slow addition of hydrochloric acid. The phenylacetamide was recrystallized from hot water and melted at 156.5–157.5°. There was obtained 80% of the theoretical amount. The phenylacetic acid was recrystallized from petrol ether and melted at 76.5–77.5°, the yield amounting to 2% of theoretical. The identical procedure was followed using acetophenone-(carbonyl)-C^{14}.

Conversion of Phenylacetic Acid from Willgerodt Reaction to Phenylacetamide.—Phenylacetic acid (100 mg.) was refluxed with 1 ml. of thionyl chloride in a microdistillation flask fitted with a reflux condenser. After ten minutes the mixture was cooled and the excess thionyl chloride, with some hydrogen chloride, was taken off under vacuum. The crude acid chloride was dissolved in 1 ml. of absolute ether and added dropwise to 5 ml. of cold concentrated ammonia. Evaporation of the ether gave crystalline phenylacetamide. To obtain the best possible yield the ammoniacal solution was evaporated to dryness and the crude amide recrystallized from hot water. Phenylacetamide obtained in this way melted at 156.7–157.5°. (The yield was 75% based on phenylacetic acid.)

Hofmann Degradation of Phenylacetamide.—Pure phenylacetamide (45 mg., 0.33 millimole) was suspended in 6.0 ml. of 0.18 molar barium hydroxide and bromide (0.67 millimole) was added to the flask by means of a lambda pipet. The receiver flask was then attached to an apparatus which contained a three-way stopcock permitting evacuation and sealing of the receiving flask. Before evacuation, however, the contents were frozen with liquid nitrogen to prevent loss of bromine. After the evacuation and sealing the flask was allowed to warm to room temperature and was shaken until all the amide dissolved in the barium hypobromite. The degradation reaction started at 70° (hot water-bath) as shown by precipitation of barium carbonate and was complete in three or four minutes. Coagulation of the precipitate was effected by immersing the flask in boiling water for an additional minute. After cooling the flask the vacuum was released by means of the stopcock. The precipitate was separated on a suction funnel and washed with two or three portions of water to remove as much benzylamine as possible.

The barium carbonate still contained traces of amine and cyanide and was reprecipitated before counting. The precipitate was therefore dissolved with concentrated sulfuric acid in an assay apparatus and the evolved carbon dioxide was collected in barium hydroxide solution.

The alkaline barium carbonate-free filtrate with washings was then slowly distilled in a microdistillation apparatus with an indented column. The oily benzylamine distilled with the first few milliliters of water. Addition of two drops of concentrated hydrochloric acid to the distillate converted the amine to its hydrochloride. To obtain the dry salt the solution was evaporated to dryness *in vacuo*. Before the benzylamine hydrochloride was oxidized it was recrystallized from butanol and melted at 256°. The yield of barium carbonate was quantitative based on phenylacetamide, while the yield of amine was 70–80% of the theoretical amount.

Decarboxylation of Phenylacetic Acid.—Phenylacetic acid (50 mg.) and 50 mg. of copper chromite catalyst were placed in a small flask fitted with a reflux condenser and a gas inlet tube. Purified quinoline (5 ml.) was added and the mixture was flushed for 20 minutes with "prepurified" nitrogen. The mixture was then heated in a sand-bath at 230° for 30 minutes with nitrogen being passed in continuously and the evolved carbon dioxide was passed with the nitrogen stream through the top of the condenser into a barium hydroxide bubbler. The reaction mixture was allowed to cool while the apparatus was flushed with nitrogen for an additional ten minutes. In order to remove traces of quinoline, the barium carbonate was dissolved in concentrated sulfuric acid and the evolved carbon dioxide reprecipitated from barium hydroxide solution, as in the treatment of the barium carbonate resulting from the Hofmann degradation of phenylacetamide. Yields of barium carbonate were 40–80% based on phenylacetic acid.

Acknowledgments.—Our thanks are due to Dr. R. W. Dodson for making available the facilities of the Brookhaven Chemistry Department and to Dr. R. B. Loftfield for valuable suggestions in the work. We are also grateful to Mr. H. C. Prosser of Brookhaven for the preparation of the methyl iodide-C^{14}.

