Chemical Studies on the Black Rot Disease of Sweet Potatoes. XVII.[*1,*2] Abnormal Semicarbazone of Ipomeanine and of Related Compounds

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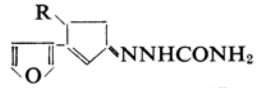
An abnormal semicarbazone, $C_{10}H_{11}O_2N_3$, was formed by the elimination of two molecules of water, when ipomeanine (I), one of the constituents of black-rotted sweet potatoes, was treated with semicarbazide by the usual procedure.[1] Kubota and Ichikawa[1] suggested, on the basis of an analogous finding by Borsche and his collaborators,[2] the formula IIa for the semicarbazone and the formula IIb for the abnormal semicarbazone of the ester III, an intermediate in the course of the synthesis of ipomeanine (I). The latter investigators gave the structure VI, the semicarbazone of 3-phenylcyclopentenone (V), for the abnormal semicarbazone of phenacylacetone (IV).

Recently, several questions have arisen about the structure II. First, the abnormal semicarbazone of ipomeanine is not regenerated to I by mild acid treatment but rather resinifies,[1] while the semicarbazone VI is easily regenerated to V under the same conditions. Secondly, the infrared spectrum of the abnormal semicarbazones is quite different from that of normal ones.[3] Thirdly, the ultraviolet maximum (265 mμ) of the semicarbazone of ipomeanine is not consistent with the structure II, since the maximum of the structure II should be more bathochromically shifted than that (263—264 mμ) of the semicarbazone of β-furylketone.[4] A reinvestigation of the structure of these semicarbazones has led us to the conclusion that the abnormal semicarbazones of ipomeanine and of the ester III possess the structures XIV and XV, respectively.

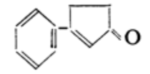
Finzi isolated a monosemicarbazone, m. p. 191°C, in the reaction of phenacylacetone (IV) and semicarbazide.[5],[*3] The monosemicarbazone was easily obtained under mild conditions. It showed an infrared band of a benzoyl carbonyl at $1690\ \mathrm{cm}^{-1}$ and a broad ultraviolet maximum at 231.5 mμ, which is assigned as an overlapping absorption of a benzoyl group and of a semicarbazone of an aliphatic ketone.[6] The structure of the monosemicarbazone must be represented as VII.

When the semicarbazone VII was allowed to stand at pH 4.7 for ten days, two kinds of crystalline products were obtained, A, $C_{12}H_{13}ON_3$, m. p. 218—219°C as the main product and B,[*4] m. p. 208—210°C, as the minor product. The product A was also obtained in a good yield by the treatment of an aqueous alcoholic solution of phenacylacetone (IV) with semicarbazide at room temperature for a long period of time, as has been described by Borsche et al.,[2] or at the refluxing temperature. They described the formation of the semicarbazone VI from phenacylacetone under

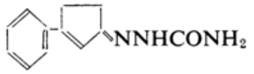


a, R=H
b, R=COOC₂H₅

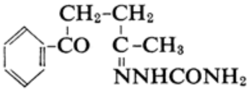
(II)



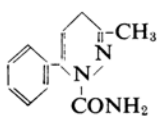
(V)



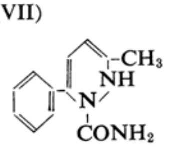
(VI)



(VII)



(VIIIa)



(VIIIb)

[*1] Part XVI, T. Kubota and T. Matsuura, *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zassi*), **79**, 490 (1958).

[*2] This work was presented at the 16th Annual Meeting of the Chemical Society of Japan, April, 1963.

[1] T. Kubota and N. Ichikawa, *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zassi*), **75**, 450 (1954).

[2] W. Borsche, W. Menz and A. Fels, *Ber.*, **41**, 199 (1908).

[3] W. H. T. Davison and P. E. Christie, *J. Chem. Soc.*, **1955**, 3389.

[4] T. Matsuura, K. Naya, N. Ichikawa and T. Kubota, This Bulletin, **35**, 1695 (1962).

