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Methyl and ethyl 2-quinolylacetate were prepared from quinoline 1-oxide *via* acetoacetic ester derivatives. Methyl 2-quinolyl, 1-isoquinolyl, 6-methoxy-3-pyridazinyl, 4-pyridyl and 2-methyl-4-pyridylacetate were synthesized from the corresponding heterocyclic *N*-oxides *via* β-aminocrotonic ester derivatives.

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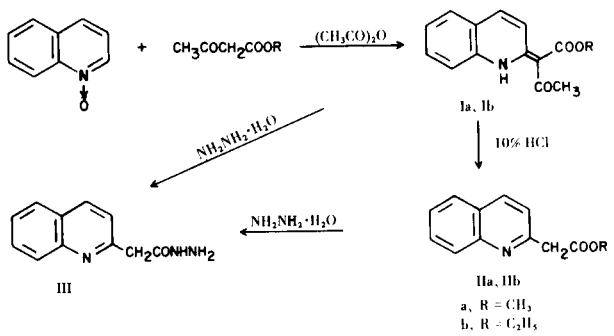
We have recently reported that 2-pyridylacethydrazide was smoothly converted into 2,3-dihydroimidazo[1,5-*a*]-pyridin-3-one, 3-(2-pyridyl)-1,2,4-oxadiazolin-5-one and 2-cyanopyridine *via* azide derivatives (1). In order to extend the scope of these reactions, it was necessary to prepare various kinds of *N*-heteroarylacetic esters as the precursors of hydrazides.

Usually, ethyl 2-pyridylacetate and its analogues are prepared by the carboxylation of picolyllithiums, followed by the esterification (2,3). They are also prepared by the reaction between picolyllithiums and diethyl carbonate (4,5) or ethyl chloroformate (6,7). The latter synthetic method can be applied to the synthesis of ethyl 2-quinolylacetate (8) and ethyl 1-isoquinolylacetate (9) and can be regarded as a general method for the preparation of π-deficient *N*-heteroarylacetic esters. However, the yields of acetates in these reactions are poor and the procedures are somewhat troublesome. In addition, the starting methyl derivatives are usually not readily available, except for some pyridine and quinoline derivatives. These disadvantages have led us to seek for the convenient preparation of such acetic ester derivatives using heterocyclic *N*-oxides as the readily available starting materials.

Hamana and Yamazaki reported a fine route to 2-alkylated quinolines by the reaction of quinoline 1-oxide with reactive methylene compounds in the presence of acetic anhydride (10). Later, a few groups extended the scope of this type of reaction by employing a variety of reactive methylene compounds or *N*-oxides (11,12). By using this method, we obtained methyl 1,2-dihydro-2-quinolylideneacetoacetate (Ia) from quinoline 1-oxide and methyl acetoacetate in 69% yield.

In the mild acid hydrolysis of compound Ia, in contrast to the acid hydrolysis of normal acetoacetic esters, the deacetylation reaction favored the hydrolysis of the ester moiety, and methyl 2-quinolylacetate (IIa), the desired compound, was obtained in a good yield (89%). Ethyl 2-quinolylacetate (IIb) was also obtained in a similar manner from quinoline 1-oxide and ethyl acetoacetate without isolating the intermediate Ib, due to the difficulties encountered in its crystallization and purification, in 39% overall yield. Baty, *et al.*, reported that the acetoacetate Ib can lead to the acetate IIb upon refluxing with sodium hydride in dimethoxyethane (11). However, our method is the more convenient one. Thus, the alkaline hydrolysis was not attempted. However, in the reaction between compound Ia and hydrazine hydrate, the deacetylation reaction also took place and 2-quinolylacethydrazide (III) was obtained. This compound was identical with the hydrazide prepared from acetate IIa.

Scheme I



M. Drobnič-Košorok, *et al.*, described that the reaction between isoquinoline 2-oxide and β-ketoesters in the presence of acetic anhydride did not yield the substituted isoquinoline with a β-ketoester group, but rather only isocarbostyril (13). 3-Picoline 1-oxide was also transformed into its pyridone derivative under similar conditions. Consequently, we needed to employ an alternative method for the introduction of acetoacetic ester or the synthetically equivalent compound to acetoacetate on the isoquinoline and pyridine nucleus.