NEW YORK, N. Y.
UPTON, N. Y. RECEIVED DECEMBER 16, 1950

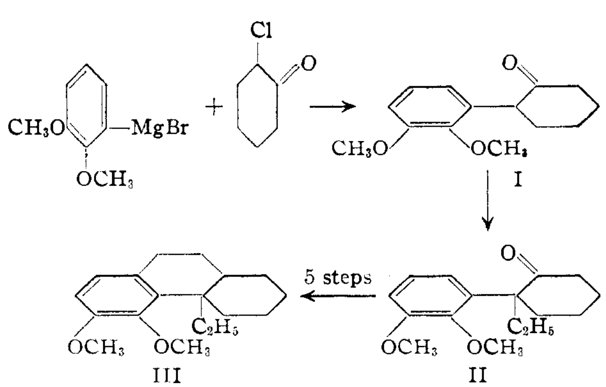
[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE OHIO STATE UNIVERSITY]

Attempted Synthesis of a Morphine Degradation Product

BY MELVIN S. NEWMAN AND WILLIAM L. MOSBY[1]

The synthesis of 2-ethyl-2-(2,3-dimethoxyphenyl)-cyclohexanone is described. This ketone is extremely unreactive as it fails to react with any of the usual carbonyl group reagents including Grignard reagents. It is reduced by lithium aluminum hydride.

In this paper are described our efforts to prepare 5,6 - dimethoxy - 4a - ethyl - 1,2,3,4,5a,9,10,10a-octahydrophenanthrene (III) a compound which, it was hoped, would provide a meeting place for synthetic and degradative operations designed to remove the last doubt concerning the structure of morphine.[2] Recent synthetic work has removed the uncertainty regarding the location of the ethaneamine side chain.[2a] The proposed synthesis is obtained briefly in the chart.



Although we have not succeeded in synthesizing III, we have made a number of observations of interest. The preparation of I as indicated[3] failed when we were unable to prepare a Grignard or organolithium reagent from 3-bromo- or 3-iodo-

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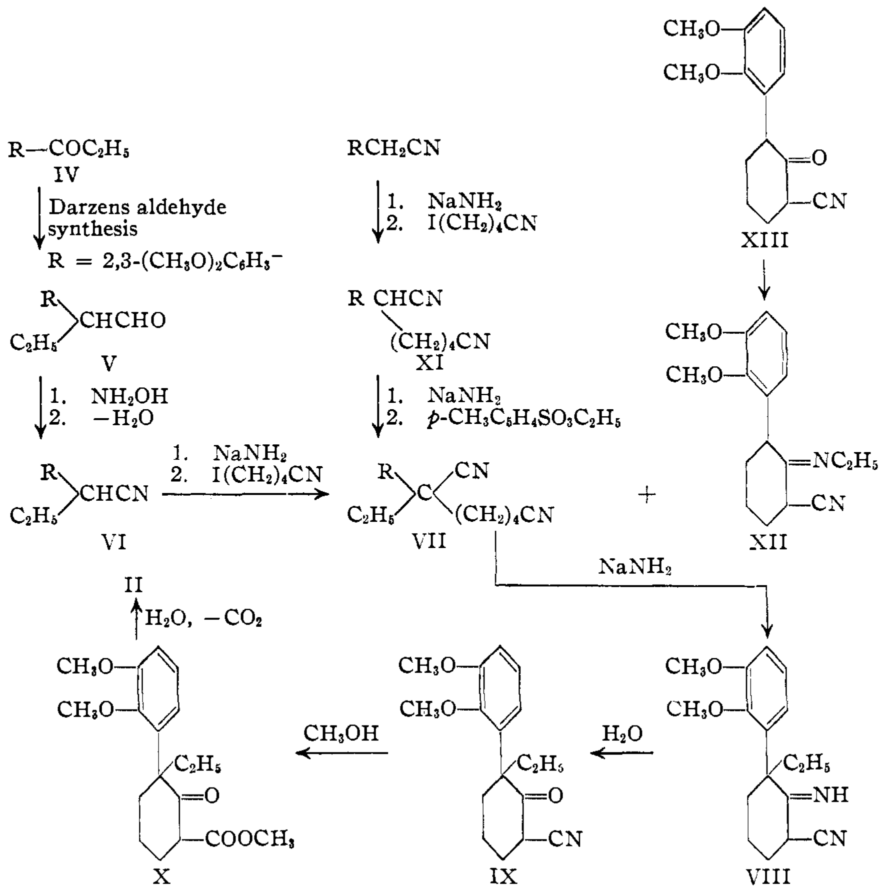
[1] Taken from the Ph.D. thesis of W. L. M., 1949. General Aniline and Film Corp., Easton, Pennsylvania.

