METHYL γ-PHENYLACETOACETATE IN THE SYNTHESIS OF DERIVATIVES OF α-AMINOINDOL-2-YL-ACETIC ACID

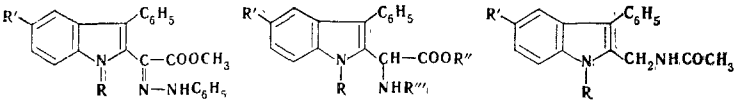
V. I. Shvedov, G. N. Kurilo,
A. A. Cherkasova, and A. N. Grinev

UDC 547.757

The cyclization of the di(phenylhydrazone) of methyl γ-phenyl-α,β-dioxobutyrate with hydrazines has given phenylhydrazones of methyl indol-2-ylglyoxylates, which have been reduced to methyl α-aminoindol-2-ylacetates. Some reactions of these compounds have been studied.

In spite of the considerable interest in amino acids of the indole series, indole derivatives containing amino acid residues in position 2 have been studied little [1-3]. By the reduction of phenylhydrazones of methyl indol-2-ylglyoxylates by a method proposed previously for the synthesis of aliphatic amino acids [4] we have obtained a number of α-aminoindol-2-ylacetic acids and their derivatives. As the initial compound we used methyl γ-phenylacetoacetate which, on azo coupling with benzenediazonium chloride, forms the α-phenylhydrazone of methyl α,β-dioxo-γ-phenylbutyrate (I). The structure of (I) was confirmed by the presence in the PMR spectrum of the signal of the protons of a γ-methylene and an imino group at 4.03 and 12.65 ppm, respectively. In the IR spectrum of this compound, the absorption band of the NH group is found in the 3170-cm^{-1} region. The displacement of the absorption band of the imino group of (I) in the low-frequency direction in the IR spectrum, and also the presence of the signal of the proton of the NH group in a very weak field in the PMR spectrum can apparently be explained by the presence of a fairly strong intramolecular hydrogen bond of the cis form of (I), as has been observed for other cases [5, 6].

When (I) was heated with asym-alkylarylhydrazines, di(arylhydrazones) were formed, and these were cyclized without isolation by the action of a methanolic solution of concentrated sulfuric acid to form phenylhydrazones of methyl indol-2-ylglyoxylates (II-IV). The derivatives (II-IV) are readily reduced by zinc in dioxane saturated with hydrogen chloride to esters of the amino acids (V-VII). In the IR spectra of compounds (V-VII), the absorption bands in the 3330-3320- and 3400-3390-cm^{-1} regions are connected with the stretching vibrations of the NH_2 groups. The hydrolysis of the ester of the amino acid (VI) with caustic potash gave a high yield of α-amino-1-benzyl-3-phenylindol-2-ylacetic acid (VIII), the reduction of (II) with zinc in a mixture on acetic acid and acetic anhydride gave the methyl ester of α-acetylamino-1-methyl-3-phenylindol-2-ylacetic acid (IX), and the hydrolysis of the latter gave the acetyl derivative of the amino acid (X). Methyl α-acetylamino-1-benzyl-3-phenylindol-2-ylacetate, obtained from (III) in the same way as (IX) was hydrolyzed, without isolation, to the acetyl derivatives of the amino acid (XI). On heating, the derivatives (X and XI) readily underwent decarboxylation, being converted into the acetylaminomethylindoles (XII and XIII).



II-XIII R = H, CH_3, $CH_2C_6H_5$; R′ = H, OCH_3; V-XI R″ = H, CH_3; R‴ = H, $COCH_3$

S. Ordzhonikidze All-Union Scientific-Research Institute of Pharmaceutical Chemistry, Moscow.
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 8, pp. 1040-1042, August, 1973. Original article submitted June 19, 1972.

TABLE 1. Phenylhydrazones of Methylindol-2-ylglyoxylates (II-IV)

Comp.	R	R′	mp, °C	Empirical formula	Found, %			Calc., %			Yield, %
					C	H	N	C	H	N	
II	CH_3	H	176—177[a]	$C_{24}H_{21}N_3O_2$	75,2	5,5	11,0	75,2	5,5	11,0	65
III	CH_3	OCH_3	161—162,5[b]	$C_{30}H_{25}N_3O_2$	78,5	5,6	9,6	78,4	5,5	9,1	70
IV	$CH_2C_6H_5$	H	204,5—205,5[a]	$C_{25}H_{23}N_3O_3$	72,6	5,6	10,4	72,6	5,6	10,2	64

[a]From ethyl acetate. [b]From methanol–dioxane (3 : 1).

