Anal. Calcd for $C_{20}H_{20}O_7N_2S_2$: C, 51.7; H, 4.3; N, 6.0; S, 13.8. Found: C, 51.4; H, 4.4; N, 6.2; S, 13.9.

The ^1H nmr spectrum had signals at τ 7.70 (three acetyl protons), 8.00 (three methyl protons on hydantoin ring), and 7.55 (methyl protons on benzene ring). The ir spectrum (in CH_2Cl_2) had bands at 5.60, 5.73 and 5.81 (sh) μ.

Registry No.—**14,** 4461-33-0; **15,** 18354-35-3; **16,** 4695-57-2; **17,** 3019-71-4; **18,** 18354-38-6; **19,** 18354-39-7; **20,** 6077-66-3; **23,** 18354-41-1; **24,** 18354-42-2; **25,** 18354-43-3; **27,** 18354-44-4; **29,** 18354-48-8; **30,** 18354-45-5; **31,** 18354-46-6; **33,** 18354-47-7.

A γ-Pyran Derivative from Pulegone and Ethyl Acetoacetate. Reformulation of a Bicyclo[3.3.1]nonenone Structure

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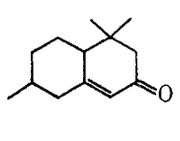
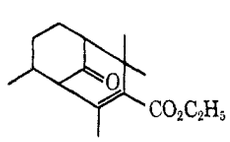
Received August 5, 1968

The crystalline solid isolated from the zinc chloride catalyzed condensation of pulegone and ethyl acetoacetate and previously identified as 3-carbethoxy-2,4,4,8-tetramethylbicyclo[3.3.1]-2-nonen-9-one is now reformulated as 3-carbethoxy-2,4,4,7-tetramethyl-5,6,7,8-tetrahydro-1,4-benzopyran by a reconsideration of its spectral properties and by hydrogenation to a tetrahydro derivative and dehydrogenation to 3-carbethoxy-2,4,4,7-tetramethyl-1,4-benzopyran.

Some time ago it was shown[1] that pulegone acetone, produced by the zinc chloride catalyzed condensation of pulegone with ethyl acetoacetate, has the constitution represented by I rather than three alternative structures proposed by other investigators.[2,3] In the meantime, Chow[4] reported the isolation of another crystalline product from the pulegone condensation, referred to here as compound B, and argued that it possessed structure II.



I



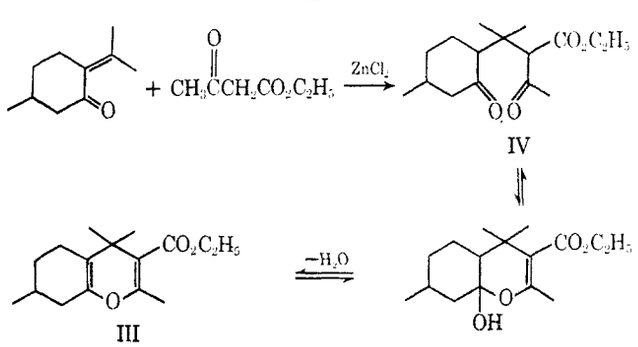
II

The exclusive reduction of the carbethoxy group in compound B by excess lithium aluminum hydride and the alleged formation of a hydrazide rather than a normal 2,4-dinitrophenylhydrazone derivative were but two of the many observations recorded by Chow[4] which do not agree with the behavior expected for a compound such as II. We have reexamined this matter and wish to report that compound B is the carbethoxypyran III and is most likely formed according to the sequence outlined in Scheme I.

When the reaction of pulegone with ethyl acetoacetate was conducted for 10 hr pulegone acetone (I) was the only crystalline product isolated. When the condensation was stopped after 2 hr, column chromatography afforded a new crystalline solid, mp 37–38°, whose physical and spectral properties were essentially identical with those of compound B reported by Chow.[4] There can be no question that the solid that we isolated is identical with the compound described by Chow.[4]

Compound B is converted into pulegone acetone by the action of zinc chloride in acetic acid[4] suggesting that its formation is reversible and that diketo ester IV eventually undergoes an irreversible intramolecular aldol condensation followed by decarbethoxylation to give I. This accounts for the fact that compound B is not found when the condensation is extended for 10 hr. Since the cyclization of IV to III produces water, it was reasoned that the yield of III might be improved if water was removed so as to prevent the hydrolysis of III to IV. When acetic anhydride was added to the reaction mixture, in order to consume the water which formed, the yield of III rose from 5 to 18% and little or no pulegone acetone formed. Unfortunately, the yield of III could not be further improved; the remainder of the material was largely accounted for as a nonvolatile, presumedly polymeric, oil.

