227–228 mμ (ε 68,500), 278 (9500), 284 (8800) (sh); $\lambda_{max}^{0.1\ N\ KOH}$ 225 mμ (ε 67,500) (sh), 276 (11,100) (sh), 282–283 (11,800), 296 (9000) (sh); ν_{max}^{KBr} 2550 (broad, *t*-amine salt), 1720 (ester C=O), 1625 and 1615 (COO^-), 1617, 1585 and 1505 (phenyl), and 1280 cm^{-1} (broad, ester, OCH_3, and OH).

Anal. Calcd for $C_{38}H_{46}N_2O_6 \cdot C_{18}H_{14}O_8$ (985.12): C, 68.28; H, 6.14; N, 2.84. Found: C, 68.47; H, 6.08; N, 3.02.

(*R*)-(−)-1-(4-Methoxybenzyl)-1,2,3,4-tetrahydro-7-methoxy-2-methyl-8-isoquinolinol (11).—To a solution of 281.5 mg (0.285 mmol) of **10** in 200 ml of methanol was added 5.15 ml of ethanol containing 38.85 mg (0.572 mmol) of sodium ethoxide. The solvent was removed under reduced pressure and the residue was extracted with ether to give 162 mg of **11** as a yellow oil: $[\alpha]^{24.9}D$ −32.2° (*c* 0.165, $CHCl_3$), $[\alpha]_{365}^{24.9}$ −326° (*c* 0.165, $CHCl_3$); for the ORD curve see Figure 2; CD (*c* 0.0464, ethanol), $[\Theta]_{300}$ 0, $[\Theta]_{278}$ −2829, $[\Theta]_{255}$ −1338, $[\Theta]_{235}$ −19,624, $[\Theta]_{230}$ −9366; $\nu_{max}^{CHCl_3}$ 3545 (OH), 1610, 1588, 1515 and 1495 (phenyl), and 1280 and 1250 cm^{-1} (OCH_3 and OH); $\lambda_{max}^{CH_3OH}$ 226 mμ (ε 21,300), 278 (3900), 284 (3600); nmr ($CDCl_3$), δ 2.31 (3 H, s, N-CH_3), 2.2–3.3 (6 H, cp, methylene protons), 3.72 and 3.81 (3 H each, s, OCH_3-4 and OCH_3-7), 4.00 (1 H, q, J = 4.5 cps, CH-1), 5.82 (1 H, b, OH), 6.55 and 6.68 (2 H, AB pattern, J = 8.5 cps, CH-5 and CH-6), 6.77 and 7.17 (4 H, A_2B_2 pattern, J = 8 cps, CH-2′, CH-3′, CH-5′ and CH-6′); mass spectrum, fragments at *m/e* 313, 312, 192 (base peak), 177.

Petaline Iodide (12a).—To the oily free base **11** (150 mg) in 20 ml of anhydrous ether was added within 20 min a solution of 1 ml of freshly distilled methyl iodide in 3 ml of anhydrous ether. The mixture was left at room temperature overnight, and the amorphous yellow precipitate was collected by filtration and washed thoroughly with ether to give 168 mg of **12a** melting between 107 and 116° after drying at 40° for 3 days under reduced pressure: for the optical rotatory dispersion curve see Figures 2 and 3; $[\alpha]^{23}D$ −4.4° (*c* 0.455, 95% ethanol); CD (*c* 0.455, 95% ethanol), $[\Theta]_{310}$ 0, $[\Theta]_{288}$ −9108, $[\Theta]_{253}$ −528, $[\Theta]_{235}$ −21,120, $[\Theta]_{225}$ −5280, $[\Theta]_{212}$ −84,480, $[\Theta]_{205}$ 0.

Petaline Reineckate (12b).—To 25 ml of an aqueous solution of **12a** (140 mg) was added a saturated aqueous solution of ammonium reineckate until no more material was precipitated. The amorphous pink precipitate was collected by filtration and dried 3 days at 50° under reduced pressure to give 128 mg of **12b**, melting between 135 and 145° dec; a mixture melting point with authentic material[9] showed no depression and the infrared spectra (KBr) were superimposable. Reprecipitation from an aqueous solution with acetone afforded, after drying at room temperature for 80 hr under reduced pressure, **12b** which melted between 126 and 134°: $[\alpha]^{23}D$ −1.5° (*c* 0.647, ethanol); ORD (*c* 0.647, ethanol), $[\alpha]_{320}$ −386°, $[\alpha]_{292}$ −850° (tr), $[\alpha]_{284}$ 0°, $[\alpha]_{270}$ +540° (pk), $[\alpha]_{253}$ 0°, $[\alpha]_{241}$ −540° (tr), $[\alpha]_{235}$ 0°, $[\alpha]_{228}$ +1620° (pk), $[\alpha]_{216}$ −1390° (tr), $[\alpha]_{212}$ −773°; CD (*c* 0.647, ethanol), $[\Theta]_{305}$ 0, $[\Theta]_{288}$ −7920, $[\Theta]_{268}$ 0, $[\Theta]_{235}$ −23,100, $[\Theta]_{223}$ −1320, $[\Theta]_{215}$ −42,900.

By paper chromatography (descending, pyridine–water 1:4, Whatman No. 1 paper), **12b** was identical with authentic material,[9] R_f 0.83. The spots were developed with modified Dragendorff reagent.[14]

Registry No.—**2**, 6068-43-5; **4**, 6077-99-2; **5**, 5890-46-0; **6**, 5890-47-1; **7b**, 16336-16-6; **8a**, 16350-27-9; **8b**, 15612-34-7; **9**, 2609-29-2; **10**, 16346-57-9; **11**, 16336-17-7; **12a**, 6392-37-6; **12b**, 16351-46-5.

Acknowledgment.—The authors thank Miss Nancey Radimer for skillful technical assistance. They also thank Dr. P. Bommer and his staff, especially Dr. V. Toome for the uv, ORD, and CD spectra, Mr. S. Traiman for the ir spectra, Dr. F. Vane for the mass spectral data, Dr. T. Williams for the nmr spectra, and Dr. F. Scheidl and his staff for performing the elemental analyses. We appreciate the help of Dr. Rachlin and his group in preparing larger amounts of starting material.

(14) B. Franck and G. Blaschke, *Ann. Chem.*, **695**, 144 (1966).

