1-piperazyl)cyclohexyl]propiophenone (XI). We have not been able to convert the products derived from aryl vinyl ketones and cyclohexanone enamines into the expected bicyclic amino ketones.

Experimental[11]

Preparation of Enamines.—A solution of 1 mole of secondary amine, 1 mole of cycloalkanone, and 1 g. of *p*-toluenesulfonic acid in 300 ml. of toluene was heated under reflux for 1 day. The water liberated was collected in a Dean–Stark trap. The solvent was distilled and the residue was either distilled *in vacuo* or recrystallized from 2-propanol. The enamines tend to decompose on standing and should be purified just prior to use.

1-(1-Cyclohexen-1-yl)-4-phenylpiperazine was prepared in 84% yield, b.p. 125–140° (0.2 mm.), m.p. 112–114° from 2-propanol.

Anal. Calcd. for $C_{16}H_{22}N_2$: N, 5.72 (basic). Found: N, 5.92.[12]

1-(1-Cyclopenten-1-yl)-4-phenylpiperazine was prepared in 61% yield, m.p. 101° from 2-propanol.

Anal. Calcd. for $C_{15}H_{20}N_2$: N, 12.27 (total). Found: N, 12.40.

1-(1-Cyclohepten-1-yl)-4-phenylpiperazine was prepared in 27% yield, b.p. 140–180° (0.2 mm.), m.p. 59–61° from 2-propanol.

Anal. Calcd. for $C_{17}H_{24}N_2$: N, 10.92 (total). Found: N, 11.09.

4a,5,6,7,8,8a-Hexahydro-8a-(4-phenyl-1-piperazyl)-4H-1-benzopyran (I).—To a stirred solution of 14.1 g. (0.0583 mole) of 1-(1-cyclohexen-1-yl)-4-phenylpiperazine in 50 ml. of dry benzene was added a solution of 4.5 g. (0.080 mole) of acrolein in 25 ml. of dry benzene over a 30-min. period (5–10°). The solution was stirred at this temperature 1 hr., allowed to stand at room temperature 5 hr., then stored overnight in the refrigerator. The white crystals which had formed were collected and washed with a small amount of benzene–ether to give 4.6 g. of I: m.p. 117–118°; $\nu_{max}^{CHCl_3}$ 1660 (—O—CH=CH—), 1150, and 1070 cm.$^{-1}$ (ether). The n.m.r. spectrum ($CDCl_3$) showed resonance peaks due to the 2- and 3-protons at τ = 3.87 (doublet) and 5.41 p.p.m. (multiplet), respectively.

The benzene–ether filtrate from above was concentrated *in vacuo* to give a white solid. Recrystallization from benzene–hexane produced 7.6 g. of crystals, m.p. 113–114°, undepressed when mixed with an analytical sample of the aminopyran. The total yield was 12.2 g. (71%).

2-(4-Phenyl-1-piperazyl)bicyclo[3.3.1]nonan-9-one (Mixture of Isomers II and III).—To a solution of 9.03 g. of I in 100 ml. of freshly distilled dimethylformamide was added 3.1 g. of triethylamine. The solution was heated in a nitrogen atmosphere for 12 hr. at 70–75°. The solvents were distilled *in vacuo* and the residue was stirred with hexane. The crude solid weighed 7.61 g., m.p. 100–105°, $\nu_{max}^{CHCl_3}$ 1710 cm.$^{-1}$ (ketone C=O). Recrystallization from hexane and a few drops of benzene followed by recrystallization from a small quantity of methanol produced an analytical sample, m.p. 128–130°.

Separation of Isomers II and III.—A 21.2-g. sample of crude bicyclic amino ketone (obtained on concentration of the solvent used in the isomerization reaction) was dissolved in benzene and chromatographed on 350 g. of Brockmann activity I neutral alumina. Elution with benzene–ether (1:1) gave 20.0 g. of crystalline material (total from thirteen 125-ml. fractions). Thin layer chromatography on Merck aluminum oxide G[13] using benzene–ether (1:1) as developer showed fractions 2 and 3 (14.5 g.) to consist mainly of compound II. Recrystallization from methanol produced an analytical sample of the equatorial isomer (II), m.p. 129–130°.

Anal. Calcd. for $C_{19}H_{26}N_2O$: C, 76.51; H, 8.72; N, 9.40. Found: C, 76.39; H, 8.74; N, 9.50.