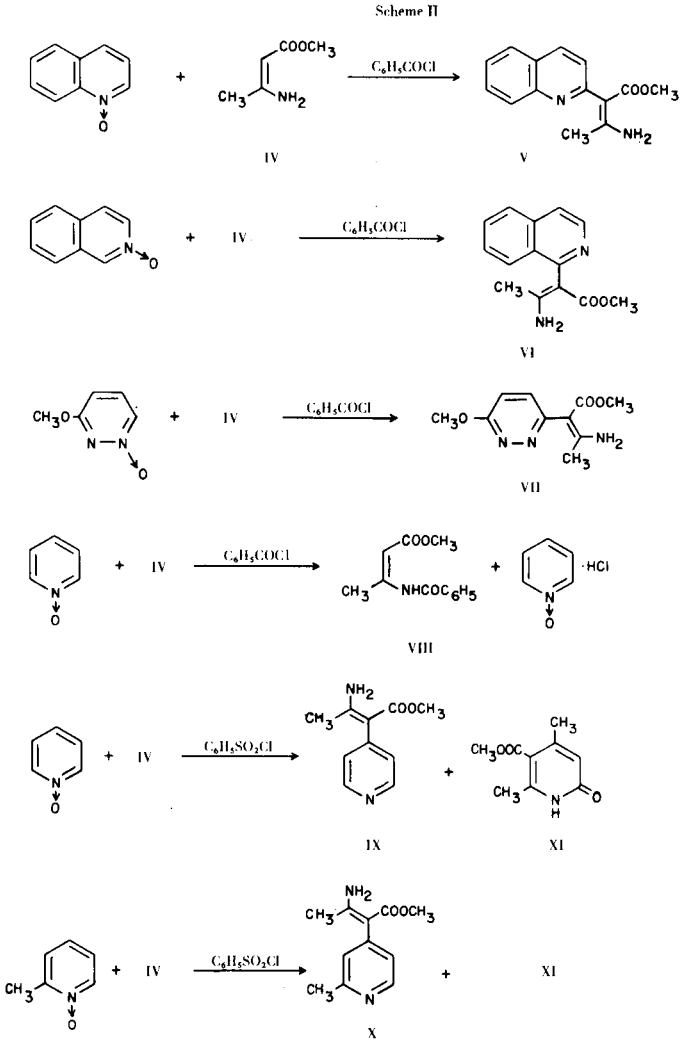
Hamana and Noda reported that quinoline 1-oxide, isoquinoline 2-oxide and pyridine 1-oxide react with the morpholine enamine of cyclohexanone in the presence of benzoyl chloride giving 2-(2-quinolyl), 2-(1-isoquinolyl) and 2-(2-pyridyl)cyclohexanone, respectively, in good yields (14). In similar fashion, they introduced various kinds of electron rich carbon compounds, for example, indoles (15) and enol ethers (16), on the heterocyclic nuclei. It is well known that β-aminocrotonic esters act as enamines in many reactions, such as the modified Hantzsh pyridine synthesis (17) and the Nenitzescu indole synthesis (18,19). Consequently, it was thought that these compounds would react with *N*-oxides under Hamana's conditions to give α-heteroaryl-β-aminocrotonic esters. In addition, since such β-aminocrotonic esters are tautomeric

with the imine of acetoacetic esters, the mild acid hydrolysis should convert these crotonic esters to the acetoacetic esters and further to the acetic esters. On the basis of these expectations, the following reactions were carried out.

Under ice-cooling, benzoyl chloride (1.1 equivalent) was added dropwise to a mixed solution of quinoline 1-oxide and methyl β-aminocrotonate (IV) (1.1 equivalent) in chloroform. After stirring at room temperature for 21 hours, the reaction mixture was treated with alkali giving methyl α-(2-quinolyl)-β-aminocrotonate (V), the expected product, in 76% yield. In a similar manner, methyl α-(1-isoquinolyl)-β-aminocrotonate (VI) and methyl α-(6-methoxy-3-pyridazinyl)-β-aminocrotonate (VII) were obtained in 58% and 48% yield, respectively, from the corresponding *N*-oxides.

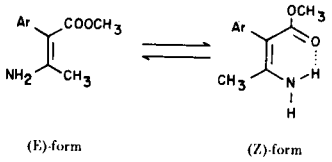
An attempted reaction between pyridine 1-oxide and compound IV under analogous conditions did not afford the desired compound but only gave methyl β-benzoylaminocrotonate (VIII) and the hydrochloride of pyridine 1-oxide as products. On the other hand, when benzenesulfonyl chloride was used as an acylating agent, pyridine 1-oxide reacted with compound IV and gave methyl α-(4-pyridyl)-β-aminocrotonate (IX) in 38% yield. Contrary to the result of an analogous reaction (14), the substitution did not occur at the 2-position on the pyridine nucleus. The confirmation of the 4-substituted product was obtained by nmr analysis. Namely, the ring protons appeared at 7.12 (H_3 and H_5) and 8.52 (H_2 and H_6) ppm in the AA'BB' pattern, which is characteristic for the spectra of 4-substituted pyridine derivatives. The reaction between 2-picoline 1-oxide and compound IV under similar condition also afforded the 4-substituted compound X in 37% yield. In these two reactions, a small amount of the pyridone derivative XI was isolated as a by-product. The formation of this compound can be rationalized by the self-condensation of IV (20).