[2] A compound, supposedly III, has been synthesized by R. Ghosh and R. Robinson, *J. Chem. Soc.*, 506 (1944). It was an oil and of unproven composition inasmuch as it might have been a mixture of stereoisomers of III and also might have had another structure.

[2a] R. Grewe, A. Mondon and E. Nolte, *Ann.*, **564**, 161 (1949); M. Gates and G. Tschudi, THIS JOURNAL, **72**, 4839 (1950); O. Schnider and J. Hellerbach, *Helv. Chim. Acta*, **33**, 1438 (1950).

[3] Compare M. S. Newman and M. Farbman, THIS JOURNAL, **66**, 1550 (1944).



veratrole. A literature survey revealed no case where a 3-haloveratrole has been converted into a Grignard reagent although such reagents have been prepared from 1,4-dimethoxy-,[4] 2,4-dimethoxy-[5] and 3,4-dimethoxy-halo-benzenes.[6] No 3,5-methoxyhalobenzene has been described and one failure to form a Grignard reagent using 2,6-dimethoxyiodobenzene is recorded.[7] The preparation of 2,3-dimethoxyphenyllithium by direct metallation of veratrole[8] has been accomplished.

The desired ketone, II, was finally obtained by cyclization of 2-ethyl-2-(2,3-dimethoxyphenyl)-pimelonitrile (VII) as shown in the chart. Once prepared, however, it proved to be so unreactive that no useful synthetic operation could be found by which to proceed. It not only failed to give any of the usual carbonyl derivatives but also proved resistant to the action of methylmagnesium iodide, giving neither addition nor enolization reactions. We were able to effect reduction by means of lithium aluminum hydride as judged by a change in the infrared absorption spectrum.[9]

Acknowledgment.—This research was supported (in part) by a research grant from the National Institutes of Health, U. S. Public Health Service, Bethesda, Md.

Experimental[10]

2,3-Dimethoxyphenyl Ethyl Ketone (IV).—The Grignard reagent from 44 g. of ethyl bromide in 100 cc. of ether was treated with 75 g. of dry cadmium chloride and the mixture was refluxed until the color test[11] indicated that no Grignard reagent was present. A solution of 20 g. of 2,3-dimethoxybenzoyl chloride[12] in 50 cc. of dry ether was added dropwise with stirring. After one additional hour at reflux the mixture was hydrolyzed. The neutral fraction was separated into ketonic and non-ketonic fractions with Girard reagent P. The non-ketonic fraction, b.p. 102–104° at 0.7 mm., gave a positive color test with ceric nitrate[13] but we were unable to prepare a 3,5-dinitrobenzoate or a phenylurethan. The yield of this fraction was appreciable (about 40%) but its nature was not investigated further. The ketone fraction b.p. 99–101° at 0.7 mm., M^{26}D 1.5210, was obtained in 30% yield. On treating with 2,4-dinitrophenylhydrazine, a yellow, more soluble derivative,[14] m.p. 131–133°, and an orange derivative, m.p. 177.0–177.5°, were obtained.

Anal. Calcd. for $C_{17}H_{18}O_6N_4$: C, 54.5; H, 4.8; N, 15.0. Found^c: C, 54.7; H, 4.8; N, 14.7.

The semicarbazone, m.p. 181–182°, also was made.

Anal. Calcd. for $C_{12}H_{17}O_3N_3$: C, 57.4; H, 6.8; N, 16.7. Found^c: C, 57.6; H, 6.9; N, 16.7.

An unsuccessful attempt to prepare this ketone by treating the diethylamide of 2,3-dimethoxybenzoic acid with ethylmagnesium bromide[15] at room temperature was made, the amide being recovered. The diethylamide, a colorless oil, b.p. 132–135° at 0.7 mm., n^{23}D 1.5240, was prepared in 88% yield from the acid chloride and diethylamine.

