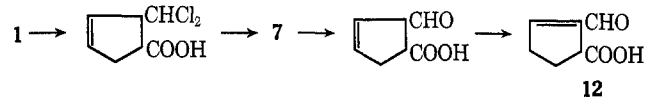
formyl substituent would be expected in the alkaline environment. The extensive formation of polymers is



attributed to condensation reactions of the aldehydic species.

Registry No.—**1**, 5307-99-3; **12**, 30758-76-0; **13**, 3128-16-3; **14**, 30698-29-4; *cis*-**15**, 30758-77-1; *trans*-**15**, 30689-38-4; **17**, 30689-39-5; **18**, 3296-49-9; **19**, 30689-41-9; **20**, 30689-42-0; **21**, 30689-43-1; **22**, 3128-15-2.

Acknowledgment.—The authors are indebted to Professor P. D. Bartlett for many helpful discussions throughout the course of this work.

A New Pyridine Synthesis *via* 4-(3-Oxoalkyl)isoxazoles[1]

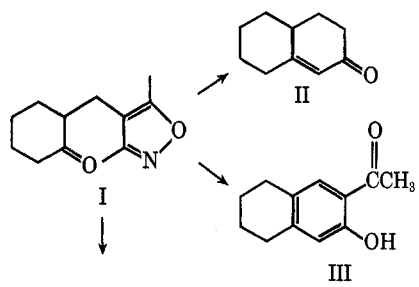
GILBERT STORK,* M. OHASHI,[2] H. KAMACHI, AND H. KAKISAWA

Department of Chemistry, Columbia University, New York, New York 10027, and the Department of Chemistry, Tokyo Kyoiku University, Otsuka, Tokyo, Japan

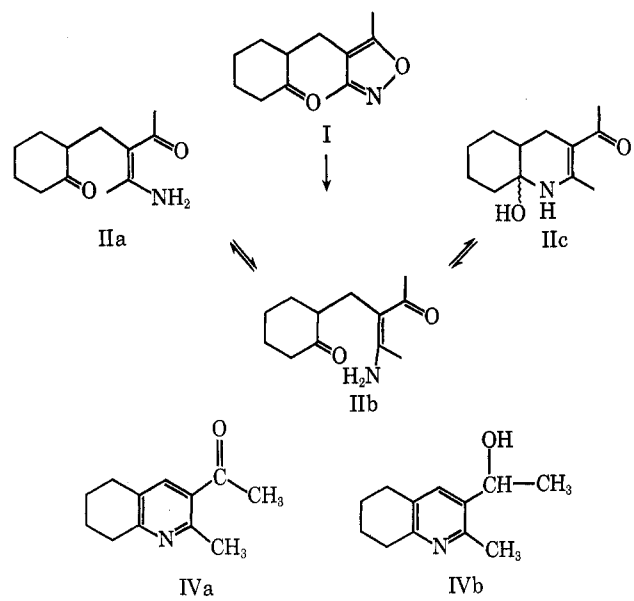
Received March 22, 1971

A general synthesis of β-acylpyridines *via* 4-(3-oxoalkyl)isoxazoles has been devised, based on the fact that these isoxazoles afford cyclic carbinolamines by reductive cleavage of their N–O linkage. Pyridines can be obtained in high yields from these carbinolamines by dehydration and oxidation.

We have developed a new synthetic method for the synthesis of β-acylpyridines *via* the transformation of suitably substituted isoxazoles. Although 3-substituted isoxazoles are stable under a variety of chemical conditions, their nitrogen–oxygen linkage exhibits high lability under special conditions, such as catalytic hydrogenation[3] or electron impact.[4] It is this lability which made possible our use of isoxazoles as masked



keto alkyl functions in synthesis and which is the basis of the new methods of annelation[5] (*e.g.*, I → II) and of benzene ring construction[6] (*e.g.*, I → III) *via* 4-(3-oxoalkyl)isoxazoles. The latter are easily prepared by the alkylation of ketones with the readily available 4-chloromethyl-3-methyl-5alkylisoxazoles.[7] We had noted during our previous investigation of the isoxazole annelation[5] that catalytic hydrogenation of 2-(3,5-dimethyl-4-isoxazolylethyl)cyclohexanone (I) gave an equilibrium mixture (IIa + IIb + IIc) which, upon heating with base, furnished a small amount of pyridines IVa and IVb in addition to the major product, $\Delta^{1,9}$-octalone-2 (II). It became clear that, if dehydration of the cyclic tautomer IIc took place faster than various hydrolytic reactions, the corresponding β-acylpyridine should be formed in high yield by mild oxidation of the dehydration product.



