New Heterocyclic Compounds Derived from 1,4-Dihydro-3(2*H*)-cinnolinone. Cyclic Hydrazides. Note I.

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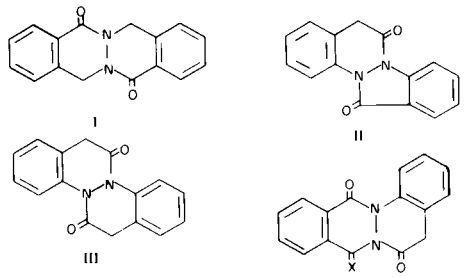
The question concerning the synthesis of the 1,4-dihydro-3(2*H*)cinnolinone was solved and some new tetracyclic derivatives are described. The structure and the synthesis of the two isomers 2-(2-carbomethoxymethylphenyl)phthalazine-1(2*H*),4(3*H*)dione and 1-(2-carbomethoxybenzoyl)-1,2-dihydrocinnolin-3(4H)one are discussed.

The noteworthy antiinflammatory activity displayed by the phthalazino[2,3-*b*]phthalazine5(14*H*),12(7*H*)dione (Diftalone-Aladione ®) (I) (1) synthesized in our laboratories by Bellasio, *et al.*, (2), prompted us to prepare a number of structurally related tetracyclic compounds (II-IV).



I

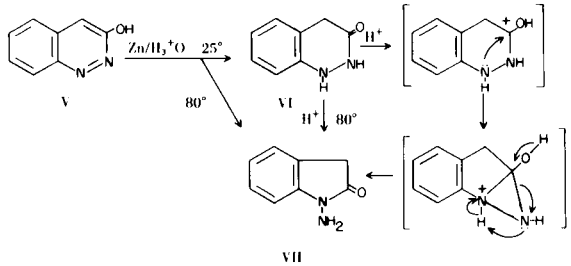
II

III

IV
a. X = H_2
b. X = O

As we looked for a method to prepare the starting tetrahydrocinnolin-3-one (VI), we found that it had been first synthesized by Neber's student Bössel (3) who, having hydrogenated the cinnolinol V with zinc and sulphuric acid, obtained a material melting at 166° to which he ascribed the formula VI.

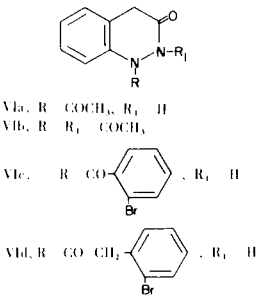
Scheme 1



VII

Later on Neber (4) corrected the melting point indicating the value of 126°. Baumgarten and *et al.* (5,6) repeating the reduction of cinnolinol with zinc and sulphuric acid in boiling ethanol, obtained the same material (m.p. 126-127°) but demonstrated the structure to be that of the *N*-aminolactam VII. Since VII very likely originated from the intermediate VI through a rearrangement which could or could not take place, depending on the reaction conditions, we tried the reduction of cinnolinol (7) in a two phase system and at room temperature. In such a way the tetrahydrocinnolinone (VI), whose mere existence had been questioned, was obtained in 78% yield. The melting point (166-167°) corresponded to that originally reported by Bössel; the absorption in the ir (ν CO; 1640 cm^{-1}) (nujol mull) markedly differed from that of "Neber's lactam" VII (ν CO: 1720 cm^{-1}) and was in agreement with the value expected for an amidic carbonyl in a six membered ring. In the nmr spectrum (DMSO-d_6), the methylene hydrogens of VI were at δ 3.42 and two separate signals at δ 8.04 and 10.05 indicated two different exchangeable protons. The *N*-amino-2-indoline (VII), on the other hand, showed a singlet at δ 3.5 due to the CH_2 and a singlet at δ 5.1 attributed to the hydrogens of the amino group.

In order to establish the conditions under which the rearrangement of cinnoline (VI) occurred, we treated it with base (ammonium or sodium hydroxide) without noticeable results. On the contrary, boiling VI with 1 equivalent of dilute hydrochloric acid for a short period, gave the rearranged compound VII nearly quantitatively. Hydrolysis and recondensation or a rearrangement of the type reported in Scheme 1 can be invoked as possible mechanisms in the formation of compound VII. The cinnolinone (VI) was further characterized as the monoacetate (VIa) and diacetate (VIb). The intermediates VIc and VId were synthesized by conventional methods.