Synthetic Quinine Analogs. I. The Synthesis and Some Chemical Transformations of 6′-Methoxy-7-oxo-8-rubene[1]

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Sodium ethoxide-catalyzed condensation of 6-methoxyquinoline-4-carboxaldehyde with 3-quinuclidinone produces 6′-methoxy-7-oxo-8-rubene in high yield. Of the two possible geometrical isomers, only that with the ketone function *trans* to the quinoline ring is formed. Reduction of the ketone affords an allylic alcohol whose *p*-nitrobenzoate is completely isomerized to the opposite geometrical isomer in refluxing acetic acid. The ketone is not ketalized by 1,2-ethanedithiol in refluxing trifluoroacetic acid but instead undergoes a remarkable condensation reaction involving one molecule of ketone, two of 1,2-ethanedithiol, and one of trifluoroacetic acid. A by-product of the reaction results from the condensation of three molecules of 1,2-ethanedithiol with two of trifluoroacetic acid. Pyrazoline derivatives of the ketone resulting from 1,3-dipolar addition of diazomethane and condensation with hydrazine are described.

As a sequel to their brilliant degradative studies which elucidated the structure of quinine,[3] Rabe and his coworkers undertook its synthesis in the 1920's.[4] While this substance constituted a rather ambitious synthetic objective for the time, a general route to the quinine skeleton was developed by which total syntheses of dihydroquinine and dihydroquinidine were accomplished in 1931.[5] In its basic form [Claisen condensation of a β-(4-piperidyl)propionate with ethyl quininate followed by decarboxylation, bromination, and cyclization], the Rabe route formed the cornerstone of most of the subsequent synthetic work in the area. Both Rabe[6] and Prelog,[7] *et al.*, used this route extensively for the preparation of synthetic quinine analogs and, in the hands of Woodward and Doering,[8] it was utilized to effect the total synthesis of quinine itself.

Much of the more recent synthetic work on the

(1) Presented at the 155th National Meeting of the American Chemical Society, San Francisco, Calif., April 1968.

(2) National Science Foundation Undergraduate Research Participant.

(3) P. Rabe, *Ber.*, **41**, 62 (1908).

(4) P. Rabe, K. Kindler, and O. Wagner, *ibid.*, **55**, 532 (1922).

(5) P. Rabe, W. Huntenburg, A. Schultze, and G. Volger, *ibid.*, **64**, 2487 (1931).

(6) (a) P. Rabe and G. Hagen, *ibid.*, **74**, 636 (1941); (b) P. Rabe and W. Schuler, *ibid.*, **76**, 318 (1943).

(7) (a) V. Prelog, P. Stern, R. Sewerth, and S. Heimbach-Juhasz, *Naturwissenschaften*, **28**, 750 (1940); (b) V. Prelog, P. Stern, R. Sewerth, and S. Heimbach-Juhasz, *Ber.*, **74**, 647 (1941).

(8) R. B. Woodward and W. E. Doering, *J. Amer. Chem. Soc.*, **66**, 849 (1944); **67**, 860 (1945).

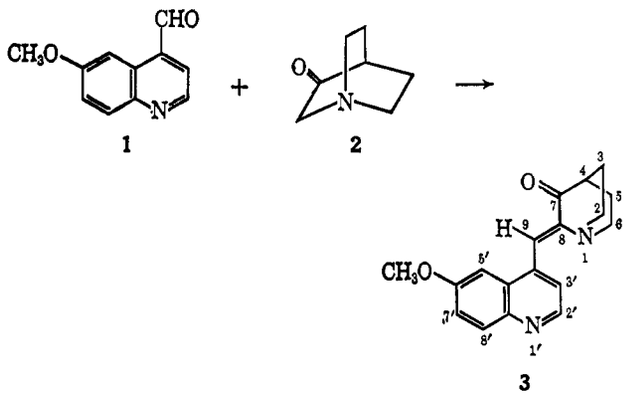
cinchona alkaloids has been directed toward the indole group. The transformation of members of the quinoline group to the indole group[9] and a total synthesis of cinchonamine,[10] the parent alkaloid of the latter, have been described.

Interest in synthetic routes to quinine and its analogs disappeared as its importance in the chemotherapy of malaria declined.[11] However, by 1963 it was clearly recognized that drug resistant strains of Plasmodium falciparum had evolved. While malarial infections with these microorganisms responded to treatment with quinine, the snythetic antimalarials which had largely replaced quinine during the two previous decades were quite ineffective.[12] As a result, quinine once again assumed a position of central importance in malaria chemotherapy. At the same time, the search for new synthetic antimalarials was taken up again and has already yielded the highly effective diaminodiphenyl sulfones.[13]

We have recently undertaken the development of new synthetic routes to the basic quinine skeleton with the twofold objective of synthesizing racemic quinine and of providing general synthetic methods for the preparation of quinine analogs. Enzymic oxidation to a carbostyril[14] seriously curtails the activity of quinine whence antipodal and racemic quinines might conceivably be far superior antimalarials to the natural product. Results from the investigation of one synthetic approach and the partial realization of the second objective are described in this paper.

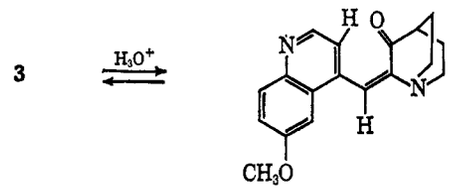
Discussion

3-Quinuclidinone (2), because of its ready availability,[15] represents an attractive precursor to the alicyclic portion of the quinine molecule. Its active methylene group is known to condense readily with aldehydes[16] and moreover the condensation, in modest yield, with quinoline-4-carboxaldehyde has been described.[17] 6-Methoxyquinoline-4-carboxaldehyde (1) was obtained by selenium dioxide oxidation of 6-methoxylepidine[18] which in turn was synthesized from *p*-anisidine and ethyl acetoacetate as first described by Rabe[5] and later modified by Elderfield and coworkers.[19] The aldehyde **1** and ketone **2** condense, in 90% yield, with sodium ethoxide as catalyst giving 6′-methoxy-7-oxo-8-rubene (**3**).



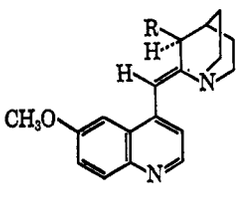
1 + **2** → **3**

Under acid catalysis, the α,β-unsaturated ketone **3** can be transformed into an equilibrium mixture of the two possible geometric isomers. However, under the conditions of the condensation reaction, only the indicated isomer (*vide infra*) of **3** is formed.