Fractions 4–6 (4.0 g.) were mixtures of II and III while fractions 7–13 (1.51 g.) consisted of compound III. An analytical sample of the axial isomer (III) was prepared by recrystallization from methanol, m.p. 100–101°; a mixture melting point with the equatorial isomer (II) was depressed, 85–90°.

Anal. Calcd. for $C_{19}H_{26}N_2O$: C, 76.51; H, 8.72; N, 9.40. Found: C, 76.62; H, 8.58; N, 9.46.

Sodium Borohydride Reduction of II.—A 1.00-g. sample of the amino ketone II was dissolved in 50 ml. of ethanol and treated with 1.2 g. of sodium borohydride. The mixture was heated under reflux 1 hr. after which excess hydrochloric acid was added. The solvent was distilled *in vacuo* and the aqueous mixture was made alkaline. A chloroform extract of the free base was concentrated *in vacuo* and the residual material was stirred with pentane to produce 0.75 g. of amino alcohol, m.p. 128–130°, $\nu_{max}^{CHCl_3}$ 3620 (free OH) and 3440 cm.$^{-1}$ (bonded OH).

Anal. Calcd. for $C_{19}H_{28}N_2O$: C, 76.00; H, 9.40; N, 9.33. Found: C, 75.80; H, 9.20; N, 9.25.

Sodium Borohydride Reduction of III.—A 0.17-g. sample of the amino ketone III in 10 ml. of ethanol was treated with 0.5 g. of sodium borohydride. The amino alcohol was isolated as described in the preceding experiment, yield 0.13 g., m.p. 145–147°. The infrared spectrum (10% in $CHCl_3$) showed no free OH absorption, but strong absorption centered at 3175 cm.$^{-1}$ was present (bonded OH). The intramolecular nature of this hydrogen bonding was shown by the fact that no free OH absorption appeared when the spectral solution was diluted.[7]

Anal. Calcd. for $C_{19}H_{28}N_2O$: C, 76.00; H, 9.40; N, 9.33. Found: C, 75.33; H, 9.24; N, 9.17.

3-Phenyl-3-[2-(4-phenyl-1-piperazyl)-2-cyclohexenyl]propiophenone (X).—A sample of the aminopyran IX (m.p. 129–130°, $\nu_{max}^{CHCl_3}$ 1660 cm.$^{-1}$) was recrystallized from methanol to give compound X in 60% yield, m.p. 135–136°, $\nu_{max}^{CHCl_3}$ 1685 (aromatic C=O) and 1645 (w, enamine C=C) cm.$^{-1}$. The n.m.r. spectrum ($CDCl_3$) showed a triplet centered at τ = 5.09 (vinyl proton) p.p.m. The analytical sample was prepared by a further recrystallization from ethanol, m.p. 134–135°; a mixture melting point with IX was depressed, 124–126°.

Anal. Calcd. for $C_{31}H_{34}N_2O$: C, 82.66; H, 7.56; N, 6.22. Found: C, 82.36; H, 7.63; N, 6.25.

3-Phenyl-3-[2-(4-phenyl-1-piperazyl)cyclohexyl]propiophenone (XI).—A 10.0-g. sample of compound X was dissolved in 250 ml. of ethyl acetate and hydrogenated in the presence of 3 g. of 10% palladium on charcoal (room temperature, 50 p.s.i.). After 12 hr., the catalyst and precipitated product were collected. The mixture was heated in ethyl acetate and the catalyst was filtered. Leaf-like crystals collected in the filtrate, yield 4.7 g., m.p. 176–177°. The filtrate, on concentration, yielded an additional 2.3 g. of product; the total yield of XI was 7.0 g. The infrared spectrum ($CHCl_3$) showed a strong band at 1685 cm.$^{-1}$ (aromatic C=O). The band at 1645 cm.$^{-1}$ (due to C=C) in the spectrum of X was absent. An analytical sample of XI was prepared by recrystallization from ethyl acetate, m.p. 176–177°.

Anal. Calcd. for $C_{31}H_{36}N_2O$: C, 82.30; H, 7.96; N, 6.19. Found: C, 82.10; H, 7.89; N, 6.17.

Acknowledgment.—The authors wish to thank Dr. Charles D. Hurd of Northwestern University for helpful discussions during the course of this work and Dr. Dale A. Stauffer and associates for the analytical services.