SCHEME I

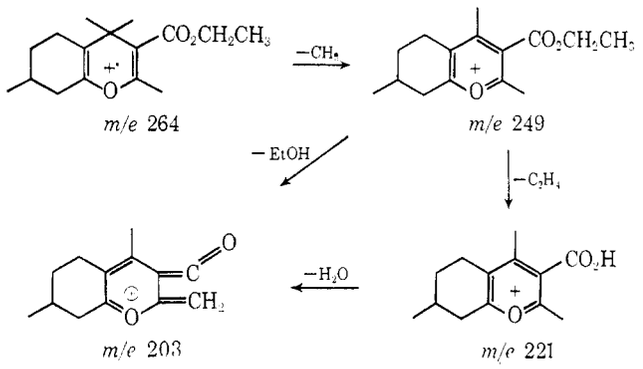


(1) J. Wolinsky and M. A. Tyrell, *Chem. Ind.* (London), 1104 (1960).
(2) P. Barbier, *C. R. Acad. Sci., Paris,* **127,** 870 (1898).
(3) L. G. Jupp, G. A. R. Kon, and E. H. Lockton, *J. Chem. Soc.,* 1639 (1928).
(4) Y. L. Chow, *Tetrahedron Lett.,* 1337 (1964).

Our investigation of compound B began with a spectral examination. The nmr spectrum of compound B displayed singlets at 1.20 and 1.23 ppm accounting for a *gem*-dimethyl group, a singlet vinyl methyl resonance at 1.90 ppm, a triplet and quartet at 1.28 and 4.11 ppm (J = 7 cps) for $-OCH_2CH_3$, and, most significantly, four protons were accounted for in the region (1.9–2.10 ppm) characteristic of allylic hydrogens. The infrared (5.82 and 6.12 μ) and ultraviolet spectra [λ_{max} 212 and 272 mμ (ϵ 2140 and 1480)] were less informative, but are consistent with what might be expected for a carbethoxypyran.[5] The ultraviolet maximum at 272 mμ offers a strong argument against the simple conjugated ester found in Chow's formulation II.

The mass spectrum of compound B showed abundant ions at *m/e* 249, 221, 219 and 203 in the high mass region. The P − 15 ion at *m/e* 249 (37% total abundance) completely dominates the spectrum and provides strong support for structure II and its fragmentation to the very stable pyrylium ion pictured in Scheme II.[6]

SCHEME II

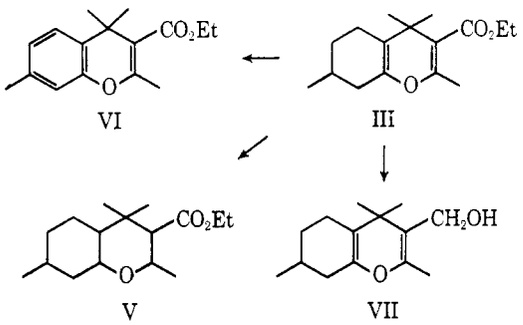


Our experience with a variety of bicyclic ketones[7] would predict that the carbonyl group in compound II would direct its fragmentation and lead to many ions of lower mass.

Compound B displays a plain positive rotatory dispersion curve which confirms the absence of a ketone group. In addition, catalytic hydrogenation gave a tetrahydro derivative, V (parent ion at *m/e* 268), rather than a dihydro derivative as reported by Chow[4] and demonstrates the presence of two carbon–carbon double bonds.

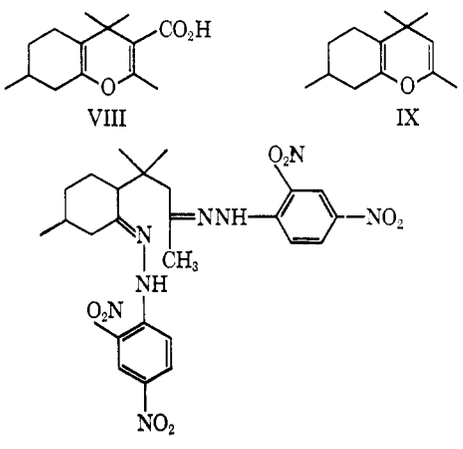
Dehydrogenation of compound B with chloranil gave the benzopyran VI whose infrared spectrum, except for new aromatic peaks, was remarkably similar to that of compound B, suggesting that a minor structural change had occurred during dehydrogenation. The mass spectral fragmentation of compound VI was also very similar to that of compound B. The formation of an aromatic ring under conditions involving minimal structural change provides another definitive argument against Chow's structure II.