Dehydration under basic conditions would be expected to be particularly easy when a carbonyl group is present in the β position to the hydroxyl group of the carbinolamines. We have examined such cases, VIa and VIb, derived from acetylacetone and ethyl acetoacetate, respectively, and have substantiated this anticipation.

Condensation of acetylacetone and 3,5-dimethyl-4-chloromethylisoxazole (V) in the presence of potassium carbonate gave, in 61% yield, the oily diketone VIa, whose structure was confirmed by the typical isoxazole fragmentation pattern in the mass spectrum[4] and by the formation of bis(3,5-dimethyl-4-isoxazolyl)methane (VII)[4] through its reaction with hydroxylamine. Catalytic hydrogenation of VIa in the presence of palladium/charcoal in triethylamine–ethyl acetate (1:1)

(1) A part of this work was announced in a short communication: M. Ohashi, H. Kamachi, H. Kakisawa, and G. Stork, *J. Amer. Chem. Soc.*, **89**, 5460 (1967).

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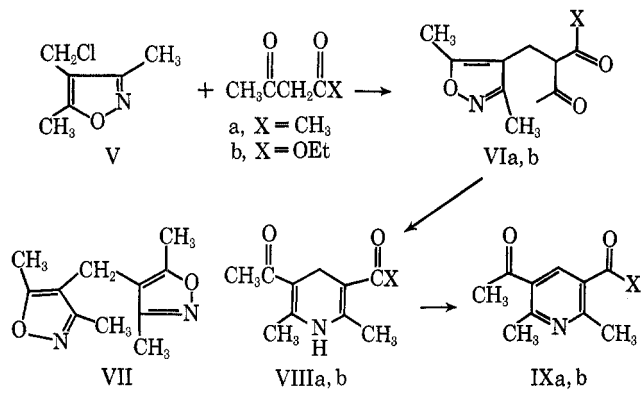
(7) G. Stork and J. E. McMurry, *J. Amer. Chem. Soc.*, **89**, 5461 (1967); N. K. Kochetkov, E. D. Khomutova, and M. V. Brazilesky, *J. Gen. Chem. USSR*, **28**, 2376 (1958).

at atmospheric pressure afforded in 74% yield yellow crystals of the known dihydropyridine VIIIa which can easily be oxidized to the corresponding pyridine IXa.[8]

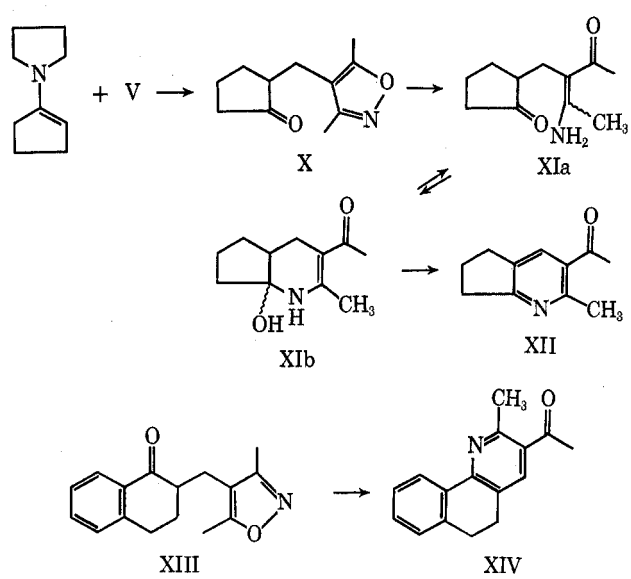
The ethyl acetoacetate analog VIb was prepared in 44% yield by alkylation of ethyl acetoacetate with V in the presence of sodium hydride in benzene–dimethylformamide. When VIb was treated as described above for VIa, it yielded the dihydropyridine VIIIb as yellow crystals, mp 148–150°. The absorption at δ 3.38 (2 H, singlet) and 5.80 (1 H, broad singlet) in the nmr spectrum indicated the presence of an isolated methylene group and a proton attached to nitrogen, respectively. The ultraviolet spectrum was also in accord with a 1,4- rather than a 1,2-dihydropyridine structure. Further confirmation was obtained by the conversion of VIIIb into the known pyridine, ethyl 5-acetyl-2,6-dimethyl-3-pyridinecarboxylate (IXb),[9] in 63% yield based on VIb, by treatment with sodium nitrite and hydrochloric acid.



