CYANOACETIC ESTERS, AMINO ACIDS, AND PYRAZOLONES[1]

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ABSTRACT

Ethyl α-substituted cyanoacetates were used to prepare hydrazides, azides, urethanes, and *dl*-α-amino-β-phenylbutyric acid, *dl*-α-amino-δ-*o*-bromophenoxyvaleric acid, and *dl*-α-amino-δ-*o*,*p*-dichlorophenoxyvaleric acid. Ethyl mono- and disubstituted cyanoacetates with hydrazine gave hydrazides which were transformed by treatment with sodium hydroxide into 4-α-phenylethyl-, 4-*m*-ethylphenoxyethyl-, 4-*o*-bromophenoxypropyl-, 4-*o*,*p*-dichlorophenoxypropyl-, 4,4-*m*-ethylphenoxyethyl-, and 4,4-*m*-methylphenoxypropyl-3-amino-5-pyrazolones. The ultraviolet absorption spectra of the pyrazolones were determined in neutral, acid, and alkaline solutions and their structures established.

INTRODUCTION

The Curtius reaction, whereby acid azides break down on heating into isocyanates and nitrogen, was applied in 1915 to the preparation of an amino acid from cyanoacetic ester by Darapsky and Hillers (3), who obtained glycine. Since that time a considerable number of amino acids (2, 4, 5, 7, 11, 12, 13, 15) have been synthesized by the same method from substituted cyanoacetic esters.

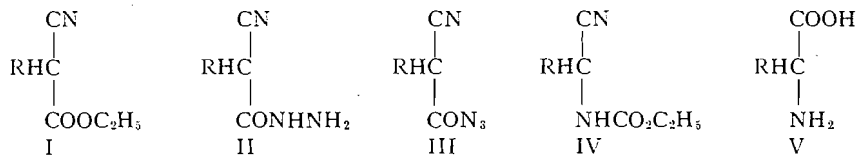
Most of the substituted cyanoacetic esters used for the preparation of amino acids gave hydrazides which were transformed by treatment with sodium hydroxide into 5-pyrazolones which were extensively studied to determine their structures (6, 8, 9, 10, 14, 15).

The object of the present work was to synthesize other amino acids and pyrazolones by the same methods and study their properties.

Substituted phenoxyalkyl bromides were prepared by a method which seems of general application (1, 16).

$$m\text{-}CH_3C_6H_4ONa + Br(CH_2)_3Br \rightarrow \gamma\text{-}m\text{-}CH_3C_6H_4O(CH_2)_3Br + NaBR.$$

By refluxing the bromides with ethyl cyanoacetate and sodium ethylate, esters (1) were obtained with yields varying from 35 to 55%.



R = aryl group. RH is replaced by R_2 in the formulae I and II for disubstituted compounds.

Hydrazine hydrate mixed with the esters (I) at room temperature gave rise

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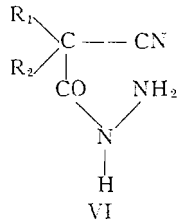
to the hydrazides (II). These were identified by their condensation products with acetone or anisaldehyde.

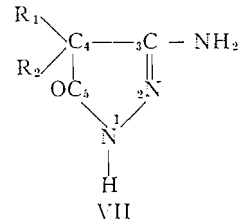
The conversion of the hydrazides into the corresponding azides (III) took place by treatment with nitrous acid, the azides being extracted with ether. On boiling the alcoholic solutions of the azides under reflux, the ethyl urethanes (IV) were formed.

The hydrolysis of the urethanes to the amino acids (V) namely, *dl*-α-amino-β-phenylbutyric acid, *dl*-α-amino-δ-*o*-bromophenoxyvaleric acid, and *dl*-α-amino-δ-*o*,*p*-dichlorophenoxyvaleric acid was effected by refluxing in hydrochloric acid (20%).