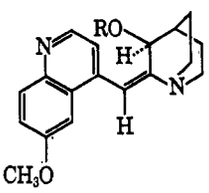


3 $\overset{H_3O^+}{\rightleftharpoons}$ **4**

Samples of isomer **4**, isolated by preparative layer chromatography, slowly rearranged to isomer **3** on standing. The assignment of structures **3** and **4** to the two ketones can be made on the basis of their ultraviolet absorption spectra. There are no serious steric interactions to inhibit coplanarity of the α,β-unsaturated ketone function and quinoline ring in ketone **3** and the resulting conjugation is reflected in an ultraviolet absorption maximum at 362 mμ. However, ketone **4** suffers severe steric interactions when these functions are coplanar and the resulting steric inhibition of resonance manifests itself in the absence of an absorption maximum above 337 mμ, the longest wavelength absorption maximum of 6-methoxyquinolines (compounds **6**, **8**, **13**, **16**, and **18** as well as **4** all show maxima between 335 and 340 mμ). The maximum at 337 mμ in compound **4** shows sufficient tailing into the visible to impart its yellow color.



5 R = OH
6, R = *p*-nitrobenzoyloxy
10, R = Cl
11, R = acetoxy



7, R = H
8, R = *p*-nitrobenzoyloxy

The α,β-unsaturated ketone **3** possesses a plane of symmetry whereby its sodium borohydride reduction produces a single (racemic) alcohol (**5**). The utilization of this alcohol as a precursor of quinine has been explored to some extent. In principle the hydroxy group can be used as a "handle" for the functionalization of C_3 (required for the introduction of a vinyl group) and can then be migrated to C_9 *via* an allylic rearrangement. Treatment with *p*-nitrobenzoyl chloride in pyridine transforms the alcohol **5** into its

(9) E. Ochiai, H. Kataoka, T. Dodo, and M. Takahashi, *Chem. Pharm. Bull.* (Tokyo), **10**, 76 (1962).
(10) C.-B. Chen, R. P. Evstigneeva, and N. A. Preobrazhenskii, *Dokl. Akad. Nauk SSSR*, **123**, 707 (1958); *Chem. Abstr.*, **53**, 7919 (1959).
(11) P. B. Russel in "Medicinal Chemistry," A. Burger, Ed., Interscience Publishers, Inc., New York, N. Y., 1960, p 814.
(12) E. H. Sadun, *Amer. J. Trop. Med. Hyg.*, **13**, 145 (1964).
(13) See E. F. Elslager and D. F. Worth, *Nature*, **206**, 630 (1965), for leading references.
(14) K. Lang and H. Keuer, *Biochem. Z.*, **329**, 277 (1957).
(15) H. U. Daeniker and C. A. Grob, *Org. Syn.*, **44**, 86 (1964); Aldrich Chemical Co., Inc., Milwaukee, Wis.
(16) (a) C. A. Grob and A. Kaiser, *Helv. Chim. Acta*, **46**, 2646 (1963); (b) A. T. Nielsen, *J. Org. Chem.*, **31**, 1053 (1966).
(17) G. R. Clemo and E. Hoggarth, *J. Chem. Soc.*, 1241 (1939).
(18) (a) C. E. Kwartler and H. G. Lindwall, *J. Amer. Chem. Soc.*, **59**, 524 (1937); (b) M. Levitz and M. T. Bogert, *J. Org. Chem.*, **10**, 341 (1945).
(19) K. N. Campbell, R. S. Tipson, R. C. Elderfield, B. K. Campbell, M. A. Clapp, W. J. Gensler, D. Morrison, and W. J. Moran, *ibid.*, **11**, 803 (1946).

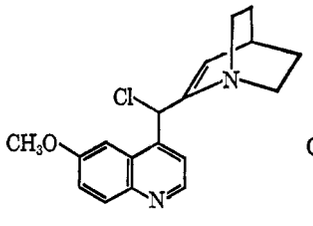
p-nitrobenzoate **6**. When this derivative was exposed to sodium acetate in refluxing acetic acid for 6 hr, it failed to yield any detectable amount of a rearranged acetate; indeed, it failed to yield any acetate. The product, compound **8**, is that resulting from isomerization of the olefinic linkage. Assignment of structures **6** and **8** to the starting material and product, respectively, is based on the nmr spectra of the two esters. Whereas the four protons of the *p*-nitrobenzoyl group appear as a singlet at 8.25 ppm in ester **6**, they give rise to a multiplet superimposed on the multiplet arising from the quinoline protons (centered at *ca.* 7.5 ppm) in the isomeric ester **8**. This is interpreted as a consequence of the close proximity of the quinoline ring and *p*-nitrobenzoyl group in ester **8**.

Both hydrolysis of *p*-nitrobenzoate **8** and sodium borohydride reduction of ketone **4** gave the same alcohol, compound **7**.

The SNi′ reaction of allylic alcohols with thionyl chloride[20] suggested a second method of transposing the oxygen function at C_7 in alcohol **5** to C_9. Treatment with thionyl chloride did in fact give some of the rearranged chloride **9**, but as a minor product. The major product was the chloride **10**. The two chlorides **9** and **10** form partially overlapping spots on thin layer chromatography and were therefore not amenable to separation. The nmr spectrum of the mixture showed signals at 3.96, 4.90, and 6.98 ppm which can be assigned to the methoxyl, C_7, and vinyl protons, respectively, of compound **10** and signals at 3.89, 6.11, and 6.48 ppm which can be assigned to the methoxyl, C_9, and vinyl protons, respectively, of compound **9**. The integration ratio of the first set of signals to the second set (4:1) indicates that the mixture consists of 80% of compound **10** and 20% of compound **9**. The alternative interpretation of the nmr spectrum as arising from a mixture of *cis–trans* isomers is not consistent with the chemical shifts observed for the C_7 and C_9 protons of compound **9**: the two isomeric alcohols **5** and **7** show vinylic proton signals at 6.92 and 6.98, respectively, and C_7 proton signals at 4.45 in each. Similarly the isomeric *p*-nitrobenzoates show vinylic proton signals at 6.95 and 7.12, respectively, and C_7 proton signals at 5.88 and 5.83, respectively.