[5] C. Finzi, *Gazz. chim. ital.*, **42**, II, 356 (1912); *Chem. Zentr.*, **1912**, II, 2082.

[*3] Finzi reported that the nitrogen analysis of a by-product, m. p. 210°C, was consistent with a monosemicarbazone.

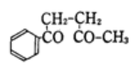
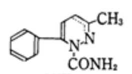
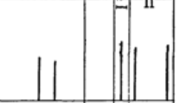
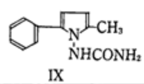
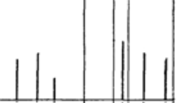
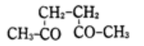
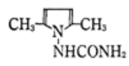
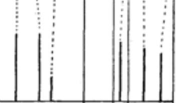
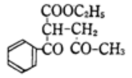
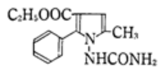
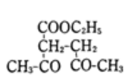
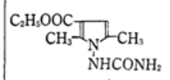
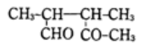
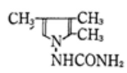
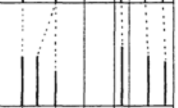
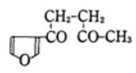
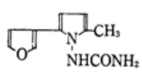
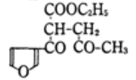
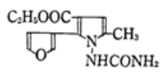
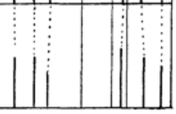
[6] K. Hirayama, in "Jikken Kagaku Koza," Vol. 1, Ed. by the Chemical Society of Japan, Maruzen Co., Tokyo (1957), pp. 63, 166.

[*4] The product B could not be isolated in several other runs.

such conditions. However VI could not be detected in our experiments. The infrared spectrum of the compound A showed no bands assigned to normal semicarbazones,[3] and elemental analyses showed that the compound A is formed by the intramolecular dehydration of the monosemicarbazone (VII) of phenacylacetone. It follows that the dihydropyridazine structure, VIIIa or VIIIb, or the pyrrylurea structure, IX, should be suggested to the compound A.

Several examples of the formation of abnormal semicarbazones, such as XI,[7] XII,[8] and XIII,[9],[*5] from 1,4-dicarbonyl compounds have been reported, as is shown in Table I. However there is no clear evidence for the pyrrylurea structure of these substances, and it still remains questionable whether the pyrrylurea structure or an alternative dihydropyridazine structure is to be chosen. On the other hand, acetonylacetone gives a normal bis-semicarbazone.[10] The treatment of the bis-semicarbazone with formic acid yields *N*-(2,5-dimethylpyrryl)-urea (X), whose structure was established by conversion to urea and 2,5-dimethylpyrrolidine.[10] The infrared spectrum of *N*-(dimethylpyrryl)urea (X) showed characteristic bands, at 3480, 3320, 3200, 1675, 1585 and 1525 cm^{-1}, which differ from the bands[3] of the usual semicarbazones in shape and position. The infrared spectrum (Table I) of the abnormal semicarbazones XI, XII, XIII, XIV (from ipomeanine (I)), and XV (from the ester III) also showed bands at 3450±30, 3300±20, 3225 ±25 (νNH), 1670±10, 1595±10, and 1535±15 cm^{-1} (νC=O and νC=C). These bands are characteristic of the pyrrylurea X. The pyrrylurea structures, XI, XII, XIII, XIV, and XV, may, therefore, be given to these abnormal semicarbazones.

TABLE I. STRUCTURES AND INFRARED BANDS OF ABNORMAL SEMICARBAZONES

1,4-Dicarbonyl compounds	Abnormal semicarbazone	Infrared bands		
		νNH	Amide I	νC=C or Amide II
 IV	 VIII			
IV	 IX			
	 X			
 XXII	 XI			
 XXI	 XII[a]			
	 XIII[b]			
 I	 XIV			
 III	 XV			

a) Bands at 3300 cm^{-1} and 3200 cm^{-1} are overlapped.
b) Cf. Ref. 9.