To obtain 3-amino-5-pyrazolones (VII), mono- and disubstituted ethyl cyanoacethydrazides (VI) were treated with sodium hydroxide.



VI



VII

R_1 = aryl group; R_2 = H or aryl group.

Four monosubstituted-3-amino-5-pyrazolones (VII, R_1 = α-phenylethyl, *m*-ethylphenoxyethyl, *o*-bromophenoxypropyl, and *o*,*p*-dichlorophenoxypropyl, R_2 = H) and two disubstituted-3-amino-5-pyrazolones (VII, both R_1 and R_2 = *m*-ethylphenoxyethyl or *m*-methylphenoxypropyl) were synthesized and their ultraviolet absorption spectra were determined.

EXPERIMENTAL*

Substituted Phenoxypropyl Bromides

In a 3 liter round-bottomed flask, fitted with a stopper carrying a long reflux condenser, a mechanical stirrer, and a separatory funnel, were placed water (1 liter), trimethylene bromide (2.47 moles), and the substituted phenol (1.95 moles). The stirrer was started and to the boiling solution was added a solution of sodium hydroxide (1.87 moles) in water (250 ml.) at such a rate that complete addition took about one hour. The mixture was refluxed for 10 to 15 hr., then cooled, and the upper water layer separated and discarded. The lower layer was washed with 5% sodium hydroxide to eliminate unreacted phenol and finally the mixture was washed with water. The solution was then distilled under reduced pressure.

The physical properties and yields of the bromides are summarized in Table I.

Substituted Cyanoacetic Esters (I)

Ethyl cyanoacetate (113 gm., 1.0 mole) was added to a clear solution of sodium ethoxide (11.5 gm. of sodium, 250 ml. of absolute ethanol) and the mixture was heated to the boiling point. After the mixture had cooled, the substituted halides (0.5 mole) were slowly added, and the reaction mixtures refluxed until

**All melting points are uncorrected.*

TABLE I
PHENOXYALKYL BROMIDES

Compound	B.p., °C.	Yield	n_D^{22}°C.	Formula	Analysis, %hal.	
					Calc.	Found
γ-*m*-Methylphenoxypropyl bromide	125–126 (6 mm.)	54	1.5389	$C_{10}H_{13}OBr$	34.9	34.7
β-*m*-Ethylphenoxyethyl bromide	143–144 (17 mm.)	50	1.5406	$C_{10}H_{13}OBr$	34.9	34.6
γ-*o*-Bromophenoxypropyl bromide	166–172 (15 mm.)	70	1.5762	$C_9H_{10}OBr_2$	54.4	53.9
γ-*o*,*p*-Dichlorophenoxypropyl bromide	158–159 (6 mm.)	79	1.5676	$C_9H_9OBrCl_2$	53.2	52.7

neutral to wet litmus paper. The alcohol was distilled off under reduced pressure and the residues poured into cold water (500 ml.). The aqueous solutions acidified with hydrochloric acid were extracted three times with ether and the combined extracts dried over anhydrous sodium sulphate. The ether was evaporated and the esters, mono- and disubstituted, were isolated by fractional distillation under reduced pressure.

The properties and yields are listed in Table II.

TABLE II
ETHYL α-SUBSTITUTED CYANOACETATES

Compound	B.p., °C.	Yield, %	n_D^{22}°C.	Formula	Nitrogen, %	
					Calc.	Found
$RCH(CN)COOC_2H_5$ R = *o*-Bromophenoxypropyl	224–232 (12 mm.), m.p. 58° to 59°C.	45		$C_{14}H_{16}O_3NBr$	4.3	4.3
o,*p*-Dichlorophenoxypropyl	197–198 (6 mm.)	38	1.5208	$C_{14}H_{15}O_3NCl_2$	4.4	4.7
$RRC(CN)COOC_2H_5$ R = *m*-Methylphenoxypropyl	184–185 (5 mm.)	57	1.4960	$C_{25}H_{31}O_4N$	3.4	3.2
m-Ethylphenoxyethyl	178–180 (6 mm.)	40	1.4978	$C_{25}H_{31}O_4N$	3.4	3.6

Substituted Cyanoacethydrazides (II)

The monosubstituted cyanoacetic esters (0.1 mole) were stirred vigorously for a few minutes with hydrazine hydrate (100%, 0.1 mole). There was evolution of heat and most of the hydrazides solidified readily. They were recrystallized from ethanol. The properties are summarized in Table III.