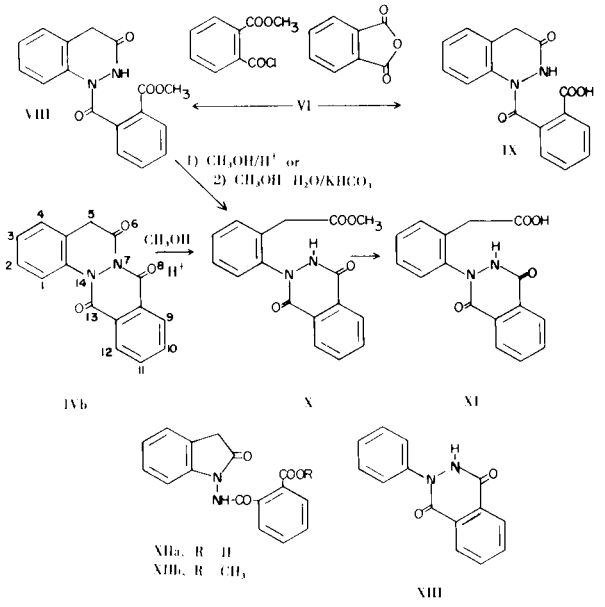


VIa, R $COOCH_3$, R_1 H
VIb, R R_1 $COCH_3$
VIc, R CO, R_1 H
VId, R CO CH_2, R_1 H

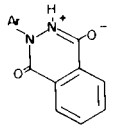
Compound VIc, when heated with copper powder in pyridine, gave the indazolo[2,1-*a*] cinnoline-(7*H*)-6,13--dione (II), although in poor yields. The cinnolino[2,1-*a*]-cinnoline-6(7*H*),13(14*H*)dione (III) was prepared from VId in the same way. Better yields of phthalazino[2,3-*a*]-cinnoline-6(5*H*),13(8*H*)dione (IVa) were obtained when 2-bromomethylbenzoyl chloride was reacted with VI in the presence of triethylamine. In a similar manner phthalazino[2,3-*a*]cinnoline-[5(*H*)],6,8,13trione (IVb) was obtained starting from phthaloyl dichloride. When IVb was heated in methanol in the presence of catalytic amount of sulfuric acid, a higher melting, less soluble compound was isolated in nearly quantitative yield. Microanalytical data as well as ir absorption, ν)CO) 1725 cm^{-1}, were in favour of a methanolysis of IVb with formation of an ester.

Two structures, namely VIII and X, arising from the ring opening between the atoms 7-8 or 6-7, seemed much more likely than the one originating from the opening of the amide linkage between the atoms 13 and 14 (Scheme II). A further structure XIIb could not be rejected *a priori*,

Scheme II



recalling the rearrangement of VI to VII. The structure of the 2-(2-carbomethoxymethylphenyl)phthalazine-2(2*H*),4-(3*H*)dione (X) was assigned to this compound on the basis of the following evidences. In the ir spectrum besides the already mentioned peak at 1725 cm^{-1} (ester carbonyl), a broad band at 3300-2400 cm^{-1} ν (NH^+ assoc.), a small band at 1630 cm^{-1} ν (CO) and a strong broad band at 1550 cm^{-1} ν (C=C) coupled with ν (C–N), indicate that in the solid state, X is present in a zwitterionic intramolecularly associated form (8). Saponification of this ester gave an acid, ν (CO) 1710 cm^{-1}, which again showed a broad band at 3400-2300 cm^{-1}, a small ν (C=O) band at 1650 cm^{-1} and a strong absorption at 1575 cm^{-1}. For direct comparison of the ir spectra, the known 2-phenylphthalazine-1(2*H*),4(3*H*)dione (XIII) (9) was synthesized. Strong association bands appeared also in the ν (NH^+) region of the spectrum of XIII (3300-2200 cm^{-1}), the ν (C=O) absorption was again of weak intensity at 1650 cm^{-1} and a strong peak at 1570-1550 cm^{-1} was observed as in the case of X and XI. A more correct formulation for X, XI and XIII in the solid state should therefore be the following:



As a further support to the attribution of structure X, we prepared the isomeric 1-(2-carbomethoxybenzoyl)-1,2-dihydrocinnolin-3(4*H*)one (VIII) and the corresponding acid IX reacting the tetrahydrocinnolinone (VI) with phthaloyl monochloride monomethylester in dioxane and triethylamine or with phthalic anhydride in pyridine, respectively. The ester (VIII) showed a peak in the ν (N–H) region at 3200 cm^{-1}, a peak at 1720 cm^{-1} assigned to the ester carbonyl and two more bands at 1690 cm^{-1} and 1650 cm^{-1} in the ν (C=O) region. The acid IX shows a sharp peak at 3300 cm^{-1} in the ν (N–H) region, a broad band (3200-2500 cm^{-1}) in the ν (O–H) region, a peak at 1720 cm^{-1} (carboxylic acid) and a band due to the two amidic carbonyls at 1650 cm^{-1}. In order to exclude the structure XIIb, the acid XIIa was prepared from *N*-amino-2-indolinone (VII) and phthalic anhydride and was shown to be different from both IX and XI. The ν (N–H) signal appears as a sharp peak at 3320 cm^{-1} and in the ν (C=O) region three peaks at 1715, 1695 and 1655 cm^{-1} indicate the carbonyl band in a five membered lactam, the carboxylic acid carbonyl and the hydrazidic carbonyl, respectively. It is interesting to mention that the ester VIII readily rearranges to the more stable isomer X on heating in methanol and mineral acid as well as under mild basic conditions.

Analogous rearrangements have been observed in related heterocyclic compounds presently under investigation.

EXPERIMENTAL

Melting points were determined in open capillary tubes and are uncorrected. Nmr spectra were determined on a Varian A/60 spectrometer using TMS as the internal reference (δ 0.0 ppm). Ir spectra were determined in nujol mull.

Tetrahydrocinnolin-3-one (VI).

To a solution of V (7) (50 g., 0.342 mole) in a two phase system of 10% sulfuric acid (1500 ml.) and ethyl acetate (1500 ml.), powdered zinc (75 g.) was added portionwise under vigorous stirring at 25°. After 45 minutes the organic layer was separated and repeated extractions were carried out with ethyl acetate. The solvent was dried and evaporated under reduced pressure to a small volume. Sufficiently pure tetrahydrocinnolin-3-one (39.5 g., 78%) was collected, m.p. 160-167°. An analytical sample was crystallized from water, m.p. 167-168°; ir: 3210 and 3160 (NH), 1640 (CO) cm^{-1}; nmr (DMSO-d_6): δ 3.42 (s, 2H, CH_2), 8.04 (s, 1H, NH-Ar), 10.05 (s, 1H, NH-CO).

Anal. Calcd. for $C_8H_8N_2O$: C, 64.85; H, 5.44; N, 18.91. Found: C, 64.98; H, 5.55; N, 18.86.

1-Amino-2-indolinone (VII) (5).

Tetrahydrocinnolin-3-one (VI) (2 g., 13.5 mmoles) in 10% hydrochloric acid (5 ml.) was heated on a boiling water bath for 15 minutes. After cooling pure 1-amino-2-indolinone (VII) (1.7 g., 85%) m.p. 126-127° was collected; ir: 3280 and 2180 (NH), 1720 (CO) cm^{-1}; nmr (DMSO-d_6): δ 3.5 (s, 2H, CH_2), 5.08 (s, 2H, NH_2).

1-Acetyltetrahydrocinnolin-3-one (VIa).

Tetrahydrocinnolin-3-one (VI) (0.5 g., 3.38 mmoles) in pyridine (2 ml.) was treated at 10° with acetic anhydride (0.316 ml., 3.38 mmoles). After 5 hours at 10° the mixture was poured in ice-cold water containing concentrated hydrochloric acid (2 ml.) and extracted with ethyl acetate. Usual work up gave a gum which was purified on a silica gel column (11 g.) eluting with chloroform-methanol mixtures. The monoacetylcinnolinone (VIa) (0.14 g., 22%) was crystallized from ethyl acetate, m.p. 146-147°; ir: 3150 (NH), 1680 (CO) cm^{-1}; nmr (deuteriochloroform): δ 2.36 (s, 3H, CH_3), 3.56 (s, 2H, CH_2), 9.8 (broad, 1H, NH).

Anal. Calcd. for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 62.96; H, 5.60; N, 14.70.

1,2-Diacetyltetrahydrocinnolin-3-one (VIb).

Tetrahydrocinnolin-3-one (VI) (3 g., 20.2 mmoles) in acetic anhydride (20 ml.) was left overnight at room temperature and then poured in ice-cold water. The solid was collected, dried and crystallized from ethanol, 2.8 g. of VIb (59.6%), m.p. 116-117°; ir: 1725 and 1690 (CO) cm^{-1}; nmr (deuteriochloroform): δ 2,17 (s, 3H, 1-$COCH_3$), 2.52 (s, 3H, 2-$COCH_3$), 3.66 (s, 2H, CH_2).