Of the two abnormal semicarbazones, A and B, obtained from phenacylacetone (IV), the infrared spectrum (Table I) of the minor product (B) showed bands assigned to the pyrrylurea structure, as has been discussed above. Therefore, the product B can be formulated as IX. Since the infrared spectrum of the major product A differs considerably from the spectrum of the pyrrylurea type of compounds, it seems that the product A may possess a dihydropyridazine structure, VIIIa or VIIIb. In spite of the similarity in structure of 1,4-dicarbonyl compounds, phenacylacetone (IV) cyclizes to give mainly the dihydropyridazine derivative under usual conditions, but ipomeanine (I) to the pyrrol derivative.

Furthermore, in the case of ethyl acetonylacetoacetate (XXI), the initial product is a normal bis-semicarbazone, which easily cyclizes to the pyrrol derivatives XII upon recrystallization from hot water. In conclusion, it is difficult to predict at present how the structural factor of the parent 1,4-dicarbonyl compounds will be affected in the formation of a normal semicarbazone or an abnormal semicarbazone, such as VIII and IX.

It is known that, in the reaction of a β-ketoester (XVI) with semicarbazide, a normal semicarbazone (XVII) is initially formed and that it in turn is converted to a 3-pyrazolone, XVIII or XIX, depending on the conditions

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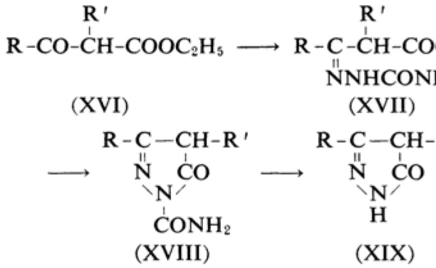
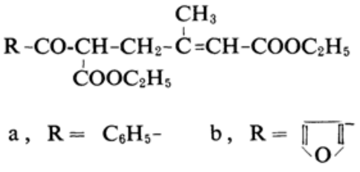
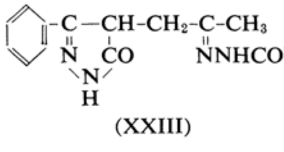
[7] W. Borsche and A. Fels, *Ber.*, **39**, 1922 (1906).
[8] G. Korschun and C. Roll, *Bull. soc. chim. France*, (4), 33, 59 (1923).
[9] W. Keller-Schierlein, M. Lj. Mihailovic and V. Prelog, *Helv. Chim. Acta*, **41**, 221 (1958).
[*5] The formations of such abnormal semicarbazones from ethyl phenacylacetoacetate, ethyl phenacylbenzoylacetate (W. Borsche and M. Spannagel, *Ann.*, **331**, 298 (1904)), and 6-methyl-2,5-heptadione (O. Wallach and F. Meister, *Ann.*, **362**, 261 (1908) and Ref. 20) were reported.
[10] E. E. Blaise, *Compt. rend.*, **172**, 221 (1921); *Chem. Zentr.*, **1921**, I, 674.

employed.[11-15] In previous reports[16,17] of this series, it was reported that the intermediate compounds XX of the syntheses of ipomeamarone and of its phenyl analog yielded abnormal semicarbazones whose structures were unknown. We can now formulate these compounds as XIX (R=β-furyl, R′=H and R=phenyl, R′=H) from the results of the elemental analyses and from the results of a comparison of the infrared spectrum with that of 5-phenyl-3-pyrazolone obtained from ethyl benzoylacetate.


(XVI) (XVII) (XVIII) (XIX)

Ethyl acetonylacetoacetate (XXI), ethyl acetonylbenzoylacetate (XXII), and the ester III, all of which have a β-ketoester group in addition to a 1,4-dicarbonyl function in the molecule, can form pyrazolone derivatives, such as XVIII and XIX, by the action of semicarbazide. In fact, ethyl acetonylbenzoylacetate (XXII) yields a pyrazolone derivative, XXIII, in addition to the abnormal semicarbazone, XI, at an elevated temperature.