Scheme II



The nmr spectrum of compound V, measured in deuteriochloroform, indicated the presence of an equilibrium between the (Z)- and (E)-forms. It is known that the olefinic C-methyl protons of β-aminocrotonic esters appear at about the same position in the spectrum of each isomer (δ (Z) = 1.8-1.9; δ (E) = 2.2-2.4) (21). Therefore, the major peak which appeared at 1.83 ppm can be assigned to the absorption of the olefinic methyl protons of the (Z)-form and the minor peak at 2.39 ppm to those of the (E)-form. The relative proportion of the (Z)- to the (E)-form is about 9:1. In the spectrum of compound VII, a slight amount of the (E)-form was also detected. For other crotonic esters, however, the (E)-form could not be detected. The characteristic low ir frequency of the ester carbonyl at about 1660 cm^{-1} also indicates that these crotonic esters exist mainly or completely in the (Z)-form, in which the chelation between the amino group and the ester carbonyl is possible (22).

Scheme III



The uv spectra of crotonic esters IV, V, VI, VII and IX are shown in Figure I. The non-coplanarity of the heterocyclic nucleus with the enaminoester moiety can be seen by comparing the enamino-ester band (around 280 nm) of the α-substituted compound with that of the non-substituted compound IV.

As we expected, the hydrolysis of the crotonic ester V with 10% hydrochloric acid under mild conditions (several minutes on a steam bath) gave methyl 2-quinolylacetate (XII) in 66% yield. This compound was completely identical with compound IIa prepared from Ia. In a similar manner, methyl 1-isoquinolylacetate (XIII) was

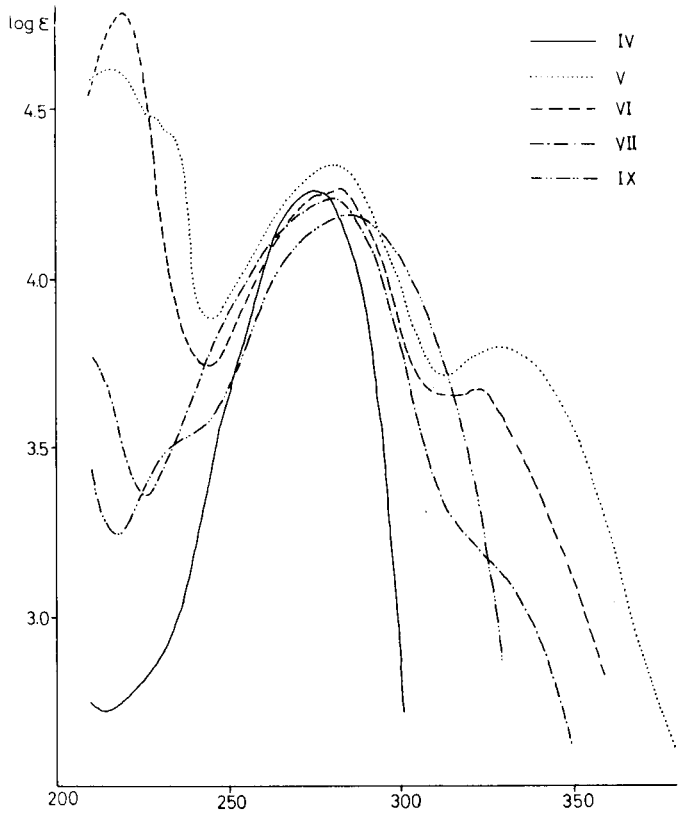


Figure I. Uv Spectra of β-Aminocrotonic Esters.

Table I

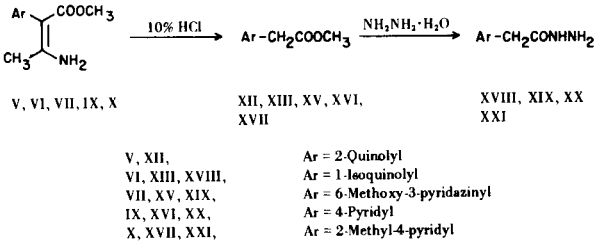
Characteristic Nmr and Ir Spectral Data of β-Aminocrotonic Esters

Compound No.	Nmr (δ ppm) (Deuteriochloroform) C=C-CH_3	Ir (cm^{-1}) (Chloroform) ν NH_2	ν C=O
IV	1.92 (a)	3490 3330	1659
V	1.83 (Z) 2.39 (E)	3490 3300	1659
VI	1.62	3490 3310	1659
VII	1.92 (Z) 2.47 (E)	3480 3290	1660
IX	1.81	3480 3300	1658
X	1.80	3480 3300	1659

(a) "High Resolution Nmr Spectra Catalog", Varian Associates, Palo Alto, 1963, Vol. 2, No. 442.

obtained in 69% yield from compound VI. However, the prolonged heating (one hour on a steam bath) converted VI into 1-methylisoquinoline (XIV). The acetates XV, XVI and XVII were also obtained from the crotonic esters VII, IX and X, respectively, by the analogous mild acid hydrolysis reaction in moderate yields. The hydrazides XVIII, XIX, XX and XXI were prepared from each of the corresponding acetates in good yields.