Derivatives of Substituted Cyanoacethydrazides

The hydrazides were dissolved in ethanol, and acetone or anisaldehyde was added to the hot solutions. If precipitation did not take place immediately,

TABLE III

α-SUBSTITUTED CYANOACETHYDRAZIDES AND DERIVATIVES

Compound	M.p., °C.	Formula	Nitrogen, %		Derivative with	M.p., °C.	Formula	Nitrogen, %	
			Calc.	Found				Calc.	Found
$RCH(CN)CONHNH_2$									
R = α-Phenylethyl	–	$C_{11}H_{13}ON_3$			Acetone	171–172	$C_{14}H_{17}ON_3$	17.3	16.8
o-Bromophenoxypropyl	99–100	$C_{12}H_{14}O_2N_3Br$	13.5	13.3	Anisaldehyde	153–154	$C_{20}H_{20}O_3N_3Br$	9.7	9.6
o,p-Dichlorophenoxypropyl	110–111	$C_{12}H_{13}O_2N_3Cl_2$	13.9	13.8	Anisaldehyde	183–184	$C_{20}H_{19}O_3N_3Cl_2$	10.0	9.9
$RRC(CN)CONHNH_2$									
R = *m*-Methylphenoxypropyl	95–96	$C_{23}H_{29}O_3N_3$	10.6	10.3	Anisaldehyde	149–150	$C_{31}H_{35}O_4N_3$	8.1	8.1
m-Ethylphenoxyethyl	140–141	$C_{23}H_{29}O_3N_3$	10.6	10.4	Anisaldehyde	183–184	$C_{31}H_{35}O_4N_3$	8.1	8.3

one drop of concentrated hydrochloric acid was added and the solutions were left standing until precipitation occurred. The products were purified by recrystallization from ethanol.

The properties are listed in Table III.

Amino Acids (V)

The hydrazides (0.05 mole) were dissolved in aqueous hydrochloric acid (15%, 100 ml.), cooled to 0°C., and covered with a layer of ether (75 ml.). Sodium nitrite (10 gm.) dissolved in water (30 ml.) was added dropwise to the mechanically stirred mixtures. The azides, on formation, passed into the ether layer. On completion of the reaction, the ether was decanted and the aqueous layers rapidly extracted with two fresh portions of ether. The extracts were combined, dried over anhydrous sodium sulphate, and filtered into absolute ethanol (75 ml.). The ether was evaporated and the azides (III) refluxed on a water bath for one hour to complete the transformation to the urethanes (IV). The alcohol was removed by distillation at reduced pressure. The urethanes were hydrolyzed to the amino acids by refluxing in aqueous hydrochloric acid (20%, 200 ml.) for 48 hr. at 140°C. The mixtures were evaporated to dryness, the residues dissolved in water, boiled with charcoal, and filtered several times. The filtrates were neutralized, concentrated to a small volume, and cooled. On the addition of acetone (2.5 liters) the amino acids precipitated. They were purified by reprecipitation in the same manner and dried in the oven at 100°C.

The following amino acids were prepared:

dl-α-amino-β-phenylbutyric acid which was identified by its hydantoin: m.p. 125–126°C. Calc. for $C_{11}H_{12}O_2N_2$: N, 13.7%. Found: N, 13.4%.

dl-α-amino-δ-*o*-bromophenoxyvaleric acid also identified by its hydantoin: m.p. 160–161°C. Calc. for $C_{12}H_{13}O_3N_2Br$: N, 8.5%. Found: 8.6%.

dl-α-amino-δ-*o*,*p*-dichlorophenoxyvaleric acid directly analyzed. Calc. for $C_{11}H_{13}O_3NCl_2$: N, 5.0%. Found: N, 4.9%.