Anal. Calcd. for $C_{13}H_{19}O_3N$: C, 65.8; H, 8.0; N, 8.9. Found^c: C, 65.6; H, 7.8; N, 5.9.

α-(2,3-Dimethoxyphenyl)-butyraldehyde, V.—To a solution of 64.7 g. (0.38 mole) of IV, 45.0 g. (0.40 mole) of ethyl chloroacetate, and 200 cc. of petroleum ether, b.p. 65–70° (Skellysolve B) was added 2 g. of sodium hydride and a few lead shot. The mixture was stirred at 35° until a steady evolution of hydrogen started (about 5 hours). Then an additional 8 g. of sodium hydride was added in portions so as to maintain the temperature near 35°. After stirring at room temperature until the evolution of hydrogen practically ceased (15 hours) the reaction mixture was poured on an

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[4] H. Kauffmann and I. Fritz, *Ber.*, **41**, 4416 (1908).

[5] H. Kauffmann and F. Kieser, *ibid.*, **45**, 2333 (1912); G. Potter, THIS JOURNAL, **48**, 3128 (1926).

[6] V. Grignard, *Compt. rend.*, **193**, 625, 2217 (1934); R. Willstatter, L. Zechmeister and W. Kindler, *Ber.*, **57**, 1938 (1924).

[7] H. Kauffman and W. Franck, *ibid.*, **40**, 4015 (1917).

[8] H. Gilman, J. Swiss and L. C. Cheney, THIS JOURNAL, **62**, 1963 (1940); E. D. Bergmann, R. Pappo and D. Ginsburg, *J. Chem. Soc.*, 1369 (1950), have reported the synthesis of I using this lithium compound.

[9] We are indebted to Mrs. Arlene Brooks, Dr. C. L. Wilson and Dr. B. Wildi for the infrared absorption spectra and aid in their interpretation.

[10] All melting points were taken by observing the melting through a magnifying glass when the crystals were electrically heated between two soft glass slides (Fisher–Johns melting point apparatus). Analyses marked ^{c} by Clark Microanalytical Laboratories, Urbana, Illinois, ^{k} by Mrs. E. Klotz, O.S.U.; and ^{p} by the microanalytical laboratory at the University of Pittsburgh.

[11] H. Gilman and K. Schultz, THIS JOURNAL, **47**, 2002 (1926).

[12] We wish to thank the Monsanto Chemical Co., for the gift of a generous sample of 2,3-dimethoxybenzaldehyde from which this acid chloride was made.

[13] F. R. Duke and G. F. Smith, *Ind. Eng. Chem., Anal. Ed.*, **12**, 201 (1940).

[14] H. Richzenbain, *Ber.*, **77**, 1 (1944), gives the m.p. as 134°.

[15] C. Beis, *Compt. rend.*, **137**, 575 (1903).

excess of dilute 5% sulfuric acid. On distillation there was obtained 69.5 g. of ethyl β-ethyl-β-(2,3-dimethoxyphenyl)-glycidate, b.p. 130–131° at 0.4 mm., $n^{25}\mathrm{D}$ 1.5040.

Anal. Calcd. for $C_{15}H_{20}O_5$: C, 64.3; H, 7.2. Found^k: C, 64.7, 64.5; H, 7.2, 7.3.

For hydrolysis a mixture of 17 g. of potassium hydroxide, 10 cc. of water, 100 cc. of alcohol and 50 g. of the glycidic ester was brought to reflux for one hour. The alcohol was removed under reduced pressure and the residue diluted with 75 cc. of water. After discarding three ether extracts of this solution and acidifying with concentrated hydrochloric acid the mixture was heated to reflux until carbon dioxide evolution ceased (74% after three hours). The aldehyde was extracted by ether and distilled to yield 25.6 g. (70%) of V, b.p. 101–103° at 0.3 mm., $n^{26}\mathrm{D}$ 1.5160. This material was used immediately in further steps. The semicarbazone m.p. 158–159°, was prepared.

Anal. Calcd. for $C_{13}H_{19}O_3N_3$: C, 58.9; H, 7.2; N, 15.7. Found^k: C, 58.2. 58.0; H, 6.9, 6.8; N, 15.8, 16.00.