(11) Melting points were taken with a Büchi capillary melting point apparatus and are uncorrected. Infrared spectra were determined with a Perkin-Elmer Model 237 grating spectrophotometer. The n.m.r. spectra were determined at 60 Mc. with a Varian Model A-60 spectrometer.

(12) Basic nitrogen values were determined by nonaqueous titration.

(13) Distributed by Brinkmann Instruments, Inc., Great Neck, Long Island, N. Y.

Lupenone and 18α-Oleanan-19α-ol-3-one from *Samadera indica*

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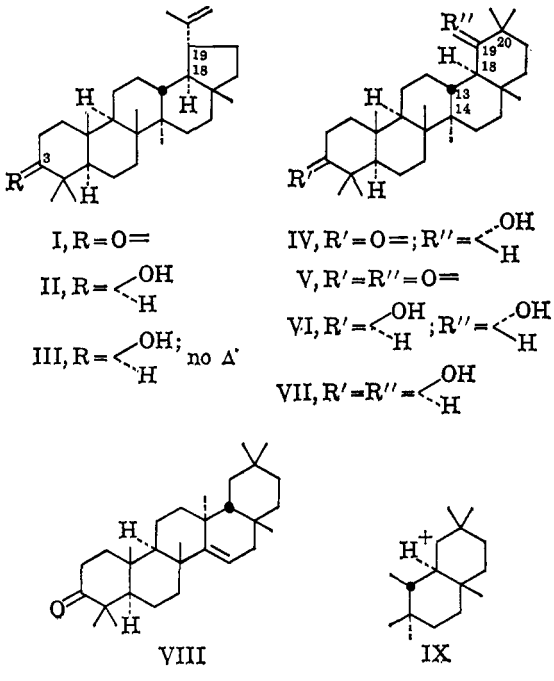
Interest in the constituents of *Samadera indica* Gärtn. (*Simarubaceae*), a tree found in Ceylon, India, and Java, originally centered on the bitter principle samaderin, first isolated in crystalline form by van

Tonningen[1] and later again by van der Marck.[2] Recently Polonsky, Zylber, and Wijesekera,[3] working with bark collected in Ceylon, showed "samaderin" to consist of at least three components, samaderins A, B, and C, all tricyclic terpenoid lactones, the structure of two of which (B and C) has now been elucidated.[4] From the petroleum ether extract of the bark the French authors isolated the triterpene, taraxerone (VIII), and the steroids, stigmastanone and stigmasterol.

In 1956 we worked up a batch of *Samadera indica* bark collected in the Travancore–Madras border area of western India with the view of studying the pharmacological properties of "samaderin." A crystalline substance answering the description of "samaderin" by van der Marck and, in the light of the work of the French investigators,[3] consisting of samaderin C contaminated with about 20% of samaderin D,[4] was readily obtained from the hexane-insoluble fraction of the ethanol extract of the bark.

The hexane-soluble fraction was distributed between hexane and 90% ethanol. The material remaining in the hexane phase yielded, on chromatography on alumina, substantial amounts of lupenone (I), the identity of which was confirmed by the preparation of the oxime and the 2,4-dinitrophenylhydrazone, and by conversion to lupeol (II) and further to lupanol (III) (see Chart I).

CHART I



Fractionation by chromatography of the products in the alcoholic phase afforded, besides additional amounts of lupenone, a hydroxy ketone $C_{30}H_{50}O_2$, m.p. 240–244°, $[\alpha]_D$ +27.5°, which was eventually recognized as the 18α-oleanan-19α-ol-3-one (IV) which Ames, Davy, Halsall, and Jones[5] had obtained from lupenone by treatment with formic acid in benzene and hydrolysis with alkali of the 19-formate which is the primary product of the reaction. Since the melting point and rotation reported by the British workers differed somewhat from ours (m.p. 229–233°, $[\alpha]_D$ +21°), the identity of the isolated hydroxy ketone remained in doubt until it had been subjected to oxidation and reduction. Thus the diketone obtained from it by chromic acid oxidation was unmistakably the 18α-oleanana-3,19-dione (V) described by Ames, *et al.*,[5] and likewise the constants of the diol prepared with sodium borohydride were those reported by these investigators for 18α-oleanana-3β,19α-diol (VI). We, furthermore, prepared from the dione V its lithium aluminum hydride reduction product, 18α-oleanana-3β,19β-diol (VII),[5] identified as the 3-monoacetate.[5]