Lithium aluminum hydride reduction of III (compound B) gave alcohol VII which displayed infrared



absorption at 5.83 and 6.0 μ. Chow[4] mistook the peak at 5.83 μ for a carbonyl stretching band. The intensity of this peak is too weak to be attributed to a carbonyl group. Doublet absorption at 5.93 and 6.1 μ is characteristic of γ-pyrans[8] and a shift to 5.83 and 6.0 μ would not be unreasonable for a γ-pyran carrying additional substituents at the 3 and 5 positions.

Chow[4] reported the oxidation of alcohol VII to an acid which we now reformulate as VIII. Decarboxylation of this acid gave an olefin which afforded a 2:1 adduct with 2,4-dinitrophenylhydrazine. The olefin and bis-2,4-DNP derivative are now assigned structures IX and X.



Finally, we comment on the reaction of pyran III with 2,4-dinitrophenylhydrazine which affords a 1:1 adduct which still retains the carbethoxy group (CH_3CH_2O– nmr signals) and is not a hydrazide deriva-

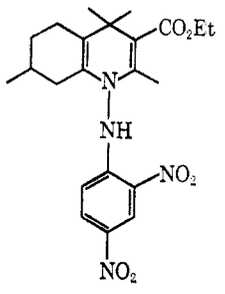
(5) The closest models for an infrared comparison are 3-carbethoxy-5,6-dihydropyrans which show absorption at 1722 and 1660 cm^{-1}; *cf.* loganin, genepin, and related glycosides [K. Sheth, E. Ramstad, and J. Wolinsky, *Tetrahedron Lett.*, 394 (1961); C. Djerassi, T. Nakano, A. N. James, L. H. Zalkow, E. J. Eisenbraun, and J. H. Shoolery, *J. Org. Chem.*, **26**, 1192 (1961)]. Ethyl-3,5-diformyl-4H-pyran [E. Winterfeldt, *Chem. Ber.*, **97**, 1959 (1964)] exhibits λ_{max} 290 mμ (ϵ 5200).

(6) The McLafferty rearrangements shown in Scheme II are documented by strong metastable ions at *m/e* 196 (249 → 221), 187 (221 → 203), and 166 (249 → 203). These fragmentations provide a strong argument against the necessity of an unpaired electron as a major driving force for the site-specific rearrangement of hydrogen to the carbonyl group in mass spectral reactions [F. W. McLafferty and T. Wachs, *J. Amer. Chem. Soc.*, **89**, 5043 (1967)]. *Cf.* M. Kraft and G. Spiteller, *Chem. Commun.*, 943 (1967), for a similar conclusion.

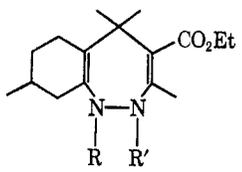
(7) D. R. Dimmel and J. Wolinsky, *J. Org. Chem.*, **32**, 2735 (1967).

(8) M. J. Jorgenson, *J. Org. Chem.*, **27**, 3224 (1962); S. Masamune, *J. Amer. Chem. Soc.*, **84**, 2452 (1962); H. W. Whitlock and N. A. Carlson, *Tetrahedron*, **20**, 2101 (1964).

tive as claimed by Chow.[4] The unique spectral properties of this derivative suggest it has the constitution represented by the dihydropyridine structure XI.

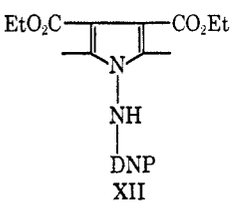


XI



XIII, R = H; R′ = 2, 4-$(NO_2)_2C_6H_3N$-
XIV, R = 2, 4-$(NO_2)_2C_6H_3$; R′ = H

XI exhibits ultraviolet maxima at 256 and 326 mμ which clearly eliminates the possibility that it is the mono-2,4-dinitrophenylhydrazone of diketo ester IV, since 2,4-DNP derivatives of saturated and unsaturated carbonyl compounds display maxima between 348 and 390 mμ.[9,10] On the other hand, the ultraviolet spectrum of XI is nearly identical with the spectra of acyl 2,4-dinitrophenylhydrazides[11] and the pyrrole XII,[12] and it is reasonable to conclude that absorption between 320 and 330 mμ characterizes ArNHN(C=X)- (Ar = 2,4-DNP) systems.