The mixture of chlorides reacted very slowly with silver acetate in refluxing acetic acid to give, as the only products isolated, the alcohol **5** and the acetate **11**. This acetate was identical with that obtained from the reaction of alcohol **5** with acetic anhydride.

Catalytic hydrogenation of the mixture of chlorides **9** and **10** in alcoholic potassium hydroxide solution gave a mixture of products from which 6′-methoxyrubane (**12**) was isolated in low yield. The two antipodal forms of this compound have been synthesized previously by Rabe.[6b]



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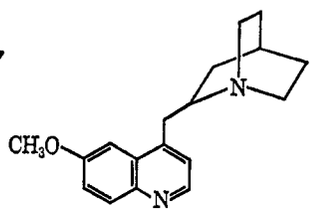
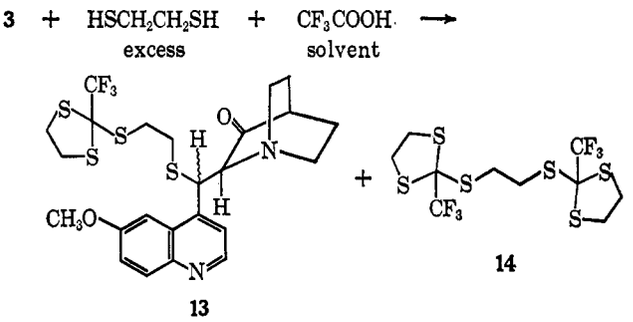


12

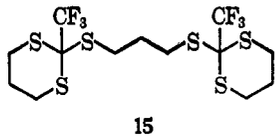
A more direct route to 6′-methoxyrubane (**12**) was anticipated in the thioketalization of the α,β-unsaturated ketone **3** followed by simultaneous hydrogenolysis and hydrogenation over Raney nickel. However, the ketone resisted all attempts to transform it into a thioketal. A reaction with 1,2-ethanedithiol takes place in refluxing trifluoroacetic acid, however the product, compound **13**, derives from sequential condensation with the dithiol, the solvent, and a second molecule of the dithiol.



13 **14**

A by-product of the reaction, compound **14**, was shown to result from a still more complex condensation in which five molecules in the reacting system combine into one.

The structure of the by-product **14** gave an essential hint in elucidating the structure of the main product **13**; hence the determination of this structure will be discussed first. The compound was obtained in 89% yield when 1,2-ethanedithiol and excess trifluoroacetic acid were heated under reflux. It is a colorless solid, readily recrystallized from ethanol without decomposition. The compound shows C–F bands at 1200 cm^{-1} in its infrared spectrum, two singlets at 3.19 and 3.52 ppm (ratio 1:2) in its proton nmr spectrum, and intense peaks at *m/e* 173 and 265 in its mass spectrum. These data, together with the analysis and observed molecular weight, can only be accommodated by structure **14**.[21] This direct condensation of a mercaptan with a carboxylic acid to form an ortho thiol ester is without precedent and is more or less unique for these two reactants. Acetic and formic acids do not condense with ethanedithiol in this manner although 1,3-propanedithiol gives, in much lower yield, the analogous product **15** with trifluoroacetic acid.[22]



15

Skeletal rearrangements attending the transformation of ketone **3** into compound **13** are precluded by the facile regeneration of **3** under a variety of conditions (heat, alumina, acetic anhydride). Compound **13** crystallizes as an ethanol solvate and this fact, combined with the thermal instability, required reduction to the alcohol **16** for molecular weight determination. The mass spectrum of compound **13** is that of the ketone

(20) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt-Dryden, New York, N. Y., 1959, p 296.

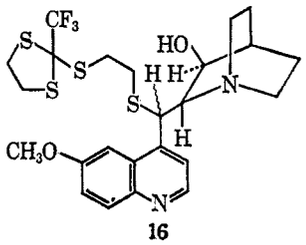
(21) A preliminary description of this reaction has been published: D. L. Coffen, *Chem. Commun.*, 1089 (1967).

(22) Compound **15** was first synthesized by Miss Patricia Garrett of our laboratory.

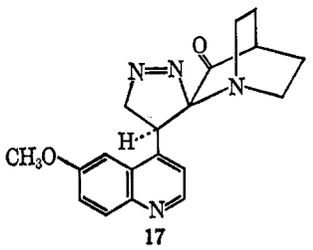
3. An infrared absorption band at 1730 cm^{-1} demonstrates that the ketone function is still present but no longer conjugated; new bands at 1150, 1175, and 1240 cm^{-1} are consistent with a compound containing C–F bonds. The nmr spectrum of a sample recrystallized from ethanol shows by a triplet at 1.20 and a quartet at 3.69 ppm (J = 7 cps) that crystalline compound **13** is a monoethanol solvate. A sample obtained by evaporating a benzene solution of **13** no longer contained these nmr bands nor an infrared band at 3300 cm^{-1}. The 100-Mc nmr spectrum of the ethanol-free sample, in comparison with the spectrum of its precursor **3**, shows the following changes: the vinyl proton singlet at 7.66 ppm has vanished; two new one-proton doublets appear at 3.71 and 5.02 ppm (J = 8 cps) and are assigned to protons at C_8 and C_9 (confirmed by spin decoupling); in addition to the methoxyl singlet at 3.89 ppm, a four-proton singlet appears at 3.20 which can be ascribed to the 1,3-dithiolane ring protons; signals from the exocyclic ethanedithiol residue are superimposed on the quinuclidine multiplets but probably give rise to triplets observed at 2.45 and 2.85 ppm (J = 8 cps).

Although compounds **13** and **16** have two and three centers of asymmetry, respectively, each of them is nevertheless obtained as a single racemate. Although it is not possible to assign stereochemistry to C_9 relative to C_8 in these compounds, the configuration indicated for C_7 in **16** can be assigned with confidence when the steric hindrance to borohydride ion attack from the upper side of **13** is considered.

The myriad products available from 1,3-dipolar addition reactions[23] suggested that numerous synthetic quinine analogs might be derivable from ketone **3** if 1,3-dipolar additions can be effected across the C_8–C_9 double bond. This possibility has been realized and demonstrated in the nearly quantitative formation of pyrazoline **17** in the reaction of ketone **3** with diazomethane. The spectroscopic properties of the adduct are in accord with structure **17**.