While lupeol "would appear to be the most widely distributed of all triterpenes,"[6] lupenone has been encountered but twice before in nature, namely, in the bark of *Alnus incana* L. Moench (gray alder tree)[7] and of *Alnus glutinosa* (black alder).[8] It is interesting that both *A. incana*[7] and *A. glutinosa*[9,10] are known to produce also taraxerone, which, as mentioned initially, has been isolated by Polonsky, *et al.*,[3] from *Samadera indica* growing in Ceylon, and that *A. glutinosa* is the source of yet another triterpenoid ketone, glutinone (alnusenone).[8,10]

As far as we know, there is no record of the previous isolation of 18α-oleanan-19α-ol-3-one (IV) (or of the related diols VI and VII) from a plant source. In view of the rather mild conditions under which formic acid effected the partial conversion of lupenone to the formate of IV (shaking of a benzene solution of the former with a large excess of the acid for 7 days at room temperature),[5] the possibility that IV was an artifact formed from lupenone during the isolation process could not be entirely discounted. Since the only acidic reagent with which the terpenes were in contact during isolation was the acid-washed alumina (Merck) used in the last chromatographic step, a benzene solution of pure lupenone was slowly percolated through a column of this adsorbent. However, even the final eluate portions emerging from the column contained only lupenone. We also considered the possibility that the alcohol used for the extraction of the bark might have been accidentally contaminated with a mineral acid or acetic acid, having particularly in mind the finding of Halsall, Jones, and Meakins[11] that lupeol, on treatment at 20° with ethanol saturated with hydrogen chloride, gives rise to 19α-chloro-18α-oleanan-3β-ol. However, nowhere in the isolation procedure were the terpenes exposed to strongly alkaline conditions such as might have effected the replacement of the chlorine substituent in this compound by hydroxyl. As regards sulfuric acid as a contaminant of the alcohol, the effect of this acid on lupeol has been studied only in acetic acid solution, where, depending on concentration, it leads to the formation either of lupenol (I,

(1) D. W. R. van Tonningen, *Arch. Pharm.*, **146**, 265 (1858).
(2) J. L. B. van der Marck, *ibid.*, **39**, 96 (1901).
(3) J. Polonsky, J. Zylber, and R. O. B. Wijesekera, *Bull. soc. chim. France*, 1715 (1962).
(4) J. Zylber and J. Polonsky, *ibid.*, 2016 (1964).
(5) T. R. Ames, G. S. Davy, T. S. Halsall, and E. R. H. Jones, *J. Chem. Soc.*, 2868 (1952).
(6) J. Simonsen and W. C. J. Ross, "The Terpenes," Vol. IV, Cambridge University Press, Cambridge, 1957, p. 339.
(7) A. A. Ryabinin and L. G. Mamyuzhina, *Zh. Obshch. Khim.*, **31**, 1033 (1961); *Chem. Abstr.*, **55**, 22501*h* (1961).
(8) Isolated as lupeol after reduction of the total ketonic fraction: S. Chapon and S. David, *Bull. soc. chim. France*, 333 (1953).
(9) J. Zellner and L. Weiss, *Monatsh. Chem.*, **46**, 309 (1926).
(10) J. H. Beaton, F. S. Spring, and R. Stevenson, *J. Chem. Soc.*, 2616 (1955).
(11) T. G. Halsall, E. R. H. Jones, and G. D. Meakins, *ibid.*, 2862 (1952).

18α-ursane skeleton) or of δ-amyrenol [olean-13(18)-en-3β-ol].[12] There is nothing in the literature to indicate that acetic acid alone affects lupeol or lupenone.

On balance of the evidence it is then reasonable to assume that the isolated oleanane derivative was not an artifact, but occurred as such in the plant. This would be well in line with the postulate of Ruzicka[13] that the cation IX functions as the biogenetic precursor of all pentacyclic terpenes having a six-membered ring E, including taraxerol.

Experimental

The melting points were taken in open Pyrex capillaries and are corrected for stem exposure. The rotation measurements were carried out in a 1-dm. semimicrotube, with chloroform as the solvent.