4-Substituted-3-amino-5-pyrazolones (VII)

The hydrazides (0.1 mole) of the ethyl substituted cyanoacetates were treated with two equivalents of sodium hydroxide (40%) and stirred for a few minutes. The mixtures were allowed to stand for three hours and diluted with water (250 ml.). The solutions were then acidified with acetic acid (50%) and allowed to cool slowly. The crystalline compounds formed were separated by filtration, washed with water, and recrystallized several times from ethanol.

Pyrazolones of both types were soluble in water, acids, and alkalies, and insoluble in ether and sodium bicarbonate solution. The 4-monosubstituted compounds, however, were more soluble in water than the 4,4-disubstituted ones. The individual properties are given in Table IV.

ULTRAVIOLET ABSORPTION SPECTRA

The ultraviolet absorption spectra were taken on a Beckman spectrophotometer Model DU in the same way as previously described (9). Results are listed in Table IV and some of the data are plotted in Figs. 1–3.

TABLE IV
4-SUBSTITUTED-3-AMINO-5-PYRAZOLONES

Compound	Formula	M.p., °C.	Analysis, %		Ultraviolet absorption maxima					
			Nitrogen		Neutral		Acid		Alkaline	
			Calc.	Found	log E_m	Å	log E_m	Å	log E_m	Å
4-(α-Phenylethyl)-	$C_{11}H_{13}ON_3$	80–81	20.7	20.5	3.46 3.66	2840 2480	2.80 3.96	2820 2380		
4-(*m*-Ethylphenoxyethyl)-	$C_{13}H_{17}O_2N_3$	135–136	17.0	16.7	3.42 3.45 3.93	2780 2720 2440	3.13 3.15 4.12	2780 2720 2260	3.21 3.26	2800 2720
4-(*o*-Bromophenoxypropyl)-	$C_{12}H_{14}O_2BrN_3$	152–153	13.5	13.2	3.62 3.62 3.96	2820 2760 2460	2.73 3.46 3.50 4.11	3000 2820 2760 2270	3.43 3.46	2840 2760
4-(*o,p*-Dichlorophenoxypropyl)-	$C_{12}H_{13}O_2Cl_2N_3$	183–184	13.9	13.6	3.44 4.18	2880 2300	3.48 4.54	2860 2300	3.32 3.38	2940 2860
4,4-(*m*-Ethylphenoxyethyl)-	$C_{23}H_{29}O_3N_3$	215–217	10.6	10.4	3.89 3.87	2790 2710	3.94 3.95	2780 2720		
4,4-(*m*-Methylphenoxypropyl)-	$C_{23}H_{29}O_3N_3$	215–216	10.6	10.5	3.96 3.94	2800 2740	3.91 3.92	2800 2740		