Scheme IV



EXPERIMENTAL

All melting points and boiling points are uncorrected. Nmr spectra were recorded on a Hitachi R-20B spectrometer for solutions in deuteriochloroform using TMS as an internal standard. Ir spectra were recorded for Nujol mulls or neat liquids on a Hitachi EPI-2 spectrometer or determined for solutions in chloroform on a JASCO IRA-2 spectrometer. Uv spectra were recorded for solutions in 95% ethanol with a Hitachi 323 spectrometer.

Methyl 1,2-Dihydro-2-quinolylideneacetoacetate (Ia).

Methyl acetoacetate (30.1 g.) was added portionwise to a solution of quinoline 1-oxide (29.7 g.) in 60 ml. of acetic anhydride, maintaining the temperature between 35° and 45° with occasional ice-cooling. After warming the solution at 35-45° for 9 hours and allowing it to stand overnight, the reaction mixture was poured into cold water. The precipitate was collected by filtration, washed with water and then with methanol giving 34.5 g. (69%) of compound Ia as yellow needles, m.p. 115-118°. This crude product was sufficiently pure for the next reaction. The sample for analysis and spectroscopy was purified by recrystallization from methanol, m.p. 119.5-120.5°; nmr: δ 2.46 (s, 3H, $COCH_3$), 3.84 (s, 3H, $COOCH_3$), 7.1-7.8 (m, 4H, ArH), 7.88 (near s, 2H, ArH), 17.4 (br s, 1H, NH); ir (nujol): 1690 (C=O) and 1632 cm^{-1} (C=O); uv λ max (log ε): 220 (4.68), 263 (sh) (4.10), 287 (4.28) and 397 nm (4.26).

Anal. Calcd. for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76. Found: C, 69.01; H, 5.30; N, 5.73.

Methyl 2-Quinolylacetate (IIa).

Compound Ia (134 g.) was added with stirring to 500 ml. of 10% hydrochloric acid over 10 minutes. After stirring for an additional 10 minutes at room temperature, the reaction mixture was made basic with aqueous sodium carbonate and extracted with chloroform. The combined extracts were washed with water, dried over sodium sulfate and evaporated. The residue was distilled *in vacuo* giving 99 g. (89%) of an orange oily liquid, b.p. 133-137°/1 mm, which solidified on standing in a refrigerator; nmr: δ 3.71 (s, 3H, $COOCH_3$), 4.03 (s, 2H, $-CH_2-$), 7.3-8.3 (m, 6H, ArH); ir (neat): 1740 (C=O) and 1170 cm^{-1} (C-O).

The picrate of IIa was prepared and recrystallized from ethanol, m.p. 155-157° dec.

Anal. Calcd. for $C_{12}H_{11}NO_2 \cdot C_6H_3N_3O_7$: C, 50.24; H, 3.28; N, 13.02. Found: C, 50.44; H, 3.16; N, 12.98.

Ethyl 2-Quinolylacetate (IIb).

Ethyl acetoacetate (100 g.) was added to a solution of quinoline

1-oxide (100 g.) in 150 ml. of acetic anhydride as described for compound Ia. After heating for 5 hours at 35-45°, the reaction mixture was cooled and poured into a solution of ice-cooled 10% hydrochloric acid (400 ml.). After stirring for 10 minutes, the acid solution was washed with chloroform several times, basified with aqueous sodium carbonate and extracted with chloroform. The extracts were washed with water, dried over sodium sulfate and evaporated. The residue was distilled *in vacuo* to give 58 g. (39%) of IIb as an orange oily liquid, b.p. 142-145°/1 mm; nmr: δ 1.24 (t, 3H, CH_2CH_3), 4.03 (s, 2H, $-CH_2-$), 4.19 (q, 2H, CH_2CH_3), 7.3-8.3 (m, 6H, ArH), J_{CH_3,CH_2} = 7 Hz; ir (neat): 1733 (C=O) and 1156 cm^{-1} (C-O).

The picrate of IIb was prepared and recrystallized from ethanol, m.p. 149-151° dec. (lit. (8) gives m.p. 148-150° dec.).

Anal. Calcd. for $C_{13}H_{13}NO_2 \cdot C_6H_3N_3O_7$: C, 51.35; H, 3.63; N, 12.61. Found: C, 51.37; H, 3.54; N, 12.51.

2-Quinolylacethydrazide (III).