α-(2,3-Dimethoxyphenyl)-butyronitrile (VI).—A mixture of 6.0 g. of hydroxylamine hydrochloride, 25 cc. of dry pyridine, 20 cc. of absolute alcohol and 5.5 g. of V was refluxed for three hours after the initial heat effect on mixing was dissipated. The oxime, b.p. 126–127° at 0.3 mm., $n^{25}\mathrm{D}$ 1.5362, was obtained as a pale yellow viscous liquid in 97% yield. This was converted into the nitrile,[16] VI, b.p. 96–97° at 0.2 mm., $n^{25}\mathrm{D}$ 1.5125, in 93% yield by heating with 10 cc. of acetic anhydride until the acetic acid formed had slowly distilled (about four hours).

Anal. Calcd. for $C_{16}H_{15}O_2N$: N, 6.8. Found^k: N, 6.6, 6.7.

2-(2,3-Dimethoxyphenyl)-2-ethylpimelonitrile (VII).[17]—To a suspension of the sodium amide prepared from 1.6 g. (0.07 mole) of sodium in 100 cc. of liquid ammonia was added 12.0 g. (0.058 mole) of VI. After stirring for one-half hour 100 cc. of toluene and 50 cc. of dry ether were added and the ammonia was allowed to evaporate overnight. A solution of 15.0 g (0.072 mole) of freshly rectified iodovaleronitrile (see below) in 50 cc. of ether was added slowly with stirring and the mixture was then brought to reflux for one-half hour. After hydrolysis with water there was obtained 12.6 g. (76%) of VII as a somewhat impure liquid, b.p. 173–180° at 0.2 mm., $n^{24}\mathrm{D}$ 1.5284. This nitrile, VII, b.p. 168–180° at 0.2 mm., $n^{26}\mathrm{D}$ 1.5290, was also formed in 56% yield by alkylating 2-(2,3-dimethoxyphenyl)-pimelonitrile (XI)[17a] with ethyl benzenesulfonate.

The δ-iodovaleronitrile used was prepared in 88% yield by adding 92 g. of δ-chlorovaleronitrile[17a] to a solution of 100 g. of sodium iodide in 500 cc. of acetone, stirring for three hours and standing for three days at about 25°. The iodonitrile was obtained as a pale yellow oil, b.p. 118–119° at 10 mm., m.p. −45.5 to −44.5°. Since it turns brown rapidly on exposure to air, no analyses were attempted but the compound used directly as prepared.

In the distillate from one preparation of VII involving the ethylation of XI, crystals separated on standing. These were removed and crystallized twice from ether. They melted at 102.5–103.0°, then solidified and remelted at 110–111.5°. Analysis permitted a structure for this compound of N-ethyl-2-cyano-2-(2,3-dimethoxyphenyl)-cyclohexanonimine (XII). This was made more probable by hydrolysis with aqueous alcoholic hydrochloric acid to 2-cyano-2-(2,3-dimethoxyphenyl)-cyclohexanone (XIII), m.p. 120.5–121.5°.

Anal. Calcd. for $C_{17}H_{22}O_2N_2$: C, 71.3; H, 7.7; N, 9.8. Found^o: C, 71.7, 71.7; H, 8.0, 7.9; N, 9.7, 9.9. Calcd. for $C_{15}H_{17}O_3N$: C, 69.5; H, 6.6; N, 5.4. Found^k: C, 69.4; H, 6.6; N, 5.4.

2-(2,3-Dimethoxyphenyl)-2-ethyl-6-cyanocyclohexanonimine (VIII).—To a suspension of sodium amide prepared in 500 cc. of liquid ammonia from 16 g. of sodium was added a solution of 182 g. (0.64 mole) of VII in 150 cc. of dry ether. After stirring for one-half hour, 150 cc. of benzene was added and the ammonia allowed to escape through a reflux condenser during 12 hours. The mixture was then refluxed for three hours and hydrolyzed by adding 500 cc. of cold water. The organic phase was washed with 5% sodium hydroxide, 2% acetic acid, saturated sodium bicarbonate, and was dried over magnesium sulfate. There was obtained 97 g. (53%) of pale yellow product, b.p. 160–165° at 0.08–0.1 mm., $n^{25}\mathrm{D}$ 1.5606, on distillation. After standing for many hours crystals appeared. On triturating with ether 32 g. (17%) of colorless solid was obtained. Three recrystallizations from ether yielded colorless crystals, m.p. 116–117°, of VIII. The non-crystalline residue was not further examined.