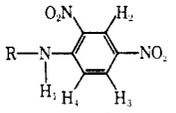
XII

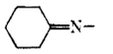
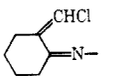
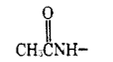
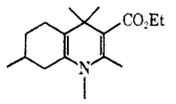
The high-field region of the nmr spectrum of XI is essentially identical with that of pyran III. The aromatic region, however, is quite distinct from that of an ordinary 2,4-DNP derivative as seen in Table I. The NH and C-4 protons are shifted upfield from their normal positions in 2,4-DNP derivatives of aldehydes and ketones, which suggests another method of distinguishing between ArNHN(C=X)- and ArNHN=C< systems.

It is conceivable that the 2,4-DNP derivative of III might be represented alternatively by XIII or XIV. These structures are rejected on the basis that the mass spectrum of the 2,4-DPN derivative displays abundant ions at 262 and 247 (100% relative abundance) attributed to loss of 2,4-DNP–NH[13] and 2,4-DNP–NH plus methyl. Furthermore, the ultraviolet spectrum of the 2,4-DNP derivative undergoes a pronounced bathochromic shift in alkaline solution consistent with the removal of the NH proton in XI and the production of a resonance stabilized anion. Removal of the NH proton in XIII or XIV cannot account for this shift.[14,15]

TABLE I

NMR SPECTRA OF 2,4-DINITROPHENYLHYDRAZINE DERIVATIVES

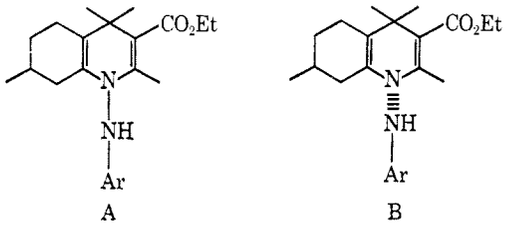


R	Registry no.	H_1	H_2[b]	H_3[c]	H_4
	1589-62-4	11.2	9.1	8.32	7.94
$CH_3CH_2CH{=}N-$[a]		11.13	9.03	8.20	7.88
	3100-86-5	11.3	9.1	8.4	8.04
	2719-07-5	10.36	9.02	8.46	7.4
		9.54	9.02	8.44	7.44

[a] G. J. Karabatsos, B. L. Shapiro, F. M. Vane, J. S. Fleming, and J. S. Ratka, *J. Amer. Chem. Soc.*, **85**, 2784 (1963). [b] $J_{2,3}$ = 2.0 cps. [c] $J_{3,4}$ = 9.6–10.0 cps.

The nmr spectrum of XI revealed certain features which are worthy of further consideration. Whereas the $-OCH_2CH_3$ protons appeared as a sharply defined quartet and the H_2 and H_3 aromatic protons were observed as a sharp doublet and a doublet of doublets, the NH resonance was composed of two signals separated by 9 Hz, the aromatic H_4 proton showed four signals instead of the usual two, and the vinyl methyl appeared as a doublet instead of the expected singlet. Long-range spin coupling was eliminated as an explanation for this phenomenon by deuterium-exchange experiments. The NH signals slowly disappeared when a deuteriochloroform solution of XI was stirred with deuterium oxide, but the four-line pattern for H_4 was unaltered. The two signal resonance for the vinyl methyl was not immediately altered, but eventually was reduced in intensity and after 6 days disappeared. Mass spectral analysis of the exchanged derivative indicated as many as six deuterium atoms had been incorporated, suggesting the exchange of two allylic protons as well as the vinyl methyl and NH protons. Stirring a deuteriochloroform solution of deuterated XI with water reversed the process. In this instance the two NH signals appeared very rapidly, whereas complete exchange of the vinyl methyl took *ca.* 9 days. XI could not be broken down into more than one component by crystallization or chromatography, leading to the conclusion that it was composed of a mixture of stable conformers resulting either from restricted rotation[16] about the N–NH bond or from slow inversion[17]