Extraction of *Samadera indica*.—The ground, dried bark (39 kg.) of *Samadera indica* was extracted by refluxing for 2 hr. with 234 l. of 95% ethanol. This was repeated twice more with fresh portions of 95% ethanol. The ethanol solution was reduced to a volume of 3 l. and then dried in trays under vacuum at 40° to give 1.871 kg. of dark brown tarry material. This material was stirred three times with 12 l. of warm (55°) hexane for 15-min. periods and the total hexane solution was evaporated to 2 l. After washing with two 1.5-l. portions of 90% ethanol and backwashing the ethanol solutions with 2 l. of hexane, the hexane solutions were concentrated to about 500 ml. After standing for 2 days at room temperature, large needles had deposited which were collected and washed with absolute ethanol. Chromatography on Merck acid-washed alumina and elution with hexane gave, after two recrystallizations from 95% ethanol, 27.9 g. (0.07% of bark) of lupenone (I), m.p. 166–169°. Further recrystallization raised the melting point to 170–171°, $[\alpha]_D$ +58.7° (*c* 0.83); lit.[14] m.p. 170.5–171.2°, $[\alpha]_D$ +57.6°.

Anal. Calcd. for $C_{30}H_{48}O$: C, 84.84; H, 11.39. Found: C, 85.19; H, 10.93.

The oxime had m.p. 278–287.5° (lit.[14] m.p. 267°).

Anal. Calcd. for $C_{30}H_{49}NO$: C, 81.94; H, 11.23; N, 3.19. Found: C, 82.11; H, 10.55; N, 3.17.

The 2,4-dinitrophenylhydrazone had m.p. 218.5–220° (lit.[14] m.p. 214°).

Anal. Calcd. for $C_{36}H_{52}N_4O_4$: C, 71.49; H, 8.67; N, 9.26. Found: C, 71.38; H, 8.50; N, 9.51.

Reduction of the ketone with sodium borohydride in methanol gave crude **lupeol (II)**, which, after two recrystallizations from ethanol, had m.p. 212–214°, $[\alpha]^{22}_D$ +27.1° (*c* 0.96); lit.[14] m.p. 215–216°, $[\alpha]_D$ +27.2°.

Anal. Calcd. for $C_{30}H_{50}O$: C, 84.44; H, 11.81. Found: C, 84.31; H, 11.75.

The acetate melted at 218–219° and had $[\alpha]^{22}_D$ +37.8° (*c* 0.696); lit.[14] m.p. 220°, $[\alpha]_D$ +47.3.

The hitherto undescribed 2,4-dinitrobenzoate was prepared from lupeol with 2,4-dinitrobenzoyl chloride and pyridine (17 hr., room temperature), m.p. 286–287°.

Anal. Calcd. for $C_{37}H_{52}N_2O_6$: C, 71.58; H, 8.44; N, 4.51. Found: C, 71.65; H, 8.32; N, 4.75.

On catalytic hydrogenation (platinum, ethanol, uptake 1 mole/mole), lupeol gave pure lupanol (III): m.p. 202–203°, $[\alpha]^{23}_D$ −14.7° (*c* 0.856); lit.[15] m.p. 206°, $[\alpha]_D$ −17.8°.

The 90% ethanol solution obtained from the above distribution with hexane was taken to dryness. The residue (125 g.) was chromatographed on 2 kg. of Merck acid-washed alumina and 1.5-l. fractions were collected. Fractions 2–4 (benzene) gave a large amount of oil from which was obtained, after recrystallization from ethanol, an additional 6 g. of lupenone. Fractions 5–10 (benzene) gave 8.38 g. of oily crystals. After four recrystallizations from ethanol, 1.03 g. of **18α-oleanan-19α-ol-3-one** (IV) was obtained: m.p. 240–244°, $[\alpha]^{22}_D$ +27.5° (*c* 1.07); lit.[5] m.p. 229–233°, $[\alpha]^{22}_D$ +21°.

Anal. Calcd. for $C_{30}H_{50}O_2$: C, 81.39; H, 11.38. Found: C, 81.40; H, 11.33.

The 2,4-dinitrophenylhydrazone had m.p. 268–270°.

Anal. Calcd. for $C_{36}H_{54}N_4O_5$: C, 69.42; H, 8.74; N, 9.00. Found: C, 69.52; H, 8.57; N, 9.22.

Attempted acetylation with acetic anhydride–pyridine at room temperature gave only starting material.