(A) A mixture of IIa (45 g.) and 80% hydrazine hydrate (35 ml.) in 200 ml. of ethanol was allowed to stand at room temperature for 4 hours. The precipitated colorless needles were collected by filtration and washed with ethanol to give 35 g. of III, m.p. 183-184°. By concentrating a mixture of the filtrate and washings, an additional 2 g. of compound III was obtained. The total yield was 37 g. (82%). Recrystallization from methanol afforded purified III, m.p. 186.5-187.5° (lit. (23) gives m.p. 183-185°); ir (nujol): 3320 (NH), 3190 (NH) and 1643 cm^{-1} (C=O).

Anal. Calcd. for $C_{11}H_{11}N_3O$: C, 65.67; H, 5.51; N, 20.88. Found: C, 65.82; H, 5.48; N, 20.86.

(B) A mixture of Ia (3.23 g.) and 80% hydrazine hydrate (10 ml.) in 80 ml. of ethanol was allowed to stand at room temperature for 10 hours. The precipitate was collected by filtration giving 1.87 g. of compound III, m.p. 186.5-187.5°. The filtrate was evaporated to dryness under reduced pressure and the residue was washed with water and filtered to give 0.38 g. of additional III, m.p. 186-187°. The total yield was 2.25 g. (86%). The ir spectra of these products were completely identical with those from the sample prepared as described in method A.

Methyl α-(2-Quinolyl)-β-aminocrotonate (V).

Benzoyl chloride (22.9 g., 0.163 mole) was added dropwise to an ice-cooled stirred solution of quinoline 1-oxide (21.5 g., 0.148 mole) and methyl β-aminocrotonate (18.8 g., 0.163 mole) in 120 ml. of chloroform. After stirring for 21 hours at room temperature, the reaction mixture was poured into water and made basic with aqueous sodium carbonate. The chloroform layer was separated and the aqueous layer was extracted with chloroform several times. The combined extracts were washed with aqueous sodium carbonate and then with water. The oily residue from the dried extracts (over sodium sulfate) was dissolved in a mixture of ether and petroleum ether and allowed to stand overnight in a refrigerator. The precipitated material was collected and recrystallized from dichloromethane/ether (charcoal) to give 27.2 g. (76%) of pale orange prisms of V, m.p. 137-138°; nmr: δ 1.83 (s, C=C-CH_3 of (Z)-form), 2.39 (s, C=C-CH_3 of (E)-form), 3.59 (s, $COOCH_3$ of (Z)-form), 3.76 (s, $COOCH_3$ of (E)-form), 7.3-8.3 (m, 6H, ArH), 4.5-9.5 (very broad, NH_2).

Anal. Calcd. for $C_{14}H_{14}N_2O_2$: C, 69.40; H, 5.83; N, 11.56. Found: C, 69.32; H, 5.83; N, 11.50.

Methyl α-(1-Isoquinolyl)-β-aminocrotonate (VI).

Benzoyl chloride (35.0 g., 0.249 mole) was added dropwise to an ice-cooled stirred solution of isoquinoline 2-oxide (32.9 g., 0.227 mole) and methyl β-aminocrotonate (28.7 g., 0.249 mole) in 190 ml. of chloroform. After stirring for 24 hours at room temperature, the yellow precipitate was collected by filtration and washed with chloroform followed by ether. The residue was dissolved in 300 ml. of water, made basic with aqueous sodium carbonate and extracted with chloroform. The residual crystals from the dried extracts (over sodium sulfate) were recrystallized from dichloromethane/ether to give 33.0 g. (58%) of colorless prisms of the hemihydrate of compound VI, m.p. 110-120° (rapid heating). This sample was dehydrated by slow heating and melted at 161.5-162.5°; nmr: δ 1.62 (s, 3H, C=C-CH_3), 3.47 (s, 3H, $COOCH_3$), 7.3-8.2 (m, 5H, ArH), 8.55 (d, 1H, H_3), 5.5-9.0 (very broad, NH_2), $J_{3,4}$ = 6 Hz.

Anal. Calcd. for $C_{14}H_{14}N_2O_2 \cdot \frac{1}{2}H_2O$: C, 66.91; H, 6.02; N, 11.15. Found: C, 66.88; H, 6.04; N, 11.02.

The anhydrous compound was obtained by sublimation at 140-150° *in vacuo* (0.3 mm Hg), m.p. 161.5-162.5°.

Anal. Calcd. for $C_{14}H_{14}N_2O_2$: C, 69.40; H, 5.83; N, 11.56. Found: C, 69.20; H, 5.79; N, 11.33.

Methyl α-(6-Methoxy-3-pyridazinyl)-β-aminocrotonate (VII).