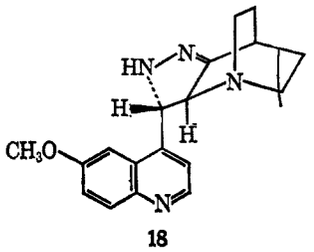


16

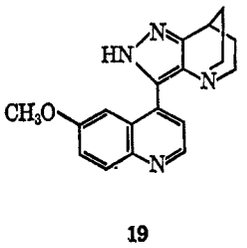


17

A second pyrazoline derivative, **18**, was obtained by warming the ketone **3** with alcoholic hydrazine. Mercuric acetate oxidation of compound **18** gave the corresponding pyrazole **19**. Structure **18**, rather than that of an α,β-unsaturated hydrazone, is assigned on the basis of the compound's nmr spectrum. The spectrum contains no vinyl proton singlet but does have two one-proton doublets at 3.11 and 4.75 ppm ($J_{8,9}$ = 4 cps). These two doublets vanish with the oxidation to pyrazole **19**. The low value of $J_{8,9}$ suggests the *trans* relationship[24] indicated for the protons at C_8 and C_9.



18



19

(23) R. Huisgen, *Angew. Chem. Intern. Ed. Engl.*, **2**, 565 (1963).

Experimental Section[25]

6′-Methoxy-7-oxo-8-rubene.—Sodium (1.56 g, 0.068 g-atom) was dissolved in absolute ethanol (60 ml) and to the resulting solution 6-methoxyquinoline-4-carboxaldehyde[18] (9.64 g, 0.0515 mol) and 3-quinuclidinone hydrochloride[15] (8.35 g, 0.0515 mol) were added. The mixture was warmed to 35°, swirled for *ca.* 5 min, and then kept at room temperature for 2 hr. Crystallization of the product was completed by slowly adding water (150 ml). The product was filtered, washed with water, and dried in air giving 14.13 g (91%) of yellow crystals. An analytical sample, recrystallized from ethanol, had mp 155–156°; ν_{max} 1710, 1620, 1510, 1230, 1095, 1035, 928, 858, and 731 cm^{-1}; λ_{max} 228 (ϵ 43,000), 250 (sh, 17,000), 337, (7300) and 362 (7200); nmr ($CDCl_3$), 2.10 (4 H, multiplet, H_3 and H_5), 2.70 (1 H, multiplet, H_4), 3.10 (4 H, multiplet H_2 and H_6), 3.96 (3 H, singlet, methoxyl), 7.32 (2 H, multiplet, $H_{5'}$ and $H_{7'}$), 7.66 (1 H, singlet, H_9), 8.04 (2 H, two doublets, three lines, $H_{3'}$ and $H_{8'}$), and 8.80 (1 H, doublet, $H_{2'}$, $J_{2'3'}$ = 5 cps); and mol wt 294 (mass spectrum).

Anal. Calcd for $C_{18}H_{18}N_2O_2$: C, 73.65; H, 6.16; N, 9.52. Found: C, 73.62; H, 6.13; N, 9.29.

Equilibration of Ketone 3 with Ketone 4.—A sample of ketone **3** (200 mg) dissolved in 6 *N* sulfuric acid was kept at room temperature for 18 hr. The solution was neutralized with aqueous sodium bicarbonate and the ketones were extracted with methylene chloride. The product showed two yellow spots on a silica gel thin-layer chromatogram ($CHCl_3$–CH_3OH 10:1), the starting material and a new spot with a lower R_f value. When material from the lower spot was eluted directly into an ultraviolet cell with ethanol, it showed a maximum at 337 mμ. The remaining product was separated by preparative layer chromatography. The ketone from the lower yellow band (68 mg) was crystallized from ethanol. This material, mp 121–123°, showed by tlc and nmr that partial conversion back to ketone **3** had occured during purification. The infrared spectrum of this material showed only minor differences from that of pure ketone **3**. The nmr spectra were also very similar with slight differences in some chemical shifts: methoxyl protons at 3.89, vinyl proton at 7.17, and $H_{2'}$ at 8.76 ppm in ketone **4**.

6′-Methoxy-7-hydroxy-8-rubene (**5**).—Ketone **3** (4.57 g, 0.0153 mol) was partially dissolved in methanol (50 ml) with warming, then treated with sodium borohydride (1.00 g, 0.026 mol) in portions while swirling. The ketone dissolved completely and the yellow color disappeared. The solution was slowly diluted with cold water (250 ml) and stored in the cold overnight. The product was filtered, washed with water, and dried in air, giving 4.51 g (98%) of colorless, crystalline alcohol, mp 153–155°. The compound had ir bands at ν_{max} 3200, 1640, 1620, 1580, 1510, 1230, 1090, 1030, 845, and 720 cm^{-1}; the nmr spectrum ($CDCl_3$) showed peaks at 1.1–3.3 (9 H, multiplets, quinuclidine H), 3.78 (3 H, singlet, methoxyl), 4.49 (1 H, broad singlet, H_7), 4.60 (1 H, broad singlet, vanished when solution was shaken with D_2O, hydroxyl), 6.92 (1 H, doublet, H_9, $J_{7,9}$ = 1.5 cps), 7.25 (2 H, multiplet, $H_{5'}$ and $H_{7'}$), 7.83 (1 H, doublet, $H_{3'}$, $J_{2'3'}$ = 4.5 cps), 8.00 (1 H, doublet, $H_{8'}$, $J_{7'8'}$ = 10 cps), and 8.64 (1 H, doublet, $H_{2'}$); and the molecular weight was 296 (mass spectrum).

6′-Methoxy-7-(*p*-nitrobenzoyloxy)-8-rubene (**6**).—A solution

(24) A. Hassner and M. J. Michelson, *J. Org. Chem.*, **27**, 3974 (1962).