(XX)


(XXIII)

Experimental[*6]

The Regeneration of the Semicarbazone (VI) of 3-Phenylcyclopent-2-en-1-one (V). — The semicarbazone VI was prepared according to the procedure of Borsche et al.[2] m. p. 232°C. A mixture of 96 mg. of the semicarbazone and 30 ml. of 5% aqueous sulfuric acid was heated at 100°C for 1.5 hr. with occasional shaking until the mixture became clear. On cooling, 3-phenylcyclopent-2-en-1-one (V) was deposited as needles, m. p. 81—82°C,[*7] whose infrared spectrum was identical with that of an authentic sample. Yield, 74%. $\lambda_{max}^{\mathrm{EtOH}}$ 284 mμ (ε 23300).

The Monosemicarbazone (VII) of Phenacylacetone (IV).—Into an ice-cooled solution of 1.0 g. of phenacylacetone[18] in 10 ml. of ethanol, a solution of 0.7 g. semicarbazide hydrochloride and 0.7 g. of anhydrous potassium acetate in 2 ml. of water was added with stirring. Precipitates were collected by filtration and recrystallized from ethanol to give 1.4 g. (48%) of the semicarbazone VII as needles, m. p. 191°C, lit. m. p. 191°C.[5] $\lambda_{max}^{\mathrm{EtOH}}$ 231.5 mμ (ε 9400).

The Formation of VIII and IX from the Monosemicarbazone (VII) of Phenacylacetone at pH 4.7 — A mixture of 72 mg. of the monosemicarbazone (VII), 72 mg. of anhydrous potassium acetate, 1.6 ml. of acetic acid. 1 m.l of water and 20 ml. of ethanol (PH 4.7) was allowed to stand at room temperature for 10 days. When the mixture was concentrated to about 10 ml. and cooled, 30 mg. (45%) of the crude VIII ("the product A" in the text) was obtained as crystals, m. p. 216—217°C. Recrystallization from ethanol yielded crystals, m. p. 218—219°C. $\lambda_{max}^{\mathrm{EtOH}}$ 285 mμ (ε 16000) and $\lambda_{\mathrm{infl.}}$ 220 mμ (ε 9600).

Found: C, 67.26; H, 6.06; N, 19.14. Calcd. for $C_{12}H_{13}ON_3$: C, 66.95; H, 6.09; N, 19.52%.

The mother liquor from VIII deposited a few milligrams of IX ("the product B" in the text), m. p. 208—210°C, which could be sublimed. $\lambda_{max}^{\mathrm{EtOH}}$ 205.5 mμ (ε 13800) and 285.5 mμ (ε 14000).

The Formation of VIII from Phenacylacetone (IV).—A mixture of 389 mg. of phenacylacetone, 390 mg. of semicarbazide hydrochloride, 390 mg. of potassium acetate, 2 ml. of water and 20 ml. of pyridine was allowed to stand at room temperature for 10 days. After concentrating, the mixture was diluted with 10 ml. of water and 285 mg. (57%) of the crude VIII, m. p. 218—219°C, which was identical with the VIII obtained above (as determined by mixed melting point and infrared spectrum determination).

When a solution of phenacylacetone, an excess of semicarbazide hydrochloride and potassium acetate in aqueous ethanol was refluxed for 5 hr., VIII was obtained in a 78% yield. In both cases, the semicarbazone (VI) of 3-phenylcyclopentenone could not be isolated.

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[11] J. Thiele and O. Stange, *Ann.*, **283**, 30 (1894).

[12] A. Sonn and W. Litten, *Ber.*, **66**, 1512 (1933).

[13] A. Michael, *J. Am. Chem. Soc.*, **41**, 424 (1919).

[14] H. C. House, J. W. Blaker and D. A. Madden, ibid., **80**, 6386 (1958).

[15] W. Borche and M. Spannagel, *Ann.*, **331**, 98 (1904).

[16] T. Matsuura, *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zassi*), **77**, 248 (1956).

[17] T. Matsuura, ibid., **78**, 389 (1957); T. Kubota and T. Matsuura, *J. Chem. Soc.*, **1958**, 735.