Anal. Calcd. for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.21; N, 12.06. Found: C, 61.85; H, 5.20; N, 11.93.

1-(2-Bromobenzoyl)tetrahydrocinnolin-3-one (VIc).

Tetrahydrocinnolin-3-one (VI) (5 g., 33.8 mmoles) dissolved in hot dioxane (160 ml.) was cooled to 15° and added first with 2-bromobenzoyl chloride (7.8 g., 35.5 mmoles) dissolved in dioxane (50 ml.) and then, dropwise, with triethylamine (3.42 g., 33.8 mmoles). Stirring was continued for 2 hours at room temperature and the mixture diluted with water and extracted with ethyl acetate. The crude VIc was purified with benzene-ether and crystallized from methanol (7.6 g., 68%), m.p. 207-208°; ir: 3150 (NH), 1675 (CO) cm^{-1}.

1-(4-Bromophenylacetyl)tetrahydrocinnolin-3-one (VId).

Tetrahydrocinnolin-3-one (VI) (5 g., 33.8 mmoles) was treated exactly as above with 2-bromophenylacetyl chloride (8.3 g., 35.5 mmoles) and reacted for 15 minutes at 20°. Work up as for VIc and crystallization from methanol gave VId (8.85 g., 76%), m.p. 192-193°; ir: 3200 and 3120 (NH), 1700 and 1670 (CO) cm^{-1}.

Anal. Calcd. for $C_{16}H_{13}BrN_2O_2$: C, 55.60; H, 3.80; N, 8.11; Br, 23.15. Found: C, 55.46; H, 4.00; N, 7.88; Br, 22.88.

Indazolo[2,1-*a*]cinnoline-(7*H*)-6,13dione (II).

A solution of VIc (10 g., 30 mmoles) in pyridine (150 ml.) was stirred at reflux temperature with copper powder (5.1 g., 80 mmoles) for 3 hours. The reaction mixture was cooled, filtered and poured into ice-water (1 l.) containing concentrated hydrochloric acid (150 ml.). Extraction with chloroform and crystallization from ethanol gave pure II (2.05 g.). Chromatography of the second crops on silica gel (chloroform) gave, after crystallization, a further quantity of pure II (1.3 g.). Total yield: 44.3%, m.p. 208-209°; ir: 1690 (CO) cm^{-1}; nmr (deuteriochloroform). δ 3.94 (s, 2H, CH_2).

Anal. Calcd. for $C_{15}H_{10}N_2O_2$: C, 71.99; H, 4.03; N, 11.20. Found: C, 71.78; H, 4.26; N, 10.90.

Cinnolino[2,1-*a*]cinnoline-6(7*H*),13(14*H*)dione (III).

A mixture of VId (7.1 g., 20.5 mmoles) and copper powder (7.1 g., 111 mmoles) in pyridine (70 ml.) was stirred at reflux for 8 hours. Work up as described above, chromatography and crystallization from methanol gave compound III (1.27 g., 28.3%), m.p. 249-250°; ir: 1680 (CO) cm^{-1}; nmr (DMSO-d_6): δ 3.91 (s, 4H, 2 CH_2). Starting material (1.25 g.) was recovered from the chromatography.

Anal. Calcd. for $C_{16}H_{12}N_2O_2$: C, 72.71; H, 4.58; N, 10.60. Found: C, 72.50; H, 4.63; N, 10.59.

Phthalazino[2,3-*a*]cinnoline-6(5*H*),13(8*H*)dione (IVa).

Compound VI (4.4 g., 29.7 mmoles) was dissolved in hot dioxane (145 ml.) and then cooled to 10°. 2-Bromomethylbenzoyl chloride (7.2 g., 30.9 mmoles) dissolved in dioxane (35 ml.) was added under stirring, followed by dropwise addition of triethylamine (6.3 g., 62 mmoles) while cooling. Stirring was continued at 20° for 30 minutes and for 2 hours at 70°. Dilution with water and extraction with ethyl acetate gave crude IVa (8 g.) which was crystallized from ethanol. Pure IVa was obtained (4.54 g., 57.8%), m.p. 206-207°; ir: 1675 (CO) cm^{-1}; nmr (deuteriochloroform): δ 3.63 (s, 2H, CH_2CO), 5.13 (s, 2H, CH_2-N).