TABLE 2. Methyl Esters of α-Amino-3-phenylindol-2-ylacetic Acids (V-VII) (R″ = CH_3; R‴ = H)

Comp.	R	R′	mp, °C	Empirical formula	Found, %				Calc., %				Yield, %
					C	H	Cl	N	C	H	Cl	N	
V	CH_3	H	94—95[a]	$C_{18}H_{18}N_2O_2$	73,5	6,1	10,5	9,5	73,5	6,2	10,7	9,5	70
HCl			189—190[b] (decomp.)	$C_{18}H_{18}N_2O_2 \cdot HCl$	62,3	5,8		7,8	65,4	5,8		8,5	
VI	$CH_2C_6H_5$	H	133—134[a]	$C_{24}H_{22}N_2O_2$	78,0	5,8	8,7	7,4	77,8	6,0	8,7	7,6	84
HCl			~150[c] (decomp.)	$C_{24}H_{22}N_2O_2 \cdot HCl$	70,7	5,6		6,7	70,8	5,7		6,9	
VII	CH_3	OCH_3	126—127[a]	$C_{19}H_{20}N_2O_3$	70,3	6,1	9,7	8,6	70,4	6,2	9,8	8,6	70
HCl			206,5—207,5[b]	$C_{19}H_{20}N_2O_3 \cdot HCl$	63,4	5,6		7,6	63,2	5,9		7,8	

[a]From methanol. [b]From methanol–ether (1 : 5). [c]From methanol–ether (1 : 10).

EXPERIMENTAL

The IR spectra were taken of the substances in the form of mulls in paraffin oil, and in the case of (I) also as a solution in carbon tetrachloride, on a Perkin–Elmer spectrophotometer. The PMR spectrum was taken in carbon tetrachloride solution on a JNM-4H-100 spectrometer with a working frequency of 100 MHz using HMDS as standard.

α-Phenylhydrazone of Methyl α,β-Dioxo-γ-phenylbutyrate (I). With stirring, 19.2 g (0.1 mole) of methyl γ-phenylacetoacetate was added to a solution of 4 g (0.1 mole) of caustic soda in 50 ml of water, the temperature not being allowed to rise above 10°C. The resulting solution was added to the diazonium salt prepared in the usual way from 9.3 g (0.1 mole) of aniline, 25 ml of concentrated hydrochloric acid, and 6.9 g (0.1 mole) of sodium nitrite, and subsequently neutralized to pH 7 with sodium acetate. The reaction mixture was stirred at 0-5°C for 1 h, and the precipitate was filtered off, washed with water and methanol, and dried. Yield 16.4 g (55.5%), mp 94-95°C (from isopropanol). PMR spectrum, δ, ppm: 3.77 ($COOCH_3$, s*); 403 (γ-CH_2, s); 7.13 (s, C_6H_5); 7.21 (s, C_6H_5); 12.65 (NH, s). Found, %: C 69.1; H 5.4; N 9.5. $C_{17}H_{16}N_2O_3$. Calculated, %: C 68.9; H 5.4; N 9.5.

Phenylhydrazones of Methyl Indol-2-ylglyoxylates (II-IV). A mixture of 0.1 mole of (I), 0.11 mole of an asymmetrical alkylarylhydrazine and 1-2 drops of acetic acid was heated at 100°C for 5 h. The water liberated was eliminated by azeotropic distillation with benzene. The residue in the flask was treated with a solution of 48 ml of concentrated sulfuric acid in 480 ml of methanol, and the mixture was boiled for 10 min. Then it was cooled, and the crystals that had separated out were filtered off, washed with water, and dried. Information on compounds (II-IV) is given in Table 1.

Methyl α-Aminoindol-2-ylacetates (V-VII). A suspension of 0.01 mole of one of compounds (II-IV) in 30 ml of dioxane was treated with 0.07 mole of zinc dust and, with stirring, 60 ml of 10% aqueous dioxane saturated with hydrogen chloride (10% by volume) was added dropwise with the temperature kept at 45-50°C. Then another 0.025 mole of zinc dust was added and the mixture was heated at 50°C for 1 h. The solid matter was filtered off and washed with dioxane. The filtrate was evaporated in vacuum, 100 ml of water was added, and it was made alkaline with an excess of ammonia and extracted with ether. The ethereal layer was washed with water and dried with magnesium sulfate. The ether was distilled off and the residue was dissolved in dry ether and the solution was acidified with a solution of hydrogen chloride in ether. The

*Singlet.

precipitate of the hydrochloride* that deposited was filtered off, washed with ether, and dried, and then this hydrochloride was dissolved in water† and the solution was made alkaline with ammonia solution.