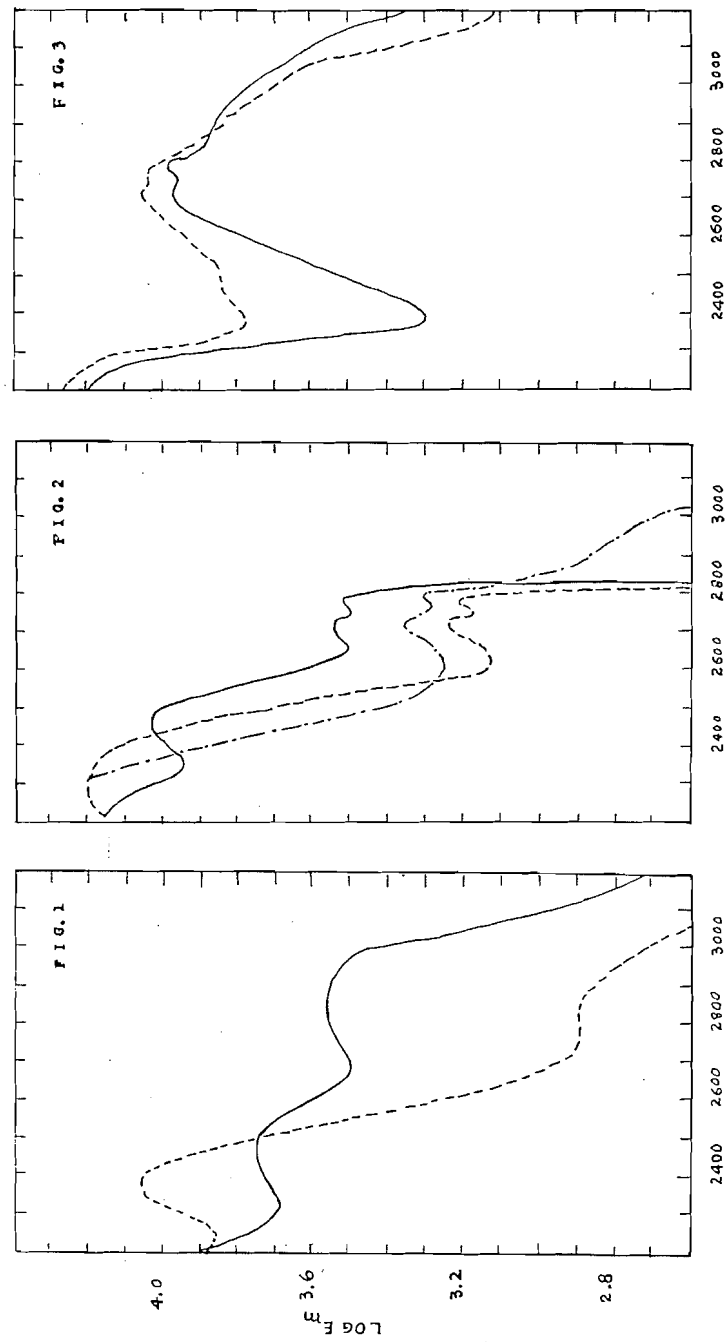
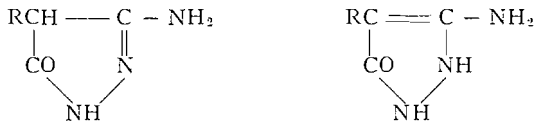


FIG. 1. Ultraviolet absorption spectrum of 4-α-phenylethyl-3-amino-5-pyrazolone: —— in neutral solution; ----- in acid solution.
FIG. 2. Ultraviolet absorption spectrum of 4-*m*-ethylphenoxyethyl-3-amino-5-pyrazolone: —— in neutral solution; ----- in acid solution; ..... in alkaline solution.
FIG. 3. Ultraviolet absorption spectrum of 4,4-di-*m*-ethylphenoxyethyl-3-amino-5-pyrazolone: —— in neutral solution; ----- in acid solution.

4-Monosubstituted-3-amino-5-pyrazolones

The spectrum of 4-α-phenylethyl-3-amino-5-pyrazolone (Fig. 1) shows a case of tautomerism as was encountered with 4-benzyl-3-amino-5-pyrazolone (9). Tautomerism occurs between the two following structures VIII and IX.



VIII IX

It has been demonstrated that pyrazolones of structure IX like 4-alkyl-3-amino-2-phenyl-5-pyrazolones (9) have their maximum absorption in the range from 2350 to 2450 Å, whereas pyrazolones of structure VIII like 4-alkyl-3-amino-5-pyrazolones absorb in the range from 2750 to 2850 Å (9).