(9) L. A. Jones, J. C. Holmes, and R. B. Seligman, *Anal. Chem.*, **28**, 191 (1956).
(10) C. J. Timmons, *J. Chem. Soc.*, 2613 (1957).
(11) A. C. Thompson and P. A. Hedin, *J. Chromatogr.*, **21**, 13 (1966).
(12) T. D. Binns and R. Brelle, *J. Chem. Soc., C*, 341 (1966).
(13) *Cf.* D. Goldsmith and C. Djerassi, *J. Org. Chem.*, **31**, 3661 (1966), for the observation of an analogous fragmentation of an $N-N(CH_3)_2$ bond in dimethylhydrazone derivatives on electron impact.
(14) G. A. Fleischer and E. C. Kendall, *ibid.*, **16**, 556 (1951); H. Reich and L. Hefle, *ibid.*, **21**, 708 (1956).
(15) F. Bohlmann, *Chem. Ber.*, **84**, 490 (1951); L. A. Jones and N. L. Mueller, *J. Org. Chem.*, **27**, 2356 (1962).
(16) B. H. Korsch and N. V. Riggs, *Tetrahedron Lett.*, 5897 (1966); Y. Shvo, E. C. Taylor, K. Mislow, and M. Raban, *J. Amer. Chem. Soc.*, **89**, 4910 (1967).
(17) A. Loewenstein, G. F. Nevmar, and J. D. Roberts, *J. Amer. Chem. Soc.*, **82**, 3599 (1960); S. G. Brois, *ibid.*, **89**, 4242 (1967); W. N. Speckamp, U. K. Dandit, and H. O. Husiman, *Tetrahedron*, **22**, 2413 (1966).



of the dihydropyridine nitrogen atom giving rise to diastereoisomers A and B.

A temperature dependence study of the nmr of XI demonstrated that NH and vinyl methyl signals collapsed to singlets at 90–100°, but the four-line aromatic H_4 pattern remained unchanged even at 130°. The 2,4-DNP XI was not stable at higher temperature. Attempts to prepare the *p*-nitrophenylhydrazone analog of XI have not met with success and it is not yet certain whether hindered rotation or slow inversion accounts for the properties of XI.

Experimental Section[18]

Reaction of Pulegone with Ethyl Acetoacetate to Give Pyran III.—A mixture of 84 g (0.553 mol) of pulegone and 84.9 g (0.653 mol) of ethyl acetoacetate was added dropwise over a 2-hr period to a vigorously stirred solution of 35.6 g (0.261 mol) of fused zinc chloride in 93 g of acetic acid and 104 g of acetic anhydride. The resulting solution was kept at room temperature for 9 days and was then added to water and extracted with ether. The ether extracts were washed with water, 5% sodium bicarbonate, and saturated salt solution. The ether was dried over anhydrous magnesium sulfate and removed under diminished pressure. Distillation afforded, after a forerun of starting materials, 40.6 g of a liquid, bp 84–103° (0.40 mm), and *ca.* 50 g of undistillable tar. The liquid was chromatographed on an acid-washed alumina column and the fraction eluting with 5% ether in pentane was recrystallized from pentane to give 13.4 g of III: mp 37–38°; ir (Nujol) 5.83 and 6.12 μ; λ_{max}^{EtOH} 212 mμ (ϵ 2140) and 272 (1480); nmr ($CDCl_3$) δ 0.98 (d, 3, $-CHCH_3$), 1.20 and 1.23 (s, 6, $>C(CH_3)_2$), 1.28 (t, 3, $-OCH_2CH_3$), 1.90 (s, 3, $-C{=}CCH_3$), and 4.11 ppm (q, 2, $-OCH_2CH_3$); $[\alpha]^{MeOH}D$ +47.6°; the ORD displayed a plain positive curve, $[\alpha]$ ($cm^{-1} \times 10^{-3}$) 49 (18), 129 (26, 362 (36), and 651° (44); the mass spectrum showed abundant ions at *m/e* 249 (100%), 221 (19%), 219 (9%), and 203 (6%) [lit. mp 37–39°; ir 1712 and 1635 cm^{-1}; λ_{max} 206 mμ (ϵ 5900) and 272 (2500), $[\alpha]D$ +47.8°].[4]

Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.73; H, 9.15. Found: C, 72.91; H, 9.32.