Anal. Calcd. for $C_{16}H_{12}N_2O_2$: C, 72.71; H, 4.58; N, 10.60. Found: C, 72.39; H, 4.45; N, 10.45.

Phthalazino[2,3-*a*]cinnoline-5(*H*)-6,8,13-trione (IVb).

To a stirred solution of VI (14.4 g., 97.2 mmoles) in dioxane (430 ml.) at 20°, phthaloyl dichloride (22 g., 108 mmoles) in dioxane (140 ml.) was added dropwise. At the same rate triethylamine (22 g., 217 mmoles) in dioxane (140 ml.) was added from a second dropping funnel. After 1 hour at 20°, the temperature was raised to 60° and maintained for one hour. The suspension was filtered hot and the filtrate was taken to dryness *in vacuo*. The residue was dissolved in methylene chloride (200 ml.) and ethanol (150 ml.) was added. Evaporation of the methyl-

ene chloride gave pure IVb (18.8 g., 69.5%), m.p. 223-226°; ir: 1775 and 1700 (CO-N-CO), 1680 (CO) cm^{-1}; nmr (deuteriochloroform): δ 3.84 (s, 2H, CH_2).

Anal. Calcd. for $C_{16}H_{10}N_2O_3$: C, 69.05; H, 3.63; N, 10.06. Found: C, 68.97; H, 3.80; N, 9.60.

1-(2-Carbomethoxybenzoyl)tetrahydrocinnolin-3-one (VIII).

To a stirred solution of VI (30 g., 203 mmoles) in dioxane (800 ml.) at 20°, phthaloyl monochloride monoethylester (44 g., 220 mmoles) in dioxane (200 ml.) was added dropwise over a 75 minute period while, at a slightly lower rate, triethylamine (20.4 g., 220 mmoles) in dioxane (150 ml.) was added from a second dropping funnel. After an additional 2 hours at 20°, triethylamine hydrochloride was filtered off and the solvent was removed *in vacuo*. Crystallization from acetone gave VIII (51.7 g., 82%, m.p. 170-179°). An analytical sample melted at 180-182° (methanol); ir: 3200 (NH), 1720 (CO, ester), 1690 and 1650 (CO) cm^{-1}; nmr (DMSO-d_6): δ 3.68 (s, 2H, CH_2), 3.72 (s, 3H CH_3), 9.5-12 (broad, 1H, NH).

Anal. Calcd. for $C_{17}H_{14}N_2O_4$: C, 65.79; H, 4.55; N, 9.03. Found: C, 65.44; H, 4.87; N, 8.80.

1-(2-Carboxybenzoyl)tetrahydrocinnolin-3-one (IX).

A stirred mixture of VI (5 g., 33.8 mmoles) and phthalic anhydride (5 g., 33.8 mmoles) in pyridine (20 ml.) was kept at room temperature with the aid of an ice-bath until solution occurred. After a further 15 hours the reaction mixture was poured into ice-water (150 ml.) containing concentrated hydrochloric acid (20 ml.). Compound IX (9 g., 90%) m.p. 191-194° was obtained. Crystallization from ethanol (95%) gave an analytical sample: m.p. 192-193°; ir: 3300 (NH), 3200-2500 (OH), 1720 (CO, acid), 1650 (CO) cm^{-1}; nmr (DMSO-d_6): δ 3.60 and 3.70 (2 s, 2H, CH_2), 9-12 (broad, 1H, OH).

Anal. Calcd. for $C_{16}H_{12}N_2O_4$: C, 64.80; H, 4.08; N, 9.46. Found: C, 64.94; H, 4.27; N, 9.41.

2-(2-Carbomethoxymethylphenyl)tetrahydrophthalazineyl,4-dione (X).

a) From IVb.

Compound IVb (8 g., 28.8 mmoles) in methanol (300 ml.) was treated with concentrated sulfuric acid (0.5 ml.) and refluxed for 3 hours. The final suspension was neutralized with 4% sodium hydroxide and most of the solvent evaporated *in vacuo*. Dilution with water, filtration of the solid and crystallization from methanol gave X (6.0 g., 67.2%), m.p. 258-260°; ir: 3300-2400 (NH^+, assoc.), 1725 (CO, ester), 1630 (CO), 1550 (C=C) cm^{-1}; nmr (DMSO-d_6): δ 3.40 (s, 3H, CH_3O), 3.68 (s, 2H, CH_2), 10-13 (broad, 1H, NH).