Anal. Calcd. for $C_{17}H_{22}O_2N_2$: C, 71.4; H, 7.7; N, 9.8. Found^p: C, 71.4, 71.4; H, 7.5, 7.5; N, 10.1, 10.0.

6-Cyano-2-(2,3-dimethoxyphenyl)-2-ethylcyclohexanone (IX).—A clear solution of 30 g. of VIII in 300 cc. of alcohol, 90 cc. of concentrated hydrochloric acid, and 90 cc. of water was refluxed for 90 minutes. After standing near 0° overnight the colorless crystals were collected, washed with cold 50% alcohol, and dried over phosphorus pentoxide *in vacuo*. On dilution of the mother liquor with 300 cc. of water and standing near 0° another drop (3.0 g.) of crystals was secured. The total yield of solid, m.p. 106–108°, was 29.8 g. (98%). A sample recrystallized from cyclohexane and from ether melted at 107.5–108.0°.

Anal. Calcd. for $C_{17}H_{21}O_3N$: C, 71.0; H, 7.3; N, 4.9. Found^p: C, 71.8; H, 7.5; N, 5.2.

6-Carbomethoxy-2-(2,3-dimethoxyphenyl)-2-ethylcyclohexanone (X).—A solution of 20 g. of IX in 200 cc. of methanol was saturated with hydrogen chloride at −60° and left in a loosely stoppered flask at room temperature for 12 hours. About 50 cc. of methanol was then distilled and the residue poured into water. The product was taken into ether and the extracts were concentrated to 50 cc. and kept at 5° for two days. The crystals were collected and a second crop from the mother liquor brought the total to 17.9 g. (78%) of good X. The analytical sample, recrystallized several times from ether, formed colorless crystals, m.p. 105–106°.

Anal. Calcd. for $C_{18}H_{24}O_5$: C, 67.5; H, 7.5. Found^o: C, 67.5; H, 7.4.

The corresponding amide, m.p. 168–169° after crystallization from alcohol, was obtained in small amount when it separated from the hydrolysis products of X (see below).

Anal. Calcd. for $C_{17}H_{23}O_4N$: C, 66.8; H, 7.5; N, 4.6. Found^o: C, 67.2; H, 7.5; N, 4.6.

2-(2,3-Dimethoxyphenyl)-2-ethylcyclohexanone (II).—A solution containing 12 g. of potassium hydroxide, 10 cc. of water, 100 cc. of alcohol and 17 g. of X was refluxed for four hours. The mixture was just acidified with concentrated hydrochloric acid and refluxed 30 minutes. About 50 cc. of solvent was distilled and the organic product isolated by ether extraction. After removal of the ether, the residue was left in a loosely stoppered flask for one month. The slowly formed crystals (small amount) proved to be the amide of X (see above). The remainder was carefully distilled to yield 9.5 g. (68%) of II, b.p. 130–131° at 0.4 mm., $n^{24}\mathrm{D}$ 1.5428.

Anal. Calcd. for $C_{16}H_{22}O_3$: C, 73.4; H, 8.4. Found^o: C, 73.4; 73.4; H, 8.4, 8.6.

This ketone, II, was recovered unchanged from attempts to: (1) form an oxime or semicarbazone; (2) form a 2,4-dinitrophenylhydrazone; (3) condense it with allylmagnesium bromide; (4) condense it with zinc and ethyl bromoacetate. Furthermore it failed to give any active hydrogen when treated with methylmagnesium iodide in butyl ether and xylene at room temperature. The carbonyl absorption band at 5.83 microns disappeared, however, on reduction with lithium aluminum hydride.

COLUMBUS, OHIO RECEIVED NOVEMBER 16, 1950

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[16] E. C. Horning and R. V. Schock, Jr., THIS JOURNAL, **70**, 2941 (1948), give b.p. 178–179 at 23 mm., $n^{25}\mathrm{D}$ 1.5157.

[17] Compare E. C. Horning, M. G. Horning and E. J. Platt, *ibid.*, (a), **69**, 2929 (1947); (b) **70**, 2072 (1948).