In the case of a monocarbonylisoxazole such as I, hydrogenation in basic media failed to afford a crystalline dihydropyridine or the cyclized carbinolamine IIc, and, consequently, dehydration of the hydrogenolysis products was carried out under acidic conditions which were used also in the oxidation step. Thus, the catalytic hydrogenation of I, prepared through the enamine alkylation[10] of cyclohexanone with V, was followed by treatment with sodium nitrite and hydrochloric acid to afford IVa, mp 46–47°, in 64% yield, after chromatography on silica gel. Absorption at 245 and 285 mμ in the uv spectrum of IVa, in addition to the presence of two methyl singlets at δ 2.56 and 2.68 and a singlet aromatic proton signal at 7.65 in the nmr spectrum, confirms the identity of IVa as 3-acetyl-2-methyl-5,6,7,8-tetrahydroquinoline.

The application of the new β-acylpyridine synthesis to the cyclopentanone analog X was also accomplished as follows. Enamine alkylation[10] of cyclopentanone with V gave the starting isoxazole (X), semicarbazone mp 211–214°, which, after hydrogenation followed by reflux in aqueous acetate buffer, furnished 3-acetyl-2-methyl-6,7-dihydro-5*H*-cyclopenta[*b*]pyridine (XII), mp 28–30°, picrate mp 132–134°. The structure followed from the spectral properties: the presence of a singlet signal for an aromatic proton at δ 7.80 ppm in the nmr spectrum, the typical absorption due to the pyridine ring at 243 and 288 mμ in the uv spectrum, a conjugated carbonyl peak at 1675 cm^{-1} in the ir spectrum, and, finally, strong peaks at *m/e* 175 (molecular ion, $C_{11}H_{13}NO$), 160 ($M^+ - CH_3$), and 132 ($M^+ - CH_3CO$) in the mass spectrum.

The formation of the pyridine ring without the use of any oxidative reagent makes it obvious that air oxidation of the dihydropyridine must have taken place during the dehydration process. This assumption was confirmed by the following observations; the hydrogenolysis product of X, which was precipitated as a white solid from the solution, must exist to a considerable extent in a ring-opened form XIa because of the presence of a strong absorption peak for a five-membered cyclic ketone at 1735 cm^{-1} in the ir spectrum. When the hydrogenated products were allowed to stand in the air for several days at room temperature, cyclization, dehydration, and air oxidation proceeded spontaneously to convert XIa to the crystalline pyridine XII quantitatively. The yield, based on X was over 50%.



In the case of the tetralone derivative XIII, the yield of pyridine was not so good as in the other cases. The starting isoxazole XIII (prepared by alkylation of 2-ethoxycarbonyl-1-tetralone[11] with V, followed by decarbethoxylation) was treated in the usual manner to afford the pyridine XIV in 21% yield based on XIII. The spectral properties of the crystalline product XIV, mp 111–112°, were all in accord with its expected structure, 2-acetyl-3-methyl-9,10-dihydro-4-azaphenanthrene. The low yield in this particular case is probably a reflection of the low reactivity of the conjugated carbonyl group of the tetralone.[12]

Experimental Section[13]

3-(3,5-Dimethyl-4-isoxazolylmethyl)pentane-2,4-dione (VIa).—Acetylacetone (9.0 g), 4-chloromethyl-3,5-dimethylisoxazole (V) (10.0 g), anhydrous potassium carbonate (9.7 g), and dry acetone