The reaction of 3-methoxypyridazine 1-oxide (13.5 g., 0.107 mole) with methyl β-aminocrotonate (13.6 g., 0.118 mole) and benzoyl chloride (16.6 g., 0.118 mole) in 150 ml. of chloroform was carried out in a similar manner as described for compound VI. Recrystallization of the crude product from benzene gave 11.4 g. (48%) of compound VII as colorless fine needles, m.p. 138-141°; nmr: δ 1.92 (s, C=C-CH_3 of (Z)-form), 2.47 (s, C=C-CH_3 of (E)-form), 3.60 (s, $COOCH_3$ of (Z)-form), 3.62 (s, $COOCH_3$ of (E)-form), 4.12 (s, 3H, OCH_3), 6.92 (d, 1H, H_5), 7.38 (d, 1H, H_4), 5-6.5 and 8-9.5 (very broad, NH_2), $J_{4,5}$ = 8.5 Hz.

Anal. Calcd. for $C_{10}H_{13}N_3O_3$: C, 53.80; H, 5.87; N, 18.83. Found: C, 53.54; H, 5.97; N, 18.85.

Reaction of Pyridine 1-Oxide with Methyl β-Aminocrotonate (IV) and Benzoyl Chloride.

Benzoyl chloride (13.5 g., 0.096 mole) was added dropwise to an ice-cooled solution of pyridine 1-oxide (8.3 g., 0.087 mole) and methyl β-aminocrotonate (11.1 g., 0.096 mole) in 40 ml. of chloroform. After stirring at room temperature for 66 hours, the precipitated material was collected by filtration and recrystallized from ethanol to give 10.9 g. of the hydrochloride of pyridine 1-oxide, m.p. 178-181° (lit. (24) gives m.p. 180-181°).

Anal. Calcd. for $C_5H_5NO \cdot HCl$: C, 45.61; H, 4.60; N, 10.65. Found: C, 45.32; H, 4.54; N, 10.64.

The filtrate was evaporated to dryness. Aqueous sodium carbonate was added to the residue and the residue was then extracted with dichloromethane. The residue from the dried extract was recrystallized from methanol to give 17.3 g. of methyl β-benzoylaminocrotonate (VIII) as colorless needles, m.p. 62-63° (lit. (25) gives m.p. 62-63°); nmr: δ 2.53 (s, 3H, C=C-CH_3), 3.72 (s, 3H, $COOCH_3$), 5.03 (s, 1H, C=C-H), 7.2-7.7 (m, 3H, ArH), 7.9-8.1 (m, 2H, ArH), 12.1 (br s, 1H, NH); ir (nujol): 3200 (NH), 1702 (C=O) and 1672 cm^{-1} (C=O).

Anal. Calcd. for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.54; H, 6.11; N, 6.52.

Methyl α-(4-Pyridyl)-β-aminocrotonate (IX) and 4,6-Dimethyl-5-methoxycarbonyl-1,2-dihydropyrid-2-one (XI).

Benzenesulfonyl chloride (35.3 g., 0.2 mole) was added dropwise to an ice-cooled stirred solution of pyridine 1-oxide (19.0 g., 0.2 mole) and methyl β-aminocrotonate (46.1 g., 0.4 mole) in 120 ml. of chloroform over 30 minutes. After stirring under ice-cooling for an additional 1.5 hours and at room temperature for 20 hours, the reaction mixture was made basic with 10% sodium carbonate. The chloroform layer was separated and the aqueous layer was

extracted with chloroform. The combined extracts were dried over sodium sulfate and evaporated under reduced pressure. Benzene was added to the residue and the deposited crystalline mass was collected by filtration and washed well with benzene and then with ether to give 12.7 g. of crude IX. The filtrate and washings were combined and evaporated to dryness. The residual oily material was passed through a column of silica gel (4 x 28 cm) using chloroform as eluent. The eluent was evaporated and the residue was triturated with ether to give 3.0 g. of colorless crystals of a mixture of IX and XI. This mixture was washed with 5% sodium hydroxide in order to remove XI giving 2.4 g. of IX. Crude IX were combined and recrystallized from benzene to give 14.5 g. (38%) of purified IX, m.p. 184.5-185.5°; nmr: δ 1.81 (s, 3H, C=C-CH_3), 3.58 (s, 3H, $COOCH_3$), 7.12 (dd, 2H, H_3 and H_5), 8.52 (dd, 2H, H_2 and H_6), 5.5-9.2 (very broad, NH_2).

Anal. Calcd. for $C_{10}H_{12}N_2O_2$: C, 62.48; H, 6.29; N, 14.58. Found: C, 62.25; H, 6.29; N, 14.62.