[*6] Melting points were uncorrected. The infrared spectra were measured in Nujol mull with a Nippon Bunko recording spectrophotometer, Model IR-S. The ultraviolet spectra were measured with a Hitachi recording spectrophotometer, Model EPS-2. The microanalyses were made by Mr. J. Goda and his associates of this Faculty.

[*7] Lit. m. p. 83—84°C. Recrystallization from ethanol gave crystals, m. p. 63—64°C, whose infrared and ultraviolet spectra were identical with those of the sample, m. p. 83—84°C. Recrystallization from water or aqueous ethanol gave crystals, m. p. 83—84°C.

[18] J. H. Helberger, *Ann.*, **522**, 269 (1963).

The Bis-semicarbazone of Acetonylacetone.—When a solution of 1.90 g. of acetonylacetone[19] in 10 ml. of ethanol was treated with a solution of 3.81 g. of semicarbazide hydrochloride and anhydrous potassium acetate in 3 ml. of water, white precipitates deposited immediately. After standing overnight, the precipitates (2.60 g., 71%) were collected and recrystallized from hot water to give the bis-semicarbazone as crystals, m. p. 225—226°C, lit. m. p. 223—224°C.[20] λ_{max}^{EtOH} 224.5 mμ (ε 21800).

The mother liquor from the bis-semicarbazone deposited crystals (20 mg.) after standing several weeks. Recrystallization from aqueous ethanol yielded crystals, m. p. 215—217°C. λ_{max}^{EtOH} 264 mμ (ε 21800). ν_{max}^{Nujol} 3460, 3200, 1680 and 1568 cm^{-1}.

Found: C, 54.83; H, 7.39. Calcd. for $C_7H_{11}ON_3$: C, 54.88; H, 7.24%.

This compound was considered to be a dimethyldihydropyridazine but it was not further investigated.

1-(2, 5-Dimethylpyrryl)urea (X). — According to the method of Blaise,[10] 100 mg. of the bis-semicarbazone of acetylacetone was mixed with 2 ml. of 50% aqueous formic acid, and then the mixture was heated at 70°C for 3 min. On cooling 27 mg. (40%) of crystals deposited; they were recrystallized from ethanol as crystals, m. p. 235—236°C, lit. m. p. 245°C.[10] λ_{max}^{EtOH} 216 mμ (ε 6710).

Found: C, 55.13; H, 7.39; N, 27.76. Calcd. for $C_7H_{11}ON_3$: C, 54.88; H, 7.24; N, 27.43%.

The Formation of XI and XXIII from Ethyl Acetonylbenzoylacetate (XXII).—a) To a solution of 1.16 g. (4.5 mmol.) of ethyl acetonylbenzoylacetate (XXII)[7] in 10 ml. of ethanol, a solution of 0.56 g. (5 mmol.) of semicarbazide hydrochloride and 0.60 g. of anhydrous potassium acetate in 3 ml. of water was added. After standing for 1 hr., precipitates (0.51 g., 39%) deposited were collected and recrystallized from water to give XI as needles, m. p. 219—221.5°C, lit. m. p. 224—226°C.[7] λ_{max}^{EtOH} 207 mμ (ε 13700) and 285 mμ (ε 4500).

Found: C, 62.78; H, 5.98; N, 14.64. Calcd. for $C_{15}H_{17}O_3N_3$: C, 62.70; H, 5.96; N, 14.63%.

b) A mixture of 1.54 g. of the ester XXII, 2.67 g. (a large excess) of semicarbazide hydrochloride, 2.7 g. of anhydrous potassium acetate, 5 ml. of water and 30 ml. of ethanol was heated under reflux for 5 hr. and then filtered while still hot in order to remove insoluble materials. After standing overnight, the filtrate deposited 0.22 g. (13%) of XI as needles, m. p. 218—220°C, which were identical with the compound obtained above (as ascertained by mixed melting point and infrared spectrum determination).