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(9) H. Henecka, *ibid.*, **82**, 41 (1949).
(10) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Amer. Chem. Soc.*, **85**, 207 (1963).
(11) W. E. Bachmann and N. L. Wendler, *ibid.*, **68**, 2580 (1949).
(12) This work was supported, in part, by a grant from the National Institutes of Health.
(13) Melting points were measured on a micro hot stage (uncorrected). Spectra were measured with the following instruments: ir, Hitachi EPI-S; uv, Hitachi ESP-3T; nmr, Hitachi H-6013; mass, Hitachi RMU-60, using an all-glass inlet system heated at 200°, ionizing energy 70 eV. Mass spectra of most of the products obtained in the course of these experiments have been summarized and interpreted in a separate paper.[4]

(30 ml) were heated under reflux for 17 hr. Ether was added to the cooled mixture and the undissolved material was filtered off. Removal of the solvent and distillation of the residue gave VIa (8.8 g, 61%): bp 134–144° (0.2 mm); ir (film) 1725, 1700 cm^{-1}; mass spectrum m/e 209 (M^+, $C_{11}H_{15}NO_3$); λ_{max}^{EtOH} 220 mμ (log ε 3.65), 251 (3.09), 306 (2.67); nmr ($CDCl_3$) δ 2.18 (s, 6), 2.23 (s, 3), ppm (s, 3).

2,6-Dimethyl-3,5-diacetyl-1,4-dihydropyridine (VIIIa).—A mixture of VIa (4.25 g) and palladium/charcoal (10%, 4.25 g) in ethyl acetate–triethylamine (1:1) was stirred in a hydrogen atmosphere at room temperature until hydrogen uptake ceased (*ca.* 21 hr). The catalyst was removed by filtration, and evaporation of the solvent gave yellow needles of VIIIa (74%): mp 209–216° (from EtOH); ir (Nujol) 1675 cm^{-1}; mass spectrum m/e 193 (M^+, $C_{11}H_{15}NO_2$); λ_{max}^{EtOH} 258 mμ (log ε 4.11), 277 (3.88), 408 (3.91); nmr ($CDCl_3$) δ 2.60 (s, 6), 2.75 ppm (s, 6).

Anal. Calcd for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.48; H, 7.76; N, 6.91.

Ethyl 2-(3,5-Dimethyl-4-isoxazolylmethyl)-3-oxobutyrate (VIb).—Sodium hydride (50% suspension, 6.0 g), washed twice with 50 ml of dry benzene to remove the coated oil, was suspended in a mixture of dry benzene (100 ml) and dimethylformamide (20 ml). Ethyl acetoacetate (7.7 g) in 40 ml of benzene was added to the above suspension with vigorous stirring. Into the mixture was added dropwise 4-chloromethyl-3,5-dimethylisoxazole (9.10 g) in benzene (40 ml). The resulting homogeneous solution was stirred under nitrogen for 15 hr, and the solution was neutralized with acetic acid and washed with water. The water layer was back-extracted with benzene and the combined organic layers were dried over magnesium sulfate. Evaporation of the solvent and distillation of the residue gave VIb: 7.50 g (44%); bp 121–135° (0.5 mm); ir (film) 1735, 1715 cm^{-1}; mass spectrum m/e 239 (M^+, $C_{12}H_{17}NO_4$); λ_{max}^{EtOH} 222 mμ (log ε 3.57), (NaOH–EtOH) 222 and 283 mμ; nmr ($CDCl_3$) δ 1.21 (t, 3, J = 7 Hz), 2.14 (s, 6), 2.27 (s, 3), 4.12 ppm (q, 2, J = 7 Hz).

2,6-Dimethyl-3-acetyl-5-carbethoxy-1,4-dihydropyridine (VIIIb).—A mixture of VIb (5.04 g) and palladium/charcoal (10%, 5.0 g) in ethyl acetate–triethylamine (1:1, 200 ml) was stirred under a hydrogen atmosphere, at room temperature, until the hydrogen uptake stopped (about 21 hr). The catalyst was removed by filtration and removal of the solvent *in vacuo* gave VIIIb, 1.50 g, as yellow crystals: mp 148–150° (from ether); mass spectrum m/e 223 (M^+, $C_{12}H_{17}NO_3$); ir (Nujol) 1650, 1700 cm^{-1}; λ_{max}^{EtOH} 244 mμ (log ε 3.90), 265 (3.62), 392 (3.57); nmr ($CDCl_3$) δ 1.30 (t, 3, J = 7 Hz), 2.17 (s, 9), 3.38 (s, 2), 4.22 (q, 2, J = 7 Hz), and 5.80 ppm (b, 1).