When pulegone, ethyl acetoacetate, and zinc chloride were heated at 90–95° for 2 hr, there was obtained two fractions, bp 70–113° (1.0 mm) and 125–150° (1.5 mm). The first fraction was largely pulegone acetone. Chromatography of the second fraction gave *ca.* 2.0 g of pyran III.

The methyl ester of III was prepared in an identical fashion employing 62.5 g of methyl acetoacetate and 108.0 g of pulegone. The fraction boiling at 86–146° (0.5 mm) was chromatographed on an alumina column to give 19 g of the liquid methyl ester. An analytical sample was obtained by vpc using a DEGS column at 190°. The spectral properties of the methyl ester were almost identical with those of III except for the absence of ethoxyl nmr resonance signals and the appearance of a methoxyl signal at 3.68 ppm. The mass spectrum displayed abundant ions at *m/e* 250 (2%), 219 (7%), 235 (100%), and 203 (55%).

Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.68; H, 9.07.

2,4-Dinitrophenylhydrazine Derivative of III.—A solution of 1.02 g of III in 10 ml of ethanol was added to a solution of 0.86 g of 2,4-dinitrophenylhydrazine and 5 ml of concentrated sulfuric acid in 30 ml of 65% aqueous ethanol. A solid immediately formed which dissolved on addition of 5 ml of ethanol. On standing overnight an orange solid was obtained. Recrystallization from 3:1 ethyl acetate:ethanol gave dark wine-colored crystals: mp 168–170.5°, ir 5.9 μ; λ_{max}^{MeOH} 215 mμ (log ϵ 4.13), 256 (3.92), and 326 (4.17); $\lambda_{max}^{0.1\ M\ NaOH}$ 222 mμ (log ϵ 3.96), 404 (4.05), and 460 (3.87) [lit. mp 178–181°; λ_{max} 326 mμ (log 4.24)].[4] The mass spectrum showed abundant ions at *m/e* 444 (4%), 429 (72%), 248 (84%), 247 (94%), 232 (22%), 220 (37%), 218 (44%), 202 (100%), 201 (75%).

Anal. Calcd for $C_{22}H_{28}N_4O_6$: C, 59.45; H, 6.35; N, 12.60. Found: C, 59.38; H, 6.43; N, 12.61.

The 2,4-DNP derivative of the corresponding methyl ester of III showed mp 171.5–172.5°.

Hydrogenation of Pyran III.—A solution of 126 mg of III in 2.5 ml of acetic acid was hydrogenated for 18 hr at atmospheric pressure using platinum oxide as catalyst. The platinum was removed by filtration and the solvent by distillation under reduced pressure. The residue was purified by vpc on a 10-ft DEGS column at 142° and the pure tetrahydropyran derivative was obtained as a colorless oil: ν_{max} 5.75 μ, showing important ions at *m/e* 268 (25%), 253 (11), 251 (17), 224 (20), 223 (27), 209 (76), 154 (65), 151 (63), 138 (52), 137 (50), 129 (75), 95 (87), 83 (83), 81 (89), 69 (95), 43 (76), and 41 (100%). Overlapping multiplets in the nmr region between 3.2–4.2 ppm accounted for four CHO-type protons. The large number of methyl resonances between 0.82 and 1.25 ppm suggested the tetrahydro derivative was a mixture of stereoisomers.

Anal. Calcd for $C_{15}H_{28}O_3$: C, 71.64; H, 10.45. Found: C, 71.92; H, 10.57.

Dehydrogenation of Pyran III.—A solution of 1.04 g (3.94 mmol) of III and 1.98 g (7.74 mmol) of chloroanil in 30 ml of *o*-xylene was heated at reflux for 2 days under a nitrogen atmosphere. The xylene was removed and pentane was added. A brown solid was removed by filtration and the filtrate was concentrated and chromatographed on an acid-washed alumina column. The fraction eluting with 5% ether–pentane was shown by nmr to be a mixture of III and the aromatic derivative VI. The two pyrans were separated by vpc using a 10-ft DEGS column at 170°. Benzopyran VI was a colorless liquid: ir 5.80 and 6.10 μ; λ_{max}^{MeOH} 215 mμ (log ϵ 3.68) and 258 (3.20); nmr (CCl_4) 6.9 (m, 3, aromatic H), 4.81 (q, 2, $-OCH_2CH_3$), 2.25 (s, 3, $ArCH_3$), 2.07 (s, 3, $C{=}CCH_3$), 1.48 (s, 6, $>C(CH_3)_2$), and 1.30 ppm (t, 3, $-OCH_2CH_3$). The mass spectrum exhibited abundant ions at *m/e* 260 (1%), 215 (15%), 245 (100%), 217 (16%), and 199 (6%).

Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 73.87; H, 7.95.

Lithium Aluminum Hydride Reduction of III.—A solution of 1.90 g (7.2 mmol) of III in 20 ml of ether was added to a suspension of 0.25 g (6.6 mmol) of lithium aluminum hydride in 20 ml of ether under a nitrogen atmosphere. After heating at reflux for 20 min, saturated ammonium chloride solution was added to the cooled solution. The mixture was filtered and the filtrate distilled to give 1.1 g of an oil which slowly solidified. Sublimation *in vacuo* gave a colorless solid: mp 68–70°; ir 3.05 μ, 5.83 (m) and 6.00 (w); λ_{max}^{MeOH} 240 mμ (sh) (ϵ 2110); nmr (CCl_4) 4.00 (s, 2, $-CH_2O$), 1.83 (s, 3, $C{=}CCH_3$), 1.10 (s, 6, $>C(CH_3)_2$) and 0.98 ppm (d, 3, J = 5 Hz, $>CHCH_3$). The mass spectrum displayed major peaks at *m/e* 222 (1%), 207 (2%), 204 (14%), 189 (100%), and 43 (22%) [lit. mp 80–82.5°;[4] ir 3640, 1710, and 1665 cm^{-1}].

Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 74.75; H, 10.15.

Oxidation of Alcohol VII to Acid VIII.—To the cooled chromium trioxide–pyridine complex, prepared by adding 1.55 g (0.0155 mol) of chromium trioxide to 20 ml of pyridine,[19] was added 1.1 g (0.0049 mol) of alcohol VII in 20 ml of pyridine. The resulting mixture was allowed to stir at 0° for 15 min and was

(18) All boiling and melting points are uncorrected. Infrared spectra were measured with Perkin-Elmer Model 221 and 137-B spectrometers. Nmr spectra were determined at 60 Mc with a Varian Associates A-60 spectrometer. Chemical shifts were measured with reference to tetramethylsilane as an internal reference. The mass spectra were measured with a Hitachi RMU-6D mass spectrometer, using an all-glass inlet system heated at 180°, a source temperature of 155°, an ionizing current of 52 μA, and an ionization energy of 75 eV. Ultraviolet spectra were determined with a Bausch and Lomb spectronic 505. The microanalyses were performed by Dr. C. S. Yeh and associates.

(19) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Amer. Chem. Soc.*, **75**, 422 (1953).

then kept at room temperature for 24 hr. The mixture was added to 100 ml of water and extracted with ether. The ether extracts were washed with 10% hydrochloric acid, water, and saturated salt solution. The ether solution was dried over anhydrous magnesium sulfate and the ether was evaporated to give 1.1 g of pyran aldehyde, ir 5.8, 6.0 and 6.2 μ, which was used directly in the next step.

The crude aldehyde was stirred in an open flask for *ca.* 40 hr. The mixture was dissolved in ether, and the ether solution was extracted with sodium bicarbonate solution. The basic extract was acidified with 5% hydrochloric acid and extracted with ether. The ether was removed to leave 0.57 g (48%) of crude acid, which was recrystallized from chloroform: mp 199–200°; ir 5.8 μ (s), 6.0 (m), 6.15 (m), and 6.25 (m); nmr (dilute solution $CDCl_3$) 2.22 (s, 3, C=CCH_3), 1.43 (s, 6, >$C(CH_3)_2$) and 1.08 ppm (d, 3, >$CHCH_3$). The mass spectrum displayed important ions at *m/e* 236 (2%), 221 (100%), 203 (3%), 43 (13%).

Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 70.44; H, 8.37.

A suspension of 100 mg of acid VIII in ether was treated with an ethereal solution of diazomethane. The solvent was evaporated affording an oil whose infrared spectrum was identical with that of the methyl ester of III.

Pyran IX.—A mixture of 0.4 g of acid VIII and 0.4 g of copper powder was heated at 220–300° resulting in the distillation of 0.2 g of liquid: ir 5.8 μ (m) and 6.0 (w); λ_{max}^{MeOH} 211 mμ (log ϵ 3.30) and 2.29 (sh) (3.14); nmr (CCl_4) δ 4.27 (q, 1, J = 1 Hz, =CH), 1.70 (d, 3, J = 1 Hz, *cis*-CH_3C=CH), 1.05 (s, 6, >$C(CH_3)_2$), and 1.02 ppm (d, 3, >$CHCH_3$). The mass spectrum exhibited important ions at *m/e* 192 (4%), 177 (100%), 135 (9%), 43 (11%).