(25) Melting points are uncorrected. Infrared spectra were measured as Nujol mulls on a Perkin-Elmer Infracord Model 137. Strong bands and those characteristic of the functional groups present are listed. Ultraviolet spectra (in 95% ethanol) and mass spectra were recorded on Cary 14 and CEC 21-103 instruments, respectively. Nmr spectra (ppm) were measured on Varian A-60A and HA-100 instruments using solvents indicated and tetramethylsilane as an internal standard. Analyses and molecular weight determinations were carried out by Galbraith Laboratories, Inc., Knoxville, Tenn. Some of the compounds with strong molecular ion peaks in their mass spectra were not analyzed.

of alcohol **5** (400 mg, 1.35 mmol) and *p*-nitrobenzoyl chloride (500 mg, 2.70 mmol) in pyridine (5 ml) was kept overnight at room temperature. The resulting mixture was diluted with methylene chloride, washed with aqueous sodium bicarbonate, dried, and evaporated. The crude product (543 mg, 91%) was recrystallized from ethanol giving colorless crystals with mp 142–145° and ir bands at ν_{max} 1720, 1625, 1580, 1525, 1500, 1350, 1320, 1265, 1225, 1105, 1025, 850, and 724 cm^{-1}. The nmr spectrum ($CDCl_3$) was essentially the same as that of the alcohol between 1 and 4 ppm. H_7 appears as a poorly resolved doublet at 5.88 and a new, four-proton singlet appears at 8.26 (*p*-nitrobenzoyl group). The quinoline and vinyl proton signals are essentially unchanged.

Anal. Calcd for $C_{25}H_{23}N_3O_5$: C, 67.41; H, 5.20; N, 9.43. Found: C, 66.19; H, 5.17; N, 9.18.

Isomerization of *p*-Nitrobenzoate 6 to *p*-Nitrobenzoate 8.—A solution of *p*-nitrobenzoate **6** (200 mg) and sodium acetate (800 mg) in acetic acid (8 ml) was heated under reflux for 6 hr. The solution was then diluted with water, neutralized with aqueous sodium bicarbonate, and extracted with methylene chloride. The dried extract was evaporated leaving 164 mg of partly crystalline, crude product, Recrystallization from ethanol gave 70 mg (35%) of pure, colorless crystals with mp 162–163° and ir bands at ν_{max} 1720, 1620, 1580, 1525, 1345, 1320, 1260, 1225, 1115, 1105, 1030, and 720 cm^{-1}. The nmr spectrum ($CDCl_3$) shows the quinuclidine protons as three multiplets between 1.0 and 3.6, the methoxyl singlet at 3.94, and H_7 at 5.83. The 7.0–8.6-ppm region of the spectrum contains at least 20 lines (10 H) of which only the $H_{2'}$ doublet at 8.48 can be assigned with confidence. The R_f value of ester **8** on tlc is distinctly lower than that of ester **6**.

Anal. Calcd for $C_{25}H_{23}N_3O_5$: C, 67.41; H, 5.20; N, 9.43. Found: C, 66.35; H, 5.34; N, 9.21.

Alcohol 7. A. By Hydrolysis of *p*-Nitrobenzoate 8.—*p*-Nitrobenzoate **8** (65 mg) was taken up in methanolic KOH (two pellets in 2 ml) andkept at room temperature for 2 hr. The solution was diluted with water and extracted with methylene chloride. The extracts were dried and evaporated leaving 36 mg (82%) of crystalline residue. Recrystallization from ethanol gave colorless crystals: mp 166–167°; ν_{max} 3150, 1640, 1620, 1580, 1505, 1230, 1045, 1035, 905, 822, and 715 cm^{-1}; nmr ($CDCl_3$), 1.1–3.4 (9 H, multiplets, quinuclidine H), 3.6 (1 H, broad singlet, hydroxyl), 3.87 (3 H, singlet, methoxyl), 4.45 (1 H, broad singlet, H_7), 6.98 (1 H, singlet, H_9), 7.25 (2 H, multiplet, $H_{5'}$ and $H_{7'}$), 7.58 (1 H, doublet, $H_{3'}$, $J_{2',3'}$ = 4.5 cps), 7.36 (1 H, doublet, $H_{8'}$, $J_{7',8'}$ = 9 cps), and 8.43 (1 H, doublet, $H_{2'}$). The molecular weight was 296 (mass spectrum); the mass spectra of alcohols **5** and **7** are nearly identical. Alcohol **7** has a distinctly lower R_f value on tlc than alcohol **5**.

B. By Reduction of Ketone 4.—The sample of ketone **4** from preparative layer chromatography (60 mg, contaminated with **3**) was repurified in the same manner. The lower yellow band was removed from the plate and added directly to a stirred solution of sodium borohydride (100 mg) in methanol (5 ml). The reaction mixture was diluted with methylene chloride, filtered through Celite to remove the silica gel, dried, and evaporated leaving 42 mg of colorless residue. The product was purified by preparative layer chromatography and recrystallization from ethanol giving 20 mg of colorless crystals, mp 163–165° (mmp 164–167°). The infrared spectrum and tlc behavior of this material are identical with those of the alcohol from method A.

6′-Methoxy-7-chloro-8-rubene (10) and 6′-Methoxy-9-chloro-7-rubene (9).—Alcohol **5** (200 mg, 0.66 mmol) was dissolved in thionyl chloride (5 ml) and the solution was refluxed for 45 min then kept at room temperature for 17 hr. Excess thionyl chloride was evaporated in a nitrogen stream. The residue was taken up in methylene chloride, washed with aqueous sodium bicarbonate, dried, and evaporated leaving 232 mg of viscous yellow oil. The product is a mixture of two compounds (tlc), crystalline in the cold but an oil at room temperature; ir bands were at ν_{max} (film) 1620, 1580, 1500, 1230, 1030, 845, 775 and 715 cm^{-1}. The nmr spectrum ($CDCl_3$) shows the quinuclidine and quinoline multiplets in the 1–3.3- and 7.2–8.8-ppm regions, respectively. Signals at 3.96 (singlet), 4.90 (quartet, $J_{4,7}$ = 3.5 cps and $J_{7,9}$ = 1.5 cps), and 6.98 (doublet, $J_{7,9}$ = 1.5 cps) in the ratio 3:1:1 are assigned to the methoxyl protons, H_7, and H_9 of chloride **10**. Signals with one-fourth of the intensity at 3.89 (singlet), 6.11 (broad singlet), and 6.48 (doublet, $J_{4,7}$ = 7 cps) in the ratio 3:1:1 are assigned to the methoxyl protons, H_9, and H_7 of chloride **9**.