18α-Oleanone-3,19-dione (V).—A solution of chromic anhydride (30 mg.) in glacial acetic acid (1 ml.) and 1 drop of water was added dropwise to 18α-oleanan-19α-ol-3-one (99 mg.) dissolved in glacial acetic acid (10 ml.). The mixture was kept at room temperature for 32 hr. and then worked up in the usual way. Two recrystallizations of the crude product from absolute ethanol gave 18α-oleanana-3,19-dione (47 mg.): m.p. 251–254°, $[\alpha]^{22}_D$ +73.7° (*c* 0.95); lit.[5] m.p. 249–252°, $[\alpha]^{20}_D$ +70°.

Anal. Calcd. for $C_{30}H_{48}O_2$: C, 81.76; H, 10.98. Found: C, 81.71; H, 10.69.

18α-Oleanana-3β,19α-diol (VI).—A solution of 18α-oleanan-19α-ol-3-one (106 mg.) in ethanol (15 ml.) was added dropwise to a stirred solution of 207 mg. of sodium borohydride in 4 ml. of ethanol. The mixture was then heated at reflux for 3 hr. After cooling, it was acidified with 10% acetic acid and diluted with water. The resulting precipitate was collected (69 mg.). The filtrate was concentrated to remove the ethanol and extracted with chloroform. The chloroform solution was washed with sodium bicarbonate and water, dried over sodium sulfate, and evaporated to give an additional 32 mg. of material. The combined solids, after two recrystallizations from methanol–chloroform, gave 72 mg. of 18α-oleanana-3β,19α-diol: m.p. 248–249°, $[\alpha]^{24}_D$ −0.7° (*c* 1.08); lit.[5] m.p. 249–249.5°, $[\alpha]^{20}_D$ −3°.

Anal. Calcd. for $C_{30}H_{52}O_2$: C, 81.02; H, 11.79. Found: C, 81.07; H, 11.64.

The 3-monoacetate, prepared by overnight treatment of the diol with acetic anhydride, after purification melted at 255.5–257° and had $[\alpha]^{20}_D$ +6.1° (*c* 0.87); lit.[5] m.p. 249–250°, $[\alpha]^{20}_D$ +7°.

Anal. Calcd. for $C_{32}H_{54}O_3$: C, 78.96; H, 11.18. Found: C, 78.97; H, 11.16.

18α-Oleanana-3β,19β-diol 3-Acetate.—A saturated ether solution of lithium aluminum hydride (2 ml.) was added to a solution of the crude dione V (27 mg.) in tetrahydrofuran (4 ml.), and the mixture was heated under reflux for 2 hr. The excess lithium aluminum hydride was decomposed by the addition of a saturated sodium sulfate solution. The organic layer was decanted and washed with 5% hydrochloric acid and saturated sodium chloride solution, dried over magnesium sulfate, and evaporated to give 29 mg. of crude 18α-oleanana-3β,19β-diol (VII), m.p. 250–260°. The infrared spectrum showed the complete absence of any carbonyl absorption.

The crude diol was treated with 1 ml. of acetic anhydride and 2 ml. of pyridine overnight at room temperature. Purification of the crude product (25 mg.) by thin layer chromatography on activity V alumina with hexane–chloroform (1:1) and recrystallization of the eluted spot from methanol gave 7 mg. of 18α-oleanana-3β,19β-diol 3-acetate: m.p. 295–297°; lit.[5] m.p. 294.5–295°.

Anal. Calcd. for $C_{32}H_{54}O_3$: C, 78.96; H, 11.18. Found: C, 79.01; H, 11.23.

(12) For a summarizing account of the isomerization of lupeol by acids, see ref. 6, pp. 364–367.

(13) L. Ruzicka, *Proc. Chem. Soc.*, 341 (1959).

(14) In ref. 6, p. 331.

(15) In ref. 6, p. 332.

Synthesis and Stereochemistry of Hydrophenanthrenes. III.[1] The Reaction of 1,3-Dicyclohexyl-1-(1,2,3,9,10,10aβ-hexahydro-7-methoxy-2α-phenanthrylcarbonyl)urea with Sodium Alkoxides

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During the course of the synthesis of hydrophenanthrene derivatives, a convenient method was required

(1) Part II of this series: Z. G. Hajos, D. R. Parrish, and M. W. Goldberg, *J. Org. Chem.*, **30**, 1213 (1965).

(2) Deceased Feb. 17, 1964.