2,6-Dimethyl-3-acetyl-5-carbethoxypyridine (IXb).—A mixture of VIb (4.21 g) and palladium/charcoal (4.0 g) in ethyl acetate–triethylamine (1:1, 150 ml) was hydrogenated as described above. The crude product of hydrogenation containing yellow needles (VIIIb) was dissolved in 50 ml of 10% hydrochloric acid. Into this solution was added dropwise a solution of sodium nitrite (1.50 g) in water (7.5 ml) and the resulting yellow solution was stirred about 3 hr. The solution was neutralized with potassium hydroxide and extracted with ether. The organic layer was dried over magnesium sulfate and evaporated to give an oil, which on distillation under reduced pressure gave IXb: 2.46 g (63%); bp 135–145° (6 mm); ir (film) 1720, 1685 cm^{-1}; λ_{max}^{EtOH} 213 mμ (log ε 4.15), 241 (3.82), 277 (3.43), 285 (3.37); nmr ($CDCl_3$) δ 1.45 (t, 3, J = 7 Hz), 2.64 (s, 3), 2.78 (s, 3), 2.85 (s, 3), 4.45 (q, 2, J = 7 Hz), and 8.50 ppm (s, 1).

2-Methyl-3-acetyl-5,6,7,8-tetrahydroquinoline (IVa).—A solution of I (856 mg) in ethyl acetate–triethylamine (1:1, 40 ml) containing palladium/charcoal (10%, 1.0 g) was hydrogenated as described above. The hydrogenation product was dissolved in 10% hydrochloric acid (12 ml). Into this solution, cooled in an ice bath, was added dropwise a solution of sodium nitrite (360 mg) dissolved in water (2 ml). The resulting solution was stirred *ca.* 17 hr. The solution was then neutralized with potassium carbonate and extracted with ether. Removal of the solvent and chromatography of the residue on alumina gave IVa (535 mg, 64%): mp 46–47°; ir (Nujol) 1685 cm^{-1}; λ_{max}^{EtOH} 242 mμ (log ε 3.67), 285 (3.67); nmr ($CDCl_3$) δ 2.56 (s, 3), 2.68 (s, 3), 7.65 ppm (s, 1); semicarbazone mp 198–199° (from ethyl acetate).

Anal. Calcd for $C_{13}H_{18}ON_4$: C, 63.39; H, 7.39; N, 22.75. Found: C, 63.69; H, 7.21; N, 22.54.

3,5-Dimethyl-4-(2-oxocyclopentylmethyl)isoxazole (X).—A solution of the pyrrolidine enamine of cyclopentanone (15.0 g)[10] and 3,5-dimethyl-4-chloromethylisoxazole (10.0 g) in dioxane (60 ml) was heated under reflux in a nitrogen atmosphere for 17 hr. Water (15 ml) was added to the above mixture and refluxing was continued for an additional 1 hr. After being cooled the solution was poured into ice–water (450 ml) and extracted with ether. The organic layer was washed successively with 5% hydrochloric acid and 5% sodium bicarbonate solution and water and then dried over magnesium sulfate. The solvent was removed *in vacuo* and the residue was distilled under reduced pressure to give X: 5.8 g (44%); bp 138–148° (0.7 mm); mass spectrum m/e 193 (M^+, $C_{11}H_{15}NO_2$); ir (film) 1740 cm^{-1}; λ_{max}^{EtOH} 223 mμ (log ε 3.67); nmr ($CDCl_3$) δ 2.24 (s, 3), 2.33 ppm (s, 3); semicarbazone mp 211–214° (from methanol).

Anal. Calcd for $C_{12}H_{18}O_2N_4$: C, 57.58; H, 7.25; N, 22.39. Found: C, 57.77; H, 7.09; N, 22.40.

3-Acetyl-2-methyl-6,7-dihydro-5*H*-cyclopenta[*b*]pyridine (XII).