α-Amino-1-benzyl-3-phenylindol-2-ylacetic Acid (VIII). To a solution of 0.3 g (5.4 mmoles) of caustic potash in 30 ml of ethanol was added 1.68 g (4.5 mmoles) of (VI), and the mixture was boiled for 1 h. Then the ethanol was distilled off and the residue was dissolved in 35 ml of water and extracted with ether. The aqueous solution was acidified with glacial acetic acid, and the precipitate was filtered off, washed with a small amount of water, and dried. Yield 1.59 g (98%), mp 151-152°C (decomp., from aqueous methanol). Found, %: C 77.3; H 5.6; N 7.9. $C_{23}H_{20}N_2O_2$. Calculated, %: C 77.5; H 5.7; N 7.9.

Methyl α-Acetylamino-1-methyl-3-phenylindol-2-ylacetate (IX). To a suspension of 4.6 g (12 mmoles) of (II) in 30 ml of glacial acetic acid were added 2.8 g (25 mmoles) of acetic anhydride and 1.2 g (15 mmoles) of fused sodium acetate, and then the reaction mixture was heated to 60°C and 9 g (0.14 mole) of zinc dust was added to it in portions over 10 min. The reaction mixture was boiled for 2 h. The sludge was filtered off and was carefully washed with hot glacial acetic acid. The combined acetic acid solutions were poured onto ice, and the precipitate was filtered off, washed with water and methanol, and dried. Yield 3.8 g (93%), mp 196-197°C (from methanol). Found, %: C 71.3; H 6.0; N 8.4. $C_{20}H_{20}N_2O_3$. Calculated, %: C 71.4; H 6.0; N 8.3.

α-Acetylamino-1-methyl-3-phenylindol-2-ylacetic Acid (Hydrate) (X). To a solution of 0.4 g (7 mmoles) of caustic potash in 30 ml of ethanol was added 1 g (3 mmoles) of (IX), and the mixture was boiled for 1 h. The product was isolated under the conditions for the synthesis of (VIII). Yield 0.75 g (75%), mp about 135°C (decomp.). The compound underwent decarboxylation during recrystallization. Found, %: C 67.1; H 5.8; N 8.1. $C_{19}H_{18}N_2O_3 \cdot H_2O$.‡ Calculated, %: C 67.0; H 5.9; N 8.2.

α-Acetylamino-1-benzyl-3-phenylindol-2-ylacetic Acid (XI). The methyl α-acetylamino-1-benzyl-3-phenylindol-2-ylacetate obtained from 4.6 g (0.01 mole) of (III) under the conditions of the synthesis of (IX), without isolation, was subjected to hydrolysis under the conditions for the synthesis of (X). The yield of (XI) was 3.27 g (87.5%). Decomp. >170°C (from ethyl acetate). Found, %: C 75.4; H 5.7; N 7.1. $C_{25}H_{22}N_2O_3$. Calculated, %: C 75.4; H 5.6; N 7.0.

2-Acetylamino-1-methyl-3-phenylindole (XII). Compound (X) (0.5 g; 1.5 mmole) was heated at 220°C in a flask with an air condenser for 3-5 min. The oily liquid formed crystallized on cooling. Yield 0.37 g (93%), mp 217-218°C (from methanol). Found, %: C 77.8; H 6.6; N 10.1. $C_{18}H_{18}N_2O$. Calculated, %: C 77.7; H 6.5; N 10.1.

2-Acetylaminomethyl-1-benzyl-3-phenylindole (XIII) was obtained under the conditions for the synthesis of (XII). Yield 98%, mp 226.5-227.5°C (from methanol). Found, %: C 81.5; H 6.2; N 7.9. $C_{24}H_{22}N_2O$. Calculated, %: C 81.3; H 6.3; N 7.9.

LITERATURE CITED

1. E. C. Kornfeld, J. Org. Chem., 16, 806 (1951).
2. H. R. Snyder and P. L. Cook, J. Amer. Chem. Soc., 78, 969 (1956).
3. S. Swaminathan and S. Sulochana, J. Org. Chem., 23, 90 (1958).
4. V. V. Feofilaktov, Zh. Obshch. Khim., 10, 247 (1957).
5. R. Abramovitch and J. Spenser, J. Chem. Soc., 3767 (1957).
6. M. N. Preobrazhenskaya, N. V. Uvarova, Yu. N. Sheinker, and N. N. Suvorov, Dokl. Akad. Nauk SSSR, 148, 1088 (1963).

*The hydrochloride of (VI) precipitated when the mixture had been allowed to stand overnight.
†The hydrochloride of (VI) was dissolved in methanol.
‡Water of crystallization found by the Karl Fischer method 6.7%, calculated 5.3%.