Anal. Calcd. for $C_{17}H_{14}N_2O_4$: C, 65.79; H, 4.55; N, 9.03. Found: C, 65.56; H, 4.76; N, 8.85.

b) From VIII with Acid.

Ester VIII (300 mg.) in methanol (10 ml.) containing traces of sulfuric acid was refluxed for 90 minutes, cooled and neutralized with aqueous sodium hydrogen carbonate solution. The solvent was removed until crystallization occurred. Compound X was collected: m.p. 257-260°. Undepressed mixed melting point with X prepared as described above and identical ir spectrum.

c) From VIII with Base.

Ester VIII (300 mg.) in methanol (10 ml.) was treated with 20% potassium hydrogen carbonate (1 ml.) and refluxed for 7 hours. Concentration to a small volume, dilution with water and acidification with acetic acid gave crystalline X, m.p. 235-247°; ir and nmr spectra identical with those obtained under a) and b).

2-(2-Carboxymethylphenyl)tetrahydrophthalazine-1,4-dione (XI).

To a suspension of X (300 mg., 0.97 mmole) in methanol (10 ml.), a 12% aqueous solution of potassium hydrate (1 ml.) was added and the resulting solution was refluxed for 1 hour. Cooling, evaporation of the methanol, dilution with water and acidification with dilute hydrochloric acid, gave XI (0.26 g., 90%) m.p. 239-246°, which was purified by solution in aqueous sodium hydrogen carbonate and precipitation with hydrochloric acid, m.p. 246-247°; ir: 3400-2300 (NH^+, assoc.), 1710 (CO, acid), 1650 (CO), 1575 (C=C) cm^{-1}; nmr (DMSO-d_6): δ 3.58 (s, 2H, CH_2), 9.2-12.5 (broad, 2H, OH and NH).

Anal. Calcd. for $C_{16}H_{12}N_2O_4$: C, 64.86; H, 4.08; N, 9.45. Found: C, 65.14; H, 4.33; N, 9.28.

1-(2-Carboxybenzoylamino)indolin-2-one (XIIa).

A mixture of VII (500 mg., 3.38 mmoles) and phthalic anhydride (500 mg., 3.38 mmoles) in pyridine (2.5 ml.) was heated on a boiling water bath for 30 minutes and left overnight at room temperature. The mixture was poured into water and the insoluble 1-phthalimidoindolin-2-one (400 mg.) was filtered off. Acidification of the filtrate with hydrochloric acid and crystallization from aqueous 30% ethanol, gave XIIa (220 mg., 22%), m.p. 271-274°; ir: 3300 (NH), 1720 (CO, cyclic), 1695 (CO, acid), 1655 (CO) cm^{-1}; nmr (DMSO-d_6): δ 3.73 (s, 2H, CH_2), 7.0-8.05 (m, 9H, aromatic and NH), 11.05 (s, 1H, OH).

Anal. Calcd. for $C_{16}H_{12}N_2O_4$: C, 64.86; H, 4.08; N, 9.46. Found: C, 64.71; H, 4.18; N, 9.56.

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REFERENCES

(1) E. Bellasio, E. Arrigoni-Martelli, *Il Farmaco, Ed. Sci.*, 27, 627 (1972).

(2) E. Bellasio and E. Testa, *ibid.*, 25, 305 (1970).

(3) G. Bössel, Inaug. Diss. Tübingen, 1925.

(4) P. W. Neber, G. Knöller, K. Herbst and A. Trissler, *Ann. Chem.*, 471, 113 (1929).

(5) H. E. Baumgarten, P. L. Creger and R. L. Zey, *J. Am. Chem. Soc.*, 82, 3977 (1960).

(6) H. E. Baumgarten, W. F. Wittman and G. J. Lehmann, *J. Heterocyclic Chem.*, 6, 333 (1969).

(7) Prepared as described by: E. J. Alford and K. Schofield, *J. Chem. Soc.*, 2102 (1952).

(8) K. Nakanishi, "Infrared Absorption Spectroscopy-Practical," Holden-Day, Inc., San Francisco and Nankodo Company Limited, Tokyo, 1962, p. 207.

(9) F. M. Rowe, J. C. Gillan and A. T. Peters, *J. Chem. Soc.*, 1808 (1935).