A.—By the procedure described above, catalytic hydrogenation of X (635 mg) with palladium/charcoal (780 mg) in ethyl acetate–triethylamine (1:1, 40 ml) gave a bluish solid which was dissolved in a mixture of sodium acetate (7.5 g), water (15 ml), and acetic acid (15 ml) and refluxed for 2 hr. After being cooled the solution was extracted with ether. Removal of the solvent and chromatography on alumina gave XII: 245 mg (60%); mp 28–30°; mass spectrum m/e 175 (M^+, $C_{11}H_{13}NO$); ir (film) 1675 cm^{-1}; λ_{max}^{EtOH} 243 mμ (log ε 3.50), 288 (3.59); nmr ($CDCl_3$) δ 2.57 (s, 3), 2.72 (s, 3), 7.80 ppm (s, 1); picrate mp 132–134°.

Anal. Calcd for $C_{17}H_{16}O_8N_4$: C, 50.50; H, 3.99; N, 13.86. Found: C, 50.63; H, 3.89; N, 14.06.

B.—Catalytic hydrogenation of X (3.82 g) as above, with palladium/charcoal (4.6 g) in ethyl acetate–triethylamine (1:1, 150 ml), gave a precipitate (XIa) which was dissolved in methanol and separated from the catalyst by filtration. The solvent was removed under reduced pressure to give a solid [ir (Nujol) 1600, 1735 cm^{-1}; λ_{max}^{EtOH} 314 mμ] which, after being washed with ether and allowed to stand for 5 days, was quantitatively transformed into XII.

2-(3,5-Dimethyl-4-isoxazolylmethyl)tetralone-1 (XIII).—A solution of ethyl 1-keto-1,2,3,4-tetrahydro-2-naphthoate (7.43 g)[11] in 50 ml of ethanol was poured into a solution of sodium ethoxide (from 0.9 g of sodium) in ethanol. Into the resulting suspension was added a solution of 3,5-dimethyl-4-chloromethylisoxazole (V) (7.0 g) in ethanol (30 ml), and the mixture was refluxed with stirring for 12 hr. The solvent was removed *in vacuo*, water was added, and the product was extracted with ether. The solvent was removed and the residue was refluxed for 24 hr with a mixture of acetic acid (75 ml), water (50 ml), and concentrated hydrochloric acid (25 ml). The mixture was evaporated to dryness and the residue was extracted with ether. The ether layer was washed with aqueous potassium carbonate and dried over magnesium sulfate. Removal of the solvent gave a crystalline residue which was recrystallized from ethanol to give XIII: mp 104–105°; 3.90 g (42%); λ_{max}^{EtOH} 245 mμ (log ε 4.15) and 294 (3.35); ir (Nujol) 1680, 1632, 1600 cm^{-1}; nmr ($CDCl_3$) δ 2.21 (s, 3), 2.31 (s, 3), 7.38 (m, 3), 8.00 ppm (m, 1); mass spectrum m/e 255 (M^+, $C_{16}H_{17}O_2N$).

Anal. Calcd for $C_{16}H_{17}O_2N$: C, 75.27; H, 6.71; N, 5.49. Found: C, 75.59; H, 6.81; N, 5.43.

2-Acetyl-3-methyl-9,10-dihydro-4-azaphenanthrene (XIV).—The isoxazolyltetralone XIII (478 mg) was hydrogenated with palladium/charcoal (10%, 250 mg) in ethyl acetate–triethylamine (1:1, 30 ml). The product, after treatment with sodium nitrite (180 mg) and 10% hydrochloric acid (15 ml), was chromatographed on alumina to give XIV: 132 mg (21%); mp 111–112° (from ethanol); λ_{max}^{EtOH} 219 mμ (log ε 4.25), 275 (4.00), 322 (4.34); nmr ($CDCl_3$) δ 2.55 (s, 3), 2.77 (s, 3), 2.91 (s, 4), 7.25 (m, 3), 7.70 (s, 1), 8.45 ppm (m, 1); mass spectrum m/e (M^+, $C_{16}H_{15}NO$).

Anal. Calcd for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90. Found: C, 81.01; H, 6.29; N, 5.71.

Registry No.—IVa, 16858-03-0; IVa semicarbazone, 16858-10-9; VIa, 16858-07-4; VIIIb, 16858-06-3; IXb, 30428-66-1; X, 16858-04-1; X semicarbazone, 16858-11-0; XII, 16858-05-2; XII picrate, 30428-69-4; XIII, 19788-42-2; XIV, 30428-71-8.