From the above mother liquor, crystals deposited after spontaneous evaporation. Recrystallization from aqueous ethanol yielded 40 mg. of XXIII as crystals, m. p. 230—231°C (decomp.). λ_{max}^{EtOH} 230 mμ (ε 16400) and $\lambda_{infl.}$ 255 mμ (ε 12300). ν_{max}^{Nujol} 3520, 3380, 3280, 2800—2300, 1680, 1650, 1570 and 1520 cm^{-1}.

Found: C, 56.38; H, 5.73; N, 25.64. Calcd. for $C_{13}H_{15}O_2N_5$: C, 57.13; H, 5.53; N, 25.63%.

The Reaction of Ethyl Acetonylacetoacetate (XXI) with Semicarbazide. — To a solution of 500 mg. of ethyl acetonylacetoacetate[19] in 30 ml. of ethanol, a solution of 275 mg. (an equimolar amount) of semicarbazide hydrochloride and 360 mg. of anhydrous potassium acetate in 5 ml. of water was gradually added. The crystals deposited were collected by filtration, washed with water and dried. The yield of the bis-semicarbazone, m. p. 186—187°C, was 285 mg. (34%). The infrared spectrum and ultraviolet spectrum (λ_{max}^{EtOH} 226 mμ (ε 17200)) showed bands characteristic of a normal semicarbazone.[3,6]

Found: C, 43.77; H, 6.90; N, 27.12. Calcd. for $C_{11}H_{20}O_4N_6$: C, 43.99; H, 6.71; N, 27.99%.

When the mother liquor from the bis-semicarbazone was allowed to stand for 1 week, 165 mg. (13%) of XII deposited as plates, m. p. 222—223°C, the melting point and infrared spectrum of which did not change after recrystallization from ethanol. λ_{max}^{EtOH} 228.5 mμ (ε 6200) and 264 mμ (ε 6300). Lit. m. p. 230°C.[8]

Found: C, 53.60; H, 6.78; N, 18.56. Calcd. for $C_{10}H_{15}O_3N_3$: C, 53.32; H, 6.71; N, 18.66%.

The Formation of XII from the Bis-semicarbazone of Ethyl Acetonylacetoacetate (XXI). — The recrystallization of the bis-semicarbazone from water or ethanol gave needles, m. p. 233—234°C. The infrared and ultraviolet spectra were identical with those of XII, m. p. 222—223°C, obtained above. The mixed melting point was 233—234°C.

Found: N, 18.68. Calcd. for $C_{10}H_{15}O_3N_3$: N, 18.66%.

5-Phenyl-3-pyrazolone (XIX; R=C_6H_5, R′=H). —This compound was prepared according to the method of House et al.,[14] m. p. 239—240°C (decomp.), lit. m. p. 242—243°C (decomp.). λ_{max}^{EtOH} 208 mμ (ε 16000), and 255 mμ (ε 16200), lit. λ_{max} 274 mμ (ε 17000). ν_{max}^{Nujol} 2800—2300, 1630, 1600 and 1550 cm^{-1}.

The Abnormal Semicarbazone (XIX; R=C_6H_5, R′=-CH_2-C(CH_3)=CH-$COOC_2H_5$)[16] of Diethyl 2-Methyl-4-benzoyl-1-butene-1,4-dicarboxylate (XXa). —λ_{max}^{EtOH} 207 mμ (ε 19000) and 248 mμ (ε 10800). ν_{max}^{Nujol} 3400, 2800—2300, 1697, 1650, 1600 and 1550—1525 cm^{-1}.

The Abnormal Semicarbazone (XIX; R=β-furyl, R′=-CH_2-C(CH_3)=$COOC_2H_5$)[17] of Diethyl 2-Methyl-4-(β-furyl)-1-butene-1,4-dicarboxylate (XXb). — ν_{max}^{Nujol} 3400, 2800—2300, 1695, 1645, 1590 and 1550 cm^{-1}. λ_{max}^{EtOH} 207 mμ (ε 19000) and 248 mμ (ε 10800).

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