In the case of 4-α-phenylethyl-3-amino-5-pyrazolone (Fig. 1), there are two absorption bands in neutral solution indicating tautomers. In acid solution, one maximum disappears leaving an inflection point at 2800 Å. There is evidence that acids catalyze the transformation of one tautomeric form (VIII) into the other (IX). This was observed with 4-benzyl-3-amino-5-pyrazolone (9).

The other 4-monosubstituted-3-amino-5-pyrazolones (Fig. 2) all have a phenoxyalkyl group in position 4, which might contribute to the absorption in addition to the pyrazolone ring. The spectra, in neutral solution, of 4-*m*-ethylphenoxyethyl-3-amino-5-pyrazolone (Fig. 2), 4-*o*-bromophenoxypropyl-3-amino-5-pyrazolone, and 4-*o*,*p*-dichlorophenoxypropyl-3-amino-5-pyrazolone are similar in shape, the pyrazolone ring is responsible for the absorption at shorter wave length, whereas the 4-substituents of the pyrazolone absorb in the range from 2750 to 2950 Å.

These spectra exclude the possibility of tautomers because in acid solution the spectra resemble very closely those in neutral media. It is believed that these compounds all have the same configuration (IX). Except at short wave lengths, the spectra in alkaline solution are all similar to those in neutral solution.

4,4-Disubstituted-3-amino-5-pyrazolones

The 4,4-disubstituted derivatives (Fig. 3) show also great similarity, a wide absorption band is observed in the range from 2600 to 3000 Å, having a maximum at about 2800 Å, which is similar to the spectrum of 4,4-dibenzyl-3-amino-5-pyrazolone (9).

The fine structure observed in the neighborhood of 2800 Å is due to the phenoxyalkyl substituent. The higher intensity of absorption observed with these disubstituted pyrazolones in comparison with the mono derivatives is due to the additive absorption of the pyrazolone chromophore and the phenoxy substituents.

These compounds have the ring structure shown above (VII).

REFERENCES

1. CLARKE, H. I. and MALM, C. J. Org. Syntheses, 9: 72. 1929.
2. DARAPSKY, A. J. prakt. Chem. 146: 250. 1936.

3. DARAPSKY, A. and HILLERS, B. J. prakt. Chem. 92: 297. 1915.
4. GAGNON, P. E. and BOIVIN, J. L. Can. J. Research, B, 26: 503. 1948.
5. GAGNON, P. E., BOIVIN, J. L., and BOIVIN, P. A. Can. J. Research, B, 28: 207. 1950.
6. GAGNON, P. E., BOIVIN, J. L., BOIVIN, P. A., and JONES, R. N. Can. J. Chem. 29: 182. 1951.
7. GAGNON, P. E., BOIVIN, J. L., and GIGUÈRE, J. Can. J. Research, B, 28: 352. 1950.
8. GAGNON, P. E., BOIVIN, J. L., and GIGUÈRE, J. Can. J. Chem. 29: 328. 1951.
9. GAGNON, P. E., BOIVIN, J. L., and JONES, R. N. Can. J. Research, B, 27: 190. 1949.
10. GAGNON, P. E., BOIVIN, J. L., and JONES, R. N. Can. J. Research, B, 28: 34. 1950.
11. GAGNON, P. E., BOIVIN, P. A., and CRAIG, H. M. Can. J. Chem. 29: 70. 1951.
12. GAGNON, P. E., GAUDRY, R., and KING, F. E. J. Chem. Soc. 13. 1944.
13. GAGNON, P. E. and NOLIN, B. Can. J. Research, B, 27: 742. 1949.
14. GAGNON, P. E., NOLIN, B., and JONES, R. N. Can. J. Chem. 29: 843. 1951.
15. GAGNON, P. E., SAVARD, K., GAUDRY, R., and RICHARDSON, E. M. Can. J. Research, B, 25: 28. 1947.
16. MARVEL, S. A. and TANENBAUM, A. L. J. Am. Chem. Soc. 44: 2645. 1922.