6′-Methoxy-7-acetoxy-8-rubene (11). A. From Chlorides 9 and 10.—The crude chloride mixture from alcohol **5** (200 mg) was stirred with silver acetate (300 mg) in acetic acid (10 ml) for **3** days at room temperature. The mixture was diluted with aqueous sodium chloride, filtered, neutralized with aqueous sodium bicarbonate, and extracted with methylene chloride. The dried extracts were evaporated leaving 179 mg of yellow gum. Separation of the crude products by preparative layer chromatography afforded 29 mg (14%) of alcohol **5** (infrared, tlc) and 75 mg (33%) of acetate **11**. The acetate formed colorless crystals from ether: mp 136–137°; ν_{max} 1730, 1660, 1620, 1580, 1500, 1245, 1230, 1035, 870, 840, and 718 cm^{-1}. The nmr ($CDCl_3$) spectrum contains signals for the quinuclidine and methoxyquinoline protons similar to those in the spectrum of the alcohol **5**. There is a new three-proton singlet at 2.16 (acetyl), H_7 appears as a poorly resolved quartet at 5.58, and H_9 appears as a broad singlet at 6.80 ppm.

Anal. Calcd for $C_{20}H_{22}N_2O_3$: C, 70.98; H, 6.55; N, 8.28. Found: C, 71.13; H, 6.37; N, 8.47.

B. From Alcohol 5.—Alcohol **5** (500 mg, 1.69 mmol) was taken up in acetic anhydride and the solution was kept overnight at room temperature. The solution was then slowly poured into cold, aqueous sodium bicarbonate. The product was extracted with methylene chloride and, after drying and evaporating, recrystallized from ether to give 470 mg (82%) of colorless crystals, identical (melting point, tlc, infrared) with that obtained by method A.

6′-Methoxyrubane (12).—The crude chloride mixture from alcohol **5** (300 mg) was taken up in a solution of potassium hydroxide (2 g) in ethanol (15 ml) and shaken with Raney nickel (0.5 g) under hydrogen at 50 psi for 16 hr. The catalyst was filtered out and washed with ethanol. The filtrate and washings were poured into water and extracted with methylene chloride giving, when dried and evaporated, 260 mg of brown oil. The most polar component of this mixture was isolated by preparative layer chromatography (silica gel) and the dihydrochloride was recrystallized twice from methylene chloride–ether giving 16 mg of colorless crystals: mp 162–164°; ν_{max} 1670, 1620, 1590, 1510, 1225, 1125, 1030, 800, and 720 cm^{-1}; molecular weight of the free base, 282 (mass spectrum).

Anal. Calcd for $C_{18}H_{22}N_2O \cdot 2HCl$: C, 60.84; H, 6.80; N, 7.88. Found: C, 60.62; H, 6.40; N, 7.92.

Compound 13.—Ketone **3** (500 mg) and 1,2-ethanedithiol (1 ml) in trifluoroacetic acid (10 ml) were heated under reflux for 16 hr. Excess trifluoroacetic acid was evaporated off and the residue was taken up in methylene chloride. This solution was washed with aqueous sodium bicarbonate, dried, and evaporated. The residue was dissolved in ethanol (4 ml) and stored in the cold for 1 week. The crystals were filtered, washed with cold ethanol, and air dried giving 750 mg (73%) of crude crystalline **13** as an ethanol (mono) solvate. Two subsequent crops of crystals were nearly pure compound **14**. Recrystallization of the main product from ethanol gave 570 mg of pure **13** in large, colorless crystals: mp 89–92° dec; ν_{max} 3250 (ethanol), 1730, 1625, 1580, 1505, 1240, 1180, 1150, 1030, 845, and 720 cm^{-1}. The nmr spectrum ($CDCl_3$, ethanol-free sample) shows three multiplets at 2.00, 2.45, and 4.00 (13 H) assigned to the quinuclidine and exocyclic ethanedithiol moiety protons, 3.20 (4 H, singlet, dithiolane ring), 3.71 (1 H, doublet, H_8, $J_{8,9}$ = 8 cps), 3.89 (3 H, singlet, methoxyl), 5.02 (1 H, doublet, H_9), 7.35, (2 H, multiplet, $H_{5'}$ and $H_{7'}$), 7.60 (1 H, doublet, $H_{3'}$, $J_{2',3'}$ = 5 cps), 8.01 (1 H, doublet, $H_{8'}$, $J_{7',8'}$ = 9.5 cps), and 8.72 (1 H, doublet, H_2').

Anal. Calcd for $C_{26}H_{33}F_3N_2O_3S_4$: C, 51.46; H, 5.48; N, 4.62; S, 21.14. Found: C, 51.40; H, 5.59; N, 4.45; S, 21.26.

Alcohol 16.—Compound **13** (50 mg) in methanol (1 ml) was treated with excess sodium borohydride and kept at room temperature for 1 hr. The solution was diluted with water and chilled and the product (42 mg, 84%) was filtered out. Recrystallization from methylene chloride–ether gave fine, colorless needles: mp 198°; ν_{max} 3200, 1620, 1580, 1240, 1170, 1145, 1070, 1030, and 829 cm^{-1}. The nmr spectrum ($CDCl_3$) shows a complex multiplet pattern in the 1.1–4.1-ppm region in which the dithiolane and methoxyl singlets appear at 3.28 and 4.00 ppm, and H_9 appears as a doublet at 5.34 ($J_{8,9}$ = 11 cps). The quinoline proton signals show only slight differences from those of compound **14**; $H_{8'}$ appears at 7.70 and $H_{2'}$ appears at 8.48 ppm.

Anal. Calcd for $C_{24}H_{29}F_3N_2O_2S_4$: C, 51.22; H, 5.19; N, 4.98; S, 22.79; mol wt, 562.78. Found: C, 51.39; H, 5.05; N, 4.60; S, 22.39; mol wt ($CHCl_3$), 564.

1,2-Bis-2(2-trifluoromethyl-1,3-dithiolanyl)thioethane (14).—A solution of 1,2-ethanedithiol (3 g, 32 mmol) in trifluoroacetic acid (20 ml) was heated under reflux for 20 hr. A second phase began to form after 3 hr. The mixture was chilled and the solid product was filtered and dried giving 4.12 g (89%) of colorless; crystals. A sample was recrystallized from ethanol: mp 85°; ν_{max} 1420, 1370, 1280, 1225, 1160, 980, 960, 890, 860, 835, 820, 708, and 693 cm^{-1}; nmr (CCl_4), 3.19 (4 H, singlet) and 3.52 ppm (8 H, singlet); mass spectrum, *m/e* 173 and 265 (no M^+ at 70 eV or at 14 eV).

Anal. Calcd for $C_{10}H_{12}F_6S_6$: C, 27.38; H, 2.76; S, 43.87; mol wt, 438.6. Found: C, 27.33; H, 2.72; S, 44.06; mol wt ($CHCl_3$), 429.