Anal. Calcd for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 81.42; H, 10.55.

Registry No.—Pulegone, 15932-80-6; ethyl acetoacetate, 141-97-9; III, 18600-02-7; III (methyl ester), 18588-64-2; XI (methyl ester), 18588-65-5; reduction product of III, 18588-66-4; VI, 18588-67-5; VIII, 18588-68-6; IX, 18588-69-7; XI, 18588-73-3.

The Synthesis of Some Fluoronitrobenzimidazoles and Their Reactivities toward Peptide Nucleophiles

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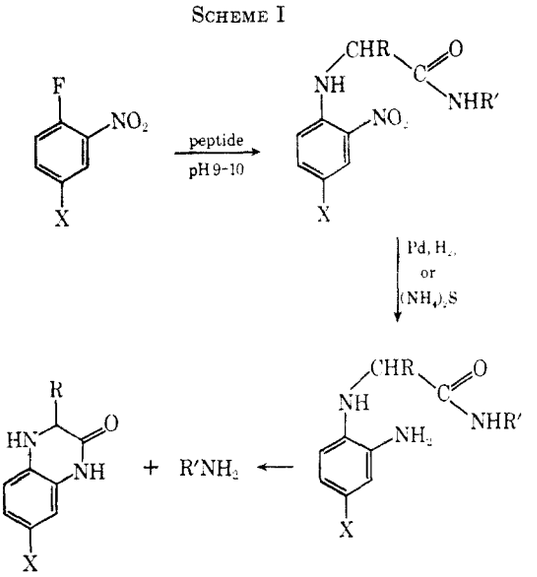
A series of mononitro- and dinitro-4-fluorobenzimidazoles has been prepared using 2-fluoroacetanilide as starting point. Assignment of position to the nitro groups is based on analyses of nmr hydrogen–fluorine coupling constants. Orientation in nitration is controlled by the fluorine atom rather than by the fused imidazole ring, except where steric factors intercede. At 25°, 5,7-dinitro-4-fluorobenzimidazole is 84 times as reactive as 2,4-dinitrofluorobenzene toward a peptide nucleophile. The enhanced reactivity is attributed primarily to the ability of the fused imidazole ring to participate in stabilization of the Meisenheimer adduct. The corresponding benzimidazole anion, as well as a series of mononitrofluorobenzimidazoles, are unreactive under the same conditions.

A series of investigations in this laboratory on the tertiary structure of proteins[1] created a need for methods for the quantitative determination of N-terminal amino acids in mixtures of polypeptides. Since neither the fluorodinitrobenzene[2] nor the phenyl isothiocyanate[2] method satisfactorily fulfilled our needs for quantitation, efforts were initiated several years ago to develop an alternative procedure.

Of the various possibilities considered, the approach first described by Holley and Holley[3] seemed attractive, primarily by virtue of the mild conditions under which peptide cleavage could be effected. In this method, the peptide is coupled with 1-fluoro-2-nitro-4-X-benzene, in which X = nitro or another electronegative, fluorine-activating substituent. The 2-nitro group of the peptide derivative is subsequently reduced, either catalytically[3] or with sulfide ion,[4] to provide an amino group as a favorably placed nucleophile for intramolecular attack on the amide bond of the N-terminal residue (Scheme I).

SCHEME I



It is obvious that the availability of a reagent with a preexisting nucleophile at position 2 would simplify

(1) L. Farber and L. A. Cohen, *Biochemistry*, **5**, 1027 (1966); J. G. Wilson and L. A. Cohen, *J. Amer. Chem. Soc.*, **85**, 564 (1963); S. Isoe and L. A. Cohen, *Arch. Biochem. Biophys.*, **127**, 522 (1968).

(2) J. L. Bailey, "Techniques in Protein Chemistry," Elsevier Publishing Co., New York, N. Y., 1962, Chapter 6.

(3) R. W. Holley and A. D. Holley, *J. Amer. Chem. Soc.*, **74**, 5445 (1962).

(4) E. Scoffone, E. Vianello, and A. Lorenzini, *Gazz. Chim. Ital.*, **87**, 354 (1957).