19}H_{16}N_2O_2$	75,1	5,3	61
IVb	190 (decomp.)	0,66	74,0	5,1	$C_{18}H_{14}N_2O_2$	74,5	4,9	50
IVc	183	0,67	68,7	5,7	$C_{13}H_{12}N_2O_2$	68,5	5,3	57
IVd	250 (decomp.)	0,50	67,6	4,8	$C_{12}H_{10}N_2O_2$	67,4	4,7	14
Va	119	0,64	75,5	5,8	$C_{20}H_{18}N_2O_2$	75,5	5,7	61
Vb	158	0,57	75,3	5,3	$C_{19}H_{16}N_2O_2$	75,1	5,3	29
Vc	113	0,57	69,6	6,0	$C_{14}H_{14}N_2O_2$	69,5	5,8	50
Vd	197,5	0,50	68,4	5,3	$C_{13}H_{12}N_2O_2$	68,5	5,3	25

*Compounds IVa, c crystallized from ethyl acetate; IVb from a mixture of ethyl acetate–hexane (1:1); IVd from a mixture of ethyl acetate–benzene (1:1); Va, c from isopropanol; Vb from a mixture of hexane–ether–isopropanol (2:1:1); Vd from benzene.
†Compounds IV a-d are benzol–ether (2:1); Va-d are benzol–ether (5:1).

TABLE 2. UV, IR, PMR, and Mass Spectra of Compounds IV and V

Compound	UV spectrum, λ_{max}, nm (log ε)	IR spectrum, cm^{-1}		PMR spectrum,* ppm				Mass spectrum, m/z (%)
		NH	C=O	2-CH_3 (s)	4-H	5-H	9(10)-R†	
IVa	241 (4,33), 310 (4,28), 338 shld. (3,86), 380 shld. (2,40)		1675 1716	3,25	4,03 s	—	5,70 s (CH_2)	
IVb	212 (4,56), 239 (4,42), 308 (4,34), 334 shld. (3,95)		1676 1713	3,22	4,10 s	—	7,00—7,60 m (C_6H_5)	
IVc	209 (4,28), 241 (4,17), 309 (4,14), 336 shld. (3,71)		1700 1746	3,18	4,02 s	—	4,02 s (CH_3)	
IVd	219 (4,39), 239 (4,22), 312 (4,18)	3340	1660 1715	3,30	4,03 s	—		214 (84), 157 (27), 129 (100), 102 (28), 77 (13)
Va	240 (4,29), 316 (4,30)		1645 1690	3,15	2,90—3,26 m		5,82 s (CH_2)	318 (94), 260 (5), 232 (9), 218 (10), 176 (18), 161 (9), 120 (16), 91 (100), 77 (23)
Vb	243 (4,05), 288 (4,27)		1680 1730	3,10	2,94—3,22 m		6,85—7,66 m (C_6H_5)	
Vc	241 (4,26), 316 (4,27)		1650 1687	3,15	2,95 broad s		3,95 s (CH_3)	242 (100), 214 (24), 201 (19), 199 (15), 197 (29), 184 (34), 173 (17), 171 (14), 157 (99), 143 (29), 140 (13), 128 (24), 115 (39)
Vd	241 (4,22), 316 (4,29)	3360	1630 1705	3,42	3,11—3,20 m		9,41 s (H)	

*PMR spectrum of compounds IVa, b, d recorded in $CDCl_3$; IVc, Va-d in $(CD_3)_2CO$. For compounds IVa-d, Va-c, PMR 80 MHz; for Vd, PMR 200 MHz.
†Compounds IVa-c, 9-R; Va-c, 10-R.

270 nm (4.17) shoulder, 286 nm (4.22). PMR spectrum [$(CD_3)_2CO$, 80 MHz]: 2.87-3.10 (m, CH_2); 2.85 (s, CH_3 of hydrazone form); 2.79 ppm (s, CH_3 of enehydrazine form). Found, %: C 70.7, H 5.8. $C_{18}H_{17}N_3O_2$. Calculated, %: C 70.4, H 5.6. 25 ml of benzene was added to the oil obtained. The precipitated enehydrazine form was filtered off and recrystallized from a mixture of benzene–methanol (2:1). Yield 0.75 g (50%), mp 195°C, Rf 0.15 (benzene–

ether, 3:1). IR spectrum (CH_2Cl_2): 3385 (NH), 1750, 1700 (C=O), 1640 cm^{-1} (C=C). UV spectrum, λ_{max} (log ε): 288 nm (4.35). PMR spectrum [$(CD_3)_2CO$, 80 MHz]: 3.00-3.15 (2H, m, CH_2); 2.79 ppm (3H, s, CH_3). Mass spectrum, m/z (%): 307 (63), 195 (23), 168 (100), 115 (5), 77 (27). Found, %: C 70.4, H 5.8. M^+ 307. $C_{18}H_{17}N_3O_2$. Calculated, %: C 70.4, H 5.6. M 307.