The alkaline washings were acidified with acetic acid and evaporated to dryness. The residue was washed with water and filtered to give 0.5 g. of compound XI as colorless crystals, m.p. 202-203.5° (benzene) (lit. (26) gives m.p. 202°); nmr: δ 2.30 (s, 3H, 4-CH_3), 2.49 (s, 3H, 6-CH_3), 3.86 (s, 3H, $COOCH_3$), 6.28 (s, 1H, H_3), 13.3 (br s, 1H, NH); ir (nujol): 1713 (C=O) and 1650 cm^{-1} (C=O).

Anal. Calcd. for $C_9H_{11}NO_3$: C, 59.66; H, 6.12; N, 7.73. Found: C, 59.59; H, 6.30; N, 7.78.

Methyl α-(2-Methyl-4-pyridyl)-β-aminocrotonate (X) and XI.

The reaction of 2-picoline 1-oxide (15.5 g., 0.142 mole) with methyl β-aminocrotonate (32.7 g., 0.284 mole) and benzenesulfonyl chloride (25.1 g., 0.142 mole) was carried out in a similar manner as described for compound IX. Recrystallization of the crude product from benzene gave 10.9 g. (37%) of compound X, m.p. 188-188.5°; nmr: δ 1.80 (s, 3H, C=C-CH_3), 2.56 (s, 3H, 2-CH_3), 3.59 (s, 3H, $COOCH_3$), 6.94 (near d, 1H, H_5), 6.99 (s, 1H, H_3), 8.43 (dd, 1H, H_6), $J_{5,6}$ = 5 Hz.

Anal. Calcd. for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84; N, 13.58. Found: C, 63.98; H, 6.91; N, 13.32.

From the alkaline washing, 0.4 g. of XI was obtained, m.p. 202-203.5°. The ir spectrum of this compound was identical with that of a specimen obtained as a by-product of IX.

Methyl 2-Quinolylacetate (XII).

A mixture of 3.74 g. of powdered V and 35 ml. of 10% hydrochloric acid was warmed on a steam bath with shaking for 6 minutes. After cooling with water, the solution was made basic with aqueous sodium carbonate and extracted with chloroform. The dried extract (sodium sulfate) was evaporated to dryness *in vacuo* to give 2.05 g. (66%) of compound XII as an orange oily liquid. The ir spectrum was superimposable upon that obtained from compound IIa.

A picrate of XII was prepared and recrystallized from ethanol, m.p. 155-156° dec.

Methyl 1-Isoquinolylacetate (XIII).

A mixture of the hemihydrate of compound VI (12.74 g.) and 130 ml. of 10% hydrochloric acid was warmed on a steam bath with shaking until the yellow color of the solution disappeared (13 minutes). After cooling with water, the solution was made basic with aqueous sodium carbonate and extracted with chloroform. The residue from the dried extract was distilled *in vacuo* to give 7.09 g. (69%) of XIII as a yellow oil, b.p. 126-128°/0.4 mm, which on standing solidified. Recrystallization from a mixture of ether and petroleum ether gave slightly yellow needles, m.p. 47-48°; nmr: δ 3.70 (s, 3H, $COOCH_3$), 4.34 (s, 2H, -CH_2-), 7.4-8.3 (m, 5H, ArH), 8.43 (d, 1H, H_3), $J_{3,4}$ = 6 Hz; ir (neat): 1640 (C=O) and 1177 cm^{-1} (C-O); uv λ max (log ε): 220 (4.79), 265 (sh) (3.64), 273 (3.71), 285 (3.64), 310 (3.50), 323 (3.59), 376 (2.54), 395 (2.67) and 417 nm (2.51).

Anal. Calcd. for $C_{12}H_{11}NO_2$: C, 71.62; H, 5.51; N, 6.96. Found: C, 71.88; H, 5.59; N, 6.97.

The picrate was prepared and recrystallized from methanol. The melting point, 196-198° dec., was determined in an evacuated capillary.

Anal. Calcd. for $C_{12}H_{11}NO_2 \cdot C_6H_3N_3O_7$: C, 50.24; H, 3.28; N, 13.02. Found: C, 50.22; H, 3.19; N, 12.90.

1-Methylisoquinoline (XIV).

A solution of 1.0 g. of the hemihydrate of VI in 10 ml. of hydrochloric acid was warmed on a steam bath for one hour. After cooling, the solution was made basic with 10% sodium carbonate and extracted with chloroform. The dried extract was evaporated *in vacuo* to give 0.4 g. of a yellow oil of compound XIV.

The picrate was prepared and recrystallized from methanol, m.p. 233.5-234.5° (lit. (27) gives m.p. 233-234°).

Anal. Calcd. for $C_{10}H_9N \cdot C_6H_3N_3O_7$: C, 51.62; H, 3.25; N, 15.05. Found: C, 51.83; H, 3.14; N, 15.19.

Methyl 6-Methoxy-3-pyridazinylacetate (XV).