1,3-Bis-2(2-trifluoromethyl-1,3-dithianyl)thiopropane (15).—A solution of 1,3-propanedithiol (4 g, 37 mmol) in trifluoroacetic acid (20 ml) was heated under reflux for 20 hr. The solution was cooled and excess trifluoroacetic acid was evaporated under reduced pressure (0.5 mm at 60°) leaving a colorless oil which exhibits carbonyl absorption at 1710 cm^{-1}. This oil was taken up in ethanol (25 ml), seeded with a crystal of product (isolated by alumina chromatography), and stored in the cold for 2 weeks. The crystals were filtered and washed with cold ethanol giving 1.86 g (32%) of product. A sample was recrystallized from ethanol: mp 54–55°; ν_{max} 1420, 1400, 1275, 1225, 1170, 1010, 884, 858, 810, 770 and 703 cm^{-1}; nmr (CCl_4), 2.0 (6 H, multiplet) and 2.94 ppm (12 H, unsymmetrical triplet); mass spectrum, *m/e* 187 and 293 (no M^+ peak).

Anal. Calcd for $C_{13}H_{18}F_6S_6$: C, 32.48; H, 3.77; S, 40.03. Found: C, 32.69; H, 3.64; S, 40.08.

Spiro-4′-(6-methoxy-4-quinolyl)-1-pyrazoline[3′.2]quinuclidin-3-one (17).—A solution of ketone **3** (500 mg) in methylene chloride (10 ml) was treated with *ca.* 0.2 *M* diazomethane in ether (50 ml). Colorless needles began to separate after 10 min. The mixture was kept in the cold for 2 days and at room temperature for 2 days, then concentrated to *ca.* 10 ml, chilled, and filtered giving 500 mg (88%) of colorless needles, mp 235–245° dec. A sample recrystallized from methylene chloride–ether had the same melting point; ir bands were at ν_{max} 1725, 1625, 1580, 1505, 1230, 1140, 1030, 850, and 820 cm^{-1}. The nmr spectrum ($CDCl_3$) contains quinuclidine proton multiplets from 1.8 to 3.2 ppm and the methoxy singlet at 3.89. H_9 appears as a quartet (1 H) at 4.21. The methylene protons of the pyrazoline ring give a cleanly resolved eight-line pattern at 4.2 arising from the splitting of an AB quartet by H_9 (J_{AB} = 18 cps, J_{A9} = 8 cps, and J_{B9} = 4 cps, confirmed by spin decoupling). The five quinoline protons appear as doublets at 6.97 ($H_{3'}$), 8.00 ($H_{8'}$), and 8.62 ($H_{2'}$), and a two-proton multiplet at 7.30 ppm.

Anal. Calcd for $C_{19}H_{20}N_4O_2$: C, 67.84; H, 5.99; N, 16.66. Found: C, 67.79; H, 6.09; N, 16.47.

5-(6-Methoxy-4-quinolyl)-3,4-(1,4-piperidylidene)-2-pyrazoline (18).—Ketone **3** (250 mg) was dissolved in ethanol (5 ml) with warming and treated with 95% hydrazine (0.5 ml). The yellow color faded with additional warming. Evaporation left 275 mg (100%) of crystalline white solid. The product crystallizes as a monohydrate. Crystals from dimethyl sulfoxide had mp 205–207° and ir bands at ν_{max} 3300, 1620, 1580, 1505, 1225, 1025, 852, and 718 cm^{-1}. The nmr spectrum (d_6-DMSO) differed from that of ketone **3** by the absence of a vinyl proton signal and the appearance of one-proton doublets at 3.11 (H_8) and 4.75 ppm (H_9, $J_{8,9}$ = 4 cps). The product had uv absorptions at λ_{max} 207 mμ (ε 34,000), 237 (43,000), and 335 (6400), and a molecular weight of 308 (mass spectrum).

Anal. Calcd for $C_{18}H_{20}N_4O \cdot H_2O$: C, 66.23; H, 6.79; N, 17.16. Found: C, 66.83; H, 6.63; N, 17.06.

5-(6-Methoxy-4-quinolyl)-3,4-(1,4-piperidylidene)pyrazole (19).—The crude pyrazoline **18** from 1 mmol of ketone **3** (294 mg) in acetic acid (5 ml) was treated with a warm solution of mercuric acietate (350 mg, 1.10 mmol) in acetic acid (10 ml). The resulting mixture was stirred at room temperature for 2 days, then poured into dilute aqueous ammonia, and extracted with methylene chloride. The crude product from evaporating the dried extracts was purified by chromatography on alumina and recrystallized from methylene chloride–ether. The pure product (179 mg, 58%) was obtained as small, colorless crystals: mp 239–243°; ν_{max} 3100, 1620, 1575, 1550, 1500, 1240, 1155, 1135, 850, and 720 cm^{-1}; λ_{max} 206 mμ (ε 26,000), 233 (34,000), 302 (7000), and 338 (7400). The nmr spectrum ($CDCl_3$–d_6-DMSO) shows quinuclidine proton signals from 1.2 to 3.0, methoxyl at 3.94, and peaks at 7.41 (1 H, quartet, $H_{7'}$, $J_{7',8'}$ = 10 cps and $J_{7',5'}$ = 3 cps), 7.65 (1 H, doublet, $H_{3'}$, $J_{2',3'}$ = 4 cps), 8.04 (2 H, two doublets, $H_{5'}$ and $H_{8'}$), and 8.82 ppm (1 H, doublet, $H_{2'}$).

Anal. Calcd for $C_{18}H_{18}N_4O$: C, 70.57; H, 5.92; N, 18.29; mol wt, 306. Found: C, 69.61; H, 6.10; N, 17.85; mol wt 306 (mass spectrum).

Registry No.—**3,** 16526-29-7; **4,** 16526-45-7; **5,** 16526-30-0; **6,** 16526-31-1; **7,** 16526-32-2; **8,** 16526-33-3; **9,** 16526-34-4; **10,** 16526-35-5; **11,** 16526-36-6; **12,** 16526-44-6; **13,** 16526-37-7; **14,** 16526-38-8; **15,** 16526-39-9; **16,** 16526-40-2; **17,** 16526-41-3; **18,** 16526-42-4; **19,** 16526-43-5.

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