General Method for Obtaining 1,3-Dioxo-1,2,3,4-tetrahydro-β-carbolines (IV) and 1,3-Dioxo-1,2,3,4,5,10-hexahydroazepino[3,4-b]indoles (V). To 5 mmole of the hydrochloride or sulfate of phenylhydrazine IIa-d was added 15-25 ml of glacial acetic acid. The mixture was saturated with dry HCl, heated to boiling, and a solution of 5 mmole of enamine I in 10 ml of glacial acetic acid was added dropwise. The reaction mixture was boiled for 1-3 h and the acetic acid was evaporated under vacuum. The residue was supplemented with 50 ml of chloroform, washed with water (2 × 20 ml), dried over $MgSO_4$, and the solvent was evaporated under vacuum. The products were separated by chromatography (column 20 × 1 cm with silica gel 40/100 mk, eluent was benzene–ether, 2:1; for azepinoindole Vb eluent was hexane–ether, 2:1). Recrystallization was carried out using a suitable solvent (Table 1). On obtaining compounds Va, c, the 10-unsubstituted azepinoindole Vd was also isolated with yield 7 and 10%, respectively. On obtaining compound IVa, the debenzylated compound – carboline IVd – was also isolated (13%).

N-Methylamide of 1-Benzyl-3-(2-carboxyethyl)-2-indolylcarboxylic Acid (VII). To 0.25 g (0.6 mmole) of 2-methyl-9-benzyl-1,3-dioxo-1,2,3,4,5,10-hexahydroazepino[3,4-b]indole (Va) was added 3 ml of acetic acid and 3 ml of concentrated HCl. The mixture was boiled until the solid had dissolved. After cooling, colorless, needleshaped crystals were precipitated. Yield 0.23 g (87%), mp 183°C (from isopropanol), Rf 0.60 (benzene–ether, 1:1). IR spectrum (KBr): 3285 (NH), 1730, 1711 (carboxyl C=O), 1640 cm^{-1} (amide C=O). UV spectrum, λ_{max} (log ε): 214 (4.46), 292 (4.13), 308 nm (3.94) shoulder. PMR spectrum ($CDCl_3$, 200 MHz): 8.01 (1H, broad s, NH); 5.55 (2H, s, CH_2Ph): 3.26 (2H, t, J = 3.5 Hz, CH_2COOH); 3.01 (2H, t, J = 3.5 Hz, $CH_2C=C$); 2.96 ppm (3H, s, CH_3). Mass spectrum, m/z (%): 336 (53), 278 (13), 277 (17), 227 (12), 218 (7), 214 (9), 120 (11), 91 (100). Found, %: C 71.8, H 6.1 M^+ 336. $C_{20}H_{20}N_2O_3$. Calculated, %: C 71.5, H 6.0. M 336.

3-(2-Carboxyethyl)-2-indolylcarboxylic Acid (IX). 5 ml of 30% KOH was added to 0.09 g (0.4 mmole) of 2-methyl-1,3-dioxo-1,2,3,4,5,10-hexahydroazepino[3,4-b]indole and the mixture was boiled for 2 h. The potassium salt which had precipitated after cooling was filtered off and dissolved in 15 ml of dilute (1:3) hydrochloric acid. The solution was then extracted with ether (3 × 10 ml), the ether extracts were dried over $MgSO_4$, and the ether was evaporated under vacuum. The residue was recrystallized from benzene, mp 190-191°C. Mass spectrum, m/z (%): 233 (80), 188 (30), 187 (60), 174 (51), 169 (52), 156 (93), 143 (13), 140 (17), 130 (79), 115 (24), 101 (16), 78 (100). According to the data of [12], mp 194-195°C.

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