A mixture of 6.2 g. of VII and 40 ml. of 10% hydrochloric acid was warmed on a steam bath for 5 minutes. After cooling with water, the solution was basified with 10% sodium carbonate and extracted with chloroform. The dried extract was evaporated and the residue was distilled *in vacuo* to give 3.4 g. (67%) of XV as yellow oil, b.p. 127-129°/2.5 mm; nmr: δ 3.72 (s, 3H, $COOCH_3$), 3.98 (s, 2H, -CH_2-), 4.11 (s, 3H, OCH_3), 6.97 (d, 1H, H_5), 7.46 (d, 1H, H_4), $J_{4,5}$ = 9 Hz; ir (neat): 1638 (C=O) and 1168 cm^{-1} (C-O).

Anal. Calcd. for $C_8H_{10}N_2O_3$: C, 52.74; H, 5.53; N, 15.38. Found: C, 52.37; H, 5.56; N, 15.30.

The picrate was prepared and recrystallized from methanol, m.p. 107-109°.

Anal. Calcd. for $C_8H_{10}N_2O_3 \cdot C_6H_3N_3O_7$: C, 40.88; H, 3.19; N, 17.03. Found: C, 40.74; H, 3.07; N, 17.28.

Methyl 4-Pyridylacetate (XVI).

This compound was prepared from compound IX in a similar manner as described for compound XV in 48% yield, b.p. 133-134°/21 mm; nmr: δ 3.62 (s, 2H, -CH_2-), 3.70 (s, 3H, $COOCH_3$), 7.23 (dd, 2H, H_3 and H_5), 8.56 (dd, 2H, H_2 and H_6); ir (neat): 1738 (C=O) and 1168 cm^{-1} (C-O).

The picrate was prepared and recrystallized from methanol, m.p. 146.5-147.5° (lit. (28) gives m.p. 146.5-147.5°).

Anal. Calcd. for $C_8H_9NO_2 \cdot C_6H_3N_3O_7$: C, 44.22; H, 3.18; N, 14.73. Found: C, 44.11; H, 3.07; N, 14.89.

Methyl 2-Methyl-4-pyridylacetate (XVII).

This compound was prepared from compound X in a similar manner as described for compound XV in 45% yield, b.p. 138-139°/21 mm; nmr: δ 2.53 (s, 3H, 2-CH_3), 3.59 (s, 2H, -CH_2-), 3.70 (s, 3H, $COOCH_3$), 7.06 (d, 1H, H_5), 7.10 (s, 1H, H_3), 8.45 (d, 1H, H_6), $J_{5,6}$ = 5 Hz; ir (neat): 1740 (C=O) and 1164 cm^{-1}

The picrate was prepared and recrystallized from methanol, m.p. 115-117°.

Anal. Calcd. for $C_9H_{11}NO_2 \cdot C_6H_3N_3O_7$: C, 45.69; H, 3.58; N, 14.27. Found: C, 45.71; H, 3.55; N, 14.37.

The following hydrazide derivatives were prepared in the usual manner.

1-Isoquinolylacethydrazide (XVIII).

This compound was prepared from acetate XIII and recrystallized from ethanol, yield 93%, m.p. 199-201°; ir (nujol): 3280 (NH), 3140 (NH) and 1649 cm^{-1} (C=O).

Anal. Calcd. for $C_{11}H_{11}N_3O$: C, 65.67; H, 5.51; N, 20.88. Found: C, 65.50; H, 5.39; N, 20.86.

6-Methoxy-3-pyridazinylacethydrazide (XIX).

This compound was prepared from acetate XV and recrystallized from ethanol, yield 94%, m.p. 149-149.5°; ir (nujol): 3280 (NH) and 1641 cm^{-1} (C=O).

Anal. Calcd. for $C_7H_{10}N_4O_2$: C, 46.15; H, 5.52; N, 30.76. Found: C, 46.26; H, 5.56; N, 30.82.

4-Pyridylacethydrazide (XX).

This compound was prepared from acetate XVI and recrystallized from ethanol/ether, yield 91%, m.p. 89-92° (lit. (6) gives m.p. 89.5-91°); ir (nujol): 3260 (NH), 3150 (NH) and 1675 cm^{-1} (C=O).

Anal. Calcd. for $C_7H_9N_3O$: C, 55.61; H, 6.00; N, 27.80. Found: C, 55.32; H, 5.93; N, 27.69.

2-Methyl-4-pyridylacethydrazide (XXI).

This compound was prepared from acetate XVII and recrystallized from ethanol/ether, yield 96%, m.p. 144.5-145.5°; ir (nujol): 3230 (NH), 3150 (NH) and 1658 cm^{-1} (C=O).

Anal. Calcd. for $C_8H_{11}N_3O$: C, 58.16; H, 6.71; N, 25.44. Found: C, 58.20; H, 6.71; N, 25.37.

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